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Highly Efficient Synthesis of Unsymmetrical 3,3'-Bis(1*H*-indol-3-yl)methanes in Water

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A simple and practical approach for the preparation of unsymmetric bis(indolyl)methanes (BIMs) was realized by Lewis acid $InBr_3$-catalyzed Friedel-Crafts reaction of indoles with 3-indolyl-substituted phthalides in water.

Keywords unsymmetric bis(indolyl)methanes, $InBr_3$, Friedel-Crafts reaction, indole, 3-indolyl-substituted phthalide

Introduction

The indole ring is widely present in a variety of biologically active compounds and has become an important structural component in many pharmaceutical agents.[1] Among various indole derivates, bis(indolyl)-methanes (BIMs) which were isolated from various terrestrial and marine natural sources exhibit a wide range of biological activities,[2] such as, promoting beneficial estrogen metabolism and inducing apoptosis in human cancer cell.[3] Especially, its various potent anticancer activities made it beginning clinical trials as a therapeutic for numerous forms of cancer. Therefore, the demand for efficient synthesis of BIMs become an increasing interest in organic synthesis.[4] Although the synthesis of symmetrical BIMs has been studied extensively over the past decades, the synthesis of unsymmetrical BIMs is still highly sought-after in synthetic community.[5] To the best of our knowledge, there were only a few reports published for the synthesis of unsymmetrical BIMs to date.[6] Vallee and co-workers reported the first synthesis of such BIMs from hydroxyamines and indoles, but the procedure was a little bit complicated.[6a] Chakrabarty and co-workers reported the preparation of BIMs through the Michael reaction of 3-(2-nitrovinyl)indole with indoles.[6b] However, the method was limited to 2,2-bis(indol-3-yl)-1-nitroethane derivatives. Ji and co-workers reported the synthesis of unsymmetrical BIMs from the reaction of indoles bearing electron-donating group with (1*H*-indol-3-yl)-(alkyl)methanols catalyzed by ammonium cerium(IV) nitrate under ultrasonic irradiation in good yields.[6c] Csaky and co-workers have synthesized unsymmetrical BIMs from gramine using an expensive catalyst.[6d] Bhuyan and co-workers reported the synthesis of 3-alkylated indoles from a three-components reaction of indole, aldehyde, and *N*,*N*-dimethylbarbituric acid, undergoing an elimination-addition reaction with another indole molecule and giving unsymmetrical BIMs in the absence of a catalyst.[6e]

Developing new and environmentally benign synthetic methods is important in organic synthesis. In recent years, organic reactions that can proceed in aqueous media have attracted great interest because of its significant environmental and economical advantages over those occurring in organic solvents.[7] Thus, it is of interest to develop a practical and general method for the synthesis of unsymmetrical BIMs in water in view of economical and environmental concerns. Following our interest in green chemistry and medicinal chemistry, we herein present a new route to synthesize unsymmetrical BIMs in pure water.

Results and Discussion

Recently, we reported the synthesis of 3-indolyl-substituted phthalides in water in the absence of a catalyst.[8] During the investigation, we observed that the product of the Friedel-Crafts reaction between indole and 2-formylbenzoic acid depended on the loading ratio of the two reactants when the reaction was performed in the presence of Lewis acid catalyst ($InBr_3$, in CH_2Cl_2, Scheme 1). When the loading ratio of reactants **1a** and **2a** was 1∶1.5, 3-indoly-substituted phthalide **3a** was obtained in 95% yield. However, when the ratio was changed to 5∶1, BIM **4a** was obtained in 94% yield. It

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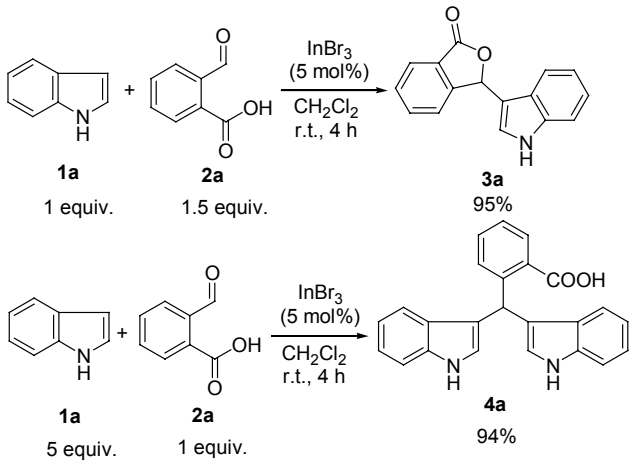
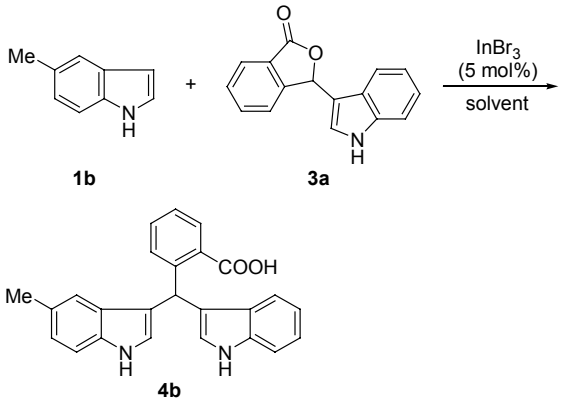
is reasonable to propose that 3-indolylsubstituted phthalide **3a** was formed first, and then it reacted with another molecule of indole **1a** to afford BIM **3a**. In vision of this, we could introduce another different substituted indole molecule to 3-indolyl-substituted phthalides in order to obtain unsymmetrical BIMs.

Scheme 1 $InBr_3$ catalysted Friedel-Crafts reaction between indole and 2-formylbenzoic acid



With this idea in mind, preliminary experiment was performed by using 5-methylindole **1b** and 3-indolyl-substituted phthalide **3a** as model substrates, CH_2Cl_2 as solvent and $InBr_3$ as catalyst. Pleasingly the reaction processed smoothly at room temperature, to afford the desired BIM **4b** in 97% yield (Table 1, Entry 1). In the view of green chemistry, we next carried out the reaction in water.

Table 1 Optimization of the reaction conditions[a]



Entry	Solvent (0.2 mol/L)	Temp./℃	Time/h	Yield[b]/%
1	CH_2Cl_2	25	5	97
2	H_2O	25	24	n.r.
3	H_2O	50	5	<10
4	H_2O	50	24	47
5	H_2O	80	5	91

[a] The reaction was performed using 5-methylindole **1b** (0.3 mmol, 1.5 equiv.), 3-indole substituted phthalide **3a** (0.2 mmol, 0.2 mol/L), $InBr_3$ (5 mol%). [b] isolated yield.

Unfortunately, there was no desired product obtained at room temperature after 24 h (Table 1, Entry 2). Then we examined the effects of the reaction temperature (Table 1, Entries 3—5). Finally, we found that the desired BIM product can be obtained in 91% yield at 80 ℃ (Table 1, Entry 5).

With the optimal reaction conditions in hand (Table 1, Entry 5), the scope of this reaction was investigated. To our delight, the 5- or 6-position-substituent of the phenyl ring of indole with either an electron-donating (Me, OMe, OBn) or -withdrawing group (Br, Cl, F) could be successfully employed to afford the corresponding BIMs in excellent yields (Table 2, Entries 1—7, yield＞90%). Also the indole with strong electron-withdrawing group (NO_2) at 6-position could give the desired BIM product in 87% yield in the standard condition. But unfortunately, the indole bearing NO_2 group at 7-position was not a suitable substrate. However, the reaction of indole with the 3-indole substituted phthalide which bears NO_2 group on the 7-position of phenyl ring of indole underwent smoothly, giving the corresponding BIM in 80% yield respectively (Table 2, Entry 9). Furthermore, this method was applicable to various 3-indolyl-substituted phthalides. With not only electron-donating group but also electron-withdrawing group at the phthalide ring, 3-indolyl-substituted phthalides were suitable substrates. The corresponding BIMs were obtained in good to excellent yields (Table 2, Entries 10—12).

Conclusions

In summary, we have developed a simple, novel and efficient synthetic protocol for the synthesis of unsymmetric BIMs by $InBr_3$-catalyzed Friedel-Crafts reaction of indoles with 3-indolyl-substituted phthalides in water in good to excellent yields. We are currently investigating the bioactivity of the BIM compounds. To our delight, preliminary experiments indicated that this BIM compounds present excellent anti-Alzheimer's Disease activity, and the results will be reported in due course.

Experimental

General procedure for synthesis of unsymmetric bis(1*H*-indol-3-yl)alkanes in water

$InBr_3$ (5 mol%) was added to a suspension of 3-indolyl substituted phthalide (0.2 mmol) and indole (0.3 mmol) in water. Then the mixture was heated to 80 ℃ until completion indicated by TLC. The reaction mixture was extracted with CH_2Cl_2 (10 mL×3). The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified on silica gel to afford the desired product.

2-((1*H*-Indol-2-yl)(5-methyl-1*H*-indol-2-yl)methyl)benzoic acid (4b) White solid; ^{1}H NMR (400 MHz, Acetone-d_6) δ: 9.90 (s, 1H), 9.79 (s, 1H), 7.91 (d, J=8.4 Hz, 1H), 7.32—7.40 (m, 4H), 7.22—7.28 (m, 2H), 7.19

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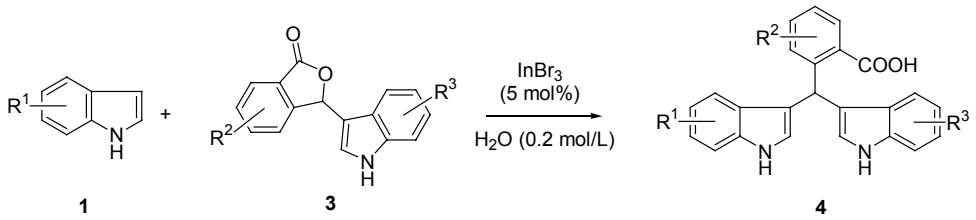
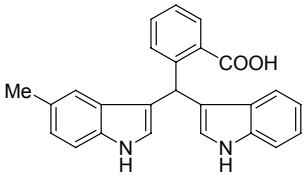
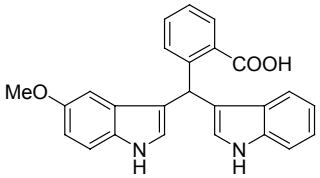
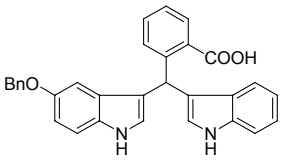
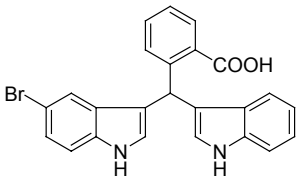
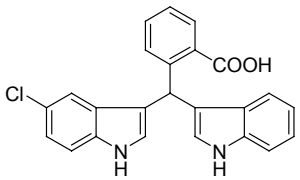
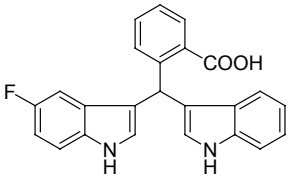
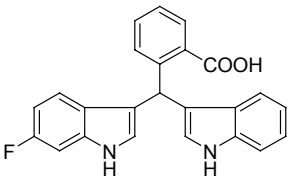
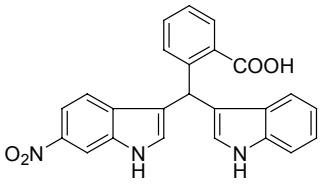
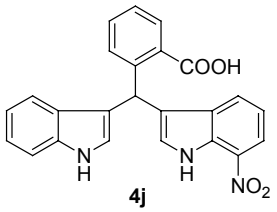
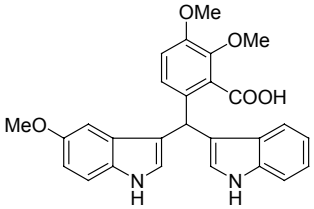
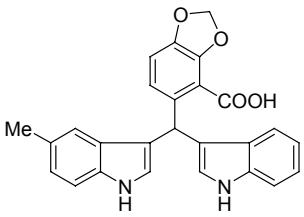
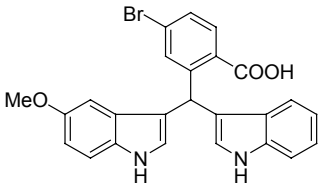
Table 2 Substrate scopes[a]



1 **3** **4**

Entry	R^1, R^2, R^3	Product	Temp./℃	Time/h	Yield[b]/%
1	5-Me, H, H	 **4b**	80	5	91
2	5-OMe, H, H	 **4c**	80	5	98
3	5-OBn, H, H	 **4d**	80	5	92
4	5-Br, H, H	 **4e**	80	5	96
5	5-Cl, H, H	 **4f**	80	5	94
6	5-F, H, H	 **4g**	80	5	90
7	6-F, H, H	 **4h**	80	5	91

Continued

Entry	R^1, R^2, R^3	Product	Temp./℃	Time/h	Yield[b]/%
8	6-NO_2, H, H	 **4i**	90	24	87
9[c]	H, H, 7-NO_2	 **4j**	90	48	80
10	5-OMe, 3,4-$(OMe)_2$, H	 **4k**	80	5	96
11	5-Me, 3,4-(OCH_2O), H	 **4l**	80	5	72
12	5-OMe, 5-Br, H	 **4m**	80	7	70

[a] The reaction was performed by using indole **2** (0.3 mmol, 1.5 equiv.), 3-indole substituted phthalide **1** (0.2 mmol, 0.2 mol/L), $InBr_3$ (5 mol%). See Supporting Information for details. [b] Isolated yield. [c] The reaction was performed by using 1*H*-indole (0.3 mmol, 1.5 equiv.), 3-(7-nitro-1*H*-indole) substituted phthalide (0.2 mmol, 0.2 mol/L), $InBr_3$ (5 mol%).

(s, 1H), 7.16 (s, 1H), 7.05 (dd, J=7.2, 7.2 Hz, 1H), 6.89 (dd, J=7.2, 7.2 Hz, 2H), 6.67 (s, 1H), 6.62 (s, 1H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 169.8, 146.7, 140.0, 136.5, 136.3, 131.9, 131.6, 131.0, 130.9, 128.5, 128.2, 128.0, 126.6, 125.0, 124.8, 124.7, 123.8, 122.1, 120.4, 120.0, 119.4, 112.1, 111.8, 35.9, 21.7; (EI-HRMS *m/z* calcd for $C_{25}H_{20}N_2O_2$ 380.1525 $[M]^+$, found 380.1521).

2-((1*H*-Indol-2-yl)(5-methoxy-1*H*-indol-2-yl)methyl)benzoic acid (4c) White solid; ^{1}H NMR (400 MHz, acetone-d_6) δ: 11.23 (s, 1H), 9.93 (s, 1H), 9.79 (s, 1H), 7.87—7.91 (m, 1H), 7.42—7.53 (m, 1H), 7.35—7.38 (m, 2H), 7.19—7.29 (m, 3H), 7.11 (s, 1H), 7.06 (dd, J=8.4, 7.2 Hz, 1H), 6.85—6.91 (m, 2H), 6.69—6.74 (m, 3H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ: 169.2, 153.6, 145.8, 137.3, 132.4, 131.1, 130.8, 130.1, 129.9, 127.8, 127.4, 125.8, 124.7, 124.0, 121.3, 119.7, 118.9, 118.8, 118.7, 118.5, 111.9, 111.3, 101.6, 54.3, 35.1; (ESI-HRMS *m/z* calcd for $C_{25}H_{20}N_2NaO_3$ 419.1372 $[M+Na]^+$, found 419.1354).

2-((5-(Benzyloxy)-1*H*-indol-2-yl)(1*H*-indol-2-yl)methyl)benzoic acid (4d) White solid; ^{1}H NMR (400 MHz, acetone-d_6) δ: 11.22 (s, 1H), 9.93 (s, 1H), 9.81 (s, 1H), 7.90 (d, J=7.2 Hz, 1H), 7.36—7.43 (m, 6H), 7.24—7.31 (m, 6H), 7.11 (s, 1H), 7.01—7.05 (m, 2H), 6.89 (dd, J=8.0, 7.2 Hz, 1H), 6.80 (d, J=8.8 Hz, 1H),

6.72 (s, 1H), 4.91 (s, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ: 169.5, 152.7, 145.8, 138.2, 137.3, 132.5, 131.1, 130.7, 130.1, 128.3, 127.7, 127.5, 127.4, 127.3, 125.8, 124.7, 124.0, 121.3, 119.6, 119.5, 118.9, 118.8, 118.5, 112.0, 111.9, 111.3, 103.2, 70.2, 35.2; (ESI-HRMS *m/z* calcd for $C_{31}H_{24}N_2NaO_3$ 495.1685 $[M+Na]^+$, found 495.1693).

2-((5-Bromo-1*H*-indol-2-yl)(1*H*-indol-2-yl)methyl)benzoic acid (4e) White solid; ^{1}H NMR (400 MHz, acetone-d_6) δ: 10.18 (d, J=13.6 Hz, 1H), 9.96 (s, 1H), 8.00 (dd, J=6.8, 6.8 Hz, 1H), 7.62 (d, J=8.4 Hz, 1H), 7.18—7.44 (m, 8H), 7.10 (dd, J=7.2, 8.0 Hz, 1H), 6.94 (dd, J=7.2, 7.2 Hz, 1H), 6.80 (s, 1H), 6.75 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ: 169.9, 145.5, 137.4, 136.0, 131.8, 130.6, 130.2, 129.3, 127.5, 126.3, 125.9, 124.3, 121.9, 121.8, 119.7, 119.3, 119.1, 119.0, 113.6, 112.1, 111.7, 35.2; (ESI-HRMS *m/z* calcd for $C_{24}H_{17}BrN_2NaO_2$ 467.0371 $[M+Na]^+$, found 467.0381).

2-((5-Chloro-1*H*-indol-2-yl)(1*H*-indol-2-yl)methyl)benzoic acid (4f) White solid; ^{1}H NMR (400 MHz, acetone-d_6) δ: 11.27 (s, 1H), 10.19 (d, J=13.6 Hz, 1H), 9.98 (s, 1H), 7.95 (dd, J=6.8, 7.2 Hz, 1H), 7.34—7.42 (m, 6H), 7.28—7.32 (m, 1H), 7.12—7.17 (m, 1H), 7.01—7.06 (m, 2H), 6.90 (dd, J=6.8, 7.2 Hz, 1H), 6.78—6.80 (m, 1H), 6.71 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ: 169.1, 145.4, 145.0, 137.3, 135.7, 131.3, 130.3, 130.0, 128.5, 127.3, 126.2, 126.0, 125.8, 124.0, 121.5, 121.4, 119.4, 119.2, 118.7, 118.6, 112.9, 112.8, 111.4, 34.9; (ESI-HRMS *m/z* calcd for $C_{24}H_{18}ClN_2O_2$ 401.1057 $[M]^+$, found 401.1707).

2-((5-Fluoro-1*H*-indol-2-yl)(1*H*-indol-2-yl)methyl)benzoic acid (4g) White solid; ^{1}H NMR (400 MHz, Acetone-d_6) δ: 10.05 (s, 1H), 9.96 (s, 1H), 7.91 (d, J=6.4Hz, 1H), 7.24—7.41 (m, 6H), 7.11 (s, 1H), 7.01—7.05 (m, 2H), 6.79—6.88 (m, 3H), 6.71 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 169.4, 158.2 (d, J=184.5 Hz), 146.3, 138.0, 134.5, 132.1, 131.0 (d, J=18.3 Hz), 128.2, 126.7 (d, J=4.4 Hz) 124.7, 122.2, 120.3, 119.6, 119.4, 113.0, 112.1, 110.3, 110.1, 105.0, 104.8, 36.0; (EI-HRMS *m/z* calcd for $C_{24}H_{17}N_2O_2F$ 384.1274 $[M]^+$, found 384.1270).

2-((6-Fluoro-1*H*-indol-2-yl)(1*H*-indol-2-yl)methyl)benzoic acid (4h) White solid; ^{1}H NMR (400 MHz, acetone-d_6) δ: 10.02 (d, J=9.2 Hz, 1H), 9.93 (s, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.34—7.45 (m, 5H), 7.25—7.30 (m, 1H), 7.23 (s, 1H), 7.15 (d, J=6.8 Hz, 1H), 7.19 (dd, J=6.8, 8.4 Hz, 1H), 6.94 (dd, J=6.8, 7.6 Hz, 1H), 6.72—6.77 (m, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ: 169.3, 159.8 (d, J=233.6 Hz), 145.6, 137.3 (d, J=7.6 Hz), 137.1, 131.4, 130.6, 130.3, 130.1, 127.4, 126.0, 124.7 (d, J=2.9 Hz), 124.2 (d, J=15.2 Hz), 121.5, 120.5 (d, J=9.5 Hz), 119.6 (d, J=15.3 Hz), 119.2, 119.0, 118.7, 111.5, 107.2 (d, J=23.8 Hz), 97.5 (d, J = 25.7 Hz), 35.1; (ESI-HRMS *m/z* calcd for $C_{24}H_{17}FN_2NaO_2$ 407.1172 $[M+Na]^+$, found 407.1189).

2-((1*H*-Indol-2-yl)(6-nitro-1*H*-indol-2-yl)methyl)benzoic acid (4i) Yellow solid; ^{1}H NMR (400 MHz, acetone-d_6) δ: 11.30 (s, 1H), 10.72 (s, 1H), 10.03 (s, 1H), 8.39 (d, J=2.4 Hz, 1H), 7.96 (d, J=8.0 Hz, 1H), 7.84 (dd, J=2.4, 8.8 Hz, 1H), 7.53 (d, J=8.8 Hz, 1H), 7.30—7.40 (m, 5H), 7.24 (s, 1H), 7.13 (d, J=6.8 Hz, 1H), 7.08 (dd, J=6.8, 7.2 Hz, 1H), 6.91 (dd, J=6.8 Hz, 6.8 Hz, 1H), 6.73 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ: 169.0, 145.1, 142.9, 137.3, 135.5, 131.9, 131.5, 130.6, 130.5, 130.0, 127.1, 126.2, 124.1, 121.5, 120.5, 119.5, 119.3, 118.7, 118.4, 113.8, 111.5, 108.3, 35.0; (ESI-HRMS *m/z* calcd for $C_{24}H_{17}N_3NaO_4$ 434.1117 $[M+Na]^+$, found 434.1139).

2-((1*H*-indol-2-yl)(7-nitro-1*H*-indol-2-yl)methyl)benzoic acid (4j) Yellow solid; ^{1}H NMR (400 MHz, acetone-d_6) δ: 10.97 (s, 1H), 10.03 (s, 1H), 8.08 (d, J=8.4 Hz, 1H), 7.97 (d, J=7.2 Hz, 1H), 7.85 (d, J=8.4 Hz, 1H), 7.36—7.41 (m, 4H), 7.27—7.32 (m, 2H), 7.04—7.11 (m, 2H), 6.94 (s, 1H), 6.91 (dd, J=7.2, 7.2 Hz, 1H), 6.74 (s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 169.6, 145.8, 138.0, 133.8, 132.4, 131.3, 130.8, 128.6, 127.9, 127.8, 127.6, 127.1, 125.0, 124.8, 122.4, 122.1, 120.1, 119.6, 119.5, 112.3, 110.9, 35.7; (EI-HRMS *m/z* calcd for $C_{24}H_{17}N_3O_4$ 411.1219 $[M]^+$, found 411.1220).

2-((1*H*-Indol-2-yl)(5-methoxy-1*H*-indol-2-yl)methyl)-4,5-dimethoxybenzoic acid (4k) White solid; ^{1}H NMR (400 MHz, acetone-d_6) δ: 9.91 (s, 1H), 9.75 (s, 1H), 7.34—7.39 (m, 2H), 7.24 (d, J=8.4 Hz, 1H), 6.98—7.05 (m, 3H), 6.89 (s, 1H), 6.87 (s, 1H), 6.75 (s, 1H), 6.68—6.71 (m, 2H), 6.00 (s, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ: 169.3, 154.5, 151.6, 146.2, 138.0, 134.8, 133.0, 131.0, 128.4, 128.1, 125.7, 125.3, 124.7, 122.1, 119.4, 119.3, 114.0, 112.6, 112.2, 112.1, 102.3, 61.4, 56.2, 55.8, 37.1; (EI-HRMS *m/z* calcd for $C_{27}H_{26}N_2O_5$ 458.1842 $[M]^+$, found 458.1856).

5-((1*H*-Indol-2-yl)(5-methyl-1*H*-indol-2-yl)methyl)benzo[*d*][1,3]dioxole-4-carboxylic acid (4l) White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.86 (s, 1H), 10.73 (s, 1H), 10.61 (s, 1H), 7.31 (d, J=7.6 Hz, 1H), 7.24 (d, J=7.6 Hz, 1H), 7.20 (d, J=8.4 Hz, 1H), 7.04 (s, 1H), 7.01 (dd, J=7.2, 6.8 Hz, 1H), 6.79—6.85 (m, 3H), 6.58—6.61 (m, 2H), 6.53—6.57 (m, 1H), 6.38 (s, 1H), 6.02 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.3, 146.2, 146.1, 137.1, 136.9, 135.5, 127.4, 127.2, 127.0, 124.5, 124.4, 123.0, 122.2, 121.4, 119.5, 118.9, 118.7, 118.7, 118.0, 116.4, 111.9, 111.7, 109.6, 102.0, 35.0, 21.8; (ESI-HRMS *m/z* calcd for $C_{26}H_{20}N_2NaO_4$ 447.1321 $[M+Na]^+$, found 447.1315).

2-((1*H*-Indol-2-yl)(5-methoxy-1*H*-indol-2-yl)methyl)-4-bromobenzoic acid (4m) White solid; ^{1}H NMR (400 MHz, acetone-d_6) δ: 10.02 (s, 1H), 9.88 (s, 1H), 7.85 (d, J=8.4 Hz, 1H), 7.58 (d, J=2.4 Hz, 1H), 7.50 (dd, J=2.4, 8.4 Hz, 1H), 7.39 (dd, J=8.4, 8.4 Hz, 2H), 7.28 (d, J=8.8 Hz, 1H), 7.12 (s, 1H), 7.08 (dd, J=8.4, 8.4 Hz, 1H), 6.92 (dd, J = 8.4, 8.4 Hz, 2H), 6.71—6.78 (m, 3H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ: 168.2, 153.8, 148.5, 137.3, 132.8, 132.3, 132.2, 130.0, 129.1, 127.5, 127.2, 125.5, 124.8, 124.1, 121.5, 119.4, 118.7, 118.2, 118.0, 112.1, 111.5, 101.3, 54.9, 35.2; (ESI-HRMS *m/z* calcd for $C_{25}H_{19}BrN_2NaO_3$

497.0477 $[M+Na]^+$, found 497.0489).

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