

## Bioisoster of Caffeic Acid: Syntheses of 1-Hydroxy-2-pyridone Analogues

Hyo Jae Jung, Ho-Joon Park, Young-Gyun Shin, Young Soo Kim,<sup>†</sup> and Sung-Hwa Yoon<sup>\*</sup>

Department of Molecular Science and Technology, Ajou University, Suwon 443-749, Korea. \*E-mail: shyoon@ajou.ac.kr

<sup>†</sup>Department of Applied Chemical Engineering, Dankook University, Cheonan 330-714, Korea

Received July 31, 2008

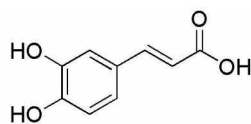
**Key Words :** Caffeic acid, DPPH, *N*-Oxide, 1-Hydroxy-2-pyridone

Caffeic acid is a naturally occurring phenolic compound that is found in many fruits, vegetables, and herbs (e.g. sage), including coffee.<sup>1,4</sup> Caffeic acid and its analogues have attracted much attention and have been studied in recent years because of their antiviral,<sup>5</sup> anti-inflammatory,<sup>6</sup> and neuroprotective properties,<sup>7</sup> and their antioxidant effects.<sup>8</sup> In particular, their antioxidative effects can be used for either the prevention of oxidative rancidity in foods or the treatment of diseases related to reactive oxygen species, such as stroke and Alzheimer's diseases.<sup>9</sup> However, since caffeic acid is not approved for direct use in food, due to it being a suspected human carcinogen based on testing in mice,<sup>10,11</sup> there is still a need to develop an analogue that has similar biological properties.

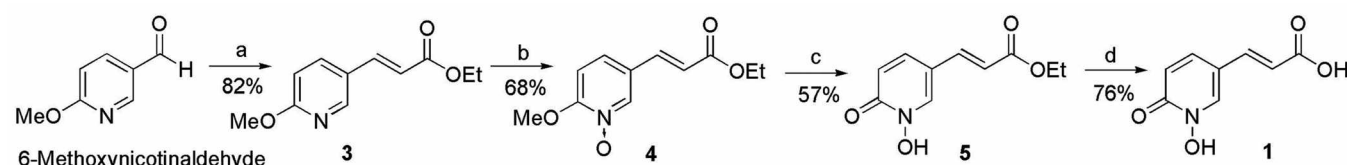
Bioisosterism is considered to be a powerful method for selecting molecular groups for drug design and lead compound development. By the application of bioisosterism, we previously found that replacing the catechol moiety in dopamine with 1-hydroxy-2-pyridone analogues resulted in similar dopaminergic activity.<sup>12</sup>

Based on those results, we replaced the functional catechol moiety in caffeic acid with 1-hydroxy-2-pyridone systems whose isosteric and isoelectric character are considered to be equivalent. Therefore, they are interchangeable in terms of their contributions to biological activity.<sup>13</sup> In this article, we describe the syntheses of two 1-hydroxy-2-pyridone analogues (compounds **1** and **2**) of caffeic acid and the evaluation of their antioxidant activities by an *in vitro* 1,1-diphenyl-2-picryl-hydrazyl free radical (DPPH) scavenging assay.<sup>14</sup>

The synthesis of the 5-substituted 1-hydroxy-2-pyridone



**Figure 1.** Structure of caffeic acid.



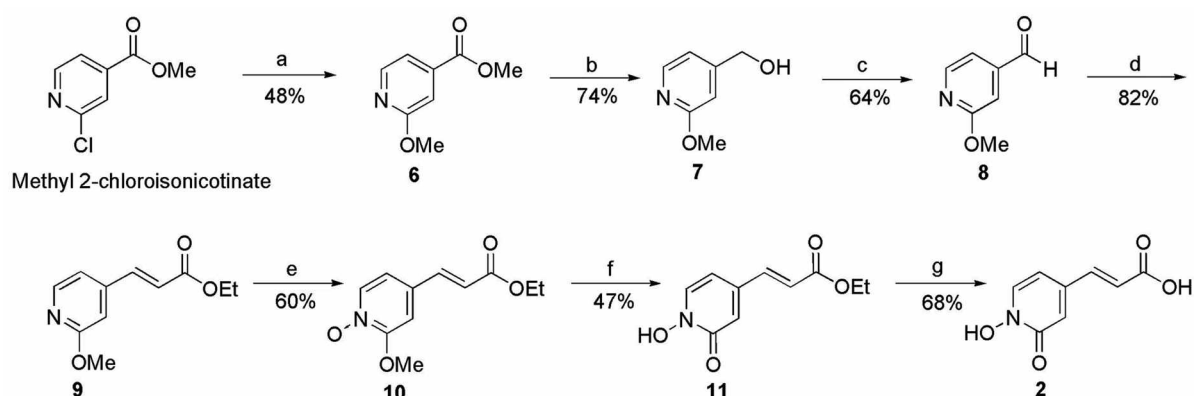
**Scheme 1.** Reagents: (a) triethyl phosphonoacetate, LiOH, THF, 4 Å molecular sieves, (b) *m*-CPBA, dichloromethane, (c) i) acetyl chloride, ii) H<sub>2</sub>O, acetone, (d) 0.5 *N* NaOH solution, THF.

analogue (**1**) is illustrated in Scheme 1. The Horner-Wadsworth-Emmons reaction<sup>15</sup> of 6-methoxynicotinaldehyde using triethyl phosphonoacetate, lithium hydroxide (LiOH), and 4 Å molecular sieves in tetrahydrofuran (THF) at room temperature gave ethyl 3-(6-methoxypyridin-3-yl)acrylate (**3**) in 82% yield. *N*-Oxidation of compound **3** with *m*-chloroperbenzoic acid (*m*-CPBA) gave the *N*-oxide compound **4** in 68% yield. Removal of the methyl group with acetyl chloride under reflux conditions, followed by hydrolysis with an acetone-water mixture gave compound **5**.<sup>16</sup> Finally, base-catalyzed hydrolysis of the ester group in **5** gave the desired 5-substituted 1-hydroxy-2-pyridone analogue (**1**).

As shown in Scheme 2, the synthesis of the 4-substituted 1-hydroxy-2-pyridone analogue (**2**) is started from methyl 2-chloroisonicotinate, due to the commercial unavailability of 2-methoxynicotinaldehyde (**8**). For the synthesis of **8**, methyl 2-chloroisonicotinate was first reacted with sodium methoxide in 1,4-dioxane to give a mixture of compound **6** and 2-chloroisonicotinic acid. The mixture resulted because de-esterification also occurred in the presence of the sodium methoxide.<sup>17</sup> Reduction of the ester compound **6** with sodium borohydride and calcium chloride in THF gave compound **7**, which was then partially oxidized with chromium (VI) oxide in dichloromethane to give compound **8**. From the aldehyde compound **8**, the target compound **2** was synthesized by the same reactions as those described for the synthesis of compound **1** from 6-methoxynicotinaldehyde (depicted in Scheme 1).

The antioxidant activities of the synthesized 1-hydroxy-2-pyridone analogues and caffeic acid were measured using the previously reported DPPH method,<sup>14</sup> and the results are shown in Table 1. Although caffeic acid showed potent radical scavenging activity, the 1-hydroxy-2-pyridone analogues did not show any activity. These results clearly indicate that the antioxidant activity of caffeic acid is mainly attributed to the catechol moiety.

In conclusion, two 1-hydroxy-2-pyridone analogues of



**Scheme 2.** Reagents: (a) sodium methoxide, 1,4-dioxane, (b)  $\text{NaBH}_4$ ,  $\text{CaCl}_2$ , THF, (c)  $\text{CrO}_3$ , dichloromethane, (d) triethyl phosphonoacetate,  $\text{LiOH}$ , THF, 4 Å molecular sieves, (e) *m*-CPBA, dichloromethane, (f) i) acetyl chloride, ii)  $\text{H}_2\text{O}$ , acetone, (g) 0.5 *N* NaOH solution, THF.

**Table 1.** Radical scavenging activities of caffeic acid and the 1-hydroxy-2-pyridone analogues

Compounds	$\text{IC}_{50}$ ( $\mu\text{M}$ )
Caffeic acid	9.74
<b>1</b>	> 600
<b>2</b>	> 600

caffeic acid were successfully synthesized from the corresponding methoxynicotinaldehydes and it was found that the analogues revealed no antioxidant activities.

### Experiments Section

**Instruments.** Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on a Varian Gemini 400 spectrometer at 400 MHz and 100 MHz, respectively. The chemical shifts given are relative to tetramethylsilane. Infrared spectra were recorded on a Jasco UV 570 UV/VIS/NIR spectrophotometer. Elemental analyses were performed using a Fisons Eager 200 instrument, Italy. Column chromatography was carried out using Merck silica gel 60 (230-400 mesh). All reactions were performed under a nitrogen atmosphere.

**Ethyl 3-(6-methoxypyridin-3-yl)acrylate (3).** Triethyl phosphonoacetate (5.21 mL, 5.89 g, 26.3 mmol) and lithium hydroxide (627 mg, 26.3 mmol) were added to a solution of 6-methoxy-3-pyridine carboxaldehyde (3.08 g, 21.9 mmol) and 4 Å molecular sieves (15.3 g) in dried THF (30 mL) at room temperature under nitrogen. The reaction mixture was stirred for 5 h at room temperature and then filtered through celite. After the solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate (100 mL). The organic layer was washed with  $\text{H}_2\text{O}$  (50 mL), 10%  $\text{NaHCO}_3$  solution (50 mL), 5% HCl solution (30 mL), and brine, and then dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After evaporation of the solvent, the crude product was recrystallized from ethyl acetate-hexane to give **3** (3.81 g, 82%) as a white solid.

mp 52 °C; IR (KBr) 1732, 1662  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.32-1.35 (m, 3H), 3.95 (s, 3H), 4.23-4.28 (m, 2H), 6.30-

6.34 (d, 1H,  $J = 15.0$  Hz), 6.73-6.75 (d, 1H,  $J = 8.8$  Hz), 7.59-7.63 (d, 1H,  $J = 16.0$  Hz), 7.73-7.76 (d, 1H,  $J = 10.8$  Hz), 8.24 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.55, 53.89, 60.62, 111.54, 117.09, 123.74, 136.20, 140.83, 148.21, 165.08, 166.62; Anal. Calcd. for  $\text{C}_{11}\text{H}_{13}\text{NO}_3$ : C, 63.76; H, 6.32; N, 6.76. Found: C, 63.83; H, 6.37; N, 6.68; ESI-MS  $m/z$ : 208  $[\text{M}+\text{H}]^+$ .

**Ethyl 3-(6-methoxypyridin-3-yl)acrylate N-oxide (4).** *m*-CPBA (4.64 g, 26.9 mmol) was added to a solution of ethyl 3-(6-methoxypyridin-3-yl)acrylate (**3**) (2.08 g, 8.96 mmol) in dichloromethane (30 mL). After the resulting mixture was stirred for 12 h at room temperature, the organic solvent was removed. The residue was chromatographed on a silica gel column using ethyl acetate/dichloromethane/methanol as an eluent (1/0/0 to 0/9/1) to give **4** (1.52 g, 68%) as a brown solid.

mp 115 °C; IR (KBr) 1707, 1636  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.32-1.36 (m, 3H), 4.06 (s, 3H), 4.24-4.29 (m, 2H), 6.37-6.41 (d, 1H,  $J = 15.6$  Hz), 6.97-7.00 (d, 1H,  $J = 8.4$  Hz), 7.44-7.50 (t, 2H,  $J = 24.0$  Hz), 8.41 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.11, 57.41, 60.71, 107.55, 120.46, 125.17, 126.40, 137.62, 138.63, 158.619, 165.38; ESI-MS:  $m/z$ : 224  $[\text{M}+\text{H}]^+$ .

**Ethyl 3-(1-hydroxy-6-oxo-1,6-dihydropyridin-3-yl)acrylate (5).** A solution of ethyl 3-(6-methoxypyridin-3-yl)acrylate N-oxide (**4**) (507 mg, 2.24 mmol) in acetyl chloride (15 mL) was refluxed for 1 h and then neutralized with 10% aqueous  $\text{NaHCO}_3$  solution. The aqueous solution was extracted with dichloromethane ( $3 \times 20$  mL). The organic layer was washed with water and then dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The organic solvent was removed. The resulting yellow residue, dissolved in small amount of acetone and water, was stirred for 10 h at room temperature. The precipitate was filtered and then dried to give **5** (271 mg, 57%) as a slightly yellow solid.

mp 147 °C; IR (KBr) 1719, 1674  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.31-1.35 (t, 3H), 4.22-4.28 (m, 2H), 6.19-6.23 (d, 1H,  $J = 16.4$  Hz), 6.72-6.75 (d, 1H,  $J = 9.6$  Hz), 7.39-7.43 (d, 1H,  $J = 15.6$  Hz), 7.60-7.63 (d, 1H,  $J = 11.6$  Hz), 7.93 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  14.40, 60.73, 114.92, 117.25, 118.61, 133.55, 135.24, 138.24, 157.86, 166.16; Anal. Calcd. for  $\text{C}_{10}\text{H}_{11}\text{NO}_4$ : C, 57.41; H, 5.30; N, 6.70. Found: C, 56.2; H,

5.38; N, 6.22; ESI-MS:  $m/z$ : 210  $[M+H]^+$ .

**3-(1-Hydroxy-6-oxo-1,6-dihydropyridin-3-yl)acrylic acid (1).** A mixture of ethyl 3-(1-hydroxy-6-oxo-1,6-dihydropyridin-3-yl)acrylate (**5**) (200 mg, 0.956 mmol) in tetrahydrofuran (10 mL), and 0.5 *N* NaOH solution (10 mL) was refluxed for 1 h. The reaction mixture was acidified with 1 *N* HCl solution to give a white precipitate. The precipitate was filtered and then recrystallized from methanol to give **1** (132 mg, 76%) as a white solid.

mp 274 °C; IR (KBr) 3238, 1713, 1636  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$  6.25-6.29 (d, 1H,  $J$  = 16.0 Hz), 6.53-6.55 (d, 1H,  $J$  = 9.2 Hz), 7.39-7.43 (d, 1H,  $J$  = 15.6 Hz), 7.82-7.84 (d, 1H,  $J$  = 9.2 Hz), 8.36 (s, 1H);  $^{13}C$  NMR (DMSO- $d_6$ )  $\delta$  112.83, 116.00, 119.33, 135.23, 138.03, 139.46, 157.47, 167.52; Anal. Calcd. for  $C_8H_7NO_4$ : C, 53.04; H, 3.89; N, 7.73. Found: C, 50.1; H, 4.21; N, 7.20; ESI-MS:  $m/z$ : 180  $[M-H]^-$ .

**Methyl 2-methoxyisonicotinate (6).** Methyl 2-chloroisonicotinate (2.03 g, 11.7 mmol) was dissolved in dry 1,4-dioxane (40 mL) and treated with sodium methoxide (1.89 g, 34.9 mmol). The resulting reaction mixture was stirred under reflux for 1 h, then cooled to room temperature, and poured into water (20 mL). The aqueous mixture was extracted with ethyl acetate (3  $\times$  20 mL), dried using  $Na_2SO_4$ , and then evaporated under reduced pressure to give **7** (955 mg, 48%) as a pale yellow oil.

IR (KBr) 2987, 1732  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.87-3.90 (d, 6H,  $J$  = 12.4 Hz), 7.22 (s, 1H), 7.31-7.32 (d, 1H,  $J$  = 4.0 Hz), 8.19-8.20 (d, 1H,  $J$  = 4.8 Hz);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  52.52, 53.72, 110.98, 115.44, 139.75, 147.30, 147.36, 164.44; ESI-MS:  $m/z$ : 168  $[M+H]^+$ .

**(2-Methoxypyridin-4-yl)methanol (7).** Powdered  $CaCl_2$  (6.64 g, 5.98 mmol) was added to a suspension of  $NaBH_4$  (339 mg, 8.97 mmol) in anhydrous THF (30 mL). After stirring this mixture at room temperature for 1.5 h, a solution of ester **6** (500 mg, 2.99 mmol) in anhydrous THF (20 mL) was added. After stirring this at room temperature for 15 h, the reaction mixture was carefully diluted with 10% NaOH solution (10 mL) and extracted with ethyl acetate (3  $\times$  10 mL). The organic layer was washed with water (2  $\times$  10 mL) and brine, and then evaporated under reduced pressure to give a crude oil. The crude product was chromatographed on a silica gel column using ethyl acetate/hexane as an eluent (1/2) to give **7** (308 mg, 74%) as a pale yellow oil.

IR (KBr) 3328, 1629  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.82 (s, 3H), 4.57 (s, 2H), 6.67 (s, 1H), 6.74-6.76 (d, 1H,  $J$  = 4.8 Hz), 7.92-7.93 (d, 1H,  $J$  = 4.4 Hz);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  53.50, 62.65, 107.10, 114.36, 146.03, 153.52, 164.07; ESI-MS:  $m/z$ : 140  $[M+H]^+$ .

**2-Methoxyisonicotinaldehyde (8).** Collins reagent was prepared by the addition of  $CrO_3$  (1.51 g, 15.1 mmol) to a solution of pyridine (2.78 g, 34.5 mmol) in  $CH_2Cl_2$  (100 mL) at 0 °C and stirred for 30 min at room temperature. (2-Methoxypyridin-4-yl)methanol (**7**) (303 mg, 2.16 mmol) in dichloromethane (100 mL) was then added and the mixture was stirred at room temperature for 30 min. The reaction mixture was filtered through celite. After the solvent was removed *in vacuo*, the residue was extracted with ethyl

acetate (3  $\times$  20 mL). The organic layer was washed with water (2  $\times$  20 mL) and brine, and evaporated under reduced pressure to give **8** (192 mg, 64%) as a yellow oil.

IR (KBr): 2929, 1725  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.90 (s, 3H), 7.04 (s, 1H), 7.20 (s, 1H), 8.27 (s, 1H), 9.90 (s, 1H);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  53.99, 111.58, 113.95, 144.31, 148.14, 164.89, 191.02; ESI-MS: 138  $m/z$ :  $[M+H]^+$

**Ethyl 3-(2-methoxypyridin-4-yl)acrylate (9).** Triethyl phosphonoacetate (0.174 mL, 197 mg, 0.875 mmol) and lithium hydroxide (21.0 mg, 0.875 mmol) were added to a solution of 2-methoxyisonicotinaldehyde (**8**) (101 mg, 0.730 mmol) and 4 Å molecular sieves (1 g) in dried tetrahydrofuran (8 mL) at room temperature under nitrogen. The reaction mixture was stirred for 1 h at room temperature and then filtered through celite. After the solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate (150 mL). The organic layer was washed with  $H_2O$  (50 mL), 10%  $NaHCO_3$  solution (50 mL), 5% HCl solution (30 mL), and brine, and then dried over anhydrous  $Na_2SO_4$ . After evaporation of the solvent, the crude product was recrystallized from ethyl acetate-hexane to give **9** (125 mg, 82%) as a colorless oil.

IR (KBr) 2981, 1719  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.32 (s, 3H), 3.94 (s, 3H), 4.24-4.30 (q, 2H), 6.50-6.54 (d, 1H,  $J$  = 16.4 Hz), 6.78 (s, 1H), 6.95-6.97 (d, 1H,  $J$  = 6.4 Hz), 7.51-7.55 (d, 1H,  $J$  = 16.4 Hz), 8.15-8.16 (d, 1H,  $J$  = 5.2 Hz);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  14.40, 53.69, 60.96, 109.85, 114.44, 122.46, 141.60, 147.30; ESI-MS:  $m/z$ : 208  $[M+H]^+$ .

**Ethyl 3-(2-methoxypyridin-4-yl)acrylate *N*-oxide (10).** *m*-CPBA (266 mg, 1.54 mmol) was added to a solution of ethyl 3-(2-methoxypyridin-4-yl)acrylate (**9**) (80.9 mg, 0.386 mmol) in dichloromethane (8 mL). The resulting mixture was stirred for 1 h at room temperature and then poured into water. The aqueous mixture was extracted with dichloromethane (3  $\times$  20 mL). The organic layer was washed with water (2  $\times$  20 mL), dried using  $Na_2SO_4$ , and then evaporated under reduced pressure to give **10** (52.3 mg, 60%) as a pale yellow solid.

mp 115 °C; IR (KBr) 3058, 1713  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.24 (s, 3H), 4.01 (s, 2H), 4.16-4.21 (q, 2H), 6.39-6.43 (d, 1H,  $J$  = 16.0 Hz), 6.95 (s, 1H), 7.00-7.01 (d, 1H,  $J$  = 6.4 Hz), 7.41-7.45 (d, 1H,  $J$  = 15.6 Hz), 8.23-8.25 (d, 1H,  $J$  = 7.2 Hz);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  14.36, 57.62, 61.26, 106.37, 115.83, 123.11, 139.17, 140.11; ESI-MS:  $m/z$ : 224  $[M+H]^+$ .

**Ethyl 3-(1-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)acrylate (11).** A solution of ethyl 3-(2-methoxypyridin-4-yl)acrylate *N*-oxide (**10**) (608 mg, 2.72 mmol) in acetyl chloride (30 mL) was refluxed for 1 h and then neutralized with 10% aqueous  $NaHCO_3$  solution. The aqueous solution was extracted with dichloromethane (3  $\times$  20 mL). The organic layer was washed with water, dried using  $Na_2SO_4$ , filtered, and then concentrated. The resulting yellow residue, dissolved in small amount of acetone and water, was stirred under reflux for 3 h. The precipitate was filtered and then dried to give **11** (267 mg, 47%) as a slightly yellow solid.

mp 164 °C; IR (KBr) 3399, 1648, 1262  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ )  $\delta$  1.32-1.36 (t, 3H), 4.24-4.30 (q, 2H), 6.41-6.46 (m,

2H), 6.77 (s, 1H), 7.41-7.44 (d, 1H,  $J = 15.6$  Hz), 7.76-7.78 (d, 1H,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  14.33, 61.12, 104.05, 118.14, 123.80, 133.37, 140.32, 143.88, 158.25, 165.42; Anal. Calcd. for  $\text{C}_{10}\text{H}_{11}\text{NO}_4$ : C, 57.41; H, 5.30; N, 6.70, Found: C, 56.67; H, 5.32; N, 6.31; ESI-MS:  $m/z$ : 210  $[\text{M}+\text{H}]^+$ .

**3-(1-Hydroxy-2-oxo-1,2-dihydropyridin-4-yl)acrylic acid (2).** A mixture of ethyl 3-(1-hydroxy-2-oxo-1,2-dihydropyridin-4-yl)acrylate (**11**) (1.00 g, 5.18 mmol) in THF (15 mL), and 0.5 N NaOH solution (15 mL) was refluxed for 3 h. The reaction mixture was acidified with 1 N HCl solution to give a white precipitate. The precipitate was filtered and then recrystallized from methanol to give **2** (589 mg, 68%) as a white solid.

mp 231 °C; IR (KBr) 3058, 1707, 1301  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ )  $\delta$  6.54-6.60 (m, 2H), 6.77 (s, 1H), 7.35-7.39 (d, 1H,  $J = 16.0$  Hz), 7.87-7.88 (d, 1H,  $J = 6.8$  Hz);  $^{13}\text{C}$  NMR ( $\text{DMSO-}d_6$ )  $\delta$  101.64, 119.58, 124.26, 135.68, 140.81, 143.23, 157.51, 166.78; Anal. Calcd. for  $\text{C}_8\text{H}_7\text{NO}_4$ : C, 53.04; H, 3.89; N, 7.73. Found: C, 52.40; H, 3.95; N, 7.48; ESI-MS:  $m/z$ : 180  $[\text{M}-\text{H}]^-$ .

**Acknowledgments.** This study was financially supported by the Post Brain Korea 21 program and SH pharmaceutical company.

## References

- Lu, Y.; Foo, L. Y.; Wong, H. *Phytochemistry* **2002**, *59*, 117.
- Lu, Y.; Foo, L. Y. *Phytochemistry* **1999**, *51*, 91.
- Lu, Y.; Foo, L. Y.; Wong, H. *Phytochemistry* **1999**, *52*, 1149.
- Lu, Y.; Foo, L. Y. *Tetrahedron Lett.* **2001**, *42*, 8223.
- King, P. J.; Ma, G.; Miao, W.; Jia, Q.; McDougall, B. R.; Reinecke, M. G.; Cornel, C.; Kuan, J.; Kim, T. R.; Robinson, W. E. *J. Med. Chem.* **1999**, *42*, 497.
- Sud'ina, G. F.; Mirzoeva, O. K.; Pushkareva, M. A.; Korshunova, G. A.; Sumbatyan, N. V.; Varfolomeev, S. D. *FEBS Lett.* **1999**, *329*, 21.
- Kim, S. R.; Kim, Y. C. *Phytochemistry* **2000**, *54*, 503.
- Chen, J. H.; Ho, C. T. *J. Agric. Food Chem.* **1997**, *45*, 2374.
- Sopheak, S.; Betty, A. L. *J. Agric. Food Chem.* **2002**, *50*, 468.
- Akihiro, H.; Masao, H.; Satoru, T.; Kumiko, O.; Tomoyuki, S.; Nobuyuki, I. *Cancer Research* **1991**, *51*, 5655.
- Lutz, U.; Lugl, S.; Bitsch, A.; Schlatter, J.; Lutz, K. *Fundamental and Applied Toxicology* **1997**, *39*, 131.
- Yoon, S.-H.; Bodor, N. S.; Simpkins, J. W. *Drug Design and Discovery* **1993**, *10*, 35.
- Friedman, H. L. *National Academy of Science National Research Council, Publication no. 206*; Washington, D. C. 1951; p 295.
- Gulcin, I. *Toxicology* **2006**, *217*, 213.
- James, M. T.; Mohamad, R. J.; Francis, C.; Carol, W. *J. Org. Chem.* **1998**, *63*, 6757.
- Choi, H.-Y.; Yoon, S.-H. *Bull. Korean Chem. Soc.* **1999**, *20*, 7.
- Krapcho, A. P.; Lovey, J. *Tetrahedron Lett.* **1973**, *14*, 957.