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Regioselective Friedel–Crafts Reactions of N-Substituted Glyoxylamide with Indoles Catalyzed by Brønsted Acid

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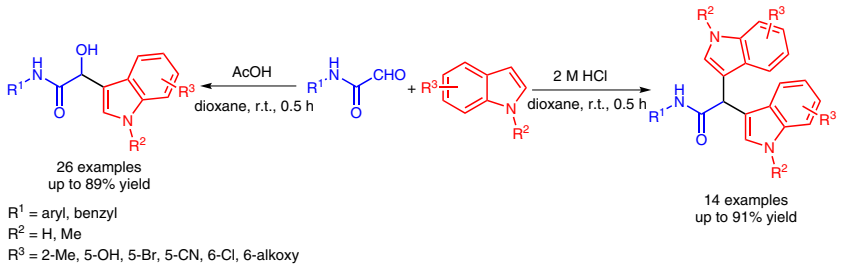
Dedicated with admiration to Professor K. Peter C. Vollhardt



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Abstract An efficient regioselective Friedel–Crafts reaction of a series of N-substituted glyoxylamide with indoles catalyzed by Brønsted acid was developed. The reactions proceeded smoothly at room temperature and the corresponding N-substituted 2-hydroxy-2-(1*H*-indol-3-yl) acetamides were afforded in moderate to good yields (up to 89%). When 2 M HCl was used, the bisindole compounds were obtained in good to excellent yield (up to 91%) resulting from a double Friedel–Crafts reaction.

Key words regioselective Friedel–Crafts reaction, Brønsted acid, N-substituted glyoxylamide, indole, N-substituted 2-hydroxy-2-(1*H*-indol-3-yl) acetamide, bisindole compound

From the early days of pharmaceutical science, indole is a key structural unit existing in a variety of natural products and drug candidates.[1] Notably, C3-substituted indole is one of the most important structural motif present in a vast array of biologically active natural products and pharmaceuticals (Figure 1).[2] The C3 substituted indole derivatives, in particular containing 1-hydroxy-1-(1*H*-indol-3-yl)propan-2-one structure moiety is an emerging new scaffold for drug discovery with a broad spectrum of biological activities including antidiabetic, analgesic, antibacterial, antitubercular, anti-inflammatory, antiangiogenic, antifungal, anticonvulsant, and some are treated as the new targets for cancer chemotherapy.[3]

Therefore, there has been a strong demand for the development of efficient methods to form the C3-functionalized indoles that contain the 1-hydroxy-1-(1*H*-indol-3-yl)propan-2-one structure moiety. Many methods have been developed for the synthesis of 1-hydroxy-1-(1*H*-indol-3-yl)propan-2-one derivatives[4] and the bisindole compounds,[5] among them Friedel–Crafts reaction, which could introduce the new carbon–carbon bond, is an important way.[6,7]

As 3-indolyl-3-hydroxy oxindole and trisindoline (Figure 2), and their derivatives, have a broad spectrum of interesting biological activities, a variety of studies on their

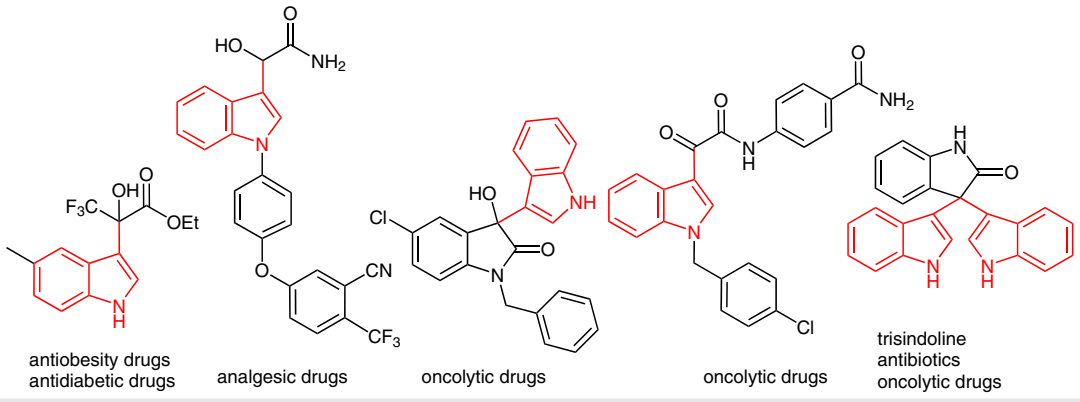


Figure 1 Selected biologically active molecules containing C3-functionalized indole moiety

synthesis methods and biological activities were reported.[8,9] However, to the best of our knowledge, the synthesis and bioactivity for their open-chain analogues N-substituted 2-hydroxy-2-(1*H*-indol-3-yl) acetamide and the bisindole compounds have not yet been reported. Herein, we report our study on the Brønsted acid catalyzed regioselective Friedel–Crafts reaction of N-substituted glyoxylamide with indoles to afford the N-substituted 2-hydroxy-2-(1*H*-indol-3-yl) acetamide and the bisindole compounds.

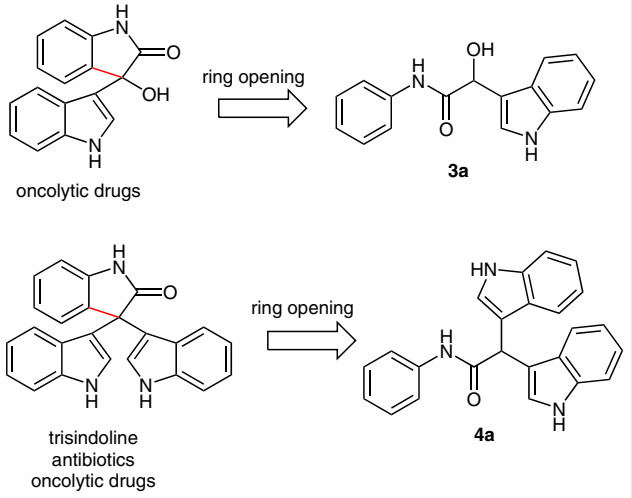


Figure 2 3-Indolyl-3-hydroxy oxindole, trisindoline, and their templates used for structural modification

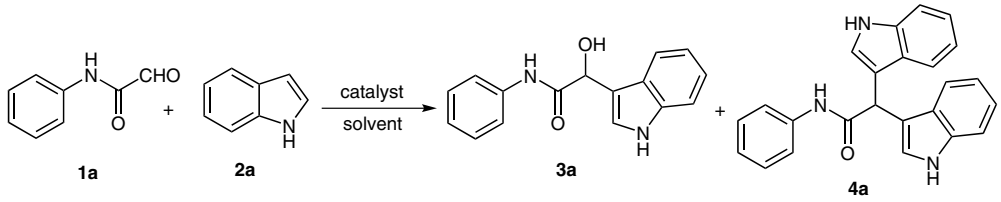
In the exploratory study of our newly proposed Friedel–Crafts reaction for the preparation of N-substituted 2-hydroxy-2-(1*H*-indol-3-yl) acetamide, we carried out a first experiment by reacting *N*-phenyl glyoxylamide (**1a**) with indole (**2a**) in the presence of $PhCO_2H$ in dioxane at room temperature (Table 1, entry 1).[10] To our delight, the desired 2-hydroxy-2-(1*H*-indol-3-yl)-*N*-phenyl acetamide (**3a**) was isolated in 76% yield. And another side product was found. Separation and confirmation of this side product suggested it was the bisindole product **4a**, as shown in Table 1. However, poor selectivity was found when a mixture of *N*-phenyl glyoxylamide with indole was treated under $PhCO_2H$ conditions. We hypothesized that the reaction selectivity could be controlled by using an appropriate Brønsted acid catalyst. Therefore, we were interested in looking for an efficient and highly selective Brønsted acid as the catalyst in the synthesis of **3a** and **4a**, respectively.

To begin our investigation, *N*-phenyl glyoxylamide (**1a**) and indole (**2a**) were chosen as the reaction substrates in the model reaction. As shown in Table 1, both catalyst and solvent had dramatic effects on this regioselective Friedel–Crafts reaction. Generally, *N*-phenyl glyoxylamide (**1a**) was reacted with indole (**2a**) at room temperature and afforded a mixture of 2-hydroxy-2-(1*H*-indol-3-yl)-*N*-phenylacetamide (**3a**) and bisindole product **4a**. Various Brønsted acid such as $PhCO_2H$, PTSA, $(CO_2H)_2$, concd HCl, HCl (2mol/L), H_3PO_4, CF_3SO_3H, $ClCH_2CO_2H$, TFA, HCO_2H, and AcOH were used (Table 1, entries 1–11). The good selectivity for **3a** was obtained by using AcOH as catalyst (Table 1, entry 11), while the formation of **4a** was nearly not observed. When the catalytic amount of concd HCl, HCl (2 mol/L), H_3PO_4, or CF_3SO_3H was employed in the reaction, only **4a** was forming rapidly and isolated (Table 1, entries 4–7) in good yield.

In addition, the screening of solvent (Table 1, entries 11–19) led to the discovery that dioxane was most suitable (Table 1, entries 11–19). Further optimization by changing the amount of AcOH revealed that, to our delight, when the addition of AcOH decreased to 5 mmol, the best result was obtained (Table 1, entry 21, 84% yield) while 1 mmol AcOH led to the incompletion of the reaction (Table 1, entry 20). Although prolonging the reaction time to 24 hours to go to completion, the product **3a** decreased a little (Table 1, entry 22). Further increasing the reaction temperature to 50 °C and even higher to 80 °C, **3a** did not increase and the reaction became complicated (Table 1, entries 23 and 24). In a word, we could selectively get the product **3a** with 84% yield by using AcOH as catalyst and dioxane as the solvent and **4a** with 89% yield by using HCl (2 mol/L) as catalyst and dioxane as the solvent.

With the optimal catalytic conditions in hand, we consequently investigated the substrate scope of the reaction. A series of regioselective Friedel–Crafts reactions of N-substituted glyoxylamide with indoles proceeded smoothly to give the corresponding products in high yields. The results are summarized in Table 2. Among various tested substrates, both electron-donating substituents such as Me and OMe at the 4-position of the benzene ring (Table 2, entries 2, 3) and electron-withdrawing substituents such as Cl, NO_2 at the 4-position (Table 2, entries 4, 6) or Cl at the 3,5-positions of the benzene ring (Table 2, entry 5) could be tolerated, and the corresponding products **3b**–**f** were isolated in moderate to good yields. Moderate yields of *N*-phenyl glyoxylamide derivatives owing electron-donating groups linked to the benzene ring were obtained (**3b**,**c**), while *N*-phenyl glyoxylamide derivatives owing electron-withdrawing groups linked to the benzene ring resulted in good yields (**3d**–**f**). These results suggested that the reactivity of the *N*-phenyl glyoxylamide derivative substrates was influenced by the electronic property of the substituent of the benzene ring of *N*-phenyl glyoxylamide derivatives. The reactivity of *N*-phenyl glyoxylamide derivatives could be reduced by an electron-donating group linked to the benzene ring. To further define the scope of this transformation, a wide range of *N*-phenyl glyoxylamide derivatives and indoles containing different substituents at the 1-, 2-, 5-, or 6-positions were reacted under the optimized reaction conditions. Indoles containing electron-withdrawing groups resulted in only moderate yields (**3i**–**o**), while good to excellent yields of indoles with electron-donating groups were obtained in most cases (**3p**–**z**). However, N-substituted gly-

Table 1 Screening Studies for the Regioselective Friedel–Crafts Reaction of *N*-Phenyl Glyoxylamide with Indole[a]



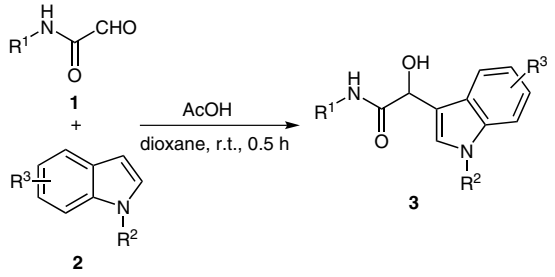
Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	$PhCO_2H$	dioxane	25	0.5	76	8
2	PTSA	dioxane	25	0.5	6	77
3	$(CO_2H)_2$	dioxane	25	0.5	42	35
4[c]	concd HCl	dioxane	25	0.5	trace	87
5[c]	HCl (2 mol/L)	dioxane	25	0.5	trace	89
6[c]	H_3PO_4	dioxane	25	0.5	trace	83
7[c]	CF_3SO_3H	dioxane	25	0.5	trace	85
8	$ClCH_2CO_2H$	dioxane	25	0.5	53	25
9	TFA	dioxane	25	0.5	8	82
10	HCO_2H	dioxane	25	0.5	69	12
11	AcOH	dioxane	25	0.5	81	trace
12	AcOH	EtOH	25	0.5	80	4
13	AcOH	MeCN	25	0.5	72	6
14	AcOH	DMSO	25	0.5	36	23
15	AcOH	THF	25	0.5	76	6
16	AcOH	acetone	25	0.5	79	4
17	AcOH	toluene	25	0.5	68	14
18	AcOH	CH_2Cl_2	25	0.5	76	8
19	AcOH	EtOAc	25	0.5	78	7
20[d]	AcOH	dioxane	25	0.5	67	trace
21[e]	AcOH	dioxane	25	0.5	84	trace
22[e]	AcOH	dioxane	25	24	82	trace
23[e]	AcOH	dioxane	50	0.5	64	15
24[e]	AcOH	dioxane	80	0.5	38	31

[a] Unless noted otherwise, reactions were performed with *N*-phenyl glyoxylamide (**1a**, 1 mmol), indole (**2a**, 1.1 mmol), and catalyst (10 mmol) in solvent (8 mL).
[b] Isolated yield.
[c] Conditions: 0.1 mmol catalyst was added.
[d] Conditions:1 mmol AcOH was added.
[e] Conditions:5 mmol AcOH was added.

oxylamide even the *N*-(4-nitrophenyl)glyoxylamide whose reactivity was preferable could not be reacted with indoles containing the strong electron-withdrawing groups such as CN or CO_2Me at the 5-position (Table 2, entries 14, 15). These results suggested that the reactivity of the indole substrate was remarkably influenced by the electronic property of the substituent of the indole. The reactivity of the indole substrate could be reduced by an electron-withdrawing group linked to indole. Therefore, these results clearly demonstrated that AcOH served as a useful Brønsted acid catalyst for the N-substituted glyoxylamide and indoles to produce the corresponding N-substituted 2-hydroxy-2-(1*H*-indol-3-yl) acetamide.

Furthermore, with optimized conditions in hand, a series of bisindole compounds resulting from the regioselective Friedel–Crafts reactions were carried out. The results were summarized in Table 3. Among various tested substrates, *N*-phenyl glyoxylamide derivatives with either electron-donating (**4b**,**c**) or electron-withdrawing substituents

Table 2 Substrate Scope in Regioelective Friedel–Crafts Reaction of N-Substituted Glyoxylamide with Indoles[a]

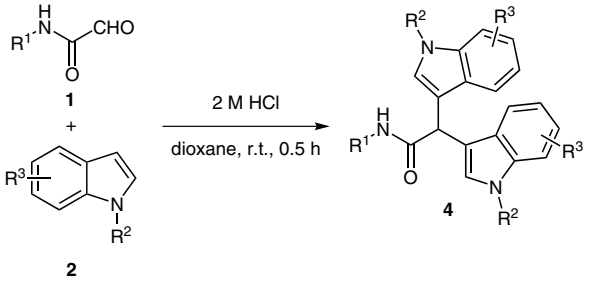


Entry	R^1	R^2	R^3	Product **3**	Yield (%)[b]
1	Ph	H	H	**3a**	84
2	4-MeC_6H_4	H	H	**3b**	71
3	4-$MeOC_6H_4$	H	H	**3c**	73
4	4-ClC_6H_4	H	H	**3d**	84
5	3,5-$Cl_2C_6H_3$	H	H	**3e**	82
6	4-$O_2NC_6H_4$	H	H	**3f**	86
7	Bn	H	H	**3g**	88
8	2-naphthyl	H	H	**3h**	79
9	Ph	H	6-Cl	**3i**	75
10[c]	4-MeC_6H_4	H	6-Cl	**3j**	66
11	4-ClC_6H_4	H	6-Cl	**3k**	73
12	4-$O_2NC_6H_4$	H	6-Cl	**3l**	78
13[c]	4-$O_2NC_6H_4$	H	5-Br	**3m**	63
14	4-$O_2NC_6H_4$	H	5-CN	–	n.r.[d]
15	4-$O_2NC_6H_4$	H	5-CO_2Me	–	n.r.[d]
16[c]	3,5-$Cl_2C_6H_3$	H	6-Cl	**3n**	61
17	Bn	H	6-Cl	**3o**	82
18	Ph	Me	6-OCH_2CO_2Et	**3p**	81
19	4-MeC_6H_4	H	5-OH	**3q**	85
20	4-MeC_6H_4	Me	6-OCH_2CO_2Et	**3r**	82
21	4-ClC_6H_4	H	2-Me	**3s**	83
22	4-ClC_6H_4	H	5-OH	**3t**	89
23	4-ClC_6H_4	Me	6-OCH_2CO_2Et	**3u**	86
24	4-ClC_6H_4	Me	6-OCH_2CONH_2	**3v**	81
25	4-BrC_6H_4	H	5-OH	**3w**	84
26	4-$O_2NC_6H_4$	Me	6-OCH_2CO_2Et	**3x**	86
27	3,5-$Cl_2C_6H_3$	Me	6-OCH_2CO_2Et	**3y**	80
28	Bn	Me	6-OCH_2CO_2Et	**3z**	85

[a] Unless noted otherwise, reactions were performed with N-substituted glyoxylamide **1** (1 mmol), indoles **2** (1.1 mmol) and AcOH (5 mmol) in dioxane (8 mL) at 25 °C for 0.5 h.
[b] Isolated yield.
[c] Reaction time was 5 h.
[d] No reaction.

(**4d**–**g**) on the benzene ring could be tolerated, and the corresponding products were isolated in good yields. The reactivity of the regioselective Friedel–Crafts reaction could be reduced by an electron-withdrawing group linked to the 5- or 6-position of indole.

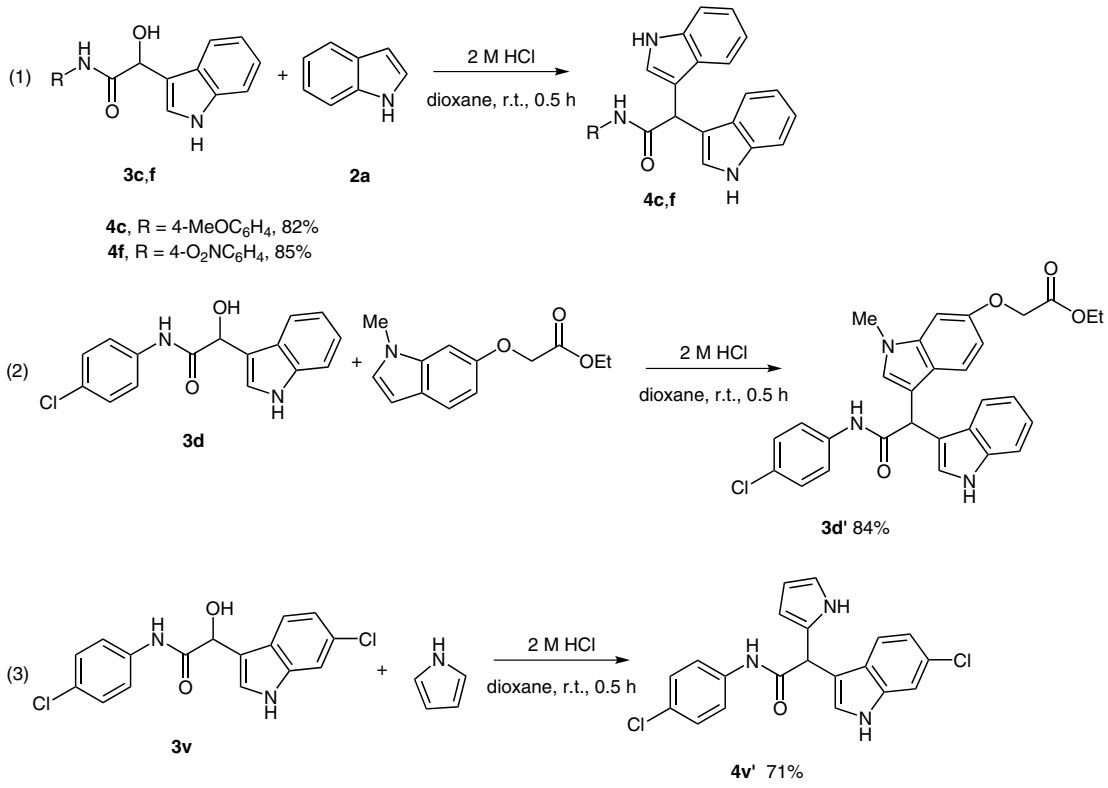
Table 3 Substrate Scope in Double Friedel–Crafts Reaction of N-Substituted Glyoxylamide with Indoles[a]



Entry	R^1	R^2	R^3	Product **4**	Yield (%)[b]
1	Ph	H	H	**4a**	89
2	3,5-$MeO_2C_6H_3$	H	H	**4b**	82
3	4-$MeOC_6H_4$	H	H	**4c**	76
4	4-ClC_6H_4	H	H	**4d**	85
5	3-ClC_6H_4	H	H	**4e**	80
6	4-$O_2NC_6H_4$	H	H	**4f**	88
7	3,5-$Cl_2C_6H_3$	H	H	**4g**	83
8	2-naphthyl	H	H	**4h**	79
9	4-MeC_6H_4	H	6-Cl	**4i**	74
10	4-MeC_6H_4	H	5-CN	**4j**	69
11	4-$MeOC_6H_4$	H	6-Cl	**4k**	71
12	4-$O_2NC_6H_4$	H	5-CN	**4l**	72
13	4-ClC_6H_4	H	2-Me	**4m**	89
14	Bn	Me	6-OCH_2CO_2Et	**4n**	87

[a] Unless noted otherwise, reactions were performed with N-substituted glyoxylamide **1** (1 mmol), indoles **2** (2 mmol), and HCl (2 mol/L, 0.1 mmol) in dioxane (8 mL) at 25 °C for 0.5 h.
[b] Isolated yield.

Moreover, the product **3** could also be transformed to **4** in the presence of a catalytic amount of HCl (2 mol/L) at room temperature. For example, **3c** and **3f** were reacted with indole and catalyzed by HCl (2 mol/L) at room temperature to afford the corresponding bisindole products **4c** and **4f** in high yields. And then, a series of different-substituted bisindole products could be obtained in the presence of **3**. For example, **3d** was reacted with ethyl 2-[(1-methyl-1*H*-indol-6-yl)oxy]acetate to afford the corresponding different substituted bisindole products **3d′**. Furthermore, **3v** could be reacted with pyrrole and catalyzed by the catalytic amount of HCl (2 mol/L) at room temperature to afford **4v′** (Scheme 1).



Scheme 1 Applications of the regioselective Friedel–Crafts reactions

In conclusion, we have demonstrated a mild and highly efficient system for the regioselective Friedel–Crafts reaction of N-substituted glyoxylamide[11] with indoles.[12] The reactions[13] proceed well for various indoles, and the Friedel–Crafts adducts are obtained in high yields. We anticipate such reactions to be a straightforward and practical way to prepare various N-substituted 2-hydroxy-2-(1*H*-indol-3-yl) acetamide and 2,2-di(1*H*-indol-3-yl)-*N*,*N*-phenylacetamide derivatives. Further work is in progress to develop catalytic enantioselective Friedel–Crafts reactions and bioactivity of the bisindole compounds.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560462.

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(12) Indoles **2** were purchased from ASTATECH and J&K Scientific Ltd. except ethyl 2-[(1-methyl-1*H*-indol-6-yl)oxy]acetate and 2-[(1-methyl-1*H*-indol-6-yl) oxy]acetamide. Ethyl 2-[(1-methyl-1*H*-indol-6-yl)oxy]acetate was synthesized according to the literature procedures, see: (a) Finefield, J. M.; Williams, R. M. *J. Org. Chem.* **2010**, *75*, 2785. (b) Akao, A.; Nonoyama, N.; Mase, T.; Yasuda, N. *Org. Process Res. Dev.* **2006**, *10*, 1178. (c) Choy, P. Y.; Lau, C. P.; Kwong, F. Y. *J. Org. Chem.* **2011**, *76*, 80. (d) Ontoria, J. M.; Marco, S. D.; Conte, I.; Francesco, M. E. D.; Gardelli, C.; Koch, U.; Matassa, V. G.; Poma, M.; Steinkühler, C.; Volpari, C.; Harper, S. *J. Med. Chem.* **2004**, *47*, 6443. 2-[(1-methyl-1*H*-indol-6-yl) oxy]acetamide was synthesized from ethyl 2-[(1-methyl-1*H*-indol-6-yl)oxy]acetate according to the literature procedures, see: (e) Kreutter, K. D.; Lu, T. B.; Lee, L.; Giardino, E. C.; Patel, S.; Huang, H.; Xu, G. Z.; Fitzgerald, M.; Haertlein, B. J.; Mohan, V.; Crysler, C.; Eisennagel, S.; Dasgupta, M.; McMillan, M.; Spurlino, J. C.; Huebert, N. D.; Maryanoff, B. E.; Tomczuk, B. E.; Damiano, B. P.; Player, M. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2865.

(13) **N-Substituted 2-Hydroxy-2-(1*H*-indol-3-yl) Acetamides 3; General Procedure**

To a stirred mixture of N-substituted glyoxylamide (1.0 mmol), indoles (1.1 mmol) in dioxane (8 mL) was added AcOH (5.0 mmol) at 25 °C for 0.5 h. After the completion of the reaction (monitored by TLC), the mixture was diluted with H_2O and extracted with EtOAc (4 × 20 mL). The organic layer was washed with sat. brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated to dryness. The crude residue was purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 80:1) to afford pure N-substituted 2-hydroxy-2-(1*H*-indol-3-yl) acetamides **3** (61–89% yield).

2,2-Di(1*H*-indol-3-yl)-*N*,*N*-phenyl Acetamide Derivatives 4; General Procedure

To a stirred mixture of N-substituted glyoxylamide (1.0 mmol), indoles (2.0 mmol) in dioxane (8 mL) was added HCl (2 mol/L, 0.1 mmol) at 25 °C for 0.5 h. After completion of the reaction (monitored by TLC), the mixture was diluted with H_2O and extracted with EtOAc (3 × 20 mL). The organic layer was washed with sat. brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated to dryness. The crude residue was purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 100:1) to afford pure 2,2-di(1*H*-indol-3-yl)-*N*,*N*-phenyl acetamide derivatives **4** (69–91% yield).

Analytical Data of Some Typical Compounds

2-Hydroxy-2-(1*H*-indol-3-yl)-*N*-phenylacetamide (3a)

Yield 84%; yellow solid, mp 150–152 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.00 (s, 1 H), 9.90 (s, 1 H), 7.70 (s, 3 H), 7.33–7.28 (m, 4 H), 7.03–6.96 (m, 3 H), 6.08 (s, 1 H), 5.32 (s, 1 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 171.9, 138.9, 136.6, 128.8, 128.0, 126.0, 124.3, 123.6, 121.4, 119.9, 118.9, 114.8, 111.7, 68.9. ESI-HRMS: *m/z* [M + Na^+] calcd for $C_{16}H_{14}N_2O_2Na$: 289.0947; found: 289.0961. Anal. Calcd: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.10; H, 5.35; N, 10.53.

2,2-Di(1*H*-indol-3-yl)-*N*-phenylacetamide (4a)

Yield 89%; yellow solid, mp 139–141 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.90 (s, 2 H), 10.34 (s, 1 H), 7.65–7.57 (m, 4 H), 7.35 (m, 2 H), 7.28 (t, *J* = 8.0 Hz, 2 H), 7.19 (s, 2 H), 7.07–7.00 (m, 3 H), 6.95 (t, *J* = 8.0 Hz, 2 H) 5.55 (s, 1 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 171.0, 138.9, 137.0, 128.8, 126.9, 126.1, 124.1, 121.5, 120.4, 119.3, 118.0, 112.8, 111.0, 42.0. ESI-HRMS: *m/z* [M + Na^+]: calcd for $C_{24}H_{19}N_3ONa$: 388.1420; found: 388.1425. Anal. Calcd: C, 78.88; H, 5.24; N, 11.50. Found: C, 78.79; H, 4.23; N, 9.49.

2-[(3-{2-[(4-chlorophenyl)amino]-1-(1*H*-indol-3-yl)-2-oxoethyl}-1-methyl-1*H*-indol-6-yl)oxy]acetate (3d′)

Yield 84%; brown solid, mp 194–196 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.92 (s, 1 H), 10.47 (s, 1 H), 7.67 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 1 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.36–7.18 (m, 2 H), 7.18 (m, 1 H), 7.07–7.04 (m, 2 H), 6.96–6.94 (m, 2 H), 6.69–6.67 (m, 1 H), 5.48 (s, 1 H), 4.77 (s, 2 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 3.67 (s, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 171.9, 169.2, 154.5, 139.3, 137.8, 136.9, 132.5, 131.0, 128.5, 127.0, 122.9, 122.1, 121.6, 121.0, 120.7, 119.8, 112.5, 109.9, 98.6, 65.6, 42.6, 40.7, 32.4, 14.2. ESI-HRMS: *m/z* [M + Na^+] calcd for $C_{29}H_{26}ClN_3O_4Na$: 538.1504; found: 538.1501. Anal. Calcd: C, 67.50; H, 5.08; N, 8.14. Found: C, 67.56; H, 5.00; N, 8.19.