A Novel Synthesis of 1-Alkyl-2-phenyl-(2,3-dihydro-) 1,8-naphthyridin-4-ones from 2-Chloronicotinic Acid

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The heterocyclic group of 1,8-naphthyridin-4-one has played a central role in pharmacological activities showing that *N*-1 alkyl substituents influence antibacterial activity and that nitrogen at position 8 controls pharmacokinetics.[1] Their derivatives possess cytotoxic activity against human tumor cells,[2] anticancer effects via inhibition of tublin polymerization,[3] and antibacterial activity.[4] Among them, Gemifloxacin (Factive®, LG Life Science Company, Daejeon, Korea), which contains 1,8-naphthy-ridin-4-one nuclei, is widely used for treating chronic bronchitis and pneumonia.[5]

The initial synthesis of 2-phenyl-1,8-naphthyridin-4-ones involves the condensation of 2-aminopyridines with ethyl benzoylacetates in the presence of polyphosphoric acid. This reaction forms pyridopyrimidyl-4-one intermediates, which are then converted to 2-phenyl-1,8-naphthyridin-4-ones by thermal rearrangement at 350 °C in low to moderate yields.[6] The substitution of ethyl 2-fluoronicotinoyl-3-ethoxyacrylates, prepared from 2-fluoronicotinic acid in three steps, by amines affords the corresponding enamino keto esters, which are then cyclized with sodium hydride or K_2CO_3 to give 1-alkyl-3-carboethoxy-1,8-naphthyridin-4-ones.[7] Alternatively, the condensation of 2-chloronicotinoyl chlorides with ethyl 3,3-dimethylaminoacrylate affords the corresponding enamino keto esters.[8] These intermediates can then be reacted with alkyl amines, followed by cyclization using K_2CO_3 in DMF to give 1-alkyl-3-carboethoxy-1,8-naphthyridin-4-ones in five steps.[9] Palladium-catalyzed tandem amination[10] of 1-(2-chloro-3-pyridyl)-3-phenyl-2-propyn-1-ones, prepared by the coupling of 2-chloro-nicotinoyl chloride with terminal alkynes, by amines using $Pd(PPh_3)_4/K_2CO_3$ affords 1-alkyl-2-phenyl-1,8-naphthyridin-4-ones in DMF at 150 °C.[11]

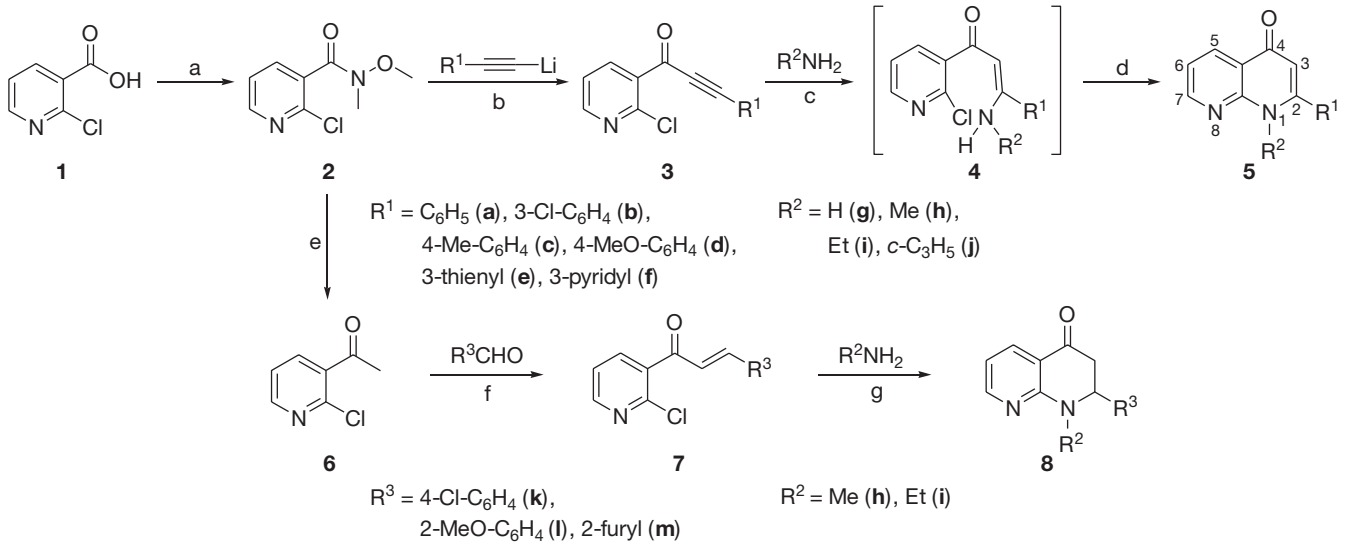
To date, few methods have been reported for the synthesis of 2,3-dihydro-1,8-naphthyridin-4-ones. The 1,4-addition of 2-aminopyridines to ethyl acrylate affords 3-(2-pyridyl-imino) propionic acids after alkaline hydrolysis, which can then be cyclized with polyphosphoric acid at 120 °C to give 2,3-dihydro-1,8-naphthyridin-4-ones in low yields.[12] The treatment of 2-chloro-3-pyridine carboxaldehyde with vinyl- magnesium bromides followed by oxidation with manganese (IV) oxide affords 1-(2-chloro-3-pyridyl)-3-alkyl-2-propen-1-ones. The 1,4-addition of these compounds and a sequential S_NAr reaction afford 1-alkyl-2,3-dihydro-1,8-naphthyridin-4-ones, but this method is effective for 2-substituted aliphatic groups.[13]

Although several methods for the synthesis of 1-alkyl-2-phenyl-1,8-naphthyridin-4-ones have been reported, some often suffer from multiple steps, harsh conditions, and low yields. Furthermore, reports on the synthesis of 1-alkyl-2-phenyl-2,3-dihydro-1,8-naphthyridin-4-ones are rare. As part our continuing study on azaflavonois,[14] we report that novel 1-alkyl-2-phenyl-(2,3-dihydro-)1,8-naphthyridin-4-ones can be efficiently synthesized from 2-chloronicotinic acid in excellent yields under mild conditions.

N-Methoxy-*N*-methyl 2-chloronicotinamide (**2**) was efficiently prepared by treating 2-chloronicotinic acid (**1**) with triethylamine and *N*-methoxy-*N*-methylcarbamoyl chloride, prepared from bis(trichloromethyl) carbonate and *N*,*O*-dimethylhydroxylamine hydrochloride, in the presence of 0.05 equiv of 4-(dimethylamino)pyridine (4-DMAP) in acetonitrile in 83% yield. This synthesis was similarly carried out according to a previous method[15] (Scheme 1). 1-(2-Chloro-3-pyridyl)-3-(hetero)aryl-2-propyn-1-ones (**3**) were successfully synthesized by reacting **2** with (hetero)arylethynyl lithiums, generated from (hetero)aryl acetylenes and methyllithium in THF for 0.5 h at 0 °C, in 78–87% yields after the usual acidic work-up (**3a**: 85%, **3b**: 78%, **3c**: 82%, **3d**: 87%, **3e**: 81%, **3f**: 85%). An attempt to prepare 1-(2-chloro-3-pyridyl)ethanone (**6**) by the direct reaction of **1** with 2 equiv of methyllithium was fruitless. However, the reaction of **2** with methyllithium proceeded smoothly in THF at 0 °C to give **6** in 90% yield after the usual acidic work-up.

The condensation of **6** with (hetero)aryl aldehydes was accomplished by the addition of 0.5 N methanolic KOH in THF at 0 °C. The reaction mixture was stirred for 2–4 h between 0 °C and room temperature (rt) and the resulting pale yellow solution was quenched with 0.5 N HCl. After the usual basic work-up, 1-(2-chloro-3-pyridyl)-3-(hetero)aryl-2-propen-1-ones (**7**) were obtained in 82–91% yields (**7k**: 89%, **7l**: 82%, **7m**: 91%). Judging from the coupling constant (J = ~16 Hz) of the two vinyl protons, the C=C bond of **7** existed exclusively in the *trans* configuration.

The synthesis of 1-alkyl-2-phenyl-1,8-naphthyridin-4-ones (**5**) was carried out by the 1,4-addition of alkyl amines and the subsequent cyclization of the enamino intermediates (**4**). For example, the addition of methylamine to a solution of 1-(2-chloro-3-pyridyl)-3-phenyl-2-propyn-1-one (**3a**) in



Scheme 1. Reagents and conditions: (a) ClCONMe(OMe), Et_3N, 0.05 equiv 4-DMAP, CH_3CN, rt, 1 h; (b) THF, 0 °C, 0.5 h; (c) THF or DME, 0 °C to rt, 0.5–3.5 h; rt, 10–36 h for **g**; (d) NaH, THF, rt, 1.5–4 h; 66 °C, 3.5 h for **j**, DME, 80 °C, 10–12 h for **g**; (e) MeLi, THF, 0 °C, 0.5 h; (f) 0.5 N KOH, THF–MeOH, 0 to rt, 2–4 h and (g) THF, rt, 4.5–24 h.

THF afforded 1-(2-chloro-3-pyridyl)-3-(*N*-methylamino)-3-phenyl-2-propen-1-one (**4a**) after 0.5 h at 0 °C in 97% yield. The characteristic ^{1}H NMR values of **4a** were identified with δ 11.24 (NH), 5.47 (=CH), and 2.99 (CH_3). However, the cyclization of **3** was carried out in a one-pot procedure without the isolation of **4**. Thus, **4** was redissolved in THF after evaporation of the solvents and treated with sodium hydride at rt. The resulting enamino anion attacked to the carbon atom at position 2 to substitute the 2-chloro group after 1.5 h to give 1-methyl-2-phenyl-1,8-naphthyridin-4-one (**5ah**) in 94% yield. In the case of cyclopropylamine, nucleophilic substitution proceeded to give 1-cyclopropyl-2-phenyl-1,8-naphthyridin-4-one (**5aj**) upon heating at 66 °C in THF for 5 h, reflecting the steric hindrance of the cyclopropyl group. Furthermore, the cyclization of 1-(2-chloro-3-pyridyl)-3-amino-3-phenyl-2-propen-1-one (**4ag**) with 1 equiv of sodium hydride afforded 2-phenyl-1,8-naphthyridin-4-one (**5ag**) in 48% yield with the recovery of **4ag** in 43% yield in DME after reflux for 24 h. The result was thought to be due to the abstraction of the proton at position 1 of **5ag** by the base, NaH. The complete conversion of **4ag** to **5ag** was expected by the use of excess NaH. Thus, the treatment of **4ag** with 2 equiv of sodium hydride afforded **5ag** in 81% yield in DME after reflux for 12 h.

The conversion of **7** to **8** was examined with methylamine in varying solvents. The treatment of 1-(2-chloro-3-pyridyl)-3-(4-chlorophenyl)-2-propen-1-one (**7k**) with methylamine in CH_2Cl_2, THF, DME, and CH_3CN at rt afforded 1-methyl-2-(4′-chlorophenyl)-2,3-dihydro-1,8-naphthyridin-4-one (**8kh**) in 65, 89, 86, and 83% yields, respectively. The reaction appeared to proceed through the 1,4-addition of alkyl amines, subsequent nucleophilic addition, and then rearomatization, which was accompanied by the liberation of alkylammonium chlorides.

After completion of the reaction, recrystallization or chromatographic separation of the extracted residue afforded **8** in 78–89% yields.

As shown in Table 1, various 1-alkyl-2-phenyl-(2,3-dihydro-)1,8-naphthyridin-4-ones were synthesized from 2-chloronicotinic acid in excellent overall yields (50–66%). Although the presence of hydrogen or a cyclopropyl group at position 1 decreased the rate of cyclization during the synthesis of **5**, the reaction proceeded smoothly in the case of methyl or ethyl groups. The reaction worked well with both electron-withdrawing groups (**5bh** and **8kh**) and electron-donating groups (**5ch**, **5dg**, **8lh**, and **8li**) of the 2-phenyl ring under the present reaction conditions. Furthermore, the synthesis of **5** and **8** which contain heteroaromatic groups such as 3-thienyl (**5eh**), 3-pyridyl (**5fi**), and 2-furyl (**8mh**) proceeded equally well in place of the phenyl ring at position 2.

Experimental

Preparation of 1-(2-chloro-3-pyridyl)-3-phenyl-2-propyn-1-one (3a) and 1-(2-chloro-3-pyridyl)ethanone (6). To a solution of **2** (473 mg, 3.0 mmol) in THF (8 mL) was added phenylethynyllithium, generated from phenylacetylene (306 mg, 3.0 mmol) and methyllithium (1.5 M in Et_2O, 2.0 mL, 3.0 mmol) for 0.5 h at 0 °C, or methyllithium (1.5 M in Et_2O, 2.0 mL, 3.0 mmol) at 0 °C. After being stirred for 0.5 h, the mixture was quenched with 0.5 N HCl (5 mL) and THF was evaporated *in vacuo*. The mixture was poured into 0.1 N HCl (30 mL) and extracted with dichloromethane (3 × 20 mL). The condensed residue was purified by silica gel column chromatography using 30% EtOAc/*n*-hexane or vacuum distillation using a Kugelrohr apparatus to give **3a** (616 mg, 85%) and **6** (420 mg, 90%), respectively. **3a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (dd, J = 4.8, 2.0 Hz, 1H),

Table 1. Synthesis of products **5** and **8** from **3** and **7**.

Entry	R^1 or R^3	R^2	Isolated yields (%)[a]
5ag	C_6H_5	H	81 (57)
5ah	C_6H_5	Me	94 (66)
5aj	C_6H_5	*c*-C_3H_5	83 (59)
5bh	3-Cl–C_6H_4	Me	93 (60)
5ch	4-Me–C_6H_4	Me	87 (59)
5dg	4-MeO–C_6H_4	H	81 (58)
5eh	3-Thienyl	Me	92 (62)
5fi	3-Pyridyl	Et	85 (60)
8kh	4-Cl–C_6H_4	Me	89 (59)
8lh	2-MeO–C_6H_4	Me	85 (52)
8li	2-MeO–C_6H_4	Et	81 (50)
8mh	2-Furyl	Me	78 (53)

[a] The numbers in parentheses indicate the overall yields from 2-chloronicotinic acid **1**.

8.34 (dd, J = 7.7, 2.0 Hz, 1H), 7.64–7.68 (m, 2H), 7.48–7.53 (m, 1H), 7.40–7.53 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 152.2, 149.5, 140.5, 133.2, 132.8, 131.2, 128.7, 122.3, 119.7, 95.6, 88.0; FT-IR (film) 2195 (C≡C), 1656 (C═O) cm^{-1}; MS *m/z* (%) 243 (M^++2, 48), 241 (M^+, 100). **6:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (dd, J = 4.8, 2.0 Hz, 1H), 7.91 (dd, J = 7.6, 2.0 Hz, 1H), 7.35 (dd, J = 7.6, 4.8 Hz, 1H), 2.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6, 151.4, 147.8, 138.4, 135.4, 122.5, 30.4; FT-IR (film) 1705 (C═O) cm^{-1} ; MS *m/z* (%) 157 (M^++2, 32), 155 (M^+, 80), 142 (100).

Preparation of 1-(2-Chloro-3-pyridyl)-3-(2-methoxyphenyl)-2-propen-1-one (7l). KOH (0.5 N in MeOH, 6.0 mL, 3.0 mmol) was added to a mixture solution of **6** (467 mg, 3.0 mmol) and 2-methoxybenzaldehyde (408 mg, 3.0 mmol) in THF at 0 °C. The mixture was stirred for 3 h between 0 °C and rt and the resulting pale yellow solution was quenched with 0.5 N HCl (6 mL). After evaporation of the solvents, the mixture was poured into a saturated $NaHCO_3$ solution (30 mL) and extracted with dichloromethane (3 × 20 mL). The condensed residue was purified by silica gel column chromatography using 30% EtOAc/*n*-hexane to give **7l** (673 mg, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (dd, J = 4.8, 2.0 Hz, 1H), 7.83 (dd, J = 7.6, 2.0 Hz, 1H), 7.82 (d, J = 16.2 Hz, 1H), 7.58 (dd, J = 7.7, 1.5 Hz, 1H), 7.35–7.43 (m, 2H), 7.26 (d, J = 16.2 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 158.9, 150.7, 147.9, 142.5, 138.3, 135.8, 132.5, 129.4, 126.1, 123.2, 122.3, 120.9, 111.4, 55.6; FT-IR (film) 1647 (C═O) cm^{-1}; MS *m/z* (%) 275 (M^++2, 7), 273 (M^+, 22), 244 (35), 242 (100).

Preparation of 1-Methyl-2-phenyl-1,8-naphthyridin-4-one (5ah). Methylamine (33 wt% in EtOH, 0.5 mL, 4.0 mmol) was added to a solution of **3a** (483 mg, 2.0 mmol) in THF (6 mL) at 0 °C. The mixture was stirred for 0.5 h between 0 °C and rt. After evaporation of the solvents, the mixture was redissolved in THF (6 mL) and the resulting solution was added to a suspended solution of sodium hydride (60% dispersion, 84 mg, 2.1 mmol) in THF (6 mL) at rt. Stirring was continued for 1.5 h and then the mixture was quenched with H_2O (2 mL). After the evaporation of THF, the mixture was poured into brine (30 mL) and extracted with ethyl acetate (3 × 20 mL). The condensed residue was recrystallized twice from 15% EtOAc/*n*-hexane to give **5ah** (444 mg, 94%). m. p. 115–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74–8.80 (m, 2H), 7.50–7.55 (m, 3H), 7.42–7.47 (m, 2H), 7.39 (dd, J = 7.9, 4.5 Hz, 1H), 6.33 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 155.6, 152.1, 151.1, 135.8, 135.6, 129.7, 128.8, 128.4, 121.5, 119.7, 113.3, 35.5; FT-IR (KBr) 1626 (C═O) cm^{-1}; MS *m/z* (%) 236 (M^+, 65), 235 (100).

Preparation of 1-Methyl-2-(2′-methoxyphenyl)-2,3-dihydro-1,8-naphthyridin-4-one (8lh)**.** Methylamine (33 wt.% in EtOH, 1.25 mL, 10.0 mmol) was added to a solution of **7l** (547 mg, 2.0 mmol) in THF (6 mL) at rt and stirred for 4.5 h. After evaporation of the solvent, the mixture was poured into a saturated $NaHCO_3$ solution (30 mL) and extracted with dichloromethane (3 × 20 mL). The condensed residue was recrystallized twice from 10% EtOAc/*n*-hexane to give 8**lh** (456 mg, 85%). m.p. 122–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (dd, J = 4.8, 2.0 Hz, 1H), 7.98 (dd, J = 7.6, 2.0 Hz, 1H), 7.18–7.25 (m, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.77 (d, J = 4.2 Hz, 2H), 6.63 (dd, J = 7.6, 4.8 Hz, 1H), 5.14 (dd, J = 7.2, 3.1 Hz, 1H), 3.84 (s, 3H), 3.18 (s, 3H), 3.17 (dd, J = 16.3, 7.3 Hz, 1H), 3.00 (dd, J = 16.3, 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 159.8, 156.9, 154.6, 135.5, 128.9 (overlapped), 126.2, 120.6, 114.5, 112.3, 111.0, 56.8, 55.1, 42.2, 35.4; FT-IR (KBr) 1668 (C═O) cm^{-1}; MS *m/z* (%) 268 (M^+, 100).

5ag, **5dg:** known compounds.[6a,11]

1-Cyclopropyl-2-phenyl-1,8-naphthyridin-4-one (5aj): m.p. 149–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (dd, J = 4.5, 2.0 Hz, 1H), 8.70 (dd, J = 7.9, 2.0 Hz, 1H), 7.53–7.58 (m, 2H), 7.48–7.53 (m, 3H), 7.38 (dd, J = 7.9, 4.5 Hz, 1H), 6.35 (s, 1H), 3.36–3.44 (m, 1H), 0.91–0.99 (m, 2H), 0.44–0.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 156.5, 153.1, 151.9, 136.6, 135.5, 129.4, 128.5, 128.3, 121.6, 119.6, 113.8, 32.0, 12.5; FT-IR (KBr) 1626 (C═O) cm^{-1}; MS *m/z* (%) 262 (M^+, 57), 261 (100).

1-Methyl-2-(3′-chlorophenyl)-1,8-naphthyridin-4-one (5bh): m.p. 181–182 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (dd, J = 4.5, 2.0 Hz, 1H), 8.74 (dd, J = 7.9, 2.0 Hz, 1H), 7.45–7.52 (m, 3H), 7.40 (dd, J = 7.9, 4.5 Hz, 1H), 7.32–7.36 (m, 1H), 6.29 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 153.8, 152.2, 151.1, 137.2, 135.8, 134.9, 130.2, 129.9, 128.5, 126.5, 121.5, 119.8, 113.3, 35.3; FT-IR (KBr) 1627 (C═O) cm^{-1}; MS *m/z* (%) 272 (M^++2, 19), 270 (M^+, 61), 271 (44), 269 (100).

1-Methyl-2-(4′-methylphenyl)-1,8-naphthyridin-4-one (5ch): m.p. 181–183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73–8.79 (m, 2H), 7.38 (dd, J = 7.9, 4.5 Hz, 1H), 7.33 (br s, 4H), 6.32 (s, 1H), 3.75 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 155.7, 152.0, 151.3, 139.8, 135.7, 132.8, 129.4, 128.3, 121.5, 119.5, 113.2, 35.3, 21.3; FT-IR (KBr) 1621 (C═O) cm^{-1}; MS *m/z* (%) 250 (M^+, 100).

1-Methyl-2-(3-thienyl)-1,8-naphthyridin-4-one (5eh): m.p. 140–142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.5, 2.0 Hz, 1H), 8.73 (dd, *J* = 7.9, 2.0 Hz, 1H), 7.54 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.50 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.37 (dd, *J* = 7.9, 4.5 Hz, 1H), 7.23 (dd, *J* = 4.9, 1.3 Hz, 1H), 6.39 (s, 1H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 152.1, 151.2, 150.7, 135.8, 135.7, 127.7, 126.9, 126.3, 121.5, 119.6, 113.3, 35.2; FT-IR (KBr) 1621 (C═O) cm^{-1}; MS *m/z* (%) 242 (M^+, 100).

1-Ethyl-2-(3-pyridyl)-1,8-naphthyridin-4-one (5fi): m. p. 112–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78–8.82 (m, 2H), 8.73–8.77 (m, 2H), 7.79–7.84 (m, 1H), 7.50 (ddd, *J* = 7.8, 4.9, 0.7 Hz, 1H), 7.40 (dd, *J* = 7.9, 4.5 Hz, 1H), 6.25 (s, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 152.3, 151.6, 150.8, 150.4, 148.6, 135.9, 135.6, 131.7, 123.3, 121.8, 119.9, 114.2, 42.0, 14.8; FT-IR (KBr) 1625 (C═O) cm^{-1}; MS *m/z* (%) 251 (M^+, 79), 250 (100).

1-Methyl-2-(4′-chlorophenyl)-2,3-dihydro-1,8-naphthyridin-4-one (8kh): viscous liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.00 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.67 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.75 (dd, *J* = 6.3, 5.0 Hz, 1H), 3.20 (dd, *J* = 16.1, 6.6 Hz, 1H), 3.16 (s, 3H), 2.87 (dd, *J* = 16.1, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 159.3, 155.0, 137.6, 135.7, 133.8, 129.3, 127.7, 114.6, 113.0, 61.6, 44.6, 35.6; FT-IR (film) 1681 (C═O) cm^{-1}; MS *m/z* (%) 274 (M^++2, 31), 272 (M^+, 94), 161 (100).

1-Ethyl-2-(2′-methoxyphenyl)-2,3-dihydro-1,8-naphthyridin-4-one (8li): m.p. 127–128 °C; ^{1}H NMR (300 MHz, CD_3COCD_3) δ 8.38 (dd, *J* = 4.7, 2.0 Hz, 1H), 7.88 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.21–7.27 (m, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 6.74–6.81 (m, 2H), 6.67 (dd, *J* = 7.5, 4.7 Hz, 1H), 5.28 (dd, *J* = 7.2, 2.7 Hz, 1H), 4.21–4.32 (m, 1H), 3.90 (s, 3H), 3.16 (dd, *J* = 16.1, 7.3 Hz, 1H), 2.99–3.10 (m, 1H), 2.88 (dd, *J* = 16.1, 2.7 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_3COCD_3) δ 191.7, 159.1, 157.0, 154.5, 134.7, 128.9, 127.1, 126.2, 120.2, 114.1, 111.9, 111.3, 54.9, 54.0, 42.0, 41.9, 12.7; FT-IR (KBr) 1676 (C═O) cm^{-1}; MS *m/z* (%) 282 (M^+, 92), 119 (100).

1-Methyl-2-(2-furyl)-2,3-dihydro-1,8-naphthyridin-4-one (8mh): m.p. 107–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.04 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.31 (d, *J* = 1.7 Hz, 1H), 6.65 (dd, *J* = 7.7, 4.8 Hz, 1H), 6.24 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.07 (d, *J* = 3.3 Hz, 1H), 4.79 (dd, *J* = 6.3, 3.3 Hz, 1H), 3.27 (s, 3H), 3.16 (dd, *J* = 16.4, 6.4 Hz, 1H), 3.01 (dd, *J* = 16.4, 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 158.6, 154.5, 152.0, 142.7, 135.6, 114.6, 113.1, 110.1, 107.6, 56.2, 41.3, 35.8; FT-IR (KBr) 1682 (C═O) cm^{-1}; MS *m/z* (%) 228 (M^+, 100).

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References

1. (a) A. S. Wagman, M. P. Wentland, In *Comprehensive Medicinal Chemistry II*, Vol. 7, J. B. Taylor, D. J. Triggle Eds., Elsevier, Oxford, 2007, p. 567; (b) S. Emami, A. Shafiee, A. Foroumadi, *Iran. J. Pharm. Res.* **2005**, 3, 123.
2. Y. J. Kim, E. A. Kim, M. L. Chung, C. Im, *Korean J. Physiol. Pharmacol.* **2009**, *13*, 511.
3. N. M. Abdullah, G. R. Rosania, K. Shedden, *PLoS One* **2009**, *4*, e4470.
4. (a) U. Shiroya, A. Poshiya, A. Patel, A. Parikh, S. Patel, *Int. J. Adv. Pharm. Res.* **2011**, *2*, 480; (b) K. Lv, J. Wu, J. Wang, M. Liu, Z. Wei, J. Cao, Y. Sun, H. Guo, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1754.
5. (a) C. Y. Hong, Y. K. Kim, J. H. Chang, S. H. Kim, H. Choi, D. H. Nam, Y. Z. Kim, J. H. Kwak, *J. Med. Chem.* **1997**, *40*, 3584; (b) K. Lv, M.-L. Liu, L.-S. Feng, L.-Y. Sun, Y.-X. Sun, Z.-Q. Wei, H.-Q. Guo, *Eur. J. Med. Chem.* **2012**, *47*, 619.
6. (a) K. Chen, S.-C. Kuo, M.-C. Hsieh, A. Mauger, C. M. Lin, E. Hamel, K.-H. Lee, *J. Med. Chem.* **1997**, *40*, 2266; (b) S.-X. Zhang, K. F. Bastow, Y. Tachibana, S.-C. Kuo, E. Hamel, A. Mauger, V. L. Narayanan, K.-H. Lee, *J. Med. Chem.* **1999**, *42*, 4081; (c) K. Chen, S.-C. Kuo, K.-H. Lee, 2-Aryl-naphthyridin-4-ones as antitumor agents, U.S. Patent 004325, 1998.
7. (a) D. Bouzard, P. D. Cesare, M. Essiz, J. P. Jacquet, P. Remuzon, A. Weber, T. Oki, M. Masuyoshi, *J. Med. Chem.* **1989**, *32*, 537; (b) T. M. Hansen, Y.-G. Gu, T. M. Rehm, P. J. Dandliker, L. E. Chovan, M. H. Bui, A. M. Nilius, B. A. Beutel, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2716.
8. S. A. Springfield, K. Marcantonio, S. Ceglia, J. Albaneze-Walker, P. G. Dormer, T. D. Nelson, J. A. Murry, *J. Org. Chem.* **2003**, *68*, 4598.
9. M. Donalisio, S. Massari, M. Argenziano, G. Manfroni, V. Cagno, A. Civra, S. Sabatini, V. Cecchetti, A. Loregian, R. Cavalli, D. Lembo, O. Tabarrini, *J. Med. Chem.* **2014**, *57*, 5649.
10. T. Zhao, B. Xu, *Org. Lett.* **2010**, *12*, 212.
11. V. O. Iaroshenko, I. Knepper, M. Zahid, R. Kuzora, S. Dudkin, A. Villinger, P. Langer, *Org. Biomol. Chem.* **2012**, *10*, 2955.
12. A. D. Settimo, G. Biagi, G. Primofiore, P. L. Ferrarini, O. Livi, A. M. Marini, *J. Heterocycl. Chem.* **1980**, *17*, 1225.
13. R. A. Bunce, S. T. Squires, B. Nammalwar, *J. Org. Chem.* **2013**, *78*, 2144.
14. (a) J. I. Lee, J. S. Youn, *Bull. Korean Chem. Soc.* **2008**, *29*, 1853; (b) Y. J. Song, J. S. Choi, J. I. Lee, *Bull. Korean Chem. Soc.* **2013**, *34*, 3117.
15. J. I. Lee, H. Park, *Bull. Korean Chem. Soc.* **2002**, *23*, 521.

