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Regioselectivity-Tunable Self-1,3-Dipolar [3+3] Cyclizations of Azomethine Ylides To Assemble Dispirooxindole-piperazines

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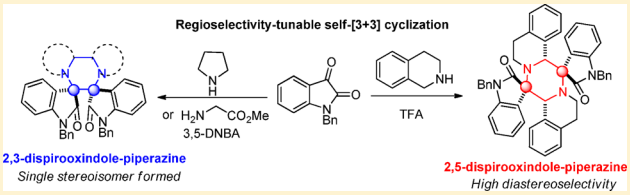
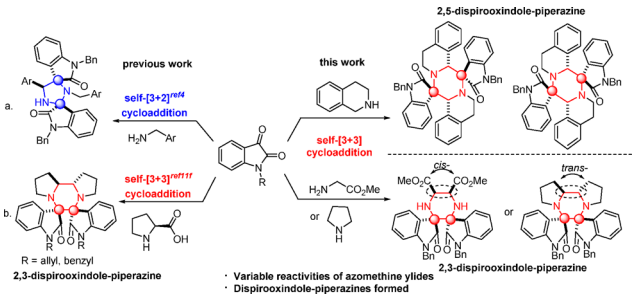
Supporting Information

ABSTRACT: A series of novel 2,3- or 2,5-dispirooxindole-piperazine ring systems were efficiently constructed through the acid-promoted self-1,3-dipolar [3+3] cyclizations of azomethine ylides derived from isatin with various primary or cyclic secondary amines. Interestingly, the regioselectivity of this self-[3+3] cyclization could be effectively tuned by varying the structural features of substrates. The unprecedented 2,5-dispirooxindole-piperazine skeleton was achieved in good diastereoselectivity by employing 1,2,3,4-tetrahydroisoquinoline, while using pyrrolidine or glycine methyl ester furnished the 2,3-dispirooxindole-piperazine scaffold in excellent diastereoselectivity (only a single isomer formed).



In recent years, 1,3-dipolar cycloaddition (1,3-DC) of azomethine ylides derived from isatins has attracted an increasing amount of interest because of their unique capability to build diverse spirooxindole ring systems.[1] Considering the interesting biological profiles of the spirooxindoles, intensive efforts have been made to explore novel reaction pathways of the azomethine ylides, allowing the rapid assembly of various heterocyclic spirooxindole motifs.[2] Notably, [3+2] cycloaddition was found to be the prevalent reaction mode for azomethine ylides, resulting in the formation of diversified five-membered spirooxindoles.[3] Very recently, we disclosed a novel self-[3+2] cyclization of azomethine ylides generated *in situ* from isatin and benzylamine (Scheme 1, equation a).[4] Consequently, a series of novel dispirooxindole-imidazolidines with potentially pronounced biological activities were prepared with high diastereoselectivities. Nevertheless, the exploration of versatile cyclizations of azomethine ylides remains demanding and challenging and would enrich the arsenal for accessing dispirooxindoles with various structural features.

Scheme 1. Self-1,3-Dipolar Cycloaddition for Constructing Various Dispirooxindole Heterocycles



It is well-known that piperazine is a basic structural motif in a broad class of organic compounds demonstrating a wide range of biological activities,[5] including antitumor,[6] antiviral,[7] antifungal,[8] and antibacterial.[9] Conceivably, the merging of piperazine with spirooxindoles might produce compounds endowed with interesting bioactivities.[10] Compared to the well-established dispirooxindole-pyrrolidine via [3+2] cycloaddition of azomethine ylides, the construction of dispirooxindole-piperizines has been rather unsuccessful.[11] In 2012, Essassi et al. reported an elegant self-[3+3] cycloaddition of azomethine ylides generated *in situ* from isatin and L-proline to prepare 2,3-dispirooxindole-piperizine.[11f] Thereafter, Banerjee and co-workers conducted mechanistic studies of the diastereoselectivities of this [3+3] cyclization.[11b] Aiming to develop efficient synthetic approaches to construct novel dispiroxindoles, we continued to direct our efforts at the rarely studied self-[3+3] cycloadditions of azomethine ylides. Herein, we disclose our unexpected findings for the acid-promoted self-[3+3] cycloaddition of azomethine ylides with tunable regioselectivities. Surprisingly, unprecedented 2,5-dispirooxindole-piperizine polycyclic scaffolds were obtained for the first time via the 1,3-dipolar cycloaddition of azomethine ylides derived from isatin with 1,2,3,4-tetrahydroisoquinoline (THIQ). Alternatively, utilization of pyrrolidine or glycine methyl ester furnished 2,3-dispirooxindole-piperizines in excellent diastereoselectivities. Moreover, this observation could significantly broaden the application of self-[3+3] cycloaddition as an efficient synthetic pathway for assembling dispiroheterocycle skeletons.

We initiated our studies by testing a self-[3+3] cycloaddition between *N*-benzylisatin (**1a**) and THIQ (**2**) to optimize

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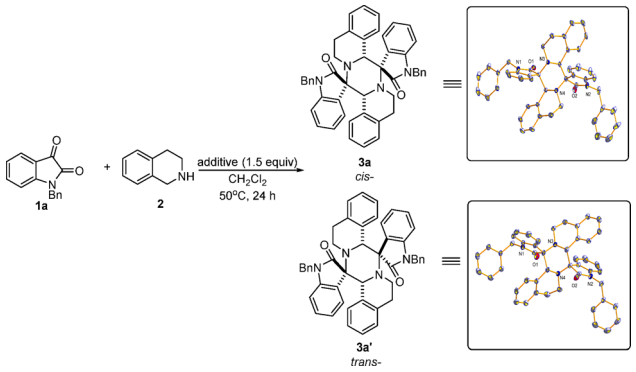
reaction parameters (Table 1). Gratifyingly, this reaction did proceed smoothly at 50 °C to afford the corresponding

Table 1. Optimization of the Self-1,3-Dipolar Cycloaddition Reaction[a]



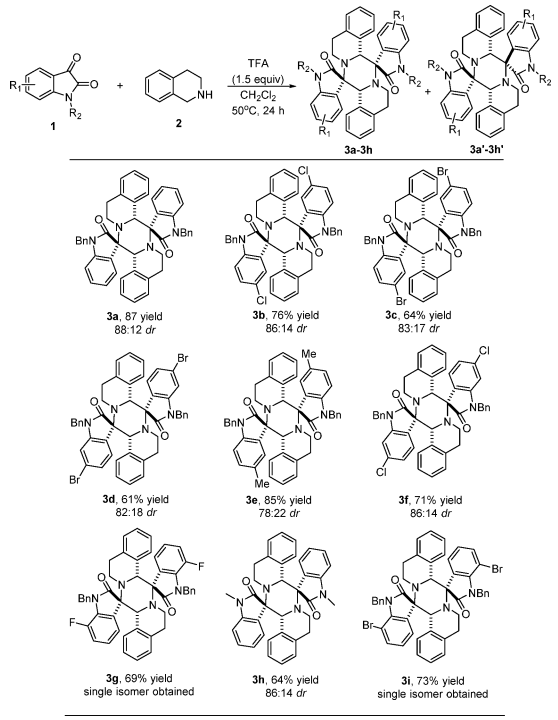
entry	additive (1.5 equiv)	time (h)	yield (%)	ratio (3a/3a′)
1	–	24	63	60/40
2	*p*-anisic acid	24	87	69/31
3	3,5-DNBA	24	86	58/42
4	benzoic acid	24	88	59/41
5	AcOH	24	89	61/39
6	**TFA**	**24**	**87**	**88/12**
7[b]	TFA	72	–[c]	–
8[d]	TFA	2	75	86/14

[a]Unless otherwise noted, the reaction was conducted in a sealed tube on a 0.4 mmol scale in CH_2Cl_2 (4 mL) with a **1a**/**2** molar ratio of 1/1.5 at 50 °C. [b]The reaction was conducted at rt. [c]Unstable product observed. [d]The reaction was conducted in toluene at 110 °C.

products. However, two separable cycloadducts were observed in a poor dr (60/40) (entry 1). Surprisingly, different from the previous reports on the formation of 2,3-dispirooxindole-piperazine,[11f] two novel 2,5-dispirooxindole-piperazine isomers (*cis* isomer as the major product) were obtained, which were confirmed by X-ray crystallographic analysis of a single crystal. Intrigued by this encouraging result, we subsequently screened additives to improve the diastereoselectivities. It was found that the addition of regular acids, including *p*-anisic acid, 3,5-dinitrobenzoic acid (3,5-DNBA), benzoic acid, and acetic acid, markedly enhanced chemical yields, albeit with similar diastereoselectivites (entries 2–5, respectively). To our delight, the addition of a stronger acid, trifluoroacetic acid (TFA; pK_a = −0.25), to the reaction system successfully delivered the desired cycloadduct in good diastereoselectivity (88/12), along with a good chemical yield (87%) (entry 6). Surprisingly, when this reaction is conducted at a lower temperature (rt) in CH_2Cl_2, only an unstable product was formed (entry 7). However, when the reaction temperature was increased to 110 °C, a slightly decreased chemical yield was obtained with good diastereoselectivity (entry 8). Accordingly, the optimized reaction conditions were fixed as follows: mixing **1a** and **2** (**1a**/**2** = 1/1.5) in CH_2Cl_2 at 50 °C.

Once the optimal conditions had been established, the substrate scope of this protocol was then studied. As shown in Scheme 2, the diversely substituted isatins were evaluated and various substituents were well tolerated. As for 5-substituted and 6-substituted *N*-benzylisatin, moderate chemical yields (64–85%) and diastereoselectivities (78/22 to 86/14) were obtained (**3b–f**). Pleasingly, utilization of 7-fluoro-*N*-benzylisatin and 7-bromo-*N*-benzylisatin afforded the corresponding cycloadduct with excellent diastereoselectivity (**3g** and **3h**, respectively, single stereoisomer formed) with satisfactory yields (69 and 73%, respectively), possibly benefiting from the steric effect induced from the substituent at position 7 of isatin. Subsequently, the influence of the protecting group on *N*-H of isatin was also studied. Similar results (**3i**, 64% yield, 86/14 dr) were obtained by utilizing *N*-methylisatin. Surprisingly, using straight isatin led to an extremely sluggish reaction, and only a trace amount of product was obtained after an even longer reaction duration. However, the employment of *N*-acetylisatin did not give the desired cycloadduct.

Scheme 2. Substrate Scope of Isatins in Self-[3+3] Cycloaddition[a]



[a]Unless otherwise noted, the reaction was conducted in a sealed tube on a 0.4 mmol scale in CH_2Cl_2 (4 mL) at 50 °C with a **1**/**2** molar ratio of 1/1.5.

Encouraged by the successful assembly of novel 2,5-dispirooxindoles-piperazines, we set out to modulate the structural features of the amine reaction partners and evaluate their effects on the reactivity in self-[3+3] cycloadditions. Depressingly, various six-membered cyclic secondary amines, including piperidine, *N*-methylpiperazine, morpholine, and pipecolinic acid, were unreactive under the optimized conditions. Interestingly, in the presence of 3,5-dinitrobenzoic acid, utilizing five-membered cyclic amine-pyrrolidine did afford the cycloadduct in 65% yield as a single stereoisomer, which was determined to be 2,3-dispirooxindole-piperazine via the NMR comparison of the resulting cycloadducts with literature data (Scheme 3).[11f] Clearly, the structural features of amines are closely related with their reactivities and reaction pathways in self-1,3-DC. As a consequence, a series of *N*-benzylisatin with different substitution patterns (5-Cl, 6-Cl, 5-F, 7-F, and 6-Br) were used to prepare the corresponding cycloadducts (**5b–f**, respectively). As a result, the excellent diastereoselectivities were consistently mantained. The chemical yield was slightly

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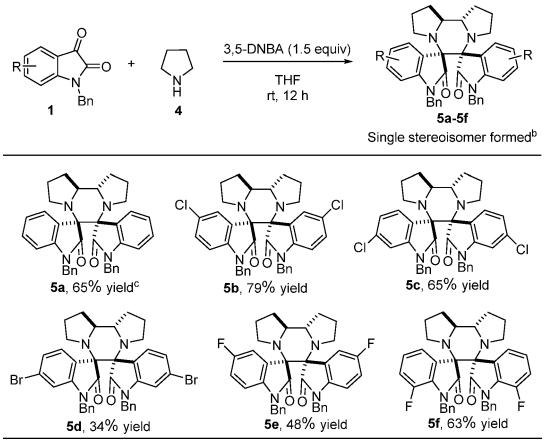
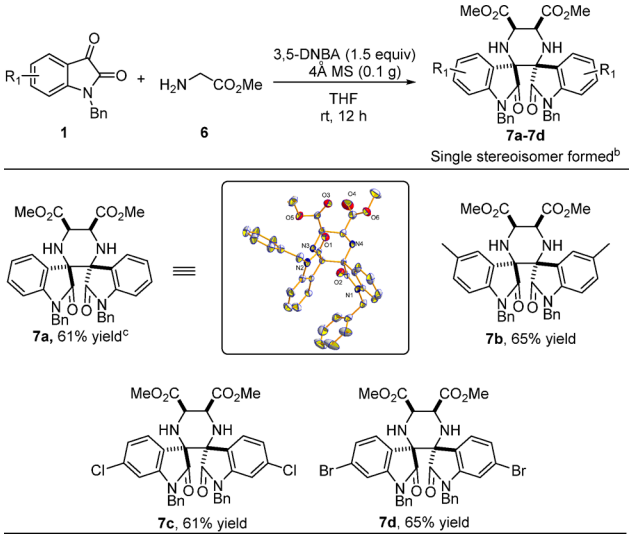
Scheme 3. Self-1,3-Dipolar Cycloaddition of Isatins with Pyrrolidine[a]



[a]Unless otherwise noted, the reaction was conducted on a 0.2 mmol scale in THF (4 mL) at rt with a **1**/**4** molar ratio of 1/1.5. [b]Determined by ^{1}H NMR. [c]Isolated yield.

Scheme 4. Self-1,3-Dipolar Cycloaddition of Isatin with Glycine Methyl Ester[a]



[a]Unless otherwise noted, the reaction was conducted on a 0.2 mmol scale in THF (4 mL) at rt with a **1**/**6** molar ratio of 1/1.5. [b]Determined by ^{1}H NMR. [c]Isolated yield.

increased to 79% in the case of the 5-Cl analogue (**5b**). In contrast, the employment of 6-Br or 5-F isatins dramatically decreased the chemical yields (**5d** and **5e**).

The substrate-dependent nature of self-[3+3] cycloaddition prompted us to extend the cyclic secondary amine to the linear primary amine and further elucidate the tunable reactivities with the change in amine reaction partner. According to our previous studies, benzylamine, a linear primary amine, proceeds via a self-[3+2] cycloaddition with isatin to give dispiroxindole-pyrrolidine.[4] It can be assumed that the electronic feature of the linear primary amine might affect the cyclization mode of the resulting azomethine ylides. Hence, glycine methyl ester, commonly used for the formation of a dipole with isatin, was evaluated for this reaction. Pleasingly, a single cycloadduct was achieved in 61% yield with glycine methyl ester was mixed with *N*-benzylisatin with the aid of 3,5-dinitrobenzoic acid and 4 Å molecular sieves (Scheme 4). Unexpectedly, after being finally elucidated by X-ray analysis, the structure of this obtained product was determined to be 2,3-dispirooxindole-piperazine **7a** with two *cis*-vincinal carboxylate groups attached to the central piperazine ring, differing from cycloadducts **5** bearing two *trans*-neighboring pyrrolidine rings. Subsequently, various substituted isatins were also employed to examine the viability of this protocol. Satisfyingly, similar chemical yields for 5-Me, 6-Cl, and 6-Br isatins were consistently obtained (**7b**–**d**, respectively).

On the basis of the experimental results and X-ray analysis, plausible reaction pathways are proposed and illustrated in Scheme 5. Imines can first be generated from the condensation between isatin and amine in the presence of acid. In the case of THIQ, the following 1,2-prototropy of imine leads to the formation of azomethine ylide **I** and slightly less stable azomethine ylide **II**.[12] Presumably, during the course of 1,3-DC of azomethine ylide **II**, the attack of the dipolarophile would enforce the inward movement of THIQ ring to the isatin ring and thereby enhance the steric hindrance.[11a] On the other hand, 1,3-DC of azomethine ylide **I** would be favored because no obvious steric hindrance would have evolved from the outward movement of the THIQ ring. As illustrated in transition state **TS-I**, contrary to the previously observed head–head cyclization mode,[11b] an unexpected head–tail [3+3] cycloaddition of two azomethine ylides **I** gives *cis*-2,5-dispirooxindole-piperazine **3a**. Besides, another head–tail cyclization between azomethine ylide **I** with the less favored **II**, as shown in transition state **TS-II**, affords *trans*-dispirooxindole-piperazine **3a′** as a minor product. Presumably, the steric interaction between two THIQ ring moieties severely impaired the head–head cycloaddition mode of **I** or **II**. In terms of glycine methyl ester, two isomeric azomethine ylides (**III** and **IV**) can be similarly formed. As shown in **TS-III**, because of the extra stabilization arising from the double secondary orbital interaction (SOI) between the orbitals of two carbonyl groups in the isatins and ester moieties, respectively,[13] a head–head [3+3] cycloaddition between azomethine ylide **III** and **IV** exclusively occurred to provide the corresponding cycloadduct **7a**. It is worth noting that this SOI between two ester groups might be responsible for the different reaction pathway from the self-1,3-DC of azomethine ylide derived from isatin with benzylamine, wherein the electronic repulsion of two phenyl rings possibly dominates the orientation of azomethine ylide and allows the self-[3+2] cyclization mode.[4] Moreover, it can be assumed that **TS-IV** is forbidden because of the existence of severe electronic interaction repulsion between phenyl moieties of isatins.

In summary, we developed the acid-promoted self-[3+3] cycloadditions of azomethine ylides derived from isatin with THIQ, pyrrolidine, or glycine methyl ester. It has been found that regioselectivities, including the head–head or head–tail reaction mode of self-[3+3] cyclization, could be tuned by modulating the structural features of the amine reaction partner. Accordingly, a variety of unprecedented 2,5- and novel 2,3-dispirooxindole-piperazines bearing two quaternary carbons and four stereogenic centers were prepared in modest to good yields with good diastereoselectivities. More importantly, these findings demonstrated the versatile utilities of self-1,3-DC in the synthesis of complex heteropolycycles.

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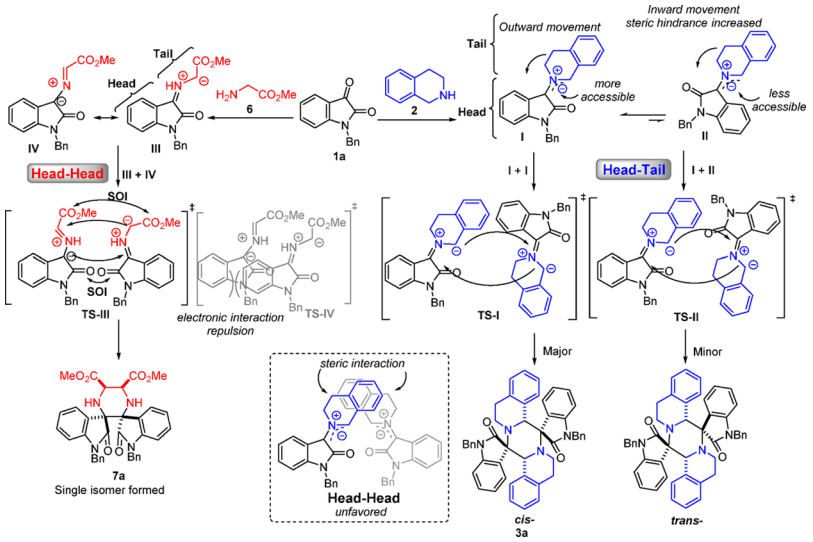
Scheme 5. Proposed Reaction Pathways



EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise noted, all the reagents were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded at 400 MHz. The chemical shifts were recorded in parts per million relative to tetramethylsilane and with the solvent resonance as the internal standard. Data were reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants (hertz), integration. ^{13}C NMR data were collected at 100 MHz with complete proton decoupling. Chemical shifts are reported in parts per million from the tetramethylsilane with the solvent resonance as the internal standard. Infrared spectra (IR) were measured with a FT-IR apparatus. High-resolution mass spectroscopy (HRMS) was performed on a TOF MS ES+ mass spectrometer, and acetonitrile was used to dissolve the sample. Column chromatography was conducted on silica gel (200−300 mesh).

General Procedures and Characterization Data of Compounds 3a−i and 3a′−i′. *N*-Substituted isatin (0.40 mmol), tetrahydroisoquinoline (0.60 mmol, 1.5 equiv), and TFA (45 μL, 0.60 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (4.0 mL) in a sealed tube. Subsequently, the resulting mixture was heated at the designated temperature. After completion of the reaction (monitored by TLC), the organic solvent was removed *in vacuo*. Then the residue was purified via flash chromatography (petroleum ether/ethyl acetate, 19/1 to 12/1) to yield the corresponding product.

Dispirooxindole-piperazine ***3a***. White solid (92.3 mg, 0.13 mmol, 77% yield): mp 238 °C dec; IR (KBr) ν 3406, 2824, 1612, 1465, 1344, 1172, 1033, 930, 866 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.77 (d, J = 6.2 Hz, 2H), 7.31−7.48 (m, 10H), 6.64−7.04 (m, 14H), 6.00 (s, 2H), 5.09 (d, J = 15.2 Hz, 2H), 4.78 (d, J = 15.2 Hz, 2H), 2.65−2.68 (m, 2H), 2.31−2.51 (m, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.3, 143.2, 136.7, 136.1, 133.1, 129.3, 129.2, 129.1, 128.8, 128.6, 128.0, 126.7, 125.8, 125.1, 124.3, 122.8, 108.9, 73.5, 59.4, 43.4, 42.5, 30.6; HRMS (TOF-ES+) m/z [M + H]$^+$ calcd for $C_{48}H_{41}N_4O_2$ 705.3230, found 705.3255.

Dispirooxindole-piperazine ***3a′***. White solid (12.6 mg, 0.02 mmol, 10% yield): mp 186−187 °C; IR (KBr) ν 3427, 2925, 2820, 1720, 1608, 1485, 1466, 1344, 1174, 1083, 949, 751 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.17 (d, J = 4.0 Hz, 1H), 7.84 (d, J = 4.0 Hz, 1H), 6.50−7.56 (m, 22H), 5.80−6.00 (m, 2H), 5.08 (d, J = 15.2 Hz, 1H), 4.71 (t, J = 14.4 Hz, 2H), 4.38 (d, J = 15.6 Hz, 1H), 2.69−3.02 (m, 2H), 2.30−2.51 (m, 6H), 1.24 (s, 1H), 0.86 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.7, 175.7, 143.3, 142.9, 138.2, 136.8, 136.5, 136.3, 132.6, 132.1, 129.9, 129.7, 129.1, 128.9, 128.6, 128.4, 128.1, 128.0, 127.4, 127.0, 125.7, 125.6, 123.0, 110.1, 108.7, 74.8, 73.6, 60.1, 59.8, 44.2, 43.3, 42.4, 31.0, 30.4; HRMS (TOF-ES+) m/z [M + H]$^+$ calcd for $C_{48}H_{41}N_4O_2$ 705.3230, found 705.3202.

Dispirooxindole-piperazine ***3b***. White solid (100.4 mg, 0.13 mmol, 65% yield): mp 243 °C dec; IR (KBr) ν 3581, 2937, 1711, 1610, 1479, 1432, 1328, 1299, 1168, 1075, 915, 810, 748 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.80 (s, 2H), 7.26−7.46 (m, 12H), 6.90 (s, 4H), 6.81 (d, J = 8.4 Hz, 2H), 6.64 (s, 4H), 5.93 (s, 2H), 5.06 (d, J = 15.6 Hz, 2H), 4.80 (d, J = 7.2 Hz, 2H), 2.51−2.66 (m, 6H), 2.32−2.34 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.6, 142.2, 136.3, 135.9, 132.3, 129.3, 129.2, 128.9, 128.6, 128.2, 127.1, 126.7 126.0, 125.0, 124.0, 123.9, 110.6, 73.7, 59.4, 43.6, 42.6, 30.6; HRMS (TOF-ES+) m/z [M + H]$^+$ calcd for $C_{48}H_{39}N_4O_2Cl_2$ 773.2450, found 773.2439.

Dispirooxindole-piperazine ***3b′***. White solid (16.6 mg, 0.021 mmol, 11% yield): mp 169−170 °C; IR (KBr) ν 3060, 2934, 2822, 1722, 1606, 1480, 1428, 1332, 1301, 1171, 1072, 950, 921, 812, 749, 699 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.28 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 1.6 Hz, 1H), 7.35−7.41 (m, 4H), 7.29−7.32 (m, 1H), 7.10−7.21 (m, 5H), 7.07 (dd, J = 8.4, 2.0 Hz), 6.91 (t, J = 7.2 Hz, 1H), 6.84 (d, J = 8.0 Hz, 2H), 6.73 (t, J = 7.2 Hz, 2H), 6.67 (dd, J = 8.4, 3.2 Hz, 2H), 6.55 (d, J = 6.4 Hz, 2H), 5.97 (d, J = 10.0 Hz, 2H), 5.88 (s, 1H), 5.76 (s, 1H), 5.08 (d, J = 15.2 Hz, 1H), 4.79 (d, J = 16.0 Hz, 1H), 4.66 (d, J = 15.2 Hz, 1H), 4.37 (d, J = 16.0 Hz, 1H), 2.94 (t, J = 10.8 Hz, 1H), 2.74 (t, J = 10.8 Hz, 1H), 2.57 (t, J = 10.8 Hz, 1H), 2.46 (dd, J = 14.8, 6.8 Hz, 2H), 2.34−2.39 (m, 1H), 2.27−2.30 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.0, 175.9, 142.3, 141.8, 138.2, 136.4, 136.2, 136.1, 132.1, 132.0, 131.5, 129.8, 129.2, 129.1, 128.9, 128.6, 128.4, 128.1, 127.7, 127.4, 127.3, 126.9, 126.6, 126.5, 126.1, 125.8, 125.6, 124.8, 111.2, 110.0, 75.3, 74.3, 60.1, 59.5, 55.4, 43.9, 43.5, 43.4, 42.5, 31.0, 30.4; HRMS (TOF-ES+) m/z [M + H]$^+$ calcd for $C_{48}H_{39}N_4O_2Cl_2$ 773.2450, found 773.2431.

Dispirooxindole-piperazine ***3c***. White solid (92.5 mg, 0.11 mmol, 53% yield): mp 245 °C dec; IR (KBr) ν 3579, 2924, 1712, 1606, 1475, 1426, 1328, 1296, 1209, 1166, 1099, 1022, 947, 915, 811, 748, 692 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.80 (d, J = 1.6 Hz, 2H), 7.45 (d, J = 7.2 Hz, 4H), 7.38−7.41 (m, 4H), 7.31−7.35 (m, 2H), 7.27 (dd, J = 8.4, 1.6 Hz, 2H), 6.90 (s, 4H), 6.81 (d, J = 8.4 Hz, 2H), 6.64 (s, 4H), 5.93 (s, 2H), 5.06 (d, J = 15.2 Hz, 2H), 4.80 (d, J = 15.2 Hz, 2H), 2.55−2.63 (m, 6H), 2.32−2.34 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.4, 142.6, 136.2, 135.9, 132.3, 132.1, 131.6, 129.2, 128.9, 128.6, 128.2, 127.1, 126.8, 126.0, 125.0, 114.5, 111.2, 73.7, 59.4, 43.4, 42.7, 30.5; HRMS (TOF-ES+) m/z [M + H]$^+$ calcd for $C_{48}H_{39}N_4O_2Br_2$ 861.1440, found 861.1427.

Dispirooxindole-piperazine ***3c′***. White solid (18.4 mg, 0.021 mmol, 11% yield): mp 270−272 °C; IR (KBr) ν 3060, 3027, 2923, 2849, 1713, 1604, 1477, 1425, 1373, 1328, 1171, 1055, 950, 810, 748, 692 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.42 (d, J = 2.0 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 7.50 (dd, J = 8.4, 1.6 Hz, 1H), 7.35−7.40 (m,

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4H), 7.29−7.32 (m, 1H), 7.10−7.21 (m, 6H), 6.91 (t, J = 7.6 Hz, 1H), 6.82−6.85 (m, 2H), 6.71−6.76 (m, 2H), 6.62 (dd, J = 8.4, 3.2 Hz, 2H), 6.54 (d, J = 6.4 Hz, 2H), 5.95−5.98 (m, 2H), 5.87 (s, 1H), 5.76 (s, 1H), 5.07 (d, J = 15.6 Hz, 1H), 4.80 (d, J = 16.0 Hz, 1H), 4.65 (d, J = 15.2 Hz, 1H), 4.36 (d, J = 16.0 Hz, 1H), 2.94 (t, J = 10.8 Hz, 1H), 2.70−2.78 (m, 1H), 2.57 (t, J = 10.4 Hz, 1H), 2.46 (dd, J = 14.8, 8.8 Hz, 2H), 2.33−2.38 (m, 1H), 2.27−2.30 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.1, 175.9, 142.9, 142.3, 138.2, 136.7, 132.7, 132.4, 132.0, 131.6, 131.5, 129.1, 128.5, 128.4, 127.8, 126.6, 125.8, 114.9, 114.3, 111.6, 110.3, 75.2, 74.3, 60.0, 59.4, 55.4, 43.9, 43.4, 42.4, 30.9, 30.3; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{48}H_{38}N_4O_2NaBr_2$ 883.1259, found 883.1270.

Dispirooxindole-piperazine ***3d***. White solid (86.7 mg, 0.10 mmol, 50% yield): mp 213 °C dec; IR (KBr) ν 3582, 2923, 2852, 1712, 1603, 1482, 1432, 1339, 1167, 1105, 1052, 867, 808, 742, 692 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.64 (d, J = 8.0 Hz, 1H), 7.46 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.2 Hz, 1H), 7.07−7.11 (m, 2H), 6.86−6.92 (m, 2H), 6.65 (dd, J = 16.4, 7.6 Hz, 2H), 5.94 (s, 1H), 5.08 (d, J = 15.2 Hz, 1H), 4.83 (d, J = 15.6 Hz, 1H), 2.69 (t, J = 12.0 Hz, 1H), 2.43−2.52 (m, 2H), 2.27−2.29 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.2, 144.8, 136.4, 136.0, 132.6, 129.2, 129.0, 128.6, 128.6, 128.2, 126.9, 126.1, 126.0, 125.7, 124.9, 122.0, 111.9, 73.3, 59.3, 43.4, 42.6, 30.5; HRMS (TOF-ES+) m/z [M + H]$^+$ calcd for $C_{48}H_{39}N_4O_2Br_2$ 861.1440, found 861.1418.

Dispirooxindole-piperazine ***3d′***. White solid (18.4 mg, 0.021 mmol, 11% yield): mp 242 °C dec; IR (KBr) ν 3582, 2923, 1718, 1638, 1594, 1452, 1156, 1093, 930, 890, 855, 730 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.08 (d, J = 7.6 Hz, 1H), 7.86 (d, J = 7.6 Hz, 1H), 7.35−7.45 (m, 4H), 7.29−7.33 (m, 2H), 7.14−7.21 (m, 4H), 7.09−7.13 (m, 1H), 6.90−6.95 (m, 3H), 6.84−6.87 (m, 2H), 6.70−6.79 (m, 3H), 6.48−6.58 (m, 2H), 6.01 (d, J = 8.0 Hz, 1H), 5.95 (s, 1H), 5.76 (s, 1H), 5.07 (d, J = 15.6 Hz, 1H), 4.74 (dd, J = 16.0, 4.8 Hz, 2H), 4.41 (d, J = 16.0 Hz, 1H), 2.88−2.95 (m, 1H), 2.74−2.82 (m, 1H), 2.41−2.44 (m, 2H), 2.25−2.32 (m, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.6, 175.8, 145.0, 144.5, 136.4, 136.3, 136.1, 131.6, 129.2, 129.0, 128.4, 128.1, 127.2, 127.0, 125.7, 122.6, 121.9, 112.7, 111.5, 74.8, 73.6, 59.8, 59.5, 43.9, 43.3, 42.2, 31.4, 30.9, 30.4; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{48}H_{38}N_4O_2NaBr_2$ 883.1259, found 883.1241.

Dispirooxindole-piperazine ***3e***. White solid (97.0 mg, 0.13 mmol, 66% yield): mp 240 °C dec; IR (KBr) ν 3582, 3033, 2939, 2905, 1704, 1600, 1490, 1156, 1029, 950, 929, 808, 753, 721, 695, 659 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.60 (s, 2H), 7.43−7.45 (m, 4H), 7.36−7.40 (m, 4H), 7.29−7.33 (m, 2H), 6.82−6.88 (m, 6H), 6.62−6.69 (m, 6H), 5.97 (s, 2H), 5.04 (d, J = 15.2 Hz, 2H), 4.75 (d, J = 15.2 Hz, 2H), 2.63−2.69 (m, 2H), 2.43−2.54 (m, 4H), 2.31−2.33 (m, 2H), 2.17 (s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.1, 141.0, 136.8, 136.1, 133.1, 131.4, 129.5, 129.4, 129.1, 128.6, 128.5, 128.0, 126.7, 125.8, 125.2, 125.0, 108.6, 73.7, 59.3, 43.4, 42.5, 30.7, 21.3; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{50}H_{44}N_4O_2Na$ 755.3362, found 755.3381.

Dispirooxindole-piperazine ***3e′***. White solid (27.7 mg, 0.038 mmol, 19% yield): mp 193−194 °C; IR (KBr) ν 3580, 3027, 2915, 1721, 1703, 1605, 1493, 1335, 1163, 1073, 945, 808, 751, 699 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.97 (s, 1H), 7.68 (s, 1H), 7.35−7.52 (m, 5H), 7.30 (t, J = 7.0 Hz, 1H), 7.14−7.16 (m, 4H), 7.08 (dd, J = 14.5, 6.5 Hz, 2H), 6.87 (t, J = 6.0 Hz, 1H), 6.78−6.82 (m, 3H), 6.68 (t, J = 7.5 Hz, 2H), 6.60 (d, J = 7.0 Hz, 2H), 6.55 (t, J = 8.5 Hz, 2H), 5.96 (s, 1H), 5.92 (d, J = 7.5 Hz, 1H), 5.77 (s, 1H), 5.05 (d, J = 15.5 Hz, 1H), 4.72 (d, J = 16.0 Hz, 1H), 4.66 (d, J = 15.5 Hz, 2H), 4.34 (d, J = 16.0 Hz, 1H), 2.91−2.96 (m, 1H), 2.77−2.83 (m, 1H), 2.40−2.44 (m, 2H), 2.35 (s, 3H), 2.31−2.35 (m, 3H), 2.18 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.7, 176.3, 141.1, 140.7, 136.4, 129.0, 128.9, 128.5, 128.35, 128.27, 127.9, 127.3, 127.0, 126.7, 126.4, 126.2, 125.7, 125.6, 125.5, 124.8, 75.2, 73.8, 61.2, 60.1, 59.7, 43.9, 43.3, 42.4, 31.0, 30.4, 21.3, 21.2; [M + H]$^+$ calcd for $C_{50}H_{45}N_4O_2$ 733.3543, found 733.3536.

Dispirooxindole-piperazine ***3f***. White solid (94.2 mg, 0.12 mmol, 61% yield): mp 238 °C dec; IR (KBr) ν 3581, 2924, 1712, 1609, 1433, 1168, 1108, 1075, 918, 864, 834, 746, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.71 (d, J = 8.8 Hz, 2H), 7.47−7.49 (m, 4H), 7.38−7.42 (m, 4H), 7.32 (t, J = 7.2 Hz, 2H), 6.94−6.96 (m, 4H), 6.85−6.92 (m, 4H), 6.63−6.67 (m, 4H), 5.96 (s, 2H), 5.08 (d, J = 15.2 Hz, 2H), 4.83 (d, J = 15.2 Hz, 2H), 2.65−2.72 (m, 2H), 2.42−2.52 (m, 4H), 2.28−2.30 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.2, 144.7, 136.4, 136.1, 133.6, 132.7, 129.2, 129.0, 128.6, 128.2, 128.1, 126.9, 126.0, 125.8, 124.9, 122.8, 109.2, 73.3, 59.3, 43.5, 42.5, 30.5; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{48}H_{38}N_4O_2NaCl_2$ 795.2270, found 295.2299.

Dispirooxindole-piperazine ***3f′***. White solid (15.6 mg, 0.021 mmol, 14% yield): mp 238 °C dec; IR (KBr) ν 3582, 2923, 1710, 1598, 1450, 1349, 1287, 1156, 1075, 1031, 986, 867, 733 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.15 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.37−7.44 (m, 4H), 7.31 (t, J = 7.2 Hz, 1H), 7.17−7.23 (m, 5H), 7.10 (d, J = 7.6 Hz, 1H), 6.97−6.99 (m, 1H), 6.91 (t, J = 7.2 Hz, 1H), 6.70−6.80 (m, 6H), 6.61 (d, J = 5.6 Hz, 1H), 6.01 (d, J = 7.6 Hz, 1H), 5.96 (s, 1H), 5.77 (s, 1H), 5.07 (d, J = 15.2 Hz, 1H), 4.75 (d, J = 16.0 Hz, 1H), 4.73 (d, J = 15.2 Hz, 1H), 4.41 (d, J = 16.0 Hz, 1H), 2.94 (t, J = 11.2 Hz, 1H), 2.76−2.82 (m, 1H), 2.43−2.55 (m, 2H), 2.28−2.33 (m, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 177.5, 175.9, 145.0, 144.9, 144.6, 144.4, 136.1, 134.2, 133.5, 132.1, 131.7, 127.2, 125.3, 122.6, 122.3, 121.9, 112.7, 111.5, 109.9, 108.9, 74.6, 73.5, 59.8, 59.7, 43.9, 43.3, 42.4, 30.9, 30.4; HRMS (TOF-ES+) m/z [M + H]$^+$ calcd for $C_{48}H_{39}N_4O_2Cl_2$ 773.2450, found 773.2477.

Dispirooxindole-piperazine ***3g***. White solid (101.8 mg, 0.14 mmol, 69% yield): mp 214 °C dec; IR (KBr) ν 3032, 2940, 2828, 1713, 1629, 1600, 1488, 1471, 1339, 1185, 1160, 1061, 924, 862, 787, 739, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.62 (d, J = 6.8 Hz, 2H), 7.39−7.40 (m, 8H), 7.33−7.35 (m, 2H), 6.89−6.96 (m, 6H), 6.85 (d, J = 7.6 Hz, 2H), 6.64−6.71 (m, 4H), 5.97 (s, 2H), 5.17 (d, J = 15.6 Hz, 2H), 4.86 (d, J = 15.6 Hz, 2H), 2.67−2.73 (m, 2H), 2.43−2.55 (m, 4H), 2.34−2.36 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.1, 146.4 (d, $^1J_{C-F}$ = 241 Hz), 137.2, 136.1, 132.4 (d, $^3J_{C-F}$ = 8.0 Hz), 129.3 (d, $^3J_{C-F}$ = 8.0 Hz), 129.0 (d, $^2J_{C-F}$ = 19 Hz), 128.1, 127.0, 125.9, 124.9, 124.1, 120.7, 117.4 (d, $^2J_{C-F}$ = 19 Hz), 73.8, 59.6, 45.3, 42.7, 30.5; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{48}H_{38}N_4O_2F_2Na$ 763.2861, found 263.2888.

Dispirooxindole-piperazine ***3h***. White solid (125.6 mg, 0.15 mmol, 73% yield): mp 232 °C dec; IR (KBr) ν 3031, 2957, 2891, 1712, 1606, 1492, 1448, 1344, 1192, 1161, 1067, 963, 928, 848, 781, 740, 700 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.88 (d, J = 7.2 Hz, 2H), 7.36−7.40 (m, 4H), 7.25−7.32 (m, 8H), 6.88−7.00 (m, 8H), 6.66 (d, J = 7.6 Hz, 2H), 5.93 (s, 2H), 5.44 (d, J = 16.4 Hz, 2H), 5.26 (d, J = 16.4 Hz, 2H), 2.71−2.77 (m, 2H), 2.45−2.48 (m, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 178.3, 140.3, 137.9, 136.2, 135.1, 132.9, 132.5, 129.0, 127.6, 127.2, 127.1, 126.0, 125.0, 124.8, 124.0, 101.4, 73.0, 60.0, 44.5, 42.9, 30.5; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{48}H_{38}N_4O_2NaBr_2$ 883.1259, found 883.1282.

Dispirooxindole-piperazine ***3i***. White solid (60.8 mg, 0.11 mmol, 55% yield): mp 237 °C dec; IR (KBr) ν 3582, 2924, 1707, 1611, 1466, 1364, 1337, 1168, 1102, 1034, 745 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.77 (d, J = 6.8 Hz, 2H), 7.08−7.12 (m, 2H), 6.86−6.94 (m, 6H), 6.81 (d, J = 6.8 Hz, 2H), 6.75 (d, J = 7.6 Hz, 2H), 6.69−6.71 (m, 2H), 5.91 (s, 2H), 3.17 (s, 6H), 2.64−2.71 (m, 2H), 2.38−2.48 (m, 4H), 2.26−2.30 (m, 2H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 177.1, 143.9, 136.2, 133.1, 129.8, 129.32, 129.27, 128.8, 126.7, 125.8, 124.7, 124.1, 122.7, 108.2, 73.8, 59.6, 42.5, 30.6, 26.1; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{36}H_{32}N_4O_2Na$ 575.2423, found 575.2440.

Dispirooxindole-piperazine ***3i′***. White solid (10.0 mg, 0.018 mmol, 9% yield): mp 199 °C dec; IR (KBr) ν 3582, 2926, 1720, 1609, 1466, 1374, 1331, 1117, 1081, 939, 751 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.14 (d, J = 6.8 Hz, 1H), 7.78 (d, J = 7.2 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 6.99−7.09 (m, 3H), 6.87−6.97 (m, 4H), 6.77−6.82 (m, 2H), 6.65−6.69 (m, 2H), 5.81 (s, 1H), 5.75 (d, J = 7.6 Hz, 1H), 5.70 (s, 1H), 3.11 (s, 3H), 2.84−2.88 (m, 1H), 2.74−2.77 (m, 1H), 2.64 (s, 3H), 2.43−2.52 (m, 1H), 2.29−2.39 (m, 3H), 2.22−2.25 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 177.5, 175.0, 144.3, 143.7, 137.9, 136.5, 132.5, 132.2, 130.0, 129.7, 129.1, 128.8, 128.5, 128.1, 127.0, 126.8, 125.7, 125.5, 125.4, 124.9, 124.2, 122.8, 122.3, 109.0, 107.7, 75.1, 73.9, 60.5, 60.2, 44.0, 42.3, 30.9, 30.4,

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26.0, 25.82, 25.79; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{36}H_{32}N_4O_2Na$ 575.2423, found 575.2418.

General Procedures and Characterization Data of Compounds 5a–f. *N*-Substituted isatin (0.40 mmol), pyrrolidine (0.6 mmol, 1.5 equiv), and 3,5-dinitrobenzoic acid (127 mg, 0.6 mmol, 1.5 equiv) were dissolved in THF (4.0 mL). The resulting mixture was then stirred at room temperature. After completion of the reaction (monitored by TLC), the organic solvent was removed *in vacuo*, and the residue was purified via flash chromatography (petroleum ether/ethyl acetate, 19/1 to 12/1) to yield the corresponding product.

Dispirooxindole-piperazine ***5a***.[11f] White solid (75.5 mg, 0.13 mmol, 65% yield): mp 157–158 °C; IR (KBr) ν 3426, 2962, 2924, 1709, 1610, 1489, 1466, 1346, 1176, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.12–7.30 (m, 12H), 7.04 (t, J = 7.6 Hz, 2H), 6.77 (t, J = 7.2 Hz, 2H), 6.52 (d, J = 8.0 Hz, 2H), 4.85 (d, J = 16.0 Hz, 2H), 4.48 (d, J = 15.6 Hz, 2H), 3.62–3.65 (m, 2H), 2.40–2.43 (m, 2H), 1.99–2.05 (m, 2H), 1.86–1.88 (m, 2H), 1.58–1.68 (m, 4H), 1.40–1.47 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.9, 143.2, 136.6, 129.6, 128.9, 127.9, 127.7, 125.8, 125.6, 122.3, 109.0, 68.1, 59.0, 47.4, 42.8, 27.5, 21.0; HRMS (TOF-ES+) m/z [M + H]$^+$ calcd for $C_{38}H_{37}N_4O_2$ 581.2917, found 581.2890.

Dispirooxindole-piperazine ***5b***.[11f] White solid (102.7 mg, 0.16 mmol, 79% yield): mp 172–173 °C; IR (KBr) ν 3404, 2965, 2813, 1709, 1606, 1486, 1331, 1172, 819, 741, 697 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.21–7.31 (m, 10H), 7.14 (d, J = 6.8 Hz, 4H), 6.59 (d, J = 8.0 Hz, 2H), 4.84 (d, J = 16.0 Hz, 2H), 4.64 (d, J = 15.6 Hz, 2H), 3.54–3.61 (m, 2H), 2.44–2.47 (m, 2H), 2.00–2.07 (m, 2H), 1.88–1.90 (m, 2H), 1.61–1.75 (m, 4H), 1.43–1.50 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.6, 142.1, 136.0, 130.0, 129.1, 127.9, 127.43, 127.37, 127.1, 125.9, 111.1, 68.2, 59.1, 47.5, 42.8, 27.4, 20.9; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{38}H_{34}N_4O_2Cl_2Na$ 671.1957, found 671.1945.

Dispirooxindole-piperazine ***5c***. White solid (84.3 mg, 0.13 mmol, 65% yield): mp 211–213 °C; IR (KBr) ν 3415, 2959, 2928, 2854, 2806, 1713, 1605, 1490, 1439, 1332, 1175, 1143, 1078, 812, 734 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.29–7.37 (m, 6H), 7.19–7.20 (m, 4H), 7.09 (d, J = 8.0 Hz, 2H), 6.74–6.79 (m, 4H), 4.83 (d, J = 15.6 Hz, 2H), 4.61 (d, J = 15.6 Hz, 2H), 3.56–3.58 (m, 2H), 2.39–2.43 (m, 2H), 1.96–2.02 (m, 2H), 1.85–1.84 (m, 2H), 1.60–1.67 (m, 4H), 1.40–1.45 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.8, 144.7, 136.3, 134.3, 129.0, 128.1, 128.0, 127.3, 124.1, 122.3, 109.5, 67.7, 59.0, 47.3, 42.7, 27.4, 20.9; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{38}H_{34}N_4O_2Cl_2Na$ 671.1957, found 671.1967.

Dispirooxindole-piperazine ***5d***. White solid (50.8 mg, 0.069 mmol, 34% yield): mp 186–187 °C; IR (KBr) ν 3410, 2914, 2871, 1712, 1594, 1455, 1165, 1150, 1059, 962, 837, 739 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.26–7.38 (m, 6H), 7.17–7.19 (m, 4H), 7.03 (d, J = 8.0 Hz, 2H), 6.89–6.91 (d, J = 8.4 Hz, 4H), 4.82 (d, J = 15.6 Hz, 2H), 4.64 (d, J = 15.6 Hz, 2H), 3.55–3.57 (m, 2H), 2.39–2.42 (m, 2H), 1.99 (q, J = 8.0 Hz, 2H), 1.85–1.87 (s, 2H), 1.58–1.70 (m, 4H), 1.40–1.45 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.7, 144.9, 136.2, 129.0, 128.1, 127.9, 127.7, 125.3, 124.6, 122.8, 112.2, 67.6, 59.0, 47.3, 42.8, 27.4, 20.9; HRMS (TOF-ES+) m/z [M + H]$^+$ calcd for $C_{38}H_{35}N_4O_2Br_2$ 737.1127, found 737.1119.

Dispirooxindole-piperazine ***5e***. White solid (59.5 mg, 0.096 mmol, 48% yield): mp 152–153 °C; IR (KBr) ν 3411, 2965, 2813, 1713, 1491, 1449, 1334, 1170, 973, 813, 695 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.23–7.29 (m, 6H), 7.14–7.16 (m, 4H), 6.98–7.01 (m, 4H), 6.57–6.60 (m, 2H), 4.84 (d, J = 16.0 Hz, 2H), 4.65 (d, J = 15.6 Hz, 2H), 3.57–3.60 (m, 2H), 2.43–2.46 (m, 2H), 2.03 (q, J = 8.0 Hz, 2H), 1.87–1.89 (m, 2H), 1.60–1.70 (m, 4H), 1.43–1.47 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.7, 158.6 (d, $^1J_{C-F}$ = 238 Hz), 139.5, 136.2, 129.0, 127.8, 127.5, 127.3 (d, $^3J_{C-F}$ = 8.0 Hz), 116.4 (d, $^2J_{C-F}$ = 23 Hz), 113.7 (d, $^2J_{C-F}$ = 25 Hz), 110.4 (d, $^3J_{C-F}$ = 8.0 Hz), 68.2, 59.1, 47.4, 42.8, 27.4, 20.9; HRMS (TOF-ES+) m/z [M + H]$^+$ calcd for $C_{38}H_{35}N_4O_2F_2$ 617.2728, found 617.2734.

Dispirooxindole-piperazine ***5f***. White solid (77.9 mg, 0.13 mmol, 63% yield): mp 180–181 °C; IR (KBr) ν 3412, 2963, 2798, 1711, 1626, 1487, 1337, 1182, 1161, 915, 775, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.24–7.36 (m, 6H), 7.13–7.15 (m, 4H), 7.00–7.06 (m, 4H), 6.78–6.83 (m, 2H), 4.98 (d, J = 16.0 Hz, 2H), 4.50 (d, J = 16.0 Hz, 2H), 3.61–3.64 (m, 2H), 2.45–2.47 (m, 2H), 2.02–2.08 (m, 2H), 1.88–1.90 (m, 2H), 1.61–1.73 (m, 4H), 1.43–1.47 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.5, 137.3, 129.6, 129.1, 129.0, 128.2, 127.8, 127.2, 123.4, 121.8, 118.1, 68.5, 58.8, 47.5, 44.6, 27.4, 20.9; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{38}H_{34}N_4O_2F_2Na$ 639.2548, found 639.2532.

General Procedures and Characterization Data of Compounds 7a–d. *N*-Substituted isatin (0.40 mmol), glycine methyl ester (0.60 mmol, 1.5 equiv), and 3,5-dinitrobenzoic acid (0.60 mmol, 1.5 equiv) were dissolved in THF (4.0 mL). The resulting mixture was then stirred at room temperature. After completion of the reaction (monitored by TLC), the organic solvent was removed *in vacuo*. Then the residue was purified via flash chromatography (petroleum ether/ethyl acetate, 19/1 to 12/1) to yield the corresponding product.

Dispirooxindole-piperazine ***7a***. White solid (77.5 mg, 0.13 mmol, 63% yield): mp 213–215 °C; IR (KBr) ν 3349, 3298, 2947, 1746, 1694, 1609, 1219, 977, 916, 735, 699, 662 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.33 (s, 1H), 7.08–7.39 (m, 14H), 6.86 (t, J = 7.2 Hz, 1H), 6.78 (t, J = 7.6 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 7.6 Hz, 1H), 5.32 (dd, J = 11.6, 4.8 Hz, 1H), 4.97 (d, J = 16.0 Hz, 1H), 4.85 (d, J = 16.0 Hz, 1H), 4.78 (d, J = 16.0 Hz, 1H), 4.55 (d, J = 15.6 Hz, 1H), 4.18 (t, J = 5.6 Hz, 1H), 4.00 (d, J = 5.6 Hz, 1H), 3.65 (s, 3H), 3.53 (s, 3H), 3.09 (d, J = 11.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.1, 173.8, 171.4, 171.1, 143.1, 143.0, 136.2, 136.1, 130.0, 129.9, 128.98, 128.95, 128.0, 127.9,127.8, 127.0, 126.9, 124.9, 124.5, 123.0, 122.9, 109.7, 109.6, 79.6, 62.3, 59.6, 52.5, 52.0, 51.7, 50.7, 43.0, 42.5; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{36}H_{32}N_4O_6Na$ 639.2220, found 639.2207.

Dispirooxindole-piperazine ***7b***. White solid (86.7 mg, 0.13 mmol, 67% yield): mp 221–222 °C; IR (KBr) ν 3331, 3034, 2938, 1705, 1611, 1492, 1354, 1214, 1160, 819, 735 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.25–7.32 (m, 6H), 7.20 (d, J = 6.4 Hz, 2H), 7.10–7.12 (m, 2H), 7.06 (s, 2H), 6.94 (d, J = 8.0 Hz, 2H), 6.53 (d, J = 8.0 Hz, 1H), 6.49 (d, J = 8.0 Hz, 1H), 5.29 (dd, J = 11.6, 4.8 Hz, 1H), 4.93 (d, J = 16.0 Hz, 1H), 4.86 (d, J = 16.0 Hz, 1H), 4.77 (d, J = 16.0 Hz, 1H), 4.55–4.65 (m, 1H), 4.16 (t, J = 5.2 Hz, 1H), 3.96 (d, J = 5.2 Hz, 1H), 3.65 (s, 3H), 3.53 (s, 3H), 3.04 (d, J = 11.6 Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.2, 173.8, 171.4, 171.2, 140.8, 140.7, 136.2, 136.1, 132.2, 132.0, 130.1, 129.1, 129.01, 128.95, 128.8, 128.0, 127.8, 127.6, 127.44, 127.37, 127.3, 127.2, 125.8, 125.4, 109.6, 109.5, 62.5, 59.8, 52.5, 52.0, 51.7, 50.8, 42.9, 42.4, 21.2, 21.1; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{38}H_{36}N_4O_6Na$ 667.2533, found 667.2557.

Dispirooxindole-piperazine ***7c***. White solid (86.3 mg, 0.13 mmol, 63% yield): mp 272–273 °C; IR (KBr) ν 3838, 2947, 1751,1716, 1606, 1214, 812, 733, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.29–7.35 (m, 8H), 7.25 (d, J = 6.8 Hz, 2H), 7.19–7.21 (m, 2H), 7.13 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 6.77–6.91 (m, 3H), 5.28 (dd, J = 10.4, 2.0 Hz, 1H), 4.78–4.99 (m, 3H), 4.61 (d, J = 15.6 Hz, 1H), 4.13–4.14 (m, 1H), 3.68 (s, 3H), 3.65 (s, 3H), 3.11 (d, J = 10.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 175.2, 173.9, 171.2, 170.9, 144.6, 135.8, 134.6, 134.4, 129.0, 128.7, 128.3, 128.2, 128.1, 127.9, 126.5, 122.8, 109.9, 62.2, 59.8, 52.5, 52.1, 51.7, 50.7, 43.0, 42.4; HRMS (TOF-ES+) m/z [M + H]$^+$ calcd for $C_{36}H_{30}N_4O_6Cl_2Na$ 707.1440, found 707.1459.

Dispirooxindole-piperazine ***7d***. White solid (103.4 mg, 0.13 mmol, 67% yield): mp 216–217 °C; IR (KBr) ν 3348, 2946, 1748, 1709, 1601, 1214, 810, 726, 698 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.99–7.36 (m, 15H), 6.93 (dd, J = 8.0, 1.6 Hz, 1H), 5.27 (dd, J = 10.4, 2.4 Hz, 1H), 4.93 (d, J = 15.6 Hz, 1H), 4.82 (s, 2H), 4,63 (d, J = 16.0 Hz, 1H), 4.13–4.18 (m, 2H), 3.68–3.73 (m, 1H), 3.65 (s, 3H), 3.52 (s, 3H), 3.09 (d, J = 10.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 174.9, 173.8, 171.3, 170.9, 144.6, 135.82, 135.79, 129.0, 128.9, 128.7,128.3, 128.1, 127.8, 125.9, 123.1, 112.6, 62.2, 59.7, 52.4, 52.1, 51.8, 50.5, 43.0, 42.7; HRMS (TOF-ES+) m/z [M + Na]$^+$ calcd for $C_{36}H_{30}N_4O_6Br_2Na$ 795.0430, found 795.0445.

X-ray Crystallography. CCDC numbers: 1421682 for **3a**, 1421681 for **3a′**, and 1021637 for **7a**.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02088.

^{1}H NMR and ^{13}C NMR spectra for compounds **3a**−**i**, **3a**′−**f**′, **3i**′, **5a**−**f**, and **7a**−**d** and X-ray structures of dispirooxindole-piperazines **3a**, **3a**′, and **7a** (PDF)

CIFs of dispirooxindole-piperazines **3a**, **3a**′, and **7a** (ZIP)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Dai, W.; Jiang, X. L.; Wu, Q.; Shi, F.; Tu, S. J. *J. Org. Chem.* **2015**, *80*, 5737−5744. (b) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2014**, *50*, 12434−12446. (c) Santos, M. M. M. *Tetrahedron* **2014**, *70*, 9735−9757. (d) Singh, S. N.; Regati, S.; Paul, A. K.; Layek, M.; Jayaprakash, S.; Reddy, K. V.; Deora, G. S.; Mukherjee, S.; Pal, M. *Tetrahedron Lett.* **2013**, *54*, 5448−5452. (e) Ding, K.; Wang, G.; Deschamps, J. R.; Parrish, D. A.; Wang, S. *Tetrahedron Lett.* **2005**, *46*, 5949−5951. (f) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−910.

(2) (a) Lanka, S.; Thennarasu, S.; Perumal, P. T. *Tetrahedron Lett.* **2014**, *55*, 2585−2588. (b) Yu, Z. B.; Liu, X. L.; Pan, B. W.; Chen, B.; Zhou, Y.; Wang, H. L. *Synth. Commun.* **2014**, *44*, 530−539. (c) Rajasekaran, T.; Karthik, G.; Sridhar, B.; Subba Reddy, B. V. *Org. Lett.* **2013**, *15*, 1512−1515. (d) Yuvaraj, P.; Reddy, B. S. R. *Tetrahedron Lett.* **2013**, *54*, 821−827. (e) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104−6155. (f) Liu, T. L.; Xue, Z. Y.; Tao, H. Y.; Wang, C. J. *Org. Biomol. Chem.* **2011**, *9*, 1980−6. (g) Tabatabaei Rezaei, S. J.; Nabid, M. R.; Yari, A.; Ng, S. W. *Ultrason. Sonochem.* **2011**, *18*, 49−53.

(3) (a) Zhao, H. W.; Yang, Z.; Meng, W.; Tian, T.; Li, B.; Song, X. Q.; Chen, X. Q.; Pang, H. L. *Adv. Synth. Catal.* **2015**, *357*, 2492−2502. (b) Naga Siva Rao, J.; Raghunathan, R. *Tetrahedron Lett.* **2012**, *53*, 854−858. (c) Kumar, R. S.; Rajesh, S. M.; Perumal, S.; Banerjee, D.; Yogeeswari, P.; Sriram, D. *Eur. J. Med. Chem.* **2010**, *45*, 411−422. (d) Thangamani, A. *Eur. J. Med. Chem.* **2010**, *45*, 6120−6126.

(4) Sun, Y. H.; Xiong, Y.; Peng, C. Q.; Li, W.; Xiao, J. A.; Yang, H. *Org. Biomol. Chem.* **2015**, *13*, 7907−7910.

(5) (a) Pinder, A. R. *Nat. Prod. Rep.* **1985**, *2*, 181−187. (b) Noravyan, A. S.; Dabaeva, V. V.; Vartanyan, S. A. *Pharm. Chem. J.* **1983**, *17*, 615−622.

(6) Zheng, M. F.; Xu, C. H.; Ma, J. W.; Sun, Y.; Du, F. F.; Liu, H.; Lin, L. P.; Li, C.; Ding, J.; Chen, K. X.; Jiang, H. L. *Bioorg. Med. Chem.* **2007**, *15*, 1815−1827.

(7) Vincetti, P.; Caporuscio, F.; Kaptein, S.; Gioiello, A.; Mancino, V.; Suzuki, Y.; Yamamoto, N.; Crespan, E.; Lossani, A.; Maga, G.; Rastelli, G.; Castagnolo, D.; Neyts, J.; Leyssen, P.; Costantino, G.; Radi, M. *J. Med. Chem.* **2015**, *58*, 4964−4975.

(8) (a) Hepperle, M.; Eckert, J.; Gala, D.; Shen, L.; Anderson Evans, C.; Goodman, A. *Tetrahedron Lett.* **2002**, *43*, 3359−3363. (b) Hepperle, M.; Eckert, J.; Gala, D. *Tetrahedron Lett.* **1999**, *40*, 5655−5659.

(9) Vembu, S.; Pazhamalai, S.; Gopalakrishnan, M. *Bioorg. Med. Chem.* **2015**, *23*, 4561−4566.

(10) (a) Mahmoodi, N.; Qian, Q.; Luk, L. Y. P.; Tanner, M. E. *Pure Appl. Chem.* **2013**, *85*, 1935−1948. (b) Lo, M. M. C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077−16086.

(11) (a) Haddad, S.; Boudriga, S.; Porzio, F.; Soldera, A.; Askri, M.; Knorr, M.; Rousselin, Y.; Kubicki, M. M.; Golz, C.; Strohmann, C. *J. Org. Chem.* **2015**, *80* (18), 9064−9075. (b) Banerjee, P.; Pandey, A. K. *RSC Adv.* **2014**, *4*, 33236−33244. (c) Shi, F.; Zhu, R. Y.; Dai, W.; Wang, C. S.; Tu, S. J. *Chem. - Eur. J.* **2014**, *20*, 2597−2604. (d) Guo, H. C.; Liu, H. L.; Zhu, F. L.; Na, R. S.; Jiang, H.; Wu, Y.; Zhang, L.; Li, Z.; Yu, H.; Wang, B.; Xiao, Y. M.; Hu, X. P.; Wang, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 12641−12645. (e) Qian, Y.; Zavalij, P. J.; Hu, W. H.; Doyle, M. P. *Org. Lett.* **2013**, *15*, 1564−1567. (f) Al Mamari, K.; Ennajih, H.; Zouihri, H.; Bouhfid, R.; Ng, S. W.; Essassi, E. M. *Tetrahedron Lett.* **2012**, *53*, 2328−2331. (g) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5334−5. (h) Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 6330−6331.

(12) Alimohammadi, K.; Sarrafi, Y.; Tajbakhsh, M.; Yeganegi, S.; Hamzehloueian, M. *Tetrahedron* **2011**, *67*, 1589−1597.

(13) (a) Lakshmi, N. V.; Thirumurugan, P.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 1064−1068. (b) Liu, H.; Dou, G. L.; Shi, D. Q. *J. Comb. Chem.* **2010**, *12*, 633−637.

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