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Palladium-catalyzed intramolecular arylation for the synthesis of tetrahydro-5*H*-benzo[6,7]azocino[5,4-*b*]indol-5-ones

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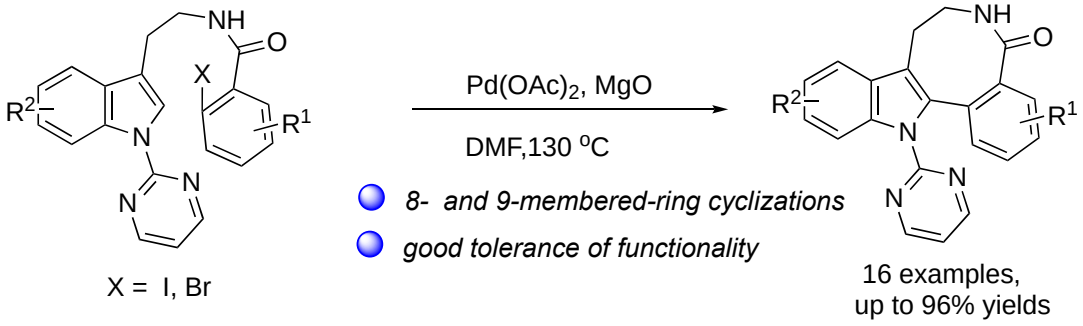
Abstract

8- and 9-membered, nitrogen-containing heterocycles are important structural motifs of many natural and synthetic compounds. Using pyrimidyl as a directing group, a variety of functionalized tetrahydro-5*H*-benzo[6,7]azocino[5,4-*b*]indol-5-one derivatives with 8- and 9-membered rings, was efficiently prepared through palladium-catalyzed intramolecular arylation (up to 96% yield). According to the control experiments, it is proposed that the mechanism of the protocol involves a C-H activation pathway.



Keywords: Indole, Arylation, Pd catalysis, Cyclization, Eight-membered, Nine-membered

Introduction

Indole compounds containing a five-, six- or seven-membered *N*-heterocycle are common, however, those with an eight-membered azocine or azocane ring are comparatively rare. [1] Indole-annulated eight-membered lactam frameworks existed in the structures of nature products such as balasubramide[2], decursivine[3], and drug candidate, 5,6,7,9-tetrahydro-8*H*-benzo[5,6]azocino[3,4-*b*]indol-8-one[4] (Figure 1).

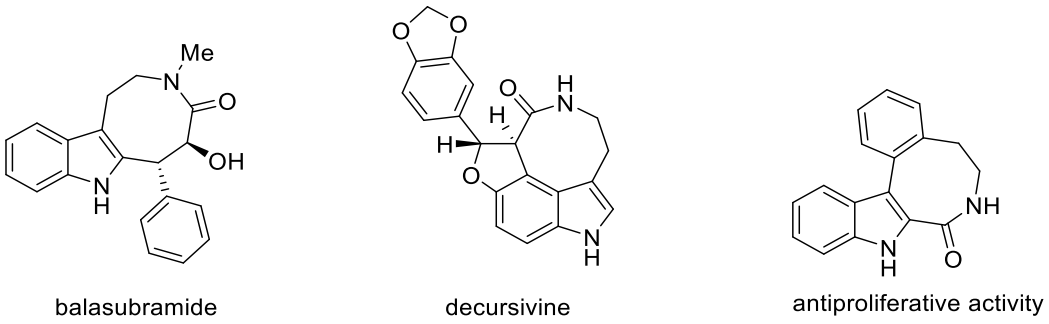
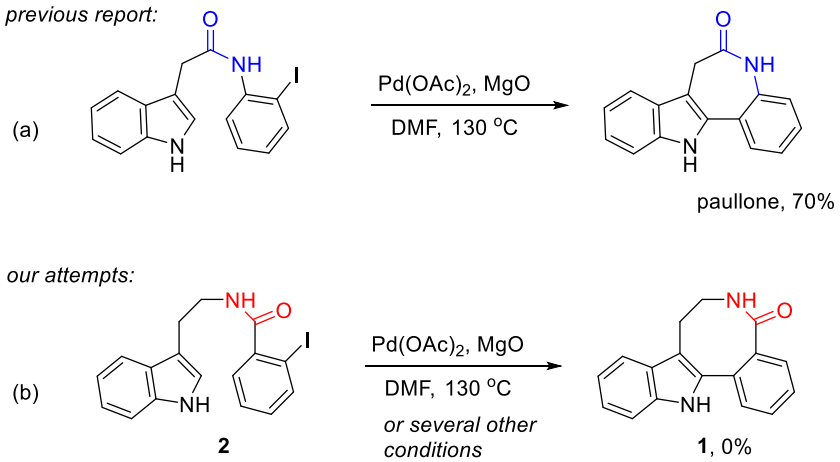


Figure1 Indole-annulated eight-membered lactams: natural products and a drug candidate.

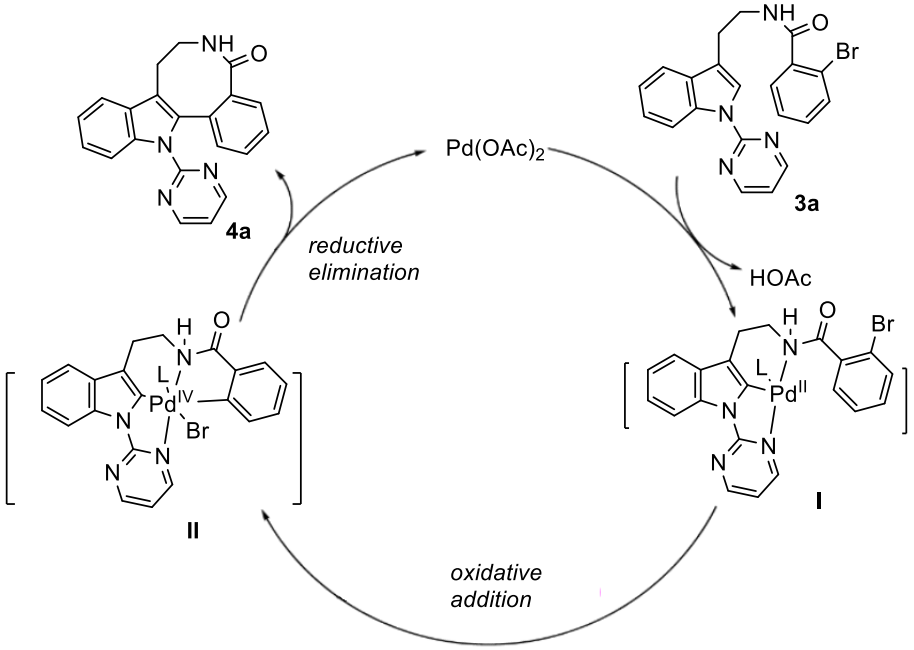
The construction of medium-sized 8- to 11-membered rings is a longstanding challenge in organic synthesis, since the kinetic and thermodynamic barriers associated with their synthesis are typically higher than for other rings sizes.[5,6] To date, no general approaches have been developed for tetrahydro-5*H*-benzo[6,7]azocino[5,4-*b*]indol-5-one **1** (Scheme 1), although some examples have been prepared through alkylative and allylative ring-opening of spiroindolines.[7,8] A Heck intramolecular coupling strategy was successfully realized to deliver paullone with a strained seven-membered ring, in 70% yield (Scheme 1a).[9] It seemed that using the above conditions or other improved conditions for Heck cyclization would possibly afford compound **1** from aryl iodide **2**, however, after identifying several Heck conditions, attempts failed to yield the desired product (Scheme 1b).



Scheme 1 Initial attempts.

These negative results led us to explore other ways to achieve the challenging intramolecular C-arylation. Pyrimidine has been used as an effective directing group in various C-2 arylations of indoles with aryl halides,[10] boronic acids,[11-13] arylsilanes[14-16] and aryl carboxylic acids.[17] We considered whether pyrimidine could serve as the directing group for palladium-catalyzed C-2-selective intramolecular arylation to produce tetrahydro-5*H*-benzo[6,7]azocino [5,4-*b*]indol-5-one derivatives, and a catalytic cycle of this Pd-catalyzed C−H arylation is

proposed in Scheme 2. The transformation occurs probably involving (1) the formation of palladacycle intermediate **I** by directing group assisted *ortho*-selective cyclometalation on the indole ring of the substrate with $Pd(OAc)_2$; (2) intramolecular oxidative addition of aromatic bromide to Pd(II) fragment provides Pd(IV) intermediate **II**; (3) C−C bond formation through reductive elimination affords the corresponding products along with the regeneration of the Pd(II) species.

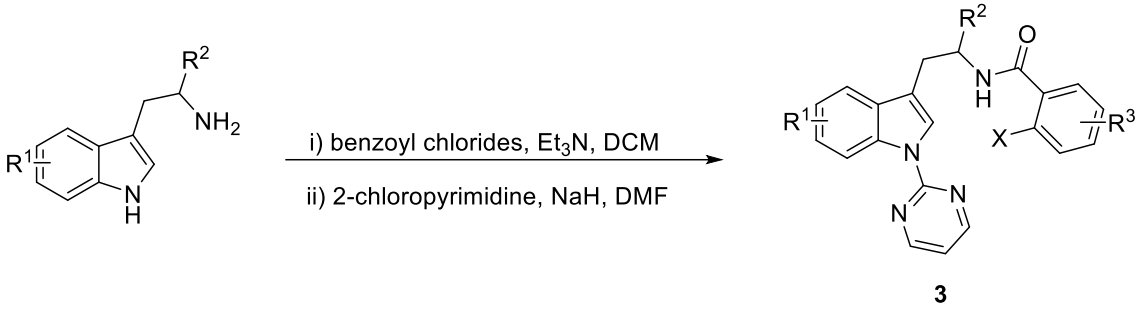


Scheme 2 Plausible mechanism for the intramolecular arylation.

Results and Discussion

With above proposal in mind, our investigation started with the preparation of precursors **3** for cyclization. Tryptamine and its derivatives were acylated with corresponding benzoyl chlorides, followed by reaction with 2-chloropyrimidine to afford a series of *N*-pyrimidyl indole derivatives (Scheme 3), amino derivative **3c** was prepared from its nitro precursor **3h** (see the Experimental Section). We chose compound **3a** as standard substrate to investigate suitable reaction conditions (Table 1). Initial screenings were performed using $Pd(OAc)_2$ with alkaline additives including $NaHCO_3$, EtONa, Et_3N, KOAc, Na_2CO_3 and MgO in DMF at 120 °C (Table 1, entries 1-6). We found that most bases could be employed in the desired transformation, among these screenings, MgO produce the best yield: compound **4a** was isolated in 92% yield. The structure of **4a** was unambiguously confirmed by NMR techniques, HRMS and single-crystal X-ray diffraction (CCDC: 2004614 contains the supplementary crystallographic data for compound **4a**. The data can be obtained free of charge from the Cambridge crystallographic data centre via www.ccdc.cam.ac.uk/structures). By contrast, when base was absent (Table 1, entry 7), **4a** was produced in decreased yield (39%). We assessed different amounts of MgO, and 3.0 equivalents was found to be optimal (Table 1, entries 8, 9). Further improvement in the yield of **4a** was achieved by enhancing the reaction temperature to 130 °C (Table 1, entry 10), however, the efficiency was reduced when it was carried out at 140 °C (Table 1, entry 11). When $Pd(OAc)_2$ was replaced by $PdCl_2$, the yield was only 32% (Table 1, entry 12). The demanding transformation also take place smoothly in other solvents such as DMA and DMSO (Table 1, entries 13, 14). Using 5 mol% of palladium led to incomplete conversion of **3a** within 16 h (Table 1, entry 15). To examine whether the desired transformation was suitable for scale-up, a gram-scale synthesis of

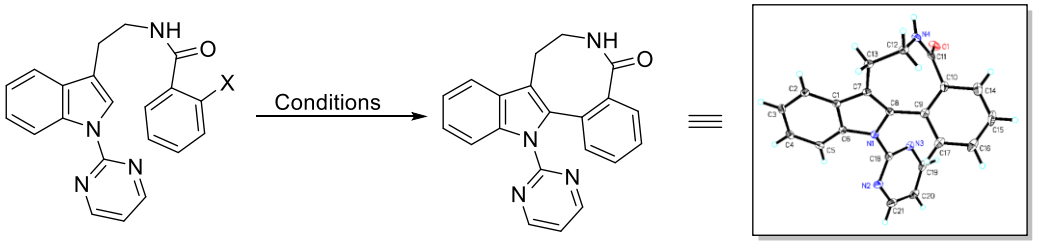
4a was also achieved with good efficiency (Table 1, entry 16). Moreover, iodide **3a'** and chloride **3a''** were both subjected to the optimal condition: **3a'** could be converted to **4a** uneventfully, however, **3a''** was did not react in this protocol (Table 1, entries 17, 18).



3

Scheme 3 Synthesis of precusors **3** for cyclization

Table 1 Conditions screened for 8-membered ring closure[a]



3a, X=Br
3a', X=I
3a'', X=Cl

4a

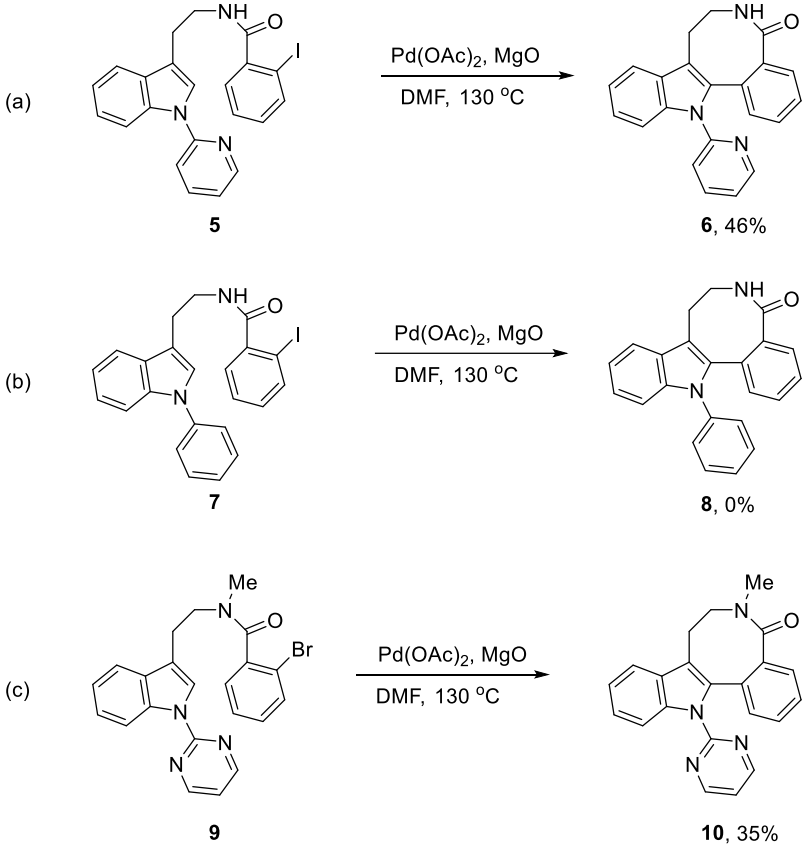
CCDC 2004614
(crystallised with CH_2Cl_2)

Entry	Catalyst/solvent/temp	Additives	Yield[b]
1	0.1 eq $Pd(OAc)_2$, DMF, 120 °C	3.0 eq $NaHCO_3$	85
2	0.1 eq $Pd(OAc)_2$, DMF, 120 °C	3.0 eq EtONa	78
3	0.1 eq $Pd(OAc)_2$, DMF, 120 °C	3.0 eq Et_3N	9
4	0.1 eq $Pd(OAc)_2$, DMF, 120 °C	3.0 eq KOAc	87
5	0.1 eq $Pd(OAc)_2$, DMF, 120 °C	3.0 eq Na_2CO_3	80
6	0.1 eq $Pd(OAc)_2$, DMF, 120 °C	3.0 eq MgO	92
7	0.1 eq $Pd(OAc)_2$, DMF, 130 °C	-	42
8	0.1 eq $Pd(OAc)_2$, DMF, 120 °C	2.0 eq MgO	88
9	0.1 eq $Pd(OAc)_2$, DMF, 120 °C	4.0 eq MgO	91
10	0.1 eq $Pd(OAc)_2$, DMF, 130 °C	3.0 eq MgO	96
11	0.1 eq $Pd(OAc)_2$, DMF, 140 °C	3.0 eq MgO	90
12	0.1 eq $PdCl_2$, DMF, 130 °C	3.0 eq MgO	32
13	0.1 eq $Pd(OAc)_2$, DMA, 130 °C	3.0 eq MgO	95
14	0.1 eq $Pd(OAc)_2$, DMSO, 130 °C	3.0 eq MgO	92
15	0.05 eq $Pd(OAc)_2$, DMF, 130 °C	3.0 eq MgO	84
16[c]	0.1 eq $Pd(OAc)_2$, DMF, 130 °C	3.0 eq MgO	92

17[d]	0.1 eq $Pd(OAc)_2$, DMF, 130 °C	3.0 eq MgO	94
18[e]	0.1 eq $Pd(OAc)_2$, DMF, 130 °C	3.0 eq MgO	0

[a] Reactions were performed using **3a** (1 mmol), base with Pd catalyst in 5.0 mL DMF for 16 h. [b] Isolated yield. [c] Reaction was performed at gram-scale: **3a** (4.8 mmol, 2.0 g) in 20.0 mL DMF. [d] Using **3a'** as substrate. [e] Using **3a''** as substrate.

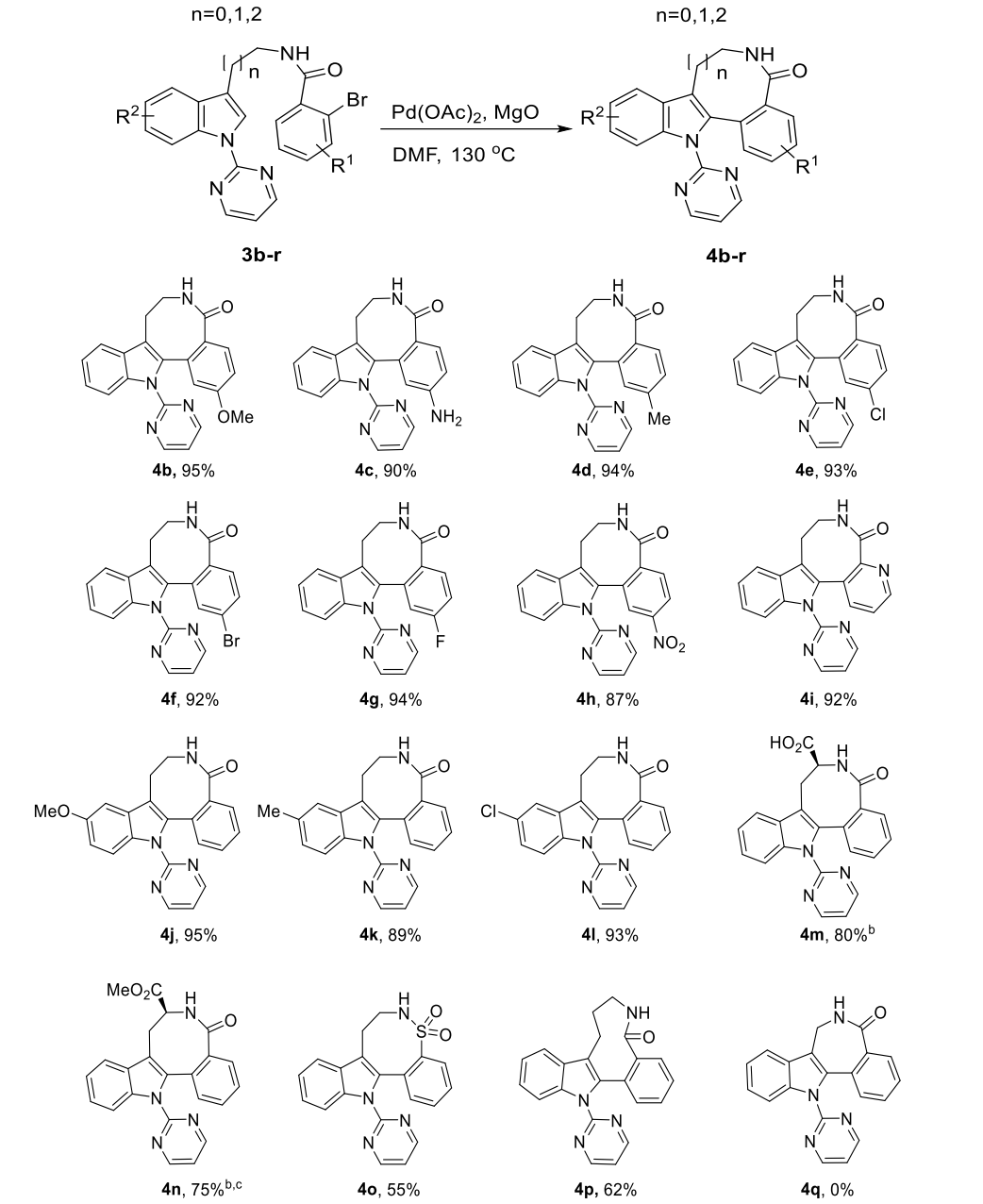
To get more insights into the mechanism of this reaction, several control experiments were performed. First, compound **5** with an *N*-2-pyridyl group on the indole nitrogen was subjected to the standard catalytic system, it gave the cyclized product **6** in only 46% yield (Scheme 4a). Next, when *N*-phenyl compound **7** was reacted, the desired C-H activation process did not occur (Scheme 4b). Furthermore, when the indole nitrogen was masked by a methyl group, precusor **9**, the corresponding cyclized product **10** could also be generated, however in a relative low yield (35%, Scheme 4c). Thus, in this transformation, both the pyrimidyl and free NH group can act as directing groups, being indispensable for highly efficient intramolecular arylation.



Scheme 4 Control experiments

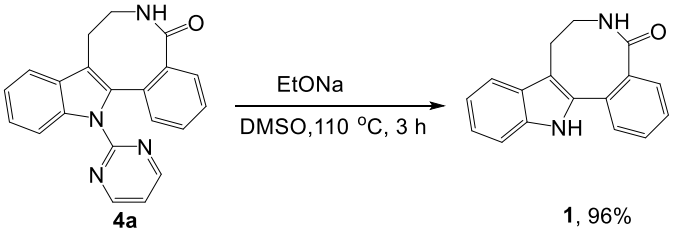
The generality of this transformation was briefly investigated (Table 2). Tetrahydro-5*H*-benzo[6,7]azocino [5,4-*b*]indol-5-one derivatives **4b-h** and **4j-l** bearing electron-donating groups (OMe, NH_2 and Me) or an electron-withdrawing substituent (Cl, Br, F and NO_2) could be produced by our protocol in good to excellent yields (75-95%). Notably, when the benzene ring was replaced by a pyridine fragment, it did not influence the efficiency, thus **4i** was obtained in 92% yield. Further, we found that using MgO led to hydrolysis of methyl ester group of methyl *N*-benzoyl-1-(pyrimidin-2-yl)-L-tryptophanate **3m**, but still the cyclization also proceeded to afford acid **4m** in 80% yield. The ester **4n** could also be obtained in 75% yield by changing the basic additive from MgO to $NaHCO_3$. Moreover, a sulfamide product **4o** could be prepared by this protocol in 55% yield. Compound **4p** with 9-membered ring was obtained in 62% yield, while 7-membered ring product **4q** could not be produced in these conditions, possibly it is not possible to form the requisite palladacycle intermediate.

Table 2 Substrates scope[a]



[a] Reactions were performed using compound **3** (1 mmol), MgO (3 mmoL), with Pd $(OAc)_2$ (0.1 mmol) in 5.0 mL DMF at 130 °C for 16-24 h, isolated yield. [b] from methy l *N*-benzoyl-1-(pyrimidin-2-yl)-*L*-tryptophanate **3m**. [c] MgO was replaced by $NaHCO_3$ (3 mmol).

Finally, to extend the synthetic practicability of this protocol, removal of the 2-pyrimidyl group from the product **4a** demonstrated. As exemplified in Scheme 5, the directing group could be readily removed in the presence of NaOEt in DMSO,[18,19] giving **1** in 96% yield.



Scheme 5. *N*-deprotection of **4a**.

Conclusions

In summary, a novel and efficient strategy to construct specific 8- or 9-membered indole-lactam skeletons has been developed, palladium-catalyzed intramolecular arylation being the core of the strategy. The reaction can proceed well with wide functional group tolerance. This work has represented a new perspective for the study of C-H bond activation. Further investigation of the extension of this method is in progress.

Experimental Section

General. All reagents used were of analytical purity. Column chromatography was carried out on silica gel. ^{1}H NMR spectra were recorded at 600 MHz and ^{13}C NMR spectra were recorded at 150 MHz and ^{19}F NMR spectra were recorded at 565 MHz. All new products were further characterized by HRMS; copies of their ^{1}H NMR and ^{13}C NMR and ^{19}F NMR spectra are provided in the Supporting Information. Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification.

Synthesis of compound 2

Triethylamine (1.26 g, 1.4 mL, 1.73 mmol) and tryptamine (1.0 g, 6.25 mmol) was dissolved in DCM (30 mL), 2-iodobenzoyl chloride (1.83 g, 946 µL, 6.875 mmol) was added dropwise to above solution at 0 ℃. After 2 h, the mixture was concentrated under reduced pressure, and diluted with EtOAc (100 mL). The organic fraction was washed with 5% $NaHCO_3$ solution (50 mL), 1N HCl solution (50 mL), brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification of crude product by flash column chromatography (DCM/MeOH=200:1 ~100:1) provided product **2** (2.39 g, 98%).

***N*-(2-(1*H*-indol-3-yl)ethyl)-2-iodobenzamide** (**2**). 2.39 g (98%); Gray solid; m.p.119.7 ~122.3℃ ; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.54 (t, *J* 7.72 Hz, 2 H), 3.33 (q, *J* 7.45 Hz, 2 H), 5.67 (s, 1 H), 7.00 - 7.05 (m, 1 H), 7.08 - 7.14 (m, 2 H), 7.20 (t, *J* 8.63 Hz, 1 H), 7.27 - 7.30 (m, 1 H), 7.30 - 7.34 (m, 1 H), 7.39 (d, *J* 9.26 Hz, 1 H), 7.71 (d, *J* 9.08 Hz, 1 H), 7.91 (d, *J* 9.08 Hz, 1 H), 8.34 (s, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 31.4, 44.5, 90.6, 107.1, 108.3, 113.7, 114.3, 116.7, 116.8, 121.1, 121.8, 121.9, 124.4, 129.2, 132.2, 134.3, 158.2. HRMS (ESI) *m/z* calcd for $C_{17}H_{15}IN_2O$ $[M+Na]^+$: 413.0116; found: 413.0121.

Synthesis of compounds 3a, 3a', 3a'', 3b, 3d-m,3o-q and 9.

Triethylamine (830 µL, 6 mmol) and amine (3 mmol) was dissolved in DCM (30 mL), benzoyl chloride (3.3 mmol) was added dropwise to above solution at 0 °C. After 2 h, the mixture was concentrated under reduced pressure, and diluted with EtOAc (50 mL). The organic fractions were washed with 5% $NaHCO_3$ solution (50 mL) and 1N HCl solution (50 mL). Then the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give a crude product which was used directly in the next step.

To a stirred solution of sodium hydride (180 mg, 4.5 mmol, 60%) in DMF at 0 °C, the above crude product was added. 2-chloropyrimidine (376 mg, 3.3 mmol), the reaction mixture was raised to 130 ℃ and stirred for 2 h. The solution was diluted with EtOAc, the organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated. Purification of crude product by flash column chromatography (PE/DCM/acetone =5:1:1~2:1:1) provided the compounds **3a**, **3a'**, **3a''**, **3b**, **3d-**, **3-q** and **9**.

2-Bromo-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3a). 756 mg (60%); White solid; m.p.92.5 ~93.7 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.14 - 3.17 (m, 2 H), 3.87 (q, *J* 6.72 Hz, 2 H), 5.98 (br. s., 1 H), 7.00 - 7.06 (m, 2 H), 7.25 - 7.28 (m, 1 H), 7.29 - 7.34 (m, 2 H), 7.35 - 7.39 (m, 1 H), 7.66 (d, *J* 7.81 Hz, 1 H), 7.81 (dd, *J* 7.99, 0.55 Hz, 1 H), 8.21 (s, 1 H), 8.68 (d, *J* 4.72 Hz, 2 H), 8.80 (d, *J* 8.36 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 26.9, 39.8, 112.6, 114.0, 116.7, 118.2, 121.7, 124.2, 127.6, 127.7, 128.8, 129.5, 130.1, 131.6, 132.2, 134.3, 137.2, 157.6, 157.7, 173.7. HRMS (ESI) *m/z* calcd for $C_{21}H_{17}BrN_4O$ $[M+Na]^+$: 443.0479; found: 443.0478.

2-Iodo-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3a'). 870 mg (62%); White solid; m.p.153.1~ 155.2 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.59 (t, *J* 7.81 Hz, 2 H), 3.42 (q, *J* 7.33 Hz, 2 H), 5.69 (s, 1 H), 6.97 - 7.04 (m, 2 H), 7.28 (s, 1 H), 7.30 - 7.34 (m, 1 H), 7.35 - 7.41 (m, 2 H), 7.72 (d, *J* 8.90 Hz, 1 H), 7.90 (d, *J* 9.08 Hz, 1 H), 8.36 (s, 1 H), 8.89 (d, *J* 5.27 Hz, 2 H), 9.02 (d, *J* 9.63 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 31.5, 44.3, 90.5, 111.2, 111.7, 112.3, 113.8, 116.6, 118.0, 118.4, 121.9, 122.2, 124.4, 124.5, 132.3, 134.5, 147.9, 148.3, 158.1. HRMS (ESI) *m/z* calcd for $C_{21}H_{17}IN_4O$ $[M+Na]^+$: 491.0324; found: 491.0339.

2-Chloro-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3a''). 654 mg (58%); White solid; m.p. 89.7~91.5 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.06 - 3.14 (m, 2 H), 3.81 - 3.87 (m, 2 H), 6.47 (s, 1 H), 6.98 (t, *J* 4.77 Hz, 1 H), 7.21 - 7.27 (m, 3 H), 7.28 - 7.32 (m, 1 H), 7.35 (td, *J* 7.75, 1.03 Hz, 1 H), 7.56 (dd, *J* 7.55, 1.67 Hz, 1 H), 7.63 (d, *J* 7.79 Hz, 1 H), 8.15 (s, 1 H), 8.63 (d, *J* 4.77 Hz, 2 H), 8.78 (d, J 8.42 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 30.4, 44.3, 111.2, 111.6, 112.1, 113.7, 114.1, 116.6, 117.9, 118.3, 121.3, 123.2, 124.3, 124.5, 126.4, 128.7, 130.5, 147.8, 148.2, 156.6. HRMS (ESI) *m/z* calcd for $C_{21}H_{17}ClN_4O$ $[M+Na]^+$: 399.0979; found: 399.0983.

3-Bromo-4-methoxy-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3b). 850 mg (63%); White solid; m.p.133.5~135.2 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.16 (t, *J* 6.72 Hz, 2 H), 3.75 (s, 3 H), 3.89 (q, *J* 6.72 Hz, 2 H), 6.18 (br. s., 1 H), 6.78 (dd, *J* 8.90, 3.09 Hz, 1 H), 7.03 - 7.06 (m, 2 H), 7.27 - 7.30 (m, 1 H) 7.35 - 7.41 (m, 2 H) 7.66 (d, *J* 7.63 Hz, 1 H), 8.21 (s, 1 H), 8.69, (d, *J* 4.72 Hz, 2 H), 8.81 (d, *J* 8.36 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.1, 39.8, 55.6, 109.4, 114.5, 115.9, 116.4, 117.0, 117.9, 118.8, 122.0, 123.6, 124.0, 130.9, 134.1, 135.8, 138.4, 157.9, 158.9, 167.4. HRMS (ESI) *m/z* calcd for $C_{22}H_{19}BrN_4O_2$ $[M+Na]^+$: 473.0582; found: 473.0583.

2-Bromo-4-methyl-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3d). 833 mg (64%); White solid; m.p. 133.5~134.7 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.32 (s, 3 H), 3.15 (t, *J* 6.73 Hz, 2 H), 3.85 - 3.93 (m, 2 H), 6.17 (br. s., 1 H), 7.04 (t, *J* 4.71 Hz, 1 H), 7.11 (d, *J* 7.85 Hz, 1 H), 7.28 (d, *J* 0.90 Hz, 1 H), 7.34 - 7.39 (m, 2 H), 7.43 (d, *J* 7.85 Hz, 1 H), 7.66 (d, *J* 7.63 Hz, 1 H), 8.20 (s, 1 H), 8.70 (d, *J* 4.71 Hz, 2 H), 8.81 (d, *J* 8.30 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 20.9, 25.1, 39.8, 115.9, 116.4, 117.1, 118.8, 119.1, 122.0, 123.6, 124.0, 128.2, 129.7, 130.9, 133.7, 134.7, 135.8, 141.8, 157.6, 158.1, 167.6. HRMS (ESI) *m/z* calcd for $C_{22}H_{19}BrN_4O$ $[M+Na]^+$: 457.0632; found: 457.0634.

2-Bromo-4-chloro-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3e). 750 mg (55%); White solid; m.p.153.5~155.1 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.15 (t, *J* 6.72 Hz, 2 H), 3.88 (q, *J* 6.54 Hz, 2 H), 6.16 (br. s., 1 H), 7.04 (t, *J* 4.81 Hz, 1 H), 7.26 - 7.29 (m, 2 H), 7.37 (t, *J* 7.72 Hz, 1 H), 7.43 (d, *J* 8.17 Hz, 1 H), 7.54 (d, *J* 1.82 Hz, 1 H), 7.64 (d, *J* 7.81 Hz, 1 H), 8.19 (s, 1 H), 8.69 (d, *J* 4.72 Hz, 2 H), 8.81 (d, *J* 8.36 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.0, 39.8, 116.0, 116.5, 116.9, 118.7, 119.8, 122.1, 123.6, 124.1, 127.8, 130.6, 130.9, 133.0, 135.8, 136.2, 136.4, 157.6, 158.1, 166.6. HRMS (ESI) *m/z* calcd for $C_{21}H_{16}BrClN_4O$ $[M+Na]^+$: 477.0087; found: 477.0088.

2,4-Dibromo-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3f). 895 mg (60%); White solid; m.p. 160.3~162.2 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.16 (t, *J* 6.72 Hz, 2 H), 3.89 (q, *J* 6.42 Hz, 2 H), 6.15 (br. s., 1 H),

7.06 (t, *J* 4.81 Hz, 1 H), 7.29 (s, 1 H), 7.36 - 7.41 (m, 2 H), 7.45 (dd, *J* 8.27, 1.73 Hz, 1 H), 7.65 (d, *J* 7.81 Hz, 1 H), 7.71 (d, *J* 1.82 Hz, 1 H), 8.20 (s, 1 H), 8.71 (d, *J* 4.72 Hz, 2 H), 8.82 (d, *J* 8.36 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.0, 39.8, 116.0, 116.5, 116.9, 118.7, 120.0, 122.1, 123.6, 124.1, 124.4, 130.7, 130.8, 130.9, 135.7, 135.8, 136.6, 157.6, 158.1, 166.7. HRMS (ESI) *m/z* calcd for $C_{21}H_{16}Br_2N_4O$ $[M+Na]^+$: 520.9580; found: 520.9583.

2-Bromo-4-fluoro-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3g). 762 mg (58%); White solid; m.p.145.5~147.1 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.16 (t, *J* 6.63 Hz, 2 H), 3.89 (q, *J* 6.54 Hz, 2 H), 6.18 (br. s., 1 H), 7.02 (td, *J* 8.22, 2.45 Hz, 1 H), 7.05 (t, *J* 4.72 Hz, 1 H), 7.25 - 7.30 (m, 2 H), 7.35 - 7.41 (m, 1 H), 7.52 (dd, *J* 8.54, 5.99 Hz, 1 H), 7.66 (d, *J* 7.63 Hz, 1 H), 8.20 (s, 1 H), 8.70 (d, *J* 4.72 Hz, 2 H), 8.82 (d, *J* 8.36 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.0, 39.8, 114.7, 114.9, 116.0, 116.5, 116.9, 118.8, 119.9, 120.4, 122.1, 123.6, 124.1, 130.9, 131.2, 134.0, 135.8, 157.6, 158.1, 161.7, 166.7. ^{19}F NMR (565 MHz, $CDCl_3$) δ -108.4 (s, 1 F). HRMS (ESI) *m/z* calcd for $C_{21}H_{16}BrFN_4O$ $[M+Na]^+$: 461.0381; found: 461.0384.

2-Bromo-4-nitro-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3h). 906 mg (65%); Yellow solid; m.p.184.8~186.2 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.18 (t, *J* 6.45 Hz, 2 H), 3.92 (q, *J* 6.48 Hz, 2 H), 6.10 (br. s., 1 H), 7.06 (t, *J* 4.81 Hz, 1 H), 7.27 - 7.30 (m, 1 H), 7.36 - 7.40 (m, 1 H), 7.60 (d, *J* 8.36 Hz, 1 H), 7.64 (d, *J* 7.63 Hz, 1 H), 8.13 (dd, *J* 8.36, 2.18 Hz, 1 H), 8.20 (s, 1 H), 8.39 (d, *J* 2.18 Hz, 1 H), 8.70 (d, *J* 4.72 Hz, 2 H), 8.81 (d, *J* 8.36 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.9, 39.8, 116.1, 116.5, 116.6, 118.7, 120.0, 122.1, 122.4, 123.7, 124.2, 128.4, 130.2, 130.7, 135.8, 143.5, 148.5, 157.5, 158.2, 165.8. HRMS (ESI) *m/z* calcd for $C_{21}H_{16}BrN_5O_3$ $[M+Na]^+$: 488.0326; found: 488.0328.

3-Bromo-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)picolinamide (3i). 670 mg (53%); White solid; m.p. 171.8~173.5 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.17 (t, *J* 6.54 Hz, 2 H), 3.91 (q, *J* 6.54 Hz, 2 H), 6.24 (br. s., 1 H), 7.06 (t, *J* 4.81 Hz, 1 H), 7.27 - 7.30 (m, 1 H), 7.36 - 7.41 (m, 2 H), 7.64 (d, *J* 7.81 Hz, 1 H), 8.21 (s, 1 H), 8.52 (d, *J* 4.90 Hz, 1 H), 8.64 - 8.74 (m, 3 H), 8.81 (d, *J* 8.54 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.0, 39.8, 116.1, 116.5, 116.6, 117.1, 118.7, 122.1, 123.5, 123.7, 124.2, 130.7, 135.8, 144.2, 148.6, 152.7, 157.5, 158.2, 165.2. HRMS (ESI) *m/z* calcd for $C_{20}H_{16}BrN_5O$ $[M+Na]^+$: 444.0428; found: 444.0430.

2-Bromo-*N*-(2-(5-methoxy-1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3j). 823 mg (61%); White solid; m.p.160.1~161.7 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.15 (t, *J* 6.72 Hz, 2 H), 3.74 (s, 3 H), 3.88 (q, J 6.72 Hz, 2 H), 6.16 (br. s., 1 H), 6.77 (dd, *J* 8.90, 3.09 Hz, 1 H), 7.01 - 7.05 (m, 2 H), 7.27 (d, *J* 0.73 Hz, 1 H), 7.33 - 7.39 (m, 2 H), 7.65 (d, *J* 7.63 Hz, 1 H), 8.19 (s, 1 H), 8.68 (d, *J* 4.72 Hz, 2 H), 8.79 (d, *J* 8.36 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.9, 39.6, 55.4, 109.2, 114.3, 115.7. 116.2, 116.8, 117.7, 118.6, 121.8, 123.4, 123.8, 130.7, 133.9, 135.6, 138.2, 157.4, 157.9, 158.7, 167.2. HRMS (ESI) *m/z* calcd for $C_{22}H_{19}Br_2N_4O_2$ $[M+Na]^+$: 473.0583; found: 473.0584.

2-Bromo-*N*-(2-(5-methyl-1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3k). 781 mg (60%); White solid; m.p.179.5~181.6 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.50 (s, 3 H), 3.14 (t, *J* 6.72 Hz, 2 H), 3.90 (q, J 6.72 Hz, 2 H), 6.16 (br. s., 1 H), 7.02 (t, *J* 4.81 Hz, 1 H), 7.19 (dd, *J* 8.45, 1.00 Hz, 1 H), 7.24 (td, *J* 7.72, 1.64 Hz, 1 H), 7.32 (td, *J* 7.49, 1.00 Hz, 1 H), 7.44 (s, 1 H), 7.50 (dd, *J* 7.63, 1.63 Hz, 1 H), 7.55 (dd, *J* 7.99, 0.73 Hz, 1 H), 8.16 (s, 1 H), 8.62 - 8.71 (m, 3 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 22.6, 29.1, 39.9, 115.7, 116.4, 118.7, 119.2, 119.7, 121.9, 122.7, 123.8, 127.5, 129.5, 131.0, 133.3, 135.8, 138.0, 157.6, 158.1, 167.6. HRMS (ESI) *m/z* calcd for $C_{22}H_{19}BrN_4O$ $[M+Na]^+$:457.0633; found: 457.0635.

2-Bromo-N-**(2-(5-chloro-1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3l).** 776 mg (57%); White solid; m.p.181.2~182.7 ºC; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.16 (t, *J* 6.72 Hz, 2 H), 3.89 (q, *J* 6.54 Hz, 2 H), 6.17 (br. s., 1 H), 7.05 (t, *J* 4.81 Hz, 1 H), 7.28 - 7.31 (m, 2 H), 7.39 (t, *J* 7.72 Hz, 1 H), 7.45 (d, *J* 8.17 Hz, 1 H), 7.56 (d, *J* 1.82 Hz, 1 H), 7.65 (d, *J* 7.81 Hz, 1 H), 8.21 (s, 1 H), 8.70 (d, *J* 4.72 Hz, 2 H), 8.82 (d, *J* 8.36 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.2, 39.7, 101.3, 112.9, 115.7, 116.8, 117.4, 119.3, 124.1, 127.5, 129.6, 130.7, 131.1, 131.7, 133.3, 137.9, 155.6, 157.5, 158.1, 167.7. HRMS (ESI) *m/z* calcd for $C_{21}H_{16}BrClN_4O$ $[M+Na]^+$:477.0085; found: 477.0088.

Methyl-*N*-(2-bromobenzoyl)-1-(pyrimidin-2-yl)-*L*-tryptophanate (3m). 788 mg (55%); Gray solid; m.p.144.7 ~146.4 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.45 - 3.59 (m, 2 H), 3.78 (s, 3 H), 5.21 (dt, *J* 7.45, 5.63 Hz, 1 H), 6.50 (d, *J* 7.63 Hz, 1 H), 7.02 - 7.09 (m, 2 H), 7.24 - 7.27 (m, 1 H), 7.29 - 7.38 (m, 3 H), 7.64 (d, *J* 7.81 Hz, 1 H), 7.85 (d, *J* 7.81 Hz, 1 H), 8.21 (s, 1 H), 8.68 (d, *J* 4.90 Hz, 2 H), 8.80 (d, *J* 8.36 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.3, 52.3, 52.9, 92.2, 113.9, 115.8, 116.1, 118.5, 121.8, 123.8, 124.3, 127.8, 128.2, 130.9, 131.0, 135.3, 139.8, 141.0, 157.3, 157.8, 168.5, 171.6. HRMS (ESI) *m/z* calcd for $C_{23}H_{19}BrN_4O_3$ [M+Na]+: 501.0530; found: 501.0533.

4-Bromo-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzenesulfonamide (3o). 780 mg (57%); Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.99 (t, *J* 7.07 Hz, 2 H), 3.34 (q, *J* 6.58 Hz, 2 H), 5.24 (t, *J* 5.72 Hz, 1 H), 7.06 (t, *J* 4.82 Hz, 1 H), 7.16 - 7.20 (m, 1 H), 7.32 (dd, *J* 7.97, 1.46 Hz, 1 H), 7.35 (d, *J* 7.18 Hz, 1 H), 7.38 - 7.41 (m, 2 H), 7.52 (dd, *J* 7.97, 1.01 Hz, 1 H), 8.08 (s, 1 H), 8.10 (dd, *J* 7.85, 1.57 Hz, 1 H), 8.70 (d, *J* 4.71 Hz, 2 H), 8.78 (d, *J* 8.30 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.4, 42.8, 115.7, 116.1, 116.5, 118.4, 119.6, 122.0, 123.8, 124.1, 127.6, 130.4, 131.4, 133.5, 134.9, 135.8, 138.5, 158.1. HRMS (ESI) *m/z* calcd for $C_{20}H_{17}BrN_4O_2S$ $[M+Na]^+$: 479.0141; found: 479.0149.

2-Bromo-*N*-(3-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)propyl)benzamide (3p). 820 mg (63%); White solid; m.p. 133.1~135.4 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.13 (q, *J* 7.27 Hz, 2 H), 2.92 (t, *J* 7.45 Hz, 2 H), 3.60 (q, *J* 6.90 Hz, 2 H), 6.08 (s, 1 H), 7.02 (t, *J* 4.72 Hz, 1 H), 7.23 - 7.27 (m, 2 H), 7.32 (td, *J* 7.49, 1.00 Hz, 1 H), 7.34 - 7.37 (m, 1 H), 7.47 (dd, *J* 7.63, 1.63 Hz, 1 H), 7.57 (dd, *J* 7.99, 0.73 Hz, 1 H), 7.60 (d, *J* 7.63 Hz, 1 H), 8.11 (s, 1 H), 8.68 (d, *J* 4.72 Hz, 2 H), 8.80 (d, *J* 8.36 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 22.6, 29.1, 39.9, 115.7, 116.4, 118.7, 119.2, 119.7, 121.9, 122.7, 123.8, 127.5, 129.5, 131.0, 131.1, 133.3, 135.8, 138.0, 157.6, 158.1, 167.6. HRMS (ESI) *m/z* calcd for $C_{22}H_{19}BrN_4O$ $[M+Na]^+$: 457.0632; found: 457.0635.

2-Bromo-*N*-((1-(pyrimidin-2-yl)-1*H*-indol-3-yl)methyl)benzamide (3q). 718 mg (59%); White solid; m.p. 226.5~228.1 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ 4.67 (d, *J* 5.63 Hz, 2 H), 7.11 - 7.13 (m, 1 H), 7.18 (t, *J* 7.45 Hz, 1 H), 7.21 - 7.28 (m, 2 H), 7.28 - 7.35 (m, 2 H), 7.53 (d, *J* 7.81 Hz, 1 H), 7.70 (d, *J* 7.63 Hz, 1 H), 8.28 (s, 1 H), 8.63 - 8.73 (m, 4 H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 34.2, 115.8, 116.1, 116.8, 118.9, 118.9, 121.5, 123.4, 123.7, 126.8, 128.4, 129.4, 130.1, 132.3, 135.0, 138.7, 156.8, 157.9, 167.2. HRMS (ESI) *m/z* calcd for $C_{20}H_{15}BrN_4O$ $[M+Na]^+$: 429.0319; found: 429.0321.

5-Bromo-*N*-methyl-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (9). 690 mg (53%); Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.48 (s, 3 H), 3.12 (t, *J* 6.72 Hz, 2 H), 3.88 (q, *J* 6.72 Hz, 2 H), 6.15 (s, 1 H), 7.01 (t, *J* 4.81 Hz, 1 H), 7.18 (dd, J 8.45, 1.00 Hz, 1 H), 7.22 (td, *J* 7.72, 1.64 Hz, 1 H), 7.30 (td, *J* 7.49, 1.00 Hz, 1 H), 7.43 (s, 1 H), 7.49 (dd, *J* 7.63, 1.63 Hz, 1 H), 7.53 (dd, *J* 7.99, 0.73 Hz, 1 H), 8.15 (s, 1 H), 8.63 - 8.69 (m, 3 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.4, 25.1, 39.8, 115.7, 116.1, 116.8, 118.7, 119.3, 123.6, 125.4, 127.4, 129.5, 131.0, 131.1, 131.5, 133.3, 134.0, 137.9, 157.5, 158.1, 167.6. HRMS (ESI) *m/z* calcd for $C_{22}H_{19}BrN_4O$ $[M+Na]^+$: 457.0634; found: 457.0635.

Synthesis of compound 3c

To a stirred solution of **3h** (500 mg, 1.07 mmol) in EtOH was added stannous chloride (1.01 g, 5.35 mmol) at 0 ℃ and the resulting mixture was stirred at 90 ℃ for 2 h. After completion, the reaction mixture was allowed to cool to rt and concentrated in vacuo. 1.0 M NaOH (20 mL) and EtOAc (30 mL) was added to the residue, and the resulting mixture was filtered through Celite. The filtrate was extracted with EtOAc and the combined organic layers were dried over Na_2SO_4 and concentrated. Purification of crude product by flash column chromatography (DCM/MeOH=100:1 ~50:1) provided the product **3c** (430 mg, 92%).

4-Amino-2-bromo-*N*-(2-(1-(pyrimidin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (3c). 430 mg (92%). White solid; m.p. 164.2~165.7 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.52 (br. s., 3 H), 3.11 (t, *J* 6.73 Hz, 2 H), 3.81 (t, *J* 6.73 Hz, 2 H), 6.52 (dd, *J* 8.53, 2.69 Hz, 1 H), 6.73 (d, *J* 2.69 Hz, 1 H), 7.02 (t, *J* 4.71 Hz, 1 H), 7.19 - 7.25 (m, 2 H), 7.33 (t, J

7.63 Hz, 1 H), 7.62 (d, *J* 7.63 Hz, 1 H), 8.14 (s, 1 H), 8.66 (d, *J* 4.71 Hz, 2 H), 8.76 (d, *J* 8.30 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.8, 39.5, 106.4, 115.8, 115.9, 116.3, 117.1, 117.8, 118.7, 122.0, 123.4, 123.9, 130.9, 133.7, 135.7, 137.9, 145.8, 157.2, 158.1, 168.2. HRMS (ESI) *m/z* calcd for $C_{21}H_{18}BrN_5O$ $[M+Na]^+$: 458.0585; found: 458.0587.

Synthesis of compound 5

To a stirred solution of sodium hydride (92 mg, 2.31 mmol, 60%) in DMF at 0 ℃, *N*-(2-(1H-indol-3-yl)ethyl)-2-bromobenzamide (600 mg, 1.54 mmol) was added. After 0.5 h, 2-chloropyridine (209 mg,1.85 mmol) was added to above solution, the reaction mixture was raised to 130 ℃ and stirred for 10 h. The solution was diluted with EtOAc, the organic layer was washed with H_2O, dried over Na_2SO_4 and concentrated. Purification of crude product by flash column chromatography (PE/DCM/acetone=5:1:1~ 2:1:1) provided the compound **5** (540 mg, 75%).

2-Iodo-*N*-(2-(1-(pyridin-2-yl)-1*H*-indol-3-yl)ethyl)benzamide (5). 600 mg (75%) Grayish-white solid; m.p.89.7 ~91.5 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.60 (t, *J* 7.72 Hz, 2 H), 3.39 (q, *J* 7.57 Hz, 2 H), 5.77 (br. s., 1 H), 6.99 - 7.04 (m, 1 H), 7.14 (dd, *J* 8.27, 5.72 Hz, 1 H), 7.21 - 7.25 (m, 1 H), 7.30 - 7.35 (m, 3 H), 7.51 (d, *J* 9.45 Hz, 1 H), 7.73 - 7.77 (m, 2 H), 7.87 - 7.92 (m, 2 H), 8.37 (d, *J* 9.45 Hz, 1 H), 8.70 - 8.75 (m, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 31.4, 44.3, 90.6, 108.9, 109.8, 111.0, 114.0, 114.6, 115.8, 117.9, 118.3, 121.9, 122.0, 123.5, 124.4, 128.4, 131.0, 132.2, 134.3, 140.2, 143.2, 158.2. HRMS (ESI) *m/z* calcd for $C_{22}H_{18}IN_3O$ $[M+Na]^+$: 490.0387; found: 490.0386.

Synthesis of compound 7

To *N*-(2-(1H-indol-3-yl)ethyl)-2-bromobenzamide (600 mg, 1.54 mmol) in toluene (10 mL), was added N,N'-dimethyl-1,2-ethanediamine (DMEDA, 88 mg, 33 µL, 0.31 mmol), CuI (29 mg, 0.15 mmol), K_3PO_4 (653 mg, 3.08 mmol) and iodobenzene 377 mg, 207 µL, 1.85 mmol), the reaction mixture was stirred at 110 ℃ for 24 h. The solution was diluted with EtOAc and filtered through Celite. The filtrate was concentrated. Purification of crude product by flash column chromatography (PE/DCM/acetone =5:1:1~2:1:1) provided compound **7** (560 mg, 78%).

2-Iodo-*N*-(2-(1-phenyl-1*H*-indol-3-yl)ethyl)benzamide (7). 560 mg (78%); white solid; m.p.84.3~86.2 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.62 (t, *J* 7.72 Hz, 2 H), 3.40 (q, *J* 7.63 Hz, 2 H), 5.73 (br. s., 1 H), 7.02 - 7.06 (m, 1 H), 7.17 - 7.21 (m, 1 H), 7.25 (t, *J* 8.81 Hz, 1 H), 7.30 - 7.39 (m, 4 H), 7.50 - 7.58 (m, 4 H), 7.62 (d, *J* 9.45 Hz, 1 H), 7.78 (d, *J* 8.90 Hz, 1 H), 7.91 (d, *J* 9.08 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 31.4, 44.5, 90.5, 106.6, 109.3, 114.0, 114.9, 117.2, 118.4, 120.1, 120.3, 121.9, 122.0, 122.4, 123.2, 124.4, 129.0, 132.0, 132.2, 134.4, 158.2. HRMS (ESI) *m/z* calcd for $C_{23}H_{19}IN_2O$ $[M+Na]^+$: 489.0432; found: 489.0434.

Synthesis of compounds 4a-q, 6, 10

Compound **3** (or **5**, **9**) (1.00 mmol), $Pd(OAc)_2$ (0.10 mmol) and magnesium oxide (3.00 mmol) in DMF (5.0 mL) was heated at 130 ℃. When the starting material was consumed (16-24 h), the reaction mixture was cooled to rt and diluted with H_2O. Then, the aqueous phase was extracted with EtOAc, the organic phase was washed with H_2O, brine, dried over Na_2SO_4 and evaporated under reduced pressure. Purification of crude product by flash column chromatography (DCM/MeOH =200:1~100:1) provided the product **4a-q**, **6**, **10**.

13-(Pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-*b*]indol-5-one (4a). 333 mg (98%); White solid; m.p.154.8~155.4 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.01 (dt, *J* 15.34, 1.87 Hz, 1 H), 3.35 (ddd, *J* 17.01, 13.83, 5.56 Hz, 1 H), 3.52 - 3.59 (m, 1 H), 3.76 (tdd, *J* 14.42, 14.42, 10.25, 3.66 Hz, 1 H), 6.88 (d, *J* 7.31 Hz, 1 H), 6.96 (t, *J* 4.77 Hz, 1 H), 7.15 (td, *J* 7.59, 1.35 Hz, 2 H), 7.23 - 7.27 (m, 1 H), 7.30 - 7.36 (m, 2 H), 7.55 (d, J 7.79 Hz, 1 H), 7.59 (dd, *J* 7.71, 1.03 Hz, 1 H), 8.13 (d, *J* 8.26 Hz, 1 H), 8.54 (d, *J* 4.93 Hz, 2 H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.1,

40.0, 112.7, 114.3, 116.9, 118.4, 121.8, 124.3, 127.8, 127.9, 129.0, 129.7, 130.3, 131.8, 132.3, 134.5, 137.4, 157.7, 157.9, 174.1. HRMS (ESI) *m/z* calcd for $C_{21}H_{16}N_4O$ $[M+H]^+$: 341.1410; found: 341.1402.

2-Methoxy-13-(pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-*b*] indol-5-one (4b). 351 mg (95%); Yellow solid; m.p.243.7~245.4 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.00 (dd, *J* 17.08, 2.00 Hz, 1 H), 3.33 (ddd, *J* 16.98, 13.90, 5.63 Hz, 1 H), 3.56 (ddd, *J* 10.54, 9.08, 4.54 Hz, 1 H), 3.76 - 3.83 (m, 1 H), 3.84 (s, 3 H), 6.70 (dd, *J* 8.54, 2.72 Hz, 1 H), 6.78 (d, *J* 8.72 Hz, 1 H), 6.97 (t, *J* 4.81 Hz, 1 H), 7.05 - 7.10 (m, 1 H), 7.11 (d, *J* 2.73 Hz, 1 H), 7.23 - 7.26 (m, 1 H), 7.30 (td, *J* 7.72, 1.09 Hz, 1 H), 7.53 (d, *J* 7.81 Hz, 1 H), 8.10 (d, *J* 8.17 Hz, 1 H), 8.56 (d, *J* 4.90 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.1, 40.1, 55.4, 111.8, 112.6, 113.5, 116.1, 116.9, 118.3, 121.7, 124.0, 124.1, 129.7, 131.7, 132.3, 135.6, 137.3, 157.8, 157.9, 159.1, 173.8. HRMS (ESI) *m/z* calcd for $C_{22}H_{18}N_4O_2$ $[M+H]^+$: 371.1518; found: 371.1508.

2-amino-13-(pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-b] indol-5-one (4c)> 319 mg (90%); Grey solid; m.p.203.7~204.6 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.87 (d, *J* 16.35 Hz, 1 H), 3.09 - 3.20 (m, 1 H), 3.35 - 3.40 (m, 1 H), 3.48 - 3.57 (m, 1 H), 5.35 (s, 2 H), 6.31 - 6.36 (m, 2 H), 6.57 (d, *J* 2.00 Hz, 1 H), 7.17 - 7.24 (m, 2 H), 7.31 (t, *J* 4.81 Hz, 1 H), 7.56 (d, *J* 7.08 Hz, 1 H), 7.78 (d, *J* 7.45 Hz, 1 H), 7.91 (dd, *J* 9.35, 4.63 Hz, 1 H), 8.73 (d, *J* 4.72 Hz, 2 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 27.1, 39.0, 111.5, 111.8, 112.6, 114.1, 117.1, 118.2, 118.3, 121.2, 123.1, 129.3, 130.8, 133.5, 136.3, 136.3, 148.2, 157.2, 158.6, 172.4. HRMS (ESI) *m/z* calcd for $C_{21}H_{17}N_5O$ $[M+H]^+$: 356.1512; found: 356.1511.

2-methyl-13-(pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-b] indol-5-one (4d): 332 mg (94%); Yellow solid; m.p.302.9~303.8℃; ^{1}H NMR (600 MHz, CDCl3) δ 2.11 (s, 3 H), 3.00 (dt, *J* 15.34, 1.87 Hz, 1 H), 3.33 (ddd, *J* 17.01, 13.83, 5.56 Hz, 1 H), 3.52 - 3.58 (m, 1 H), 3.72 - 3.83 (m, 1 H), 6.70 (s, 1 H), 6.96 (t, J 4.77 Hz, 1 H), 7.00 (d, *J* 5.09 Hz, 1 H), 7.13 (dd, *J* 7.79, 0.79 Hz, 1 H), 7.23 - 7.27 (m, 1 H), 7.32 (td, *J* 7.67, 1.19 Hz, 1 H), 7.48 (d, *J* 7.79 Hz, 1 H), 7.54 (d, *J* 7.79 Hz, 1 H), 8.12 (d, *J* 8.27 Hz, 1 H), 8.55 (d, J 4.77 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.0, 27.1, 40.0, 112.6, 114.2, 116.8, 118.4, 121.8, 124.2, 127.9, 128.5, 129.7, 130.9, 131.7, 131.8, 132.6, 137.4, 139.0, 157.8, 174.2. HRMS (ESI) *m/z* calcd for $C_{22}H_{18}N_4O$ $[M+H]^+$: 355.1563; found: 355.1569.

2-chloro-13-(pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-b] indol-5-one (4e): 347 mg (93%); Yellow solid; m.p.237.5~238.4 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.03 (d, *J* 17.80 Hz, 1 H), 3.37 (ddd, *J* 17.12, 13.76, 5.63 Hz, 1 H), 3.59 (dt, *J* 15.12, 4.70 Hz, 1 H), 3.72 - 3.80 (m, 1 H), 6.92 (d, *J* 1.63 Hz, 1 H), 7.01 (t, *J* 4.81 Hz, 2 H), 7.28 - 7.30 (m, 1 H), 7.33 (dd, *J* 8.27, 1.91 Hz, 1 H), 7.36 (t, *J* 7.63 Hz, 1 H), 7.55 (dd, *J* 12.63, 8.08 Hz, 2 H), 8.22 (d, *J* 8.36 Hz, 1 H), 8.58 (d, *J* 4.72 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.1, 40.0, 113.2, 115.2, 117.0, 118.5, 122.1, 124.8, 127.9, 129.4, 129.6, 130.2, 130.9, 132.9, 133.9, 135.0, 137.6, 157.6, 157.9, 173.0. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}ClN_4O$ $[M+H]^+$: 375.1023; found: 375.1013.

2-bromo-13-(pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-b] indol-5-one (4f): 384 mg (92%); Yellow solid; m.p.259.9~261.7 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.03 (dd, *J* 7.08, 1.82 Hz, 1 H), 3.36 (ddd, *J* 17.08, 13.81, 5.63 Hz, 1 H), 3.59 (ddd, *J* 10.58, 9.13, 4.45 Hz, 1 H), 3.71 - 3.82 (m, 1 H), 6.96 - 7.04 (m, 2 H), 7.08 (d, *J* 1.09 Hz, 1 H), 7.28 - 7.30 (m, 1 H), 7.34 - 7.38 (m, 1 H), 7.45 - 7.50 (m, 2 H), 7.56 (d, *J* 7.81 Hz, 1 H), 8.21 (d, *J* 8.36 Hz, 1 H), 8.58 (d, *J* 4.72 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 7.1, 40.0, 113.1, 115.2, 117.1, 118.6, 122.1, 123.1, 124.8, 129.5, 129.6, 130.8, 133.1, 133.3, 134.0, 137.5, 157.6, 157.9, 173.1. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}BrN_4O$ $[M+H]^+$: 419.0510; found: 419.0507.

2-fluoro-13-(pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-b] indol-5-one (4g): 336 mg (94%); Pale yellow solid; m.p.174.9~176.8 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.03 (dd, *J* 17.08, 1.63 Hz, 1 H), 3.37 (ddd, *J* 17.12, 13.85, 5.54 Hz, 1 H), 3.56 - 3.63 (m, 1 H), 3.71 - 3.82 (m, 1 H), 6.63 (dd, *J* 9.63, 2.54 Hz, 1 H), 7.01 (t, *J* 4.81 Hz, 1 H), 7.06 (td, *J* 8.36, 2.54 Hz, 1 H), 7.10 (d, *J* 6.90 Hz, 1 H), 7.28 - 7.31 (m, 1 H), 7.34 - 7.38 (m, 1 H), 7.57 (d, *J* 7.63 Hz, 1 H), 7.59 (dd, *J* 8.54, 5.81 Hz, 1 H), 8.20 (d, *J* 8.36 Hz, 1 H), 8.58 (d, *J* 4.90 Hz, 2 H); ^{13}C

NMR (151 MHz, $CDCl_3$) δ 27.1, 40.0, 113.0, 114.8, 115.0, 115.1, 117.2, 118.6, 122.1, 124.8, 129.5, 130.1, 130.8, 131.0, 134.4, 137.5, 157.6, 158.0, 162.0, 163.6, 173.2; ^{19}F NMR (565 MHz, $CDCl_3$) δ -111.8. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}FN_4O$ $[M+H]^+$: 359.1313; found: 359.1308.

2-nitro-13-(pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-b] indol-5-one (4h): 335 mg (87%); Yellow solid; m.p.174.9~176.8 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.97 (d, *J* 17.08 Hz, 1 H), 3.23 - 3.31 (m, 1 H), 3.40 - 3.50 (m, 2 H), 7.25 - 7.33 (m, 2 H), 7.37 (t, *J* 7.63 Hz, 1 H), 7.53 (d, *J* 2.18 Hz, 1 H), 7.70 (t, *J* 8.90 Hz, 2 H), 8.09 (d, *J* 8.36 Hz, 1 H), 8.20 (dd, *J* 8.54, 2.18 Hz, 1 H), 8.43 (dd, *J* 8.72, 5.27 Hz, 1 H), 8.69 (d, *J* 4.72 Hz, 2 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 30.8, 34.0, 112.8, 115.7, 118.3, 119.1, 122.1, 122.5, 124.7, 124.8, 129.0, 129.6, 129.7, 132.3, 136.8, 141.3, 147.1, 156.5, 158.7, 170.0. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}N_5O_3$ $[M+H]^+$: 386.1260; found: 386.1253.

13-(Pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-pyrido[3',2':6,7]azocino[5,4-*b*]indol-5-one (4i). 314 mg (92%); Grey solid; m.p. 278.5~280.5 ºC; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.05 (dt, *J* 15.71, 1.32 Hz, 1 H), 3.39 (ddd, *J* 17.21, 13.76, 5.54 Hz, 1 H), 3.57 - 3.63 (m, 1 H), 3.66 - 3.74 (m, 1 H), 6.98 (t, *J* 4.81 Hz, 1 H), 7.27 - 7.30 (m, 1 H), 7.35 - 7.42 (m, 2 H), 7.48 (d, *J* 5.09 Hz, 1 H), 7.56 (d, *J* 7.81 Hz, 1 H), 8.17 (s, 1 H), 8.26 (d, *J* 8.36 Hz, 1 H), 8.53 (d, *J* 4.72 Hz, 2 H), 8.56 (d, *J* 5.09 Hz, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.1, 39.9, 113.4, 116.1, 117.1, 118.5, 121.6, 122.2, 125.0, 127.5, 128.7, 129.6, 137.4, 141.0, 148.5, 150.9, 157.5, 158.0, 171.8. HRMS (ESI) *m/z* calcd for $C_{20}H_{15}N_5O$ $[M+H]^+$: 342.1368; found: 342.1372.

10-Methoxy-13-(pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-*b*] indol-5-one (4j). 351 mg (95%); White solid; m.p. 154.7~156.4 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.98 (dd, *J* 17.08, 2.00 Hz, 1 H), 3.29 (ddd, *J* 17.03, 13.85, 5.63 Hz, 1 H), 3.56 (ddd, *J*10.54, 9.08, 4.54 Hz, 1 H), 3.72 - 3.81 (m, 1 H), 3.89 (s, 3 H), 6.89 (d, *J* 7.45 Hz, 2 H), 6.93 (t, *J* 4.81 Hz, 1 H), 6.94 - 6.99 (m, 2 H), 7.16 (td, *J* 7.58, 1.18 Hz, 1 H), 7.34 (td, *J* 7.54, 0.91 Hz, 1 H), 7.55 - 7.61 (m, 1 H), 8.09 (d, *J* 8.72 Hz, 1 H), 8.51 (d, *J* 4.90 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.2, 40.0, 55.8, 100.8, 113.4, 113.9, 114.1, 116.7, 127.8, 127.9, 129.0, 130.3, 130.4, 132.0, 132.4, 133.0, 134.4, 155.6, 157.7, 157.8, 174.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{18}N_4O_2$ $[M+H]^+$: 371.1514; found 371.1508.

10-Methyl-13-(pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-*b*] indol-5-one (4k). 315 mg (89%); Yellow solid; m.p.177.7~179.4 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.99 (s, 3 H), 2.84 - 2.90 (m, 1 H), 3.17 - 3.25 (m, 1 H), 3.39 - 3.45 (m, 1 H), 3.57 - 3.68 (m, 1 H), 6.55 (d, *J* 10.35 Hz, 1 H), 6.88 (dt, *J* 7.36, 4.77 Hz, 1 H), 6.99 (s, 1 H), 6.99 - 7.03 (m, 1 H), 7.10 - 7.15 (m, 1 H), 7.16 - 7.21 (m, 1 H), 7.31 - 7.35 (m, 1 H), 7.41 - 7.45 (m, 1 H), 7.87 - 8.03 (m, 1 H), 8.43 (dd, *J* 9.26, 4.72 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.3, 29.5, 45.2, 115.3, 116.6, 117.8, 120.2, 121.6, 123.7, 124.6, 127.6, 128.2, 128.7, 131.7, 132.1, 133.2, 136.2, 138.3, 157.4, 157.5, 172.4. HRMS (ESI) *m/z* calcd for $C_{22}H_{18}N_4O$ $[M+H]^+$: 355.1568; found 355.1559.

10-Chloro-13-(pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-*b*] indol-5-one (4l). 347 mg (93%); White solid; m.p.258.1~260.7 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.96 (dd, *J* 17.08, 2.00 Hz, 1 H), 3.26 (ddd, *J* 17.08, 13.81, 5.63 Hz, 1 H), 3.55 (ddd, *J* 10.63, 9.08, 4.63 Hz, 1 H), 3.73 (tdd, *J* 14.40, 14.40, 10.17, 3.72 Hz, 1 H), 6.86 (d, *J* 7.63 Hz, 1 H), 6.98 (t, *J* 4.81 Hz, 1 H), 7.08 (d, *J* 4.72 Hz, 1 H), 7.16 (td, *J* 7.63, 1.09 Hz, 1 H), 7.25 (dd, *J* 8.72, 2.00 Hz, 1 H), 7.36 (td, *J* 7.54, 0.91 Hz, 1 H), 7.49 (d, *J* 1.82 Hz, 1 H), 7.55 - 7.61 (m, 1 H), 8.06 (d, *J* 8.90 Hz, 1 H), 8.53 (d, *J* 4.90 Hz, 2 H) ; ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.0, 39.9, 113.6, 114.0, 117.2, 118.0, 124.4, 127.4, 128.0, 128.1, 129.0, 130.2, 130.9, 131.3, 133.7, 134.5, 135.7, 157.5, 158.0, 173.9. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}ClN_4O$ $[M+H]^+$: 375.1019; found 375.1013.

(*S*)-5-Oxo-13-(pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-*b*] indole-7-carboxylic acid (4m). 307 mg (80%); [□]$_D$ = -24 (0.01g/mL, MeOH); Brown solid; m.p.213.4~215.8 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.26 - 3.37 (m, 2 H), 4.43 (ddd, *J* 12.13, 9.95, 4.63 Hz, 1 H), 6.77 (d, *J* 7.63 Hz, 1 H), 7.20 (td, *J* 7.63, 1.09 Hz, 1 H), 7.24 - 7.28 (m, 1 H), 7.28 - 7.33 (m, 2 H), 7.37 (t, *J* 7.27 Hz, 1 H), 7.45 (d, *J* 7.27 Hz, 1 H), 7.66 (d, *J* 7.81 Hz, 1 H), 7.95 (d, *J* 8.17 Hz, 1 H), 8.13 (d, *J* 11.63 Hz, 1 H), 8.68 (d, *J* 4.90 Hz, 2 H), 13.13 (s, 1 H) ; ^{13}C NMR (151 MHz,

DMSO-d_6) δ 30.0, 53.8, 112.8, 113.9, 118.8, 119.2, 122.2, 124.6, 128.3, 128.4, 129.3, 129.4, 130.6, 131.0, 132.5, 135.5, 137.0, 156.9, 159.1, 171.1, 172.3. HRMS (ESI) *m/z* calcd for $C_{22}H_{16}N_4O_3$ [M+H]$^+$: 385.1303; found 385.1301.

Methyl-(*S*)-5-oxo-13-(pyrimidin-2-yl)-6,7,8,13- tetrahydro-5*H*-benzo [6,7] azocino [5,4-*b*] indole-7-carboxylate (4n). 298.5 mg (75%); [⍰]$_D$ = -17 (0.01g/mL, MeOH); White solid; m.p. 268.2 ~269.7 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.29 - 3.46 (m, 2 H), 3.84 (s, 3 H), 4.73 (ddd, *J* 13.12, 9.31, 4.27 Hz, 1 H), 6.57 (d, *J* 9.63 Hz, 1 H), 6.92 (d, *J* 7.63 Hz, 1 H), 6.97 (t, *J* 4.81 Hz, 1 H), 7.19 (td, *J* 7.63, 1.27 Hz, 1 H), 7.26 - 7.29 (m, 1 H), 7.35 (qd, *J* 7.78, 1.00 Hz, 2 H), 7.54 (d, *J* 7.81 Hz, 1 H), 7.62 (dd, *J* 7.72, 1.00 Hz, 1 H), 8.16 (d, *J* 8.18 Hz, 1 H), 8.53 (d, *J* 4.90 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 30.9, 52.9, 53.8, 112.9, 113.2, 117.1, 118.2, 122.1, 124.6, 128.0, 128.1, 129.1, 129.5, 130.4, 131.6, 132.2, 134.3, 137.2, 157.6, 157.9, 171.5, 171.7. HRMS (ESI) *m/z* calcd for $C_{23}H_{18}N_4O_3$ [M+H]$^+$: 399.1454; found 399.1457.

13-(Pyrimidin-2-yl)-6,7,8,13-tetrahydrobenzo[7,8][1,2]thiazocino[6,5-b]indole 5,5-dioxide (4o).207 mg (55%); White solid; m.p.167.2~170.8 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.06 (dd, *J* 14.53, 10.90 Hz, 1 H), 3.03 (ddd, *J* 14.03, 10.49, 8.36 Hz, 1 H), 3.30 (dd, *J* 14.90, 5.81 Hz, 1 H), 3.42 - 3.48 (m, 1 H), 7.10 (d, *J* 7.08 Hz, 1 H), 7.25 - 7.30 (m, 2 H), 7.32 - 7.37 (m, 1 H), 7.41 (td, *J* 7.45, 1.09 Hz, 1 H), 7.54 - 7.59 (m, 2 H), 7.70 (d, *J* 7.63 Hz, 1 H), 8.08 - 8.13 (m, 1 H), 8.31 (d, *J* 8.36 Hz, 1 H), 8.68 (d, *J* 4.72 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 25.0, 42.1, 113.8, 117.8, 118.4, 118.5, 121.8, 123.9, 128.0, 128.3, 128.4, 130.0, 130.5, 131.5, 134.4, 136.3, 142.4, 156.8, 158.4. HRMS (ESI) *m/z* calcd for $C_{20}H_{16}N_4O_2S$ [M+H]$^+$: 377.1079 found 377.1072.

14-(Pyrimidin-2-yl)-7,8,9,14-tetrahydrobenzo[3,4]azonino[5,6-b]indol-5(6*H*)-one (4p). 220 mg (62%); Yellow solid; m.p.245.3~247.3 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.75 (t, *J* 4.37 Hz, 2 H), 2.30 - 2.40 (m, 1 H), 3.06 - 3.18 (m, 2 H), 3.32 (d, *J* 13.35 Hz, 1 H), 5.76 (dd, *J* 9.85, 4.13 Hz, 1 H), 6.92 (t, *J* 4.77 Hz, 1 H), 7.28 - 7.30 (m, 1 H), 7.33 (dd, *J* 7.47, 1.27 Hz, 1 H), 7.35 (td, *J* 7.75, 1.19 Hz, 1 H), 7.41 - 7.48 (m, 2 H), 7.52 (dd, *J* 7.31, 1.11 Hz, 1 H), 7.59 (d, *J* 7.63 Hz, 1 H), 8.45 (d, *J* 8.26 Hz, 1 H), 8.48 (d, *J* 4.77 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 24.3, 29.5, 45.2, 115.3, 116.6, 117.8, 120.2, 121.6, 123.7, 124.6, 127.5, 128.2, 128.7, 131.7, 132.1, 133.2, 136.2, 138.3, 157.4, 157.5, 172.4. HRMS (ESI) *m/z* calcd for $C_{22}H_{18}N_4O$ [M+H]$^+$: 355.1567 found 355.1559.

13-(Pyridin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-b]indol-5-one (6). 156 mg (46%); Yellow solid; m.p.218.2~220.7 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.04 (dd, *J* 16.89, 2.18 Hz, 1 H), 3.38 (ddd, *J* 16.76, 13.94, 5.63 Hz, 1 H), 3.57 (ddd, *J* 10.45, 8.99, 4.54 Hz, 1 H), 3.72 - 3.80 (m, 1 H), 6.48 (d, *J* 7.99 Hz, 1 H), 6.90 (d, *J* 7.45 Hz, 1 H), 7.10 (ddd, *J* 7.31, 4.95, 0.82 Hz, 1 H), 7.15 (td, *J* 7.63, 1.27 Hz, 1 H), 7.21 - 7.29 (m, 3 H), 7.34 (td, *J* 7.58, 1.00 Hz, 1 H), 7.42 (td, *J* 7.77, 1.91 Hz, 1 H), 7.55 - 7.59 (m, 2 H), 7.74 (d, *J* 8.17 Hz, 1 H), 8.59 - 8.62 (m, 1 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 27.0, 40.2, 111.7, 112.4, 118.4, 121.1, 121.1, 122.1, 123.9, 127.8, 128.4, 128.9, 129.3, 130.1, 131.6, 131.7, 135.3, 137.7, 137.8, 148.7, 151.6, 174.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{17}N_3O$ [M+H]$^+$: 340.1457 found 340.1450.

6-Methyl-13-(pyrimidin-2-yl)-6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-b] indol-5-one (10). 124 mg (35%); Yellow solid; m.p.235.3~237.3 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.48 (s, 3 H), 2.95 - 3.00 (m, 1 H), 3.31 (ddd, *J* 17.03, 13.85, 5.63 Hz, 1 H), 3.54 (ddd, *J* 10.58, 8.95, 4.45 Hz, 1 H), 3.76 (tdd, *J* 14.42, 14.42, 10.22, 3.63 Hz, 1 H), 6.89 (d, *J* 7.81 Hz, 1 H), 6.92 (t, *J* 4.81 Hz, 2 H), 7.12 - 7.17 (m, 2 H), 7.30 - 7.35 (m, 2 H), 7.58 (dd, *J* 7.63, 0.73 Hz, 1 H), 8.04 (d, *J* 8.36 Hz, 1 H), 8.51 (d, *J* 4.90 Hz, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.4, 27.1, 40.0, 112.6, 114.0, 116.7, 118.2, 125.8, 127.6, 127.8, 128.9, 129.9, 130.3, 131.2, 132.1, 132.4, 134.5, 135.8, 157.8, 157.8, 174.0. HRMS (ESI) *m/z* calcd for $C_{22}H_{18}N_4O$ [M+H]$^+$: 355.1467 found 355.1458.

Synthesis of compound 1

Compound **4a** (340 mg, 1.00 mmoL) and sodium ethoxide (272 mg, 4.0 mmoL) were added to DMSO (10 mL). The mixture was heated at 110 °C with stirring until compound **4a** has been consumed (3 h). The reaction

mixture was cooled to rt and diluted with H_2O. The aqueous phase was extracted with EtOAc. Then, the combined organic phase was washed with H_2O, brine, dried over Na_2SO_4 and evaporated under reduced pressure. Purification of crude product by flash column chromatography provided the product **1** (251 mg, 96%).

6,7,8,13-tetrahydro-5*H*-benzo[6,7]azocino[5,4-*b*]indol-5-one (1). 251 mg (96%); White solid; m.p.282.6 ~285.3 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.80 - 2.93 (m, 1 H), 3.15 - 3.27 (m, 1 H), 3.38 - 3.49 (m, 1 H), 3.59 - 3.72 (m, 1 H), 7.00 (dd, *J* 7.72, 7.18 Hz, 1 H), 7.05 - 7.11 (m, 1 H), 7.19 - 7.26 (m, 1 H), 7.30 (d, *J* 7.99 Hz, 1 H), 7.36 (td, *J* 7.18, 1.82 Hz, 1 H), 7.38 - 7.47 (m, 4 H), 10.09 (s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 26.8, 39.6, 107.5, 110.5, 117.6, 118.4, 121.5, 127.4, 127.7, 128.3, 129.0, 129.2, 130.8, 131.3, 134.3, 135.9, 172.5. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}N_2O$ $[M+H]^+$: 263.1190 found 263.1184

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of compounds **2**, **3 a–r**, **9**, **5**, **7**, **4 a–q**, **6**, **10** and **1** are given in the Supplementary Material file associated with this manuscript.

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