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A FACILE SYNTHESIS OF SYMMETRICAL AND UNSYMMETRICAL BIS(INDOLYL)ACETAMIDES MEDIATED BY PROTIC ACID

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Abstract – We report the preparation of symmetrical bis(indolyl)acetamides using the dimerization of 2-hydroxy-(2-indolyl)acetamides and unsymmetrical bis(indolyl)acetamides *via* electrophilic substitution of indoles with 2-hydroxy-(2-indolyl)acetamides. Both conversions were mediated by protic acid in THF at room temperature.

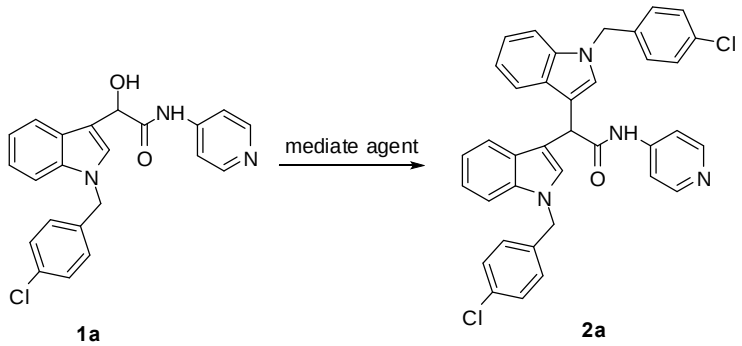
INTRODUCTION

Bis(indolyl)alkanes are one of the most important classes of bioactive compounds.[1] Therefore, improved syntheses of both symmetrical and unsymmetrical bis(indolyl)alkanes have been developed.[2] Generally, symmetrical bis(indolyl)alkanes are obtained from the condensation of indoles with aldehydes or ketones in the presence of protic or Lewis acids.[3] Recently, several unsymmetrical bis(indolyl)alkanes have been synthesized using $ClSiMe_3$ catalysis,[4,5] TLC-grade silica gel under microwave irradiation,[6] and ceric ammonium nitrate (CAN) under ultrasonic irradiation.[7] However, there is no report on the biological activity of bis(indolyl)acetamides and synthesis of bis(indolyl)acetamides has only rarely been reported.[8] Owing to the similar structures of bis(indolyl)alkanes and bis(indolyl)acetamides (two indole or substituted indole units in a molecule), we consider that to develop a facile method for the preparation of bis(indolyl)acetamides and to investigate their biological activity are of some significance. Herein, we report a facile preparation of symmetrical bis(indolyl)acetamides using the dimerization of 2-hydroxy-(2-indolyl)acetamides and unsymmetrical bis(indolyl)acetamides *via* electrophilic substitution of indoles with 2-hydroxy-(2-indolyl)acetamides.

RESULTS AND DISCUSSION

Our research began with the observation that the dimerization of 2-hydroxy-(2-indolyl)acetamide **1a** mediated by HBr in THF afforded symmetrical bis(indolyl)acetamide **2a** (Table 1, Entry 2). First, we investigated the effects of a variety of protic and Lewis acids on this reaction using **1a** as a model compound. The reaction was very sluggish when concentrated HCl was used as a mediate agent; **1a** still remained after 72 h (as monitored by TLC). Reactions mediated by $AlCl_3$, $BF_3{\cdot}Et_2O$ and TsOH gave low to moderate yields, while no reaction occurred when acetic acid was used as a mediate agent. Surprisingly, H_2SO_4 promoted the reaction in moderate yield in only 10 min, while HNO_3 required long reaction time but provided a better yield. Next, we investigated the solvent effects on the H_2SO_4-mediated reaction. A trace amount of **2a** was obtained in CH_2Cl_2, while no desired product was given in $MeNO_2$. The reaction proceeded slowly to give **2a** in 15.4% yield with residual **1a** in CS_2. No bis(indolyl)acetamide **2a** was obtained when MeOH and EtOH were used as the solvent, but etherification of **1a** with the alcohols was observed (Table 1 and Scheme 1).

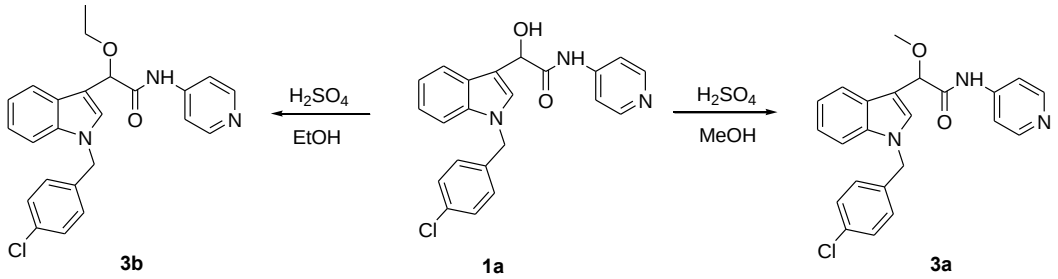
Table 1. Mediate agent and solvent screening for the synthesis of bis(indolyl)acetamide **2a**[a]



1a **2a**

Entry	Mediate agent	Solvent	Time(h)	Yield(%)[b]
1	None	THF	48	n.r.[c]
2	HBr	THF	1	55.4
3	HCl	THF	72	40.0[d]
4	$AlCl_3$	THF	11	26.7
5	$BF_3{\cdot}Et_2O$	THF	6	58.1
6	AcOH	THF	48	n.r.[c]
7	TsOH	THF	10	48.6
8	HNO_3	THF	48	73.3
9	H_2SO_4	THF	10 min	66.7
10	H_2SO_4	CH_2Cl_2	36	trace
11	H_2SO_4	$MeNO_2$	1	n.d.[e]
12	H_2SO_4	CS_2	48	15.4[d]
13	H_2SO_4	MeOH	1	n.d.[e]
14	H_2SO_4	EtOH	1	n.d.[e]

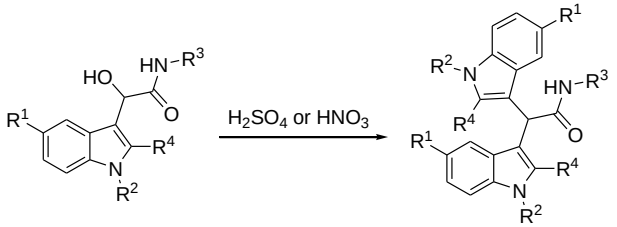
[a]Reaction conditions: **1a** (0.5 mmol) and mediate agent (1.0 mmol) in solvent (5 mL) at room temperature. [b]Isolated yield. [c]No reaction. [d]Starting material remained. [e]No desired product.



Scheme 1. Etherification of **1a** with MeOH and EtOH

Based on the above results, we explored the scope of this dimerization using various 2-hydroxy-(2-indolyl)acetamides mediated by H_2SO_4 or HNO_3 in THF. As is shown in Table 2, 2-hydroxy-(2-indolyl)acetamides, including those with bromo substituents on the indole ring, proved to be good substrates mediated by H_2SO_4 (Table 2, Entries 4 and 5). However, the H_2SO_4-mediated reactions of 2-hydroxy-(2-indolyl)acetamides with indole rings unsubstituted at the N-atom gave complex mixtures with no desired products (Table 2, Entries 3 and 6). HNO_3 was able to mediate the reactions of 2-hydroxy-(2-indolyl)acetamides with indole rings unsubstituted at the N-atom but failed for those with bromo-substituted and *N*-substituted indole rings.

Table 2. Synthesis of symmetrical bis(indolyl)acetamides **2a**-**2g** mediated by H_2SO_4 and HNO_3[a]



1a-1g 2a-2g

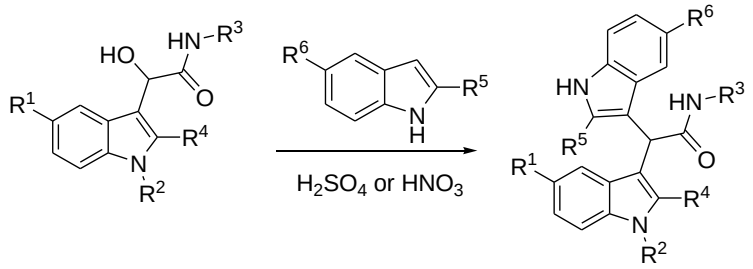
Entry	**2**	R^1	R^2	R^3	R^4	Mediate agent	Time	Yield (%)[b]
1	**2a**	H	4-$ClC_6H_4CH_2$	4-C_5H_4N	H	H_2SO_4	10 min	66.7
						HNO_3	48 h	73.3
2	**2b**	H	Me	4-C_5H_4N	H	H_2SO_4	6 h	22.8
						HNO_3	48 h	30.8
3	**2c**	H	H	4-C_5H_4N	H	H_2SO_4	2 h	n.d.[c]
						HNO_3	4 h	47.3
4	**2d**	Br	4-$ClC_6H_4CH_2$	4-C_5H_4N	H	H_2SO_4	1 h	93.5
						HNO_3	48 h	n.r.[d]
5	**2e**	Br	Me	4-C_5H_4N	H	H_2SO_4	10 min	85.7
						HNO_3	48 h	n.r.[d]
6	**2f**	Br	H	4-C_5H_4N	H	H_2SO_4	2 h	n.d.[c]
						HNO_3	24 h	75.0
7	**2g**	H	4-$ClC_6H_4CH_2$	CMe_3	H	H_2SO_4	3 h	44.1
						HNO_3	24 h	60.0

[a]Reaction conditions: **1** (0.5 mmol) and mediate agent (1.0 mmol) in THF (5 mL) at room temperature. [b]Isolated yield. [c]No desired product. [d]No reaction.

We speculated that symmetrical bis(indolyl)acetamides were obtained *via* an electrophilic substitution reaction. To provide support for our speculation and increase the diversity of bis(indolyl)acetamides, we

attempted to synthesize unsymmetrical bis(indolyl)acetamides through electrophilic substitution reactions of indoles with 2-hydroxy-(2-indolyl)acetamides. Unsymmetrical bis(indolyl)acetamide **4a** was obtained in 20.4% yield, together with the symmetrical bis(indolyl)acetamide **2a** in 44.3% yield, when mediated by H_2SO_4 at room temperature using a 1:2 molar ratio of indole to **1a**. However, when the molar ratio of indole and **1a** was adjusted to 1:1, unsymmetrical bis(indolyl)acetamide **4a** was obtained in 67.3% yield, with only a trace amount of symmetrical bis(indolyl)acetamide **2a**. Based on this reaction, unsymmetrical bis(indolyl)acetamides **4a**-**4g** were synthesized in moderate to excellent yields *via* the reaction of 2-hydroxy-(2-indolyl)acetamides with substituted indoles in a 1:1 molar ratio (Table 3 and Table 4). It was observed that the substitution reaction of the 3-methylindole occurred exclusively at the 2-position.

Table 3. Synthesis of unsymmetrical bis(indolyl)acetamides **4a**-**4e** mediated by H_2SO_4 and HNO_3[a]

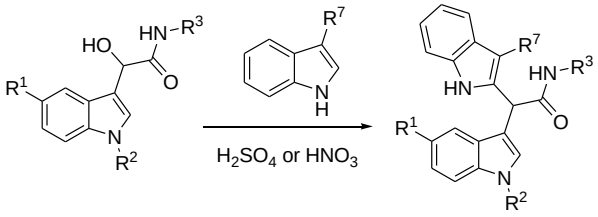


1a, 1g, and 1h **4a-4e**

Entry	**4**	R^1	R^2	R^3	R^4	R^5	R^6	Mediate agent	Time	Yield (%)[b]
1	**4a**	H	4-$ClC_6H_4CH_2$	4-C_5H_4N	H	H	H	H_2SO_4	10 min	67.3
								HNO_3	24 h	69.4
2	**4b**	H	4-$ClC_6H_4CH_2$	4-C_5H_4N	H	Me	H	H_2SO_4	10 min	55.6
								HNO_3	40 h	76.6
3	**4c**	H	4-$ClC_6H_4CH_2$	4-C_5H_4N	H	H	Br	H_2SO_4	0.5 h	82.5
								HNO_3	72 h	73.7
4	**4d**	H	H	4-C_5H_4N	Me	H	H	H_2SO_4	10 min	63.2
								HNO_3	4 h	84.2
5	**4e**	H	4-$ClC_6H_4CH_2$	CMe_3	H	H	H	H_2SO_4	10 min	85.1
								HNO_3	9 h	63.8

[a]Reaction conditions: **1** (0.5 mmol), indole or substituted indoles (0.5 mmol) and mediate agent (1.0 mmol) in THF (5 mL) at room temperature. [b]Isolated yield.

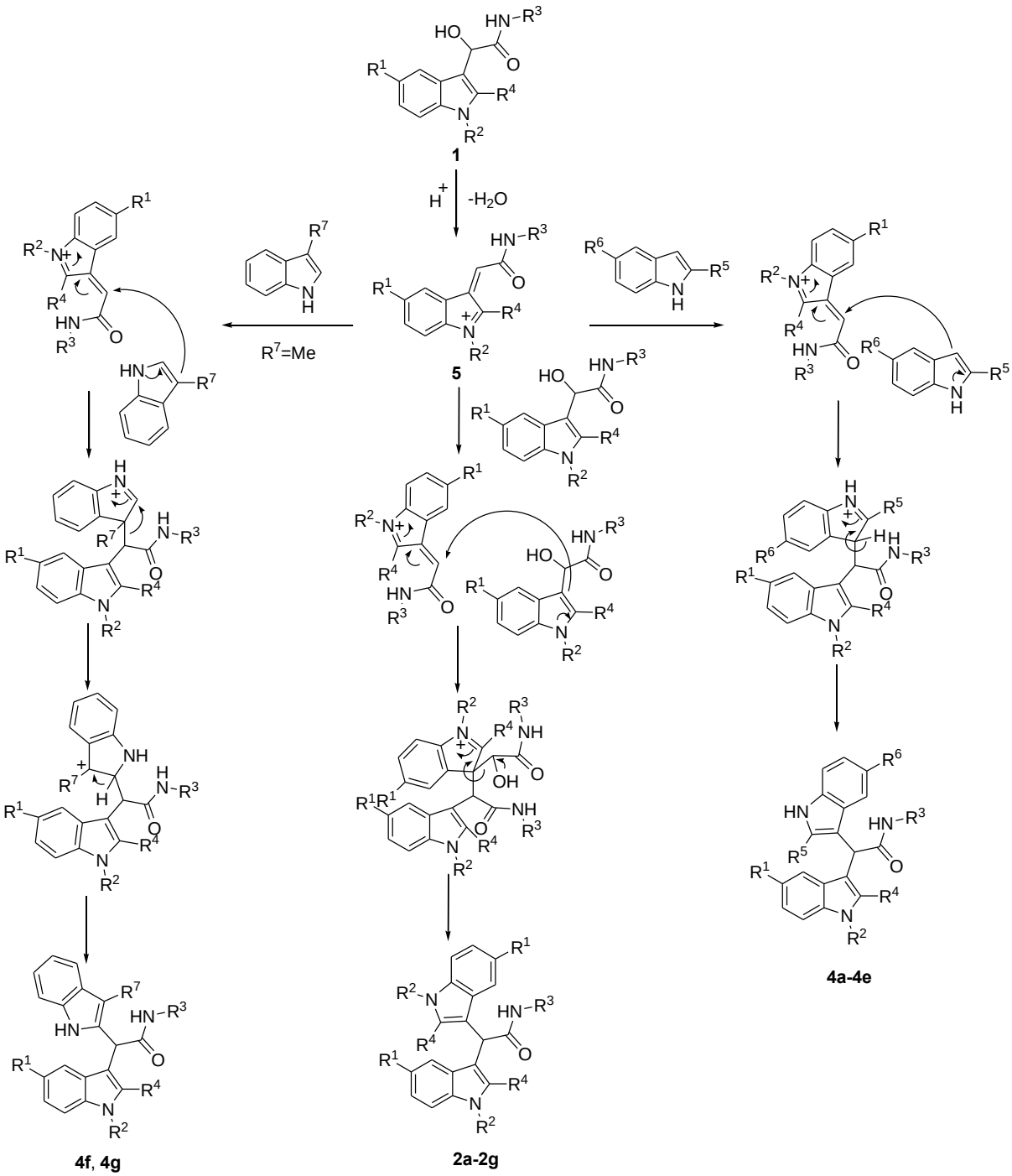
Table 4. Synthesis of unsymmetrical bis(indolyl)acetamides **4f** and **4g** mediated by H_2SO_4 and HNO_3[a]



1a, 1g **4f**, **4g**

Entry	**4**	R^1	R^2	R^3	R^7	Mediate agent	Time	Yield (%)[b]
1	**4f**	H	4-$ClC_6H_4CH_2$	4-C_5H_4N	Me	H_2SO_4	10 min	86.0
						HNO_3	49 h	80.0
2	**4g**	H	4-$ClC_6H_4CH_2$	CMe_3	Me	H_2SO_4	10 min	91.7
						HNO_3	4.5 h	76.6

[a]Reaction conditions: **1** (0.5 mmol), 3-methylindole (0.5 mmol) and mediate agent (1.0 mmol) in THF (5 mL) at room temperature. [b]Isolated yield.



Scheme 2. A plausible mechanism for the synthesis of symmetrical and unsymmetrical bis(indolyl)acetamides

A reasonable mechanism for the above reactions is proposed in Scheme 2. First, azafulvenium salt **5** is generated by dehydroxylation.[9] Dehydroxylation might be caused by the high sensitivity of 2-hydroxy-(2-indolyl)acetamide **1** to acid. Next, azafulvenium salt **5** undergoes further reaction with a second molecule of 2-hydroxy-(2-indolyl)acetamide or indole or substituted indoles to form symmetrical and unsymmetrical bis(indolyl)acetamides, respectively. The rearrangement of 2-hydroxy-(2-indolyl)acetamides with 3-methylindole, which results in the substitution at the 2-position of 3-methylindole, is worthy of note.[10]

In summary, we have demonstrated a facile synthesis of symmetrical bis(indolyl)acetamides *via* the dimerization of 2-hydroxy-(2-indolyl)acetamides and unsymmetrical bis(indolyl)acetamides *via* the electrophilic substitution of indoles with 2-hydroxy-(2-indolyl)acetamides mediated by protic acid at room temperature. Easy availability of the cheap reagent and mild reaction conditions of the present methodology make it a highly attractive protocol for synthesis of diverse and new bioactive symmetrical and unsymmetrical bis(indolyl)acetamides.

EXPERIMENTAL

All commercially available reagents and solvents were employed without further purification. Melting points were determined in a Büchi Melting Point B-540 apparatus and were uncorrected. Infrared spectra were recorded in a Bruker IFS-55 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in Bruker ARX 300 MHz or 600 MHz, using TMS as the internal standard. Chemical shift values were reported in δ (ppm) and coupling constants in hertz. ESI mass spectra were performed using an Aiglent 1100. High resolution mass spectrometry (HRMS) were obtained using a Bruker MicroTOF QII Time of Flight mass spectrometer. Column chromatography was performed on silica gel H and analytical TLC data on silica gel HF_{254}.

Starting Matericals

2-Hydroxy-(2-indolyl)acetamides were prepared by the reduction of substituted indol-3-yl-2-oxoacetamides with $NaBH_4$ in methanolic THF at room temperature. The substituted indol-3-yl-2-oxoacetamides were prepared by reference 11.

General procedure for preparation of 2-hydroxy-(2-indolyl)acetamides 1a-1h

To a solution of corresponding indol-3-yl-2-oxoacetamide (4 mmol) in THF (10 mL) and MeOH (10 mL) cooled in an ice bath was added $NaBH_4$ (2 mmol). Then the mixture was stirred at room temperature until TLC analysis showed that the starting material had been completely converted. The reaction was quenched at 0 °C with aqueous NH_4Cl and extracted three times with CH_2Cl_2. After the organic layers were dried (Na_2SO_4), the solvents were concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel with PE-EtOAc.

2-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-2-hydroxy-*N*-(pyridin-4-yl)acetamide (1a)

Yield 82.3%; white solid; mp 182.9-184.6 °C (PE-THF); IR 3425.7, 1664.3, 1583.3, 1497.2 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.36-5.43 (m, 3H), 6.29 (d, 1H, J = 4.6 Hz), 7.02 (t, 1H, J = 7.3 Hz), 7.10 (t, 1H, J = 7.1 Hz), 7.24 (d, 2H, J = 8.4 Hz), 7.38 (d, 2H, J = 8.4 Hz), 7.42 (d, 1H, J = 8.1 Hz), 7.52 (s, 1H), 7.74 (d, 1H, J = 6.8 Hz), 7.76 (d, 2H, J = 6.0 Hz), 8.41 (d, 2H, J = 6.0 Hz), 10.37 (s, 1H); ESI-MS *m/z*: 389.9 $[M - H]^-$.

2-Hydroxy-2-(1-methyl-1*H*-indol-3-yl)-*N*-(pyridin-4-yl)acetamide (1b)

Yield 70.8%; white solid; mp 187.7-188.4 °C (PE-THF); IR 3374.6, 1691.2, 1598.0, 1528.2 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.76 (s, 3H), 5.38 (d, 1H, J = 4.5 Hz), 6.24 (d, 1H, J = 4.5 Hz), 7.03 (t, 1H, J = 7.7 Hz), 7.15 (t, 1H, J = 7.4 Hz), 7.35 (s, 1H), 7.40 (d, 1H, J = 8.2 Hz), 7.71-7.78 (m, 3H), 8.42 (d, 2H, J = 6.2 Hz), 10.35 (s, 1H); ESI-MS *m/z*: 280.1 $[M - H]^-$.

2-Hydroxy-2-(1*H*-indol-3-yl)-*N*-(pyridin-4-yl)acetamide (1c)

Yield 43.8%; white solid; mp 180.5-182.3 °C (PE-THF); IR 3312.7, 3044.2, 1689.6, 1601.6, 1584.5, 1512.7 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.38 (d, 1H, J = 4.3 Hz), 6.22 (d, 1H, J = 4.4 Hz), 6.98 (t, 1H, J = 7.6 Hz), 7.08 (t, 1H, J = 7.2 Hz), 7.34-7.40 (m, 2H), 7.72 (d, 1H, J = 7.9 Hz), 7.76 (d, 2H, J = 6.1 Hz), 8.41 (d, 2H, J = 5.9 Hz), 10.34 (s, 1H), 11.05 (s, 1H); ESI-MS *m/z*: 266.0 $[M - H]^-$.

2-[1-(4-Chlorobenzyl)-5-bromo-1*H*-indol-3-yl]-2-hydroxy-*N*-(pyridin-4-yl)acetamide (1d)

Yield 66.2%; pale yellow solid; mp 133.4-136.2 °C (PE-THF); IR 3351.5, 2852.0, 1690.1, 1583.2, 1510.4 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.39 (d, 1H, J = 4.6 Hz), 5.41 (s, 2H), 6.38 (d, 1H, J = 4.5 Hz), 7.19-7.27 (m, 3H), 7.38 (d, 2H, J = 8.3 Hz), 7.43 (d, 1H, J = 8.8 Hz), 7.58 (s, 1H), 7.75 (d, 2H, J = 5.6 Hz), 7.96 (d, 1H, J = 1.3 Hz), 8.43 (d, 2H, J = 5.3 Hz), 10.41 (s, 1H); ESI-MS *m/z*: 470.0 $[M + H]^+$.

2-(5-Bromo-1-methyl-1*H*-indol-3-yl)-2-hydroxy-*N*-(pyridin-4-yl)acetamide (1e)

Yield 73.3%; white solid; mp 184.1-186.0 °C (PE-THF); IR 3326.7, 2859.5, 1697.2, 1602.9, 1585.3, 1511.1 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.76 (s, 3H), 5.37 (d, 1H, J = 4.2 Hz), 6.33 (d, 1H, J = 4.4 Hz), 7.26 (dd, 1H, J = 1.3, 8.7 Hz), 7.37-7.42 (m, 2H), 7.75 (d, 2H, J = 5.9 Hz), 7.95 (d, 1H, J = 1.2 Hz), 8.42 (d, 2H, J = 5.9 Hz), 10.38 (s, 1H); ESI-MS *m/z*: 360.0 $[M + H]^+$.

2-(5-Bromo-1*H*-indol-3-yl)-2-hydroxy-*N*-(pyridin-4-yl)acetamide (1f)

Yield 83.1%; white solid; mp 198.3-199.9 °C (PE-THF); IR 3299.4, 1686.2, 1585.3, 1512.5 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 5.37 (d, 1H, J = 3.4 Hz), 6.28 (d, 1H, J = 3.4 Hz), 7.19 (dd, 1H, J = 1.7, 8.5 Hz), 7.34 (d, 1H, J = 8.5 Hz), 7.42 (d, 1H, J = 2.0 Hz), 7.75 (d, 2H, J = 5.8 Hz), 7.93 (s, 1H), 8.42 (d, 2H, J = 6.1 Hz), 10.36 (s, 1H), 11.25 (s, 1H); ESI-MS *m/z*: 346.0 $[M + H]^+$.

2-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-*N*-*tert*-butyl-2-hydroxyacetamide (1g)

Yield 90.8%; white solid; mp 168.4-170.3 °C (PE-THF); IR 3385.5, 3253.4, 2966.0, 1651.9, 1524.2 cm^{-1};

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.30 (s, 9H), 5.06 (d, 1H, J = 5.0 Hz), 5.38 (s, 2H), 5.85 (d, 1H, J = 5.0 Hz), 7.00 (t, 1H, J = 7.7 Hz), 7.09 (t, 1H, J = 7.4 Hz), 7.23 (d, 2H, J = 8.3 Hz), 7.32 (s, 1H), 7.34-7.44 (m, 4H), 7.67 (d, 1H, J = 7.7 Hz); ESI-MS *m/z*: 393.1 $[M + Na]^+$.

2-Hydroxy-2-(2-methyl-1*H*-indol-3-yl)-*N*-(pyridin-4-yl)acetamide (1h)

Yield 51.8%; white solid; mp 214.0-214.9 °C (PE-THF); IR 3400.9, 3329.2, 3300.3, 3054.3, 1694.3, 1601.1, 1582.1, 1508.1 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.42 (s, 3H), 5.35 (d, 1H, J = 3.8 Hz), 6.13 (d, 1H, J = 3.8 Hz), 6.88 (t, 1H, J = 7.5 Hz), 6.97 (t, 1H, J = 7.4 Hz), 7.24 (d, 1H, J = 7.9 Hz), 7.57 (d, 1H, J = 7.7 Hz), 7.79 (d, 2H, J = 6.1 Hz), 8.41 (d, 2H, J = 6.0 Hz), 10.33 (s, 1H), 10.94 (s, 1H); ESI-MS: *m/z* 280.1 $[M - H]^-$.

General procedure for preparation of compounds 2a, 2b, 2d, 2e, and 2g mediated by H_2SO_4

H_2SO_4 (1 mmol) was added dropwise to a solution of corresponding 2-hydroxy-(2-indolyl)acetamide (0.5 mmol) in THF (5 mL). Then the mixture was stirred at room temperature until TLC analysis showed that the starting material had been completely converted. Water (15 mL) was added and the resulting solution was alkalized to pH 9-10 with triethylamine. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed successively with water and brine. After the organic layers were dried (Na_2SO_4), the solvents were concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel with EtOAc.

General procedure for preparation of compounds 2a-2c, 2f, and 2g mediated by HNO_3

HNO_3 (1 mmol) was added dropwise to a solution of corresponding 2-hydroxy-(2-indolyl)acetamide (0.5 mmol) in THF (5 mL). Then the mixture was stirred at room temperature until TLC analysis showed that the starting material had been completely converted. Water (15 mL) was added and the resulting solution was alkalized to pH 9-10 with triethylamine. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed successively with water and brine. After the organic layers were dried (Na_2SO_4), the solvents were concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel with EtOAc.

2,2-Bis[1-(4-chlorobenzyl)-1*H*-indol-3-yl]-*N*-(pyridin-4-yl)acetamide (2a)

White solid; mp 234.9-235.5 °C (PE-EtOAc); IR 3318.9, 1674.0, 1591.1, 1511.0 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 5.40 (s, 4H), 5.61 (s, 1H), 6.98 (t, 2H, J = 7.5 Hz), 7.08 (t, 2H, J = 7.5 Hz), 7.16 (d, 4H, J = 8.4 Hz), 7.34 (d, 4H, J = 8.4 Hz), 7.37-7.40 (m, 4H), 7.57 (d, 2H, J = 7.8 Hz), 7.62 (d, 2H, J = 6.2 Hz), 8.42 (d, 2H, J = 6.0 Hz), 10.80 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 42.4, 48.7, 110.7, 113.4, 113.8, 119.4, 119.8, 122.0, 127.6, 128.1, 128.9, 129.3, 132.4, 136.6, 137.9, 146.4, 150.9, 172.4; ESI-HRMS: calcd for $C_{37}H_{29}Cl_2N_4O$, 615.1721; found, 615.1721 $[M + H]^+$.

2,2-Bis(1-methyl-1*H*-indol-3-yl)-*N*-(pyridin-4-yl)acetamide (2b)

White solid; mp 239.1-239.7 °C (PE-EtOAc); IR 3327.5, 1675.2, 1589.5, 1510.0 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.74 (s, 6H), 5.58 (s, 1H), 7.00 (t, 2H, J = 7.5 Hz), 7.14 (t, 2H, J = 7.5 Hz), 7.19 (s, 2H), 7.40 (d, 2H, J = 8.2 Hz), 7.59 (d, 2H, J = 7.7 Hz), 7.61 (d, 2H, J = 5.4 Hz), 8.40 (d, 2H, J = 4.1 Hz), 10.74 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 32.3, 41.6, 109.7, 112.2, 113.2, 118.6, 118.8, 121.2, 126.8, 128.1, 136.7, 145.9, 150.4, 172.2; ESI-HRMS: calcd for $C_{25}H_{23}N_4O$, 395.1866; found, 395.1863 $[M + H]^+$.

2,2-Bis(1*H*-indol-3-yl)-*N*-(pyridin-4-yl)acetamide (2c)

White solid; mp 250.1-251.4 °C (PE-EtOAc); IR 3406.8, 1677.2, 1592.5, 1521.4 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.59 (s, 1H), 6.95 (t, 2H, J = 7.2 Hz), 7.06 (t, 2H, J = 7.1 Hz), 7.20 (d, 2H, J = 2.0 Hz), 7.36 (d, 2H, J = 8.0 Hz), 7.58 (d, 2H, J = 7.8 Hz), 7.62 (d, 2H, J = 5.6 Hz), 8.40 (d, 2H, J = 4.1 Hz), 10.76 (s, 1H), 10.95 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 42.0, 111.5, 113.0, 113.2, 118.4, 118.8, 121.0, 123.8, 126.5, 136.3, 146.0, 150.4, 172.3; ESI-HRMS: calcd for $C_{23}H_{19}N_4O$, 367.1554; found, 367.1555 $[M + H]^+$.

2,2-Bis[1-(4-chlorobenzyl)-5-bromo-1*H*-indol-3-yl]-*N*-(pyridin-4-yl)acetamide (2d)

White solid; mp 228.1-230.0 °C; IR 3383.6, 1664.4, 1589.8, 1508.1 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.43 (s, 4H), 5.56 (s, 1H), 7.17-7.21 (m, 6H), 7.34-7.41 (m, 6H), 7.59 (s, 2H), 7.62 (d, 2H, J = 5.9 Hz), 7.70 (d, 2H, J = 1.2 Hz), 8.44 (d, 2H, J = 5.2 Hz), 10.79 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 41.8, 48.3, 111.7, 112.1, 112.5, 113.4, 121.7, 124.0, 128.6, 128.8, 129.1, 132.0, 134.8, 137.0, 145.7, 150.4, 171.3; ESI-HRMS: calcd for $C_{37}H_{27}Br_2Cl_2N_4O$, 770.9923; found, 770.9926 $[M + H]^+$.

2,2-Bis(5-bromo-1-methyl-1*H*-indol-3-yl)-*N*-(pyridin-4-yl)acetamide (2e)

White solid; mp 274.3-275.9 °C (PE-EtOAc); IR 3442.3, 1708.1, 1593.5, 1509.3 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.76 (s, 6H), 5.54 (s, 1H), 7.26 (dd, 2H, J = 1.8, 8.7 Hz), 7.32 (s, 2H), 7.42 (d, 2H, J = 8.7 Hz), 7.59 (d, 2H, J = 5.9 Hz), 7.74 (d, 2H, J = 1.4 Hz), 8.43 (d, 2H, J = 5.7 Hz), 10.71 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 32.6, 41.1, 111.3, 111.5, 112.1, 113.3, 121.0, 123.7, 128.3, 129.8, 135.4, 145.7, 150.4, 172.6; ESI-HRMS: calcd for $C_{25}H_{21}Br_2N_4O$, 551.0077; found, 551.0075 $[M + H]^+$.

2,2-Bis(5-bromo-1*H*-indol-3-yl)-*N*-(pyridin-4-yl)acetamide (2f)

White solid; mp 183.4-185.5 °C (PE-EtOAc); IR 3419.4, 1672.5, 1591.3, 1508.4 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.54 (s, 1H), 7.18 (dd, 2H, J = 1.7, 8.6 Hz), 7.36 (d, 2H, J = 8.4 Hz), 7.33 (d, 2H, J = 2.3 Hz), 7.61 (d, 2H, J = 6.2 Hz), 7.72 (d, 2H, J = 1.4 Hz), 8.43 (d, 2H, J = 6.0 Hz), 10.72 (s, 1H), 11.23 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 41.7, 111.2, 112.4, 113.3, 113.7, 121.1, 123.6, 125.6, 128.2, 135.0, 145.8, 150.4, 171.8; ESI-HRMS: calcd for $C_{23}H_{17}Br_2N_4O$, 522.9764; found, 522.9767 $[M + H]^+$.

2,2-Bis[1-(4-chlorobenzyl)-1*H*-indol-3-yl]-*N*-*tert*-butylacetamide (2g)

White solid; mp 259.6-261.5 °C (PE-EtOAc); IR 3402.3, 3285.5, 1645.7, 1549.0, 1491.5, 1464.0 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.26 (s, 9H), 5.35 (s, 1H), 5.37 (s, 4H), 6.95 (t, 2H, *J* = 7.3 Hz), 7.06 (t, 2H, *J* = 7.3 Hz), 7.14 (d, 4H, *J* = 8.4 Hz), 7.22 (s, 2H), 7.34 (d, 4H, *J* = 8.4 Hz), 7.37 (d, 2H, *J* = 8.3 Hz), 7.55 (d, 2H, *J* = 7.8 Hz), 7.85 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 28.5, 41.1, 48.1, 50.1, 110.0, 114.5, 118.6, 119.5, 121.2, 127.2, 127.4, 128.4, 128.8, 131.8, 136.0, 137.6, 171.3; ESI-HRMS: calcd for $C_{36}H_{33}Cl_2N_3ONa$, 616.1893; found, 616.1890 $[M + Na]^+$.

2-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-2-methoxy-*N*-(pyridin-4-yl)acetamide (3a)

The same procedure with the preparation of compound **2a** mediated by H_2SO_4 except using MeOH instead of THF as a solvent. White solid; mp 171.0-172.2 °C (MeOH); IR 3293.2, 1677.8, 1588.9, 1510.3 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 3.37 (s, 3H), 5.15 (s, 1H), 5.43 (s, 2H), 7.04 (t, 1H, *J* = 7.5 Hz), 7.13 (t, 1H, *J* = 7.2 Hz), 7.22 (d, 2H, *J* = 8.1 Hz), 7.38 (d, 2H, *J* = 8.2 Hz), 7.44 (d, 1H, *J* = 8.1 Hz), 7.59 (s, 1H), 7.69-7.76 (m, 3H), 8.43 (d, 2H, *J* = 5.2 Hz), 10.44 (s, 1H); ESI-MS *m/z*: 404.0 $[M - H]^-$.

2-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-2-ethoxy-*N*-(pyridin-4-yl)acetamide (3b)

The same procedure with the preparation of compound **2a** mediated by H_2SO_4 except using MeOH instead of THF as a solvent. White solid; mp 163.4-165.0 °C (MeOH); IR 3282.6, 3033.4, 1678.2, 1586.0, 1510.4 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.21 (t, 3H, *J* = 7.0 Hz), 3.49-3.66 (m, 2H), 5.24 (s, 1H), 5.42 (s, 2H), 7.04 (t, 1H, *J* = 7.4 Hz), 7.12 (t, 1H, *J* = 7.6 Hz), 7.22 (d, 2H, *J* = 8.4 Hz), 7.37 (d, 2H, *J* = 8.4 Hz), 7.43 (d, 1H, *J* = 8.1 Hz), 7.55 (s, 1H), 7.70 (d, 2H, *J* = 6.2 Hz), 7.74 (d, 1H, *J* = 7.8 Hz), 8.43 (d, 2H, *J* = 5.8 Hz), 10.35 (s, 1H); ESI-MS *m/z*: 420.1 $[M + H]^+$.

General procedure for preparation of compounds 4a-4g mediated by H_2SO_4

To a solution of corresponding 2-hydroxy-(2-indolyl)acetamide (0.5 mmol) and indole (0.5 mmol) in THF (5 mL), H_2SO_4 (1 mmol) was added dropwise. Then the mixture was stirred at room temperature until TLC analysis showed that the starting material had been completely converted. Water (15 mL) was added and the resulting solution was alkalized to pH 9-10 with triethylamine. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed successively with water and brine. After the organic layers were dried (Na_2SO_4), the solvents were concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel with EtOAc.

General procedure for preparation of compounds 4a-4g mediated by HNO_3

To a solution of corresponding 2-hydroxy-(2-indolyl)acetamide (0.5 mmol) and indole (0.5 mmol) in THF (5 mL), HNO_3 (1 mmol) was added dropwise. Then the mixture was stirred at room temperature until TLC analysis showed that the starting material had been completely converted. Water (15 mL) was added and the resulting solution was alkalized to pH 9-10 with triethylamine. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed successively with water and brine.

After the organic layers were dried (Na_2SO_4), the solvents were concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel with EtOAc.

2-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-2-(1*H*-indol-3-yl)-*N*-(pyridin-4-yl)acetamide (4a)

White solid; mp 154.4-156.0 °C (PE-EtOAc); IR 3414.4, 3318.9, 1681.6, 1589.7, 1510.5 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.40 (s, 2H), 5.61 (s, 1H), 6.93-7.01 (m, 2H), 7.04-7.11 (m, 2H), 7.18 (d, 2H, J = 8.4 Hz), 7.21 (d, 1H, J = 2.1 Hz), 7.33-7.40 (m, 5H), 7.57-7.60 (m, 2H), 7.62 (d, 2H, J = 6.4 Hz), 8.42 (d, 2H, J = 6.2 Hz), 10.77 (s, 1H), 10.97 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 42.0, 48.2, 110.2, 111.6, 112.8, 113.1, 113.3, 118.5, 118.9, 119.2, 121.1, 121.4, 123.8, 126.4, 127.2, 127.6, 128.5, 128.8, 131.9, 136.0, 136.3, 137.4, 145.9, 150.4, 172.1; ESI-HRMS: calcd for $C_{30}H_{24}ClN_4O$, 491.1633; found, 491.1633 $[M + H]^+$.

2-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-2-(2-methyl-1*H*-indol-3-yl)-*N*-(pyridin-4-yl)acetamide (4b)

White solid; mp 240.1-241.2 °C (PE-EtOAc); IR 3401.1, 3243.7, 1671.3, 1589.5, 1508.5 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.42 (s, 3H), 5.40 (s, 2H), 5.54 (s, 1H), 6.84 (t, 1H, J = 7.7 Hz), 6.89-6.96 (m, 2H), 7.05 (t, 1H, J = 7.8 Hz), 7.15-7.23 (m, 3H), 7.28 (d, 1H, J = 7.8 Hz), 7.33-7.39 (m, 3H), 7.61 (d, 2H, J = 6.4 Hz), 7.64 (d, 1H, J = 8.7 Hz), 8.40 (d, 2H, J = 6.0 Hz), 10.61 (s, 1H), 10.88 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 12.0, 41.6, 48.1, 107.6, 110.2, 110.3, 113.1, 113.3, 118.1, 118.7, 118.8, 119.4, 119.9, 121.4, 127.3, 127.4, 127.7, 128.4, 128.8, 131.8, 133.0, 135.1, 136.1, 137.6, 146.0, 150.4, 172.0; ESI-HRMS: calcd for $C_{31}H_{26}ClN_4O$, 505.1789; found, 505.1788 $[M + H]^+$.

2-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-2-(5-bromo-1*H*-indol-3-yl)-*N*-(pyridin-4-yl)acetamide (4c)

White solid; mp 175.5-177.0 °C (PE-EtOAc); IR 3407.6, 1673.0, 1592.3, 1508.1 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 5.41 (s, 2H), 5.57 (s, 1H), 6.97 (t, 1H, J = 7.1 Hz), 7.08 (t, 1H, J = 7.0 Hz), 7.14-7.21 (m, 3H), 7.32-7.42 (m, 6H), 7.53 (d, 1H, J = 7.8 Hz), 7.61 (d, 2H, J = 6.2 Hz), 7.75 (s, 1H), 8.42 (d, 2H, J = 6.2 Hz), 10.76 (s, 1H), 11.21 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 42.0, 48.2, 110.3, 111.2, 112.4, 112.7, 113.3, 113.7, 119.0, 119.1, 121.5, 121.6, 123.6, 125.6, 127.2, 127.6, 128.3, 128.6, 128.9, 131.9, 135.1, 136.1, 137.5, 145.9, 150.5, 171.9; ESI-HRMS: calcd for $C_{30}H_{23}BrClN_4O$, 569.0738; found, 569.0732 $[M + H]^+$.

2-(1*H*-Indol-3-yl)-2-(2-methyl-1*H*-indol-3-yl)-*N*-(pyridin-4-yl)acetamide (4d)

White solid; mp 186.4-188.4 °C (PE-EtOAc); IR 3401.8, 3302.1, 1670.0, 1592.7, 1510.2 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.41 (s, 3H), 5.52 (s, 1H), 6.83-6.97 (m, 3H), 7.04 (t, 1H, J = 7.8 Hz), 7.08 (d, 1H, J = 1.8 Hz), 7.22 (d, 1H, J = 7.9 Hz), 7.31 (d, 1H, J = 8.1 Hz), 7.34 (d, 1H, J = 8.1 Hz), 7.61 (d, 2H, J = 6.2 Hz), 7.67 (d, 1H, J = 7.8 Hz), 8.40 (d, 2H, J = 5.7 Hz), 10.57 (s, 1H), 10.86-10.87 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 12.0, 41.7, 107.9, 110.3, 111.5, 113.0, 113.3, 118.1, 118.3, 118.4, 119.4, 119.9, 121.0, 123.5, 126.7, 127.8, 133.0, 135.1, 136.3, 146.1, 150.3, 172.2; ESI-HRMS: calcd for

$C_{24}H_{21}N_4O$, 381.1710; found, 381.1709 $[M + H]^+$.

2-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-*N*-*tert*-butyl-2-(1*H*-indol-3-yl)acetamide (4e)

White solid; mp 188.0-189.7 °C (PE-EtOAc); IR 3400.2, 3286.1, 1655.0, 1547.3, 1491.7, 1455.8 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.26 (s, 9H), 5.33 (s, 1H), 5.37 (s, 2H), 6.92-6.98 (m, 2H), 7.00-7.08 (m, 3H), 7.15 (d, 2H, J = 8.4 Hz), 7.22 (s, 1H), 7.31-7.38 (m, 4H), 7.54 (d, 1H, J = 8.1 Hz), 7.57 (d, 1H, J = 8.0 Hz), 7.82 (s, 1H), 10.80 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ: 28.5, 41.1, 48.1, 50.1, 110.0, 111.4, 114.4, 114.8, 118.1, 118.6, 119.1, 119.4, 120.8, 121.2, 123.4, 126.8, 127.3, 127.5, 128.4, 128.8, 131.8, 136.0, 136.3, 137.6, 171.5; ESI-HRMS: calcd for $C_{29}H_{28}ClN_3ONa$, 492.1813; found, 492.1815 $[M + Na]^+$.

2-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-2-(3-methyl-1*H*-indol-2-yl)-*N*-(pyridin-4-yl)acetamide (4f)

White solid; mp 171.4-171.8 °C (PE-EtOAc); IR 3429.5, 3056.4, 1695.1, 1591.7, 1508.4 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 2.36 (s, 3H), 5.41 (d, 2H, J = 1.9), 5.69 (s, 1H), 6.91-7.03 (m, 3H), 7.09 (t, 1H, J = 7.4 Hz), 7.24 (d, 2H, J = 8.4 Hz), 7.33-7.48 (m, 7H), 7.63 (d, 2H, J = 6.3 Hz), 8.45 (d, 2H, J = 6.2 Hz), 10.56 (s, 1H), 10.86 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.6, 41.8, 48.4, 106.3, 110.3, 111.3, 111.6, 113.4, 117.9, 118.1, 118.5, 119.2, 120.7, 121.7, 127.0, 127.6, 128.1, 128.5, 129.0, 131.6, 131.9, 135.7, 135.9, 137.2, 145.6, 150.5, 170.6; ESI-HRMS: calcd for $C_{31}H_{26}ClN_4O$, 505.1789; found, 505.1787 $[M + H]^+$.

2-[1-(4-Chlorobenzyl)-1*H*-indol-3-yl]-*N*-*tert*-butyl-2-(3-methyl-1*H*-indol-2-yl)acetamide (4g)

White solid; mp 221.5-222.7 °C (PE-EtOAc); IR 3419.2, 3289.8, 1641.3, 1549.4, 1490.3, 1460.3 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 1.28 (s, 9H), 2.31 (s, 3H), 5.38 (d, 2H, J = 4.3 Hz), 5.43 (s, 1H), 6.68-7.01 (m, 3H), 7.06 (t, 1H, J = 7.7 Hz), 7.21 (d, 2H, J = 8.4 Hz), 7.30 (s, 1H), 7.32-7.40 (m, 5H), 7.48 (d, 1H, J = 7.8 Hz), 8.04 (d, 1H, J = 8.0 Hz), 10.32 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 8.5, 28.4, 40.8, 48.3, 50.4, 105.3, 110.1, 111.3, 113.4, 117.6, 117.9, 118.8, 118.9, 120.2, 121.4, 127.1, 127.2, 128.2, 128.4, 128.9, 131.9, 133.3, 135.5, 135.8, 137.3, 170.2; ESI-HRMS: calcd for $C_{30}H_{30}ClN_3ONa$, 506.1970; found, 506.1967 $[M + Na]^+$.

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