Synthesis of an 4-Oxo-1,4-dihydropyridinomethylidene Substituted 2-Indolinone

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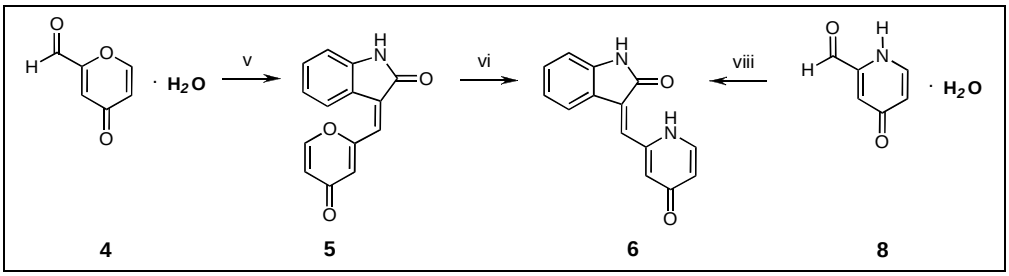

The (*Z*)-3-substituted 2-indolinone **6** was prepared using the aldehydes **4** and **8** unknown up to now and 2-indolinone.

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The 3-substituted 2-indolinones have been designed as a novel class of tyrosine kinase inhibitors, which exhibit selectivity toward different receptor tyrosine kinases (RTKs) [1]. Investigations led to SU 5416, which is a potent and selective inhibitor of the vascular endothelial growth factor receptor (VEGF, Flk-1/KDR) that inhibits tyrosine kinase catalysis, tumor vascularization and growth of multiple tumor types [2]. In order to get a similar compound to SU 5416, which contains the 2-indolinone pharmacophore, compound **6** was prepared (Figure 1).

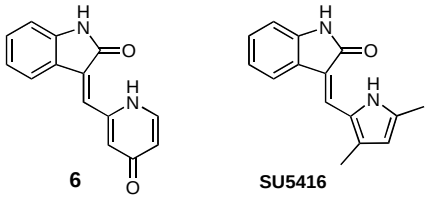
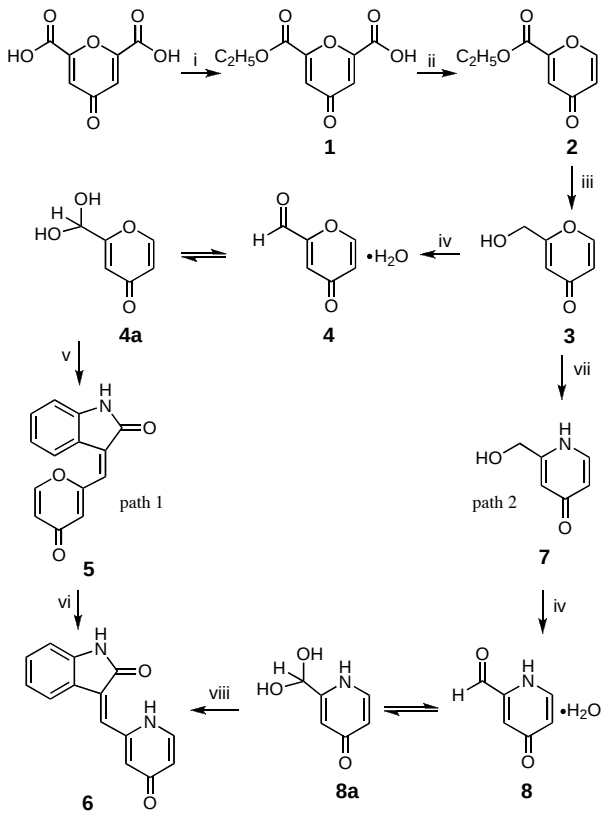


Figure 1

The 3-substituted 2-indolinone **6** was prepared following path 1 in Scheme 1. The synthesis is starting with chelidonic acid, which is partially esterified by 5% alcoholic hydrogen chloride to give the monoethyl chelidonate **1** [3]. After decarboxylation of **1** the resulting ethyl comanate **2** [3] was reduced by sodium borohydride to give the 2-hydroxymethyl-4-pyrone **3** [4]. The following oxidation in the presence of manganese (IV) dioxide led to the desired aldehyde-hydrate **4**, which exists in equilibrium with the geminale diol-structure (6:4).

Scheme 1

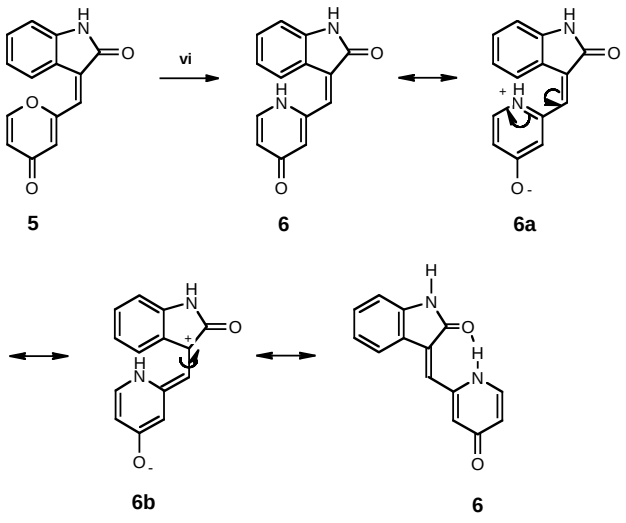


i, 5% ethanolic hydrochloric acid; ii, 230°C; iii, sodium borohydride, methanol, -20°C; iv, methanol/acetone/dichloromethane (1:1:1), activated manganese (IV) dioxide, 50°C; v, pyridine, 2-indolinone, ΔT; vi, ammonium acetate, glacial acetic acid, ΔT; vii, ammonium carbonate (10%), ammonia (25%), ΔT; viii, piperidine, 2-indolinone.

Compound **5**, which interestingly is the *E*-isomer (Scheme 1), is formed from the aldehyde **4** and 2-indolinone by Knoevenagel-condensation. With respect to the pharmacological results the *Z*-isomer is desired [1]. The last stage therefore is to realize ring-transformation connected with *E-Z*-isomerization (**5** → **6**). This is possible using ammonium acetate in glacial acetic acid. A lot of resonance structures exist for compound **6**, from which, for example, structure **6b** permits rotation between the pyridone-subunit and the 2-indolinone structure. The formation of the *Z*-isomer is preferred, due to the intramolecular hydrogen-bond interaction between the N-1' of the pyridone ring and the C-2 carbonyl oxygen atom of the 2-indolinone ring (Scheme 2).

The conception of the synthesis also allows to prepare the 3-substituted 2-indolinone **6** following path 2 in Scheme 1. A ring-transformation of the 2-hydroxymethyl-4-pyrone **3** in the presence of ammonium carbonate in ammonia is required to get the hydroxymethylpyridone **7**. Oxidation using manganese (IV) dioxide led to the desired aldehyde-hydrate **8** that also exists in equilibrium with the geminale diol-structure (2:8). The desired *Z*-isomer, compound **6**, is formed under the conditions of a Knoevenagel-reaction (Scheme 1).

Scheme II



vi, ammonium acetate, glacial acetic acid, ΔT

The 3-substituted 2-indolinones may exist as either the *Z*- or *E*-isomer depending on the characteristics of the substituents at the C-3 position of the 3-substituted 2-indolinone. In compound **5** the orientation, due to the double bond, is *E*, which was determined by X-ray technique. Figure 2 shows the results of X-ray analysis together with the numbering scheme.

An X-ray analysis of compound **6** could not be executed, due to the poor crystal quality. Only extreme thin needle shaped crystals with diameters of less than 0.02 mm could be obtained. In no case could one single crystalline needle be isolated.

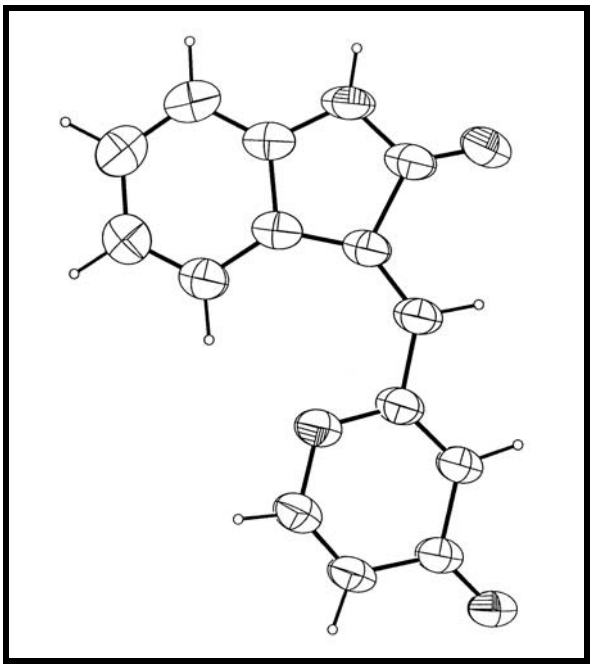


Figure 2. Structure of compound **5**, generated with ORTEP [5].

The geometry of compound **6** was demonstrated using NOESY-1D analysis. After having been irradiated with the frequency of the vinyl proton, the signal intensity of H-4 and H-3' increased. Irradiation with the frequency of H-4 led to an increase in the signal intensity of the vinyl proton and H-5. The only conceivable explanation therefore is the Z-isomer of compound **6** (Figure 3).

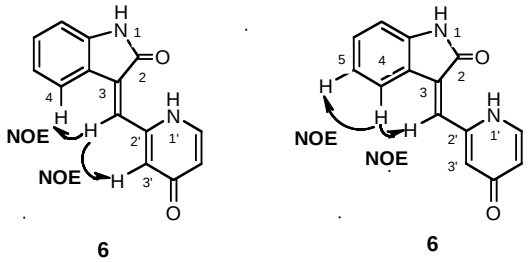


Figure 3

EXPERIMENTAL

Melting points (mp) were determined on a Lindström apparatus and are uncorrected. The infrared (ir) spectra were recorded on a Perkin-Elmer 297 spectrometer. The nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz on a Bruker AC 300 spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to

Table 1

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for Compound **5**. U (eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	X	Y	Z	U (eq)
C(1)	3877(1)	3514(2)	808(1)	51(1)
C(2)	4256(1)	4934(3)	1432(1)	60(1)
C(3)	4639(1)	6673(3)	1402(1)	68(1)
C(4)	4646(1)	7036(3)	752(1)	70(1)
C(5)	4273(1)	5661(3)	123(1)	65(1)
C(6)	3901(1)	3921(2)	160(1)	54(1)
N(7)	3498(1)	2341(2)	-405(1)	61(1)
C(8)	3191(1)	881(2)	-179(1)	55(1)
O(8)	2802(1)	-651(2)	-554(1)	70(1)
C(9)	3432(1)	1559(2)	632(1)	50(1)
C(10)	3213(1)	271(3)	983(1)	53(1)
C(11)	3340(1)	382(2)	1744(1)	52(1)
C(12)	3203(1)	-1246(2)	2056(1)	53(1)
C(13)	3355(1)	-1107(2)	2824(1)	53(1)
O(13)	3273(1)	-2628(2)	3140(1)	69(1)
C(14)	3615(1)	939(3)	3181(1)	64(1)
C(15)	3723(1)	2482(3)	2828(1)	74(1)
O(16)	3607(1)	2267(2)	2121(1)	69(1)

Table 2

Bond Length [Å] and Angles [°] for Compound **5**.

C(1)-C(2)	1.389(2)
C(1)-C(6)	1.4101(19)
C(1)-C(9)	1.456(2)
C(2)-C(3)	1.380(2)
C(2)-H(2)	0.967(17)
C(3)-C(4)	1.387(3)
C(3)-H(3)	1.006(19)
C(4)-C(5)	1.377(3)
C(4)-H(4)	1.002(19)
C(5)-C(6)	1.373(2)
C(5)-H(5)	0.96(2)
C(6)-N(7)	1.391(2)
N(7)-C(8)	1.356(2)
N(7)-H(7)	0.88(2)
C(8)-O(8)	1.210(2)
C(8)-C(9)	1.5231(19)
C(9)-C(10)	1.341(2)
C(10)-C(11)	1.4558(18)
C(10)-H(10)	0.972(16)
C(11)-C(12)	1.337(2)
C(11)-O(16)	1.3557(19)
C(12)-C(13)	1.448(2)
C(12)-H(12)	0.969(16)
C(13)-O(13)	1.2343(18)
C(13)-C(14)	1.432(2)
C(14)-C(15)	1.318(2)
C(14)-H(14)	0.94(2)
C(15)-O(16)	1.3623(19)
C(15)-H(15)	0.96(2)
C(2)-C(1)-C(6)	117.80(15)
C(2)-C(1)-C(9)	135.49(13)
C(6)-C(1)-C(9)	106.71(13)
C(3)-C(2)-C(1)	119.83(15)
C(3)-C(2)-H(2)	122.2(10)
C(1)-C(2)-H(2)	117.9(10)
C(2)-C(3)-C(4)	120.90(18)
C(2)-C(3)-H(3)	120.3(11)
C(4)-C(3)-H(3)	118.8(11)
C(5)-C(4)-C(3)	120.68(18)
C(5)-C(4)-H(4)	118.1(11)
C(3)-C(4)-H(4)	121.2(11)
C(6)-C(5)-C(4)	118.19(15)
C(6)-C(5)-H(5)	120.1(11)

Table 2 (continued)

C(4)-C(5)-H(5)	121.7(11)
C(5)-C(6).-N(7)	127.31(14)
C(5)-C(6)-C(1)	122.60(15)
N(7)-C(6)-C(1)	110.09(14)
C(8)-N(7)-C(6)	111.35(13)
C(8)-N(7)-H(7)	124.1(12)
C(6)-N(7)-H(7)	124.4(12)
O(8)-C(8)-N(7)	126.16(13)
O(8)-C(8)-C(9)	127.42(14)
N(7)-C(8)-C(9)	106.42(14)
C(10)-C(9)-C(1)	138.28(13)
C(10)-C(9)-C(8)	116.27(14)
C(1)-C(9)-C(8)	105.42(12)
C(9)-C(10)-C(11)	131.82(15)
C(9)-C(10)-H(10)	116.6(9)
C(11)-C(10)-H(10)	111.5(9)
C(12)-C(11)-O(16)	121.66(13)
C(12)-C(11)-C(10)	122.94(15)
O(16)-C(11)-C(10)	115.40(13)
C(11)-C(12)-C(13)	121.71(14)
C(11)-C(12)-H(12)	118.1(10)
C(13)-C(12)-H(12)	120.2(10)
O(13)-C(13)-C(14)	123.57(13)
O(13)-C(13)-C(12)	122.60(14)
C(14)-C(13)-C(12)	113.83(13)
C(15)-C(14)-C(13)	120.83(14)
C(15)-C(14)-H(14)	117.7(12)
C(13)-C(14)-H(14)	121.4(12)
C(14)-C(15)-O(16)	123.74(16)
C(14)-C(15)-H(15)	127.0(13)
O(16)-C(15)-H(15)	109.2(13)
C(11)-O(16)-C(15)	118.0 (13)

Table 3

Hydrogen Coordinates (x 10^4) and Isotropic Displacement Parameters (Å^2 x 10^3) for Compound **5**.

	X	Y	Z	U(eq)
H(2)	4245(9)	4650(30)	1879(10)	70(5)
H(3)	4911(11)	7720(30)	1850(11)	81(6)
H(4)	4907(11)	8320(30)	720(11)	78(5)
H(5)	4268(11)	5900(30)	-335(12)	79(5)
H(7)	3421(11)	2340(30)	-867(13)	81(6)
H(10)	2931(9)	-1010(20)	699(9)	54(4)
1H(12)	3004(10)	-2550(30)	1756(10)	63(5)
H(14)	3697(11)	1240(30)	3661(12)	82(6)
H(15)	3903(13)	3900(30)	3023(13)	95(6)

tetramethyl silane as the internal standard. The coupling constants (J) are quoted in Hz. The ^{13}C nmr spectra were recorded on a DPX 400 BRUKER. The mass spectra (electron impact) were obtained on a CH-7A-Varian MAT (70 eV). Elemental analyses were performed on a Perkin-Elmer Elementae-Vario EL. Silica gel 60 (Merck, 230-400 mesh) and silica gel plates (Merck, 60 F_{254}) were used for flash chromatography and tlc. The petroleum ether, used for recrystallization, had a bp of 40-70°C. Dichloromethane was distilled from phosphorous pentoxide. Anhydrous methanol and ethanol were obtained after reflux over small amounts of magnesium and distillation. All other reagents were obtained from commercial suppliers and used without further purification.

6-(Ethoxycarbonyl)-4-oxo-4*H*-pyran-2-carboxylic acid (1). Chelidonic acid (120 g, 6.45 moles) was refluxed with 600 mL ethanolic hydrochloric acid (5%) for 3 hours. After cooling to -10°C the reaction mixture was stirred for one hour. The solid

Table 4

Torsion Angles [°] for Compound **5**.

C(6)-C(1)-C(2)-C(3)	0.0(2)
C(9)-C(1)-C(2)-C(3)	179.42(16)
C(1)-C(2)-C(3)-C(4)	0.5(3)
C(2)-C(3)-C(4)-C(5)	-0.3(3)
C(3)-C(4)-C(5)-C(6)	-0.4(3)
C(4)-C(5)-C(6)-N(7)	-179.44(16)
C(4)-C(5)-C(6)-C(1)	1.0(2)
C(2)-C(1)-C(6)-C(5)	-0.8(2)
C(9)-C(1)-C(6)-C(5)	179.65(13)
C(2)-C(1)-C(6)-N(7)	179.57(13)
C(9)-C(1)-C(6)-N(7)	0.03(16)
C(5)-C(6)-N(7)-C(8)	-178.84(15)
C(1)-C(6)-N(7)-C(8)	0.76(18)
C(6)-N(7)-C(8)-O(8)	178.85(15)
C(6)-N(7)-C(8)-C(9)	-1.17(17)
C(2)-C(1)-C(9)-C(10)	-2.1(3)
C(6)-C(1)-C(9)-C(10)	177.34(18)
C(2)-C(1)-C(9)-C(8)	179.88(17)
C(6)-C(1)-C(9)-C(8)	-0.70(15)
O(8)-C(8)-C(9)-C(10)	2.6(2)
N(7)-C(8)-C(9)-C(10)	-177.40(13)
O(8)-C(8)-C(9)-C(1)	-178.88(15)
N(7)-C(8)-C(9)-C(1)	1.14(15)
C(1)-C(9)-C(10)-C(11)	1.5(3)
C(8)-C(9)-C(10)-C(11)	179.36(15)
C(9)-C(10)-C(11)-C(12)	-167.36(16)
C(9)-C(10)-C(11)-O(16)	12.9(2)
O(16)-C(11)-C(12)-C(13)	-1.9(2)
C(10)-C(11)-C(12)-C(13)	178.34(14)
C(11)-C(12)-C(13)-O(13)	-175.92(15)
C(11)-C(12)-C(13)-C(14)	3.4(2)
O(13)-C(13)-C(14)-C(15)	177.20(18)
C(12)-C(13)-C(14)-C(15)	-2.1(3)
C(13)-C(14)-C(15)-C(16)	-0.7(3)
C(12)-C(11)-O(16)-C(15)	-1.1(2)
C(10)-C(11)-O(16)-C(15)	178.72(12)
C(14)-C(15)-O(16)-C(11)	2.4(3)

material was collected by filtration and washed with ether (3 x 150 mL) to yield product **1** as pale brown crystals: Yield 101.2 g (74%), mp 218-220°C, ir (potassium bromide): 3072 (CH olef.), 2986 (CH aliph.), 1758, 1650 (C=O), 1173 (C-O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.01 (m, 2H, H3 and H5), 4.37 (m, 2H, O-*CH_2*-CH_3), 1.32 ppm (m, 3H, O-CH_2-*CH_3*); ms: (m/z) 212 ($M^{+\cdot}$, 60%).

Ethyl 4-oxo-4*H*-2-pyran-carboxylate (2). Compound **1** (56 g, 0.6 moles) was heated to 230°C in portions of approximately 4 x 14 g in a flask with air condenser. A pale yellow liquid was produced, already partially crystallized in the air condenser. Flash chromatography (ethyl acetate/ethanol (9:1)) of the crude reaction compound yielded the pure white compound **2**: Yield 11 g (25%), mp 96-98°C, ir (potassium bromide): 3056 (CH), 2991 (CH), 1729, 1621 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.21 (d, 1H, *J*= 5.9, H6), 6.90 (d, 1H, *J*= 2.6 Hz, H3), 6.48 (dd, 1H, *J*= 2.6 Hz, *J*= 5.9 Hz, H5), 4.35 (q, 2H, *J*= 7.2 Hz, O-*CH_2*-CH_3), 1.31 ppm (t, 3H, *J*= 7.2 Hz, O-CH_2-*CH_3*); ms: (m/z) 168 ($M^{+\cdot}$, 100%).

2-(Hydroxymethyl)-4*H*-pyran-4-one (3). A solution of 11 g (88.7 mmoles) of compound **2** in 114 mL dry methanol was cooled to -20°C at which time 3.6 g (95.2 mmoles) sodium borohydride was added and the reaction mixture was stirred at -20°C for one hour. 50 mL of the solvent were evaporated and the remaining suspension was poured onto 100 mL ice water.

Table 5

Crystal data and Structure Refinement for Compound **5**.

Formula	$C_{14}H_9N0_3$
Formula weight	239.22
Temperature	293 K
Wavelength	1.54180 A
Crystal system/Space group	monoclinic/C2/c
Unit cell dimensions	a = 20.780(9) Å α = 90.00(3) deg. b = 6.323(3) Å β = 125.87(3) deg. c = 20.931(6) Å γ = 90.00(4) deg.
Volume	2228.6(16) $Å^3$
Z, calculated density	8, 1.426 Mg/m^3
Absorption coefficient	0.843 mm^{-1}
F(000)	992
Crystal size	0.44 x 0.26 x 0.08 mm
Theta range for data collection	4.76 to 65.02 deg.
Index ranges	-24<=g<=24/0<=k<=7/-24<=1<=24
Reflections collected/unique	3817/1911 [R(int) = 0.0250]
Completeness to 2theta = 65.02	100.0 %
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1911/0/200
Goodness-of-fit on F^2	1.044<41
Final R indices [I<2sigma(I)]	R1 = 0.0313, wR2 = 0.0852
R indices (all data)	R1 = 0.0460, wR2 = 0.0921
Extinction coefficient	0.00128 (14)
Largest diff. peak and hole	0.130 and -0.143 e..A^{-3}

This aqueous solution was neutralized with sulfuric acid (10%) and concentrated. The reaction mixture was refluxed in 100 mL ethyl acetate/ethanol (9:1) for ten minutes, dried over sodium sulphate and concentrated. The brown oil obtained was purified by flash chromatography (silica gel, ethyl acetate/ethanol (9:1)) and recrystallized with ethanol and petroleum ether to give white crystals: Yield 5.6 g (50%), mp 66°C, ir (potassium bromide): 3389, 3214 (OH), 2911, 2853 (CH), 1661 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 8.11 (d, 1H, *J*= 5.4 Hz, H6), 6.23 (m, 2H, H3 and H5), 5.66 (t, 1H, *J*= 6.0 Hz, OH), 4.29 ppm (d, 2H, *J*= 6.0 Hz, CH_2), ms: (m/z) 126 ($M^{+\cdot}$, 90%). *Anal*. Calcd for $C_6H_6O_3$ (126.1): C, 57.14 H, 4.80. Found: C, 57.11 H, 4.86.

4-Oxo-4*H*-pyran-2-carbaldehyde hydrate (4) and 2-Dihydroxymethyl-4*H*-pyran-4-one (4a). To a solution of 150 mg (1.2 mmoles) of compound **3** in 20 mL methanol/ acetone/ dichloromethane (1:1:1) was added 200 mg manganese (IV) dioxide and the reaction mixture was stirred at 60°C for four hours. Every hour another 200 mg of manganese (IV) dioxide was added after which the suspension was filtered and the solvents were removed by evaporation. The precipitated solid was purified by flash chromatography (silica gel, ethyl acetate/ ethanol, 8:2) and recrystallized with ethyl acetate and *n*-hexane to give pale yellow crystals: Yield 1.02 g (38%, **4**, **4a**), ir (potassium bromide): 3245 (OH), 3075 (CH), 1659, 1647 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6) of **4**: δ 9.64 (s, 1H, CHO), 8.29 (d, 1H, *J*= 5.8 Hz, H6), 7.06 (d, 1H, *J*= 2.6 Hz, H3), 6.48 (dd, 1H, *J*= 2.6 Hz, *J*= 5.8 Hz, H5) ppm; ^{1}H-nmr (dimethyl sulfoxide-d_6) of **4a**: δ 8.14 (d, 1H, *J*= 5.8 Hz, H6), 6.84 (d, 2H, *J*= 5.5 Hz, 2 OH), 6.32 (d, 1H, *J*= 2.5 Hz, H3), 6.25 (dd, 1H, *J*= 2.5 Hz, *J*= 5.8 Hz, H5), 5.47 ppm (1H, m, HO-*CH*-OH); ms: (m/z) 124 ($M^{+\cdot}$, 71%). *Anal*. Calcd for $C_6H_4O_3$•H_2O: (142.1): C, 53.51 H, 3.88. Found: C, 53.20 H, 3.78.

(*E*)-3-((4-Oxo-4*H*-pyran-2-yl)methylene)indolin-2-one (5). A mixture of 240 mg (1.7 mmoles) of compounds **4**, **4a** and 250 mg (1.9 mmoles) indolin-2-one were dissolved in 15 mL pyridine and refluxed for 30 minutes. The reaction mixture was poured onto ice and treated with 15 mL concentrated hydrochloric acid (pH 2-3). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). Then the organic layer was dried with sodium sulfate and concentrated. The crude compound was recrystallized from ethanol to yield orange crystals: Yield 200 mg (45%), mp 254°C, ir (potassium bromide): 3081 (CH), 1717 (CO-NH), 1649, 1630 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 10.76 (s, 1H, NH), 8.47 (d, 1H, *J*= 5.8 Hz, H6'), 8.07 (d, 1H, *J*= 7.8 Hz, H4), 7.35 (t, 1H, *J*= 7.8 Hz, H6), 7.17 (s, 1H, CH), 7.02 (t, 1H, *J*= 7.8 Hz, H5), 6.92 (d, 1H, *J*= 2.5 Hz, H3'), 6.90 (d, 1H, *J*= 7.8 Hz, H7), 6.43 ppm (dd, 1H, *J*= 2.5 Hz, *J*= 5.8 Hz, H5'), ^{13}C-nmr (dimethyl sulfoxide-d_6): δ 177.8, 167.9, 160.1, 155.9 (C6') 144.5, 131.9 (C6), 131.6, 127.1 (C4), 123.9 (CH=), 121.9 (C5), 120.9 (C3'), 119.8, 116.8 (C5'), 110.2 (C7); ms: (m/z) 239 ($M^{+\cdot}$, 100%). *Anal*. Calcd for $C_{14}H_9NO_3$ (239.2): C, 70.29 H, 3.79 N, 5.86. Found: C, 69.99 H, 3.71 N, 5.73.

(*Z*)-3-((4-Oxo-1,4-dihydropyridine-2-yl)methylene)indolin-2-one (6). ***Method A:*** A solution of 80 mg (0.3 mmoles) of compound **5** and 20 mg ammonium acetate in 30 mL glacial acetic acid was refluxed for three hours. The reaction mixture was poured onto 200 mL ice/water and neutralized with saturated sodium carbonate solution. The aqueous layer was concentrated and resolved in a mixture of ethyl acetate/ethanol (8:2). The precipitated salts were removed and the organic layer was purified by flash chromatography (silica gel, ethyl acetate/ethanol (8:2)) and recrystallized from ethanol to yield red crystals.

Method B: The reaction mixture of 37 mg (0.3 mmoles) of compounds **8/8a**, 40 mg (0.3 mmoles) of 2-indolinone and 2 drops of piperidine in 5 mL ethanol was refluxed for two hours and concentrated. The reaction product was purified by flash chromatography (silica gel, ethyl acetate/ ethanol, 8:2) and recrystallized from ethanol to yield red crystals: mp 256°C, ir (potassium bromide): 3059, 2920 (CH), 1681 (CO-NH), 1603 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 13.65 (m, 1H, NH1'), 11.37 (s, 1H, NH1), 7.91 (m, 1H, H6'), 7.77 (d, 1H, *J*= 7.2 Hz, H4), 7.66 (s, 1H, CH=), 7.32 (t, 1H, *J*= 6.9 Hz, H6), 7.09 (t, 1H, *J*= 7.2 Hz, H5), 6.93 (d, 1H, *J*= 6.9 Hz, H7), 6.58 (s, 1H, H3'), 6.15 ppm (d, 1H, *J*= 5.9 Hz, H5'); ms: (m/z) 238 ($M^{+\cdot}$, 83%). *Anal*. Calcd for $C_{14}H_{10}N_2O_2 \bullet H_2O$ (256.3): C, 65.62 H, 4.72 N, 10.93. Found: C, 65.68 H, 4.74 N, 10.92.

2-(Hydroxymethyl)-1,4-dihydropyridine-4-one (7). A solution of 2 g (15.8 mmoles) of compound **3** and 30 mL of ammonium carbonate (10%) and ammonia (25%) (1:1) was refluxed for one hour. The reaction mixture was poured onto ice and the pH was adjusted to 6 with sulfuric acid (10%). The solution was stirred with a mixture of ethyl acetate and ethanol (9:1) to eliminate the organic impurities. The aqueous layer was concentrated and the residue was refluxed with ethanol (50 mL) for ten minutes. The organic layers were combined and dried with sodium sulfate and concentrated. The resulting light brown oily product was recrystallized from ethanol to give a white compound: Yield 1.3 g (66%), mp 197°C, ir (potassium bromide): 3426 (OH), 3080, 2926 (CH), 1512 cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 11.08 (br, 1H, NH), 7.69 (m, 1H, H6), 6.26 (m, 1H, H5), 6.15 (s, 1H, H3), 5.50 (m, 1H, OH), 4.36 ppm (m, 2H, CH_2), ms: (m/z) 125 ($M^{+\cdot}$, 49%). *Anal*. Calcd for $C_6H_7NO_2$ (125.1): C, 57.59 H, 5.64 N, 11.20. Found: C, 57.68 H, 5.78 N, 11.26.

4-Oxo-1,4-dihydro-pyridine-2-carbaldehyde hydrate (8) and **2-(Dihydroxymethyl)-1,4-dihydropyridine-4-one (8a).** To a solution of 1.3 g (10.4 mmoles) of compound **7** in 20 mL methanol/ acetone/dichloromethane (1:1:1) was added 1.5 g manganese (IV) dioxide and the reaction mixture was stirred at 60°C for four hours. Every hour were added another 1.5 g of manganese (IV) dioxide, after which the suspension was filtered and the solvents were removed by evaporation. The precipitated solid was purified by flash chromatography (silica gel, ethyl acetate) and recrystallized with ethyl acetate and ethanol to give pale yellow crystals: Yield (**8**, **8a**) 87.3 mg (71%), mp 148-153°C, ir (potassium bromide): 3431 (OH, NH), 1632 (C=O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6) of **8**: δ 10.65 (s, 1H, NH), 9.94 (s, 1H, CHO), 8.15 (m, 1H, H6), 6.92 (s, 1H, H3), 6.66 ppm (m, 1H, H5); ^{1}H-nmr (dimethyl sulfoxide-d_6) of **8a**: δ 11.16 (s, 1H, NH), 7.47 (m, 1H, H6), 6.79 (d, 2H, *J*= 6.4 Hz, 2 OH), 6.11 (m, 1H, H3), 5.98 (m, 1H, H5), 5.57 ppm (t, 1H, *J*= 6.4 Hz, HO-*CH*-OH); ms: (m/z) 123 ($M^{+\cdot}$, 26%). *Anal*. Calcd for $C_6H_5NO_2 \bullet H_2O$ (141.1): C, 52.56 H, 4.82 N, 10.22. Found: C, 52.69 H, 4.79 N, 10.05.

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