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Highly diastereoselective synthesis of imidazolidine-dispirooxindoles via three-component [3+2] cycloadditions of isatins, 2-(aminomethyl)pyridine and isatin-based imines

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Abstract: In the presence of of Et_3N, the [3+2] cycloaddition of isatins, 2-(aminomethyl)pyridine and isatin-based imines proceeded readily, and furnished novel imidazolidine-dispirooxindoles in up to 84% yield with up to >99:1 diastereoselectivity. The relative configuration of the imidazolidine-dispirooxindoles was firmly confirmed on the basis of X-ray single crystal structure analysis. The reaction mechanism was assumed to account for the diastereoselective formation of the imidazolidine-dispirooxindoles.

Introduction

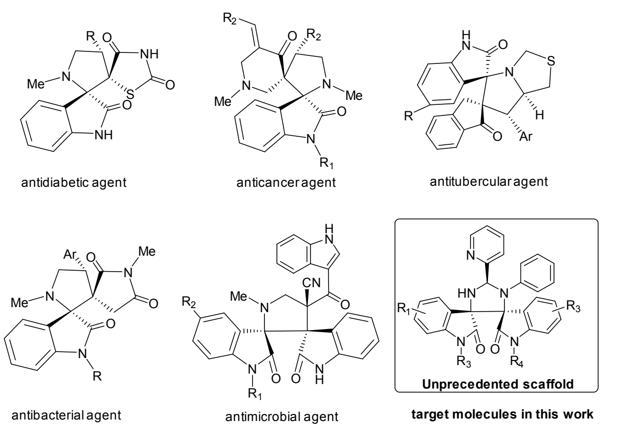

Figure 1 Representative bioactive dispirooxindoles

Dispirooxindoles constitute a class of structurally and stereochemically diverse and complex chemical entities, and exhibit a wide range of important biological activities, for example, antidiabetic, anticancer, antitubercular, antibacterial as well as antimicrobial activities as summarized in Figure 1.[1] Since the biological and medicinal importance with dispirooxindoles, organic chemists and medicinal chemists have been involved in developing useful and powerful methodologies for the synthesis of dispirooxindoles with potential biological activities.[2] Among the known synthetic methodologies, the [3+2] cycloaddition of azomethine ylides with various substituted dipolarophiles served as the main tools for the construction of dispirooxindoles.[3] In particular, most of the present pyrrolidine-dispirooxindoles were easily and efficiently produced by means of the [3+2] cycloaddition of isatin-derived azomethine ylides with various olefin-based dipolarophiles.[4] In spite of the progress made in the synthesis of an array of dispirooxindoles, it is still highly needed to develop more efficient and concise methodologies for the synthesis of dispirooxindoles bearing structural and stereochemical diversity.

In the recent years, the diastereoselective construction of structurally unique dispirooxindoles consisting of two spirooxindole motifs has gained attentions from several research groups. For example, in 2012 Yuan and co-workers reported the diastereoselective synthesis of dispiro[imidazolidine-2-thione]bisoxindoles through [3+2]cycloaddtion of 3-isothiocyanato oxindoles with isatinimines.[5] In the same year, Taylor research group carried out the diastereoselective construction of spirocyclic bisoxindoles via a double C-H, Ar-H coupling process.[6] In 2015, by following a similar self-cycloaddition strategy, Yang[7] and Thennarsu[8] research groups individually contributed to the first diastereoselective synthesis of imidazolidine-dispirooxindoles including two spirooxindoles at 2,5-positions of imidazolidine ring by treating azomethine ylides with isatin-based imines as shown in

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Copies of NMR for Imidazolidine-Dispirooxindoles **4**; X-ray single crystal structure analysis data for **4de**

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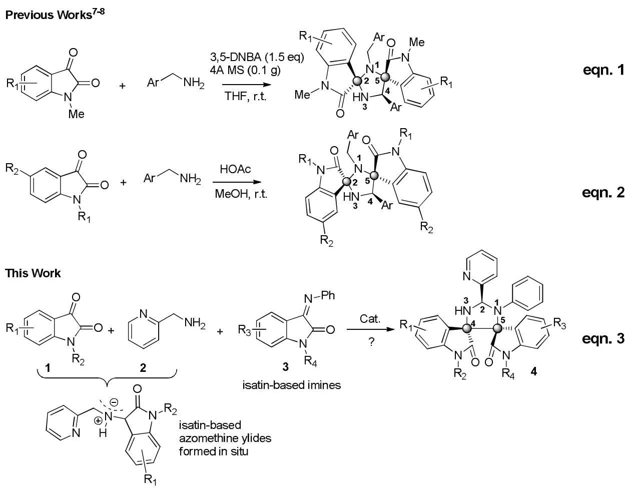
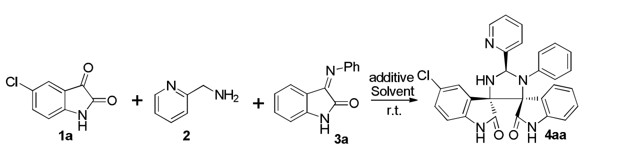
Scheme 1 (eqn. 1 & eqn. 2). In our work, we first designed the distereoselective three-component [3+2] cycloadditions of isatins, 2-(aminomethyl)pyridine and isatin-based imines for the construction of a series of novel imidazolidine-dispirooxindoles bearing two spirooxindoles at 4,5-positions of imidazolidine ring as outlined in Scheme 1 (eqn. 3). The [3+2] cycloadditions underwent smoothly, thus providing the designed unprecedented imidazolidine-dispirooxindoles in desirable chemical yields with high diastereoselectivities.



Scheme 1 Diastereoselective synthesis of imidazolidine-dispirooxindoles

Results and discussion

Table 1 Optimization of reaction conditions[a]

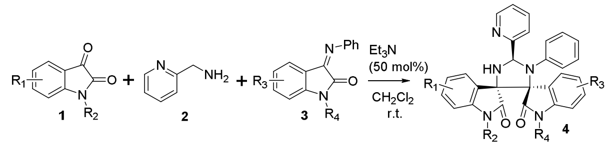


Entry	Solvent	Additive	Time (h)	Yield[b] (%)	dr[c]
1	THF	-	24	42	53:47
2	Toluene	-	24	15	90:10
3	CH_2Cl_2	-	24	53	83:17
4	CH_3CN	-	24	33	84:16
5	EtOH	-	24	19	72:28
6	CH_2Cl_2	CuI	40	trace	-
7	CH_2Cl_2	$Yb(OTf)_3$	40	31	18:81
8	CH_2Cl_2	$MgSO_4$	40	44	72:28
9	CH_2Cl_2	$PhCO_2H$	40	55	70:30
10	CH_2Cl_2	2,2'-Biphenol	40	61	73:27
11	CH_2Cl_2	Stearic acid	40	58	74:26
12	CH_2Cl_2	Quinine	40	52	85:15
13	CH_2Cl_2	Pyridine	40	64	76:24
14	CH_2Cl_2	DIPEA	40	51	85:15
15	CH_2Cl_2	DMAP	40	48	85:15
16	CH_2Cl_2	DBN	40	47	86:14
17	CH_2Cl_2	DBU	40	35	88:12
18	CH_2Cl_2	TBD	40	58	81:19
19	CH_2Cl_2	Et_3N (5 mol%)	72	58	88:12
20	CH_2Cl_2	Et_3N (10 mol%)	72	65	88:12
21	CH_2Cl_2	Et_3N (20 mol%)	72	58	89:11
22	CH_2Cl_2	Et_3N (30 mol%)	72	61	89:11
23	CH_2Cl_2	Et_3N (50 mol%)	72	70	92:8

[a] Reaction was conducted with 5-Cl-isatin **1a** (0.1mmol), 2-(aminomethyl)pyridine **2** (0.1mmol), isatin-based imine **3a** (0.1 mmol) in the absence or presence of 10 mol% of additive in the indicated solvents (0.5 mL) at room temperature. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy.

Initially, under the different reaction conditions, we examined the three-component [3+2] cycloadditionof **1a**, **2** and **3a** as shown in Table 1. Without any additives, we screened a series of solvents, and found that the use of CH_2Cl_2 gave **4aa** in better chemical yield with comparable diastereoselectivity (Table 1, entries 1-5). Moreover, Lewis acids and protonic acids as additives could cause the different loss in chemical yield and diastereoselectivity (Table 1, entries 6-11). At last, we examined a variety of organic bases as additives as well as catalytic loading of Et_3N, and discovered that 50 mol% of Et_3N behaved most efficiently, and furnished **4aa** in 70% yield with 92:8 dr (Table 1, entries 12-23). Considering the chemical yield and diastereoselectivity of **4aa** comprehensively, we determined the optimal reaction conditions as below: **1a**:**2**:**3a** = 1:1:1, 50 mol% Et_3N, CH_2Cl_2, room temperature.

Table 2 Extension of substrate scope[a]



Entry	**1** (R_1, R_2)	**3** (R_3, R_4)	Yield[b] (%)	dr[c]
1	**1a**(5-Cl, H)	**3a**(H, H)	70(**4aa**)	92:8
2	**1b** (H, H)	**3a** (H, H)	76(**4ba**)	>99:1
3	**1b** (H, H)	**3b** (5-MeO, H)	63(**4bb**)	85:15
4	**1a**(5-Cl, H)	**3c**(5-Cl, H)	77(**4ac**)	>99:1
5	**1a**(5-Cl, H)	**3b** (5-MeO, H)	70(**4ab**)	88:12
6	**1c** (5-MeO, H)	**3c** (5-Cl, H)	83(**4cc**)	67:33
7	**1c**(5-MeO, H)	**3b** (5-MeO, H)	61(**4cb**)	>99:1
8	**1d** (H, Bn)	**3a** (H, H)	80(**4da**)	75:25
9	**1e** (H, Me)	**3a**(H, H)	71(**4ea**)	76:24
10	**1d** (H, Bn)	**3d** (H, Me)	78(**4dd**)	>99:1
11	**1b** (H, H)	**3d** (H, Me)	63(**4bd**)	>99:1
12	**1d** (H, Bn)	**3e** (H, Bn)	81(**4de**)	>99:1
13	**1f** (5-F, H)	**3e** (H, Bn)	61(**4fe**)	>99:1
14	**1a** (5-Cl, H)	**3e** (H, Bn)	83(**4ae**)	>99:1
15	**1g** (6-Cl, H)	**3e** (H, Bn)	63(**4ge**)	>99:1
16	**1h** (5-Br, H)	**3e** (H, Bn)	78(**4he**)	>99:1
17	**1i** (6-Br, H)	**3e** (H, Bn)	61(**4ie**)	>99:1
18	**1b** (H, H)	**3e** (H, Bn)	84(**4be**)	>99:1
19	**1j** (5-Me, H)	**3e** (H, Bn)	78(**4je**)	>99:1
20	**1c** (5-MeO, H)	**3e** (H, Bn)	64(**4ce**)	>99:1
21	**1b** (H, H)	**3f**(5-Cl, Bn)	84((**4bf**)	>99:1
22	**1b** (H, H)	**3g**(5-Br, Bn)	81(**4bg**)	>99:1
23	**1b** (H, H)	**3h** (5-Me, Bn)	77(**4bh**)	>99:1
24	**1b** (H, H)	**3i** (5-MeO, Bn)	75(**4bi**)	>99:1
25[d]	**1a**(5-Cl, H)	**3a**(H, H)	NR[e]	-

[a] Reactions were conducted with Isatins **1** (0.1mmol), 2-(aminomethyl)pyridine **2** (0.1mmol), Isatin-based imines **3** (0.1mmol), Et_3N (0.05mmol) in CH_2Cl_2 (0.5ml) at room temperature for 72 h. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy. [d] Benzylamine was used. [e] No reaction

Subsequently, we extended the reaction scope as outlined in Table 2 under the optimal reaction conditions by using variable substrates **1** and **3**. In most cases, the [3+2] cycloadditions gave products **4** in the acceptable chemical yields with excellent diastereoselectivities (entries 1-2, 4, 7, 10-24). As for other cases, products **4** were formed in 63-80% chemical yields with 67:33-88:12 diastereoselectivities (entries 3, 5-6 and 8-9). Surprisingly, we found that the [3+2] cycloaddition of **1a**, benzylamine and **3a** did not take place at all (entry 25). Moreover, the use of single crystal X-ray analysis determined the relative configuration of **4de** as presented in Figure 2.[9] Based on the relative configuration of **4de**, the relative configurations of other imidazolidine-dispirooxindoles **4** were similarly assigned as shown in Table 2.

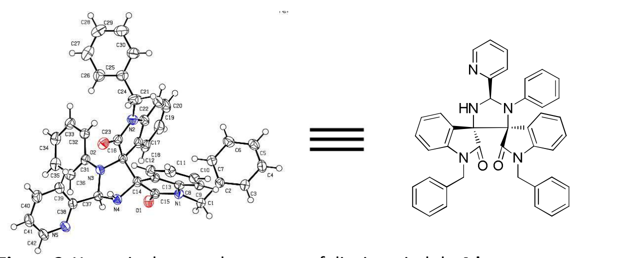
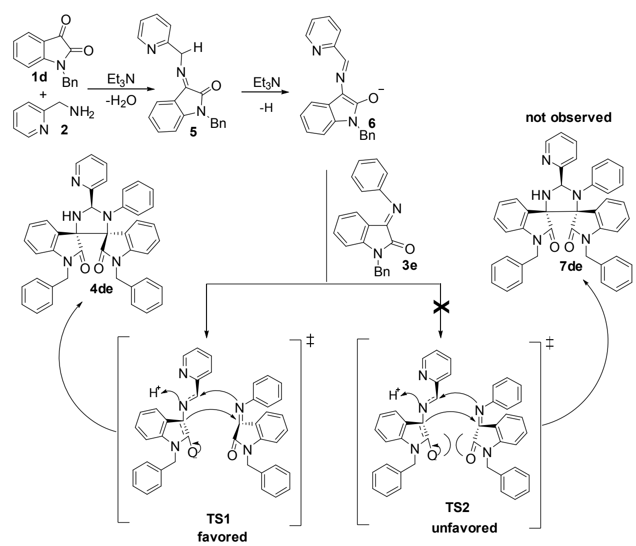


Figure 2 X-ray single crystal structure of dispirooxindole **4de**



Scheme 2 Proposed mechanism for [3+2] cycloaddition

To shed light on the formation and diastereoselectivity of **4de**, we proposed the mechanism for the [3+2] cycloaddition as illustrated in Scheme 2. Initially, under catalysis of Et_3N, isatin **1d** condenses easily with 2-(aminomethyl)pyridine **2** to afford imine **5**. Subsequently, the deprotonation of imine **5** with Et_3N give rise to enolate **6**. Finally, the cyclization of the resulted enolate **6** with imine **3e** formed diastereoisomer **4de** via the transition state **TS1**. In our case, the formation of diastereoisomer **7de** was not observed through the transition state **TS2**. With the aid of molecular model, it was found that two 2-indolinone rings have a face-to-face overlap in the transition state **TS2**, and the stronger electronstatic repulsion exists between the two π systems; in comparison, this type of electronstatic repulsion decrease remarkably in the transition state **TS1** owing to the parallel-displaced orientation between the two 2-indolinone rings.[10] Therefore, the transition state **TS1** is more stable than the transition state **TS2**. Noticeably, the [3+2] cycloaddition prefer to adopt the transition state **TS1** to lead to formation of thermodynamically more stable diastereoisomer **4de** instead of diastereoisomer **7de** bearing the severe steric hindrance between the two 2-indolinone moieties. Overall, it was deduced that the preference for the transition state **TS1** over the transition state **TS2** account for the excellent diastereoselectivity in the [3+2] cycloaddition.

Conclusions

In conclusion, by means of Et_3N-catalyzed [3+2] cycloaddition of isatin-derived azomethine ylides with isatin-based imines, we first accomplished the synthesis of imidazolidine-dispirooxindoles featuring two spirooxindoles at 4,5-positions of the imidazolidine ring. Significantly, our methodology not only enriched the synthetic chemistry of imidazolidine-dispirooxindoles, but also benefited to the discovery of novel dispirooxindoles with potential biological activities. At present, the design and stereoselective synthesis of new type of dispirooxindoles is undergoing in our lab, and will be reported in due course.

Experimental Section

General methods

Unless noted otherwise, all reagents were commercially available and used without further purification. All solvents were distilled from the appropriate drying agents immediately before use. Reactions were monitored by TLC carried out on 0.25 mm SDS silica gel coated glass plates (60F254) and compounds were detected with UV light. The compound melting point was determined by a melting point instrument. NMR spectra were recorded on 400 MHz instrument and calibrated using tetramethylsilane (TMS) as internal reference. High resolution mass spectra (HRMS) were recorded under electrospray ionization (ESI) conditions.

Typical procedure for the diastereoselective synthesis of imidazolidine-dispirooxindoles 4

Triethylamine (0.05 mmol, 6.9 µL, 5.0 mg) was added to a mixture of isatins **1** (0.1 mmol), 2-(aminomethyl)pyridine **2** (0.1 mmol, 9.8 µL, 10.8 mg) and Isatin-based imines **3** (0.1 mmol) in anhydrous CH_2Cl_2 (0.5 mL). The reaction was stirred at room temperature for 72 hours. After completion of the reaction, the crude product was purified by flash column chromatography on silica gel (petroleum ether / ethyl acetate = 1:2) to afford the pure products **4** as white powder (61-84% yield; 67:33- >99:1 dr).

4aa: Reaction time: 72 h; yield: 70% (0.07 mmol, 34.5 mg); white powder, mp>320 ℃; dr = 92:8; ^{1}H NMR (400 MHz, DMSO): δ 10.90 (s, 1H), 10.51 (s, 1H), 8.58 (s, 1H), 8.46 (d, J = 7.2Hz, 1H), 7.77 (s, 1H), 7.56 (s, 1H), 7.31-7.25 (m, 2H), 14 (s, 1H), 6.89-6.63 (m, 7H), 6.44 (d, J = 6.0Hz, 1H), 6.06 (s, 2H), 4.50 (d, J = 8.4Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 178.5, 175.9, 160.6, 148.6, 142.7, 142.6, 142.5, 137.6, 130.6, 130.2, 128.6, 127.3, 126.5, 126.0, 125.6, 124.0, 123.6, 122.9, 122.1, 118.0, 115.9, 111.3, 110.6, 79.5, 74.7, 73.5; HRMS(ESI) calculated for $C_{28}H_{21}ClN_5O_2$ (M + H$^+$): 494.13783, found 494.13620.

4ba: Reaction time: 72 h; yield: 76% (0.076 mmol, 34.9 mg); white powder, mp>320 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.47 (s, 2H), 8.58 (d, J = 4.0Hz, 1H), 8.45 (d, J = 8.0Hz, 1H), 7.79 (t, J = 7.6Hz, 1H), 7.50 (d, J = 7.6Hz, 1H), 7.32 (t, J = 5.6Hz, 1H), 7.20 (t, J = 7.6Hz, 1H), 7.12 (t, J = 7.6Hz, 1H), 6.97-6.88 (m, 2H), 6.82-6.61 (m, 6H), 6.43 (t, J = 7.2Hz, 1H), 6.04 (d, J = 6.0Hz, 2H), 4.14 (d, J = 5.2Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 178.7, 175.8, 160.6, 148.8, 144.7, 142.7, 142.6, 137.7, 130.7, 128.5, 127.3, 125.9, 124.0, 123.4, 123.3, 123.2, 122.1, 122.0, 117.9, 115.9, 110.5, 109.9, 79.5, 74.9, 73.3; HRMS(ESI) calculated for $C_{28}H_{22}N_5O_2$ (M + H$^+$): 460.17680, found 460.17548.

4bb: Reaction time: 72 h; yield: 63% (0.063 mmol, 30.8 mg); white powder, mp>320 ℃; dr = 85:15; ^{1}H NMR (400 MHz, DMSO): δ 10.63 (s, 1H), 10.48 (s, 1H), 8.58 (d, J = 4.0Hz, 1H), 8.45 (d, J = 8.0Hz, 1H), 7.78 (t, J = 7.6Hz, 1H), 7.51 (d, J = 8.0Hz, 1H), 7.31 (t, J = 5.6Hz, 1H), 7.19 (d, J = 8.0Hz, 1H), 6.95 (t, J = 7.6Hz, 1H), 6.82 (t, J = 7.6Hz, 2H), 6.72-6.62 (m, 4H), 6.54 (s, 1H), 6.45 (t, J = 7.2Hz, 2H), 6.06 (d, J = 6.8Hz, 2H), 4.11 (d, J = 9.2Hz, 1H), 3.52 (s, 3H);^{13}C NMR (100 MHz, DMSO):δ 178.5, 175.7, 160.6, 154.8, 148.8, 143.5, 142.7, 137.7, 136.0, 130.7, 128.6, 125.9, 124.6, 124.0, 123.4, 123.3, 122.1, 117.9, 115.9, 114.8, 113.9, 110.7, 109.9, 79.6, 75.0, 73.4, 55.7; HRMS(ESI) calculated for $C_{29}H_{24}N_5O_3$ (M + H$^+$): 490.18737, found 490.18607.

4ac: Reaction time: 72 h; yield: 77% (0.077 mmol, 40.6 mg); white powder, mp>320 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 11.04 (s, 1H), 10.69 (s, 1H), 8.56 (d, J = 4.4Hz, 1H), 8.42 (d, J = 8.0Hz, 1H), 7.78 (t, J = 7.6Hz, 1H), 7.53 (d, J = 2.0Hz, 1H), 7.33-7.20 (m, 3H), 6.87-6.94 (m, 3H), 6.76 (d, J = 8.4Hz, 1H), 6.68-6.63 (m, 2H), 6.49 (t, J = 7.2Hz, 1H), 6.06 (d, J = 6.8Hz, 2H), 4.61 (d, J = 8.8Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 178.1, 175.9, 160.3, 148.6, 142.3, 141.7, 137.6, 130.8, 130.1, 128.8, 126.9, 126.5, 126.2, 126.1, 125.2, 125.1, 124.1, 126.6, 118.5, 115.9, 112.1, 111.4, 79.5, 75.0, 73.4; HRMS(ESI) calculated for $C_{28}H_{20}Cl_2N_5O_2$ (M + H$^+$): 528.09886, found 528.09767.

4ab: Reaction time: 72 h; yield: 70% (0.07 mmol, 36.6 mg); white powder, mp>320 ℃; dr = 88:12; ^{1}H NMR (400 MHz, DMSO): δ 10.75 (s, 1H), 10.58 (s, 1H), 8.56 (d, J = 4.4Hz, 1H), 8.45 (d, J = 8.0Hz, 1H), 7.77 (t, J = 8.0Hz, 1H), 7.55 (d, J = 2.0Hz, 1H), 7.33-7.25 (m, 2H), 6.82 (t, J = 7.6Hz, 2H), 6.74-6.71 (m, 1H), 6.66-6.63 (m, 3H), 6.50 (d, J = 2.4Hz, 1H), 6.45 (t, J = 7.2Hz, 1H), 6.06 (d, J = 7.2Hz, 2H), 4.48 (d, J = 8.8Hz, 1H), 3.52 (s, 3H);^{13}C NMR (100 MHz, DMSO):δ 178.2, 175.9, 160.5, 154.8, 148.6, 142.6, 142.4, 137.6, 135.8, 130.6, 128.6, 126.5, 126.0, 125.5, 124.4, 124.0, 123.6, 118.0, 115.9, 114.8, 114.1, 111.3, 110.8, 79.5, 74.8, 73.5, 55.7; HRMS(ESI) calculated for $C_{29}H_{23}ClN_5O_3$ (M + H$^+$): 524.14839, found 524.14740.

4cc: Reaction time: 72 h; yield: 83% (0.083 mmol, 43.5 mg); white powder, mp>320 ℃; dr = 67:33; ^{1}H NMR (400 MHz, DMSO): δ 10.96 (s, 1H), 10.41 (s, 1H), 8.58 (d, J = 4.4Hz, 1H), 8.41 (d, J = 7.6Hz, 1H), 7.79 (t, J = 7.2Hz, 1H), 7.34-7.28 (m, 1H), 7.23-7.16 (m, 2H), 6.87-

6.73 (m, 5H), 6.68-6.63 (m, 1H), 6.57 (d, *J* = 8.4Hz, 1H), 6.48 (t, *J* = 7.6Hz, 1H), 6.06 (s 2H), 4.30 (d, *J* = 9.2Hz, 1H), 3.70 (s, 3H);^{13}C NMR (100 MHz, DMSO):δ 178.3, 175.8, 160.3, 155.1, 148.8, 142.5, 141.8, 137.7, 136.4, 129.9, 128.8, 127.0, 126.0, 125.4, 125.2, 124.2, 124.1, 123.4, 118.3, 115.9, 115.4, 113.3, 112.0, 110.3, 79.7, 75.4, 73.4, 55.9; HRMS(ESI) calculated for $C_{29}H_{23}ClN_5O_3$ (M + H$^+$): 524.14839, found 524.14746.

4cb: Reaction time: 72 h; yield: 61% (0.061 mmol, 31.7 mg); white powder, mp>320 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.66 (s, 1H), 10.30 (s, 1H), 8.58 (d, *J* = 4.0Hz, 1H), 8.44 (d, *J* = 7.6Hz, 1H), 7.78 (t, *J* = 7.2Hz, 1H), 7.32 (t, *J* = 2.0Hz, 1H), 7.18 (s, 1H), 6.84-6.63 (m, 6H), 6.54 (s, 2H), 6.44 (t, *J* = 7.2Hz, 1H), 6.05 (d, *J* = 7.2Hz, 2H), 4.14 (d, *J* = 9.2Hz, 1H), 3.69 (s, 3H), 3.51 (s, 3H);^{13}C NMR (100 MHz, DMSO):δ 178.5, 175.7, 160.5, 155.0, 154.8, 148.8, 142.7, 137.7, 136.5, 135.9, 128.6, 124.6, 124.5, 124.0, 123.3, 117.9, 115.9, 115.2, 114.9, 113.9, 113.3, 110.7, 110.2, 79.7, 75.3, 73.5, 55.9, 55.7; HRMS(ESI) calculated for $C_{30}H_{26}N_5O_4$ (M + H$^+$): 520.19793, found 520.19666.

4da: Reaction time: 72 h; yield: 80% (0.08 mmol, 44 mg); white powder, mp 251-253 ℃; dr = 75:25; ^{1}H NMR (400 MHz, DMSO): δ 10.77 (s, 1H), 8.58 (d, *J* = 4.8Hz, 1H), 8.48 (d, *J* = 8.0Hz, 1H), 7.80 (t, *J* = 7.6Hz, 1H), 7.61 (d, *J* = 7.6Hz, 1H), 7.34 (t, *J* = 4.8Hz, 1H), 7.20-7.16 (m, 4H), 7.02 (t, *J* = 7.6Hz, 1H), 6.85-6.71 (m, 9H), 6.53 (d, *J* = 8.0Hz, 1H), 6.45 (t, *J* = 7.2Hz, 1H), 6.07 (d, *J* = 7.2Hz, 2H), 4.88 (d, *J* = 16.0Hz, 1H), 4.52 (d, *J* = 16.0Hz, 1H), 4.35 (d, *J* = 9.2Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 178.7, 174.2, 160.6, 148.7, 143.9, 142.9, 142.6, 137.3, 135.7, 130.8, 130.0, 128.9, 127.6, 127.5, 127.3, 125.9, 124.1, 123.4, 123.1, 123.0, 122.9, 122.2, 118.1, 116.0, 110.7, 109.7, 79.5, 74.7, 73.6, 42.7; HRMS(ESI) calculated for $C_{35}H_{28}N_5O_2$ (M + H$^+$): 550.22375, found 550.22229.

4ea: Reaction time: 72 h; yield: 71% (0.071 mmol, 33.6 mg); white powder, mp 266-269 ℃; dr = 76:24; ^{1}H NMR (400 MHz, DMSO): δ 10.76 (s, 1H), 8.58 (d, *J* = 4.0Hz, 1H), 8.47 (d, *J* = 8.0Hz, 1H), 7.78 (t, *J* = 7.6Hz, 1H), 7.55 (d, *J* = 7.6Hz, 1H), 7.33-7.28 (m, 2H), 7.10 (t, *J* = 7.6Hz, 1H), 7.03 (t, *J* = 7.6Hz, 1H), 6.82-6.67 (m, 7H), 6.43 (t, *J* = 7.2Hz, 1H), 6.06 (d, *J* = 7.2Hz, 2H), 4.27 (d, *J* = 9.2Hz, 1H), 2.85 (s, 3H);^{13}C NMR (100 MHz, DMSO):δ 178.4, 174.2, 160.6, 148.8, 144.7, 142.7, 142.6, 137.7, 130.9, 130.1, 128.6, 126.8, 125.5, 124.1, 123.4, 122.9, 122.7, 122.6, 121.7, 118.0, 115.9, 110.5, 108.9, 79.7, 74.9, 73.5, 25.8; HRMS(ESI) calculated for $C_{29}H_{24}N_5O_2$ (M + H$^+$): 474.19245, found 474.19119.

4dd: Reaction time: 72 h; yield: 78% (0.078 mmol, 44 mg); white powder, mp 114-116 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 8.59 (d, *J* = 4.0Hz, 1H), 8.55 (d, *J* = 8.0Hz, 1H), 7.78 (t, *J* = 7.2Hz, 1H), 7.53 (d, *J* = 7.6Hz, 1H), 7.35-7.26 (m, 2H), 7.19-7.16 (m, 4H), 7.02-6.95 (m, 2H), 6.88-6.76 (m, 7H), 6.53 (d, *J* = 7.6Hz, 1H), 6.45 (t, *J* = 7.6Hz, 1H), 6.04 (d, *J* = 6.8Hz, 2H), 4.86 (d, *J* = 15.6Hz, 1H), 4.52 (d, *J* = 15.6Hz, 1H), 4.47 (d, *J* = 8.8Hz, 1H), 3.08 (s, 3H);^{13}C NMR (100 MHz, DMSO):δ 176.9, 174.1, 160.5, 148.7, 144.1, 143.9, 142.5, 137.7, 135.7, 130.9, 130.1, 128.9, 128.6, 127.6, 127.3, 126.9, 125.5, 124.1, 123.5, 122.8, 122.7, 122.6, 122.4, 118.2, 116.2, 109.7, 109.6, 79.6, 74.9, 73.5, 42.7, 26.5; HRMS(ESI) calculated for $C_{36}H_{30}N_5O_2$ (M + H$^+$): 564.23940, found 564.23779.

4bd: Reaction time: 72 h; yield: 63% (0.063 mmol, 29.8 mg); white powder, mp 253-255 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.44 (s, 1H), 8.59 (d, *J* = 4.4Hz, 1H), 8.50 (d, *J* = 8.0Hz, 1H), 7.79 (t, *J* = 7.6Hz, 1H), 7.40 (d, *J* = 7.6Hz, 1H), 7.33 (t, *J* = 5.6Hz, 1H), 7.24-7.16 (m, 2H), 6.92 (d, *J* = 7.2Hz, 3H), 6.87-6.77 (m, 3H), 6.72 (d, *J* = 9.2Hz, 1H), 6.59 (d, *J* = 7.6Hz, 1H), 6.43 (t, *J* = 8.0Hz, 1H), 6.00 (d, *J* = 7.2Hz, 2H), 4.24 (d, *J* = 9.2Hz, 1H), 3.07 (s, 3H);^{13}C NMR (100 MHz, DMSO):δ 176.9, 175.7, 160.6, 148.8, 144.0, 143.4, 142.6, 137.7, 130.8, 130.1, 128.6, 126.8, 125.4, 124.1, 123.4, 123.1, 122.6, 122.5, 121.8, 118.0, 117.7, 116.0, 110.0, 109.4, 79.6, 75.1, 73.3, 26.4; HRMS(ESI) calculated for $C_{29}H_{24}N_5O_2$ (M + H$^+$): 474.19245, found 474.19101.

4de:Reaction time: 72 h; yield: 81% (0.081 mmol, 51.8 mg); white powder, mp 108-110 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 8.60 (d, *J* = 4.0Hz, 1H), 8.53 (d, *J* = 8.0Hz, 1H), 7.82 (t, *J* = 7.2Hz, 1H), 7.56 (d, *J* = 7.6Hz, 1H), 7.35-7.32 (m, 1H), 7.25-7.10 (m, 10H), 6.94-6.91 (m, 2H), 6.84-6.72 (m, 7H), 6.57 (d, *J* = 8.0Hz, 1H), 6.44 (t, *J* = 8.8Hz, 1H), 6.05 (d, *J* = 7.2Hz, 2H) , 4.90 (s, 2H), 4.86 (d, *J* = 16.0Hz, 1H), 4.56 (d, *J* = 8.4Hz, 1H), 4.54 (d, *J* = 16.0Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 177.1, 174.5, 160.6, 148.7, 144.0, 143.6, 142.4, 137.8, 136.2, 135.7, 130.8, 130.1, 129.0, 128.5, 127.9, 127.8, 127.6, 127.3, 126.0, 124.1, 123.5, 123.0, 122.9, 122.8, 122.7, 118.3, 116.2, 110.4, 109.8, 79.6, 74.9, 73.5, 43.6, 42.7; HRMS(ESI) calculated for $C_{42}H_{34}N_5O_2$ (M + H$^+$): 640.27070, found 640.26917.

4fe: Reaction time: 72 h; yield: 61% (0.061 mmol, 34.6 mg); white powder, mp 277-279 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.43 (s, 1H), 8.58 (d, *J* = 4.4Hz, 1H), 8.48 (d, *J* = 8.0Hz, 1H), 7.80 (t, *J* = 7.2Hz, 1H), 7.34-7.25 (m, 5H), 7.14-7.04 (m, 4H), 6.98 (d, *J* = 7.6Hz, 1H), 6.83 (t, *J* = 7.6Hz, 1H), 6.77-6.72 (m, 4H), 6.66 (m, 1H), 6.43 (t, *J* = 7.2Hz, 1H), 6.02 (d, *J* = 7.2Hz, 2H), 5.05 (d, *J* = 15.6Hz, 1H), 4.84 (d, *J* = 15.6Hz, 1H), 4.62 (d, *J* = 8.8Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 176.9, 176.4, 160.6, 157.0, 148.6, 143.6, 142.4, 139.7, 137.7, 136.1, 130.2, 129.0, 128.5, 127.9, 127.4, 127.2, 124.1, 123.6, 122.9, 122.6, 118.3, 116.3, 110.3, 79.3, 75.2, 73.4, 43.6; HRMS(ESI) calculated for $C_{35}H_{27}FN_5O_2$ (M + H$^+$): 568.21433, found 568.21271.

4ae: Reaction time: 72 h; yield: 83% (0.083 mmol, 48.4 mg); white powder, mp 285-287 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.54 (s, 1H), 8.58 (d, *J* = 4.0Hz, 1H), 8.49 (d, *J* = 8.0Hz, 1H), 7.80 (t, *J* = 7.6Hz, 1H), 7.54 (s, 1H), 7.34-7.26 (m, 5H), 7.14 (t, *J* = 7.6Hz, 1H), 7.04 (s, 2H), 6.96 (d, *J* = 7.6Hz, 1H), 6.82 (d, *J* = 7.6Hz, 1H), 6.77-6.66 (m, 5H), 6.43 (t, *J* = 7.2Hz, 1H), 6.02 (d, *J* = 6.0Hz, 2H), 5.08 (d, *J* = 15.6Hz, 1H), 4.79 (d, *J* = 15.6Hz, 1H), 4.73 (d, *J* = 8.0Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 176.9, 176.3, 160.6, 148.6, 143.6, 142.6, 142.4, 137.6, 136.1, 130.7, 130.2, 129.1, 128.5, 127.9, 127.4, 127.2, 126.8, 126.4, 125.6, 124.0, 123.7, 122.9, 122.6, 118.3, 116.2, 111.4, 110.3, 79.7, 74.9, 73.5, 43.6; HRMS(ESI) calculated for $C_{35}H_{27}ClN_5O_2$ (M + H$^+$): 584.18478, found 584.18353.

4ge:Reaction time: 72 h; yield: 63% (0.063 mmol, 36.8 mg); white powder, mp 172-174 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.55 (s, 1H), 8.58 (d, *J* = 4.4Hz, 1H), 8.49 (d, *J* = 8.0Hz, 1H), 7.80 (t, *J* = 7.6Hz, 1H), 7.42 (d, *J* = 8.0Hz, 1H), 7.34-7.27 (m, 4H), 7.15 (t, *J* = 7.6Hz, 1H), 7.06 (d, *J* = 2.0Hz, 2H), 6.94 (d, *J* = 7.2Hz, 1H), 6.86-6.71

(m, 6H), 6.67 (s, 1H), 6.43 (t, *J* = 7.2Hz, 1H), 6.02 (d, *J* = 7.2Hz, 2H), 4.98 (d, *J* = 15.6Hz, 1H), 4.85 (d, *J* = 15.6Hz, 1H), 4.53 (d, *J* = 8.4Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 176.9, 176.4, 160.7, 148.6, 145.0, 143.5, 142.4, 137.7, 136.2, 135.2, 130.2, 128.9, 128.5, 127.9, 127.8, 127.7, 127.1, 124.1, 123.6, 122.8, 122.6, 122.4, 122.0, 118.3, 116.1, 110.3, 110.0, 79.5, 74.6, 73.3, 43.6; HRMS(ESI) calculated for $C_{35}H_{27}ClN_5O_2$ (M + H^+): 584.18478, found 584.18384.

4he: Reaction time: 72 h; yield: 78% (0.078 mmol, 49 mg); white powder, mp 289-291 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.51 (s, 1H), 8.57 (d, *J* = 4.4Hz, 1H), 8.49 (d, *J* = 8.0Hz, 1H), 7.80 (t, *J* = 7.2Hz, 1H), 7.66 (s, 1H), 7.44 (d, *J* = 8.0Hz, 1H), 7.34-7.27 (m, 4H), 7.13 (t, *J* = 7.6Hz, 1H), 7.05 (s, 2H), 6.95 (d, *J* = 7.6Hz, 1H), 6.84-6.70 (m, 5H), 6.62 (d, *J* = 8.0Hz, 1H), 6.43 (t, *J* = 7.2Hz, 1H), 6.01 (d, *J* = 6.0Hz, 2H), 5.07 (d, *J* = 15.6Hz, 1H), 4.97 (d, *J* = 15.6Hz, 1H), 4.73 (d, *J* = 8.4Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 176.9, 176.2, 160.6, 148.6, 143.5, 143.0, 142.4, 137.6, 136.1, 133.5, 130.2, 129.5, 129.1, 128.5, 127.9, 127.4, 127.2, 126.0, 124.0, 123.7, 122.9, 122.6, 118.3, 116.1, 114.1, 112.0, 110.3, 79.6, 74.9, 73.5, 43.6; HRMS(ESI) calculated for $C_{35}H_{27}BrN_5O_2$ (M + H^+): 628.13426, found 628.13330.

4ie: Reaction time: 72 h; yield: 61% (0.061 mmol, 38.3 mg); white powder, mp 175-177 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.53 (s, 1H), 8.57 (d, *J* = 4.8Hz, 1H), 8.48 (d, *J* = 8.0Hz, 1H), 7.80 (t, *J* = 7.2Hz, 1H), 7.79-7.15 (m, 5H), 7.06 (t, *J* = 7.6Hz, 1H), 7.05 (d, *J* = 3.6Hz, 2H), 7.00 (d, *J* = 2.0Hz, 1H), 6.98 (d, *J* = 1.6Hz, 1H), 6.95-6.70 (m, 6H), 6.43 (t, *J* = 7.2Hz, 1H), 6.01 (d, *J* = 6.8Hz, 2H), 5.10 (d, *J* = 15.6Hz, 1H), 4.84 (d, *J* = 15.6Hz, 1H), 4.53 (d, *J* = 8.4Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 176.9, 176.3, 160.7, 148.6, 145.1, 143.5, 142.4, 137.7, 136.2, 130.2, 128.9, 128.5, 128.1, 127.9, 127.8, 127.7, 127.1, 124.9, 124.1, 123.7, 123.5, 122.9, 122.8, 122.6, 118.3, 116.1, 112.8, 110.3, 79.5, 74.7, 73.2, 43.6; HRMS(ESI) calculated for $C_{35}H_{27}BrN_5O_2$ (M + H^+): 628.13426, found 628.13385.

4be:Reaction time: 72 h; yield: 84% (0.084 mmol, 46.2 mg); white powder, mp 248-250 ?; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.45 (s, 1H), 8.59 (d, *J* = 4.0Hz, 1H), 8.50 (d, *J* = 8.0Hz, 1H), 7.81 (t, *J* = 7.2Hz, 1H), 7.46 (d, *J* = 7.2Hz, 1H), 7.33 (t, *J* = 5.6Hz, 1H), 7.25-7.21 (m, 4H), 7.14-7.07 (m, 3H), 6.98 (d, *J* = 7.6Hz, 1H), 6.88-6.71 (m, 6H), 6.65 (d, *J* = 7.6Hz, 1H), 6.43 (t, *J* = 6.8Hz, 1H), 6.10 (d, *J* = 6.8Hz, 2H), 4.93 (d, *J* = 15.6Hz, 1H), 4.86 (d, *J* = 15.6Hz, 1H), 4.35 (d, *J* = 8.0Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 177.1, 176.1, 160.6, 148.8, 143.5, 142.5, 137.8, 136.2, 130.8, 130.0, 129.0, 128.5, 127.9, 127.7, 127.2, 126.0, 124.1, 123.4, 122.8, 122.2, 118.2, 116.1, 110.2, 110.0, 79.7, 75.1, 73.3, 43.6; HRMS(ESI) calculated for $C_{35}H_{28}N_5O_2$ (M + H^+): 550.22375, found 550.22229.

4je: Reaction time: 72 h; yield: 78% (0.078 mmol, 44 mg); white powder, mp 233-235 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.26 (s, 1H), 8.59 (d, *J* = 4.4Hz, 1H), 8.49 (d, *J* = 8.0Hz, 1H), 7.80 (t, *J* = 7.6Hz, 1H), 7.34-7.21 (m, 5H), 7.12 (t, *J* = 8.0Hz, 1H), 7.05 (d, *J* = 7.6Hz, 1H), 6.99 (d, *J* = 7.2Hz, 3H), 6.82 (t, *J* = 7.2Hz, 1H), 6.77-6.72 (m, 3H), 6.67 (d, *J* = 7.6Hz, 1H), 6.55 (d, *J* = 7.6Hz, 1H), 6.43 (t, *J* = 7.2Hz, 1H), 6.02 (d, *J* = 7.2Hz, 2H), 5.04 (d, *J* = 15.6Hz, 1H), 4.81 (d, *J* = 15.6Hz, 1H), 4.27 (d, *J* = 9.2Hz, 1H), 2.08 (s, 3H);^{13}C NMR (100 MHz, DMSO):δ 177.2, 176.1, 160.7, 148.8, 143.7, 142.6, 141.0, 137.7, 136.2, 131.2, 131.0, 129.0, 128.5, 127.8, 127.3, 127.2, 126.8, 124.1, 123.5, 123.4, 122.8, 122.7, 118.1, 116.1, 110.2, 109.8, 79.7, 75.1, 73.4, 43.5, 21.1; HRMS(ESI) calculated for $C_{36}H_{30}N_5O_2$ (M + H^+): 564.23940, found 564.23816.

4ce: Reaction time: 72 h; yield: 64% (0.064 mmol, 37.1 mg); white powder, mp 221-224 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.23 (s, 1H), 8.59 (d, *J* = 4.0Hz, 1H), 8.48 (d, *J* = 8.0Hz, 1H), 7.81 (t, *J* = 7.6Hz, 1H), 7.33 (t, *J* = 5.6Hz, 1H), 7.24 (s, 3H), 7.14-7.10 (m, 2H), 7.00 (d, *J* = 7.2Hz, 3H), 6.83-6.68 (m, 6H), 6.58 (d, *J* = 8.8Hz, 1H), 6.43 (t, *J* = 7.2Hz, 1H), 6.01 (d, *J* = 6.4Hz, 2H), 5.06 (d, *J* = 16.0Hz, 1H), 4.83 (d, *J* = 16.0Hz, 1H), 4.38 (d, *J* = 8.8Hz, 1H), 3.55 (s, 3H);^{13}C NMR (100 MHz, DMSO):δ 177.1, 176.1, 160.6, 155.2, 148.7, 143.6, 142.6, 137.8, 136.5, 136.1, 130.1, 129.0, 128.5, 127.8, 127.4, 127.3, 124.4, 124.1, 123.4, 122.8, 118.2, 116.1, 116.0, 112.9, 110.5, 110.2, 79.8, 75.4, 73.4, 55.7, 43.5; HRMS(ESI) calculated for $C_{36}H_{30}N_5O_3$ (M + H^+): 580.23432, found 580.23254.

4bf:Reaction time: 72 h; yield: 84% (0.084 mmol, 49 mg); white powder, mp 274-276 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.60 (s, 1H), 8.59 (d, *J* = 4.8Hz, 1H), 8.45 (d, *J* = 8.0Hz, 1H), 7.82 (t, *J* = 7.2Hz, 1H), 7.44 (d, *J* = 7.6Hz, 1H), 7.36-7.33 (m, 1H), 7.27-7.22 (m, 5H), 7.04-7.01 (m, 2H), 6.93 (s, 1H), 6.89 (t, *J* = 10.4Hz, 1H), 6.86-6.74 (m, 3H), 6.69 (t, *J* = 9.6Hz, 2H), 6.48 (t, *J* = 7.6Hz, 1H), 6.02 (d, *J* = 7.2Hz, 2H), 4.93 (d, *J* = 15.6Hz, 1H), 4.85 (d, *J* = 15.6Hz, 1H), 4.48 (d, *J* = 8.4Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 176.7, 176.2, 160.3, 148.7, 143.4, 142.5, 142.3, 137.8, 135.8, 131.0, 130.0, 129.1, 128.7, 128.0, 127.7, 126.9, 126.8, 126.2, 125.1, 124.1, 123.4, 123.1, 122.4, 118.6, 116.2, 111.7, 110.2, 79.7, 75.4, 73.2, 43.7; HRMS(ESI) calculated for $C_{35}H_{28}ClN_5O_2$ (M + H^+): 584.18478, found 584.18414.

4bg:Reaction time: 72 h; yield: 81% (0.081 mmol, 50.8 mg); white powder, mp 280-282 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.58 (s, 1H), 8.59 (d, *J* = 4.0Hz, 1H), 8.45 (d, *J* = 8.0Hz, 1H), 7.82 (t, *J* = 7.2Hz, 1H), 7.44 (d, *J* = 7.2Hz, 1H), 7.36-7.32 (m, 2H), 7.25 (s, 4H), 7.05-7.02 (m, 3H), 6.87 (t, *J* = 7.6Hz, 1H), 6.80 (t, *J* = 7.6Hz, 2H), 6.71-6.67 (m, 3H), 6.48 (t, *J* = 6.8Hz, 1H), 6.01 (d, *J* = 5.6Hz, 2H), 4.92 (d, *J* = 15.6Hz, 1H), 4.85 (d, *J* = 15.6Hz, 1H), 4.48 (d, *J* = 8.8Hz, 1H);^{13}C NMR (100 MHz, DMSO):δ 176.6, 176.2, 160.3, 148.7, 143.4, 142.9, 142.2, 137.8, 135.8, 132.8, 131.0, 130.2, 129.5, 129.2, 129.1, 128.7, 128.0, 127.8, 127.7, 126.2, 125.4, 124.1, 123.4, 123.1, 122.4, 118.6, 117.6, 116.1, 114.7, 112.2, 110.2, 79.7, 75.4, 73.1, 43.6; HRMS(ESI) calculated for $C_{35}H_{28}BrN_5O_2$ (M + H^+): 628.13426, found 628.13348.

4bh:Reaction time: 72 h; yield: 77% (0.077 mmol, 43.4 mg); white powder, mp 225-228 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.51 (s, 1H), 8.59 (d, *J* = 4.0Hz, 1H), 8.49 (d, *J* = 8.0Hz, 1H), 7.80 (t, *J* = 8.0Hz, 1H), 7.45 (d, *J* = 7.6Hz, 1H), 7.32 (t, *J* = 5.6Hz, 1H), 7.25-7.20 (m, 4H), 7.07 (d, *J* = 2.8Hz, 2H), 6.93 (d, *J* = 7.6Hz, 1H), 6.88-6.84 (m, 2H), 6.77-6.71 (m, 3H), 6.66-6.61 (m, 2H), 6.43 (t, *J* = 7.2Hz, 1H), 6.00 (d, *J* = 7.2Hz, 2H), 4.87 (s, 2H), 4.30 (d, *J* = 9.2Hz, 1H), 2.03 (s, 3H);^{13}C NMR (100 MHz, DMSO):δ 177.0, 176.2, 160.7, 148.7, 143.5, 142.5, 141.2, 137.8, 136.3, 131.4, 130.8, 130.4, 129.0, 128.5, 127.9, 127.8, 127.6, 126.0, 124.1, 123.4, 122.2, 118.0, 115.9, 110.0, 79.8, 75.1, 73.2, 43.6, 21.2; HRMS(ESI) calculated for $C_{36}H_{30}N_5O_2$ (M + H^+): 564.23940, found 564.23840.

4bi: Reaction time: 72 h; yield: 75% (0.075 mmol, 43.4 mg); white powder, mp 219-221 ℃; dr>99:1; ^{1}H NMR (400 MHz, DMSO): δ 10.50 (s, 1H), 8.59 (d, *J* = 4.4Hz, 1H), 8.49 (d, *J* = 8.0Hz, 1H), 7.80 (t, *J* = 7.6Hz, 1H), 7.46 (d, *J* = 7.6Hz, 1H),7.34-7.21 (m, 5H), 7.07 (d, *J* = 2.8Hz, 2H), 6.87 (d, *J* = 7.6Hz, 1H), 6.78-6.60 (m, 7H), 6.45 (t, *J* = 7.2Hz, 1H), 6.03 (d, *J* = 7.2Hz, 2H), 4.89 (d, *J* = 15.6Hz, 1H), 4.84 (d, *J* = 15.6Hz, 1H), 4.31 (d, *J* = 9.2Hz, 1H), 3.51 (s, 3H);^{13}C NMR (100 MHz, DMSO):δ 176.7, 176.1, 160.6, 155.3, 148.8, 143.5, 142.5, 137.8, 136.7, 136.3, 130.8, 129.0, 128.6, 127.9, 127.8, 126.1, 124.3, 124.1, 123.4, 123.3, 122.2, 118.2, 116.1, 115.0, 113.6, 110.5, 110.0, 79.7, 75.3, 73.3, 55.7, 43.6; HRMS(ESI) calculated for $C_{36}H_{30}N_5O_3$ (M + H^+): 580.23432, found 580.23279.

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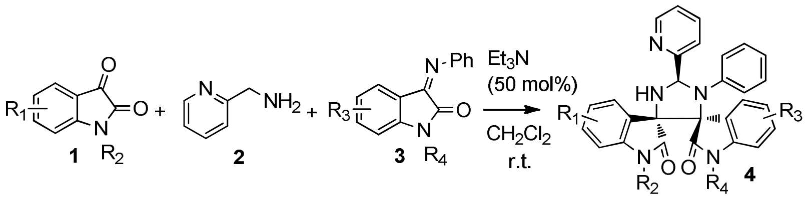
11. †Electronic Supplementary Information (ESI) available.

Graphical and textual abstract



24 samples in total
up to 84% yield
up to >99:1 dr