

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

Shaozhong WANG,^a Liya CAO,^a Haijian SHI,^a Yanmei DONG,^a Jianwei SUN,^a and Yuefei HU^{*,b}

^a Department of Chemistry, Nanjing University; Nanjing 210093, P. R. China; and ^b Department of Chemistry, Tsinghua University; Beijing 100084, P. R. China. Received August 16, 2004; accepted October 7, 2004

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 alkoxy substituted 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 IC₅₀ 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 inhibitors¹¹⁾ 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.

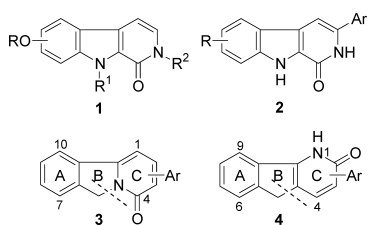
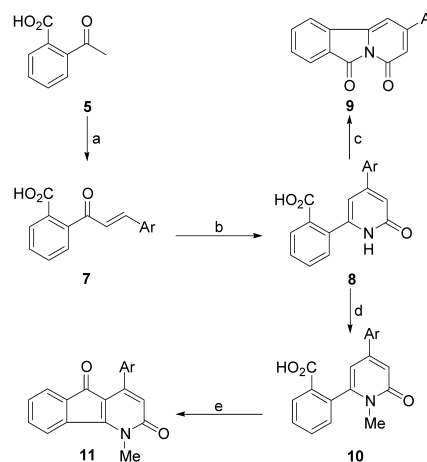


Chart 1

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) BtCH₂CONH₂, NaOH, EtOH, reflux, 6 h, 60–75%; (c) xylene, reflux, 8 h, 89–98%. (d) 2.0 N aq. NaOH, (MeO)₂SO₂, 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 ₆ H ₅	90	151–152	1696, 1648
b	4-CH ₃ C ₆ H ₄	90	165–166	1693, 1637
c	4- <i>i</i> -PrC ₆ H ₄	92	152–153	1669, 1604
d	4-FC ₆ H ₄	90	135–137	1692, 1644
e	4-ClC ₆ H ₄	88	165–166	1689, 1666
f	2-ClC ₆ H ₄	88	134–135	1689, 1666
g	4-MeOC ₆ H ₄	90	132–133	1690, 1649
h	3-MeOC ₆ H ₄	88	128–129	1713, 1610
i	2-Furyl	95	135–136	1711, 1611
j	2-Thienyl	90	134–135	1691, 1658

* To whom correspondence should be addressed. e-mail: yfh@mail.tsinghua.edu.cn

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 ₆ H ₅	63	98	83	92	f	2-ClC ₆ H ₄	68	90	75	85
b	4-CH ₃ C ₆ H ₄	65	96	80	90	g	4-MeOC ₆ H ₄	75	95	80	90
c	4- <i>i</i> -PrC ₆ H ₄	60	90	81	92	h	3-MeOC ₆ H ₄	73	91	78	88
d	4-FC ₆ H ₄	70	92	87	90	i	2-Furyl	60	89	80	85
e	4-ClC ₆ H ₄	68	90	85	90	j	2-Thienyl	62	90	81	86

p-nitrobenzaldehydes, failed to afford the expected chalcones.

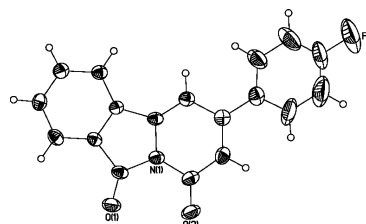
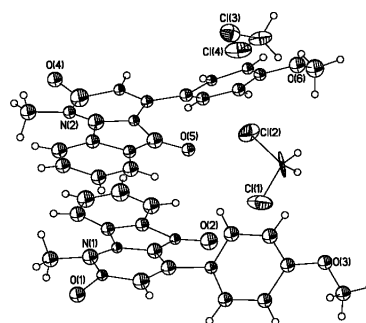
Among the methods for preparation of 3-unsubstituted 2-pyridone,^{27–37} [3+3] annulation between chalcone and C–N fragment connected with a leaving group displayed high convenience and efficiency, such as *N*-(2-carbamoylmethyl)-pyridinium ylide,^{29–33} 2-acetamidoacetamide³⁴ or 2-(benzotriazol-1-yl)acetamide.^{35–37} 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)acetamide³⁵ 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, H₂SO₄, CH₃SO₃H, TFA, ZnCl₂, AlCl₃ or SnCl₄ 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 Me₂SO₄ 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 intramolecular *C*-acylation smoothly catalyzed by

Fig. 1. Structure of Compound **9d**Fig. 2. Structure of Compound **11g**

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 ¹H-NMR spectra respectively, the singlet signals appearing at δ 6.94–6.41 ppm in ¹H-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

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 CDCl₃ with TMS as internal reference. The *J* values are given in Hz. MS spectra were obtained on a VG-ZAB-MS 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), BtCH₂CONH₂ (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; ¹H-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 C₁₈H₁₃NO₃: 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; ¹H-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 C₁₉H₁₅NO₃: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.65; H, 5.00; N, 4.41.

2-[4-(4-Isopropylphenyl)-2-pyridon-6-yl]benzoic Acid (**8c**): mp 222–223 °C (MeOH); IR cm⁻¹: 3025, 1660, 1629; ¹H-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 C₁₉H₁₅NO₃: 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; ¹H-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 C₁₈H₁₂FNO₃: 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; ¹H-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 C₁₈H₁₂ClNO₃: C, 66.37; H, 3.71; N, 4.30. Found: C, 66.35; H, 3.79; N, 4.28.

2-[4-(2-Chlorophenyl)-2-pyridon-6-yl]benzoic Acid (**8f**): mp 267–269 °C (MeOH); IR cm⁻¹: 3097, 1718, 1619; ¹H-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 C₁₈H₁₂ClNO₃: 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; ¹H-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 C₁₉H₁₅NO₄: 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; ¹H-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 C₁₉H₁₅NO₄: 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; ¹H-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 C₁₆H₁₁NO₄: 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; ¹H-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 C₁₆H₁₁NO₃S: 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; ¹H-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); ¹³C-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 C₁₈H₁₁NO₂: 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; ¹H-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 C₁₉H₁₃NO₂: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.32; H, 4.59; N, 4.72.

2-(4-Isopropylphenyl)pyrido[2,1-*a*]isoindole-4,6-dione (**9c**): mp 237–239 °C (xylene); IR cm⁻¹: 3068, 1782, 1755, 1674, 1617; ¹H-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 C₂₁H₁₉NO₂: 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; ¹H-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 C₁₈H₁₀FNO₂: 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; ¹H-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 C₁₈H₁₀ClNO₂: 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; ¹H-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 C₁₈H₁₀ClNO₂: 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; ¹H-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 C₁₉H₁₃NO₃: 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; ¹H-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 C₁₉H₁₃NO₃: 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; ¹H-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 C₁₆H₉NO₃: 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, 1767, 1673, 1619; ¹H-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 C₁₆H₉NO₂S: 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 (2.0N, 20 ml) was added Me₂SO₄ (10 mmol) and aqueous solution of NaOH (2.0N, 80 ml) simultaneously at 0 °C. Then the mixture was stirred for another 2h at the same temperature and neutralized by aqueous HCl (2.0N). 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; ¹H-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 C₁₉H₁₅NO₃: 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; ¹H-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 C₂₀H₁₇NO₃: 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; ¹H-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 C₂₂H₂₁NO₃: 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; ¹H-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 C₁₉H₁₄FNO₃: 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; ¹H-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 C₁₉H₁₄ClNO₃: 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; ¹H-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 C₁₉H₁₄ClNO₃: C, 67.16; H, 4.15; N, 4.12. Found: C, 67.37; H, 4.36; N, 4.06.

2-[1-Methyl-4-(4-methoxyphenyl)-2-pyridon-6-yl]benzoic Acid (10g): mp 218—220 °C (EtOH); IR cm⁻¹: 1697, 1634, 1608; ¹H-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 C₂₀H₁₇NO₄: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.66; H, 5.17; N, 4.13.

2-[1-Methyl-4-(3-methoxyphenyl)-2-pyridon-6-yl]benzoic Acid (10h): mp 261—262 °C (EtOH); IR cm⁻¹: 1705, 1637, 1572; ¹H-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 C₂₀H₁₇NO₄: 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; ¹H-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 C₁₇H₁₃NO₄: 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; ¹H-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 C₁₇H₁₃NO₃S: 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-1H-in-

deno[1,2-*b*]pyridine-2,5-dione (11a—j) Under the N₂, 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 NaHCO₃, the mixture was extracted with CH₂Cl₂. The combined organic layers were washed with water and dried over Na₂SO₄. The solvent was removed to yield a residue, which was purified by recrystallization to give compound **11** (Table 3).

4-Phenyl-1-methyl-1H-indeno[1,2-*b*]pyridine-2,5-dione (11a): mp 188—190 °C (CH₂Cl₂/PE); IR cm⁻¹: 1704, 1661; ¹H-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 C₁₉H₁₃NO₂: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.41; H, 4.65; N, 4.80.

4-(4-Methylphenyl)-1-methyl-1H-indeno[1,2-*b*]pyridine-2,5-dione (11b): mp 204—206 °C (CH₂Cl₂/PE); IR cm⁻¹: 1712, 1661; ¹H-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 C₂₀H₁₅NO₂: C, 79.72; H, 5.02; N, 4.65. Found: C, 79.79; H, 5.06; N, 4.63.

4-(4-Isopropylphenyl)-1-methyl-1H-indeno[1,2-*b*]pyridine-2,5-dione (11c): mp 140—142 °C (CH₂Cl₂/PE); IR cm⁻¹: 1716, 1698, 1656; ¹H-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 C₂₂H₁₉NO₂: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.08; H, 5.90; N, 4.30.

4-(4-Fluorophenyl)-1-methyl-1H-indeno[1,2-*b*]pyridine-2,5-dione (11d): mp 202—204 °C (CH₂Cl₂/PE); IR cm⁻¹: 1708, 1659; ¹H-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 C₁₉H₁₂FNO₂: C, 74.75; H, 3.96; N, 4.59. Found: C, 74.75; H, 4.02; N, 4.58.

4-(4-Chlorophenyl)-1-methyl-1H-indeno[1,2-*b*]pyridine-2,5-dione (11e): mp 220—222 °C (CH₂Cl₂/PE); IR cm⁻¹: 1712, 1679, 1664; ¹H-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 C₁₉H₁₂ClNO₂: C, 70.92; H, 3.76; N, 4.35. Found: C, 70.92; H, 3.81; N, 4.33.

4-(2-Chlorophenyl)-1-methyl-1H-indeno[1,2-*b*]pyridine-2,5-dione (11f): mp 194—196 °C (CH₂Cl₂/PE); IR cm⁻¹: 1704, 1677, 1660; ¹H-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 C₁₉H₁₂ClNO₂: C, 70.92; H, 3.76; N, 4.35. Found: C, 70.92; H, 3.84; N, 4.31.

4-(4-Methoxyphenyl)-1-methyl-1H-indeno[1,2-*b*]pyridine-2,5-dione (11g): mp 118—120 °C (CH₂Cl₂/PE); IR cm⁻¹: 1718, 1650, 1628, 1611; ¹H-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); ¹³C-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 C₂₀H₁₅NO₃: C, 75.70; H, 4.76; N, 4.41. Found: C, 75.69; H, 4.69; N, 4.39.

4-(3-Methoxyphenyl)-1-methyl-1H-indeno[1,2-*b*]pyridine-2,5-dione (11h): mp 168—170 °C (CH₂Cl₂/PE); IR cm⁻¹: 1709, 1664, 1604; ¹H-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 C₂₀H₁₅NO₃: C, 75.70; H, 4.76; N, 4.41. Found: C, 75.78; H, 4.82; N, 4.33.

4-(2-Furyl)-1-methyl-1H-indeno[1,2-*b*]pyridine-2,5-dione (11i): mp 232—234 °C (CH₂Cl₂/PE); IR cm⁻¹: 1699, 1647; ¹H-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 C₁₇H₁₁NO₃: C, 73.64; H, 4.00; N, 5.05. Found: C, 73.74; H, 3.95; N, 5.14.

4-(2-Thienyl)-1-methyl-1H-indeno[1,2-*b*]pyridine-2,5-dione (11j): mp 178—180 °C (CH₂Cl₂/PE); IR cm⁻¹: 1703, 1655; ¹H-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 C₁₇H₁₁SNO₂: C, 69.61; H, 3.78; N, 4.77. Found: C, 69.63; H, 3.68; N, 4.78.

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- Crystal data of compound **9d**: C₁₈H₁₀FNO₂, *M*=291.27, Orthorhombic; *a*=13.185(5) Å, *b*=4.852(2) Å, *c*=21.305(6) Å; *V*=1320.8(8) Å³, *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*>2σ(*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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