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AN EFFICIENT SOLVENT- AND CATALYST-FREE SYNTHESIS OF BICYCLIC PYRIDONES WITH HIGH MOLECULAR DIVERSITY VIA CASCADE REACTION

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Abstract – Two efficient cascade routes for synthesis of substituted bicyclic pyridines under solvent- and catalyst-free conditions have been developed. One is conducted by refluxing the reaction mixture of heterocyclic ketene amins (HKAs), triethoxymethane and dicarbonyl compounds. The other one is proceeded with HKAs and diethyl ethoxymethylenemalonate (EMME) under ultrasound irradiation. Both routes for preparation of bicyclic 2-pyridones carried out with low cost and easy available substrates and achieved diversity of target compounds in good yields efficiently and environmental-friendly.

Amongst the numerous multifused *N*-heterocycles, bicyclic pyridones containing a ring-junction nitrogen are frequently found in pharmacophores and natural products,¹ such as hydroxycamptothecin,² topotecan,³ irinotecan,⁴ huperzine A,⁵ etc. (Figure 1). Bicyclic pyridones have been proved to be the inhibitors of thrombin,⁶ acetylcholinesterase,⁷ human rhinovirus (HRV) 3C protease (3CP)⁸ and reported as the agents with anticancer,⁹ antimicrobial,¹⁰ anti-HIV,¹¹ antidiabetic¹² or antifungal¹³ biological activities. Owing to the biologically and structurally interesting properties, a large number of synthetic methods for the construction of bicyclic pyridone compounds have been established. Among them, aza-ene reaction,¹⁴ aza-Michael addition,¹⁵ aza-Diels-Alder reaction¹⁶ and cross-coupling reaction^{12,17} have been widely explored to synthesize pyridone derivatives. The condensation reaction of enamines and alkoxymethylenemalonate¹⁸ is another important method for pyridine synthesis. However, the previous methods require

use of solvents, catalysts, bases or acids, such as 1,4-dioxane, toluene, acetonitrile, Cu_2O , ruthenium or palladium. A rapid synthetic route for the construction of 2-pyridones under catalyst- and solvent-free reaction conditions from enamino esters and diethyl ethoxymethylenemalonate at high temperature (130°C)¹⁹ was reported in 2016. Thus, developing environmental-friendly and efficient methods to provide bicyclic pyridone material basis for the development of wider applications is an inevitable trend.

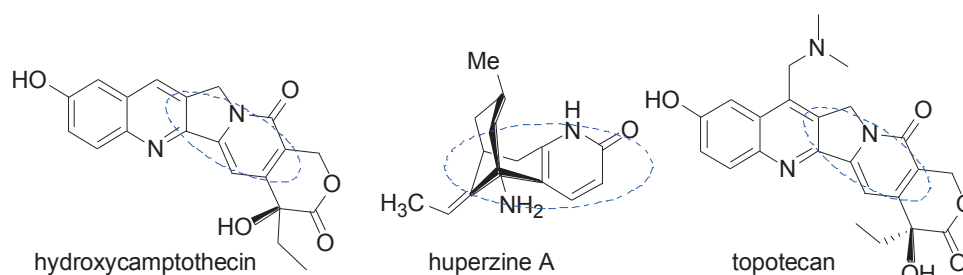
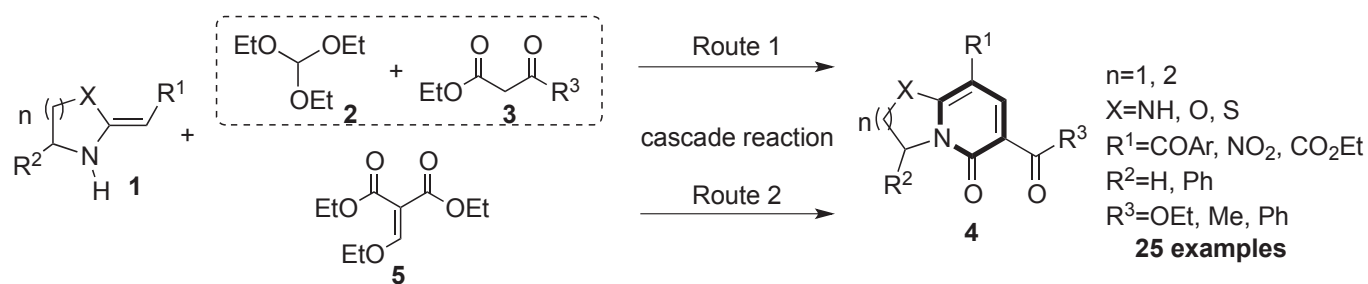


Figure 1. Bicyclic pyridone derivatives with biological activities

Cascade synthesis is an effective strategy for composition of functional molecules in modern organic synthesis.²⁰ The processes of cascade reaction involve multiple bond formations in one pot, which avoid lengthy separation process and purification of intermediates¹⁶ while increasing product yields and reducing in pollution.¹⁷ As a part of our continuous interest directed toward the development of new methodologies, we utilized the enamino esters analogues polynucleophilic heterocyclic ketene animals (HKAs) to construct diversified bicyclic pyridones via cascade reaction.

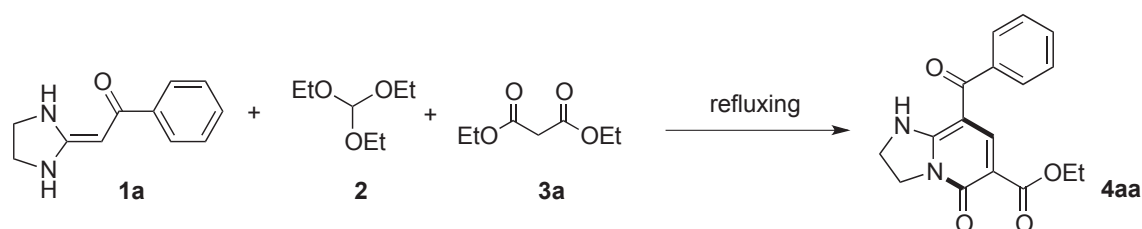
In this paper, two solvent- and catalyst-free cascade synthesis protocols with HKAs have been designed for the preparation of highly substituted 2-bicyclic pyridones. Firstly, we used HKAs and different types of dicarbonyl compounds (aliphatic malonic acid diethyl ester, 3-oxobutyric acid ethyl ester and aromatic 3-oxo-3-phenylpropionic acid ethyl ester) with triethoxymethane as substrates (Scheme 1, Route 1). At the same time, we found another novel cascade synthesis of bicyclic pyridones with EMME and HKAs including five-/six-membered HKAs, *N*, *O*-acetals or *N*, *S*-acetals (Scheme 1, Route 2).



Scheme 1. Synthesis of dicyclopriodones with HKAs

To optimize the reaction conditions, we chose HKAs **1a**, triethoxymethane **2** and diethyl malonate **3a** as the model substrates (Table 1). After the screening of solvents (1 mL; EtOH, MeCN, dioxane or acetone), catalysts (0.1 mmol; acetic acid, triethylamine, BuOK or NaH) (entries 1-4 and entries 4-8) and the ratio of **1a**, **2** and **3a**, we found that the optimal reaction conditions for synthesis of bicyclic pyridones were refluxing the reaction mixture of **1a**: **2**: **3a**=1.0: 1.2: 1.2 for 35 min under solvent- and catalyst-free conditions (entry 9) with an isolated product of a good yield (82%).

Table 1. Optimization of three-component reaction conditions^a



Entry	1a : 2 : 3a	Solvent	Catalyst	Time (h)	Yield ^b (%)
1	1.0:1.2:1.2	EtOH	-	1.0	35
2	1.0:1.2:1.2	MeCN	-	1.0	44
3	1.0:1.2:1.2	1,4-dioxane	-	1.0	53
4	1.0:1.2:1.2	acetone	-	1.0	49
5	1.0:1.2:1.2	-	acetic acid	2.0	43
6	1.0:1.2:1.2	-	triethylamine	2.0	52
7	1.0:1.2:1.2	-	BuOK	2.0	34
8	1.0:1.2:1.2	-	NaH	2.0	23
9	1.0:1.2:1.2	-	-	0.5	82
10	1.2:1.0:1.0	-	-	0.5	75
11	1.0:1.2:1.0	-	-	0.5	66

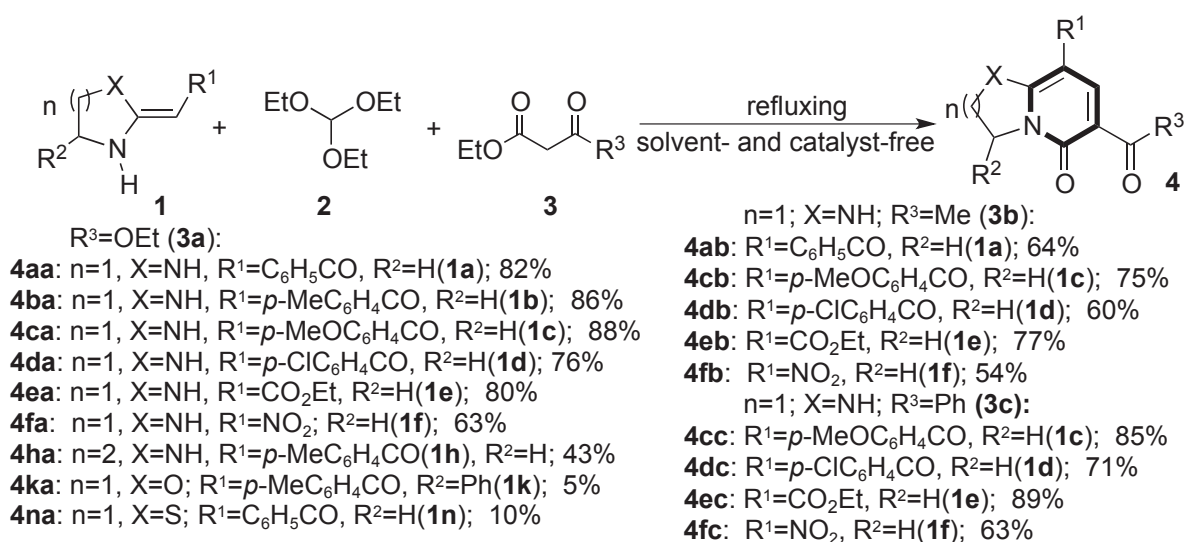
^aUnless otherwise specified, the reaction was performed by refluxing the reaction mixture of **1a**, **2** and **3a** under solvent- and catalyst-free conditions; ^bIsolated yields based on HKA **1a**.

To demonstrate the utility of the optimal reaction conditions for this three-component cascade synthesis of bicyclic pyridones, we used different HKAs as synthetic building blocks (Scheme 2). The results showed that structures of the HKAs influenced the reactivity and product yields significantly. Five-membered HKAs (**1a-1f**) proved to be more active than the six-membered ones (**1h**), giving higher yields of the desired compounds. Moreover, the reactivity of HKAs was increased with the electron-rich properties of the α -C atoms (**1b** and **1c**). The stronger electron-withdrawing groups HKA contains, the lower reactivity the substrate possesses (**1d** and **1f**). *N*, *O*-Acetal and *N*, *S*-acetal gave much lower yields of bicyclic pyridones (**1k** and **1n**).

Next we studied the tolerance of this three-component reaction towards different dicarbonyl compounds. Both aromatic and aliphatic dicarbonyl compounds were suitable for this transformation, and prolonging

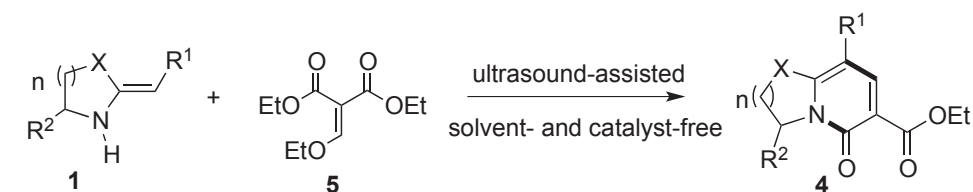
the reaction time aromatic 3-oxo-3-phenylpropionic acid ethyl ester (Scheme 2, **3c**) furnished the products in relatively higher yields with respect to aliphatic 3-oxobutyric acid ethyl ester (Scheme 2, **3a** and **3b**). While HKAs showed the same tendency, that the reactivity was decreased with the electron-poor properties of α -carbon (Scheme 2, **1d** and **1f**).

Diethyl ethoxymethylenemalonate (EMME) **5** can be prepared with the commercially available raw materials triethoxymethane **2** and diethyl malonate **3**. In order to extend functional group variations of bicyclic pyridones and provide more powerful basis for the analysis of reaction mechanism, we chose EMME and HKAs as substrates to form the desired products under solvent-free conditions with no catalyst. The reaction of HKA **1g** and EMME **5** could afford bicyclic pyridone **4ga** in the yield 61% after magnetic stirring at room temperature for 24 h. While shorter reaction time and higher product yields of this reaction can be obtained under ultrasonic irradiation. When the reaction carried out at 25-30 °C by sonicating for 5 h, the product **4ga** afforded in 82% yield.



Scheme 2. Synthesis of dicyclopyridones by three-component cascade reaction

With the optimized conditions in hand, the scope and generality of the reactions were evaluated with electronically diverse five-membered HKAs (Scheme 3, **1a-1f**), six-membered HKAs (Scheme 3, **1g-1j**), *N*, *O*-acetals (Scheme 3, **1k-1m**) and *N*, *S*-acetals (Scheme 3, **1n-1p**). This reaction showed the generality with respect to the substrate scope against HKAs and afforded bicyclic pyridones from **1g-1p** in much higher yields than the three-component proposal. The HKAs bearing an electron-donating group at the *para*-positions of phenyl rings (Scheme 3, **1b**, **1c**, **1e**, **1h**, **1i**, **1l** and **1o**) furnished the products in slightly higher yields. *N*, *O*-Acetal substituted with phenyl group next to the secondary amine (Scheme 3, **1k**) was tolerated well in this reaction.



n=1; X=NH:

4aa: R¹=C₆H₅CO, R²=H(**1a**); 70%

4ba: R¹=*p*-MeC₆H₄CO, R²=H(**1b**); 71%

4ca: R¹=*p*-MeOC₆H₄CO, R²=H(**1c**); 75%

4da: R¹=*p*-ClC₆H₄CO, R²=H(**1d**); 67%

4ea: R¹=CO₂Et, R²=H(**1e**); 83%

4fa: R¹=NO₂, R²=H(**1f**); 59%

n=1; X=O:

4ka: R¹=C₆H₅CO, R²=Ph(**1k**); 78%

4la: R¹=*p*-MeOC₆H₄CO, R²=H(**1l**); 80%

4ma: R¹=*p*-ClC₆H₄CO, R²=H(**1m**); 72%

n=2; X=NH:

4ga: R¹=C₆H₅CO, R²=H(**1g**); 82%

4ha: R¹=*p*-MeC₆H₄CO, R²=H(**1h**); 84%

4ia: R¹=*p*-MeOC₆H₄CO, R²=H(**1i**); 85%

4ja: R¹=*p*-ClC₆H₄CO, R²=H(**1j**); 76%

n=1, X=S:

4na: R¹=C₆H₅CO, R²=H(**1n**); 71%

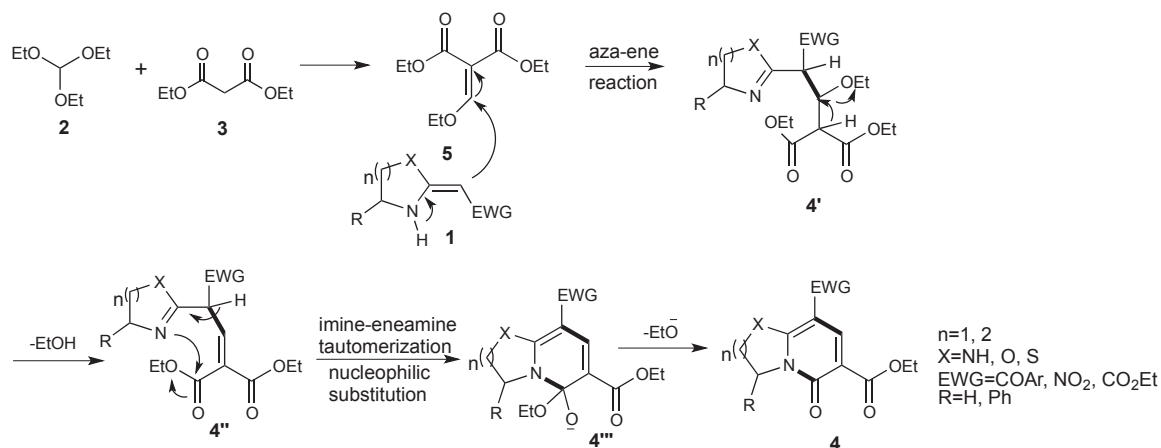
4oa: R¹=*p*-MeC₆H₄CO, R²=H(**1o**); 75%

4pa: R¹=*p*-ClC₆H₄CO, R²=H(**1p**); 69%

Reaction conditions: HKAs (1.0 mmol) and EMME (5.0 mmol) were sonicated at 25-30 °C in the water bath with an ultrasonic washer for 5 h. The reaction temperature was controlled by adding cool water or ice into the bath water and observed with a mercurial thermometer; All yields isolated by Column chromatography were shown on 1.0 mmol scale based on HKAs.

Scheme 3. Synthesis of dicyclopyridones by two-component cascade reaction

A proposed mechanism for the one-pot cascade reaction was depicted in Scheme 4. Triethoxymethane **2** reacted with diethyl malonate **3a** to form EMME **5**. Due to the conjugation of electron-donating amino groups and the electron-withdrawing group (COR or NO₂) with a double bond, the α-carbon of HKAs possesses much higher electron density, which acted as a nucleophile to attack the electron deficient double bond of EMME that is influenced by two electrophilic carbonyl groups to form **4'** possibly via an aza-ene mechanism. Then, the terminal ethoxyl group of **4'** was easily removed a molecule of ethanol to give **4''**. Bicyclic 2-pyridone **4** as the final product was obtained after a process of imine-eneamine tautomerization, nucleophilic substitution, cyclization and an elimination of ethoxy moiety.



Scheme 4. Proposed mechanism for the three-component cascade reaction

To summarize, we have developed two efficient cascade routes to synthesize substituted bicyclic pyridones under solvent-free and catalyst-free conditions. One was conducted by refluxing the reaction mixture of HKAs **1**, triethoxymethane **2** and dicarbonyl compounds **3**. The five-membered HKAs can react with dicarbonyl compounds either aromatic 3-oxo-3-phenylpropionic acid ethyl ester or aliphatic 3-oxobutyric acid ethyl ester/diethyl malonate and triethoxymethane to form dicyclopriidones in moderate to good yields. The other one is proceeded with HKAs and EMME under ultrasound irradiation. The five-/six-membered HKAs, *N*, *O*-acetals and *N*, *S*-acetals were suitable for the transformation of desired products. These two routes complement with each other, more pyridine ketones with different substituting groups have been synthesized, and the correctness of reaction mechanism has been further proved. Mechanistically, this three-component cascade reaction proceeds via Michael reaction to form EMME, then EMME reacted with HKAs via aza-ene reaction, and the products obtained after a process of nucleophilic substitution. Both routes for preparation of bicyclic 2-pyridones carried out with low cost and easy available substrates and achieved diversity of target compounds in good yields efficiently and environmental-friendly.

EXPERIMENTAL

All compounds were characterized by full spectroscopic data. The melting points were determined on X-5 melting point apparatus without correction. NMR spectra were recorded on a Bruker AVANCE III 400 spectrometer (^1H NMR: 400 MHz, ^{13}C NMR: 100 MHz) in CDCl_3 or $\text{DMSO}-d_6$, chemical shifts (d) are expressed in ppm, and J values are given in Hz. IR spectra (KBr pellet) were detected by a Thermo Nicolet iS10 FT-IR instrument. The reaction monitoring and purity determination of the substrates were accomplished by thin layer chromatography (TLC) on silica gel PolyGram SILG/UV 254 plates. HRMS were performed on an Agilent LC/MSD TOF instrument. Column chromatography was performed on silica gel (200-300 mesh).

Starting Materials. The HKAs used in this work were synthesized according to the literature,²¹ other chemicals and solvents were purchased from chemical companies and used without further purification.

Typical procedure for the preparation of bicyclic pyridones (4):

Route 1. The three-component cascade reaction: 1.0 mmol of the HKA **1** was added followed by 1.2 mmol of triethoxymethane **2** and corresponding dicarbonyl compound **3** (1.2 mmol), the mixture was refluxed for 30-65 min, the reaction was monitored by thin-layer chromatography using EtOAc/petroleum ether (8: 1, by vol.) as developing system. When HKAs were consumed completely, the reaction was terminated. The residue was purified by silica gel column chromatography (EtOAc: petroleum ether = 5: 1).

Route 2. Synthesis of dicyclopriidones with HKAs and EMME: HKAs **1a-p** (1.0 mmol) and EMME **5**

(5.0 mmol) were added into the reaction tube, all reactions were carried out at 25-30 °C under ultrasonic irradiation for 5 h. The reaction mixture was purified by flash silica gel column chromatography (CH₂Cl₂: MeOH = 25: 1) to afford product **4** as white solid in isolated yield from 59% to 85%.

8-Benzoyl-7-oxo-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylic acid ethyl ester (4aa): White needle-like crystals; Mp 226-228 °C (Ref. 234-236 °C²²); ¹H NMR (400 MHz, CDCl₃): δ 8.75 (br, 1H, NH), 8.51 (s, 1H, CH), 7.49-7.58 (m, 5H, ArH), 4.26-4.33 (m, 4H, CH₂CH₃ and NCH₂), 4.06 (t, *J* = 9.64, 2H, NHCH₂), 1.32 (t, *J* = 7.04, 3H, CH₃).

8-(4-Methylbenzoyl)-7-oxo-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylic acid ethyl ester (4ba): White needle-like crystals; Mp 203-205 °C (Ref. 203-205 °C²²); ¹H NMR (400 MHz, CDCl₃): δ 8.79 (br, 1H, NH), 8.54 (s, 1H, CH), 7.49 (d, *J* = 7.84, 2H, ArH), 7.30 (d, *J* = 8.40, 2H, ArH), 4.28-4.31 (m, 4H, CH₂CH₃ and CONCH₂), 4.02-4.06 (m, 2H, NHCH₂), 2.44 (s, 3H, ArCH₃), 1.34 (t, *J* = 7.04, 3H, CH₃).

8-(4-Methoxybenzoyl)-7-oxo-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylic acid ethyl ester (4ca): White needle-like crystals; Mp 213-215 °C; IR (KBr) (ν_{max}, cm⁻¹) 3452, 3340, 2984, 1727, 1669, 1609, 1561, 1256, 1230, 1174, 842 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.64 (br, 1H, NH), 8.49 (s, 1H, CH), 7.51 (d, *J* = 8.40, 2H, ArH), 6.91 (d, *J* = 8.40, 2H, ArH), 4.20-4.25 (m, 4H, CH₂CH₃ and CONCH₂), 3.97 (t, *J* = 9.56, 2H, NHCH₂), 3.81 (s, 3H, OCH₃), 1.26 (t, *J* = 7.08, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 190.8, 164.1, 161.4, 157.4, 148.7, 129.7, 129.6, 112.8, 105.6, 96.7, 59.7, 54.5, 42.6, 42.1, 13.4; HRMS (ESI-TOF⁺): *m/z* Calcd for C₁₈H₁₈O₅N₂Na [(M+Na)⁺] 365.1108; found, 365.1107.

8-(4-Chlorobenzoyl)-7-oxo-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylic acid ethyl ester (4da): White needle-like crystals; Mp 278-279 °C (Ref. 280-281 °C²²); ¹H NMR (400 MHz, CDCl₃): δ 8.79 (br, 1H, NH), 8.42 (s, 1H, CH), 7.51-7.45 (m, 4H, ArH), 4.25-4.32 (m, 4H, CH₂CH₃ and CONCH₂), 4.04 (t, *J* = 9.96, 2H, NHCH₂), 1.32 (t, *J* = 7.08, 3H, CH₃).

7-Oxo-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6,8-dicarboxylic acid diethyl ester (4ea): White needle-like crystals; Mp 211-213 °C; IR (KBr) (ν_{max}, cm⁻¹) 3390, 2986, 2318, 1728, 1667, 1644, 1567, 1238, 1176, 1150, 861, 783, 695 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.62 (br, 1H, NH), 7.56 (s, 1H, NH), 4.23-4.35 (m, 6H, CH₂CH₃, and CONCH₂), 3.97 (t, *J* = 9.48, 2H, NCH₂), 1.36 (q, *J* = 6.84, 6H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 165.5, 165.0, 158.5, 157.4, 147.4, 107.2, 88.7, 60.6, 60.6, 44.0, 43.0, 14.4; HRMS (ESI-TOF⁺): *m/z* Calcd for C₁₃H₁₆O₅N₂Na [(M+Na)⁺] 303.0951; found, 303.0950.

8-Nitro-7-oxo-1,2,3,7-tetrahydroimidazo[1,2-*a*]pyridine-6-carboxylic acid ethyl ester (4fa): Red needle-like crystals; Mp 274-275 °C; IR (KBr) (ν_{max}, cm⁻¹) 3331, 3082, 2987, 1734, 1652, 1618, 1571, 1276, 1161, 1103, 863, 764, 702 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.76 (br, 1H, NH), 8.61 (s, 1H, CH), 4.19 (q, *J* = 7.04, 2H, CH₂CH₃), 4.09 (t, *J* = 9.00, 2H, CONCH₂), 3.88 (t, *J* = 10.20, 2H, NCH₂), 1.25 (q, *J* = 7.04, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 168.2, 162.0, 157.2, 145.6, 118.1, 111.8,

65.4, 49.3, 48.8, 19.4; HRMS (ESI-TOF⁺): *m/z* Calcd for C₁₀H₁₁O₅N₃Na [(M+Na)⁺] 276.0591; found, 276.0591.

9-Benzoyl-8-oxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrimidine-7-carboxylic acid ethyl ester (4ga):

White needle-like crystals; Mp 178-180 °C; IR (KBr) (ν_{\max} , cm⁻¹) 3442, 3112, 2972, 1735, 1697, 1613, 1589, 1252, 1179, 1136, 864, 760, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 11.18 (br, 1H, NH), 8.41 (s, 1H, CH), 7.45 (d, *J* = 3.24, 5H, ArH), 4.23 (t, *J* = 7.00, 2H, CH₂CH₃), 4.05 (d, *J* = 4.56, 2H, CONCH₂), 3.51 (s, 2H, NHCH₂), 2.09 (s, 2H, CH₂), 1.26 (t, *J* = 7.04, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 194.8, 165.3, 158.6, 155.8, 149.6, 139.1, 131.0, 128.4, 128.4, 103.8, 98.2, 60.6, 39.4, 38.6, 19.1, 14.3; HRMS (ESI-TOF⁺): *m/z* Calcd for C₁₈H₁₈O₄N₂Na [(M+Na)⁺] 349.1159; found, 349.1155.

9-(4-Methylbenzoyl)-8-oxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrimidine-7-carboxylic acid ethyl ester (4ha):

White needle-like crystals; mp 183-185 °C; IR (KBr) (ν_{\max} , cm⁻¹) 3442, 3123, 2974, 1697, 1611, 1589, 1180, 1137, 1067, 1016, 865, 779, 738 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 11.24 (br, 1H, NH), 8.50 (s, 1H, CH), 7.43 (d, *J* = 7.64, 2H, COArH), 7.28 (d, *J* = 7.08, 2H, ArH), 4.29 (q, *J* = 7.08, 2H, CH₂CH₃), 4.11 (t, *J* = 5.76, 2H, CONCH₂), 3.56 (s, 2H, NHCH₂), 2.43 (s, 3H, ArCH₃), 2.15 (t, *J* = 5.32, 2H, CH₂), 1.32 (t, *J* = 7.08, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 194.8, 165.5, 158.6, 155.8, 149.7, 141.5, 136.4, 129.1, 128.6, 103.6, 98.3, 60.6, 39.3, 38.6, 21.5, 19.2, 14.4; HRMS (ESI-TOF⁺): *m/z* Calcd for C₁₉H₂₀O₄N₂Na [(M+Na)⁺] 363.1315; found, 363.1313.

9-(4-Methoxybenzoyl)-8-oxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrimidine-7-carboxylic acid ethyl ester (4ia):

White needle-like crystals; mp 150-152 °C; IR (KBr) (ν_{\max} , cm⁻¹) 3439, 3378, 2875, 1732, 1654, 1598, 1215, 1173, 1114, 865, 781, 734 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 11.21 (br, 1H, NH), 8.54 (s, 1H, CH), 7.54 (d, *J* = 7.96, 2H, COArH), 6.99 (d, *J* = 8.04, 2H, ArH), 4.31 (q, *J* = 7.16, 2H, CH₂CH₃), 4.13 (t, *J* = 5.72, 2H, CONCH₂), 3.90 (s, 3H, ArOCH₃), 3.57 (s, 2H, NHCH₂), 2.16 (t, *J* = 5.52, 2H, CH₂), 1.34 (t, *J* = 7.04, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 193.9, 165.5, 162.1, 158.6, 155.8, 149.6, 131.6, 130.7, 113.7, 103.4, 98.3, 60.6, 55.5, 39.4, 38.6, 19.2, 14.4; HRMS (ESI-TOF⁺): *m/z* Calcd for C₁₉H₂₀O₅N₂Na [(M+Na)⁺] 379.1264; found, 379.1261.

9-(4-Chlorobenzoyl)-8-oxo-1,3,4,8-tetrahydro-2H-pyrido[1,2-a]pyrimidine-7-carboxylic acid ethyl ester (4ja):

White needle-like crystals; Mp 278-279 °C; IR (KBr) (ν_{\max} , cm⁻¹) 3441, 3138, 2826, 1725, 1653, 1609, 1577, 1263, 1199, 1122, 864, 695 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.80 (br, 1H, NH), 8.12 (s, 1H, CH), 7.60 (d, *J* = 8.20, 2H, COArH), 7.51 (d, *J* = 8.24, 2H, ArH), 4.09 (q, *J* = 7.00, 2H, COOCH₂), 3.90 (t, *J* = 5.08, 2H, CONCH₂), 3.51 (s, 2H, NHCH₂), 2.01 (s, 2H, CH₂), 1.15 (t, *J* = 7.04, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 192.3, 164.8, 157.9, 155.6, 148.7, 138.6, 135.9, 130.4, 129.0, 102.7, 98.1, 60.0, 39.8, 38.9, 18.8, 14.7; HRMS (ESI-TOF⁺): *m/z* Calcd for C₁₈H₁₇O₄N₂ClNa [(M+Na)⁺] 383.0769; found, 383.0764.

8-Benzoyl-7-oxo-3-phenyl-2,3-dihydro-7H-oxazolo[3,2-a]pyridine-6-carboxylic acid ethyl ester

(4ka): White needle-like crystals; Mp 171-172 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3382, 3135, 1735, 1669, 1644, 1593, 1235, 1168, 1138, 863, 794, 756, 700 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.68 (s, 1H, CH), 7.73 (d, $J = 7.60$, 1H, COArH), 7.59 (t, $J = 7.56$, 1H, COArH), 7.50 (t, $J = 7.44$, 2H, COArH), 7.50 (t, $J = 7.44$, 2H, COArH), 7.36-7.42 (m, 3H, ArH), 7.32 (d, $J = 8.24$, 2H, ArH), 5.82 (dd, $J_1 = 8.80$, $J_2 = 3.04$, 1H, OCH₂), 5.11 (t, $J = 9.16$, 1H, ArCHN), 4.85 (dd, $J_1 = 9.20$, $J_2 = 3.08$, 1H, OCH₂), 4.23-4.34 (m, 2H, CH₂CH₃), 1.30 (t, $J = 7.09$, 3H, CH₂CH₃); ^{13}C NMR (100 MHz, CDCl_3): δ 189.9, 164.1, 161.2, 156.3, 149.7, 138.1, 136.7, 132.5, 129.4, 129.0, 128.5, 126.6, 112.3, 99.0, 78.1, 61.1, 59.5, 14.3; HRMS (ESI-TOF⁺): m/z Calcd for C₂₃H₁₉O₅NNa [(M+Na)⁺] 412.1155; found, 412.1158.

8-(4-Methoxybenzoyl)-7-oxo-2,3-dihydro-7H-oxazolo[3,2-a]pyridine-6-carboxylic acid ethyl ester

(4la): White needle-like crystals; Mp 165-167 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3381, 3135, 1735, 1658, 1636, 1600, 1257, 1234, 1159, 863, 799 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.61 (s, 1H, CH), 7.71 (d, $J = 8.08$, 2H, ArH), 6.96 (d, $J = 7.96$, 2H, ArH), 4.91 (t, $J = 8.80$, 2H, OCH₂), 4.33-4.41 (m, 4H, CH₂CH₃ and CONCH₂), 3.87 (t, $J = 6.44$, 3H, OCH₃), 1.35 (t, $J = 7.20$, 3H, CH₂CH₃); ^{13}C NMR (100 MHz, CDCl_3): δ 188.5, 164.2, 163.3, 160.9, 157.1, 149.5, 131.6, 130.3, 113.7, 113.5, 111.4, 99.6, 70.4, 61.1, 55.5, 43.8, 14.3; HRMS (ESI-TOF⁺): m/z Calcd for C₁₈H₁₇O₆NNa [(M+Na)⁺] 366.0948; found, 366.0950.

8-(4-Chlorobenzoyl)-7-oxo-2,3-dihydro-7H-oxazolo[3,2-a]pyridine-6-carboxylic acid ethyl ester

(4ma): White needle-like crystals; Mp 162-164 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3435, 2995, 1726, 1647, 1548, 1255, 1175, 860, 678 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.61 (s, 1H, CH), 7.63 (d, $J = 8.08$, 2H, ArH), 7.45 (d, $J = 8.12$, 2H, ArH), 4.92 (t, $J = 8.88$, 2H, OCH₂), 4.33-4.42 (m, 4H, CH₂CH₃ and CONCH₂), 1.36 (t, $J = 7.20$, 3H, CH₂CH₃); ^{13}C NMR (100 MHz, CDCl_3): δ 188.4, 163.9, 161.2, 157.0, 149.1, 138.8, 136.4, 130.4, 128.8, 111.9, 105.6, 99.0, 70.6, 61.2, 43.7, 14.3; HRMS (ESI-TOF⁺): m/z Calcd for C₁₇H₁₄O₅NCINa [(M+Na)⁺] 370.0453; found, 370.0453.

8-Benzoyl-7-oxo-2,3-dihydro-7H-thiazolo[3,2-a]pyridine-6-carboxylic acid ethyl ester (4na):

Yellow-brown needle-like crystals; Mp 177-179 °C; IR (KBr) (ν_{\max} , cm^{-1}) 3423, 3063, 2990, 1796, 1644, 1623, 1562, 1246, 1194, 1137, 864, 703 cm^{-1} ; ^1H NMR (400 MHz, DMSO-*d*₆): δ 8.24 (s, 1H, CH), 7.57-7.65 (m, 5H, ArH), 4.47 (t, $J = 8.32$, 2H, CH₂CH₃), 4.16 (q, $J = 7.04$, 2H, CONCH₂), 3.49 (t, $J = 8.32$, 2H, SCH₂), 1.19 (t, $J = 7.08$, 3H, CH₂CH₃); ^{13}C NMR (100 MHz, DMSO-*d*₆): δ 191.0, 165.3, 164.3, 157.3, 146.1, 137.7, 132.4, 129.1, 128.9, 112.6, 110.4, 60.8, 51.3, 28.2, 14.6; HRMS (ESI-TOF⁺): m/z Calcd for C₁₇H₁₅O₄NNaS [(M+Na)⁺] 352.0614; found, 352.0613.

8-(4-Methoxybenzoyl)-7-oxo-2,3-dihydro-7H-thiazolo[3,2-a]pyridine-6-carboxylic acid ethyl ester

(4oa): Light yellow granule crystals; Mp 202-204 °C ; IR (KBr) (ν_{\max} , cm^{-1}) 3438, 2992, 1699, 1677, 1572, 1266, 1193, 1149, 870, 795, 719 cm^{-1} ; ^1H NMR (400 MHz, DMSO-*d*₆): δ 8.26 (s, 1H, CH), 7.52 (d, $J = 7.76$, 2H, ArH), 7.38 (d, $J = 7.84$, 2H, ArH), 4.46 (t, $J = 8.28$, 2H, CH₂CH₃), 4.16 (d, $J = 7.04$, 2H, CONCH₂), 3.47 (t, $J = 8.28$, 2H, SCH₂), 2.41 (s, 3H, ArOCH₃), 1.20 (t, $J = 7.08$, 3H, CH₂CH₃); ^{13}C NMR

(100 MHz, DMSO-*d*₆): δ 190.7, 165.1, 164.4, 157.3, 146.1, 142.7, 134.9, 129.6, 129.2, 112.5, 110.6, 60.8, 51.3, 28.2, 21.6, 14.6; HRMS (ESI-TOF⁺): *m/z* Calcd for C₁₈H₁₇O₄NNaS [(M+Na)⁺] 366.0770; found, 366.0770.

8-(4-Chlorobenzoyl)-7-oxo-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-6-carboxylic acid ethyl ester (4pa): Light yellow granule crystals; Mp 217-219 °C; IR (KBr) (ν_{\max} , cm⁻¹) 3440, 3016, 1741, 1665, 1630, 1575, 1244, 1190, 1137, 862, 770, 699 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.20 (s, 1H, CH), 7.64 (m, 4H, ArH), 4.47 (t, *J* = 8.32, 2H, CH₂CH₃), 4.18 (d, *J* = 7.08, 2H, CONCH₂), 3.48 (t, *J* = 8.36, 2H, SCH₂), 1.21 (t, *J* = 7.08, 3H, CH₂CH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 189.9, 165.4, 164.3, 157.2, 145.9, 137.2, 136.4, 130.9, 129.3, 112.8, 110.3, 60.9, 51.3, 28.3, 14.6; HRMS (ESI-TOF⁺): *m/z* Calcd for C₁₇H₁₄O₄NCINaS [(M+Na)⁺] 386.0224; found, 386.0225.

6-Acetyl-8-benzoyl-2,3-dihydro-1H-imidazo[1,2-*a*]pyridin-5-one (4ab): White needle-like crystals; Mp 293-294 °C; IR (KBr) (ν_{\max} , cm⁻¹) 3412, 3292, 1665, 1598, 1159, 1073, 977, 953, 860, 548 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.24 (br, 1H, NH), 7.46-7.50 (m, 3H, ArCH), 7.39-7.43 (m, 2H, ArCH), 5.65 (d, *J* = 8.40, 1H, CH), 4.22-4.27 (m, 2H, CONCH₂), 3.93 (t, *J* = 9.40, 2H, NHCH₂), 1.70 (d, *J* = 6.40, 3H, COCH₃); ¹³C NMR (100 MHz, CDCl₃): δ 194.8, 160.6, 157.3, 152.1, 143.4, 130.9, 128.4, 127.5, 109.3, 99.0, 77.3, 43.4, 42.7, 23.6; HRMS (ESI-TOF⁺): *m/z* Calcd for C₁₆H₁₅O₃N₂ [(M+H)⁺] 283.1077; found, 283.1075.

6-Acetyl-8-(4-methoxybenzoyl)-2,3-dihydro-1H-imidazo[1,2-*a*]pyridin-5-one (4cb): White needle-like crystals; Mp 191-193 °C; IR (KBr) (ν_{\max} , cm⁻¹) 3409, 1658, 1607, 1443, 1165, 1075, 975, 950, 861 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.76 (br, 1H, NH), 7.49-7.52 (m, 2H, ArCH), 6.91-6.94 (m, 2H, ArCH), 5.67 (d, *J* = 6.40, 1H, CH), 4.24 (t, *J* = 8.80, 2H, CONCH₂), 3.90 (t, *J* = 9.20, 2H, NHCH₂), 3.86 (s, 3H, ArOCH₃), 1.79 (s, 3H, COCH₃); ¹³C NMR (100 MHz, CDCl₃): δ 194.0, 162.4, 160.6, 156.8, 152.1, 134.4, 130.2, 113.7, 108.9, 99.0, 55.4, 43.6, 42.6, 23.3 cm⁻¹; HRMS (ESI-TOF⁺): *m/z* Calcd for C₁₇H₁₇O₄N₂ [(M+H)⁺] 313.1183; found, 313.1178.

6-Acetyl-8-(4-chlorobenzoyl)-2,3-dihydro-1H-imidazo[1,2-*a*]pyridin-5-one (4db): White needle-like crystals; Mp 126-127 °C; IR (KBr) (ν_{\max} , cm⁻¹) 3332, 1602, 1577, 1549, 1451, 1160, 1088, 951, 862, 848 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.24 (br, 1H, NH), 7.71 (d, *J* = 8.52, 2H, ArCH), 7.42 (d, *J* = 8.52, 2H, ArCH), 5.24 (s, 1H, CH), 3.59 (d, *J* = 6.08, 2H, CONCH₂), 3.46 (d, *J* = 5.88, 2H, NHCH₂), 3.34 (s, 3H, COCH₃); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 194.2, 193.5, 160.2, 157.9, 139.9, 137.2, 134.2, 133.5, 129.6, 128.8, 98.3, 44.9, 44.8, 21.2 cm⁻¹; HRMS (ESI-TOF⁺): *m/z* Calcd for C₁₆H₁₄O₃N₂Cl [(M+H)⁺] 317.0687; found, 317.0689.

6-Acetyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-8-carboxylic acid ethyl ester (4eb): White needle-like crystals; Mp 136-138 °C; IR (KBr) (ν_{\max} , cm⁻¹) 3388, 1676.1, 1630, 1584, 1551, 1442, 1370, 1157, 1074, 951, 861 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.73 (br, 1H, NH), 5.65 (s, 1H, CH), 4.27 (q, *J*

= 7.12, 2H, CH_2CH_3), 4.20 (t, $J = 8.84$, 2H, $CONCH_2$), 3.87 (t, $J = 9.28$, 2H, $NHCH_2$), 2.36 (s, 3H, $COCH_3$), 1.35 (t, $J = 7.12$, 3H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 160.6, 157.3, 153.7, 108.7, 88.7, 60.2, 43.7, 42.3, 23.8, 14.4 cm^{-1} ; HRMS (ESI-TOF⁺): m/z Calcd for $C_{12}H_{15}O_4N_2 [(M+H)^+]$ 251.1026; found, 251.1026.

6-Acetyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (4fb): White needle-like crystals; Mp 174-176 °C; IR (KBr) (ν_{max} , cm^{-1}) 3428, 3296, 1678, 1649, 1612, 1560, 1209, 1161, 1075, 952, 861 cm^{-1} ; 1H NMR (400 MHz, $DMSO-d_6$): δ 9.82 (br, 1H, NH), 8.59 (s, 1H, CH), 4.10-4.15 (m, 2H, $CONCH_2$), 3.89-3.94 (m, 2H, $NHCH_2$), 2.49 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $DMSO-d_6$): δ 198.7, 164.3, 157.4, 144.3, 144.1, 119.7, 49.3, 49.0, 44.1, 35.5 cm^{-1} ; HRMS (ESI-TOF⁺): m/z Calcd for $C_9H_9O_4N_3 [(M+H)^+]$ 224.0666; found, 224.0668.

6-Benzoyl-8-(4-methoxybenzoyl)-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (4cc): White needle-like crystals; Mp 262-264 °C; IR (KBr) (ν_{max} , cm^{-1}) 3430, 1584, 1440, 1159, 1074, 950, 860, 548 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 7.81 (br, 1H, NH), 7.77-7.80 (m, 1H, ArH), 7.77 (s, 1H, CH), 7.56 (t, $J = 7.44$, 1H, ArH), 7.48 (t, $J = 7.40$, 1H, ArH), 7.43 (t, $J = 7.80$, 2H, ArH), 7.34 (t, $J = 7.80$, 2H, ArH), 7.14 (d, $J = 8.64$, 1H, ArH), 6.78 (d, $J = 8.64$, 1H, ArH), 4.60 (s, 4H, $NHCH_2$ and $CONCH_2$), 3.72 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $DMSO-d_6$): δ 194.2, 193.5, 160.2, 157.9, 148.5, 139.9, 137.7, 137.2, 134.2, 133.5, 130.6, 129.6, 129.4, 129.2, 128.8, 125.0, 124.3, 114.6, 98.3, 55.6, 44.9, 44.8 cm^{-1} ; HRMS (ESI-TOF⁺): m/z Calcd for $C_{22}H_{19}O_4N_2 [(M+H)^+]$ 375.1339; found, 375.1340.

6-Benzoyl-8-(4-chlorobenzoyl)-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (4dc): White needle-like crystals; Mp 275-277 °C; IR (KBr) (ν_{max} , cm^{-1}) 3413, 1685, 1654, 1585, 1448, 1161, 1074, 947, 860, 547 cm^{-1} ; 1H NMR (400 MHz, $DMSO-d_6$): δ 7.79 (br, 1H, NH), 7.74-7.77 (m, 1H, ArH), 7.73 (s, 1H, CH), 7.57-7.63 (m, 2H, ArH), 7.46-7.51 (m, 2H, ArH), 7.42-7.44 (m, 2H, ArH), 7.24 (d, $J = 8.36$, 2H, ArH), 4.44 (s, 4H, $NHCH_2$ and $CONCH_2$); ^{13}C NMR (100 MHz, $DMSO-d_6$): δ 193.9, 193.4, 157.7, 148.4, 147.5, 139.3, 137.7, 134.6, 134.3, 133.5, 131.9, 130.9, 129.6, 129.4, 128.8, 125.1, 124.7, 98.0, 45.0, 44.7 cm^{-1} ; HRMS (ESI-TOF⁺): m/z Calcd for $C_{21}H_{16}O_3N_2Cl [(M+H)^+]$ 379.0844; found, 379.0848.

6-Benzoyl-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-a]pyridine-8-carboxylic acid ethyl ester (4ec): White needle-like crystals; Mp 187-189 °C; IR (KBr) (ν_{max} , cm^{-1}) 3456, 1701, 1658, 1631, 1563, 1448, 1230, 1078, 996, 547 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$): δ 8.26 (br, 1H, NH), 7.88-7.91 (m, 3H, ArH), 7.77-7.79 (m, 2H, ArH), 6.29 (s, 1H, CH), 4.86 (t, $J = 8.76$, 2H, $CONCH_2$), 4.52 (t, $J = 9.20$, 2H, $NHCH_2$), 4.44 (q, $J = 7.12$, 2H, CH_2CH_3), 1.32 (t, $J = 7.12$, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 160.3, 157.1, 156.1, 141.3, 127.4, 127.3, 127.2, 109.2, 87.8, 59.7, 43.9, 42.7, 13.3 cm^{-1} ; HRMS (ESI-TOF⁺): m/z Calcd for $C_{17}H_{17}O_4N_2 [(M+H)^+]$ 313.1183; found, 313.1184.

6-Benzoyl-8-nitro-2,3-dihydro-1H-imidazo[1,2-a]pyridin-5-one (4fc): White needle-like crystals; Mp 234-236 °C; IR (KBr) (ν_{max} , cm^{-1}) 3406, 1664, 1644, 1622, 1605, 1563, 1487, 1161, 1121, 1073, 984, 948,

860, 548 cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.79 (br, 1H, NH), 8.29 (s, 1H, CH), 7.71-7.73 (m, 2H, ArH), 7.59-7.63 (m, 1H, ArH), 7.48 (t, $J = 7.76$, 2H, ArH), 4.12 (t, $J = 9.08$, 2H, CONCH_2), 3.93 (t, $J = 9.20$, 2H, NHCH_2); ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ 192.2, 158.7, 152.6, 139.5, 138.5, 133.0, 129.5, 128.6, 116.7, 113.8, 44.5, 44.1 cm^{-1} ; HRMS (ESI-TOF $^+$): m/z Calcd for $\text{C}_{14}\text{H}_{12}\text{O}_4\text{N}_3$ [(M+H) $^+$] 286.0822; found, 286.0822.

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