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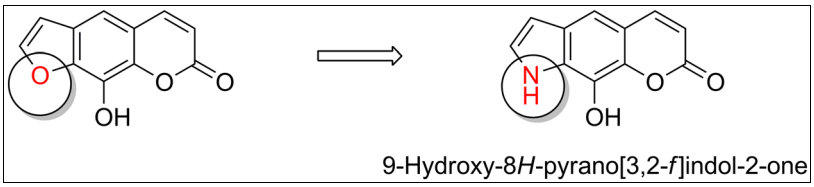

A simple and efficient approach to synthesize a novel pyrrolocoumarin 9-hydroxy-8*H*-pyrano[3,2-*f*]indol-2-one **(7)** has been described. Starting from vanillin, the key intermediate 7-methoxy-1*H*-indol-6-yl propiolate **(6)** was synthesized in six steps. Then, the target compound was obtained by forming pyrone-ring and demethylation simultaneously in one step. A plausible mechanism invoking $PtCl_4$ catalyzed one-step reaction of cyclization and demethylation was also presented.

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INTRODUCTION

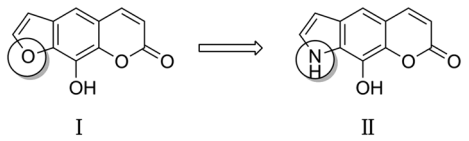
Furocoumarins are natural products that occur in a large number of umbelliferous plants, citrus fruits, and certain herbal medicines [1]. Especially, 8-hydroxypsoralen (9-hydroxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one, (**I**)) is a linear 6,7-furocoumarin. It and its analogs exhibit broad spectrum of pharmacological activities, such as anti-oxidative activity, anti-inflammatory, and anti-fungicidal [2]. Moreover, it has been shown to possess anti-HIV, anti-cancer effects, anti-depressant, and β-secretase inhibitory [3]. In recent years, the particular of tricyclic aromatic fused structure has gained considerable attentions by pharmacologists and chemists. However, 8-hydroxypsoralen and its analogs have undesirable side effects, such as genotoxicity, risk of skin cancers, and chromosomal aberrations [4]. These toxic effects are due to their cross-linking with DNA [5]. In light of these aspects, the development of low toxicity, high efficiency, and benign compounds will be a beneficial and interesting challenge. For the reasons mentioned earlier, we maintained the skeleton structure of (**I**) and replaced the oxygen of furan-ring with NH, constructing a novel pyrrolocoumarin 9-hydroxy-8*H*-pyrano[3,2-*f*]indol-2-one (**II**) (Fig. 1).

RESULTS AND DISCUSSION

Structurally, there are two main synthetic strategies to construct the pyrrolocoumarin skeleton, namely indol-ring construction and pyrone-ring construction. Among these methods, the methodology fusing an indol-ring (especially including substituent group) on a pyrone nucleus has been traditionally and widely applied for the synthesis of pyrrolocoumarin and its analogs. However, only a few papers described methods for construction of pyrone-ring on unsubstituent indol-ring by intramolecular cyclization reaction. In this paper, we presented a short and efficient synthesis route to (**II**). The reagents and reaction conditions are depicted in Scheme 1.

Precursor compounds **1–3** were synthesized using a modification of the previously reported procedures, and the overall yield was up to 71% in three steps. On the basis of the ordinary reaction condition (H_2O, NaOH), tetrahydrofuran (THF) rather than diethyl ether hydrophilic and high solubility had to be employed. Vanillin was esterified with Ac_2O in anhydrous THF to give acetic acid 4-formyl-2-methoxy-phenyl ester (**1**). Then, the reaction of **1** with an excess of fuming nitric acid resulted in the formation of acetic acid 4-formyl-2-methoxy-3-nitro-phenyl ester (**2**) under −20°C by selective nitration. The by-product was isolated by ice water/ethanol (5:1). Further, hydrolysis of **2** afforded 4-hydroxy-3-methoxy-2-nitro-benzaldehyde (**3**) as a yellow crystal (sensitive to light). The melting points and the spectral data were consistent with the compounds **1–3** reported in literature [6].

The literature procedure has been previously reported to give β-dinitrostyrene compounds (containing a phenolic hydroxyl group) via demethylation or hydrolysis. But there were only a few methods to get these kinds of compounds directly from unprotected phenolic hydroxyl compounds and nitromethane as raw materials [7]. Thus, the classical Henry reaction of **3** with nitromethane was transformed to 4-hydroxy-3-methoxy-2, β-dinitrostyrene (**4**) in the presence of ammonium acetate in acetic acid in 74% yield. We found the yield of **4** was only related to the temperature without the dosage of ammonium acetate and acetic acid. Then, reductive cyclization of **4** with 10% Pd/C, acetic acid, and ammonium formate to provide the key



I II

Figure 1. Structures of 8-hydroxypsoralen (**I**) and 9-hydroxy-8*H*-pyrano [3,2-*f*]indol-2-one (**II**).

intermediate 6-hydroxy-7-methoxyindole (**5**) as a white crystal in 38% yield.

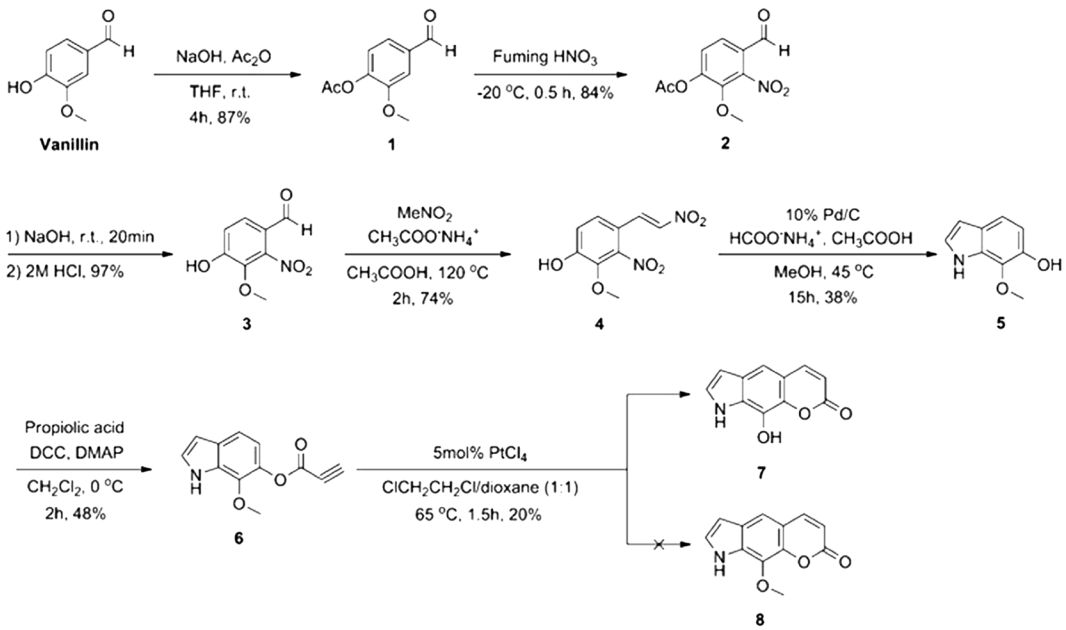
In order to perform the direct conversion of **5** into 9-methoxy-8*H*-pyrano[3,2-*f*]indol-2-one (**8**) under the Pechmann reaction, we used the classical malic acid/H_2SO_4 as reaction system. Unfortunately, this reaction failed to give the expected **8**, affording only the derivative of malic acid upon gas chromatography/mass spectrometry analysis. Moreover, different kinds of catalysts were tested for this purpose, such as $ZnCl_2$, $AlCl_3$, P_2O_5, $POCl_3$, benzenesulfonic acid, and polyphosphoric acid. However, no products were obtained. That is, a possible indol-ring of **5** was not conducive to the formation of pyrone-ring in these acid conditions. Through inspecting the chemical attributes of **5**, it was found that **5** was very sensitive to oxidizing agents in the presence of acids or bases. Beyond that, **5** also be quickly darkened in organic solvents under photocatalysis, but was highly stable in solid form. Therefore, in order to avoid the decomposition of **5**, it was significant to develop a simple and environmentally friendly synthetic method.

On the basis of the strategy previously described in the literature [8], 7-methoxy-1*H*-indol-6-yl propiolate **6** was prepared by condensation of the phenolic hydroxyl in **5** with propiolic acid using dicyclohexylcarbodiimide and 4-(dimethylamino) pyridine at 0°C in 48% yield. It was interesting to note that **6** skipped the step of construction of **8** and was directly converted into the six-membered heterocyclic ring of 9-hydroxy-8*H*-pyrano[3,2-*f*]indol-2-one (**7**), which was obtained under 65°C for 1.5 h using 5 mol % of $PtCl_4$ as a catalyst in 1,2-dichloroethane/1,4-dioxane (1:1) in 20% yield.

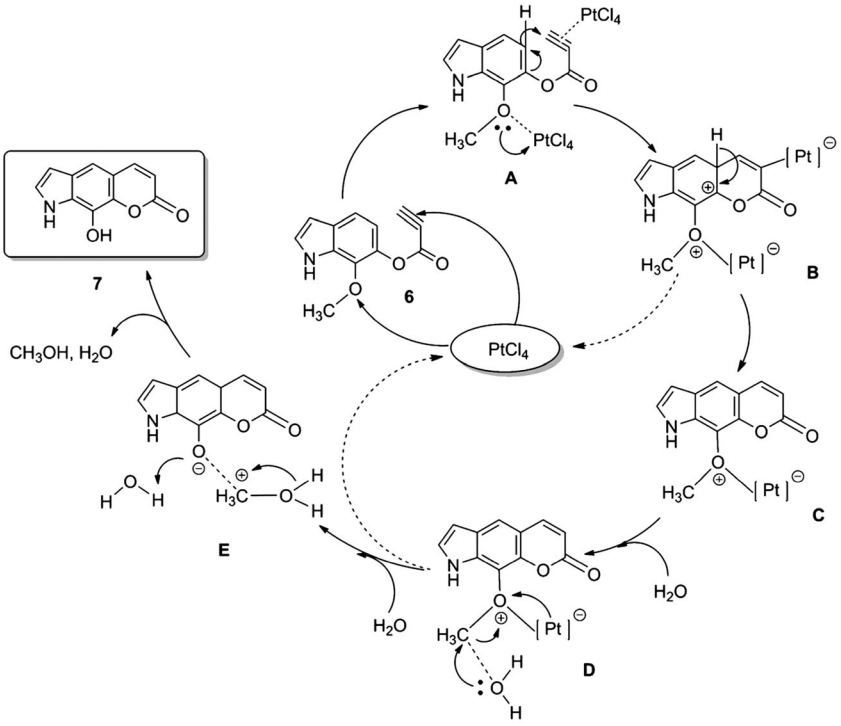
To the best of our knowledge, $PtCl_4$ is mainly used as a cyclization reagent in chemical reaction [9,10]. Before this study, there were few reports and studies on demethylation of methyl ether. The efficient $PtCl_4$ catalyzed one-step reaction of cyclization and demethylation was likely related to the position of propiolate group and methoxyl group of **6**.

The exact mechanism of this abnormal reaction is not clear. Here, a plausible mechanism for one-step reaction of cyclization and demethylation under the catalysis of $PtCl_4$ is shown in Scheme 2. First, the $PtCl_4$ coordinates to the alkyne of **6** and the oxygen of methoxyl group to give the intermediate **A** simultaneously. Later, the intramolecular electrophilic aromatic substitution occur at the aromatic ring of intermediate **A**, and the oxygen of methoxyl group is attached to $PtCl_4$, affording intermediate **B**. Upon deprotonation and rehybridization of the carbon center as well as rearomatization, the $PtCl_4$ is removed from intermediate **B** to generate intermediate **C**. Subsequently, in the post-processing step, H_2O act as a nucleophile to facilitate the hydration to generate intermediate **D**. Accordingly, another $PtCl_4$ is removed from intermediate **D** to give intermediate **E**, including the negative-charged oxygen through electron transfer in the

Scheme 1. Synthesis route of 9-hydroxy-8*H*-pyrano[3,2-*f*]indol-2-one (**7**).



Scheme 2. Possible mechanism for $PtCl_4$ catalyzed one-step reaction of cyclization and demethylation affording **7**.



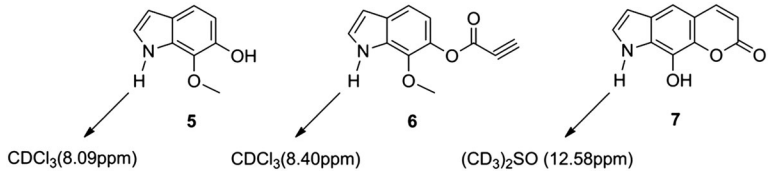


Figure 2. Characteristic N–H proton signals in the ^{1}H-NMR spectra of **5**, **6,** and **7**.

intramolecular. Then, the intermediate **E** undergoes a rapid hydride transfer from O-H of water to the negative-charged oxygen of intermediate **E** to give the target compound **7**.

The synthesis of indol homologous compounds **5**, **6,** and **7** were distinguished by characteristic signals in their ^{1}H-NMR spectra corresponding to the shift of indol N–H proton, respectively (Fig. 2). Contrast to **5**, the signal of N–H proton in **6** displayed a characteristic of field shifting to $\delta = 8.40$ ppm due to the deshielding effect of propargyl ester. In compound **7**, the deshielding effect of pyrone-ring is even lower as the signal of N–H proton shift to lower field in indol region appearing at $\delta = 12.58$ ppm.

CONCLUSIONS

In conclusion, we have described an efficient method for the first total synthesis of a novel pyrrolocoumarin 9-hydroxy-8*H*-pyrano[3,2-*f*]indol-2-one. The catalysis of $PtCl_4$ was to be worth investigating for one-step reaction of cyclization and demethylation, although the transformation rate was low. Further biological study of 9-hydroxy-8*H*-pyrano[3,2-*f*]indol-2-one and the synthesis of modified derivatives are currently underway in our group.

EXPERIMENTAL

Melting points were measured on an X-4 microscope melting point apparatus (Henan, China) and were uncorrected. Infrared spectra were recorded on a Shimadzu Fourier transform Fourier transform infrared 440 spectrometer (SHIMADZU, Japan) in the 4000–500 cm^{-1} range. NMR spectra were recorded on a Bruker AVANCE 400 MH_Z spectrometer (Bruker, Germany) in $CDCl_3$ or DMSO-d_6. The chemical shifts (δ values) are given in parts per million downfield from tetramethylsilane as the internal reference. The molecular weights were performed on a Shimadzu GC-MS-QP2010 spectrometer (SHIMADZU, Japan). High resolution mass spectra were recorded on Bruker micrOTOF-Q II spectrometer (Bruker, Karlsruhe, Germany). All the solvents and chemicals were obtained from commercial sources and were used without further purification unless otherwise stated. The synthetic procedure was controlled by the method of thin-layer chromatography (TLC) on 0.25 mm silica gel plates (60 GF-254, Qindao

Ocean Chemical Company, China) and visualized with ultraviolet light (Shanghai, China). The products were purified by recrystallization or flash chromatography. Column chromatography was carried out on silica gel (300–400 mesh, Qindao Ocean Chemical Company, China).

Acetic acid 4-formyl-2-methoxy-phenyl ester (1). Vanillin (10.00 g, 65.72 mmol) was dissolved in 6% aqueous sodium hydroxide solution (50 mL), and acetic anhydride (10.60 mL, 112.34 mmol) in dry THF (60 mL) was added dropwise. The mixture was vigorously stirred at RT for 4 h. THF was removed under reduced pressure. The residue was extracted with ethyl acetate (2 × 50 mL). The organic phase was washed with brine solution and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was washed with ice ethanol (3 × 10 mL) and dried to give **1** as white needles, 11.10 g (87%), mp 76–77°C (lit. [6a] mp 77° C, no range given); R_f = 0.64 (petroleum ether–EtOAc, 2:1); IR (KBr): 2960, 2847, 1750 (C═O), 1680 (C═O), 1279, 1209 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.35 (s, 3 H, $COCH_3$), 3.91 (s, 3 H, OCH_3), 7.23 (d, J = 7.6 Hz, 1 H, ArH), 7.52–7.46 (m, 2 H, ArH), 9.95 (s, 1 H, CHO); ^{13}C-NMR ($CDCl_3$): δ 20.75 ($CO\underline{C}H_3$), 56.18 ($O\underline{C}H_3$), 110.89, 123.51, 124.84, 135.31, 145.00, 152.04 (C-aryl), 168.46 ($\underline{C}OCH_3$), 191.16 ($\underline{C}HO$); MS (EI, *m/z*): 194 $[M]^+$. The spectral data are in agreement with literature values.

Acetic acid 4-formyl-2-methoxy-3-nitro-phenyl ester (2). To a solution of fuming nitric acid (40 mL) was slowly added **1** (10.00 g, 51.50 mmol) over 20 min at −20°C. The resulting mixture was stirred at this temperature for 0.5 h. Then, the reaction mixture was poured into ice water (200 mL). The precipitate was filtered, washed with ice water:ethanol (5:1,v/v) and dried to give **2** as a white solid, 10.30 g (84%), mp 84–85°C (lit. [6c] mp 87°C, no range given); R_f = 0.40 (petroleum ether–EtOAc, 2:1); IR (KBr): 2960, 2870, 1776 (C═O), 1709 (C═O), 1550 and 1373 (NO_2), 1277, 1182 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.42 (s, 3 H, $COCH_3$), 3.96 (s, 3 H, OCH_3), 7.45 (d, J = 8.4 Hz, 1 H, ArH), 7.72 (d, J = 8.4 Hz, 1 H, ArH), 9.91 (s, 1 H, CHO); ^{13}C-NMR ($CDCl_3$): δ 20.94 ($CO\underline{C}H_3$), 63.10 (OCH3), 125.66, 126.17, 126.25, 144.55, 145.71, 149.23 (C-aryl), 167.63 ($\underline{C}OCH_3$), 185.81 ($\underline{C}HO$); MS (EI, *m/z*): 239 $[M]^+$. The spectral data are in agreement with literature values.

4-Hydroxy-3-methoxy-2-nitro-benzaldehyde (3). To a stirred solution of 7% aqueous sodium hydroxide solution (60 mL) was slowly added **2** (10.30 g, 43.06 mmol), and the mixture was stirred at RT for 0.5 h. The reaction mixture was acidified with 2 M HCl at 0°C. The precipitate was filtered, washed with ice water, and dried to give **3** in dark as a yellow solid, 8.23 g (97%), mp 135–136°C (lit. [6a] mp 137°C, no range given); R_f = 0.16 (petroleum ether–EtOAc, 2:1); IR (KBr): 3276 (OH), 2959, 2928, 1670 (C═O), 1575, 1540 and 1373 (NO_2), 1317, 1275, 1202 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.98 (s, 3 H, OCH_3), 6.40 (s, 1 H, OH), 7.22 (d, J = 8.4 Hz, 1 H, ArH), 7.66 (d, J = 8.4 Hz, 1 H, ArH), 9.81 (s, 1 H, CHO); ^{13}C-NMR ($CDCl_3$): δ 63.11 ($O\underline{C}H_3$), 117.71, 120.96, 128.42, 139.12, 144.53, 155.25 (C-aryl), 185.80 ($\underline{C}HO$); MS (EI, *m/z*): 197 $[M]^+$. The spectral data are in agreement with literature values.

4-Hydroxy-3-methoxy-2,β-dinitrostyrene (4). To a solution of **3** (8.23 g, 41.75 mmol) in acetic acid (100 mL), ammonium acetate (8.00 g, 103.79 mmol) and nitromethane (7.64 g, 125.16 mmol) were added under nitrogen and stirred at 120°C for 2 h (or until the reaction was complete as judged by silica gel TLC in CH_2Cl_2). The mixture was then cooled to 40° C and poured into ice water (300 mL). The mixture was extracted with CH_2Cl_2 (7 × 100 mL). The organic phase was washed with water (2 × 100 mL) and brine solution (2 × 100 mL), dried over anhydrous Na_2SO_4, then the solvent was concentrated in vacuum. The residue was purified by flash chromatography (silica gel; CH_2Cl_2) to give **4** as a yellow solid, 7.38 g (74%), mp 164–166°C; R_f = 0.20 (CH_2Cl_2); IR (KBr): 3414(OH), 3109, 2945, 2928, 2852, 1603, 1525 and 1342 (NO_2), 1298, 1220, 1064 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 3.97 (s, 3 H, OCH_3), 7.44 (s, 1 H, $C\underline{H}CHNO_2$), 7.58 (s, 1 H, $CHC\underline{H}NO_2$), 8.25 (d, J = 13.2 Hz, 1 H, ArH), 8.44 (d, J = 13.2 Hz, 1 H, ArH), 10.88 (s, 1 H, OH); ^{13}C-NMR ($CDCl_3$): δ 61.53 ($O\underline{C}H_3$), 112.59, 119.34, 124.67 (C-aryl), 130.94 ($\underline{C}HCHNO_2$), 138.86 ($CHCHNO_2$), 139.34, 146.42, 154.98 (C-aryl); MS (EI, *m/z*): 240 $[M]^+$; HR-ESI-MS: *m/z* calcd for $C_9H_8N_2O_6$ $[M + Na]^+$ 263.0280; found, 263.0223.

6-Hydroxy-7-methoxyindole (5). Under nitrogen, to a solution of **4** (0.50 g, 2.08 mmol) in dry methanol (10 mL), 10% Pd/C (0.05 g) and acetic acid (0.10 mL) were added and stirred at RT for 20 min. Then, ammonium acetate (1.21 g, 19.19 mmol) was added and stirred at RT for 15 h. The Pd/C was filtered and washed with methanol. The combined solvents were evaporated, and the crude residue was subjected to column chromatography (silica gel; petroleum ether–acetone, 3:1) to obtain **5** as a white crystal, 0.13 g (38%), mp 85°C (lit. [11] mp 85°C); R_f = 0.53 (petroleum ether–acetone, 2:1); IR (KBr): 3495 (OH), 3420 (NH), 3105, 2947, 2843, 1620, 1506, 1411, 1333, 1236, 1202, 1047, 725 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.98 (s, 3 H, OCH_3), 5.27 (s, 1 H, OH), 6.50 (s, 1 H, H-pyrrol), 6.81 (d, J = 8.4 Hz, 1 H, ArH), 7.11 (s, 1 H, H-pyrrol), 7.25 (s, 1 H, ArH), 8.09 (s, 1 H, NH); ^{13}C-NMR ($CDCl_3$): δ 60.82 ($O\underline{C}H_3$), 103.40 (C-pyrrol), 110.30, 116.61, 123.30 (C-aryl), 124.14 (C-pyrrol), 129.20, 131.78, 143.42 (C-aryl); MS (EI, *m/z*): 163.1 $[M]^+$.

7-Methoxy-1*H*-indol-6-yl propiolate (6). Under nitrogen, a solution of propiolic acid (0.67 mL, 10.90 mmol) in dry CH_2Cl_2 (50 mL) was stirred at 0°C for 10 min. Then, dicyclohexylcarbodiimide (2.25 g, 10.90 mmol) in dry CH_2Cl_2 (5 mL) was added. A white precipitate formed after stirred 15 s. A solution of **5** (1.18 g, 7.23 mmol) in anhydrous CH_2Cl_2 (2 mL) was added to the reaction mixture. Lastly, 4-dimethylamiopryidine (0.12 g, 0.98 mmol) was dissolved in dry CH_2Cl_2 and added dropwise to the stirring solution. The reaction was stirred under nitrogen at 0°C until complete consumption of **5** was monitored by TLC (2 h), and then the mixture was concentrated in vacuum. The solid residue was suspended in EtOAc, filtered, and the filtrate was washed with brine. The collected organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The solid residue was purified by chromatography (silica gel; petroleum ether–acetone, 3:1) to obtain **6** as a white solid, 0.74 g (48%), mp 112–113°C; R_f = 0.60 (petroleum ether–acetone, 2:1); IR (KBr): 3392 (NH), 3259 (C≡CH), 2941, 2810, 2123 (C≡C), 1732 (C═O), 1600, 1500, 1338, 1242, 1200, 1057, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.09 (s, 1 H, C≡C$\underline{H}$), 4.00 (s, 3 H, OCH_3), 6.55 (s, 1 H, H-pyrrol), 6.85 (d, J = 8.8 Hz, 1 H, ArH), 7.23 (s, 1 H, H-pyrrol), 7.34 (d, J = 8.8 Hz, 1 H, ArH), 8.40 (s, 1 H, NH); ^{13}C-NMR ($CDCl_3$): δ 61.08 ($O\underline{C}H_3$), 74.24(C≡$\underline{C}$H), 103.41 (C-pyrrol), 115.00 ($\underline{C}$≡CH), 115.98 (C-aryl), 125.16 (C-pyrrol), 128.59, 129.37, 136.05, 136.89 (C-aryl), 151.35

(C=O); MS (EI, *m/z*): 215 $[M]^+$; HR-ESI-MS: *m/z* calcd for $C_{12}H_9NO_3$ $[M+Na]^+$ 238.0480; found, 238.0428.

9-Hydroxy-8*H*-pyrano[3,2-*f*]indol-2-one (7). To a solution of **6** (0.74 g, 3.44 mmol) in 1,4-dioxane and 1,2-dichloroethane (1:1, 10 mL), 5 mol% $PtCl_4$ (0.06 g) was added. The mixture was stirred under nitrogen at 65°C for 1.5 h, then extracted with EtOAc (3 × 50 mL) after the $PtCl_4$ was filtered. The combined solvents were evaporated, and the crude residue was subjected to column chromatography (silica gel; petroleum ether–acetone, 3:1) to obtain **7** as a light brown solid, 0.14 g (20%), mp 175–176°C; R_f = 0.39 (petroleum ether–acetone, 2:1); IR (KBr): 3475 (OH), 3238 (NH), 3092, 2926, 2852, 1780 (C=O), 1636, 1500, 1402, 1188, 1024, 760 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 5.76 (d, J = 9.2 Hz, 1 H, H-pyrano), 6.33 (s, 1 H, OH), 6.52 (d, J = 5.2 Hz, 1 H, H-pyrrol), 6.87 (d, J = 9.6 Hz, 1 H, H-pyrano), 7.40 (s, 1 H, ArH), 7.62 (d, J = 5.2 Hz, 1 H, H-pyrrol), 12.58 (s, 1 H, NH); ^{13}C-NMR (DMSO-d_6): δ 89.38 (C-pyrrol), 108.58 (C-pyrano), 122.00, 124.20 (C-aryl), 124.94 (C-pyrrol), 126.74, 130.87, 133.04 (C-aryl), 155.73 (C-pyrano), 173.75 (C-aryl), 178.94 (C=O); MS (EI, *m/z*): 201.0 $[M]^+$; HR-ESI-MS: *m/z* calcd for $C_{11}H_7NO_3$ $[M+Na]^+$ 224.0324; found, 224.0301.

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