Article

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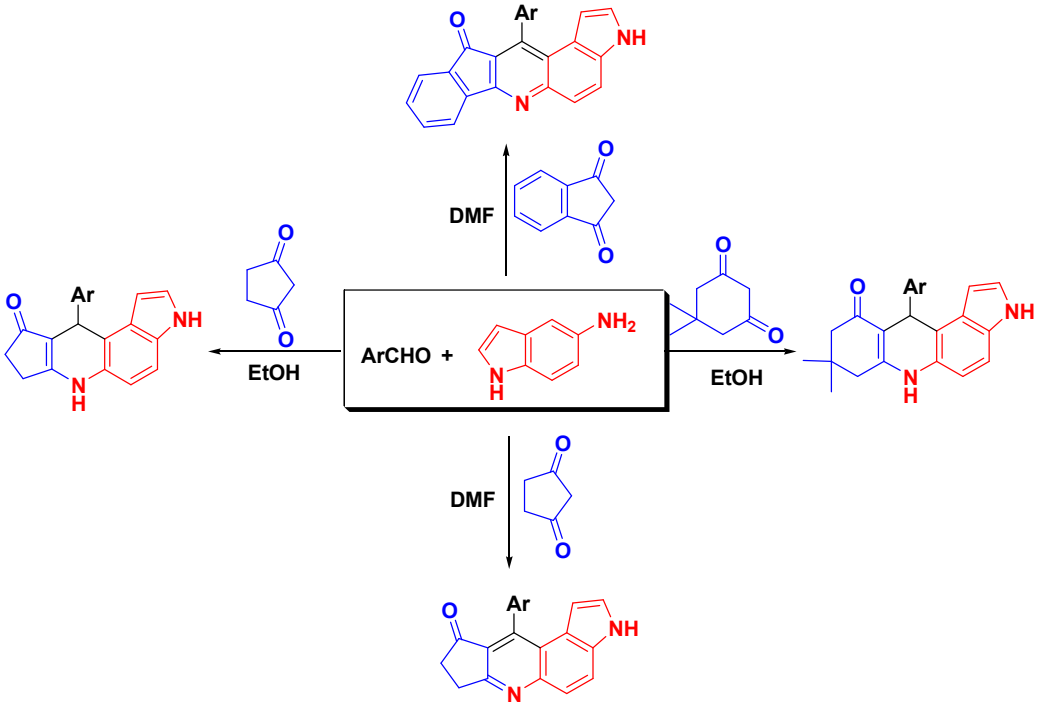

Combinatorial Synthesis of Pyrrolo[3,2-*f*]quinoline and Pyrrolo[3,2-*a*]acridine Derivatives via Three-Component Reaction under Catalyst-Free Conditions

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Abstract—A combinatorial synthesis of pyrrolo[3,2-*f*]quinoline and pyrrolo[3,2-*a*]acridine derivatives is described by a three-component reaction of aromatic aldehyde, 1*H*-indol-5-amine and 1,3-dicarbonyl compounds with catalyst-free conditions. The 1,3-dicarbonyl compounds include 5,5-dimethylcyclohexane-1,3-dione, cyclopentane-1,3-dione and 2*H*-indene-1,3-dione. It is interesting that the designed reactions gave aromatized or un-aromatized products, which depend on the reaction temperature and reactants of 1,3-dicarbonyl compounds.

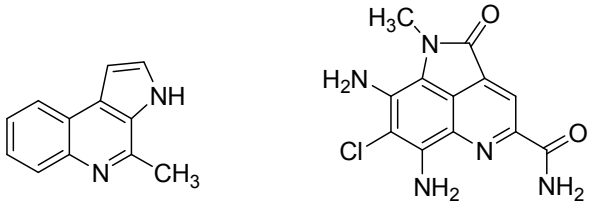
Keywords: pyrrolo[3,2-*f*]quinoline, pyrrolo[3,2-*a*]acridine, 1*H*-indol-5-amine, catalyst-free, synthesis

1. Introduction

Acridine occurs in a large number of natural products and attracts much attention due to its widely biological activities. Its derivatives produce remarkable effects as pharmaceuticals including anti-bacterial,[1] anti-cancer,[2-3] anti-tumour,[4-5] ribonucleolytic,[6] anti-angiogenic[7] and anti-fungicidal activities.[8] It is well known that the three-component reaction of arylamine, aromatic aldehyde and cyclic 1,3-dicarbonyl compound is an efficient method to synthesize these potentially active heterocycles.[9] As a member of this family, pyrroloacridine contains both pyrrole and acridine moieties, which may afford unique biological activities for screening. Therefore, a simple, mild, and versatile preparation of pyrroloacridines in one-pot reaction is still highly desirable.

In addition, pyrroloquinoline is a skeleton of natural alkaloids. For example, *Marinoquinoline* A (Figure 1, left) is isolated from the gliding bacterium *Ohtaekwangia kribbensis*, and shows weak antibacterial and antifungal activities and moderate cytotoxicity against four growing mammalian cell lines.[10] Another important alkaloid containing pyrroloquinoline is *Ammosamide* B (Figure 1, right),

which is well known for its anti-tumour activity.[11] Its derivatives also have attracted much attention recently due to the other remarkable biological and pharmacological activities, such as anti-oxidative,[12] cytotoxic,[13] anti-cancer,[14] photochemotherapeutic[15] and anti-viral activity.[16] Therefore, a considerable effort has been made for the synthesis of pyrroloquinoline annulated heterocyclic derivatives due to their wide applications.[17-22] As a continuation of our research devoted to the new methods for the preparation of heterocycles via multi-component reactions,[23] we describe here the synthesis of pyrrolo[3,2-*f*]quinoline and pyrrolo[3,2-*a*]acridine derivatives by a three-component reaction of aromatic aldehyde, 1*H*-indol-5-amine and 1,3-dicarbonyl compounds under catalyst-free conditions.

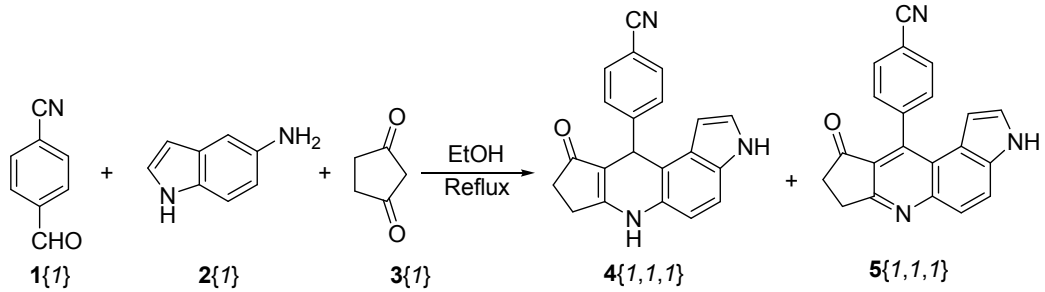


Marinoquinoline A *Ammosamide* B

Figure 1. The interesting alkaloids containing pyrroloquinoline

2. Results and discussion

Treatment of 4-cyanobenzaldehyde **1**{*1*}, 1*H*-indol-5-amine **2**{*1*}, and cyclopentane-1,3-dione **3**{*1*} in refluxing EtOH without catalysts, resulted in the corresponding 10-(4-cyanophenyl)-6,7,8,10-tetrahydrocyclopenta[*b*]pyrrolo[3,2-*f*] quinolin-9(3*H*)-one derivatives **4**{*1*,*1*,*1*} in high yield (Scheme 1).



1{*1*} **2**{*1*} **3**{*1*} **4**{*1*,*1*,*1*} **5**{*1*,*1*,*1*}

Scheme 1. Reaction of **1**{*1*}, **2**{*1*} and **3**{*1*}

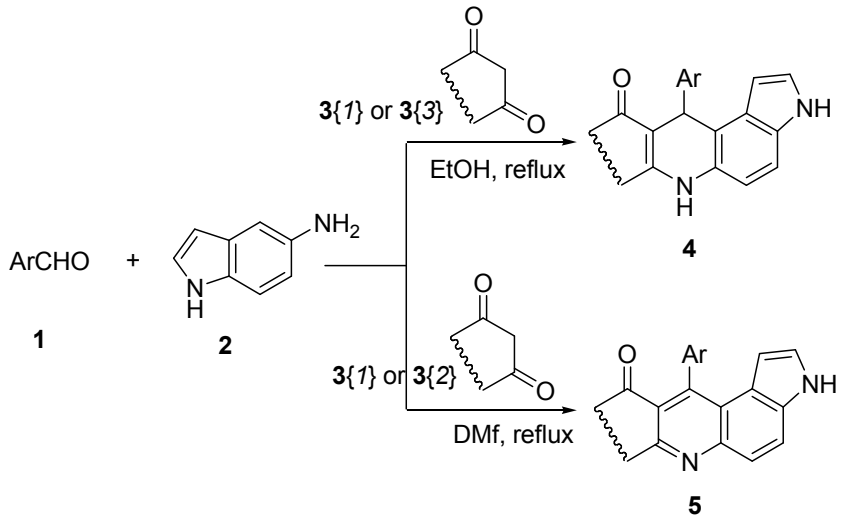
In our lab, the screening of catalysts was carried out first, for example, KF/Al_2O_3, piperidine and DBU (Table 1, entries 4-6), taking the reaction of 4-cyanobenzaldehyde **1**{*1*}, **2**{*1*}, and **3**{*1*} as a model. It was found that no catalyst,

the reaction could take place and give **4**{*1*,*1*,*1*} in high yields (93 %). The solvents, such as CH_3OH, EtOH, benzene and THF (entries 3, 7-10), were also tested to this reaction, the EtOH gave the best result. Furthermore, the product was collected by filtration without further purification, when the EtOH solution was cooled to room temperature after the completion of the reaction. It was interesting that the same reaction gave the aromatized cyclopenta[*b*]pyrrolo[3,2-*f*]quinolin-9(3*H*)-one derivatives **5**{*1*,*1*,*1*} in 68 % yield at 80 ºC along with 11 % yield of **4**{*1*,*1*,*1*} in DMF. The yield of **5**{*1*,*1*,*1*} was also gradually raised with the increase of temperature, and it gave the highest yield of 84 % at reflux in DMF for 6 hours (entries 8-11).

Table 1. Synthetic results of **4**{*1*,*1*,*1*} and **5**{*1*,*1*,*1*} under different reaction conditions[a]

Entry	temperature (°C)	Catalyst(mol%)	Time(h)	Solvent	Yields (**4**/**5**, %)[b]
1	r.t.	-	10	EtOH	Trace/0
2	50	-	16	EtOH	68/0
3	**Reflux**	**-**	**10**	**EtOH**	**93/0**
4	Reflux	KF/Al_2O_3	10	EtOH	90/0
5	Reflux	Piperidine	10	EtOH	90/0
6	Reflux	DBU	10	EtOH	87/0
7	80	-	8	CH_3OH	87/0
8	Reflux	-	14	CH_3CN	82/0
9	Reflux	-	16	Benzene	89/0
10	Reflux	-	14	THF	85/0
11	80	-	10	DMF	11/68
12	100	-	10	DMF	0/78
13	**Reflux**	**-**	**6**	**DMF**	**0/84**

[a] Reagents and conditions: 4-cyanobenzaldehyde **1**{*1*} (0.140 g, 1.0 mmol), **2**{*1*} (0.213 g, 1.0 mmol), **3**{*1*} (0.133 g, 1.0 mmol), solvent (10 mL). [b] Isolated yields.



Scheme 2. Reaction of **1**, **2** and **3**

The interesting and selective reaction depending on the reaction temperature, inspired us to test other 1,3-dicarbonyl compounds in this type of reaction. 2*H*-Indene-1,3-dione **3**{*2*} was chosen firstly for its similarity to cyclopentane-1,3-dione. It was found that the products were easily oxidized by air, even if the designed reactions were treated at slightly lower temperature in EtOH, they all aromatized to 12-arylindeno[1,2-*b*]pyrrolo[3,2-*f*]quinolin-11(3*H*)-one derivatives in high yields without catalysts (Scheme 2). Perhaps, the large conjugative system promotes the centre 1,4-dihydropyrdine (1,4-DHP) ring to be easy oxidized by air.

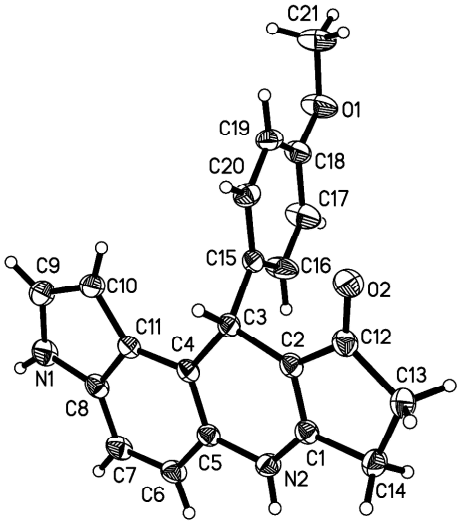


Figure 2. The crystal structure of **4**{*8*,*1*,*1*} with a molecule of DMF being deleted for clarity.

It was reported [24-27] that most of 1,4-DHP rings are stable in air, so above-mentioned results raised an interesting question: why were they so easily oxidized by air? With this question, the single crystal of **4**{*8*,*1*,*1*} was grown by slow evaporation at room temperature, and determined by CCD diffractometer. The crystal structure of **4**{*8*,*1*,*1*} is shown in Figure 2. X-ray diffraction analysis indicates that all the atoms (C(1)-C(5)/N(2)) on the center 1,4-DHP ring are coplanar, with mean deviation being 0.0249 Å, which is obviously different from those of similar structures.[28,29] Perhaps, the planar 1,4-DHP ring is oxidized more readily than the distorted ones (boat, or half-chair confirmation). It is also found in the crystal structure of **4**{*8*,*1*,*1*} that the adjacent five-membered ring (C(1)/C(2)/C(12)-C(14)) is also a planar structure, with mean deviation being 0.009 Å. Therefore, we think that the coplanar 1,4-DHP is just because of the outer five-membered planar ring. Otherwise, the 1,4-DHP would change to normal distorted confirmation, and it would be stable in air.

With this idea in mind, we selected the third 1,3-dicarbonyl compound to instead of five-membered planar ring. 5,5-Dimethylcyclohexane-1,3-dione **3**{*3*} (dimedone is not a planar structure) was subjected to react with **1** and **2**{*1*} without catalysts. The un-aromatized 8,9-dihydro-8,8-dimethyl-11-aryl-3*H*-pyrrolo[3,2-*a*]acridin-10(6*H*,7*H*, 11*H*)-one derivatives were obtained as we expected, whether they were treated in refluxing EtOH or DMF.

In order to confirm our assumption, we also grew the single crystals of **4**{*23*,*1*,*3*}, and its crystal structure is shown in Figure 3. X-ray diffraction analysis demonstrates that the 1,4-DHP is slightly distorted, adopting a skew boat confirmation as expected. The atoms of C(1), C(2) C(4) and C(5) are coplanar, with atoms C(3) and N(1) deviating from the defined plane by 0.222(2) and 0.106(2) Å, respectively. The outer six-membered ring adopts a half-chair confirmation as expected, and the atom C(7) deviates from the plane (C(4)-C(6)/C(8)/C(9)) by 0.640 (2) Å.

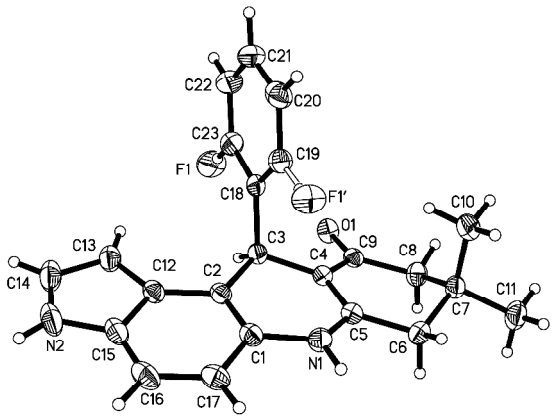


Figure 3. The crystal structure of **4**{*19*,*1*,*3*}

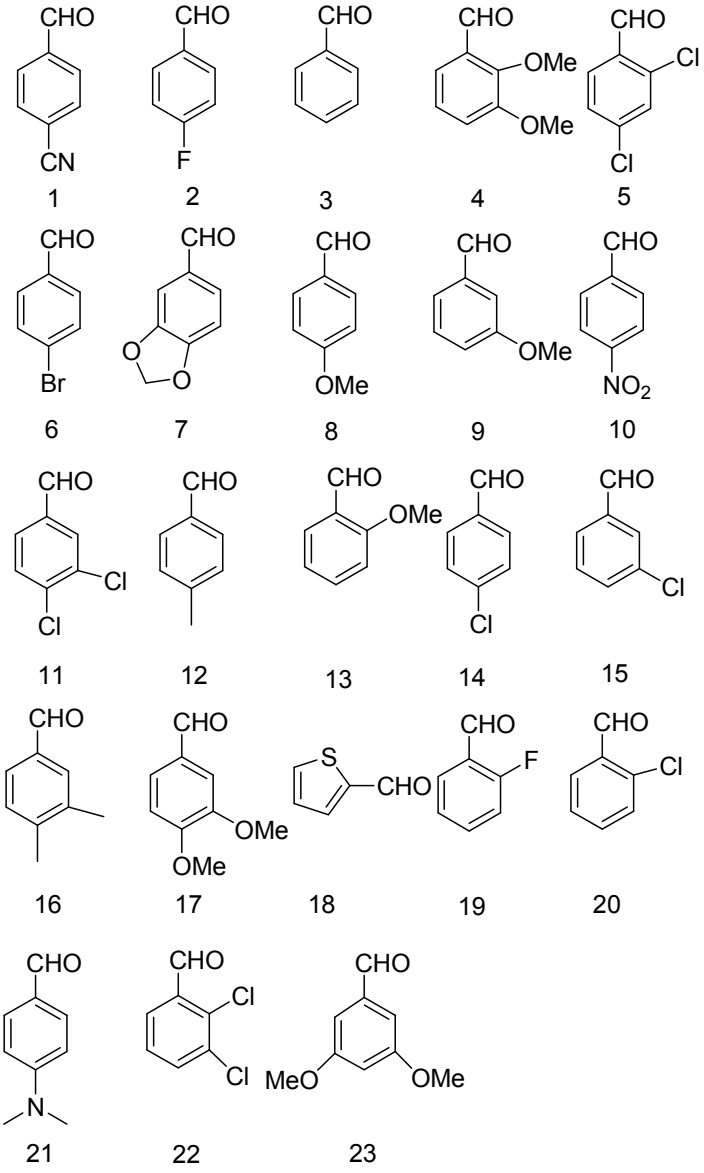
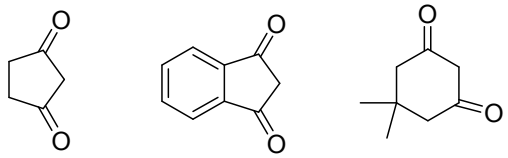


Figure 4. Diversity of aldehydes **1**{*1-23*}



1 2 3

Figure 5. Diversity of 1,3-dicarbonyl compounds **3**{*1-3*}

Table 2. The reaction time and yields of the products **4**[a]

entry	Ar	time (h)	products	Isolated yields (%)
1	4-CNC_6H_4	6	**4**{*1*,*1*,*1*}	87
2	4-FC_6H_4	6	**4**{*2*,*1*,*1*}	90
3	C_6H_5	7	**4**{*3*,*1*,*1*}	92
4	2,3-$(MeO)_2C_6H_3$	8	**4**{*4*,*1*,*1*}	86
5	2,4-$Cl_2C_6H_3$	5	**4**{*5*,*1*,*1*}	90
6	4-BrC_6H_4	6	**4**{*6*,*1*,*1*}	84
7	Piperonyl	8	**4**{*7*,*1*,*1*}	88
8	4-$MeOC_6H_4$	9	**4**{*8*,*1*,*1*}	90
9	3-$MeOC_6H_4$	6	**4**{*9*,*1*,*1*}	94
10	4-$NO_2C_6H_4$	5	**4**{*10*,*1*,*1*}	92
11	4-BrC_6H_4	6	**4**{*6*,*1*,*3*}	92
12	Piperonyl	10	**4**{*7*,*1*,*3*}	95
13	3-$MeOC_6H_4$	8	**4**{9,*1*,*3*}	90
14	3,4-$Cl_2C_6H_3$	6	**4**{*11*,*1*,*3*}	90
15	4-MeC_6H_4	6	**4**{*12*,*1*,*3*}	91
16	2-$MeOC_6H_4$	8	**4**{*13*,*1*,*3*}	89
17	4-ClC_6H_4	5	**4**{*14*,*1*,*3*}	90
18	3-ClC_6H_4	6	**4**{*15*,*1*,*3*}	95
19	3,4-$(CH_3)_2C_6H_3$	10	**4**{*16*,*1*,*3*}	96
20	3,4-$(MeO)_2C_6H_3$	10	**4**{*17*,*1*,*3*}	96
21	2-Thienyl	6	**4**{*18*,*1*,*3*}	95
22	2-FC_6H_4	8	**4**{*19*,*1*,*3*}	87

[a] Reaction condition: EtOH (10 mL), **1** (1.0 mmol), **2**{*1*} (0.132 g, 1.0 mmol) and **3** (1.0 mmol), reflux.

Table 3. The reaction time and yields of the products **5**[a]

entry	Ar	time (h)	products	Isolated yields (%)
1	4-CNC_6H_4	10	**5**{*1*,*1*,*1*}	84
2	C_6H_5	16	**5**{*3*,*1*,*1*}	84
3	2,4-$Cl_2C_6H_3$	12	**5**{*5*,*1*,*1*}	92
4	3,4-$Cl_2C_6H_3$	15	**5**{*11*,*1*,*1*}	87
5	4-MeC_6H_4	16	**5**{*12*,*1*,*1*}	90
6	2-$MeOC_6H_4$	18	**5**{*13*,*1*,*1*}	83
7	3-ClC_6H_4	10	**5**{*15*,*1*,*1*}	88
8	2-ClC_6H_4	10	**5**{*20*,*1*,*1*}	90

9	4-$Me_2NC_6H_4$	12	**5**{*21*,*1*,*1*}	90
10	2,3-$Cl_2C_6H_3$	12	**5**{*22*,*1*,*1*}	89
11	3,5-$(MeO)_2C_6H_3$	18	**5**{*23*,*1*,*1*}	92
12	2,4-$Cl_2C_6H_3$	10	**5**{*5*,*1*,*2*}	87
13	4-BrC_6H_4	10	**5**{*6*,*1*,*2*}	90
14	Piperonyl	10	**5**{*7*,*1*,*2*}	90
15	3-$MeOC_6H_4$	10	**5**{*9*,*1*,*2*}	95
16	3,4-$Cl_2C_6H_3$	10	**5**{*11*,*1*,*2*}	88
17	4-MeC_6H_4	9	**5**{*12*,*1*,*2*}	87
18	2-$MeOC_6H_4$	8	**5**{*13*,*1*,*2*}	96
19	4-ClC_6H_4	7	**5**{*14*,*1*,*2*}	92
20	3-ClC_6H_4	7	**5**{*15*,*1*,*2*}	90
21	3,4-$(CH_3)_2C_6H_3$	12	**5**{*16*,*1*,*2*}	85
22	2-ClC_6H_4	8	**5**{*20*,*1*,*2*}	94
23	3,5-$(MeO)_2C_6H_3$	12	**5**{*23*,*1*,*2*}	92

[a] Reaction condition: DMF (10 mL), **1** (1.0 mmol), **2**{*1*} (0.132 g, 1.0 mmol) and **3** (1.0 mmol), reflux.

3. Conclusion

In summary, a three-component reaction of aromatic aldehyde, 1*H*-indol-5-amine and 1,3-dicarbonyl compounds including 5,5-dimethylcyclohexane-1,3-dione, cyclopentane-1,3-dione and 2*H*-indene-1,3-dione was studied under catalyst-free conditions, with pyrrolo[3,2-*f*]quinoline and pyrrolo[3,2-*a*]acridine derivatives being obtained in high yields. The advantages of this procedure include mild reaction conditions, high yields, one-pot operational simplicity, and with catalyst-free conditions.

4. Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr pellet. ^{1}H NMR spectra was obtained from a solution in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using a Bruker-micro-TOF-Q-MS analyzer.

General procedure for the syntheses of 4.

A dry 50 mL flask was charged with aromatic aldehyde **1** (1.0 mmol), 1*H*-indol-5-amine **2** (0.132 g, 1.0 mmol), 1,3-dicarbonyl compounds **3** (1.0 mmol) and

EtOH (10 mL). The reaction mixture was stirred at reflux for 5-10 h. After the completion of the reaction, as indicated by TLC, the products **4** were obtained as pale yellow power or crystals, when the mixture was allowed to down to room temperature.

10-(4-Methoxyphenyl)-6,7,8,10-tetrahydrocyclopenta[*b*]pyrrolo[3,2-*f*]quinolin-9(3*H*)-one **4**{*8*,*1*,*1*}: M. p. 289~291 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 2.18~2.28 (m, 2H, CH_2), 2.62~2.67 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3), 5.18 (s, 1H, CH), 6.19 (s, 1H, ArH), 6.70 (d, J = 8.0 Hz, 2H, ArH), 6.84 (d, J = 8.4 Hz, 1H, ArH), 7.08 (d, J = 8.0 Hz, 2H, ArH), 7.16 (s, 1H, ArH), 7.24 (d, J = 8.0 Hz, 1H, ArH), 9.92 (s, 1H, NH), 10.98 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): 23.9, 33.2, 37.9, 54.8, 99.8, 110.6, 111.2, 111.6, 113.1, 114.8, 125.3, 126.9, 128.6, 129.1, 132.7, 139.5, 157.0, 164.9, 199.4. IR (KBr): 3247, 3076, 3036, 2922, 2837, 2805, 2717, 2576, 1689, 1613, 1561, 1510, 1453, 1436, 1354, 1341, 1293, 1253, 1191, 1175, 1161, 1125, 1033, 989, 892, 836, 749, 725, 697 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{21}H_{19}N_2O_2$ $[M + H]^+$ 331.1447, found 331.1442.

General procedure for the syntheses of 5.

A dry 50 mL flask was charged with aldehyde **1** (1.0 mmol), 1*H*-indol-5-amine **2** (0.132 g, 1.0 mmol), 1,3-dicarbonyl compounds **3** (1.0 mmol) and DMF (10 mL). The reaction mixture was stirred at reflux for 8-18 h. After the completion of the reaction, as indicated by TLC, a little water was added to the mixture at reflux. The products **5** were obtained as pale yellow power or crystals, when the mixture was allowed to down to room temperature.

10-(2,3-Dichlorophenyl)-7,8-dihydrocyclopenta[*b*]pyrrolo[3,2-*f*]quinolin-9(3*H*)-one **5**{*22*,*1*,*1*}: M. p. > 300 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 2.73~2.79 (m, 2H, CH_2), 3.31~3.36 (m, 2H, CH_2), 5.15 (s, 1H, ArH), 7.32~7.35 (m, 2H, ArH), 7.55~7.59 (m, 1H, ArH), 7.82 (d, J = 9.2 Hz, 1H, ArH), 7.89 (d, J = 8.0 Hz, 1H, ArH), 8.05 (d, J = 8.8 Hz, 1H, ArH), 11.92 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 100 MHz): 27.7, 36.2, 103.3, 119.7, 120.7, 121.3, 122.5, 123.0, 125.1, 128.6, 129.0, 129.9, 130.6, 132.0, 132.5, 138.4, 140.9, 149.5, 167.9, 203.6. IR (KBr): 3449, 3034, 2927, 1704, 1570, 1538, 1488, 1456, 1429, 1414, 1368, 1341, 1311, 1275, 1185, 1166, 1149, 1099, 1044,

892, 797, 742 cm^{-1}. HRMS (ESI, *m/z*): Calcd for $C_{20}H_{13}N_2OCl_2$ $[M + H]^+$ 367.0405, found 367.0391.

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Supporting Information Available. Characterized data including NMR, IR and HRMS of **4** and **5**, and crystallographic information files (CIF) of **4**{*8*,*1*,*1*} and **4**{*19*,*1*,*3*}, this material is available free of charge via the Internet at http://pubs.acs.org.

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