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Synthesis of latonduine derivatives via intramolecular Heck reaction

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Abstract—The synthesis of indole ring-fused benzazepinone series as latonduine derivatives has been developed via an intramolecular Heck reaction. The scope has been enlarged not only to indole moiety but also to pyrrolo and benzo[*b*]thiophene nuclei. Several derivatives prepared have been evaluated in vitro for their antiproliferative activities on breast cancer cell lines. Some of them showed promising cytotoxic activities.

1. Introduction

Latonduines A and B have been isolated from the Indonesian sponge *Stylissa carteri* (Fig. 1).[1] These natural products appear to be related to the well-known pyrrolo[2,3-*c*]azepin-8-one family (aldisine, hymenialdisine, stevensine, hymenin, and spongiacidins).[2] Latonduine A and latonduine B ethyl ester were found inactive in cytotoxicity assays against a panel of human cancer lines and for enzyme inhibition against a panel of protein kinases. Latonduine A has been synthesized in five steps from 4,5-dibromo-*N*-[2-(1,3-dioxolan-2-yl)ethyl]pyrrole-2-carboxamide.[1]

In our laboratory, we focused on the synthesis of latonduine derivatives **I** (Fig. 1) where the pyrrole and the pyrimidine nuclei were replaced, respectively, by heterocycle and benzene moieties. In a previous communication,[3] we have reported the general sequence using an intramolecular Heck coupling[4] as key reaction to reach the *N*-protected derivatives. According to the same approach, Beccalli et al. have recently disclosed the synthesis of *N*-methyl six-membered latonduine and paullone derivatives.[5,6] In this paper, we detail the strategy for obtaining the non-protected or *N*-methyl derivatives **I**. Amongst the products prepared, some of them were evaluated for their in vitro cytotoxicity against human breast cancer cell lines.

2. Results and discussion

Compounds **3a–d** were prepared in two steps from the commercially available ethyl-1*H*-indole-2-carboxylate **1a**, methyl 4-methoxy-1*H*-indole-2-carboxylate **1b**, ethyl 5-methoxy-1*H*-indole-2-carboxylate **1c**, and methyl 6-methoxy-1*H*-indole-2-carboxylate **1d** (Scheme 1). N-Alkylation of **1a–d** was performed in the presence of sodium hydride and ethoxymethyl chloride (EOMCl) to afford **2** in good yield. Saponification of **2** gave the desired 1-(ethoxymethyl)-1*H*-indole-2-carboxylic acids **3** in near-quantitative yield. The 5,8-dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one derivatives **9a–d** were prepared from **3a–d** in four or five steps (Scheme 2). The amidification of **3** was achieved using DMAP, EDCI, and freshly prepared 2-iodobenzylamine **4**.[7] The compounds **5** were obtained in 85–95% yield. Attempts of Heck reaction on **5a** or *N*-methyl derivatives of **5a** and **5b** led to low yield of cyclized compounds (15–17% yield). Boc protection of the amide nitrogen of **5** was carried out under classical conditions (Boc_2O and DMAP) to afford **6**

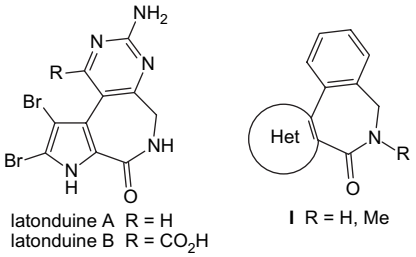

Figure 1.

Keywords: Indole; Heck; Intramolecular cyclization; Cytotoxic agent.
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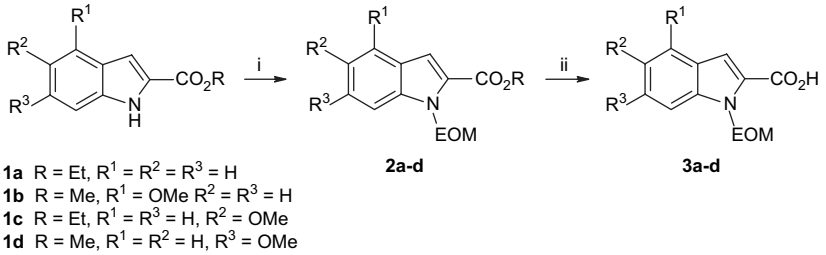


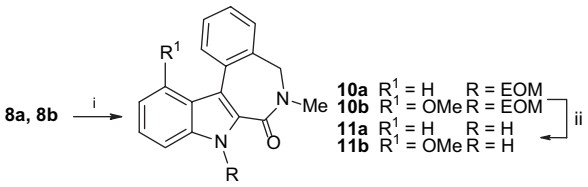
Scheme 1. (i) NaH, DMF, EOMCl, 0 °C to rt, 15 h, **2a**=97%, **2b**=96%, **2c**=95%, **2d**=87%; (ii) LiOH·H_2O, EtOH or MeOH, reflux, 2 h, **3a**=98%, **3b**=99%, **3c**=96%, **3d**=97%.

Table 1. Heck reaction on compounds **6a–d**

6	R^1	R^2	R^3	7	Yield (%)
6a	H	H	H	**7a**	96
6b	OMe	H	H	**7b**	90
6c	H	OMe	H	**7c**	93
6d	H	H	OMe	**7d**	96

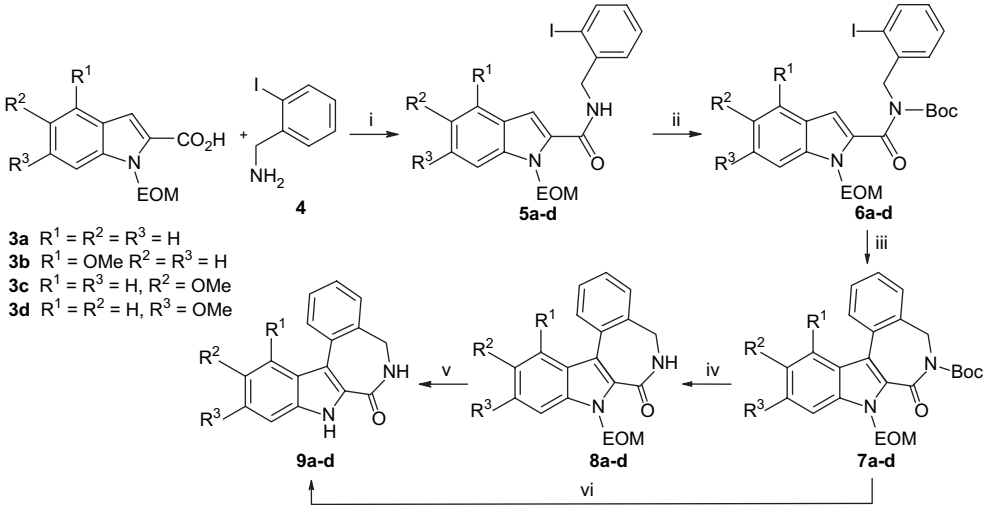
in near-quantitative yield. The intramolecular ring closure of **6** was performed in the presence of $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.1 equiv), and silver carbonate (2 equiv) in DMF at 100 °C for 1 h to give **7** in excellent yield (Table 1). The difference of reactivity between **5**, *N*-methyl **5** and **6** can be explained by the presence of the bulky group on amide, which favors a more reactive conformation.[8,9] Removal of protecting groups on **7** could be carried out in one or two-step procedures according to the final derivatives envisaged. Sequential deprotection of **7** was achieved by removal of the *N*-Boc group (1 N NaOH and 1,4-dioxane) and then the *N*-EOM group (1 N HCl and 1,4-dioxane) to afford, respectively, **8** and **9** in good yield. Compounds **9** could also be obtained from **7** in fair yield by a one pot treatment in acidic conditions (1 N HCl and 1,4-dioxane). It should be noted that the ^{1}H NMR spectrum of **9b** in DMSO-d_6 at room temperature showed a mixture of rotamers, while on raising the temperature to 120 °C the coalescence of the signals was observed.

N-Methyl derivatives **11a** and **11b** were prepared in two steps (Scheme 3). N-Alkylation of **8a** and **8b** afforded **10a** and **10b** in 99% yield. EOM deprotection of **10** gave **11a** and **11b**, respectively, in 92 and 36% yield.

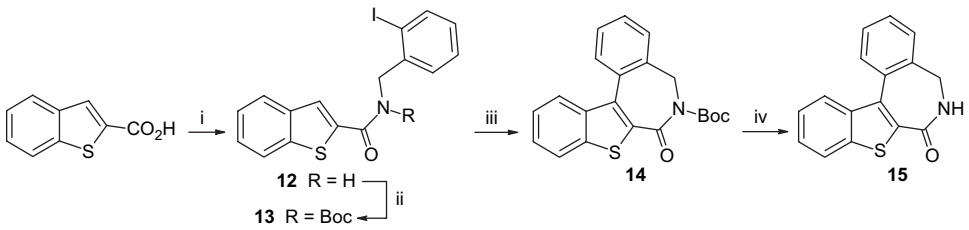


Scheme 3. (i) NaH, ICH_3, THF, 0 °C to rt, 4 h, **10a**,**b**=99%; (ii) 1 N HCl, 1,4-dioxane, 80 °C, 2 h, **11a**=92%, **11b**=36%.

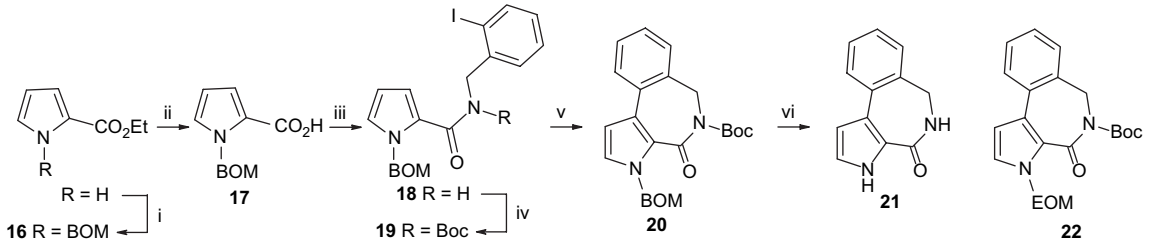
In the case of the preparation of benzo[*b*]thiophene derivative (Scheme 4), the amides **12** and **13** were prepared from commercially available benzo[*b*]thiophene-2-carboxylic acid and 2-iodobenzylamine **4** according to the procedure described for indole derivatives **5** and **6**. Heck cyclization procedure was applied on **13** to afford **14** in 82% yield (in this reaction, final derivative **15** was also isolated in 8% yield). Removal of the Boc group of **14** was effective by treatment with a solution of trifluoroacetic acid in dichloromethane at room temperature to give **15** in 88% yield. The same assay in basic medium (1 N NaOH and 1,4-dioxane) led to the degradation of **14**.



Scheme 2. (i) EDCI, DMAP, CH_2Cl_2, 0 °C to rt, 24 h, **5a**=95%, **5b**=91%, **5c**=90%, **5d**=85%; (ii) Boc_2O, DMAP, CH_3CN, rt, overnight, **6a**–**d**=99%; (iii) $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Ag_2CO_3, DMF, 100 °C, 1 h, see Table 1; (iv) 1 N NaOH, 1,4-dioxane, 80 °C, 1 h, **8a**=80%, **8b**=93%, **8c**=65%, **8d**=73%; (v) 1 N HCl, 1,4-dioxane, 80 °C, 2 h, **9a**=94%, **9b**=42%, **9c**=97%, **9d**=81%; (vi) 1 N HCl, 1,4-dioxane, 80 °C, 5 h, **9a**=79%, **9b**=42%, **9c**=65%, **9d**=63%.



Scheme 4. (i) Compound **4**, EDCI, DMAP, CH_2Cl_2, 0 °C to rt, 24 h, 77%; (ii) Boc_2O, DMAP, CH_3CN, rt, overnight, 99%; (iii) $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Ag_2CO_3, DMF, 100 °C, 1 h, 82%; (iv) TFA, CH_2Cl_2, rt, 1 h, 88%.



Scheme 5. (i) NaH, DMF, BOMCl, 0 °C to rt, 15 h, 99%; (ii) $LiOH{\cdot}H_2O$, EtOH, reflux, 2 h, quantitative; (iii) **4**, EDCI, DMAP, CH_2Cl_2, 0 °C to rt, 24 h, 95%; (iv) Boc_2O, DMAP, CH_3CN, rt, overnight, 99%; (v) $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Ag_2CO_3, DMF, 140 °C, 1 h, 85%; (vi) $Pd(OH)_2$, H_2 (1 atm), EtOH/THF, 4:1, rt, 2 h, then 1 N NaOH, 1,4-dioxane, 80 °C, 1 h, 88%.

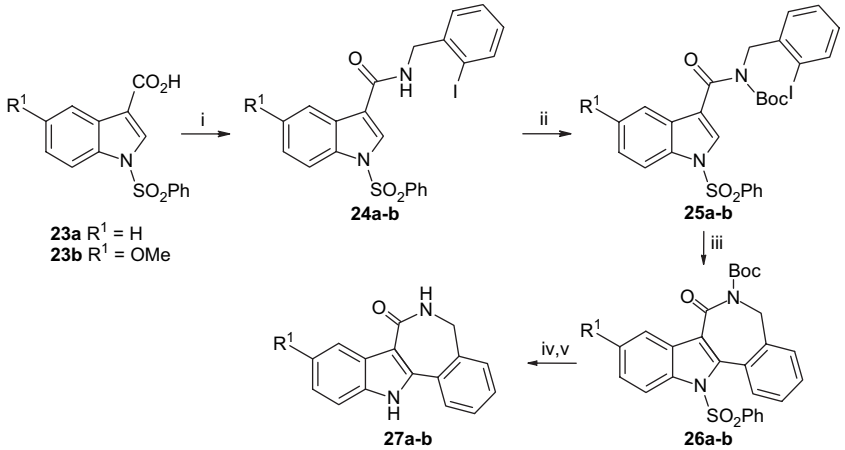
Pyrrole derivative **21**, close latonduine scaffold, was prepared in fair yield from commercially available ethyl-1*H*-pyrrole-2-carboxylate (Scheme 5). N-Alkylation of this latter compound was performed in the presence of sodium hydride and benzyloxymethyl chloride (BOMCl) to afford **16** in near-quantitative yield. Saponification of **16** gave the desired 1-(benzyloxymethyl)-1*H*-pyrrole-2-carboxylic acid **17** in quantitative yield. Amides **18** and **19** were obtained in good yield. The intramolecular cyclization of protected amide **19** required the modification of experimental parameters as reported in Table 2. Thus, the ring closure reaction was improved (**20**, 85% yield) when 0.1 equiv of $Pd(OAc)_2$ was used and the cyclization was performed at 140 °C.

Table 2. Heck reaction on compound **19**

Catalyst (equiv)	Temp (°C)	Time (h)	**20**, yield (%)	**19**, recovered yield (%)
0.05	100	2.5	62	36
0.1	100	2.5	76	20
0.1	140	1	85	—

Moreover, we used the *N*-BOM derivative **20** instead of *N*-EOM derivative **22** (previously prepared in our laboratory)[3] to access the desired pyrrole **21**. Removal of the *N*-Boc group of **22** in basic medium was highly effective (1 N NaOH and 1,4-dioxane, quantitative yield). Unfortunately, EOM deprotection in 1 N HCl led to complete degradation of the starting material. Similarly, the cleavage of the *N*-BOM group of **20** by hydrogenolysis followed by removal of the *N*-Boc group afforded **21** in 88% yield.

Using the same synthetic sequence, 5,12-dihydroindolo[3,2-*d*][2]benzazepin-7(6*H*)-one derivatives **27**, close analogue of paullones,[10] were obtained from 1*H*-indole-3-carboxylic acids **23a**[9] and **23b** (Scheme 6). Compound **23b** was



Scheme 6. (i) Compound **4**, EDCI, DMAP, CH_2Cl_2, 0 °C to rt, 24 h, **24a**=82%, **24b**=76%; (ii) Boc_2O, DMAP, CH_3CN, rt, overnight, **25a**,**b**=99%; (iii) $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Ag_2CO_3, DMF, 100 °C, 2 h, **26a**=92%, **26b**=96%; (iv) TFA, CH_2Cl_2, rt, 2 h; (v) 1 M TBAF, THF, 70 °C, 30 min, **27a**=40%, **27b**=43% (two-step yield).

Table 3. Percentage growth-inhibition of MCF-7 cells treated with compounds **9a**, **9c**, **9d**, **15**, **21**, and **27** at 1 μM for 72 h

Compounds	**9a**	**9c**	**9d**	**15**	**21**	**27a**	**27b**
Growth-inhibition[a] (%)	70.2	27	64	17	4.5	5.8	4.8

[a] Inhibition of MCF-7 cell proliferation was measured by the MTT assay.

prepared by oxidation of 5-methoxy-1-(phenylsulfonyl)-indole-3-carboxaldehyde[11] in 81% yield. In this case, the cyclization reaction of **25** was performed in the presence of 0.1 equiv of palladium catalyst at 100 °C for 2 h to afford **26** in 92–96% yield.[3] A two-step deprotection sequence was developed to reach compounds **27**. Removal of the *N*-Boc group was first carried out by treatment of **26** with trifluoroacetic acid in dichloromethane at room temperature followed by the second deprotection in the presence of TBAF in refluxing THF. The derivatives **27a** and **27b** were obtained in 40–43% yield (two-step yield).

The MCF-7 breast adenocarcinoma cell line was used to assess the cytotoxic potential of compounds **9a**, **9c**, **9d**, **15**, **21**, **27a** and **27b**. The best antiproliferative activity was found for 5,8-dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one derivatives **9a** and **9d** (Table 3). From this preliminary screening, growth-inhibitory activity (IC_{50}) of lead compounds **9a** and **9b** was determined on MCF-7 and MDA-MB231 cancer cell lines (Table 4). These compounds showed significant cytotoxic activity. Structure–activity relationship studies are in progress to improve the potency of this new indole series.

Table 4. Growth-inhibitory activity of compounds **9a** and **9d**

Compounds	Cell lines IC_{50} (μM)[a,b]	
	MCF-7	MDA-MB231
9a	1.2	3
9d	0.6	4

[a] MTT assay.
[b] Values obtained for mean of three different experiments.

3. Conclusion

In conclusion, we have developed an efficient and straightforward synthesis for new heterocyclic ring-fused benzazepinone scaffolds via intramolecular Heck coupling reaction. The 5,8-dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one series shows significant and encouraging cytotoxic activity. This synthetic approach will be applied for the preparation of marine natural product latonduines.

4. Experimental

4.1. General experimental procedures

Melting points were measured with a Büchi Tottoli SMP-20 heating unit and are uncorrected. IR spectra were recorded with a Perkin–Elmer spectrum one spectrophotometer. NMR spectra were recorded with an AVANCE 300 Bruker spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C. Chemical shifts are expressed in parts per million (ppm) relative to TMS. Mass spectra were recorded with a Perkin–Elmer SCIEX API spectrometer and Thermo Finnigan Mat 95 XL. Elemental analyses were performed on a Thermoquest Flash 1112 series EA analyzer. TLC was conducted on precoated silica gel plates (Merck $60F_{254}$) and the spots were visualized under UV light. Flash chromatography was carried out on column using flash silica gel 60 Merck (40–63 mm) with the indicated solvents (petroleum ether (PE): bp 40–60 °C). All reactions requiring anhydrous conditions were conducted in flame-dried apparatus.

4.2. General procedure for EOM protection

At 0 °C, sodium hydride (636 mg, 15.9 mmol, 60% dispersed in oil) was added to a solution of **1** (10.6 mmol) in anhydrous DMF (21 mL). The reaction mixture was stirred for 1 h at room temperature and ethoxymethyl chloride (1.97 mL, 21.2 mmol) was added dropwise. The final solution was stirred for 15 h at room temperature. The solvent was evaporated in vacuo. The residue was taken up in H_2O (10 mL) and extracted with CH_2Cl_2 (5×10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography to give **2**.

4.2.1. Ethyl 1-(ethoxymethyl)-1*H*-indole-2-carboxylate (2a). According to the general procedure, compound **2a** was prepared from **1a**. Chromatography eluent: PE/EtOAc 95:5; yield: 97%; oil; IR (film) ν 3070, 2978, 1709, 1522, 1314, 1249, 1210, 1094, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (t, 3H, J=7.2 Hz, CH_3), 1.41 (t, 3H, J=7.2 Hz, CH_3), 3.50 (q, 2H, J=7.2 Hz, CH_2), 4.39 (q, 2H, J=7.2 Hz, CH_2), 6.04 (s, 2H, CH_2), 7.19 (t, 1H, J=8.2 Hz, H_5), 7.35–7.40 (m, 2H, H_3+H_6), 7.58 (d, 1H, J=8.5 Hz, H_7), 7.68 (d, 1H, J=7.9 Hz, H_4); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 15.1 (CH_3), 60.8 (CH_2), 63.9 (CH_2), 73.4 (CH_2), 111.4 (CH), 112.2 (CH), 121.4 (CH), 122.6 (CH), 125.6 (CH), 126.4 (C), 127.9 (C), 139.9 (C), 162.1 (CO); MS (IS) m/z 248 $(M+H)^+$. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.33; H, 7.13; N, 5.77.

4.2.2. Methyl 1-(ethoxymethyl)-4-methoxy-1*H*-indole-2-carboxylate (2b). According to the general procedure, compound **2b** was prepared from **1b**. Chromatography eluent: PE/EtOAc 85:15; yield: 96%; white solid; mp 71–72 °C (EtOAc/PE); IR (KBr) ν 3000, 2956, 1724, 1615, 1438, 1232, 1186, 1092, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (t, 3H, J=7.2 Hz, CH_3), 3.49 (q, 2H, J=7.2 Hz, CH_2), 3.90 (s, 3H, CH_3), 3.95 (s, 3H, CH_3), 6.00 (s, 2H, CH_2), 6.55 (d, 1H, J=7.7 Hz, H_5), 7.16 (d, 1H, J=8.5 Hz, H_7), 7.29 (t, 1H, J=8.1 Hz, H_6), 7.47 (s, 1H, H_3); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 51.8 (CH_3), 55.5 (CH_3), 63.9 (CH_2), 73.7 (CH_2), 100.6 (CH), 104.4 (CH), 110.1 (CH), 117.8 (C), 126.3 (C), 126.8 (CH), 141.4 (C), 154.7 (C), 162.4 (CO); MS (IS) m/z 264 $(M+H)^+$. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.80; H, 6.40; N, 5.19.

4.2.3. Ethyl 1-(ethoxymethyl)-5-methoxy-1*H*-indole-2-carboxylate (2c). According to the general procedure, compound **2c** was prepared from **1c**. Chromatography eluent: PE/EtOAc 9:1; yield: 95%; white solid; mp 63–64 °C (EtOAc/PE); IR (KBr) ν 3000, 2978, 1709, 1517, 1464, 1382, 1212, 1082 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (t, 3H, J=7.2 Hz, CH_3), 1.41 (t, 3H, J=7.2 Hz, CH_3), 3.48 (q, 2H,

J=7.2 Hz, CH_2), 3.85 (s, 3H, CH_3), 4.37 (q, 2H, J=7.2 Hz, CH_2), 5.99 (s, 2H, CH_2), 7.02–7.06 (m, 2H, H_4+H_6), 7.26 (s, 1H, H_3), 7.47 (d, 1H, J=8.7 Hz, H_7); ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3), 15.2 (CH_3), 55.8 (CH_3), 60.8 (CH_2), 63.8 (CH_2), 73.6 (CH_2), 102.8 (CH), 111.7 (CH), 112.4 (CH), 116.9 (CH), 126.7 (C), 128.2 (C), 135.3 (C), 155.2 (C), 162.0 (CO); MS (IS) m/z 278 $(M+H)^+$. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.12; H, 6.99; N, 4.98.

4.2.4. Methyl 1-(ethoxymethyl)-6-methoxy-1*H*-indole-2-carboxylate (2d). According to the general procedure, compound **2d** was prepared from **1d**. Chromatography eluent: PE/EtOAc 85:15; yield: 87%; white solid; mp 57–58 °C (EtOAc/PE); IR (KBr) ν 3014, 2964, 1705, 1620, 1464, 1212 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J=7.2 Hz, CH_3), 3.51 (q, 2H, J=7.2 Hz, CH_2), 3.89 (s, 6H, $2CH_3$), 6.00 (s, 2H, CH_2), 6.86 (dd, 1H, J=2.2, 8.8 Hz, H_5), 6.98 (d, 1H, J=2.2 Hz, H_7), 7.28 (s, 1H, H_3), 7.54 (d, 1H, J=8.8 Hz, H_4); ^{13}C NMR ($CDCl_3$) δ 14.8 (CH_3), 51.2 (CH_3), 55.1 (CH_3), 63.3 (CH_2), 73.0 (CH_2), 93.1 (CH), 112.3 (CH), 112.5 (CH), 120.2 (C), 123.1 (CH), 126.1 (C), 140.7 (C), 158.8 (C), 161.9 (CO); MS (IS) m/z 264 $(M+H)^+$. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32; O, 24.31. Found: C, 63.63; H, 6.35; N, 5.15.

4.3. General procedure for the saponification

Lithium hydroxide monohydrate (507 mg, 12.1 mmol) and H_2O (2 mL) were added to a solution of **2** (10.1 mmol) in ethanol or methanol (28 mL). The reaction mixture was stirred at reflux for 2 h and the solvent was evaporated. The residue was taken up in H_2O (5 mL), acidified with 1 N HCl, and extracted with EtOAc (3×10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The solid was then recrystallized from EtOAc or EtOAc/PE to afford **3**.

4.3.1. 1-(Ethoxymethyl)-1*H*-indole-2-carboxylic acid (3a). According to the general procedure, compound **3a** was prepared from **2a**. Yield: 98%; white solid; mp 139–141 °C (EtOAc/PE); IR (KBr) 3100–2500, 3042, 2984, 1677, 1519, 1432, 1391, 1259, 1235, 1087, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (t, 3H, J=7.2 Hz, CH_3), 3.52 (q, 2H, J=7.2 Hz, CH_2), 6.04 (s, 2H, CH_2), 7.22 (t, 1H, J=8.2 Hz, H_5), 7.41 (t, 1H, J=8.2 Hz, H_6), 7.52 (s, 1H, H_3), 7.60 (d, 1H, J=8.5 Hz, H_7), 7.72 (d, 1H, J=7.9 Hz, H_4); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 64.0 (CH_2), 73.5 (CH_2), 111.5 (CH), 114.8 (CH), 121.7 (CH), 123.0 (CH), 126.3 (C), 126.4 (CH), 126.8 (C), 140.5 (C), 167.2 (CO); MS (IS) m/z 218 $(M-H)^+$. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.06; H, 6.07; N, 6.45.

4.3.2. 1-(Ethoxymethyl)-4-methoxy-1*H*-indole-2-carboxylic acid (3b). According to the general procedure, compound **3b** was prepared from **2b**. Yield: 99%; white solid; mp 154–155 °C (EtOAc); IR (KBr) ν 3100–2500, 2958, 1674, 1517, 1498, 1264, 1243, 1186, 1079, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J=7.2 Hz, CH_3), 3.51 (q, 2H, J=7.2 Hz, CH_2), 3.97 (s, 3H, CH_3), 6.02 (s, 2H, CH_2), 6.56 (d, 1H, J=7.7 Hz, H_5), 7.15 (d, 1H, J=8.5 Hz, H_7), 7.33 (t, 1H, J=8.1 Hz, H_6), 7.65 (s, 1H, H_3); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 55.5 (CH_3), 64.0 (CH_2), 73.8 (CH_2), 100.7 (CH), 104.4 (CH), 112.4 (CH), 117.9 (C), 125.5 (C), 127.6 (CH), 142.0 (C), 154.9 (C), 166.9 (CO); MS (IS) m/z 248 $(M-H)^+$. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.55; H, 5.98; N, 5.65.

4.3.3. 1-(Ethoxymethyl)-5-methoxy-1*H*-indole-2-carboxylic acid (3c). According to the general procedure, compound **3c** was prepared from **2c**. Yield: 96%; white solid; mp 146–147 °C (EtOAc/PE); IR (KBr) ν 3100–2500, 2973, 1674, 1524, 1431, 1226, 1093, 827 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J=7.2 Hz, CH_3), 3.50 (q, 2H, J=7.2 Hz, CH_2), 3.86 (s, 3H, CH_3), 6.00 (s, 2H, CH_2), 7.07–7.09 (m, 2H, H_4+H_6), 7.42 (s, 1H, H_3), 7.49 (d, 1H, J=9.8 Hz, H_7); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 55.8 (CH_3), 63.9 (CH_2), 73.6 (CH_2), 102.7 (CH), 112.5 (CH), 114.1 (CH), 118.0 (CH), 126.6 (C), 127.0 (C), 135.9 (C), 155.3 (C), 167.0 (CO); MS (IS) m/z 248 $(M-H)^+$. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.88; H, 6.21; N, 5.73.

4.3.4. 1-(Ethoxymethyl)-6-methoxy-1*H*-indole-2-carboxylic acid (3d). According to the general procedure, compound **3d** was prepared from **2d**. Yield: 97%; white solid; mp 149–151 °C (EtOAc); IR (KBr) ν 3100–2500, 2939, 1673, 1620, 1498, 1441, 1225, 1126 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3H, J=7.2 Hz, CH_3), 3.53 (q, 2H, J=7.2 Hz, CH_2), 3.90 (s, 3H, CH_3), 6.01 (s, 2H, CH_2), 6.88 (dd, 1H, J=2.2, 8.8 Hz, H_5), 6.98 (d, 1H, J=2.2 Hz, H_7), 7.46 (s, 1H, H_3), 7.57 (d, 1H, J=8.8 Hz, H_4); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 55.7 (CH_3), 63.8 (CH_2), 73.5 (CH_2), 93.4 (CH), 113.3 (CH), 115.1 (CH), 120.6 (C), 123.8 (CH), 125.7 (C), 141.8 (C), 159.7 (C), 166.9 (CO); MS (IS) m/z 248 $(M-H)^+$. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.66; H, 5.98; N, 5.71.

4.4. General procedure for peptidic coupling

Under argon atmosphere, indole **3** (4.29 mmol), DMAP (0.52 g, 4.29 mmol), and EDCI (0.91 g, 4.72 mmol) were added to a solution of 2-iodobenzylamine **4** (1.10 g, 4.72 mmol) in CH_2Cl_2 (45 mL) at 0 °C. The mixture was stirred for 4 h at 0 °C and then for 20 h at room temperature. H_2O (10 mL) was added, the mixture was acidified with 6 N HCl solution (pH 1–2), and extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried over Na_2SO_4, then filtered and concentrated in vacuo to give a crude solid, which was washed with Et_2O to afford **5**.

4.4.1. 1-(Ethoxymethyl)-*N*-(2-iodobenzyl)-1*H*-indole-2-carboxamide (5a). According to the general procedure, compound **5a** was prepared from **3a**. Yield: 95%; white solid; mp 141–142 °C (washing Et_2O); IR (KBr) ν 3292, 2978, 1630, 1538, 1343, 1265, 1091, 1067, 1013, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 3H, J=7.2 Hz, CH_3), 3.51 (q, 2H, J=7.2 Hz, CH_2), 4.67 (d, 2H, J=5.9 Hz, CH_2), 5.91 (s, 2H, CH_2), 7.01 (t, 1H, J=7.7 Hz, H_{ar}), 7.03 (s, 1H, H_{ar}), 7.08 (br t, 1H, J=5.9 Hz, NH), 7.18 (t, 1H, J=7.5 Hz, H_{ar}), 7.31–7.37 (m, 2H, H_{ar}), 7.47 (d, 1H, J=7.5 Hz, H_{ar}), 7.53 (d, 1H, J=8.3 Hz, H_{ar}), 7.64 (d, 1H, J=7.7 Hz, H_{ar}), 7.87 (d, 1H, J=7.9 Hz, H_{ar}); ^{13}C NMR (DMSO-d_6) δ 14.9 (CH_3), 47.6 (CH_2), 63.1 (CH_2), 72.5 (CH_2), 98.4 (C), 106.6 (CH), 111.2 (CH), 120.9 (CH),

121.7 (CH), 124.2 (CH), 126.0 (C), 127.7 (CH), 128.3 (CH), 129.0 (CH), 131.9 (C), 138.5 (C), 138.9 (CH), 140.5 (C), 161.9 (CO); MS (IS) *m/z* 435 $(M+H)^+$. Anal. Calcd for $C_{19}H_{19}IN_2O_2$: C, 52.55; H, 4.41; N, 6.45. Found: C, 52.43; H, 4.50; N, 6.40.

4.4.2. 1-(Ethoxymethyl)-*N*-(2-iodobenzyl)-4-methoxy-1*H*-indole-2-carboxamide (5b). According to the general procedure, compound **5b** was prepared from **3b**. Yield: 91%; white solid; mp 158–159 °C (washing Et_2O); IR (KBr) ν 3266, 2970, 1623, 1531, 1373, 1257, 1098, 1016, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 (t, 3H, J=7.2 Hz, CH_3), 3.50 (q, 2H, J=7.2 Hz, CH_2), 3.95 (s, 3H, CH_3), 4.66 (d, 2H, J=6.0 Hz, CH_2), 5.92 (s, 2H, CH_2), 6.56 (d, 1H, J=7.5 Hz, H_{ar}), 6.92 (t, 1H, J=6.0 Hz, NH), 7.00 (t, 1H, J=7.7 Hz, H_{ar}), 7.12 (s, 1H, H_{ar}), 7.13 (d, 1H, J=7.5 Hz, H_{ar}), 7.26 (t, 1H, J=7.7 Hz, H_{ar}), 7.34 (t, 1H, J=7.5 Hz, H_{ar}), 7.46 (d, 1H, J=7.5 Hz, H_{ar}), 7.86 (d, 1H, J=7.9 Hz, H_{ar}); ^{13}C NMR (DMSO-d_6) δ 14.9 (CH_3), 47.6 (CH_2), 55.2 (CH_3), 63.0 (CH_2), 72.7 (CH_2), 98.4 (C), 100.7 (CH), 104.2 (CH), 104.3 (CH), 116.7 (C), 125.4 (CH), 127.8 (CH), 128.3 (CH), 129.0 (CH), 130.3 (C), 138.9 (CH), 140.0 (C), 140.6 (C), 153.5 (C), 161.7 (CO); MS (IS) *m/z* 465 $(M+H)^+$. Anal. Calcd for $C_{20}H_{21}IN_2O_3$: C, 51.74; H, 4.56; N, 6.03. Found: C, 52.01; H, 4.68; N, 6.14.

4.4.3. 1-(Ethoxymethyl)-*N*-(2-iodobenzyl)-5-methoxy-1*H*-indole-2-carboxamide (5c). According to the general procedure, compound **5c** was prepared from **3c**. Yield: 90%; white solid; mp 161–162 °C (washing Et_2O); IR (KBr) ν 3265, 2964, 1630, 1546, 1471, 1382, 1235, 1091, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (t, 3H, J=7.2 Hz, CH_3), 3.49 (q, 2H, J=7.2 Hz, CH_2), 3.84 (s, 3H, CH_3), 4.66 (d, 2H, J=6.0 Hz, CH_2), 5.86 (s, 2H, CH_2), 6.95 (s, 1H, H_{ar}), 7.00 (dd, 1H, J=2.3, 9.1 Hz, H_{ar}), 7.01–7.05 (m, 3H, H_{ar}+NH), 7.35 (t, 1H, J=7.5 Hz, H_{ar}), 7.42 (d, 1H, J=9.1 Hz, H_{ar}), 7.47 (d, 1H, J=7.5 Hz, H_{ar}), 7.86 (d, 1H, J=7.9 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 48.6 (CH_2), 55.8 (CH_3), 64.0 (CH_2), 73.7 (CH_2), 99.2 (C), 102.7 (CH), 106.9 (CH), 111.8 (CH), 115.8 (CH), 126.9 (C), 128.7 (CH), 129.6 (CH), 130.0 (CH), 132.8 (C), 134.4 (C), 139.7 (CH), 140.4 (C), 155.2 (C), 162.0 (CO); MS (IS) *m/z* 465 $(M+H)^+$. Anal. Calcd for $C_{20}H_{21}IN_2O_3$: C, 51.74; H, 4.56; N, 6.03. Found: C, 51.98; H, 4.69; N, 6.23.

4.4.4. 1-(Ethoxymethyl)-*N*-(2-iodobenzyl)-6-methoxy-1*H*-indole-2-carboxamide (5d). According to the general procedure, compound **5d** was prepared from **3d**. Yield: 85%; white solid; mp 164–165 °C (washing Et_2O); IR (KBr) ν 3278, 2903, 2840, 1620, 1536, 1236, 1212, 1090, 1014, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (t, 3H, J=7.2 Hz, CH_3), 3.52 (q, 2H, J=7.2 Hz, CH_2), 3.88 (s, 3H, CH_3), 4.65 (d, 2H, J=6.0 Hz, CH_2), 5.90 (s, 2H, CH_2), 6.84 (dd, 1H, J=2.2, 8.8 Hz, H_{ar}), 6.91 (br t, 1H, J=6.0 Hz, NH), 6.95–7.03 (m, 3H, H_{ar}), 7.34 (t, 1H, J=7.5 Hz, H_{ar}), 7.46 (d, 1H, J=7.7 Hz, H_{ar}), 7.50 (d, 1H, J=8.8 Hz, H_{ar}), 7.86 (d, 1H, J=7.8 Hz, H_{ar}); ^{13}C NMR (DMSO-d_6) δ 14.9 (CH_3), 47.5 (CH_2), 55.4 (CH_3), 63.0 (CH_2), 72.4 (CH_2), 93.9 (CH), 98.3 (C), 107.0 (CH), 111.6 (CH), 120.0 (C), 122.5 (CH), 127.6 (CH), 128.3 (CH), 129.0 (CH), 130.7 (C), 138.9 (CH), 139.8 (C), 140.6 (C), 157.6 (C), 161.9 (CO); MS (IS) *m/z* 465 $(M+H)^+$. Anal. Calcd for $C_{20}H_{21}IN_2O_3$: C, 51.74; H, 4.56; N, 6.03. Found: C, 51.66; H, 4.44; N, 5.95.

4.5. General procedure for Boc protection

A solution of amide **5** (4.24 mmol), Boc_2O (1.48 g, 6.78 mmol), and a catalytic amount of DMAP in acetonitrile (65 mL) was stirred overnight at room temperature. After evaporation of the solvent, the residue was partitioned between EtOAc (30 mL) and H_2O (20 mL). The two phases were separated and the aqueous phase was extracted with EtOAc (2×30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography to give **6**.

4.5.1. *tert*-Butyl {[1-(ethoxymethyl)-1*H*-indol-2-yl]carbonyl}(2-iodobenzyl)carbamate (6a). According to the general procedure, compound **6a** was prepared from **5a**. Chromatography eluent: PE/EtOAc 85:15; yield: 99%; white solid; mp 108–109 °C (EtOAc/PE); IR (KBr) ν 2975, 1734, 1659, 1460, 1338, 1318, 1212, 1144, 1094, 983, 742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.16 (t, 3H, J=7.2 Hz, CH_3), 1.19 (s, 9H, $3CH_3$), 3.55 (q, 2H, J=7.2 Hz, CH_2), 4.99 (s, 2H, CH_2), 5.82 (s, 2H, CH_2), 6.95 (s, 1H, H_{ar}), 6.95–6.99 (m, 1H, H_{ar}), 7.19 (t, 1H, J=7.1 Hz, H_{ar}), 7.28–7.38 (m, 3H, H_{ar}), 7.58 (d, 1H, J=8.5 Hz, H_{ar}), 7.66 (d, 1H, J=7.9 Hz, H_{ar}), 7.85 (d, 1H, J=7.9 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3), 27.6 ($3CH_3$), 54.3 (CH_2), 64.0 (CH_2), 73.6 (CH_2), 83.6 (C), 97.7 (C), 109.1 (CH), 111.1 (CH), 121.4 (CH), 122.3 (CH), 125.2 (CH), 126.3 (C), 126.9 (CH), 128.5 (CH), 128.9 (CH), 133.0 (C), 139.0 (C), 139.5 (CH+C), 153.5 (CO), 165.8 (CO); MS (IS) *m/z* 535 $(M+H)^+$. Anal. Calcd for $C_{24}H_{27}IN_2O_4$: C, 53.94; H, 5.09; N, 5.24. Found: C, 54.23; H, 4.99; N, 5.33.

4.5.2. *tert*-Butyl {[1-(ethoxymethyl)-4-methoxy-1*H*-indol-2-yl]carbonyl}(2-iodobenzyl)carbamate (6b). According to the general procedure, compound **6b** was prepared from **5b**. Chromatography eluent: PE/EtOAc 9:1; yield: 99%; oil; IR (film) ν 2976, 1735, 1666, 1518, 1497, 1438, 1368, 1258, 1147, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, 3H, J=7.2 Hz, CH_3), 1.21 (s, 9H, $3CH_3$), 3.53 (q, 2H, J=7.2 Hz, CH_2), 3.95 (s, 3H, CH_3), 4.97 (s, 2H, CH_2), 5.81 (s, 2H, CH_2), 6.55 (dd, 1H, J=7.7 Hz, H_{ar}), 6.92–6.98 (m, 1H, H_{ar}), 7.10 (s, 1H, H_{ar}), 7.15 (d, 1H, J=8.3 Hz, H_{ar}), 7.24–7.37 (m, 3H, H_{ar}), 7.84 (d, 1H, J=7.5 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3), 27.7 ($3CH_3$), 54.4 (CH_2), 55.4 (CH_3), 63.9 (CH_2), 73.8 (CH_2), 83.6 (C), 97.7 (C), 100.6 (CH), 104.1 (CH), 107.5 (CH), 117.5 (C), 126.4 (CH), 126.9 (CH), 128.5 (CH), 128.8 (CH), 131.5 (C), 139.5 (CH), 139.7 (C), 140.6 (C), 153.7 (CO), 154.6 (C), 165.6 (CO); MS (IS) *m/z* 565 $(M+H)^+$. Anal. Calcd for $C_{25}H_{29}IN_2O_5$: C, 53.20; H, 5.18; N, 4.96. Found: C, 53.24; H, 5.08; N, 5.06.

4.5.3. *tert*-Butyl {[1-(ethoxymethyl)-5-methoxy-1*H*-indol-2-yl]carbonyl}(2-iodobenzyl)carbamate (6c). According to the general procedure, compound **6c** was prepared from **5c**. Chromatography eluent: PE/EtOAc 95:5; yield: 99%; foam; IR (film) ν 2981, 1734, 1664, 1523, 1369, 1265, 1211, 1147, 739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, 3H, J=7.2 Hz, CH_3), 1.20 (s, 9H, $3CH_3$), 3.53 (q, 2H, J=7.2 Hz, CH_2), 3.86 (s, 3H, CH_3), 4.98 (s, 2H, CH_2), 5.77 (s, 2H, CH_2), 6.87 (s, 1H, H_{ar}), 6.93–7.06 (m, 3H,

H_{ar}), 7.27–7.37 (m, 2H, H_{ar}), 7.47 (d, 1H, J=8.9 Hz, H_{ar}), 7.85 (d, 1H, J=7.9 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 15.0 (CH_3), 27.6 ($3CH_3$), 54.2 (CH_2), 55.6 (CH_3), 63.8 (CH_2), 73.6 (CH_2), 83.4 (C), 97.6 (C), 102.6 (CH), 108.7 (CH), 112.0 (CH), 116.3 (CH), 126.6 (C), 126.8 (CH), 128.4 (CH), 128.8 (CH), 133.2 (C), 134.3 (C), 139.4 (CH), 139.5 (C), 153.4 (CO), 155.1 (C), 165.6 (CO); MS (IS) m/z 565 $(M+H)^+$. Anal. Calcd for $C_{25}H_{29}IN_2O_5$: C, 53.20; H, 5.18; N, 4.96. Found: C, 53.40; H, 5.05; N, 4.88.

4.5.4. *tert*-Butyl {[1-(ethoxymethyl)-6-methoxy-1*H*-indol-2-yl]carbonyl}(2-iodobenzyl)carbamate (6d). According to the general procedure, compound **6d** was prepared from **5d**. Chromatography eluent: PE/EtOAc 95:5; yield: 99%; white solid; mp 121–122 °C (EtOAc/PE); IR (KBr) 2975, 1711, 1665, 1619, 1493, 1313, 1143, 1101, 974, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3H, J=7.2 Hz, CH_3), 1.21 (s, 9H, $3CH_3$), 3.56 (q, 2H, J=7.2 Hz, CH_2), 3.89 (s, 3H, CH_3), 4.96 (s, 2H, CH_2), 5.81 (s, 2H, CH_2), 6.85 (dd, 1H, J=2.3, 8.8 Hz, H_{ar}), 6.91–6.99 (m, 3H, H_{ar}), 7.30–7.37 (m, 2H, H_{ar}), 7.52 (d, 1H, J=8.8 Hz, H_{ar}), 7.84 (d, 1H, J=7.9 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 27.7 ($3CH_3$), 54.5 (CH_2), 55.7 (CH_3), 63.9 (CH_2), 73.7 (CH_2), 83.4 (C), 93.5 (CH), 97.8 (C), 110.7 (CH), 112.8 (CH), 120.5 (C), 123.3 (CH), 127.1 (CH), 128.5 (CH), 128.9 (CH), 132.0 (C), 139.6 (CH), 139.7 (C), 140.6 (C), 153.8 (CO), 159.0 (C), 165.6 (CO); MS (IS) m/z 565 $(M+H)^+$. Anal. Calcd for $C_{25}H_{29}IN_2O_5$: C, 53.20; H, 5.18; N, 4.96. Found: C, 53.33; H, 5.25; N, 4.88.

4.6. General procedure for Heck coupling

A mixture of **6** (1.87 mmol), PPh_3 (49 mg, 0.18 mmol), $Pd(OAc)_2$ (21 mg, 0.09 mmol), and silver carbonate (1.03 g, 3.74 mmol) in anhydrous DMF (40 mL) was vigorously stirred at 100 °C for 1 h. After cooling, the solvent was removed in vacuo. The residue was taken up in CH_2Cl_2, filtered over Celite®, and rinsed with CH_2Cl_2. The solvent was evaporated in vacuo and the crude residue was purified by flash chromatography (PE/EtOAc 85:15) to give **7**.

4.6.1. 8-(Ethoxymethyl)-7-oxo-5,6,7,8-tetrahydroindolo-[2,3-*d*][2]benzazepine-6-carboxylic acid *tert*-butyl ester (7a). According to the general procedure, compound **7a** was prepared from **6a**. Yield: 96%; white solid; mp 104–106 °C (EtOAc/PE); IR (KBr) ν 2978, 1708, 1677, 1462, 1368, 1325, 1282, 1146, 1100, 965, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J=7.2 Hz, CH_3), 1.55 (s, 9H, $3CH_3$), 3.53–3.65 (m, 2H, CH_2), 4.26 and 5.17 (d, 1H, J=14.7 Hz, CH_2), 5.93 and 6.18 (d, 1H, J=10.7 Hz, CH_2), 7.27–7.57 (m, 5H, H_{ar}), 7.71 (d, 1H, J=8.5 Hz, H_{ar}), 8.03–8.08 (m, 2H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 15.2 (CH_3), 28.2 ($3CH_3$), 48.9 (CH_2), 64.2 (CH_2), 74.3 (CH_2), 83.6 (C), 111.9 (CH), 121.3 (C), 122.1 (2CH), 124.6 (C), 126.3 (CH), 127.4 (CH), 128.3 (CH), 128.6 (CH), 128.7 (CH), 129.4 (C), 132.9 (C), 136.2 (C), 139.8 (C), 150.8 (CO), 161.6 (CO); MS (IS) m/z 407 $(M+H)^+$. Anal. Calcd for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.26; H, 6.60; N, 6.97.

4.6.2. 8-(Ethoxymethyl)-12-methoxy-7-oxo-5,6,7,8-tetrahydroindolo[2,3-*d*][2]benzazepine-6-carboxylic acid *tert*-butyl ester (7b). According to the general procedure, compound **7b** was prepared from **6b**. Yield: 90%; white solid; mp 145–146 °C (EtOAc/PE); IR (KBr) ν 2972, 1717, 1684, 1462, 1280, 1259, 1147, 1098, 763 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J=7.2 Hz, CH_3), 1.56 (s, 9H, $3CH_3$), 3.52–3.64 (m, 2H, CH_2), 3.86 (s, 3H, CH_3), 4.33 and 5.15 (d, 1H, J=14.3 Hz, CH_2), 5.88 and 6.11 (d, 1H, J=10.7 Hz, CH_2), 6.65 (d, 1H, J=7.5 Hz, H_{ar}), 7.26–7.45 (m, 5H, H_{ar}), 7.95 (d, 1H, J=7.5 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 15.2 (CH_3), 28.2 ($3CH_3$), 49.3 (CH_2), 55.0 (CH_3), 64.1 (CH_2), 74.4 (CH_2), 83.5 (C), 101.7 (CH), 104.6 (CH), 114.7 (C), 121.5 (C), 126.9 (CH), 127.0 (CH), 127.1 (2CH), 129.2 (C), 132.4 (C), 132.5 (CH), 135.5 (C), 141.4 (C), 150.8 (CO), 155.6 (C), 161.3 (CO); MS (IS) m/z 437 $(M+H)^+$. Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.66; H, 6.50; N, 6.42.

4.6.3. 8-(Ethoxymethyl)-11-methoxy-7-oxo-5,6,7,8-tetrahydroindolo[2,3-*d*][2]benzazepine-6-carboxylic acid *tert*-butyl ester (7c). According to the general procedure, compound **7c** was prepared from **6c**. Yield: 93%; white solid; mp 157–158 °C (EtOAc/PE); IR (KBr) ν 2967, 1760, 1662, 1618, 1496, 1348, 1259, 1103, 767 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.14 (t, 3H, J=7.2 Hz, CH_3), 1.55 (s, 9H, $3CH_3$), 3.50–3.66 (m, 2H, CH_2), 3.88 (s, 3H, CH_3), 4.26 and 5.16 (d, 1H, J=15.0 Hz, CH_2), 5.90 and 6.14 (d, 1H, J=10.7 Hz, CH_2), 7.14 (dd, 1H, J=2.3, 9.0 Hz, H_{ar}), 7.39 (t, 1H, J=7.5 Hz, H_{ar}), 7.45 (d, 1H, J=2.3 Hz, H_{ar}), 7.52–7.58 (m, 2H, H_{ar}), 7.61 (d, 1H, J=9.0 Hz, H_{ar}), 8.01 (d, 1H, J=7.5 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 28.1 ($3CH_3$), 48.8 (CH_2), 55.8 (CH_3), 64.1 (CH_2), 74.4 (CH_2), 83.4 (C), 102.5 (CH), 112.8 (CH), 117.3 (CH), 120.6 (C), 124.8 (C), 127.1 (CH), 128.0 (CH), 128.3 (CH), 128.6 (CH), 129.7 (C), 133.1 (C), 135.0 (C), 136.0 (C), 150.8 (CO), 155.8 (C), 161.5 (CO); MS (IS) m/z 437 $(M+H)^+$. Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.99; H, 6.56; N, 6.55.

4.6.4. 8-(Ethoxymethyl)-10-methoxy-7-oxo-5,6,7,8-tetrahydroindolo[2,3-*d*][2]benzazepine-6-carboxylic acid *tert*-butyl ester (7d). According to the general procedure, compound **7d** was prepared from **6d**. Yield: 96%; white solid; mp 147–149 °C (EtOAc/PE); IR (KBr) ν 2974, 1712, 1664, 1615, 1455, 1325, 1281, 1206, 1148, 1104, 1076, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3H, J=7.2 Hz, CH_3), 1.55 (s, 9H, $3CH_3$), 3.57–3.68 (m, 2H, CH_2), 3.93 (s, 3H, CH_3), 4.25 and 5.15 (d, 1H, J=14.5 Hz, CH_2), 5.92 and 6.12 (d, 1H, J=10.7 Hz, CH_2), 6.95 (dd, 1H, J=2.3, 9.0 Hz, H_{ar}), 7.10 (d, 1H, J=2.3 Hz, H_{ar}), 7.38 (t, 1H, J=7.5 Hz, H_{ar}), 7.50–7.55 (m, 2H, H_{ar}), 7.91 (d, 1H, J=9.0 Hz, H_{ar}), 7.99 (d, 1H, J=7.7 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 15.2 (CH_3), 28.2 ($3CH_3$), 48.9 (CH_2), 55.7 (CH_3), 64.1 (CH_2), 74.4 (CH_2), 83.4 (C), 93.9 (CH), 113.4 (CH), 118.8 (C), 122.0 (C), 123.0 (CH), 127.3 (CH), 128.3 (CH+C), 128.5 (CH), 128.6 (CH), 132.9 (C), 136.2 (C), 141.2 (C), 150.9 (CO), 159.5 (C), 161.6 (CO); MS (IS) m/z 437 $(M+H)^+$. Anal. Calcd for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.62; H, 6.33; N, 6.47.

4.7. General procedure for Boc deprotection

A solution of **7** (1.23 mmol) and 1 N NaOH (8 mL) in 1,4-dioxane (25 mL) was stirred at 80 °C for 1 h. After cooling, the

solution was neutralized with 1 N HCl solution (pH 6–7) and extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography to afford **8**.

4.7.1. 8-(Ethoxymethyl)-5,8-dihydroindolo[2,3-*d*][2]-benzazepin-7(6*H*)-one (8a). According to the general procedure, compound **8a** was prepared from **7a**. Chromatography eluent: PE/EtOAc 1:1; yield: 80%; white solid; mp 180–181 °C (EtOAc); IR (KBr) ν 3364, 2975, 1640, 1455, 1303, 1090, 1073, 931, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, 3H, J=7.2 Hz, CH_3), 3.50–3.62 (m, 2H, CH_2), 4.09 (dd, 1H, J=6.9, 14.7 Hz, CH_2), 4.26 (dd, 1H, J=5.9, 14.7 Hz, CH_2), 5.92 and 6.24 (d, 1H, J=10.7 Hz, CH_2), 6.39 (br s, 1H, NH), 7.27–7.53 (m, 5H, H_{ar}), 7.70 (d, 1H, J=8.5 Hz, H_{ar}), 8.00 (d, 1H, J=7.5 Hz, H_{ar}), 8.05 (d, 1H, J=8.3 Hz, H_{ar}); ^{13}C NMR (DMSO-d_6) δ 15.0 (CH_3), 44.3 (CH_2), 63.4 (CH_2), 73.0 (CH_2), 111.7 (CH), 118.4 (C), 121.0 (CH), 121.7 (CH), 124.1 (C), 125.1 (CH), 127.1 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 130.2 (C), 132.5 (C), 138.3 (C), 138.4 (C), 162.7 (CO); MS (IS) m/z 307 $(M+H)^+$. Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.41; H, 6.01; N, 9.08.

4.7.2. 8-(Ethoxymethyl)-12-methoxy-5,8-dihydroindolo-[2,3-*d*][2]benzazepin-7(6*H*)-one (8b). According to the general procedure, compound **8b** was prepared from **7b**. Chromatography eluent: PE/EtOAc 2:3; yield: 93%; white solid; mp 168–169 °C (EtOAc/PE); IR (KBr) ν 3323, 2972, 1666, 1459, 1306, 1263, 1152, 1081, 852, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (t, 3H, J=7.2 Hz, CH_3), 3.47–3.62 (m, 2H, CH_2), 3.86 (s, 3H, CH_3), 4.06 (dd, 1H, J=6.8, 14.4 Hz, CH_2), 4.30 (dd, 1H, J=6.2, 14.4 Hz, CH_2), 5.87 and 6.19 (d, 1H, J=10.7 Hz, CH_2), 6.33 (br s, 1H, NH), 6.67 (d, 1H, J=7.7 Hz, H_{ar}), 7.27–7.43 (m, 5H, H_{ar}), 7.86 (d, 1H, J=8.1 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 15.2 (CH_3), 45.9 (CH_2), 55.1 (CH_3), 64.1 (CH_2), 74.2 (CH_2), 101.8 (CH), 104.5 (CH), 115.1 (C), 120.9 (C), 126.3 (CH), 126.4 (CH), 126.8 (CH), 127.0 (CH), 129.1 (C), 132.8 (C), 132.8 (CH), 137.1 (C), 140.7 (C), 155.4 (C), 164.1 (CO); MS (IS) m/z 337 $(M+H)^+$. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.16; H, 6.20; N, 8.46.

4.7.3. 8-(Ethoxymethyl)-11-methoxy-5,8-dihydroindolo-[2,3-*d*][2]benzazepin-7(6*H*)-one (8c). According to the general procedure, compound **8c** was prepared from **7c**. Chromatography eluent: PE/EtOAc 35:65; yield: 65%; foam; IR (film) ν 3274, 2971, 1644, 1499, 1469, 1306, 1225, 1092, 1077, 795 cm^{-1}; ^1H NMR (DMSO-d_6, only one rotamer) δ 1.02 (t, 3H, J=7.2 Hz, CH_3), 3.32–3.48 (m, 2H, CH_2), 3.83 (s, 3H, CH_3), 3.97 (dd, 1H, J=5.3, 14.3 Hz, CH_2), 4.08 (dd, 1H, J=6.6, 14.3 Hz, CH_2), 5.84 and 6.10 (d, 1H, J=10.7 Hz, CH_2), 7.08 (dd, 1H, J=2.3, 8.9 Hz, H_{ar}), 7.35–7.40 (m, 2H, H_{ar}), 7.46–7.55 (m, 2H, H_{ar}), 7.68 (d, 1H, J=8.9 Hz, H_{ar}), 7.96 (d, 1H, J=7.2 Hz, H_{ar}), 8.55 (t, 1H, J=6.0 Hz, NH); ^{13}C NMR (DMSO-d_6) δ 14.9 (CH_3), 44.3 (CH_2), 55.4 (CH_3), 63.2 (CH_2), 73.0 (CH_2), 101.8 (CH), 112.7 (CH), 115.5 (CH), 117.9 (C), 124.4 (C), 126.8 (CH), 127.7 (CH), 127.8 (CH), 128.2 (CH), 130.6 (C), 132.6 (C), 133.4 (C), 138.1 (C), 155.1 (C), 162.6 (CO); MS (IS) m/z 337 $(M+H)^+$. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.63; H, 6.12; N, 8.44.

4.7.4. 8-(Ethoxymethyl)-10-methoxy-5,8-dihydroindolo-[2,3-*d*][2]benzazepin-7(6*H*)-one (8d). According to the general procedure, compound **8d** was prepared from **7d**. Chromatography eluent: PE/EtOAc 3:7; yield: 73%; white solid; mp 188–189 °C (EtOAc/PE); IR (KBr) ν 3280, 2968, 1620, 1439, 1337, 1300, 1220, 1170, 1077, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (t, 3H, J=7.2 Hz, CH_3), 3.55–3.63 (m, 2H, CH_2), 3.94 (s, 3H, CH_3), 4.08 (dd, 1H, J=7.0, 14.6 Hz, CH_2), 4.25 (dd, 1H, J=6.0, 14.6 Hz, CH_2), 5.88 and 6.18 (d, 1H, J=10.7 Hz, CH_2), 6.23 (br s, 1H, NH), 6.95 (dd, 1H, J=2.3, 9.0 Hz, H_{ar}), 7.11 (d, 1H, J=2.3 Hz, H_{ar}), 7.32–7.39 (m, 2H, H_{ar}), 7.47–7.52 (m, 1H, H_{ar}), 7.91 (d, 1H, J=9.0 Hz, H_{ar}), 7.95 (d, 1H, J=7.9 Hz, H_{ar}); ^{13}C NMR (DMSO-d_6) δ 15.0 (CH_3), 44.3 (NCH_2), 55.6 (OCH_3), 63.3 (CH_2), 72.9 (OCH_2), 94.3 (CH), 112.2 (CH), 118.1 (C), 118.9 (C), 121.9 (CH), 127.1 (CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 129.1 (C), 132.5 (C), 138.2 (C), 139.7 (C), 158.2 (C), 162.7 (CO); MS (IS) m/z 337 $(M+H)^+$. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.33; H, 5.88; N, 8.36.

4.8. General procedure for EOM deprotection

A solution of **8** (0.16 mmol) and 1 N HCl (1.6 mL) in 1,4-dioxane (3.5 mL) was stirred at 80 °C for 2 h. After cooling, the solution was neutralized with a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (2×10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography to afford **9**.

4.8.1. 5,8-Dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one (9a). According to the general procedure, compound **9a** was prepared from **8a**. Chromatography eluent: CH_2Cl_2/MeOH 98.5:1.5; yield: 94%; white solid; mp >210 °C (washing with cold MeOH); IR (KBr) ν 3300–3100, 2980, 1651, 1615, 1524, 1471, 1331, 1048, 739 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.07 (d, 2H, J=5.3 Hz, CH_2), 7.20 (t, 1H, J=7.4 Hz, H_{ar}), 7.30–7.35 (m, 2H, H_{ar}), 7.46–7.55 (m, 3H, H_{ar}), 7.94 (d, 1H, J=7.7 Hz, H_{ar}), 8.00 (d, 1H, J=8.1 Hz, H_{ar}), 8.40 (t, 1H, J=5.3 Hz, NH), 12.03 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 44.7 (CH_2), 112.8 (CH), 116.1 (C), 120.7 (CH), 120.9 (CH), 124.4 (CH), 124.5 (C), 126.4 (CH), 127.3 (CH), 128.2 (CH), 128.3 (CH), 130.0 (C), 133.4 (C), 136.6 (C), 137.0 (C), 163.6 (CO); MS (IS) m/z 249 $(M+H)^+$. Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.35; H, 4.92; N, 11.37.

4.8.2. 12-Methoxy-5,8-dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one (9b). According to the general procedure, compound **9b** was prepared from **8b**. Chromatography eluent: CH_2Cl_2/MeOH 98.5:1.5; yield: 42%; white solid; mp >210 °C (EtOAc/PE); IR (KBr) ν 3349, 3221, 2940, 1638, 1582, 1500, 1465, 1443, 1353, 1260, 1101, 757, 742 cm^{-1}; ^1H NMR (DMSO-d_6, 120 °C, only one rotamer) δ 3.83 (s, 3H, CH_3), 4.08 (d, 2H, J=5.5 Hz, CH_2), 6.67 (d, 1H, J=7.7 Hz, H_{ar}), 7.15–7.39 (m, 5H, H_{ar}), 7.78 (d, 1H, J=7.9 Hz, H_{ar}), 8.08 (br s, 1H, NH), 11.70 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 44.9 (CH_2), 54.9 (CH_3), 100.7

(CH), 105.6 (CH), 114.6 (C), 116.7 (C), 125.2 (CH), 125.9 (CH), 126.6 (CH), 126.9 (CH), 129.5 (C), 131.4 (CH), 133.2 (C), 136.5 (C), 138.2 (C), 154.6 (C), 163.1 (CO); MS (IS) *m/z* 279 $(M+H)^+$. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.11; H, 6.91; N, 9.89.

4.8.3. 11-Methoxy-5,8-dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one (9c). According to the general procedure, compound **9c** was prepared from **8c**. Chromatography eluent: CH_2Cl_2/MeOH 98.5:1.5; yield: 97%; white solid; mp 130 °C dec (EtOAc/Et_2O); IR (KBr) ν 3340, 3234, 2969, 1629, 1521, 1502, 1469, 1221, 1151, 1027, 767, 731 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.82 (s, 3H, CH_3), 4.05 (d, 2H, J=5.1 Hz, CH_2), 6.99 (dd, 1H, J=2.3, 8.9 Hz, H_{ar}), 7.32 (t, 1H, J=7.0 Hz, H_{ar}), 7.39–7.55 (m, 4H, H_{ar}), 7.96 (d, 1H, J=7.7 Hz, H_{ar}), 8.35 (t, 1H, J=5.1 Hz, NH), 11.89 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 44.7 (CH_2), 55.4 (CH_3), 101.6 (CH), 113.6 (CH), 115.3 (CH), 115.7 (C), 124.6 (C), 126.2 (CH), 126.9 (CH), 128.2 (2CH), 130.4 (C), 131.8 (C), 133.6 (C), 136.8 (C), 154.5 (C), 163.6 (CO); MS (IS) *m/z* 279 $(M+H)^+$. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.55; H, 5.01; N, 10.17.

4.8.4. 10-Methoxy-5,8-dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one (9d). According to the general procedure, compound **9d** was prepared from **8d**. Chromatography eluent: CH_2Cl_2/MeOH 98:2; yield: 81%; white solid; mp >210 °C ($CHCl_3$); IR (KBr) ν 3300–3129, 2950, 1633, 1528, 1460, 1294, 1241, 1166, 1028, 751 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.82 (s, 3H, CH_3), 4.05 (d, 2H, J=4.5 Hz, CH_2), 6.84 (br d, 1H, J=8.9 Hz, H_{ar}), 6.97 (s, 1H, H_{ar}), 7.29–7.48 (m, 3H, H_{ar}), 7.86 (d, 1H, J=8.9 Hz, H_{ar}), 7.89 (d, 1H, J=7.9 Hz, H_{ar}), 8.26 (br t, 1H, J=4.5 Hz, NH), 11.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 44.7 (CH_2), 55.2 (CH_3), 94.5 (CH), 111.6 (CH), 116.5 (C), 118.7 (C), 121.8 (CH), 126.4 (CH), 127.2 (CH), 128.1 (CH), 128.2 (CH), 128.8 (C), 133.3 (C), 136.9 (C), 137.7 (C), 157.6 (C), 163.6 (CO); MS (IS) *m/z* 279 $(M+H)^+$. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.67; H, 5.21; N, 10.22.

4.9. General procedure for N-alkylation

At 0 °C, sodium hydride (26 mg, 0.63 mmol, 60% dispersed in oil) was added to a solution of **8** (0.42 mmol) in anhydrous THF (1.5 mL). The reaction mixture was stirred for 10 min at room temperature and iodomethane (32 μL, 0.51 mmol) was added dropwise. The mixture was stirred for 4 h at room temperature. The solvent was evaporated in vacuo. The residue was taken up in H_2O (5 mL) and extracted with CH_2Cl_2 (2×5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (PE/EtOAc 3:2) to give **10**.

4.9.1. 8-(Ethoxymethyl)-6-methyl-5,8-dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one (10a). According to the procedure described for **10**, compound **10a** was prepared from **8a**. Yield: 99%; white solid; mp 143–144 °C (EtOAc/PE); IR (KBr) ν 2972, 1627, 1519, 1387, 1328, 1080, 754 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, 3H, J=7.2 Hz, CH_3), 3.22 (s, 3H, CH_3), 3.52–3.62 (m, 2H, CH_2), 4.06 and 4.48 (d, 1H, J=14.5 Hz, CH_2), 5.91 and 6.19 (d, 1H, J=10.7 Hz, CH_2), 7.26–7.55 (m, 5H, H_{ar}), 7.69 (d, 1H, J=8.3 Hz, H_{ar}), 8.01 (d, 1H, J=7.9 Hz, H_{ar}), 8.03 (d, 1H, J=8.3 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 15.1 (CH_3), 34.3 (CH_3), 53.6 (CH_2), 64.0 (CH_2), 74.0 (CH_2), 111.6 (CH), 119.3 (C), 121.2 (CH), 121.6 (CH), 124.6 (C), 125.2 (CH), 126.9 (CH), 127.5 (CH), 128.3 (CH), 128.5 (CH), 130.5 (C), 133.1 (C), 135.6 (C), 138.6 (C), 161.5 (CO); MS (IS) *m/z* 321 $(M+H)^+$. Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.25; H, 6.36; N, 8.87.

4.9.2. 8-(Ethoxymethyl)-12-methoxy-6-methyl-5,8-dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one (10b). According to the procedure described for **10**, compound **10b** was prepared from **8b**. Yield: 99%; white solid; mp 145–147 °C (EtOAc/PE); IR (KBr) ν 2980, 1642, 1567, 1499, 1438, 1391, 1325, 1260, 1097, 752 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.01 (t, 3H, J=7.2 Hz, CH_3), 3.08 (s, 3H, CH_3), 3.32–3.47 (m, 2H, CH_2), 3.80 (s, 3H, CH_3), 4.28 and 4.34 (d, 1H, J=14.7 Hz, CH_2), 5.82 and 6.03 (d, 1H, J=10.7 Hz, CH_2), 6.73–6.76 (m, 1H, H_{ar}), 7.29–7.44 (m, 4H, H_{ar}), 7.51 (d, 1H, J=7.4 Hz, H_{ar}), 7.80 (d, 1H, J=7.7 Hz, H_{ar}); ^{13}C NMR (DMSO-d_6) δ 15.4 (CH_3), 34.2 (CH_3), 53.2 (CH_2), 55.5 (CH_3), 63.9 (CH_2), 73.6 (CH_2), 102.4 (CH), 104.7 (CH), 114.2 (C), 119.1 (C), 126.7 (CH), 127.3 (2CH), 127.5 (CH), 130.6 (C), 132.1 (CH), 132.5 (C), 136.0 (C), 140.3 (C), 155.1 (C), 161.0 (CO); MS (IS) *m/z* 351 $(M+H)^+$. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.72; H, 6.41; N, 8.14.

4.9.3. 6-Methyl-5,8-dihydroindolo[2,3-*d*][2]benzazepin-7(6*H*)-one (11a). According to the procedure described for **9**, compound **11a** was prepared from **10a**. Recrystallization from EtOAc; yield: 92%; white solid; mp >210 °C (EtOAc); IR (KBr) ν 3203, 2930, 1621, 1525, 1331, 1241, 1110, 746 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.15 (s, 3H, CH_3), 4.32 (s, 2H, CH_2), 7.20 (t, 1H, J=7.1 Hz, H_{ar}), 7.30–7.39 (m, 2H, H_{ar}), 7.50–7.62 (m, 3H, H_{ar}), 7.96 (d, 1H, J=7.7 Hz, H_{ar}), 8.00 (d, 1H, J=7.9 Hz, H_{ar}), 12.03 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 34.5 (CH_3), 52.7 (CH_2), 112.7 (CH), 115.7 (C), 120.6 (CH), 120.7 (CH), 124.2 (C), 124.3 (CH), 126.3 (CH), 127.0 (CH), 128.4 (2CH), 130.4 (C), 133.2 (C), 135.2 (C), 136.5 (C), 161.7 (CO); MS (IS) *m/z* 263 $(M+H)^+$. Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.93; H, 5.27; N, 10.55.

4.9.4. 12-Methoxy-6-methyl-5,8-dihydroindolo[2,3-*d*]-[2]benzazepin-7(6*H*)-one (11b). According to the procedure for **9**, compound **11b** was prepared from **10b**. Chromatography eluent: CH_2Cl_2/MeOH 99:1; yield: 36%; yellow solid; mp >210 °C (EtOAc); IR (KBr) ν 3215, 2930, 1617, 1507, 1445, 1354, 1260, 1109, 757 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.13 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 4.27 and 4.35 (d, 1H, J=14.5 Hz, CH_2), 6.65 (d, 1H, J=7.7 Hz, H_{ar}), 7.12 (d, 1H, J=8.1 Hz, H_{ar}), 7.21–7.42 (m, 3H, H_{ar}), 7.50 (d, 1H, J=7.3 Hz, H_{ar}), 7.78 (d, 1H, J=7.7 Hz, H_{ar}), 12.03 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 34.3 (CH_3), 53.0 (CH_2), 54.9 (CH_3), 100.7 (CH), 105.5 (CH), 114.4 (C), 116.4 (C), 125.2 (CH), 125.6 (CH), 126.9 (CH), 127.1 (CH), 129.9 (C), 131.0 (CH), 133.0 (C), 134.6 (C), 138.1 (C), 154.6 (C), 161.2 (CO); MS (IS) *m/z* 293 $(M+H)^+$. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 74.18; H, 5.44; N, 9.73.

4.9.5. *N*-(2-Iodobenzyl)benzo[*b*]thiophene-2-carboxamide (12). According to the procedure described for **5**, compound **12** was prepared from benzo[*b*]thiophene-2-carboxylic acid and **4**. Yield: 77%; white solid; mp 165–166 °C (washing Et_2O); IR (KBr) ν 3255, 3056, 1619, 1544, 1408, 1286, 1010, 875, 740 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.45 (d, 2H, J=5.5 Hz, CH_2), 7.05 (t, 1H, J=7.5 Hz, H_{ar}), 7.32–7.50 (m, 4H, H_{ar}), 7.88 (d, 1H, J=7.7 Hz, H_{ar}), 7.95–7.97 (m, 1H, H_{ar}), 8.02–8.05 (m, 1H, H_{ar}), 8.20 (s, 1H, H_{ar}), 9.32 (t, 1H, J=5.5 Hz, NH); ^{13}C NMR (DMSO-d_6) δ 48.0 (CH_2), 98.6 (C), 122.8 (CH), 125.0 (CH), 125.2 (CH), 125.3 (CH), 126.3 (CH), 128.1 (CH), 128.4 (CH), 129.1 (CH), 139.0 (CH), 139.2 (C), 139.5 (C), 140.2 (C), 140.3 (C), 161.7 (CO); MS (IS) m/z 394 $(M+H)^+$. Anal. Calcd for $C_{16}H_{12}INOS$: C, 48.87; H, 3.08; N, 3.56. Found: C, 49.13; H, 3.19; N, 3.39.

4.9.6. *tert*-Butyl (benzo[*b*]thiophen-2-ylcarbonyl)(2-iodobenzyl)carbamate (13). According to the procedure described for **6**, compound **13** was prepared from **12**. Chromatography eluent: PE/EtOAc 95:5; yield: 99%; oil; IR (film) ν 2977, 1735, 1670, 1518, 1458, 1365, 1342, 1226, 1147, 1013, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (s, 9H, $3CH_3$), 4.98 (s, 2H, CH_2), 6.96 (t, 1H, J=7.5 Hz, H_{ar}), 7.26–7.47 (m, 4H, H_{ar}), 7.78 (s, 1H, H_{ar}), 7.84–7.86 (m, 3H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 27.6 ($3CH_3$), 54.8 (CH_2), 83.9 (C), 97.7 (C), 122.7 (CH), 125.0 (CH), 125.4 (CH), 126.8 (CH), 127.1 (CH), 128.4 (CH), 128.5 (CH), 128.9 (CH), 138.3 (C), 138.7 (C), 139.4 (C), 139.5 (CH), 141.3 (C), 153.1 (CO), 167.2 (CO); MS (IS) m/z 494 $(M+H)^+$. Anal. Calcd for $C_{21}H_{20}INO_3S$: C, 51.13; H, 4.09; N, 2.84. Found: C, 50.88; H, 3.94; N, 2.77.

4.9.7. 7-Oxo-5,7-dihydro-6*H*-benzo[*b*]thieno[2,3-*d*][2]benzazepine-6-carboxylic acid *tert*-butyl ester (14). A mixture of **14** (105 mg, 0.21 mmol), PPh_3 (5.6 mg, 0.02 mmol), $Pd(OAc)_2$ (2.4 mg, 0.01 mmol), and silver carbonate (117 mg, 0.42 mmol) in anhydrous DMF (4 mL) was vigorously stirred at 100 °C for 1 h. After cooling, the solvent was removed in vacuo. The residue was taken up in CH_2Cl_2, filtered over Celite®, and rinsed with CH_2Cl_2. The solvent was evaporated in vacuo and the crude residue was purified by flash chromatography (PE/EtOAc 95:5) to afford **14** (64 mg, 82%) as a white solid, starting material **13** (10 mg, 10%) and **15** (4.8 mg, 8%). Mp 162–163 °C (EtOAc/PE); IR (KBr) ν 2980, 1726, 1665, 1458, 1369, 1289, 1152, 1092, 744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 9H, $3CH_3$), 4.30 and 5.28 (d, 1H, J=14.7 Hz, CH_2), 7.45–7.60 (m, 5H, H_{ar}), 7.93 (d, 1H, J=8.3 Hz, H_{ar}), 7.95 (d, 1H, J=7.9 Hz, H_{ar}), 8.15 (d, 1H, J=7.9 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 28.1 ($3CH_3$), 48.4 (CH_2), 83.9 (C), 123.0 (CH), 125.2 (CH), 125.5 (CH), 127.2 (CH), 128.6 (CH), 128.9 (2CH), 129.0 (CH), 132.9 (C), 136.8 (C), 137.0 (C), 137.2 (C), 137.7 (C), 141.3 (C), 151.1 (CO), 163.3 (CO); MS (IS) m/z 366 $(M+H)^+$. Anal. Calcd for $C_{21}H_{19}NO_3S$: C, 69.02; H, 5.24; N, 3.83. Found: C, 69.29; H, 5.33; N, 3.96.

4.9.8. 5,6-Dihydrobenzo[*b*]thieno[2,3-*d*][2]benzazepin-7-one (15). At room temperature, trifluoroacetic acid (600 μL, 8.08 mmol) was added to a solution of compound **14** (73 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (3 mL). After stirring for 1 h at room temperature, H_2O (5 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2×5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The solid was then recrystallized from EtOAc to afford **15** (46 mg, 88%). White solid; mp >210 °C (EtOAc); IR (KBr) ν 3270, 2900, 1645, 1521, 1464, 1407, 772 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.11 (d, 2H, J=5.5 Hz, CH_2), 7.49–7.59 (m, 5H, H_{ar}), 7.87 (d, 1H, J=7.5 Hz, H_{ar}), 8.09–8.16 (m, 2H, H_{ar}), 8.73 (br t, 1H, J=5.5 Hz, NH); ^{13}C NMR (DMSO-d_6) δ 44.4 (CH_2), 123.3 (CH), 124.6 (CH), 125.4 (CH), 126.7 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 128.7 (CH), 132.3 (C), 135.2 (C), 136.6 (C), 137.2 (C), 139.2 (C), 139.4 (C), 164.1 (CO); MS (IS) m/z 266 $(M+H)^+$. Anal. Calcd for $C_{16}H_{11}NOS$: C, 72.43; H, 4.18; N, 5.28. Found: C, 72.43; H, 4.09; N, 5.33.

4.9.9. Ethyl 1-(benzyloxymethyl)-1*H*-pyrrole-2-carboxylate (16). At 0 °C, sodium hydride (216 mg, 5.39 mmol, 60% dispersed in oil) was added to a solution of ethyl-1*H*-pyrrole-2-carboxylate (500 mg, 3.59 mmol) in anhydrous DMF (17 mL). The reaction mixture was stirred for 1 h at room temperature and benzyloxymethyl chloride (996 μL, 7.18 mmol) was added dropwise. The mixture was stirred for 15 h at room temperature. The solvent was evaporated in vacuo. The residue was taken up in H_2O (10 mL) and extracted with CH_2Cl_2 (5×20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (PE/EtOAc 95:5) to afford **16** (930 mg, 99%) as an oil. IR (film) ν 3035, 2980, 1704, 1537, 1418, 1317, 1236, 1113, 739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (t, 3H, J=7.2 Hz, CH_3), 4.31 (q, 2H, J=7.2 Hz, CH_2), 4.51 (s, 2H, CH_2), 5.78 (s, 2H, CH_2), 6.21 (t, 1H, J=3.2 Hz, $H_{pyrrole}$), 7.01–7.04 (m, 2H, $H_{pyrrole}$), 7.28–7.37 (m, 5H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 59.5 (CH_2), 69.7 (CH_2), 76.0 (OCH_2), 108.5 (CH), 118.6 (CH), 122.2 (C), 127.3 (3CH), 128.0 (2CH), 128.4 (CH), 137.1 (C), 160.5 (CO); MS (IS) m/z 260 $(M+H)^+$. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.66; H, 6.71; N, 5.43.

4.9.10. 1-(Benzyloxymethyl)-1*H*-pyrrole-2-carboxylic acid (17). According to the general procedure described for **3**, compound **17** was prepared from **16**. Yield: quantitative; white solid; mp 93–94 °C (EtOAc/PE); IR (KBr) ν 3100–2500, 1681, 1537, 1443, 1314, 1254, 1129, 1072, 905, 739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.52 (s, 2H, CH_2), 5.78 (s, 2H, CH_2), 6.26 (dd, 1H, J=2.5, 3.8 Hz, $H_{pyrrole}$), 7.08 (dd, 1H, J=1.7, 2.5 Hz, $H_{pyrrole}$), 7.18 (dd, 1H, J=1.7, 3.8 Hz, $H_{pyrrole}$), 7.29–7.38 (m, 5H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 70.4 (CH_2), 76.6 (CH_2), 109.6 (CH), 121.5 (CH), 121.8 (C), 128.0 (3CH), 128.5 (2CH), 130.2 (CH), 137.2 (C), 166.0 (CO); MS (IS) m/z 230 $(M-H)^+$. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.44; H, 6.78; N, 6.16.

4.9.11. 1-(Benzyloxymethyl)-*N*-(2-iodobenzyl)-1*H*-pyrrole-2-carboxamide (18). According to the general procedure described for **5**, compound **18** was prepared from **17** and **4**. Yield: 95%; white solid; mp 98–99 °C (washing Et_2O); IR (KBr) ν 3304, 2900, 1629, 1542, 1522, 1468, 1311, 1253, 1075, 748 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.51 (s, 2H, CH_2), 4.60 (d, 2H, J=5.9 Hz, CH_2), 5.76 (s,

2H, CH_2), 6.17 (dd, 1H, J=2.8, 3.2 Hz, $H_{pyrrole}$), 6.70–6.72 (m, 2H, $H_{pyrrole}$+NH), 6.93 (br s, 1H, $H_{pyrrole}$), 6.98 (t, 1H, J=7.5 Hz, H_{ar}), 7.25–7.31 (m, 6H, H_{ar}), 7.42 (d, 1H, J=7.5 Hz, H_{ar}), 7.84 (d, 1H, J=7.9 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 48.2 (CH_2), 70.4 (CH_2), 76.7 (CH_2), 99.1 (C), 108.6 (CH), 114.2 (CH), 126.4 (C), 127.3 (CH), 127.9 (2CH), 128.0 (CH), 128.6 (2CH), 128.7 (CH), 129.4 (CH), 129.9 (CH), 137.3 (C), 139.6 (CH), 140.7 (C), 161.5 (CO); MS (IS) m/z 447 $(M+H)^+$. Anal. Calcd for $C_{20}H_{19}IN_2O_2$: C, 53.83; H, 4.29; N, 6.28. Found: C, 54.13; H, 4.42; N, 6.52.

4.9.12. *tert*-Butyl {[1-(benzyloxymethyl)-1*H*-pyrrol-2-yl]-carbonyl}(2-iodobenzyl)carbamate (19). According to the general procedure described for **6**, compound **19** was prepared from **18**. Chromatography eluent: PE/EtOAc 9:1; yield: 99%; oil; IR (film) ν 2971, 1732, 1655, 1532, 1425, 1331, 1213, 1143, 965, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H, $3CH_3$), 4.52 (s, 2H, CH_2), 4.90 (s, 2H, CH_2), 5.68 (s, 2H, CH_2), 6.23 (dd, 1H, J=2.6, 3.8 Hz, $H_{pyrrole}$), 6.75 (dd, 1H, J=1.7, 3.8 Hz, $H_{pyrrole}$), 6.90–6.96 (m, 1H, H_{ar}), 7.05 (dd, 1H, J=1.7, 2.6 Hz, $H_{pyrrole}$), 7.27–7.35 (m, 7H, H_{ar}), 7.82 (d, 1H, J=7.7 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 27.8 ($3CH_3$), 54.4 (CH_2), 70.2 (CH_2), 76.5 (CH_2), 83.0 (C), 97.6 (C), 108.8 (CH), 118.5 (CH), 127.0 (CH), 127.3 (C), 127.9 (CH), 128.0 (2CH), 128.2 (CH), 128.4 (CH), 128.5 (2CH), 128.7 (CH), 137.3 (C), 139.4 (CH), 139.9 (C), 153.7 (CO), 164.6 (CO); MS (IS) m/z 547 $(M+H)^+$. Anal. Calcd for $C_{25}H_{27}IN_2O_4$: C, 54.95; H, 4.98; N, 5.13. Found: C, 55.25; H, 5.16; N, 5.26.

4.9.13. 8-(Benzyloxymethyl)-7-oxo-5,6,7,8-tetrahydropyrrolo[2,3-*d*][2]benzazepine-6-carboxylic acid *tert*-butyl ester (20). A mixture of **19** (492 mg, 0.90 mmol), PPh_3 (47 mg, 0.18 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol), and silver carbonate (496 mg, 1.80 mmol) in anhydrous DMF (18 mL) was vigorously stirred at 140 °C for 1 h. After cooling, the solvent was removed in vacuo. The residue was taken up in CH_2Cl_2, filtered over Celite®, and rinsed with CH_2Cl_2. The solvent was evaporated in vacuo and the crude residue was purified by flash chromatography (PE/EtOAc 9:1) to give **20** (320 mg, 85%) as an oil. IR (film) ν 2978, 1714, 1673, 1454, 1406, 1332, 1148, 1083, 941, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9H, $3CH_3$), 4.19 and 5.10 (d, 1H, J=14.7 Hz, CH_2), 4.59 (s, 2H, CH_2), 5.60 and 6.20 (d, 1H, J=9.8 Hz, CH_2), 6.56 (d, 1H, J=2.8 Hz, $H_{pyrrole}$), 7.21 (d, 1H, J=2.8 Hz, $H_{pyrrole}$), 7.27–7.33 (m, 6H, H_{ar}), 7.40–7.45 (m, 2H, H_{ar}), 7.68 (d, 1H, J=7.5 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 28.0 ($3CH_3$), 48.8 (CH_2), 70.7 (CH_2), 77.7 (CH_2), 82.8 (C), 107.6 (CH), 123.4 (C), 126.9 (CH), 127.3 (CH), 127.7 (2CH), 127.8 (CH), 128.1 (CH), 128.4 (2CH), 128.5 (CH), 129.4 (CH), 130.8 (C), 133.5 (C), 134.9 (C), 137.3 (C), 151.1 (CO), 161.0 (CO); MS (IS) m/z 419 $(M+H)^+$. Anal. Calcd for $C_{25}H_{26}N_2O_4$: C, 71.75; H, 6.26; N, 6.69. Found: C, 71.52; H, 6.10; N, 6.53.

4.9.14. 5,8-Dihydropyrrolo[2,3-*d*][2]benzazepin-7(6*H*)-one (21). A suspension of **20** (105 mg, 0.25 mmol) and $Pd(OH)_2$ (53 mg, 50% w/w) in ethanol/THF (10 mL, 4:1) was stirred under H_2 (1 bar) for 2 h at room temperature. The catalyst was removed by filtration and the filtrate was evaporated in vacuo. The residue obtained was used in the next step without further purification. A solution of the crude product and 1 N NaOH (1.25 mL) in 1,4-dioxane (4 mL) was stirred at 80 °C for 1 h. After cooling, the solution was neutralized with 1 N HCl solution (pH 2–3) and extracted with EtOAc (3×10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The solid was finally recrystallized from EtOAc to afford **21** (44 mg, 88%) as a white solid. Mp 209–210 °C (EtOAc); IR (KBr) ν 3350–3050, 2906, 1631, 1593, 1511, 1461, 1130, 1089, 754 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.01 (d, 2H, J=5.1 Hz, CH_2), 6.58 (t, 1H, J=2.6 Hz, $H_{pyrrole}$), 7.05 (t, 1H, J=2.6 Hz, $H_{pyrrole}$), 7.24 (t, 1H, J=7.3 Hz, H_{ar}), 7.32–7.39 (m, 2H, H_{ar}), 7.62 (d, 1H, J=7.7 Hz, H_{ar}), 7.88 (br t, 1H, J=5.1 Hz, NH), 11.80 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 45.0 (CH_2), 106.8 (CH), 122.5 (CH), 124.1 (C), 125.3 (C), 126.3 (CH), 126.4 (CH), 127.8 (2CH), 134.1 (C), 135.5 (C), 163.4 (CO); MS (IS) m/z 199 $(M+H)^+$. Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.88; H, 5.16; N, 14.23.

4.9.15. 5-Methoxy-1-(phenylsulfonyl)-1*H*-indole-3-carboxylic acid (23b). To a solution of 5-methoxy-1-(phenylsulfonyl)-indole-3-carboxaldehyde (379 mg, 1.20 mmol) in dioxane/H_2O (14 mL, 4:1) was added $NaClO_2$ (176 mg, 1.93 mmol) followed by sulfamic acid (664 mg, 6.85 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature. A saturated $NaHCO_3$ solution (15 mL) was added with precaution to the solution and the final mixture was stirred for 30 min. The solution was concentrated and the residue was dissolved in EtOAc. The organic solution was washed with 3 N HCl and H_2O. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The solid was recrystallized from EtOAc to give **23b** (323 mg, 81%) as a white solid. Mp >210 °C (EtOAc); IR (KBr) ν 3135–2600, 1680, 1430, 1380, 1200, 970 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.77 (s, 3H, CH_3), 7.02 (dd, 1H, J=2.5, 9.1 Hz, H_6), 7.50 (d, 1H, J=2.5 Hz, H_4), 7.63 (t, 2H, J=7.7 Hz, H_{ar}), 7.75 (t, 1H, J=7.4 Hz, H_{ar}), 7.86 (d, 1H, J=9.1 Hz, H_7), 8.10 (d, 2H, J=7.9 Hz, H_{ar}), 8.29 (s, 1H, H_2), 12.81 (br s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 55.4 (CH_3), 103.7 (CH), 114.0 (C), 114.1 (CH), 114.7 (CH), 127.1 (2CH), 128.7 (C), 128.8 (C), 130.1 (2CH), 132.4 (CH), 135.2 (CH), 136.5 (C), 156.8 (C), 164.4 (CO); MS (IS) m/z 332 $(M+H)^+$. Anal. Calcd for $C_{16}H_{13}NO_5S$: C, 58.00; H, 3.95; N, 4.23. Found: C, 58.34; H, 4.08; N, 4.36.

4.9.16. *N*-(2-Iodobenzyl)-1-(phenylsulfonyl)-1*H*-indole-3-carboxamide (24a). According to the procedure described for **5**, compound **24a** was prepared from **23a**[9] and **4**. A catalytic amount of DMAP was used. Yield: 82%; white solid; mp 204–206 °C (washing CH_2Cl_2); IR (KBr) ν 3264, 3067, 2950, 1625, 1560, 1382, 1097, 744, 690 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.44 (d, 2H, J=5.5 Hz, CH_2), 7.03–7.09 (m, 1H, H_{ar}), 7.30–7.41 (m, 4H, H_{ar}), 7.65 (t, 2H, J=7.7 Hz, H_{ar}), 7.75 (t, 1H, J=7.4 Hz, H_{ar}), 7.89 (d, 1H, J=7.7 Hz, H_{ar}), 7.93 (d, 1H, J=7.9 Hz, H_{ar}), 8.05 (d, 2H, J=8.0 Hz, H_{ar}), 8.16 (d, 1H, J=8.1 Hz, H_{ar}), 8.67 (s, 1H, H_{ar}), 8.97 (br t, 1H, J=5.5 Hz, NH); ^{13}C NMR (DMSO-d_6) δ 47.5 (CH_2), 98.8 (C), 112.9 (CH), 116.3 (C), 122.3 (CH), 124.2 (CH), 125.4 (CH), 126.9 (2CH), 128.4 (2CH+C), 128.5 (CH), 129.1 (CH), 130.1 (2CH), 133.9 (C), 135.1 (CH), 136.6 (C), 139.0 (CH), 140.6 (C), 162.7 (CO); MS

(IS) *m/z* 517 $(M+H)^+$. Anal. Calcd for $C_{22}H_{17}IN_2O_3S$: C, 51.17; H, 3.32; N, 5.43. Found: C, 50.97; H, 3.22; N, 5.35.

4.9.17. *N*-(2-Iodobenzyl)-5-methoxy-1-(phenylsulfonyl)-1*H*-indole-3-carboxamide (24b). According to the procedure described for **5**, compound **24b** was prepared from **23b** and **4**. A catalytic amount of DMAP was used. Yield: 76%; white solid; mp >210 °C (washing CH_2Cl_2); IR (KBr) ν 3308, 3070, 2936, 2822, 1630, 1552, 1378, 1093, 752, 693 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.75 (s, 3H, CH_3), 4.43 (d, 2H, J=5.5 Hz, CH_2), 6.99 (dd, 1H, J=2.6, 9.0 Hz, H_{ar}), 7.03–7.09 (m, 1H, H_{ar}), 7.36–7.44 (m, 2H, H_{ar}), 7.62–7.67 (m, 3H, H_{ar}), 7.75 (t, 1H, J=7.4 Hz, H_{ar}), 7.82 (d, 1H, J=9.0 Hz, H_{ar}), 7.89 (d, 1H, J=7.5 Hz, H_{ar}), 8.01 (d, 2H, J=8.0 Hz, H_{ar}), 8.64 (s, 1H, H_{ar}), 8.96 (br t, 1H, J=5.5 Hz, NH); ^{13}C NMR (DMSO-d_6) δ 47.5 (CH_2), 55.3 (CH_3), 98.8 (C), 104.2 (CH), 113.8 (CH), 114.6 (CH), 116.1 (C), 126.8 (2CH), 128.4 (2CH), 128.5 (C), 129.0 (CH), 129.1 (CH), 129.6 (C), 130.1 (2CH), 135.0 (CH), 136.6 (C), 139.0 (CH), 140.6 (C), 156.5 (C), 162.8 (CO); MS (IS) *m/z* 547 $(M+H)^+$. Anal. Calcd for $C_{23}H_{19}IN_2O_4S$: C, 50.56; H, 3.51; N, 5.13. Found: C, 50.79; H, 3.45; N, 5.26.

4.9.18. *tert*-Butyl (2-iodobenzyl){[1-(phenylsulfonyl)-1*H*-indol-3-yl]carbonyl}carbamate (25a). According to the procedure described for **6**, compound **25a** was prepared from **24a**. Chromatography eluent: PE/EtOAc 95:5; yield: 99%; white solid; mp 85–87 °C (Et_2O/PE); IR (KBr) ν 3065, 2977, 2872, 1723, 1677, 1447, 1383, 748, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, 9H, $3CH_3$), 5.00 (s, 2H, CH_2), 6.96 (t, 1H, J=7.5 Hz, H_{ar}), 7.24–7.39 (m, 4H, H_{ar}), 7.48 (t, 2H, J=7.7 Hz, H_{ar}), 7.59 (t, 1H, J=7.4 Hz, H_{ar}), 7.80 (d, 1H, J=7.7 Hz, H_{ar}), 7.85 (d, 1H, J=7.9 Hz, H_{ar}), 7.95 (d, 2H, J=8.0 Hz, H_{ar}), 8.00 (d, 1H, J=8.1 Hz, H_{ar}), 8.08 (s, 1H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 27.5 ($3CH_3$), 54.4 (CH_2), 83.9 (C), 97.8 (C), 113.7 (CH), 119.4 (C), 121.5 (CH), 124.5 (CH), 125.6 (CH), 127.1 (CH), 127.3 (2CH), 128.0 (C), 128.5 (CH), 129.0 (CH), 129.7 (2CH), 130.2 (CH), 134.5 (C), 134.6 (CH), 137.9 (C), 139.6 (CH), 139.7 (C), 153.1 (CO), 167.1 (CO); MS (IS) *m/z* 617 $(M+H)^+$. Anal. Calcd for $C_{27}H_{25}IN_2O_5S$: C, 52.61; H, 4.09; N, 4.54. Found: C, 52.66; H, 4.09; N, 4.50.

4.9.19. *tert*-Butyl (2-iodobenzyl){[5-methoxy-1-(phenylsulfonyl)-1*H*-indol-3-yl]carbonyl}carbamate (25b). According to the procedure described for **6**, compound **25b** was prepared from **24b**. Chromatography eluent: PE/EtOAc 85:15; yield: 99%; white solid; mp 131–132 °C (Et_2O); IR (KBr) ν 3070, 2976, 2824, 1732, 1670, 1448, 1376, 1092, 724, 693 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.93 (s, 9H, $3CH_3$), 3.74 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 7.03–7.08 (m, 2H, H_{ar}), 7.15 (d, 1H, J=2.5 Hz, H_{ar}), 7.18 (d, 1H, J=7.4 Hz, H_{ar}), 7.43 (t, 1H, J=7.0 Hz, H_{ar}), 7.64 (t, 2H, J=7.6 Hz, H_{ar}), 7.75 (t, 1H, J=7.3 Hz, H_{ar}), 7.90 (d, 1H, J=7.6 Hz, H_{ar}), 7.93 (d, 1H, J=9.1 Hz, H_{ar}), 8.13 (d, 2H, J=8.0 Hz, H_{ar}), 8.36 (s, 1H, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 27.6 ($3CH_3$), 54.4 (CH_2), 55.8 (CH_3), 83.9 (C), 97.9 (C), 103.4 (CH), 114.5 (CH), 115.4 (CH), 119.0 (C), 127.2 (2CH), 127.4 (CH), 128.5 (CH), 129.0 (CH), 129.1 (2C), 129.7 (2CH), 130.8 (CH), 134.5 (CH), 137.8 (C), 139.6 (CH), 139.8 (C), 153.2 (CO), 157.4 (C), 167.3 (CO); MS (IS) *m/z* 647 $(M+H)^+$. Anal. Calcd for $C_{28}H_{27}IN_2O_6S$: C, 52.02; H, 4.21; N, 4.33. Found: C, 51.78; H, 4.11; N, 4.45.

4.9.20. 12-(Phenylsulfonyl)-7-oxo-5,6,7,12-tetrahydroindolo[3,2-*d*][2]benzazepine-6-carboxylic acid *tert*-butyl ester (26a). According to the procedure described for **7**, compound **26a** was prepared from **25a**. In this case, $Pd(OAc)_2$ (10 mol %) and PPh_3 (20 mol %) were used. The reaction mixture was stirred at 100 °C for 2 h. Chromatography eluent: PE/EtOAc 9:1; yield: 92%; white solid; mp 154 °C dec (Et_2O); IR (KBr) ν 3078, 2978, 1759, 1693, 1446, 1387, 756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (s, 9H, $3CH_3$), 3.66 and 5.09 (d, 1H, J=14.5 Hz, CH_2), 7.12 (br d, 2H, J=8.5 Hz, H_{ar}), 7.20 (t, 2H, J=8.5 Hz, H_{ar}), 7.37–7.58 (m, 6H, H_{ar}), 7.97–8.00 (m, 1H, H_{ar}), 8.16 (br d, 1H, J=7.7 Hz, H_{ar}), 8.34 (d, 1H, J=8.3 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 28.1 ($3CH_3$), 47.8 (CH_2), 83.8 (C), 117.6 (CH), 121.7 (C), 122.8 (CH), 126.0 (CH), 126.5 (2CH), 126.6 (CH), 127.5 (2CH), 128.7 (2CH+C), 129.7 (C), 130.3 (CH), 133.4 (CH), 134.2 (CH), 135.7 (C), 136.5 (C), 138.6 (C), 141.9 (C), 151.1 (CO), 162.7 (CO); MS (IS) *m/z* 489 $(M+H)^+$. Anal. Calcd for $C_{27}H_{24}N_2O_5S$: C, 66.38; H, 4.95; N, 5.73. Found: C, 66.11; H, 4.82; N, 5.70.

4.9.21. 9-Methoxy-12-(phenylsulfonyl)-7-oxo-5,6,7,12-tetrahydroindolo[3,2-*d*][2]benzazepine-6-carboxylic acid *tert*-butyl ester (26b). According to the procedure described for **7**, compound **26b** was prepared from **25b**. In this case, $Pd(OAc)_2$ (10 mol %) and PPh_3 (20 mol %) were used. The reaction mixture was stirred at 100 °C for 2 h. Chromatography eluent: PE/EtOAc 85:15; yield: 96%; white solid; mp 146 °C dec (EtOAc/PE); IR (KBr) ν 3099, 2975, 2843, 1749, 1652, 1446, 1389, 756, 699 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.45 (s, 9H, $3CH_3$), 3.79 (s, 3H, CH_3), 3.88 and 5.10 (d, 1H, J=14.8 Hz, CH_2), 7.12 (dd, 1H, J=2.6, 9.1 Hz, H_{ar}), 7.17 (d, 2H, J=8.1 Hz, H_{ar}), 7.41 (t, 2H, J=7.9 Hz, H_{ar}), 7.48 (d, 1H, J=2.6 Hz, H_{ar}), 7.54–7.64 (m, 4H, H_{ar}), 7.89–7.91 (m, 1H, H_{ar}), 8.11 (d, 1H, J=9.1 Hz, H_{ar}); ^{13}C NMR ($CDCl_3$) δ 28.1 ($3CH_3$), 47.8 (CH_2), 55.8 (CH_3), 83.8 (C), 104.3 (CH), 116.3 (CH), 118.6 (CH), 121.6 (C), 126.5 (2CH), 127.4 (CH), 127.5 (CH), 128.8 (2CH+C), 130.3 (CH), 131.0 (C), 132.8 (C), 133.5 (CH), 134.2 (CH), 135.6 (C), 136.4 (C), 142.6 (C), 150.9 (CO), 158.2 (C), 163.0 (CO); MS (IS) *m/z* 519 $(M+H)^+$. Anal. Calcd for $C_{28}H_{26}N_2O_6S$: C, 64.85; H, 5.05; N, 5.40. Found: C, 65.00; H, 5.16; N, 5.53.

4.10. General procedure for both deprotection

To a solution of **26** (0.20 mmol) in anhydrous CH_2Cl_2 (4 mL) at room temperature was added trifluoroacetic acid (1 mL, 13.46 mmol). After stirring for 2 h, H_2O (20 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2×20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a crude solid, which was engaged in the next step without further purification. The crude product was dissolved in anhydrous THF (5 mL) and 1 M tetrabutylammonium fluoride (1.0 mL) was added. The resulting solution was refluxed for 30 min, then solvent was evaporated and the crude solid was recrystallized from methanol to afford **27**.

4.10.1. 5,12-Dihydroindolo[3,2-*d*][2]benzazepin-7(6*H*)-one (27a). According to the general procedure described for

27, compound **27a** was prepared from **26a**. Yield: 40%; white solid; mp >210 °C (MeOH); IR (KBr) ν 3320–3171, 3049, 2978, 1623, 1573, 1489, 1448, 742 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.09 (d, 2H, J=5.3 Hz, CH_2), 7.14 (t, 1H, J=7.3 Hz, H_{ar}), 7.24 (t, 1H, J=7.3 Hz, H_{ar}), 7.45–7.56 (m, 4H, 3H_{ar}+NH), 7.83–7.85 (d, 2H, J=7.3 Hz, H_{ar}), 8.07 (d, 1H, J=7.9 Hz, H_{ar}), 12.06 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 44.4 (CH_2), 109.4 (C), 111.4 (CH), 120.5 (CH), 121.6 (CH), 123.0 (CH), 126.7 (CH), 127.9 (C), 128.0 (CH), 128.1 (CH), 128.9 (CH), 130.4 (C), 136.3 (C), 137.9 (C), 138.4 (C), 166.8 (CO); MS (IS) m/z 249 $(M+H)^+$. Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.53; H, 5.01; N, 11.41.

4.10.2. 9-Methoxy-5,12-dihydroindolo[3,2-*d*][2]benzazepin-7(6*H*)-one (27b). According to the general procedure described for **27**, compound **27b** was prepared from **26b**. Yield: 43%; white solid; mp >210 °C (CH_2Cl_2); IR (KBr) ν 3350–3180, 3000, 2957, 2843, 1622, 1490, 1466, 1033, 741 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.78 (s, 3H, CH_3), 4.07 (d, 2H, J=5.1 Hz, CH_2), 6.88 (dd, 1H, J=2.6, 8.9 Hz, H_{ar}), 7.39 (d, 1H, J=8.9 Hz, H_{ar}), 7.43–7.55 (m, 3H, 2H_{ar}+NH), 7.58 (d, 1H, J=2.6 Hz, H_{ar}), 7.80–7.82 (m, 2H, H_{ar}), 11.96 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 44.5 (CH_2), 55.3 (CH_3), 102.9 (CH), 109.1 (C), 112.2 (CH), 113.4 (CH), 126.5 (CH), 128.0 (CH), 128.1 (CH), 128.5 (C), 128.8 (CH), 130.5 (C), 131.3 (C), 138.2 (2C), 154.3 (C), 167.0 (CO); MS (IS) m/z 279 $(M+H)^+$. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.54; H, 4.98; N, 9.99.

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