Preparation of 2-Pyridone-Containing Tricyclic Alkaloid Derivatives as Potential Inhibitors of Tumor Cell Proliferation by Regioselective Intramolecular *N*- and *C*-Acylation of 2-Pyridone

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A novel and practical preparation of 2-pyridone-containing tricyclic alkaloid derivatives was developed. By regioselective intramolecular *N*- and *C*-acylation of 2-(4-aryl-2-pyridon-6-yl)benzoic acid, a pair of structural isomers 2-aryl pyrido[2,1-*a*]isoindole-4,6-diones and 4-aryl 1-methyl-1*H*-indeno[1,2-*b*]-pyridine-2,5-diones, as potential inhibitors of tumor cell proliferation, were prepared respectively.

Key words synthesis; tricyclic alkaloid; 2-pyridone; intramolecular *N*-acylation; intramolecular *C*-acylation

Recently, A-ring alkoxyl subsitituted β-carbolin-1-ones (**1**, Chart 1) were reported to inhibit colon and lung tumors in a patent literature.[1)] Subsequently, we found that 3-aryl β-carbolin-1-ones (**2**) inhibit the proliferation of HeLa cells with IC_{50} values in the low micromolar range and that the aromatic substitution on C3 in **2** proved to be essential for their biological activity.[2,3)] To broaden the scope of previous studies, aryl-substituted 2-pyridone-containing derivatives, such as pyrido[2,1-*a*]isoindole-4-one (**3**) and 1*H*-indeno[1,2-*b*]pyridine-2-one (**4**), were designed as our synthetic targets to make it possible to probe their structure–activity relationships.

Some alkaloids having frameworks of **3** and **4** occur in nature,[4—7)] whose analogues were synthesized more often in laboratories for their potent bioactivities as receptor ligands,[8—10)] enzyme inhibitors[11)] or anti-tumor agents.[12,13)] Since **3** and **4** are a pair of structural isomers, it is reasonable to expect that they could be prepared from a common precursor, which should have a structure of 6-substituted 2-pyridone allowing a disconnection between methylene and C-ring in **3** and **4** (Chart 1). However, neither such precursor nor procedure has been employed for this purpose so far.[14—26)] Since the methods for preparation of 3-unsubstituted 2-pyridone have been well established in recent years,[27—37)] herein we report a novel synthetic route to **3** and **4** as shown in Chart 2. The route starts from an aldol condensation between 2-acetylbenzoic acid (**5**) and aryl aldehyde (**6**) to yield chalcone (**7**), which subsequently undergoes a [3+3] annulation to give 2-(2-pyridon-6-yl)benzoic acid (**8**). Serving as a common precursor, **8** goes through an intramolecular *N*-acylation to produce 2-aryl pyrido[2,1-*a*]isoindole-4,6-diones (**9**), or carries out an intramolecular *C*-acylation to yield 4-aryl 1-methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-diones (**11**) regioselectively.

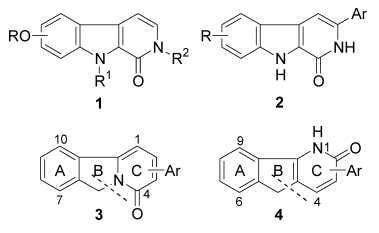
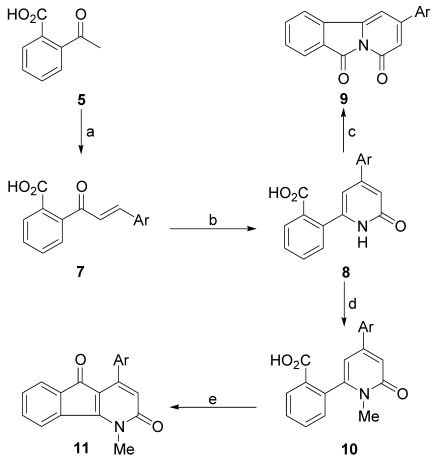


Chart 1

Results and Discussion

Preparation of 2-Aryl Pyrido[2,1-*a*]isoindole-4,6-diones (9a—j) Following the known procedure,[38)] the mixtures of 2-acetylbenzoic acid (**5**) and aryl aldehydes **6a**—**j** were treated respectively with NaOH in aqueous EtOH at room temperature for 20 h. As shown in Table 1, the corresponding products 2-(3-aryl acryloyl)benzoic acids (**7a**—**j**) were yielded conveniently in high yields. However, the aryl aldehydes bearing an electron-withdrawing group, such as *o*-, *m*-,



Conditions: (a) ArCHO (**6**), NaOH, aq. EtOH, rt, 20 h, 88-95%. (b) $BtCH_2CONH_2$, NaOH, EtOH, reflux, 6 h, 60-75%; (c) xylene, reflux, 8 h, 89-98%. (d) 2.0 N aq. NaOH, $(MeO)_2SO_2$, 0 °C, 2 h, 89-92%; (e) PPA, 120 °C, 0.5 h, 85-92%.

Chart 2

Table 1. The Yields and Physical Properties of Compounds **7a**—**j**

7	Ar	Yield (%)	mp (°C)	IR (cm^{-1})
a	C_6H_5	90	151—152	1696, 1648
b	4-$CH_3C_6H_4$	90	165—166	1693, 1637
c	4-*i*-PrC_6H_4	92	152—153	1669, 1604
d	4-FC_6H_4	90	135—137	1692, 1644
e	4-ClC_6H_4	88	165—166	1689, 1666
f	2-ClC_6H_4	88	134—135	1689, 1666
g	4-$MeOC_6H_4$	90	132—133	1690, 1649
h	3-$MeOC_6H_4$	88	128—129	1713, 1610
i	2-Furyl	95	135—136	1711, 1611
j	2-Thienyl	90	134—135	1691, 1658

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Table 2. The Yields of Compounds **8**—**11**

8—11	Ar	Yield (%)				8—11	Ar	Yield (%)			
		8	9	10	11			8	9	10	11
a	C_6H_5	63	98	83	92	**f**	2-ClC_6H_4	68	90	75	85
b	4-$CH_3C_6H_4$	65	96	80	90	**g**	4-$MeOC_6H_4$	75	95	80	90
c	4-*i*-PrC_6H_4	60	90	81	92	**h**	3-$MeOC_6H_4$	73	91	78	88
d	4-FC_6H_4	70	92	87	90	**i**	2-Furyl	60	89	80	85
e	4-ClC_6H_4	68	90	85	90	**j**	2-Thienyl	62	90	81	86

p-nitrobenzaldehydes, failed to afford the expected chalcones.

Among the methods for preparation of 3-unsubstituted 2-pyridone,[27—37] [3+3] annulation between chalcone and C–C–N fragment connected with a leaving group displayed high convenience and efficiency, such as *N*-(2-carbamoylmethyl)-pyridinium ylide,[29—33] 2-acetamidoacetamide[34] or 2-(benzotriazol-1-yl)acetamide.[35—37] By scanning the conditions, the best yield (63%) of desired 2-pyridone **8a** was obtained when chalcone **7a** was refluxed with 2-(benzotriazol-1-yl)acetamide[35] in the presence of NaOH for 6 h. Under similar conditions, other compounds **7b**—**j** were annulated to give the corresponding products **8b**—**j** in 60—75% yields. It is worthy to note that the heterocycles **8i**—**j** showed good toleration of the conditions (Table 2).

Usually, intramolecular *N*-acylation of amides can be well accomplished in refluxing acetic anhydride for several hours.[39,40] But it failed in our case largely due to the poor solubility of both substrates and products in refluxing acetic anhydride. Fortunately, the intramolecular *N*-acylation of **8a** was achieved successfully in almost quantitative yield by refluxing it in xylene for 8 h with a Dean–Stark trap. Similarly, the *N*-acylation of **8b**—**j** yielded the corresponding **9b**—**j** in 85—96% yields (Chart 2, Table 2). Since the products **9a**—**j** have much less solubility in xylene at room temperature, they were collected cleanly by filtration in the work-up procedure. The structure of compound **9d** was confirmed by its single crystal X-ray diffraction analysis (Fig. 1).[41]

Preparation of 4-Aryl 1-Methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-diones (11a—j) To the best of our knowledge, no successful intramolecular *C*-acylation of 2-pyridone has been reported in literature. In a few samples of intermolecular *C*-acylation of *N*-alkylated 2-pyridones, very harsh conditions were employed.[42—44] Therefore, it was not surprising that our attempts to *C*-acylate **8a** under Friedel–Crafts conditions catalyzed by PPA, H_2SO_4, CH_3SO_3H, TFA, $ZnCl_2$, $AlCl_3$ or $SnCl_4$ failed. We hypothesized that those undesired results might be caused by the presence of the active proton on nitrogen in **8a** and *N*-alkylation of **8a** was required.

2-Pyridone has two tautomeric forms (hydroxy and oxo forms) under basic conditions and it normally yields *O*- or/and *N*-alkylated products mainly depending upon the media used.[45—50] It is interesting to observe that *N*-methylated product **10a** was obtained regioselectively in 83% yield when **8a** was treated by Me_2SO_4 in 2.0 M aqueous solution of NaOH at 0 °C for 2 h. Under the same conditions, **8b**—**j** were also *N*-methylated to give the corresponding products **10b**—**j** in 75—87% yields smoothly.

In agreement with our expectation, compound **10a** took place an intramolecuar *C*-acylation smoothly catalyzed by PPA at 120 °C for 0.5 h to give the desired product **11a** in high yield (92%). Under the similar conditions, intramolecular *C*-acylation of **10b**—**j** yielded the corresponding **11b**—**j** in 85—92% yields. As the long-range coupling of protons on C3 and C5 in **10a**—**j** displays two doublet signals at δ 6.75—6.60 ppm and δ 6.40—6.06 ppm in their ^{1}H-NMR spectra respectively, the singlet signals appearing at δ 6.94—6.41 ppm in ^{1}H-NMR spectra of **11a**—**j** are in full agreement with their structural assignments. In addition, the structure of **11g** was confirmed by its single crystal X-ray diffraction analysis (Fig. 2).[51]

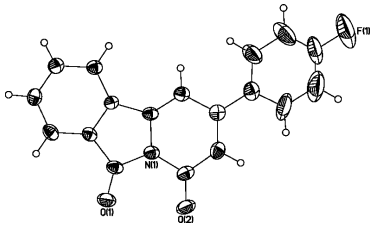

Fig. 1. Structure of Compound **9d**

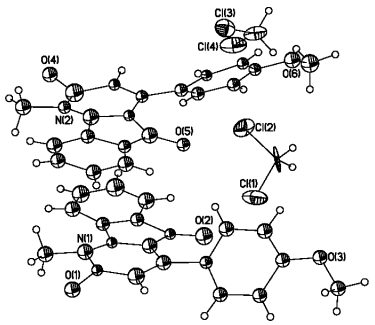

Fig. 2. Structure of Compound **11g**

In summary, a novel synthetic route was developed for the preparation of 2-aryl pyrido[2,1-*a*]isoindole-4,6-dione (**9**) and 4-aryl 1-methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (**11**) by using 2-(4-aryl-2-pyridon-6-yl)benzoic acid (**8**) as a common precursor. By refluxing compound **8** in xylene for 8 h, an intramolecular *N*-acylation was accomplished to yield alkaloid **9** in high yield. While, alkaloid **11** was achieved satisfactorily by an intramolecular *C*-acylation when *N*-methylated **8** was heated with PPA for 0.5 h.

Experimental

The IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer as KBr pellets. The NMR spectra were recorded on a Bruker ACF-300 spectrometer in $CDCl_3$ with TMS as internal reference. The *J* values are given in Hz. MS spectra were obtained on a VG-ZAB-HS mass spectrometer with 70 eV. The elemental analyses were performed on a Perkin-Elmer 240C instrument. PE is petroleum ether (60—90 °C).

A General Procedure for the Preparation of 2-(3-Aryl acryloyl)benzoic Acids (7a—j) To a stirred cold solution (ice-bath) of 2-acetylbenzoic acid (**5**, 3.28 g, 20 mmol) and aryl aldehyde (**6**, 20 mmol) in EtOH (10 ml) was added an aqueous solution of NaOH (1.5 M, 20 ml). After stirred at room temperature for another 20 h, the resultant mixture was poured into ice-water and neutralized by aqueous HCl (6.0 M). The crude product as solid was collected by filtration and recrystallized from EtOAc to give compound **7**. Some properties of **7a**—**j** were showed in Table 1.

A General Procedure for the Preparation of 2-(4-Aryl 2-pyridon-6-yl)benzoic Acid (8a—j) The mixture of compound **7** (10 mmol), $BtCH_2CONH_2$ (1.76 g, 10 mmol) and NaOH (1.4 g, 35 mmol) in EtOH (60 ml) was heated to reflux for 6 h. After compound **7** was exhausted completely (monitored by TLC), most of the solvent was evaporated. The residue then was poured into ice-water and neutralized by aqueous HCl (6.0 M). The crude product as solid was collected and was recrystallized from MeOH to give compound **8** (Table 2).

2-(4-Phenyl-2-pyridon-6-yl)benzoic Acid (**8a**): mp 260—262 °C (MeOH); IR cm^{-1}: 3038, 1661, 1634, 1595; ^{1}H-NMR (DMSO-d_6) δ: 7.93 (1H, d, J=7.5), 7.75—7.72 (2H, m), 7.69—7.54 (3H, m), 7.51—7.46 (3H, m), 6.60 (1H, s), 6.48 (1H, s); MS-FAB m/z: 291 (M^+, 0.3%), 273 (100). *Anal.* Calcd for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.30; H, 4.66; N, 4.83.

2-[4-(4-Methylphenyl)-2-pyridon-6-yl]benzoic Acid (**8b**): mp 267—268 °C (MeOH); IR cm^{-1}: 3028, 1664, 1627, 1595; ^{1}H-NMR (DMSO-d_6) δ: 7.92 (1H, d, J=7.6), 7.69—7.53 (5H, m), 7.27 (2H, d, J=8.2), 6.57 (1H, s), 6.46 (1H, s), 2.35 (3H, s); MS-FAB m/z: 306 (M+1, 3.6%), 91 (100). *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.65; H, 5.00; N, 4.41.

2-[4-(4-Isoproylphenyl)-2-pyridon-6-yl]benzoic Acid (**8c**): mp 222—223 °C (MeOH); IR cm^{-1}: 3025, 1660, 1629; ^{1}H-NMR (DMSO-d_6) δ: 7.92 (1H, dd, J=7.6, 1.1), 7.68—7.64 (3H, m), 7.61—7.53 (2H, m), 7.34 (2H, d, J=8.2), 6.58 (1H, d, J=1.3), 6.46 (1H, s), 2.95—2.91 (1H, m), 1.22 (6H, d, J=6.9); MS-FAB m/z: 334 (M+1, 10.2%), 59 (100). *Anal.* Calcd for $C_{19}H_{15}NO_4$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.60; H, 5.80; N, 4.21.

2-[4-(4-Fluorophenyl)-2-pyridon-6-yl]benzoic Acid (**8d**): mp 276—278 °C (MeOH); IR cm^{-1}: 3090, 1691, 1632, 1599; ^{1}H-NMR (DMSO-d_6) δ: 7.94 (1H, d, J=7.5), 7.83—7.79 (2H, m), 7.68—7.54 (3H, m), 7.30 (2H, t, J=8.7), 6.60 (1H, s), 6.49 (1H, s); MS-FAB m/z: 310 (M+1, 15.4%), 91 (100). *Anal.* Calcd for $C_{18}H_{12}FNO_3$: C, 69.90; H, 3.91; N, 4.53. Found: C, 69.83; H, 4.06; N, 4.35.

2-[4-(4-Chlorophenyl)-2-pyridon-6-yl]benzoic Acid (**8e**): mp 306—308 °C (MeOH); IR cm^{-1}: 3043, 1662, 1627, 1594; ^{1}H-NMR (DMSO-d_6) δ: 7.94 (1H, d, J=7.5), 7.78 (2H, d, J=8.5), 7.68—7.51 (5H, m), 6.62 (1H, s), 6.49 (1H, s); MS-FAB m/z: 328 (M+3, 0.8%), 326 (M+1, 2.5), 91 (100). *Anal.* Calcd for $C_{18}H_{12}ClNO_3$: C, 66.37; H, 3.71; N, 4.30. Found: C, 66.35; H, 3.76; N, 4.24.

2-[4-(2-Chlorophenyl)-2-pyridon-6-yl]benzoic Acid (**8f**): mp 267—269 °C (MeOH); IR cm^{-1}: 3097, 1718, 1619; ^{1}H-NMR (DMSO-d_6) δ: 7.90 (1H, d, J=7.5), 7.74—7.43 (7H, m), 6.35 (1H, s), 6.21 (1H, s); MS-FAB m/z: 328 (M+3, 1.6%), 326 (M+1, 1.9), 55 (100). *Anal.* Calcd for $C_{18}H_{12}ClNO_3$: C, 66.37; H, 3.71; N, 4.30. Found: C, 66.35; H, 3.79; N, 4.28.

2-[4-(4-Methoxyphenyl)-2-pyridon-6-yl]benzoic Acid (**8g**): mp 254—256 °C (MeOH); IR cm^{-1}: 3010, 1668, 1630, 1604; ^{1}H-NMR (DMSO-d_6) δ: 7.92 (1H, d, J=7.5), 7.73—7.53 (5H, m), 7.02 (2H, d, J=8.5), 6.55 (1H, s), 6.46 (1H, s), 3.81 (3H, s); MS-FAB m/z: 322 (M+1, 0.5%), 91 (100). *Anal.* Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.08; H, 4.83; N, 4.37.

2-[4-(3-Methoxyphenyl)-2-pyridon-6-yl]benzoic Acid (**8h**): mp 178—180 °C (MeOH); IR cm^{-1}: 3241, 1685, 1612, 1602; ^{1}H-NMR (DMSO-d_6) δ: 7.93 (1H, dd, J=7.4, 1.0), 7.69—7.54 (3H, m), 7.39 (1H, t, J=7.8), 7.30—7.23 (2H, m), 7.03—7.00 (1H, m), 6.62 (1H, d, J=1.6), 6.50 (1H, s), 3.82 (3H, s); MS-FAB m/z: 322 (M+1, 25.0%), 91 (100). *Anal.* Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.08; H, 4.64; N, 4.34.

2-[4-(2-Furyl)-2-pyridon-6-yl]benzoic Acid (**8i**): mp 256—258 °C (MeOH); IR cm^{-1}: 3110, 1670, 1633, 1576; ^{1}H-NMR (DMSO-d_6) δ: 7.95 (1H, d, J=7.6), 7.87 (1H, s), 7.69—7.57 (2H, m), 7.50 (1H, d, J=7.3), 7.25 (1H, d, J=3.4), 6.65 (1H, t, J=1.6), 6.56 (1H, s), 6.49 (1H, s); MS-FAB m/z: 282 (M+1, 3.7%), 91 (100). *Anal.* Calcd for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.94; N, 4.98. Found: C, 68.28; H, 4.02; N, 4.94.

2-[4-(2-Thienyl)-2-pyridon-6-yl]benzoic Acid (**8j**): mp 250—252 °C (MeOH); IR cm^{-1}: 3109, 1668, 1628, 1573; ^{1}H-NMR (DMSO-d_6) δ: 7.95 (1H, d, J=7.4), 7.75—7.71 (2H, m), 7.69—7.57 (2H, m), 7.52 (1H, d, J=7.4), 7.20—7.17 (1H, m), 6.54 (1H, d, J=1.3), 6.48 (1H, s); MS-FAB m/z: 298 (M+1, 12.2%), 91 (100). *Anal.* Calcd for $C_{16}H_{11}NO_3S$: C, 64.63; H, 3.73; N, 4.71. Found: C, 64.67; H, 3.99; N, 4.63.

A General Procedure for the Preparation of 2-Aryl Pyrido[2,1-*a*]isoindole-4,6-dione (9a—j) The solution of compound **8** (3 mmol) in xylene (60 ml) was heated to reflux to move continuously out the water with a Dean–Stark equipment. After 8 h (monitored by TLC), it was cooled to room temperature. The precipitated yellowish crystals were collected to get pure compound **9** (Table 2).

2-Phenylpyrido[2,1-*a*]isoindole-4,6-dione (**9a**): mp 266—268 °C (xylene); IR cm^{-1}: 3053, 1783, 1751, 1675, 1616; ^{1}H-NMR δ: 8.02 (1H, d, J=7.6), 7.82—7.74 (2H, m), 7.68—7.62 (3H, m), 7.57—7.51 (3H, m), 6.94 (1H, d, J=1.4), 6.80 (1H, d, J=1.4); ^{13}C-NMR δ: 165.4, 160.6, 151.9, 141.0, 136.8, 135.4, 134.9, 131.6, 130.7, 129.6, 127.7, 127.0, 126.3, 121.7, 121.2, 102.5; MS m/z: 275 (M+2, 1.5%), 274 (M+1, 12.6), 273 (M^+, 60.5), 245 (100). *Anal.* Calcd for $C_{18}H_{11}NO_2$: C, 79.11; H, 4.06; N, 5.13. Found: C, 79.00; H, 4.12; N, 5.13.

2-(4-Methylphenyl)-pyrido[2,1-*a*]isoindole-4,6-dione (**9b**): mp 264—266 °C (xylene); IR cm^{-1}: 3061, 1782, 1754, 1674, 1617; ^{1}H-NMR δ: 8.03 (1H, d, J=7.5), 7.82—7.74 (2H, m), 7.64—7.56 (3H, m), 7.33 (2H, d, J=8.0), 6.94 (1H, d, J=1.2), 6.79 (1H, d, J=1.1), 2.45 (3H, s); MS m/z: 289 (M+2, 2.5%), 288 (M+1, 22.7), 287 (M^+, 100). *Anal.* Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.32; H, 4.59; N, 4.72.

2-(4-Isoproylphenyl)-pyrido[2,1-*a*]isoindole-4,6-dione (**9c**): mp 237—239 °C (xylene); IR cm^{-1}: 3068, 1782, 1755, 1674, 1617; ^{1}H-NMR δ: 8.04 (1H, d, J=7.3), 7.82—7.74 (2H, m), 7.63—7.60 (3H, m), 7.39 (2H, d, J=7.7), 6.95 (1H, s), 6.80 (1H, s), 3.06—2.96 (1H, m), 1.32 (6H, d, J=6.9); MS m/z: 317 (M+2, 3.4%), 316 (M+1, 25.4), 315 (M^+, 100). *Anal.* Calcd for $C_{21}H_{19}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.98; H, 5.29; N, 4.56.

2-(4-Fluorophenyl)-pyrido[2,1-*a*]isoindole-4,6-dione (**9d**): mp 276—278 °C (xylene); IR cm^{-1}: 3061, 1784, 1758, 1673, 1616; ^{1}H-NMR δ: 8.03 (1H, d, J=7.6), 7.82—7.74 (2H, m), 7.69—7.60 (3H, m), 7.26—7.18 (2H, m), 6.89 (1H, d, J=1.5), 6.75 (1H, d, J=1.5); MS m/z: 292 (M+1, 20.7%), 291 (M^+, 100). *Anal.* Calcd for $C_{18}H_{10}FNO_2$: C, 74.22; H, 3.46; N, 4.81. Found: C, 74.16; H, 3.52; N, 4.76.

2-(4-Chlorophenyl)-pyrido[2,1-*a*]isoindole-4,6-dione (**9e**): mp 306—308 °C (xylene); IR cm^{-1}: 3062, 1784, 1758, 1673, 1609; ^{1}H-NMR δ: 8.04 (1H, d, J=7.5), 7.83—7.75 (2H, m), 7.66—7.60 (3H, m), 7.51 (2H, d, J=8.2), 6.88 (1H, s), 6.77 (1H, s); MS m/z: 310 (M+3, 3.5%), 309 (M+2, 27.5), 308 (M+1, 18.1), 307 (M^+, 100). *Anal.* Calcd for $C_{18}H_{10}ClNO_2$: C, 70.25; H, 3.28; N, 4.55. Found: C, 70.29; H, 3.36; N, 4.51.

2-(2-Chlorophenyl)-pyrido[2,1-*a*]isoindole-4,6-dione (**9f**): mp 270—271 °C (xylene); IR cm^{-1}: 3062, 1784, 1760, 1677, 1620; ^{1}H-NMR δ: 8.04 (1H, d, J=7.5), 7.75 (2H, d, J=3.9), 7.66—7.59 (1H, m), 7.54—7.52 (1H, m), 7.45—7.39 (3H, m), 6.80 (1H, d, J=1.1), 6.63 (1H, d, J=1.1); MS m/z: 310 (M+3, 5.9%), 309 (M+2, 35.8), 308 (M+1, 19.7), 307 (M^+, 100). *Anal.* Calcd for $C_{18}H_{10}ClNO_2$: C, 70.25; H, 3.28; N, 4.55. Found: C, 70.19; H, 3.53; N, 4.40.

2-(4-Methoxyphenyl)-pyrido[2,1-*a*]isoindole-4,6-dione (**9g**): mp 260—262 °C (xylene); IR cm^{-1}: 3066, 1784, 1751, 1673, 1617; ^{1}H-NMR δ: 8.02 (1H, d, J=7.5), 7.82—7.73 (2H, m), 7.65—7.58 (3H, m), 7.03 (2H, d, J=8.7), 6.93 (1H, d, J=1.4), 6.74 (1H, d, J=1.5), 3.90 (3H, s); MS m/z: 305 (M+2, 2.6%), 304 (M+1, 20.9), 303 (M^+, 100). *Anal.* Calcd for $C_{19}H_{13}NO_3$: C, 75.24; H, 4.32; N, 4.62. Found: C, 75.23; H, 4.48; N, 4.57.

2-(3-Methoxyphenyl)-pyrido[2,1-*a*]isoindole-4,6-dione (**9h**): mp 206—208 °C (xylene); IR cm^{-1}: 3060, 1763, 1677, 1620, 1597; ^{1}H-NMR δ: 8.02 (1H, d, J=7.6), 7.78 (dd, 2H, J=16.9, 7.7), 7.62 (1H, t, J=7.3), 7.44 (1H, t, J=7.9), 7.25 (1H, t, J=6.2), 7.16 (1H, t, J=2.0), 7.05 (1H, dd, J=8.2, 1.9), 6.92 (1H, d, J=1.3), 6.79 (1H, d, J=1.3), 3.89 (3H, s); MS m/z: 305 (M+2, 2.6%), 304 (M+1, 21.6), 303 (M^+, 100). *Anal.* Calcd for $C_{19}H_{13}NO_3$: C, 75.24; H, 4.32; N, 4.62. Found: C, 75.24; H, 4.33; N, 4.50.

2-(2-Furyl)-pyrido[2,1-*a*]isoindole-4,6-dione (**9i**): mp 267—268 °C (xylene); IR cm^{-1}: 3120, 1764, 1744, 1689, 1634, 1610, 1593; ^{1}H-NMR δ: 8.02 (1H, d, J=7.5), 7.83—7.74 (2H, m), 7.64—7.59 (2H, m), 6.99 (1H, d, J=3.3), 6.95 (1H, s), 6.84 (1H, s), 6.62 (1H, t, J=1.5); MS m/z: 264 (M+1, 16.6%), 263 (M^+, 100). *Anal.* Calcd for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N, 5.34. Found: C, 73.13; H, 3.49; N, 5.29.

2-(2-Thienyl)-pyrido[2,1-*a*]isoindole-4,6-dione (**9j**): mp 268—270 °C (xylene); IR cm^{-1}: 3085, 1781, 1757, 1673, 1619; ^{1}H-NMR δ: 8.0 (1H, d, J=7.5), 7.85—7.75 (2H, m), 7.65—7.53 (3H, m), 7.22—7.19 (1H, m), 6.92 (1H, d, J=1.0), 6.79 (1H, d, J=1.0); MS m/z: 281 (M+2, 5.5%), 280 (M+1, 17.1), 279 (M^+, 100). *Anal.* Calcd for $C_{16}H_9NO_2S$: C, 68.80; H, 3.25; N, 5.01. Found: C, 68.84; H, 3.30; N, 4.96.

A General Procedure for the Preparation of 2-(4-Aryl 1-methyl-2-pyridon-6-yl)benzoic Acid (10a—j) To a stirred solution of **8** (5 mmol) in

aqueous solution of NaOH (2.0 N, 20 ml) was added Me_2SO_4 (10 mmol) and aqueous solution of NaOH (2.0 N, 80 ml) simultaneously at 0 °C. Then the mixture was stirred for another 2 h at the same temperature and neutralized by aqueous HCl (2.0 N). The precipitated solid was collected and the crude product was purified by recrystallization to give compound **10** (Table 2).

2-(1-Methyl-4-phenyl-2-pyridon-6-yl)benzoic Acid (**10a**): mp 258—260 °C (EtOH); IR cm^{-1}: 1698, 1636, 1574; ^{1}H-NMR (DMSO-d_6) δ: 8.04 (1H, dd, J=7.7, 1.3), 7.78—7.64 (4H, m), 7.55—7.52 (1H, m), 7.48—7.44 (3H, m), 6.73 (1H, d, J=2.0), 6.38 (1H, d, J=2.0), 3.10 (3H, s); MS m/z: 307 (M+2, 3.3%), 306 (M+1, 19.7), 305 (M^+, 100). *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.74; H, 5.03; N, 4.39.

2-[1-Methyl-4-(4-methylphenyl)-2-pyridon-6-yl]benzoic Acid (**10b**): mp 223—225 °C (EtOH); IR cm^{-1}: 1694, 1631, 1574; ^{1}H-NMR (DMSO-d_6) δ: 8.05 (1H, d, J=7.6), 7.75 (1H, t, J=7.4), 7.68—7.56 (3H, m), 7.53 (1H, d, J=6.9), 7.26 (2H, d, J=7.9), 6.70 (1H, d, J=1.9), 6.37 (1H, d, J=1.9), 3.09 (3H, s), 2.34 (3H, s); MS m/z: 320 (M+1, 3.2%), 319 (M^+, 13.9), 57 (100). *Anal.* Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.20; H, 5.40; N, 4.40.

2-[1-Methyl-4-(4-isopropylphenyl)-2-pyridon-6-yl]benzoic Acid (**10c**): mp 278—280 °C (EtOH); IR cm^{-1}: 1694, 1634, 1576; ^{1}H-NMR (DMSO-d_6) δ: 8.05 (1H, dd, J=7.7, 1.1), 7.75 (1H, td, J=7.5, 1.4), 7.69—7.64 (3H, m), 7.52 (1H, dd, J=7.5, 1.0), 7.32 (2H, d, J=8.3), 6.71 (1H, d, J=2.0), 6.36 (1H, d, J=2.0), 3.09 (3H, s), 2.94—2.90 (1H, m), 1.20 (6H, d, J=6.9); MS m/z: 349 (M+2, 3.7%), 348 (M+1, 24.7), 347 (M^+, 100). *Anal.* Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.10; H, 6.03; N, 4.02.

2-[1-Methyl-4-(4-fluorophenyl)-2-pyridon-6-yl]benzoic Acid (**10d**): mp 164—166 °C (EtOH); IR cm^{-1}: 1704, 1636, 1551; ^{1}H-NMR (DMSO-d_6) δ: 8.06 (1H, d, J=7.5), 7.84—7.79 (2H, m), 7.74 (1H, d, J=7.3), 7.66 (1H, t, J=6.8), 7.53 (1H, d, J=7.3), 7.28 (2H, t, J=8.8), 6.73 (1H, d, J=1.8), 6.39 (1H, d, J=1.9), 3.09 (3H, s); MS m/z: 325 (M+2, 3.9%), 324 (M+1, 18.5), 323 (M^+, 100). *Anal.* Calcd for $C_{19}H_{14}FNO_3$: C, 70.58; H, 4.36; N, 4.33. Found: C, 70.51; H, 4.40; N, 4.32.

2-[1-Methyl-4-(4-chlorophenyl)-2-pyridon-6-yl]benzoic Acid (**10e**): mp 250—251 °C (EtOH); IR cm^{-1}: 1701, 1635, 1575; ^{1}H-NMR (DMSO-d_6) δ: 8.06 (1H, dd, J=7.7, 1.3), 7.80—7.73 (3H, m), 7.69—7.64 (1H, m), 7.54—7.49 (3H, m), 6.75 (1H, d, J=2.0), 6.40 (1H, d, J=2.0), 3.09 (3H, s); MS m/z: 341 (M+2, 15.3%), 340 (M+1, 20.7), 339 (M^+, 68.7), 294 (100). *Anal.* Calcd for $C_{19}H_{14}ClNO_3$: C, 67.16; H, 4.15; N, 4.12. Found: C, 67.00; H, 4.21; N, 4.09.

2-[1-Methyl-4-(2-chlorophenyl)-2-pyridon-6-yl]benzoic Acid (**10f**): mp 304—306 °C (EtOH); IR cm^{-1}: 1711, 1640, 1574; ^{1}H-NMR (DMSO-d_6) δ: 8.03 (1H, d, J=7.5), 7.74 (1H, t, J=7.5), 7.65 (1H, t, J=7.6), 7.57—7.51 (2H, m), 7.44—7.42 (3H, m), 6.45 (1H, s), 6.06 (1H, s), 3.12 (3H, s); MS m/z: 340 (M+1, 1.6%), 339 (M^+, 2.8), 43 (100). *Anal.* Calcd for $C_{19}H_{14}ClNO_3$: C, 67.16; H, 4.15; N, 4.12. Found: C, 67.37; H, 4.36; N, 4.06.

2-[1-Methyl-4-(4-methoxylphenyl)-2-pyridon-6-yl]benzoic Acid (**10g**): mp 218—220 °C (EtOH); IR cm^{-1}: 1697, 1634, 1608; ^{1}H-NMR (DMSO-d_6) δ: 8.05 (1H, d, J=7.6), 7.77—7.63 (4H, m), 7.52 (1H, d, J=7.4), 6.99 (2H, d, J=8.5), 6.68 (1H, d, J=1.4), 6.36 (1H, d, J=1.4), 3.79 (3H, s), 3.08 (3H, s); MS m/z: 337 (M+2, 3.2%), 336 (M+1, 20.4), 335 (M^+, 100). *Anal.* Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.66; H, 5.17; N, 4.13.

2-[1-Methyl-4-(3-methoxylphenyl)-2-pyridon-6-yl]benzoic Acid (**10h**): mp 261—262 °C (EtOH); IR cm^{-1}: 1705, 1637, 1572; ^{1}H-NMR (DMSO-d_6) δ: 8.05 (1H, d, J=7.7), 7.75 (1H, t, J=7.4) 7.66 (1H, t, J=7.6), 7.53 (1H, d, J=7.5), 7.37 (1H, t, J=7.8), 7.28 (1H, d, J=7.9), 7.24 (1H, m), 7.02—6.99 (1H, m), 6.74 (1H, d, J=2.0), 6.40 (1H, d, J=2.0), 3.81 (s, 3H), 3.09 (s, 3H); MS m/z: 336 (M+1, 24.6%), 335 (M^+, 67.9), 44 (100). *Anal.* Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.63; H, 5.17; N, 4.10.

2-[1-Methyl-4-(2-furyl)-2-pyridon-6-yl]benzoic Acid (**10i**): mp 230—232 °C (EtOH); IR cm^{-1}: 1706, 1639, 1575; ^{1}H-NMR (DMSO-d_6) δ: 8.05 (1H, dd, J=7.6, 1.0), 7.86 (1H, d, J=1.5), 7.75 (1H, td, J=7.4, 1.3), 7.66 (1H, td, J=7.6, 1.3), 7.51 (1H, dd, J=7.5, 0.9), 7.24 (1H, d, J=3.4), 6.65—6.63 (2H, m), 6.40 (1H, d, J=1.9), 3.06 (3H, s); MS m/z: 297 (M+2, 2.6%), 296 (M+1, 15.0), 295 (M^+, 79.9), 250 (100). *Anal.* Calcd for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.25; H, 4.30; N, 4.52.

2-[1-Methyl-4-(2-thienyl)-2-pyridon-6-yl]benzoic Acid (**10j**): mp 242—244 °C (EtOH); IR cm^{-1}: 1701, 1635, 1575; ^{1}H-NMR (DMSO-d_6) δ: 8.06 (1H, dd, J=7.7, 1.1), 7.79—7.64 (4H, m), 7.52 (1H, dd, J=7.5, 1.1), 7.18—7.15 (1H, m), 6.64 (1H, d, J=2.1), 6.39 (1H, d, J=2.1), 3.06 (3H, s); MS m/z: 313 (M+2, 6.2%), 312 (M+1, 11.8), 311 (M^+, 60.8), 279 (100). *Anal.* Calcd for $C_{17}H_{13}NO_3S$: C, 65.58; H, 4.21; N, 4.50. Found: C, 65.63; H, 4.20; N, 4.60.

A General Procedure for the Preparation of 4-Aryl 1-Methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (11a—j) Under the N_2, a mixture of compound **10** (3 mmol) in PPA (10 ml) was heated to 120 °C for 0.5 h. Then the resultant mixture was cooled to room temperature and poured into ice-water. After neutralization by solid $NaHCO_3$, the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water and dried over Na_2SO_4. The solvent was removed to yield a residue, which was purified by recrystalliation to give compound **11** (Table 3).

4-Phenyl-1-methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (**11a**): mp 188—190 °C (CH_2Cl_2/PE); IR cm^{-1}: 1704, 1661; ^{1}H-NMR δ: 7.76 (1H, d, J=7.4), 7.64 (1H, dd, J=6.9, 1.3), 7.56—7.45 (7H, m), 6.41 (1H, s), 4.04 (3H, s); MS m/z: 289 (M+2, 2.4%), 288 (M+1, 19.6), 287 (M^+, 100). *Anal.* Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.41; H, 4.65; N, 4.80.

4-(4-Methylphenyl)-1-methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (**11b**): mp 204—206 °C (CH_2Cl_2/PE); IR cm^{-1}: 1712, 1661; ^{1}H-NMR δ: 7.76 (1H, d, J=7.2), 7.65 (1H, dd, J=7.5, 1.4), 7.56—7.45 (2H, m), 7.42 (2H, d, J=8.0), 7.27 (2H, d, J=7.6), 6.41 (1H, s), 4.05 (3H, s), 2.44 (3H, s); MS m/z: 303 (M+2, 2.7%), 302 (M+1, 20.6), 301 (M^+, 100). *Anal.* Calcd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65. Found: C, 79.79; H, 5.06; N, 4.63.

4-(4-Isopropylphenyl)-1-methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (**11c**): mp 140—142 °C (CH_2Cl_2/PE); IR cm^{-1}: 1716, 1698, 1656; ^{1}H-NMR δ: 7.76 (1H, d, J=6.9), 7.66 (1H, dd, J=6.6, 1.6), 7.57—7.45 (4H, m), 7.33 (2H, d, J=8.1), 6.44 (1H, s), 4.06 (3H, s), 2.99 (1H, m), 1.32 (6H, d, J=6.9); MS m/z: 331 (M+2, 2.8%), 330 (M+1, 22.1), 329 (M^+, 100). *Anal.* Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.08; H, 5.90; N, 4.30.

4-(4-Fluorophenyl)-1-methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (**11d**): mp 202—204 °C (CH_2Cl_2/PE); IR cm^{-1}: 1708, 1659; ^{1}H-NMR δ: 7.77 (1H, d, J=6.9), 7.66 (1H, dd, J=6.8, 1.4), 7.55—7.48 (4H, m), 7.15 (2H, t, J=8.6), 6.39 (1H, s), 4.05 (3H, s); MS m/z: 307 (M+2, 2.3%), 305 (M^+, 100). *Anal.* Calcd for $C_{19}H_{12}FNO_2$: C, 74.75; H, 3.96; N, 4.59. Found: C, 74.75; H, 4.02; N, 4.58.

4-(4-Chlorophenyl)-1-methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (**11e**): mp 220—222 °C (CH_2Cl_2/PE); IR cm^{-1}: 1712, 1679, 1664; ^{1}H-NMR δ: 7.78 (1H, d, J=6.9), 7.67 (1H, d, J=6.9), 7.58—7.51 (2H, m), 7.48—7.41 (4H, m), 6.38 (1H, s), 4.06 (3H, s); MS m/z: 324 (M+3, 6.4%), 323 (M+2, 34.7), 322 (M+1, 27.9), 321 (M^+, 100). *Anal.* Calcd for $C_{19}H_{12}ClNO_2$: C, 70.92; H, 3.76; N, 4.35. Found: C, 70.92; H, 3.81; N, 4.33.

4-(2-Chlorophenyl)-1-methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (**11f**): mp 194—196 °C (CH_2Cl_2/PE); IR cm^{-1}: 1704, 1677, 1660; ^{1}H-NMR δ: 7.76 (1H, d, J=7.1), 7.61 (1H, dd, J=6.9, 0.5), 7.53—7.46 (3H, m), 7.42—7.35 (2H, m), 7.28—7.25 (1H, m), 6.35 (1H, s), 4.06 (3H, s); MS m/z: 324 (M+3, 0.7%), 323 (M+2, 2.3), 322 (M+1, 1.5), 321 (M^+, 7.6), 286 (100). *Anal.* Calcd for $C_{19}H_{12}ClNO_2$: C, 70.92; H, 3.76; N, 4.35. Found: C, 70.92; H, 3.84; N, 4.31.

4-(4-Methoxylphenyl)-1-methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (**11g**): mp 118—120 °C (CH_2Cl_2/PE); IR cm^{-1}: 1718, 1650, 1628, 1611; ^{1}H-NMR δ: 7.76 (1H, d, J=7.2), 7.66 (1H, dd, J=6.7, 1.1), 7.56—7.46 (4H, m), 6.99 (2H, d, J=8.7), 6.40 (1H, s), 4.05 (3H, s), 3.88 (3H, s); ^{13}C-NMR δ: 188.0, 163.5, 161.1, 160.9, 150.7, 136.9, 135.7, 133.7, 132.3, 130.5, 128.6, 124.2, 123.7, 115.1, 113.7, 55.7, 32.6; MS m/z: 319 (M+2, 3.3%), 318 (M+1, 23.3), 317 (M^+, 100). *Anal.* Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41. Found: C, 75.69; H, 4.69; N, 4.39.

4-(3-Methoxylphenyl)-1-methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (**11h**): mp 168—170 °C (CH_2Cl_2/PE); IR cm^{-1}: 1709, 1664, 1604; ^{1}H-NMR δ: 7.77 (1H, d, J=6.8), 7.66 (1H, dd, J=6.6, 1.5), 7.58—7.47 (2H, m), 7.38 (1H, t, J=7.8), 7.06—7.00 (3H, m), 6.46 (1H, s), 4.07 (3H, s), 3.87 (3H, s); MS m/z: 319 (M+2, 4.2%), 318 (M+1, 21.3), 317 (M^+, 100). *Anal.* Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41. Found: C, 75.78; H, 4.82; N, 4.33.

4-(2-Furyl)-1-methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (**11i**): mp 232—234 °C (CH_2Cl_2/PE); IR cm^{-1}: 1699, 1647; ^{1}H-NMR δ: 8.10 (1H, d, J=3.5), 7.73 (1H, d, J=6.9), 7.69 (1H, dd, J=6.0, 1.3), 7.57 (1H, s), 7.55—7.46 (2H, m), 6.94 (1H, s), 6.60—6.58 (1H, m), 4.02 (3H, s); MS m/z: 278 (M+1, 18.2%), 277 (M^+, 100). *Anal.* Calcd for $C_{17}H_{11}NO_3$: C, 73.64; H, 4.00; N, 5.05. Found: C, 73.74; H, 3.95; N, 5.14.

4-(2-Thienyl)-1-methyl-1*H*-indeno[1,2-*b*]pyridine-2,5-dione (**11j**): mp 178—180 °C (CH_2Cl_2/PE); IR cm^{-1}: 1703, 1655; ^{1}H-NMR δ: 7.89 (1H, dd, J=3.7, 0.9), 7.79—7.76 (1H, m), 7.72—7.69 (1H, m), 7.58—7.47 (3H, m), 7.19—7.16 (1H, m), 6.63 (1H, s), 4.05 (3H, s); MS m/z: 295 (M+2, 5.3%), 294 (M+1, 19.7), 293 (M^+, 100). *Anal.* Calcd for $C_{17}H_{11}SNO_2$: C, 69.61; H, 3.78; N, 4.77. Found: C, 69.63; H, 3.68; N, 4.78.

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41) Crystal data of compound **9d**: $C_{18}H_{10}FNO_2$, M=291.27, Orthorhombic; a=13.185(5) Å, b=4.852(2) Å, c=21.305(6) Å; V=1320.8(8) Å^3, T=298(2) K; space group: P21/a; Z=4, Absorption coefficient: 0.106 mm^{-1}, 3041 reflections measured, 2364 unique (R_{int}=0.1411); Final R indices [I>2sigma(I)]: R_1=0.0866, wR_2=0.2489; R indices (all data): R_1=0.2284, wR_2=0.3298. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 222744.
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51) Crystal data of compound **11g**: $(C_{20}H_{15}NO_3)_2(CH_2Cl_2)_2$, M=804.51, Orthorhombic; a=7.412(2) Å, b=21.360(5) Å, c=23.310(7) Å; V=3690.4(17) Å^3, T=298(2) K; space group: P212121; Z=4, Absorption coefficient: 0.374 mm^{-1}, 4164 reflections measured, 3933 unique (R_{int}=0.0358); Final R indices [I>2sigma(I)]: R_1=0.0563, wR_2=0.1482; R indices (all data): R=0.1983, wR_2=0.1930. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 222745.