

银催化 2-芳基吲哚与马来酰亚胺 C—H 键烷基化反应

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摘要 发展了一种银催化高效高区域选择性的 2-芳基吲哚 C-3 位烷基化反应. 在温和条件下, 能以高达 97% 的收率得到目标化合物, 且该方法操作简单, 不需要外加氧化剂.

关键词 银催化; 2-芳基吲哚; 马来酰亚胺; 烷基化

Silver-Catalyzed C—H Alkylation of 2-Arylindoles with Maleimides

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Abstract A highly efficient and regioselective C-3-alkylation of 2-arylindoles with maleimides has been developed using Ag(I) as catalyst. 3-(2-Aryl-1H-indol-3-yl)pyrrolidine-2,5-diones were afforded with high yields (up to 97%) under relatively mild reaction conditions. The method features operational simplicity and avoiding external oxidant.

Keywords silver-catalyzed; 2-arylindoles; maleimides; alkylation

1 Introduction

Indolylsuccinimide, an important motif of aza-heterocycles, frequently emerges in natural products^[1] and drug candidates^[2] due to their noteworthy biological activities,^[3] as well as drug candidates that exhibit high kinase selectivity and anticancer activity.^[4] They are also useful synthetic intermediates for construction of complicate heterocyclic frameworks.^[5] For examples, compound **A** is a mood stabilizer and able to stimulate steroidogenesis.^[6] Compound **B**, with remarkable antiangiogenic activity, was discovered from 2,3-diarylmalimide derivatives.^[7] Compound **C**, one clinical candidate, shows great potency in IDO-1 human whole blood assay.^[8] Additionally, compounds **D** and **E** exhibit good chemical activities in term of fluorescence (FL), chemiluminescence (CL), and bioluminescence (BL) (Figure 1).^[9]

Traditionally, indolylsuccinimides were prepared starting from indolylmagnesium bromides and bromomaleimides.^[10] Moreover, they have also been catalyzed by the conjugate addition of indoles to α,β -unsaturated compounds in the presence of Lewis acid.^[11] Recently, transi-

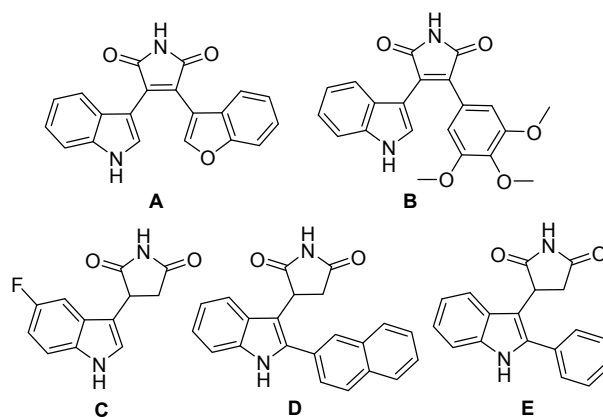


Figure 1 Examples illustrating the importance of indolylsuccinimides

tion-metal-catalyzed coupling reactions have been widely applied in indolylsuccinimides synthesis. For example, Zhao group^[12] developed the Michael addition and oxidative dehydrogenation reaction of indoles with maleimides promoted by AlCl_3 , obtaining 3-substituted indoles in high yields with excellent regioselectivity. Then, this group^[13]

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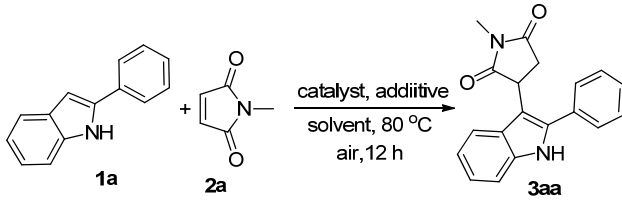
extended the regioselective tandem oxidative coupling reactions from both free and protected (NH) indoles with maleimides catalyzed by palladium. Despite these methods have contributed greatly to this field, there still exist some respective limitations, such as requirement of long reaction times, excess oxidant, pre-functionalized substrates and low efficiency. Therefore, developing high efficiency and convenient method is considerable. Silver salts have concurrently been developed as a newly emerging metal catalyst due to its excellent catalytic activity, high selectivity, long service life, convenient after-treatment, and ease of removal.^[14] With our ongoing efforts to the clean transition-metal-catalyzed C—H bond functionalization,^[15] herein, we disclose a Ag(I)-catalyzed alkylation of 2-arylindoles with maleimides to synthesize 3-(2-aryl-1*H*-indol-3-yl)pyrrolidine-2,5-dione with high yields and excellent regioselectivity, avoiding external oxidants under relatively mild reaction conditions.

2 Results and discussion

Our initial experiment was performed with 2-phenylindole (**1a**) and *N*-methylmaleimide (**2a**) as model substrates to optimize the reaction conditions (Table 1). In the presence of 20 mol% AgNTf₂, the reaction of indole **1a** with **2a** in 1,2-dichloroethane (DCE) at 80 °C under air atmosphere afforded the expected product **3aa** in 56% yield (Table 1, Entry 1). The structural and regiochemical assignments of compound **3aa** were confirmed by X-ray crystallographic analysis (Figure 2).^[16] To our delight, the yield increased significantly to 86% when 1.0 equiv. of AcOH was added (Table 1, Entry 2). The silver salts, including AgSbF₆, AgOTf, AgBF₄, Ag₂CO₃, AgOAc, Ag-TFA, were tested. AgNTf₂ was proved to be an optimal catalyst (Table 1, Entries 2~8). Then, an extensive survey of acids (AcOH, HCOOH, TFA, MSA, Ac₂O, PivOH) was performed (Table 1, Entries 9~13). PivOH afforded **3aa** in the highest yield of 93% (Table 1, Entry 13). Both raising and lowering the amount of PivOH resulted in lower yield of the target product **3aa** (Table 1, Entries 14, 15). Next, several additional parameters were altered in an attempt to further improve yield. It was observed that the solvent played a crucial role. Among the solvents tested, CCl₄ was the optimal choice (Table 1, Entries 15~21). Finally, 80 °C was determined to be the optimal reaction temperature. The yield reduced significantly when the reaction temperature decreased or increased (Table 1, Entries 22~24). Subsequently, the loading of 5 mol% AgNTf₂ was most appropriate (Table 1, Entry 24). Moreover, the control experiment indicated that PivOH could not promote the reaction in the absence of the Ag catalyst (Table 1, Entry 25).

With the optimized reaction conditions in hand, we turned our attention to the scope of the substrates for this transformation (Table 2). The reaction was compatible with a variety of 2-phenylindoles affording the desired products in moderate to good yields. A wide range of ma-

Table 1 Optimization of the reaction conditions^a



Entry	Catalyst	Additive	Solvent	Yield ^b /%
1	AgNTf ₂	—	DCE	56
2	AgNTf ₂	AcOH	DCE	86
3	AgSbF ₆	AcOH	DCE	70
4	AgOTf	AcOH	DCE	78
5	AgBF ₄	AcOH	DCE	82
6	Ag ₂ CO ₃	AcOH	DCE	NR
7	AgOAc	AcOH	DCE	NR
8	AgTFA	AcOH	DCE	Trace
9	AgNTf ₂	HCOOH	DCE	89
10	AgNTf ₂	TFA ^c	DCE	73
11	AgNTf ₂	MSA ^d	DCE	92
12	AgNTf ₂	Ac ₂ O	DCE	80
13	AgNTf ₂	PivOH	DCE	93
14 ^e	AgNTf ₂	PivOH	DCE	54
15 ^f	AgNTf ₂	PivOH	DCE	61
16	AgNTf ₂	PivOH	DMF	NR
17	AgNTf ₂	PivOH	CH ₃ OH	32
18	AgNTf ₂	PivOH	CH ₃ CN	NR
19	AgNTf ₂	PivOH	Toluene	86
20	AgNTf ₂	PivOH	CHCl ₃	89
21	AgNTf ₂	PivOH	CCl ₄	96
22 ^g	AgNTf ₂	PivOH	CCl ₄	97
23 ^h	AgNTf ₂	PivOH	CCl ₄	78
24 ⁱ	AgNTf ₂	PivOH	CCl ₄	82
25	—	PivOH	CCl ₄	NR

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (20 mol%), and additive (1.0 equiv) at 80 °C for 12 h in solvent (2.0 mL) under air. ^b Isolated yield. ^c TFA: trifluoroacetic acid. ^d MSA: methanesulfonic acid. ^e PivOH (0.5 equiv). ^f PivOH (2.0 equiv.). ^g **1a** (0.1 mmol), **2a** (0.12 mmol), AgNTf₂ (5 mol%). ^h At 60 °C. ⁱ At 100 °C.

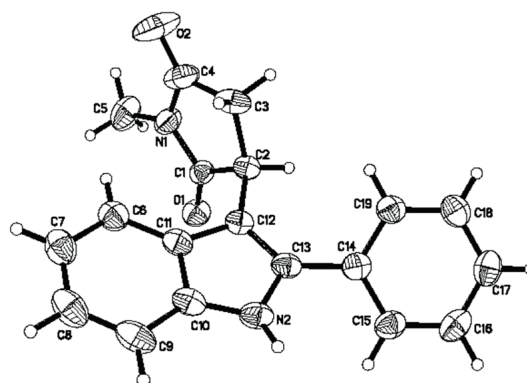
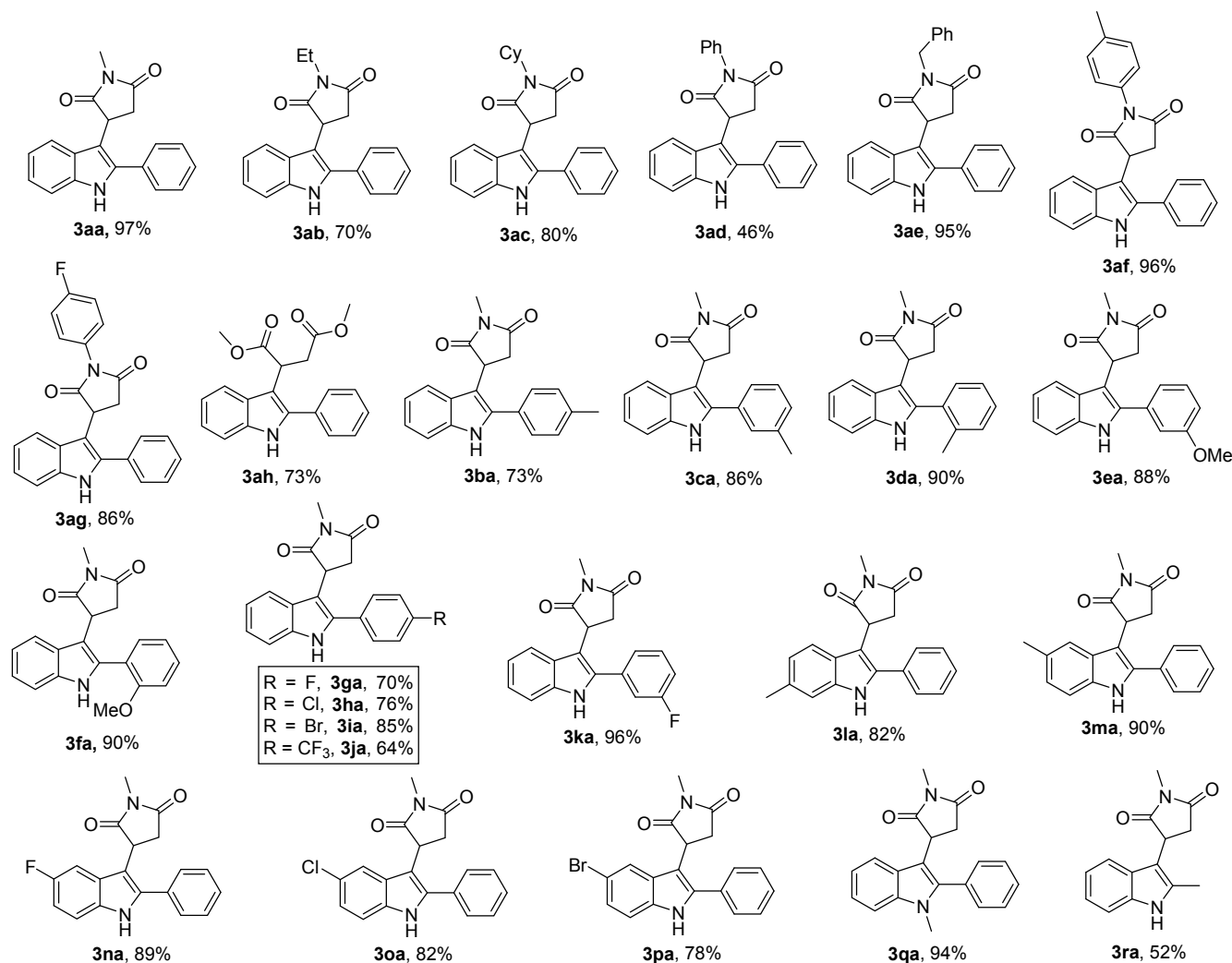
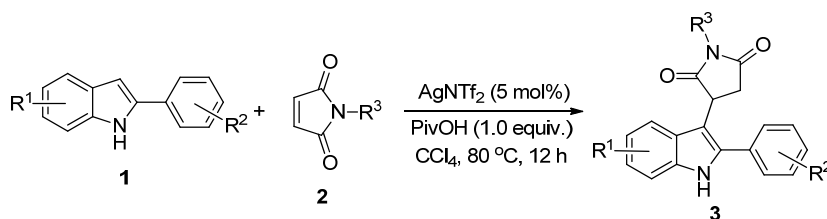


Figure 2 X-ray molecular structure of the product **3aa**

leimides were firstly evaluated in the reaction with 2-phenylindole (**1a**) (Table 2, **3aa**~**3ah**). The maleimides with *N*-alkyl substituted (such as Me, Et, and cyclohexyl) maleimides gave the desired products (**3aa**, 97%; **3ab**,

Table 2 Scope of substrates^{a,b}

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), AgNTf₂ (5 mol%), and PivOH (1.0 equiv.) at 80 °C for 12 h in CCl₄ (2.0 mL) under air. ^b Isolated yield.

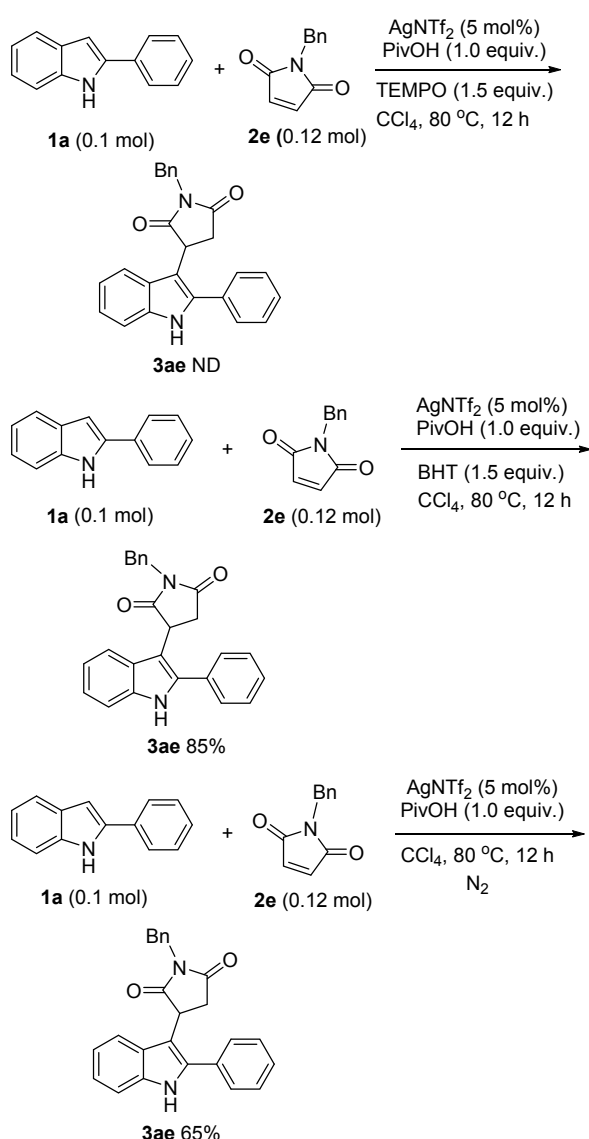
70%; **3ac**, 80%) in good to excellent yields. *N*-Phenyl maleimide (**3ad**, 46%) obtained a medium yield, perhaps due to its good conjugate structure with maleimide ring. *N*-Benzyl functionalities readily furnished the desired product **3ae** in 95% yield. Additionally, evaluation of electronic effects on the aryl ring of *N*-aryl maleimides turned out great yields (**3af**, and **3ag**, 96%, and 86%). And the dimethyl maleate (**3ah**, 73%) also had a good transformation in the reaction.

Then, substituted 2-phenylindoles with *N*-methyl maleimide were subjected to the optimized reaction conditions. It was found that the identity of the 2-phenylindoles substituents has no obviously influence the reaction yields.

Generally, 4'-methyl, 3'-methyl, 2'-methyl 2-phenylindoles afforded excellent yields (**3ba**, 73%; **3ca**, 86%; **3da**, 90%). And 3'-methoxy, 2'-methoxy 2-phenylindoles could obtain good yields (**3ea**, 88%; **3fa**, 90%). Then, 2-phenylindoles with halogen and trifluoromethyl generally have slightly lower yields (**3ga**, 70%; **3ha**, 76%; **3ia**, 85%; **3ja**, 64%). These results suggest that electron-withdrawing substituents could slightly decrease the reactivity of the 2-phenylindoles by reducing the nucleophilicity of the 3-position. Additionally, halogens on the indole ring (**3la**, **3ma**, **3na**, **3oa**, and **3pa**) were tolerated and given excellent yields, providing useful synthetic handles for further functionalization. In addition, *N*-methyl-2-phenylindole could give

the product **3qa** in 94% yield, and 2-methylindole was also applied to this catalytic system, giving the product **3ra** in 52% yield.

Some control experiments were conducted to gain insight into the reaction mechanism (Scheme 1). When the radical scavenger 2,2,6,6-tetramethylpiperidinoxy (TEMPO) was affiliated to the reaction system, the desired product **3ae** was not detected. Considering the selective oxidation of TEMPO may hinder the reaction, we switched to 2,6-di-*tert*-butyl-4-methylphenol (BHT), which had little influence on the yield of the product **3ae**. In addition, when the reaction was performed under N₂ atmosphere, the desired product **3ae** was obtained in 65% yield. These results indicated that the radical process was ruled out, and molecular oxygen does not play a crucial role in this reaction.



Scheme 1 Control experiments

On the basis of the results obtained and previous literatures,^[17] a plausible mechanism for the reaction is proposed and depicted in Figure 3. Initially, *N*-methylmale-

imide (**2a**) was activated by Ag(I) to form intermediate **A**. Then electrophilic attack of 2-phenylindole to the intermediate **A** gave intermediate **B**, which delivered the desired product **3aa** and catalytically active Ag(I) through protodemetalation. In the catalytic cycle, Ag(I) as a catalyst promotes the procedure by increasing the electrophilic ability of α,β -unsaturated compounds.^[17a,18]

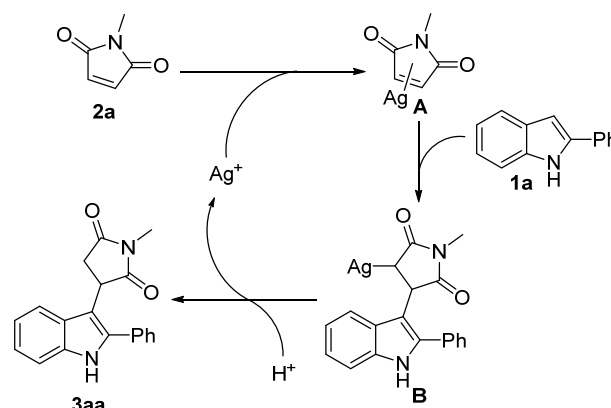


Figure 3 Plausible reaction mechanism

3 Conclusions

In summary, the alkylation of 2-arylindole with maleimides has been developed using silver(I) as catalyst. Under the optimized reaction conditions, a broad range of 3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-diones were conveniently obtained in moderate to excellent yields under relatively mild reaction conditions.

4 Experimental section

4.1 General experimental information

All reactions were carried out under an air atmosphere (≈ 15 mL volume) equipped with a magnetic stirring element. Unless otherwise stated, all commercial reagents were used without additional purification. Column chromatography was undertaken on silica gel (200~300 mesh) using a proper eluent system. ¹H NMR, ¹⁹F NMR, and ¹³C NMR spectra were recorded on a spectrometer at 400, 376 and 100 MHz, respectively, with deuterated chloroform as solvent. The chemical shifts δ are reported relative to tetramethylsilane ($\delta = 0$) or residual CHCl₃ ($\delta = 77.00$). High-resolution mass spectrometry (HRMS) was performed on a Q-TOF spectrometer using electrospray ionization (ESI). X-ray analysis was performed with a single-crystal X-ray diffractometer. The 2-arylindoles^[19] and maleimides^[20] were prepared according to references. The solvents and reagents were obtained from the commercial suppliers and used without further purification.

4.2 General synthesis procedure

A mixture of 2-phenylindole (0.1 mmol), *N*-methylmaleimide (0.12 mmol), AgNTf₂ (5 mol%) and PivOH (0.1 mmol) in carbon tetrachloride (2 mL) in a sealed tube was stirred at 80 °C for 12 h. After cooling to room temperature, the mixture was purified by column chromatography

on silica gel (EtOAc/petroleum ether, $V:V=1:3$) to afford the desired product **3aa**.

Methyl-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3aa**): Pale yellow solid. 29.5 mg, 97% yield. m.p. 184~186 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.33 (s, 1H), 7.60~7.57 (m, 2H), 7.48~7.39 (m, 3H), 7.35 (d, $J=8.2$ Hz), 7.25~7.15 (m, 2H), 7.10~7.07 (m, 1H), 4.39 (t, $J=7.1$ Hz, 1H), 3.12 (s, 3H), 3.09 (t, $J=7.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 179.0, 176.8, 137.6, 136.0, 131.9, 129.1, 128.8, 128.7, 126.1, 122.8, 120.5, 118.2, 111.6, 107.7, 37.9, 36.2, 25.2; HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{17}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 305.1285, found 305.1287.

Ethyl-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3ab**): White solid. 22.2 mg, 70% yield. m.p. 193~195 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.49 (s, 1H), 7.61~7.59 (m, 2H), 7.49~7.41 (m, 3H), 7.33 (t, $J=8.0$ Hz), 7.23~7.19 (m, 2H), 7.13~7.09 (m, 1H), 4.39 (t, $J=7.2$ Hz, 1H), 3.73 (dd, $J=7.1$, 14.5 Hz, 2H), 3.09 (d, $J=7.8$ Hz, 2H), 1.21 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 178.8, 176.7, 137.6, 136.1, 131.9, 129.0, 128.8, 128.6, 126.1, 122.7, 120.4, 118.2, 111.7, 107.7, 37.8, 36.2, 34.2, 13.1; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 319.1441, found 319.1444.

Cyclohexyl-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3ac**): White solid. 29.6 mg, 80% yield. m.p. 224~226 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.32 (s, 1H), 7.61~7.59 (m, 2H), 7.47~7.40 (m, 3H), 7.32 (t, $J=8.2$ Hz, 1H), 7.20~7.16 (m, 2H), 7.10~7.06 (m, 1H), 4.30 (t, $J=7.1$ Hz, 1H), 4.18~4.09 (m, 1H), 3.03 (s, 1H), 3.01 (s, 1H), 2.33~2.17 (m, 2H), 1.83 (d, $J=13.1$ Hz, 2H), 1.65 (d, $J=10.4$ Hz, 3H), 1.36~1.19 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 179.0, 176.9, 137.6, 136.1, 131.9, 129.1, 128.8, 128.6, 126.1, 122.7, 120.4, 118.3, 111.6, 108.1, 52.2, 37.5, 35.9, 28.9, 25.9, 25.1; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 373.1911, found 373.1913.

Phenyl-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3ad**): White solid. 16.7 mg, 46% yield. m.p. 117~119 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.30 (s, 1H), 7.69~7.67 (dd, $J=1.7$, 8.3 Hz, 2H), 7.55~7.52 (m, 2H), 7.51~7.49 (m, 2H), 7.48~7.45 (m, 2H), 7.42~7.39 (m, 4H), 7.27~7.25 (m, 1H), 7.20~7.16 (m, 1H), 4.60 (dd, $J=6.6$, 8.5 Hz, 1H), 3.30 (dd, $J=3.3$, 8.7 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 177.8, 175.7, 137.7, 136.1, 132.1, 131.9, 129.3, 129.2, 128.9, 128.8, 128.7, 126.5, 126.2, 122.9, 120.7, 118.2, 111.7, 107.9, 38.0, 36.3; HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{19}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 367.1441, found 367.1447.

1-Benzyl-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3ae**): White solid. 36.1 mg, 96% yield. m.p. 105~107 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.62 (s, 1H), 7.54~7.51 (dd, $J=2.4$, 6.1 Hz, 4H), 7.40~7.38 (m, 6H), 7.22 (d, $J=8.0$ Hz, 1H), 7.17~7.13 (m, 1H), 6.97~6.91 (m, 2H), 4.84 (dd, $J=13.9$, 26.5 Hz, 2H), 4.40 (dd, $J=5.9$, 8.9 Hz, 1H), 3.12~2.99 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 178.9, 176.5, 137.6, 136.1, 135.7, 131.9, 129.30, 129.0, 128.8, 128.7, 128.6, 128.2, 126.0, 122.6, 120.2, 118.3, 111.7, 107.6, 42.9, 37.9, 36.2; HRMS (ESI) calcd

for $\text{C}_{25}\text{H}_{21}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 381.1598, found 381.1600.

3-(2-Phenyl-1*H*-indol-3-yl)-1-(*p*-tolyl)pyrrolidine-2,5-dione (**3af**): White solid. 37.8 mg, 95% yield. m.p. 125~127 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.45 (s, 1H), 7.43~7.37 (m, 1H), 7.36~7.34 (m, 1H), 7.31~7.27 (m, 2H), 7.20~7.16 (m, 1H), 7.15~7.06 (m, 3H), 4.37 (dd, $J=5.2$, 6.6 Hz, 1H), 3.13 (s, 3H), 3.10 (t, $J=4.4$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 178.1, 176.0, 138.9, 137.7, 136.1, 131.9, 123.0, 129.5, 129.08, 129.1, 128.9, 128.7, 126.3, 126.2, 122.7, 120.6, 118.1, 111.8, 107.8, 38.0, 36.3, 21.3; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{21}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 381.1598, found 381.1601.

1-(4-Fluorophenyl)-3-(2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3ag**): Pale red solid. 33.0 mg, 86% yield. m.p. 115~117 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.31 (s, 1H), 7.62 (dd, $J=1.7$, 8.2 Hz, 2H), 7.50~7.43 (m, 3H), 7.38~7.32 (m, 4H), 7.24~7.20 (m, 1H), 7.18~7.12 (m, 3H), 4.55 (dd, $J=6.4$, 8.3 Hz, 1H), 3.25 (dd, $J=3.2$, 8.9 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 177.8, 175.6, 164.2, 160.8, 137.8, 136.1, 131.8, 129.2, 128.9, 128.8, 128.4, 128.3, 122.9, 120.7, 118.0, 116.4, 116.2, 111.8, 38.0, 36.2; ^{19}F NMR (376 MHz, CDCl_3) δ : -112.14 (s); HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{18}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 385.1347, found 385.1350.

3-(2-Phenyl-1*H*-indol-3-yl)hexane-2,5-dione (**3ah**): White solid. 22.2 mg, 73% yield. m.p. 180~182 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.13 (s, 1H), 7.74 (d, $J=8.0$ Hz, 1H), 7.67 (t, $J=1.4$ Hz, 2H), 7.53~7.49 (m, 2H), 7.46~7.41 (m, 1H), 7.38 (d, $J=8.0$ Hz, 2H), 7.24~7.20 (m, 1H), 7.16~7.12 (m, 1H), 4.57 (dd, $J=4.7$, 10.6 Hz, 1H), 3.69 (s, 3H), 3.62 (s, 3H), 3.58~3.46 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 173.9, 172.4, 136.2, 135.8, 132.3, 129.1, 128.8, 128.5, 127.1, 122.5, 120.3, 120.1, 111.0, 108.7, 52.4, 51.8, 38.5, 36.2; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 306.1489, found 306.1492.

Methyl-3-(2-(*p*-tolyl)-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3ba**): White solid. 23.2 mg, 73% yield. m.p. 198~200 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.35 (s, 1H), 7.53 (d, $J=7.9$ Hz, 2H), 7.41 (d, $J=8.2$ Hz, 1H), 7.32 (d, $J=7.9$ Hz, 2H), 7.25~7.17 (m, 2H), 7.14~7.09 (m, 1H), 4.42 (t, $J=6.9$ Hz, 1H), 3.17 (s, 3H), 3.13 (t, $J=6.4$ Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 179.0, 176.9, 138.8, 137.7, 135.9, 128, 128.9, 128.7, 126.2, 122.7, 120.5, 118.1, 111.5, 107.4, 37.9, 36.2, 25.2, 21.4; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 319.1441, found 319.1447.

1-Methyl-3-(2-(*m*-tolyl)-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3ca**): Pale red solid. 27.4 mg, 86% yield. m.p. 201~203 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.28 (s, 1H), 7.43 (d, $J=6.2$ Hz, 2H), 7.40 (d, $J=7.5$ Hz, 2H), 7.28 (s, 1H), 7.26~7.21 (m, 1H), 7.19 (d, $J=7.7$ Hz, 1H), 7.14~7.10 (m, 1H), 4.44 (dd, $J=6.2$, 8.4 Hz, 1H), 3.17 (s, 3H), 3.12 (dd, $J=4.2$, 9.1 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 179.0, 176.9, 138.9, 137.7, 135.9, 131.8, 129.5, 129.4, 129.0, 126.2, 125.9, 122.7, 120.5, 118.2, 111.6, 107.6, 37.9, 36.2, 25.2, 21.6; HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 319.1441, found

319.1447.

Methyl-3-(2-(*o*-tolyl)-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3da**): White solid. 28.7 mg, 90% yield. m.p. 112~114 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.35 (s, 1H), 7.33~7.29 (m, 3H), 7.26 (d, *J*=7.2 Hz, 1H), 7.21~7.16 (m, 3H), 7.11~7.07 (m, 1H), 3.99 (dd, *J*=5.6, 9.3 Hz, 1H), 2.95 (s, 3H), 3.01~2.86 (m, 2H), 2.23 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 178.7, 176.9, 138.2, 136.7, 135.8, 131.3, 131.2, 130.5, 129.3, 125.8, 122.5, 120.3, 117.9, 111.5, 108.9, 37.7, 36.3, 25.0, 20.1; HRMS (ESI) calcd for C₂₀H₁₉N₂O₂ [M + H]⁺ 319.1441, found 319.1442.

3-(2-(3-Methoxyphenyl)-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (**3ea**): Pale red solid. 29.4 mg, 88% yield. m.p. 98~100 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.35 (s, 1H), 7.39~7.34 (m, 2H), 7.21~7.18 (m, 1H), 7.17~7.16 (m, 2H), 7.15 (t, *J*=0.9 Hz, 1H), 7.10~7.06 (m, 1H), 6.67~6.94 (m, 1H), 4.42 (t, *J*=7.3 Hz, 1H), 3.83 (s, 3H), 3.12 (s, 3H), 3.09 (d, *J*=7.3 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 179.0, 176.9, 160.0, 137.50, 136.0, 133.2, 130.2, 126.1, 122.8, 121.0, 120.5, 118.2, 114.4, 114.3, 111.6, 107.7, 55.4, 37.9, 36.1, 25.2; HRMS (ESI) calcd for C₂₅H₂₁N₂O₂ [M + H]⁺ 335.1390, found 335.1396.

3-(2-(2-Methoxyphenyl)-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (**3fa**): White solid. 29.4 mg, 88% yield. m.p. 98~100 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.37 (s, 1H), 7.38~7.33 (m, 2H), 7.21~7.14 (m, 4H), 6.69~6.94 (m, 1H), 4.41 (t, *J*=7.6 Hz, 1H), 3.83 (s, 3H), 3.12 (s, 3H), 3.08 (d, *J*=7.3 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 179.0, 176.9, 159.9, 137.5, 136.0, 133.2, 130.2, 126.1, 122.8, 121.0, 120.5, 118.2, 114.4, 114.2, 111.7, 107.7, 55.4, 37.9, 36.1, 25.2; HRMS (ESI) calcd for C₂₅H₂₁N₂O₂ [M + H]⁺ 335.1390, found 335.1394.

3-(2-(4-Fluorophenyl)-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (**3ga**): White solid. 29.4 mg, 88% yield. m.p. 106~108 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.21 (s, 1H), 7.63~7.59 (m, 2H), 7.38 (d, *J*=8.0 Hz, 1H), 7.24~7.16 (m, 3H), 7.15 (t, *J*=1.2 Hz, 1H), 7.12~7.09 (m, 1H), 4.32 (t, *J*=7.6 Hz, 1H), 3.15 (s, 3H), 3.12 (d, *J*=7.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 178.9, 176.7, 163.1 (d, *J*=249.6 Hz), 136.6, 136.0, 130.7 (d, *J*=8.6 Hz), 127.9, 126.0, 122.9, 120.7, 118.2, 116.2 (d, *J*=22.1 Hz), 111.6, 107.9, 37.8, 36.0, 25.3; ¹⁹F NMR (376 MHz, CDCl₃) δ: -112.14 (s); HRMS (ESI) calcd for C₁₉H₁₆FN₂O₂ [M + H]⁺ 323.1190, found 323.1194.

3-(2-(4-Chlorophenyl)-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (**3ha**): Pale red solid. 25.6 mg, 76% yield. m.p. 217~219 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.21 (s, 1H), 7.59~7.56 (m, 2H), 7.48~7.45 (m, 2H), 7.39 (d, *J*=7.8 Hz, 1H), 7.26~7.21 (m, 1H), 7.16 (t, *J*=7.7 Hz, 1H), 7.13~7.09 (m, 1H), 4.33 (t, *J*=7.4 Hz, 1H), 3.15 (s, 3H), 3.12 (d, *J*=7.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 178.8, 176.7, 136.4, 136.1, 134.9, 130.3, 130.1, 129.4, 126.0, 123.1, 120.7, 118.3, 111.7, 108.2, 37.8, 36.0, 25.3; HRMS (ESI) calcd for C₁₉H₁₆ClN₂O₂ [M + H]⁺ 339.0895, found 339.0899.

3-(2-(4-Bromophenyl)-1*H*-indol-3-yl)-1-methylpyrro-

lidine-2,5-dione (**3ia**): Pale red solid. 32.3 mg, 85% yield. m.p. 237~239 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.22 (s, 1H), 7.62~7.60 (m, 2H), 7.52~7.49 (m, 2H), 7.39 (d, *J*=8.2 Hz, 1H), 7.25~7.21 (m, 1H), 7.16 (t, *J*=7.7 Hz, 1H), 7.13~7.09 (m, 1H), 4.33 (t, *J*=7.4 Hz, 1H), 3.15 (s, 3H), 3.11 (d, *J*=7.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 178.8, 176.7, 136.4, 136.1, 132.3, 130.7, 130.3, 126.0, 123.1, 123.1, 120.7, 118.3, 111.7, 108.2, 37.8, 36.0, 25.3; HRMS (ESI) calcd for C₁₉H₁₆BrN₂O₂ [M + H]⁺ 383.0390, found 383.0392.

1-Methyl-3-(2-(4-(trifluoromethyl) phenyl)-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3ja**): White solid. 23.7 mg, 64% yield. m.p. 210~212 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.39 (s, 1H), 7.70 (s, 4H), 7.36 (d, *J*=8.2 Hz, 1H), 7.25~7.21 (m, 1H), 7.16 (t, *J*=7.6 Hz, 1H), 7.13~7.09 (m, 1H), 4.35 (t, *J*=7.6 Hz, 1H), 3.16 (s, 3H), 3.13 (d, *J*=7.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 178.8, 176.6, 136.3, 136.0, 135.3, 129.0, 126.1, 126.1, 126.0, 126.0, 125.9, 123.4, 120.9, 118.5, 111.8, 108.9, 37.8, 36.0, 25.3; ¹⁹F NMR (376 MHz, CDCl₃) δ: -62.61 (s); HRMS (ESI) calcd for C₂₀H₁₆F₃N₂O₂ [M + H]⁺ 373.1158, found 373.1159.

3-(2-(3-Fluorophenyl)-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (**3ka**): Pale red solid. 30.9 mg, 96% yield. m.p. 106~108 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.33 (s, 1H), 7.46~7.31 (m, 4H), 7.23~7.19 (m, 1H), 7.17~7.12 (m, 2H), 7.08 (dd, *J*=0.9, 7.9 Hz, 1H), 4.38 (dd, *J*=6.6, 8.2 Hz, 1H), 3.14 (s, 3H), 3.12 (t, *J*=6.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 178.9, 176.7, 136.2 (d, *J*=1.8 Hz), 136.1, 133.9 (d, *J*=7.9 Hz), 130.8, 130.7, 125.9, 124.5 (d, *J*=3.1 Hz), 123.1, 120.6, 118.3, 115.7 (d, *J*=3.2 Hz), 115.5 (d, *J*=1.5 Hz), 111.8, 108.2, 37.8, 36.1, 25.3; ¹⁹F NMR (376 MHz, CDCl₃) δ: -111.37 (s); HRMS (ESI) calcd for C₁₉H₁₆FN₂O₂ [M + H]⁺ 323.1190, found 323.1192.

Methyl-3-(6-methyl-2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3la**): White solid. 28.5 mg, 90% yield. m.p. 216~218 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.23 (s, 1H), 7.56~7.53 (m, 2H), 7.45~7.41 (m, 2H), 7.40~7.36 (m, 1H), 7.11 (s, 1H), 7.04~7.01 (d, *J*=8.1 Hz, 1H), 6.09 (dd, *J*=1.0, 8.1 Hz, 1H), 4.35 (t, *J*=7.1 Hz, 1H), 3.11 (s, 3H), 3.06 (d, *J*=7.6 Hz, 2H), 2.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 179.1, 176.9, 136.9, 136.5, 132.7, 132.0, 129.0, 128.7, 128.5, 123.9, 122.2, 117.8, 111.6, 107.5, 37.9, 36.2, 25.2, 21.7; HRMS (ESI) calcd for C₂₀H₁₉N₂O₂ [M + H]⁺ 319.1441, found 319.1444.

Methyl-3-(5-methyl-2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3ma**): White solid. 26.0 mg, 82% yield. m.p. 216~218 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.15 (s, 1H), 7.60~7.58 (m, 2H), 7.49~7.42 (m, 3H), 7.26 (t, *J*=8.4 Hz, 1H), 7.04~7.02 (dd, *J*=1.5, 8.4 Hz, 1H), 6.90 (d, *J*=0.8 Hz, 1H), 4.38 (t, *J*=7.6 Hz, 1H), 3.14 (s, 3H), 3.09 (d, *J*=7.6 Hz, 2H), 2.41 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 179.0, 176.9, 137.7, 134.4, 132.0, 129.8, 129.1, 128.6, 126.4, 124.4, 117.8, 111.3, 107.1, 37.9, 36.1, 25.3, 21.7; HRMS (ESI) calcd for C₂₀H₁₉N₂O₂ [M + H]⁺ 319.1441, found 319.1443.

3-(5-Fluoro-2-phenyl-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (**3na**): White solid. 30.1 mg, 89% yield. m.p. 108~110 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.27 (s, 1H), 7.59~7.56 (m, 2H), 7.51~7.44 (m, 3H), 7.30 (dd, *J*=4.5, 8.9 Hz, 1H), 6.98~6.93 (m, 1H), 6.80 (dd, *J*=2.3, 9.3 Hz, 1H), 4.36 (dd, *J*=5.5, 9.6 Hz, 1H), 3.14 (s, 3H), 3.11~2.99 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 178.8, 176.5, 158.0 (d, *J*=236.1 Hz), 139.4, 132.5, 131.5, 129.1, 128.9, 128.7, 126.4 (d, *J*=9.8 Hz), 112.4 (d, *J*=9.8 Hz), 111.1 (d, *J*=25.8 Hz), 107.7 (d, *J*=4.9 Hz), 103.5 (d, *J*=24.6 Hz), 37.7, 36.0, 25.3; ¹⁹F NMR (376 MHz, CDCl₃) δ: -122.66 (s); HRMS (ESI) calcd for C₁₉H₁₆F-N₂O₂ [M+H]⁺ 323.1190, found 323.1193.

3-(5-Chloro-2-phenyl-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (**3oa**): White solid. 27.7 mg, 82% yield. m.p. 122~124 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.27 (s, 1H), 7.59~7.56 (m, 2H), 7.51~7.44 (m, 3H), 7.30 (dd, *J*=4.5, 8.9 Hz, 1H), 6.98~6.93 (m, 1H), 6.80 (dd, *J*=2.3, 9.3 Hz, 1H), 4.36 (dd, *J*=5.5, 9.6 Hz, 1H), 3.14 (s, 3H), 3.11~2.99 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 178.6, 176.4, 139.1, 134.3, 131.4, 129.2, 129.1, 128.8, 127.2, 126.1, 123.2, 117.6, 112.6, 107.4, 37.7, 36.1, 25.4; HRMS (ESI) calcd for C₁₉H₁₆ClN₂O₂ [M+H]⁺ 339.0895, found 339.0897.

3-(5-Bromo-2-phenyl-1*H*-indol-3-yl)-1-methylpyrrolidine-2,5-dione (**3pa**): Pale red solid. 29.9 mg, 78% yield. m.p. 112~114 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.27 (s, 1H), 7.59~7.56 (m, 2H), 7.51~7.44 (m, 3H), 7.30 (dd, *J*=4.5, 8.9 Hz, 1H), 6.98~6.93 (m, 1H), 6.80 (dd, *J*=2.3, 9.3 Hz, 1H), 4.36 (dd, *J*=5.5, 9.6 Hz, 1H), 3.14 (s, 3H), 3.11~2.99 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 178.6, 176.3, 138.9, 134.6, 131.3, 129.2, 129.1, 128.8, 127.9, 125.7, 120.7, 113.7, 113.0, 107.3, 37.7, 36.1, 25.4; HRMS (ESI) calcd for C₁₉H₁₆BrN₂O₂ [M+H]⁺ 383.0390, found 383.0390.

1-Methyl-3-(1-methyl-2-phenyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3qa**): White solid. 29.5 mg, 94% yield. m.p. 165~168 °C; ¹H NMR (400 MHz, CDCl₃) δ: 7.52~7.48 (m, 5H), 7.36 (d, *J*=8.2 Hz, 1H), 7.28~7.21 (m, 2H), 7.11 (t, *J*=7.6 Hz, 1H), 4.16 (dd, *J*=5.5, 9.6 Hz, 1H), 3.14 (s, 3H), 3.11~2.99 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 179.0, 176.9, 135.5, 133.2, 126.0, 121.6, 119.9, 117.1 (2C), 110.9 (2C), 106.8, 37.7, 36.2, 25.2, 11.6.

1-Methyl-3-(2-methyl-1*H*-indol-3-yl)pyrrolidine-2,5-dione (**3ra**): White solid. 7.3 mg, 52% yield. m.p. 108~110 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.17 (s, 1H), 7.23 (d, *J*=8.0 Hz, 2H), 7.12~7.08 (m, 1H), 7.07~7.00 (m, 2H), 4.18 (dd, *J*=5.2, 9.6 Hz, 1H), 3.20~3.13 (m, 4H), 2.99~2.90 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 179.0, 176.9, 135.5, 133.2, 126.0, 121.6, 119.9, 117.1, 110.9, 106.8, 37.7, 36.2, 25.2, 11.6.

Supporting Information ¹H NMR, ¹⁹F NMR and ¹³C NMR spectra of the **3aa**~**3ah** and **3ba**~**3ra**, and X-ray crystallographic data of **3aa**. The Supporting Information is available free of charge via the Internet at

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