EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201403292

A General and Efficient Method to Access Tetracyclic Spirooxindole Derivatives

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Keywords: Anionic condensation / Reduction / Cyclization / Selective deprotection / Tetracyclic spirooxindole / Spiro compounds

An efficient, simple, and convenient synthetic procedure for the synthesis of tetracyclic spirooxindole derivatives, starting from *N*-protected isatins and 2-fluoropyridine, was successfully developed. It enables the facile formation of a new class of spirooxindoles in which the oxindole core is fused with various heterocycles at the C-3 position.

Introduction

Spiroheterocycles are of great interest due to their conformational restriction, which is associated with their broad range of physical and biochemical properties.[1] In particular, polycyclic spirooxindole systems have emerged as attractive synthetic targets because of their prevalence in a number of biologically active compounds and natural products.[2] A survey of the literature showed that the biological potential can be related to the framework of the spiro ring.[3] For example, the simplest tricyclic skeleton, horsfiline (**Ia**; Figure 1), in which the oxindole moiety is linked with a pyrrolidine, is an alkaloid found in the plant *Horsfildea superb* Warb and used in traditional herbal medicine for its antitumor activity. Two other spirooxindole alkaloids of the same type also used as antitumor compounds are coerulescine (**Ib**) from the blue canary grass *Phalaris coerulescens* and elacomine (**II**) from *Elaeagnus commutate*.[4]

Spirobrassinin (**III**) and its analogues are a particular class of spirooxindole phytoalexins, isolated from the plant family *Cruciferae*, which exhibit potent antitumor, antimicrobial, and oviposition stimulant biological activities,[5] whereas compound **IV** was characterized as a hit compound for new inhibitors of β-secretase (BCAE-1) involved in Alzheimer's disease,[6] and compound **V** (XEN 907), connected to a dihydrobenzofuran unit, displayed strong analgesic activity.[7]

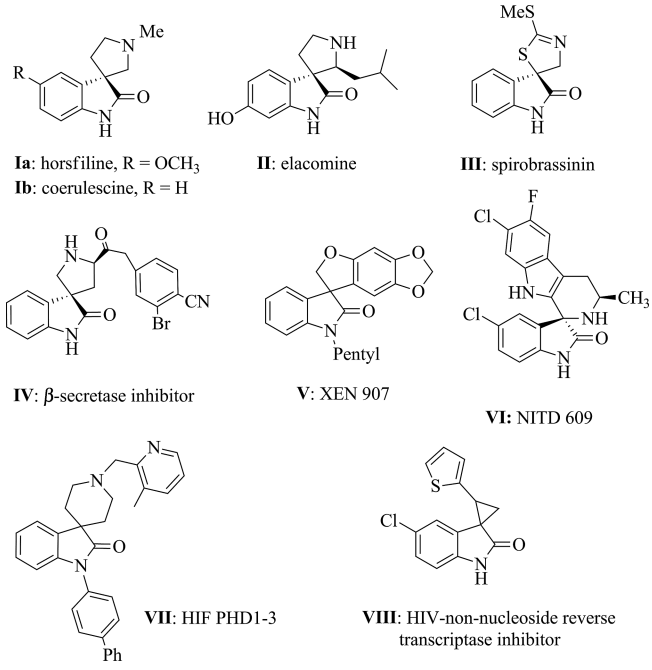

Figure 1. Spirooxindoles with interesting biological activities.

Spirocyclic oxindoles fused with piperidine systems are used as an antimalarial agent (cipargamine, NITD-609, **VI**; Figure 1)[8] or for the treatment of anemia (HIF PHD 1–3, **VII**),[9]whereas compound **VIII**, in which the spirooxindole unit is fused with a cyclopropane system, was shown to be a potent HIV-1 non-nucleoside reverse transcriptase inhibitor.[10]

Thus, many methods have appeared in the literature, all directed towards the synthesis of this highly valuable struc-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403292.

tural motif.[3] In this context, we focused our efforts on the development of a general route for the synthesis of biologically active polycyclic spirooxindoles fused with five-, six-, or seven-membered heterocycle systems, condensed in each case with a pyridine core (Figure 2).

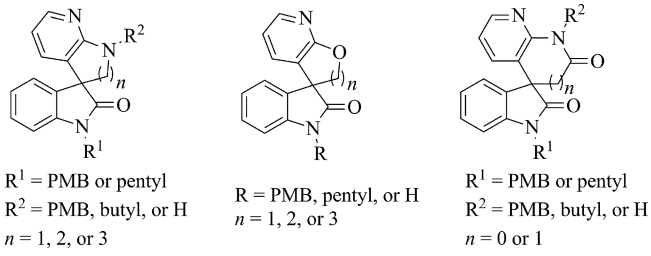
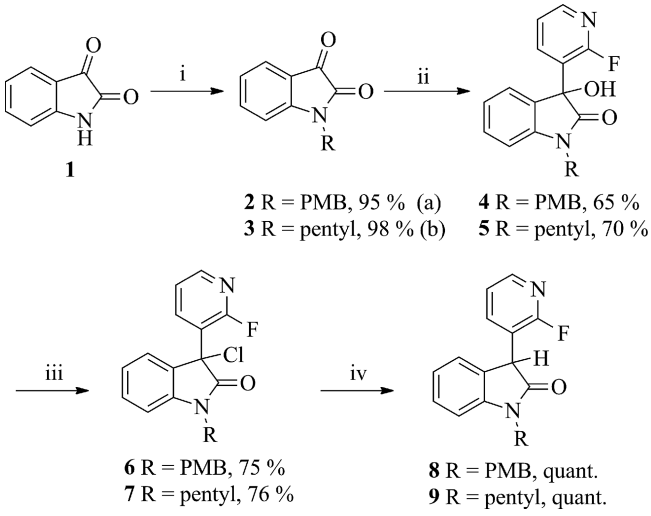


Figure 2. Targeted molecules.

We wish to describe our results here. All products were obtained from derivatives **4** or **5** as common starting materials, themselves prepared from *N*-substituted isatins **2**[11] and **3**,[12] conveniently prepared in turn from commercial isatin (Scheme 1). Three series of new spirooxindole derivatives were efficiently synthesized (Figure 2), containing a five-, six-, or seven-membered heterocycle with

* an amine function (in the first series)
* an ether function (in the second series)
* an amide function (in the third series).



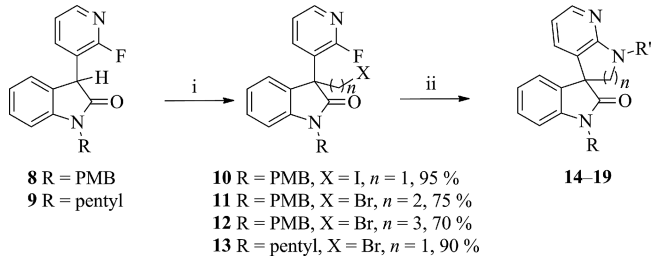
Scheme 1. Synthesis of compounds **8** and **9**. (i) (a) 4-methoxybenzyl chloride, K_2CO_3, KI, DMF, 120 °C, 4 h; (b) 1-bromopentane, NaH, DMF, room temp., 12 h; (ii) 2-fluoropyridine, LDA, THF, –78 °C, 4 h, then **2** or **3**, –78 °C to room temp., 6 h; (iii) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C, 2 h; (iv) Zn, THF/AcOH (7:3), room temp., 3 h.

Results and Discussion

One straightforward method for the synthesis of these products is to use a 3-substituted 3-hydroxyindole derivative in a key step. Intermediates of this kind and their synthetic potential have been extensively described,[13] and have generally been obtained through the addition of a nucleophile to a carbonyl group in the indole 3-position. In our case, we decided to use 2-fluoropyridine, selective *ortho*-lithiation of which with LDA[14] efficiently furnished the resulting 3-lithio derivative. Condensation of this with *N*-protected isatins **2** or **3** afforded compounds **4** and **5**, respectively, in good yields. Dehydroxylation of compounds **4** and **5** was achieved in two steps by treatment with $SOCl_2$ and pyridine in dichloromethane at 0 °C for 2 h[15] and then with zinc dust in a THF/AcOH mixture at room temperature for 3 h[16] to afford compounds **8** and **9**, our pivotal structures, in good yields (Scheme 1).

Spirooxindoles Containing Five-, Six-, or Seven-Membered Heterocycles Incorporating Amine Functions

Alkylation of compounds **8** and **9** variously with diodomethane, dibromomethane, 1,2-dibromoethane, or 1,3-dibromopropane in the presence of potassium hydroxide in DMF[17] gave the corresponding alkylated products **10** (95%), **11** (75%), **12** (70%), and **13** (90%) (Scheme 2).



Scheme 2. Spirooxindoles **14**–**19**. (i) KOH, DMF, dihaloalkane (diiodomethane for **10**, 1,2-dibromoethane for **11**, 1,3-dibromopropane for **12**, and dibromethane for **13**), room temp., 2 h; (ii) butylamine or 4-methoxybenzylamine, dioxane, microwaves, 200 °C, 3 h.

S_N2 substitution and S_NAr cyclization were achieved in a one-step[18] fashion by treatment with butylamine or 4-methoxybenzylamine under microwave irradiation conditions (200 °C, 3 h.), and allowed the convenient synthesis of a series of spirooxindoles **14**–**19** in good yield (Table 1).

N-Deprotection of compound **15** was next envisaged, by standard procedures.[19] No reaction at all was achieved with the use of TFA at room temperature during 12 h, TFA at 100 °C for 1 h, or H_2/Pd-C in methanol at room temperature over 4 h (Table 2). However, when the reaction was carried out with TFA in dichloromethane in the presence of 10 equiv. of triflic acid, at room temperature overnight, *N*-deprotected product **20** was obtained in excellent yield (90%).[20]

Selective deprotection of compounds **18** and **19** was conducted with trifluoroacetic acid at 100 °C over 30 min under microwave conditions and furnished compounds **21** and

Table 1. Synthesis of compounds **14**–**19**.

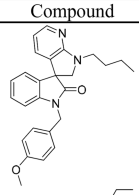
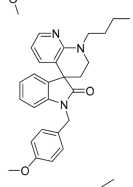
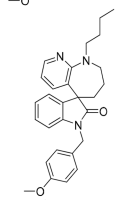
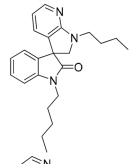
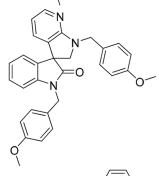
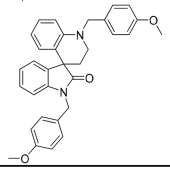
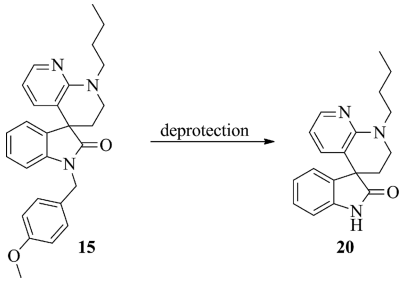
Entry	R	R′	*n*	Compound	Yield [%]
1	PMB	butyl	1 (**14**)		85
2	PMB	butyl	2 (**15**)		90
3	PMB	butyl	3 (**16**)		68
4	pentyl	butyl	1 (**17**)		80
5	PMB	PMB	1 (**18**)		75
6	PMB	PMB	2 (**19**)		78

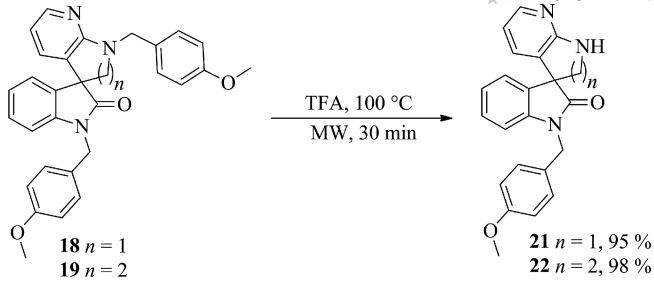
Table 2. Attempted PMB removal.



Entry	Conditions	Result
1	TFA, 12 h, r.t.	s.m.[a]
2	TFA, 1 h, microwaves, 100 °C	s.m.
3	H_2, Pd-C, P = 1 atm, MeOH, 4 h, r.t.	s.m.
4	TFA, triflic acid 10 equiv., CH_2Cl_2, 12 h, r.t.	**20** (90%)

[a] s.m.: starting material, CH_2Cl_2/dichloromethane.

22 in excellent yields (95% and 98% respectively; Scheme 3). Under these conditions no deprotection of the lactam function was observed.



Scheme 3. Selective deprotection of compounds **18** and **19**.

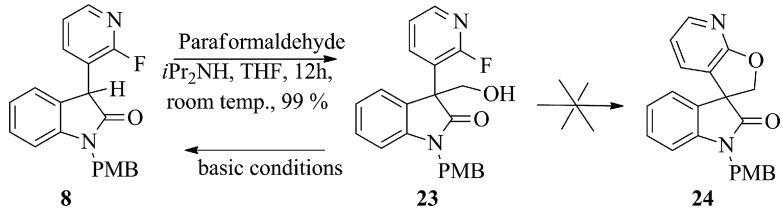
Spirooxindoles Containing Five-, Six-, or Seven-Membered Heterocycles Incorporating Ether Functions

To extend the methodology we decided to prepare spirooxindoles of type **24**, in which the oxindole core was fused with a tetrahydrofuran system. Hydroxymethylation of compound **8** at the C-3 position was performed in THF at room temperature in the presence of 10 equiv. of paraformaldehyde and 4 equiv. of diisopropylamine for 12 h to give compound **23** in a quantitative yield.[21] However, all attempts to transform compound **23** into **24** by S_NAr cyclization in basic medium[22] were not successful, with only compound **8** being obtained by a retro-aldol process (Scheme 4).

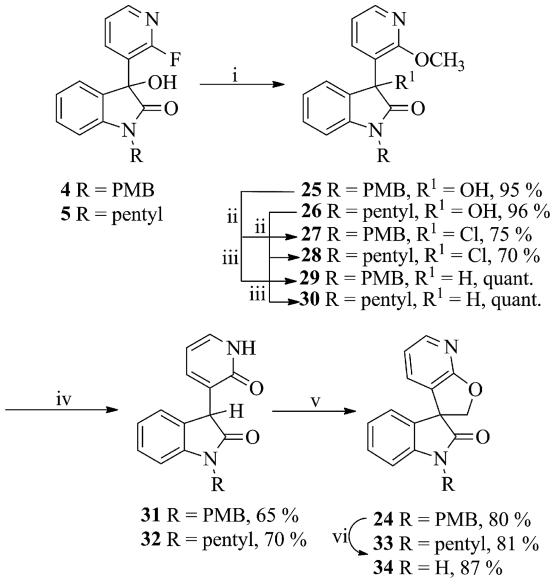
In the face of such failure, we went back to the first approach, starting from compounds **4** and **5**. Treatment of **4** with sodium methoxide in methanol for 12 h furnished **25** (95% yield); likewise, **5** led to **26** in a similar yield (96%). Dehydroxylation of compounds **25** and **26** was achieved, as described previously, in two steps, firstly by treatment with $SOCl_2$ and pyridine in dichloromethane at 0 °C for 2 h to give **27** and **28** (75 and 70% yield, respectively), and then by treatment with zinc dust in a THF/AcOH mixture at room temperature for 3 h to afford compounds **29** and **30** in near quantitative yield (Scheme 5).

Hydrolysis of compounds **29** and **30** was carried out with HCl (3 N) in a H_2O/dioxane mixture (1:1) at 80 °C over 12 h,[23] with the corresponding pyridones **31** and **32** being isolated in good yields. Further treatment of intermediates **31** and **32** with chloroiodomethane in DMF at room temperature in the presence of Cs_2CO_3 for 12 h afforded the cyclized compounds **24** and **33** in 80% and 81% yields, respectively (Scheme 5). The structure of compound **33** was confirmed by X-ray diffraction (Figure 3). Finally, *N*-deprotected product **34** was obtained in good yield (87%) by use of TFA and 10 equiv. of triflic acid in dichloromethane at room temperature overnight.

The corresponding six- and seven-membered heterocycles **41** and **42** were prepared from compound **8** by treatment with sodium hydride, followed by alkylation with methyl bromoacetate or methyl 3-bromopropionate at 0 °C for 2 h[25] to afford **35** (98%) or **36** (80%). Saponification of the corresponding esters was carried out with NaOH (2 N) in MeOH at room temperature overnight to give **37**



Scheme 4. Attempts to cyclize compound **23**.



Scheme 5. Synthesis of spirooxindoles **24**, **33**, and **34**. (i) MeONa, MeOH, reflux, 12 h; (ii) $SOCl_2$, pyridine, CH_2Cl_2, 0 °C, 2 h; (iii) Zn, THF/AcOH, room temp., 3 h; (iv) HCl (3 N), dioxane, 80 °C, 12 h; (v) chloroiodomethane, Cs_2CO_3, DMF, room temp., 12 h; (vi) TFA, triflic acid, CH_2Cl_2, room temp., 12 h.

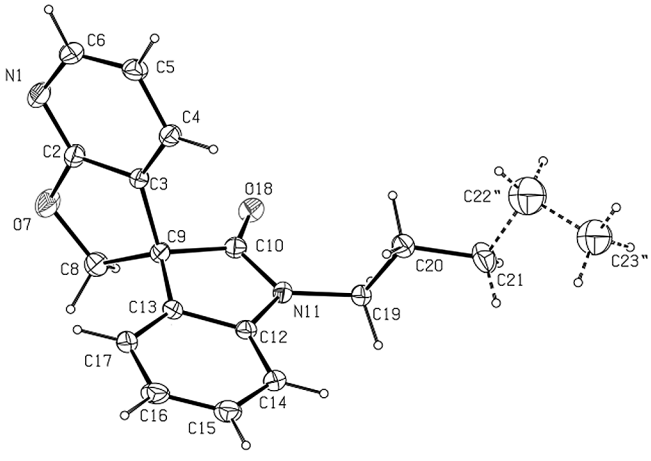
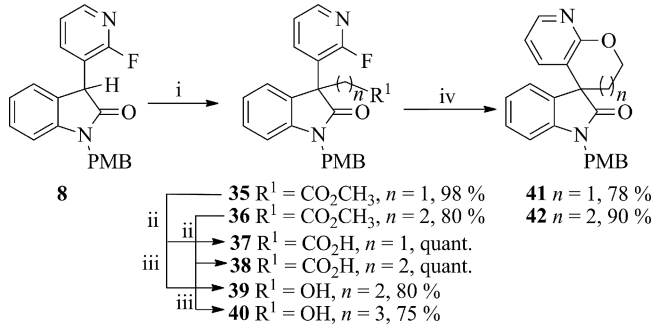


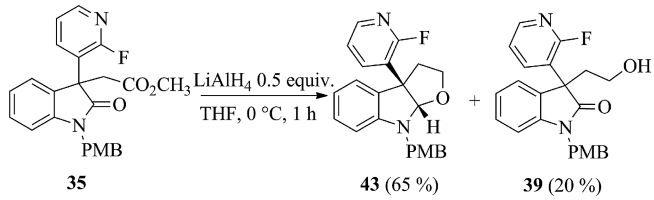
Figure 3. ORTEP view of compound **33**[24] (two positions of the disordered lateral chain C22 and C23 have been omitted to allow better visibility of the chemical structure).

and **38** in quantitative yields, and the resulting acids were transformed into mixed anhydrides by treatment with ethyl chloroformate in the presence of triethylamine at 0 °C in THF for 0.5 h. Reduction of these anhydrides with $NaBH_4$ in EtOH at ambient temperature overnight afforded the alcohols **39** and **40** in very good yields (Scheme 6). Finally, compounds **39** and **40** were cyclized in THF at 150 °C in the presence of 1 equiv. of NaH under microwave irradiation conditions for 2 h to give compounds **41** and **42** in good yields[22] after purification (Scheme 6).



Scheme 6. Synthesis of spirooxindoles **41** and **42**. (i) Methyl bromoacetate or methyl 3-bromopropionate, NaH, THF, 0 °C, 2 h; (ii) NaOH (2 N), MeOH, room temp., 12 h; (iii) (a) ethyl chloroformate, Et_3N, THF, 0 °C, 0.5 h; (b) $NaBH_4$, EtOH, room temp., 12 h; (iv) NaH, THF, 150 °C, microwaves, 2 h.

Attempts to reduce ester **35** directly to alcohol **39** with $LiAlH_4$ (0.5 or 1 equiv.) were unsuccessful, with a mixture of compounds **43** and **39** being obtained (Scheme 7). Compound **43**, the main compound obtained in both cases, was the result of molecular trapping of the alcohol on the transient iminium ion. The relative stereochemistry was determined by X-ray diffraction (Figure 4) and is in accordance with compounds obtained by the same methodology.[26]



Scheme 7. Reduction of ester **35** with $LiAlH_4$.

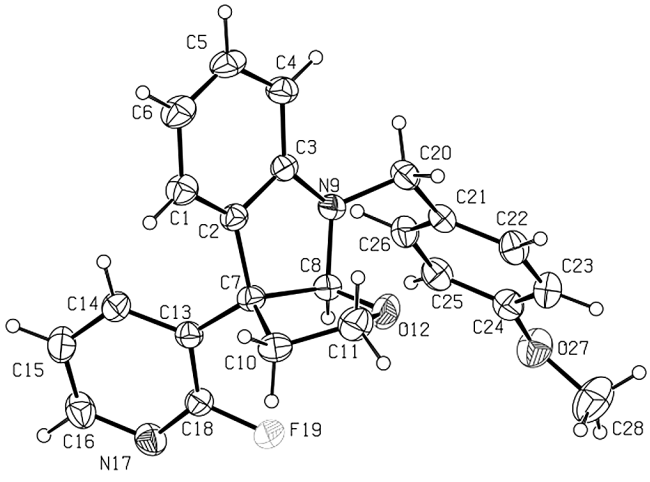
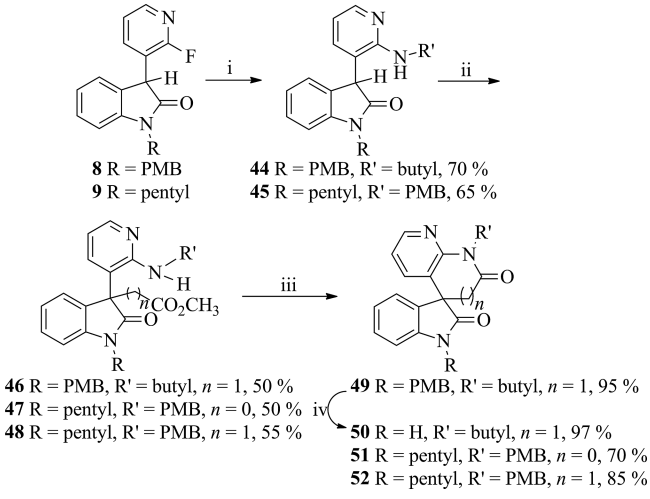


Figure 4. ORTEP view of compound **43**.[24]

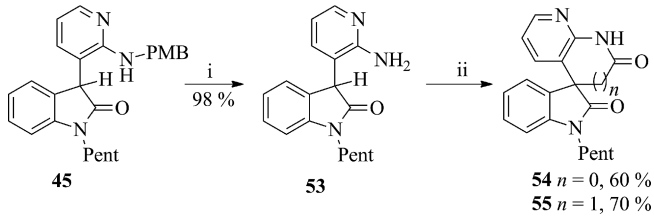
Spirooxindoles Containing Five- or Six-Membered Heterocycles Incorporating Amide Functions

Compounds **8** and **9** were also employed in the synthesis of spirooxindoles containing five- or six-membered N-heterocycles incorporating lactam functions. Treatment of compounds **8** and **9** with butylamine or 4-methoxybenzylamine in dioxane at 180 °C for 3 h under microwave irradiation conditions led to substitution of the fluorine atom by the amine[18] group and afforded **44** and **45** in good yields. These were converted into **46**, **47**, and **48** by treatment with methyl chloroformate or methyl bromoacetate in THF at 0 °C in the presence of 2 equiv. of NaH for 2 h. Finally, compounds **46**, **47**, and **48** were cyclized in methanol in the presence of Et_3N at 100 °C under microwave irradiation conditions for 2 h to give compounds **49**, **50**, and **51** in good to excellent yields after purification (Scheme 8). As in the case of compound **20**, use of triflic acid (10 equiv., TFA, CH_2Cl_2, room temperature, overnight) was necessary to obtain the *N*-deprotected product **50** in an excellent yield of 97%.



Scheme 8. Synthesis of spirooxindoles **49**–**52**. (i) Butylamine or 4-methoxybenzylamine, dioxane, 180 °C, microwaves, 3 h; (ii) methyl chloroformate or methyl bromoacetate, NaH, THF, 0 °C, 2 h; (iii) MeOH, Et_3N, 100 °C, microwaves, 2 h; (iv) TFA, triflic acid, CH_2Cl_2, room temp., 12 h.

Alternatively, compound **45** was *N*-deprotected by use of TFA at 100 °C under microwave irradiation conditions for 30 min to give **53** in excellent yield. Treatment of **53** with methyl chloroformate or methyl bromoacetate in the presence of triethylamine furnished a crude product that was then cyclized under microwave irradiation conditions at 100 °C for 1 h to afford **54** or **55** in good yields after purification (Scheme 9).



Scheme 9. Synthesis of spirooxindoles **54** and **55**. (i) TFA, 100 °C, microwaves, 30 min; (ii) methyl chloroformate or methyl bromoacetate, Et_3N, THF, room temp., 12 h, then 100 °C, microwaves, 1 h.

Conclusions

We have developed a synthetic route to new spirooxindoles fused with five-, six-, or seven-membered heterocycle moieties. A library of a wide variety of original tetracyclic spirooxindoles was obtained in moderate to good yields by starting from two key intermediates: 3-(2-fluoropyridin-3-yl)-3-hydroxy-1-[(4-methoxyphenyl)methyl]indolin-2-one (**4**) and 3-(2-fluoropyridin-3-yl)-3-hydroxy-1-pentylindolin-2-one (**5**). This method opens the way to a general synthesis of tetracyclic spirooxindole systems, major skeletons for designing biologically active compounds. Further studies and investigation of the properties of these molecules are currently in progress in our laboratory.

Experimental Section

General: Microwave-assisted reactions were carried out with a Biotage Initiator Microwave synthesis instrument with internal temperatures measured with an IR sensor. The reactions were monitored by thin-layer chromatography (TLC) analysis on silica gel (60 F254) plates. Spots were visualized with UV light at 254 nm and 356 nm. Column chromatography was performed with silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points (m.p.) were obtained with a melting point apparatus with a digital thermometer in open capillary tubes and are reported without correction. ^1H and ^{13}C NMR spectra were recorded with a Bruker DPX 400 MHz instrument in $CDCl_3$ or [D_6]DMSO. The chemical shifts are reported in parts per million (δ scale), and all coupling constant (J) values are in Hertz [Hz]. The following abbreviations are used to explain the multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). IR absorption spectra were obtained with a Perkin–Elmer Paragon 1000 PC spectrometer, and values are reported in cm^{-1}. HRMS was performed with a Maxis Bruker 4G instrument, and spectra were recorded with a time-of-flight mass spectrometer fitted with an electrospray (ESI).

General Method to Prepare Compounds 4 and 5: 2-Fluoropyridine (9.7 g, 0.1 mol) was added slowly to a cold (–75 °C) solution of lithium diisopropylamide, which had been prepared previously by treatment of diisopropylamine (10.1 g, 0.1 mol) with butyllithium (62.5 mL, 0.1 mol) in THF (250 mL) at 0 °C for 30 min. The resulting yellow mixture was stirred at –78 °C for 4 h before addition of compound **2** (26.7 g, 0.1 mol) or **3** (21.7 g, 0.1 mol) in THF (75 mL) solution. Stirring was continued at –78 °C for 6 h, before hydrolysis with an aqueous solution of NH_4Cl at room temperature. The aqueous phase was extracted with ethyl acetate, and the organic phase was washed with water and brine, dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (petroleum ether/EtOAc 7:3) to give product **4** or **5**.

3-(2-Fluoropyridin-3-yl)-3-hydroxy-1-(4-methoxybenzyl)indolin-2-one (4): M.p. 94 °C; yield 65%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.81 (s, 3 H), 3.98 (s, 1 H), 4.81 (d, J = 15.5 Hz, 1 H), 5.05 (d, J = 15.5 Hz, 1 H), 6.82 (d, J = 7.9 Hz, 1 H), 6.90 (d, J = 8.6 Hz, 2 H), 7.01 (t, J = 7.5 Hz, 1 H), 7.09 (d, J = 6.7 Hz, 1 H), 7.22–7.31 (m, 2 H), 7.33 (d, J = 8.6 Hz, 2 H), 8.15 (d, J = 4.8 Hz, 1 H), 8.40 (ddd, J = 9.6, 7.6, 1.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 43.8, 55.3, 74.6 (d, J = 5.3 Hz), 110.1, 114.3 (2×CH), 121.6 (d, J = 4.2 Hz), 122.9 (d, J = 28.2 Hz), 123.5, 124.4, 127.0, 128.7, 128.8, 129.3, 130.4, 138.6 (d, J = 4.4 Hz), 143.1, 147.8 (d, J = 14.9 Hz), 159.2, 159.3 (d, J = 239.0 Hz), 175.9 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3306, 2838, 1719, 1609, 1576, 1513, 1487, 1245, 1174, 1065, 1028, 835, 749, 676, 649 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{17}FN_2O_3$ $[M + H]^+$ 365.1296; found 365.1294.

3-(2-Fluoropyridin-3-yl)-3-hydroxy-1-pentylindolin-2-one (5): M.p. 92 °C; yield 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (t, J = 6.9 Hz, 3 H), 1.34–1.49 (m, 4 H), 1.66–1.83 (m, 2 H), 3.61–3.73 (m, 1 H), 3.81–3.88 (m, 1 H), 4.15 (s, 1 H), 6.94 (d, J = 7.8 Hz, 1 H), 7.03 (td, J = 7.5, 0.8, Hz, 1 H), 7.09 (d, J = 6.1 Hz, 1 H), 7.25–7.27 (m, 1 H), 7.36 (td, J = 7.7, 1.4 Hz, 1 H), 8.11–8.13 (m, 1 H), 8.35 (ddd, J = 9.6, 7.6, 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.4, 26.8, 29.0, 40.0, 74.6 (d, J = 5.3 Hz), 109.1, 121.6 (d, J = 4.2 Hz), 123.0, 123.3, 124.5, 129.5, 130.4, 138.5, 143.4, 147.0 (d, J = 14.8 Hz), 159.3 (d, J = 240.6 Hz), 175.8 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3336, 2956, 2931, 2871, 1702, 1609, 1487, 1430, 1361, 1241, 1140, 1121, 1099, 926, 860, 750, 695, 676 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{19}FN_2O_2$ $[M + H]^+$ 315.1503; found 315.1502.

General Method to Prepare Compounds 6 and 7: Thionyl chloride (4.1 mL, 56.7 mmol) was added dropwise to a solution of hydroxyindole **4** (13.76 g,37.8 mmol) or **5** (11.87 g,37.8 mmol) and pyridine (6.2 mL, 75.6 mmol) in CH_2Cl_2 (80 mL), cooled to 0 °C in a round-bottomed flask. The reaction solution was stirred at 0 °C for 2 h. Water (60 mL) was then added, and the mixture was extracted with CH_2Cl_2 (3× 100 mL). The combined extracts were washed with brine and then dried with $MgSO_4$ prior to concentration. Purification by column chromatography (petroleum ether/EtOAc, 8:2) afforded chlorooxindole **6** (10.85 g) or **7** (9.56 g), each as an oil.

3-Chloro-3-(2-fluoropyridin-3-yl)-1-(4-methoxybenzyl)indolin-2-one (6): Yellow oil; yield 75%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.81 (s, 3 H), 4.95 (d, J = 15.5 Hz, 1 H), 5.05 (d, J = 15.5 Hz, 1 H), 6.83 (d, J = 7.9 Hz, 1 H), 6.91 (d, J = 8.7 Hz, 2 H), 7.02 (td, J = 7.5, 0.6, Hz, 1 H), 7.11 (dd, J = 7.4, 0.8 Hz, 1 H), 7.25 (dd, J = 7.8, 1.1 Hz, 1 H), 7.34 (d, J = 8.6 Hz, 2 H), 7.39 (ddd, J = 7.4, 4.9, 1.7 Hz, 1 H), 8.24 (dd, J = 3.5, 1.4 Hz, 1 H), 8.55 (ddd, J = 9.8, 7.6, 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 44.1, 55.3, 64.2 (d, J = 6.2 Hz), 110.2, 114.3 (2 CH), 119.7 (d, J = 26.8 Hz), 121.8 (d, J = 4.3 Hz), 123.6, 124.4, 126.9, 128.7 (2 CH), 129.5, 130.7, 140.8 (d, J = 3.2 Hz), 142.0, 148.0 (d, J = 15.1 Hz), 159.02 (d, J = 240.2 Hz), 159.3, 172.4 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2935, 2837, 1732, 1605, 1512, 1488, 1467, 1424, 1380, 1271, 1244, 1175, 1113, 1034, 938, 925, 824, 805, 755, 706, 684, 668, 638 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{16}ClFN_2O_2$ $[M + H]^+$ 383.0957; found 383.0955.

3-Chloro-3-(2-fluoropyridin-3-yl)-1-pentylindolin-2-one (7): Yellow oil; yield 76%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (t, J = 7.1 Hz, 3 H), 1.31–1.52 (m, 4 H), 1.72–1.89 (m, 2 H), 3.71–3.97 (m, 2 H), 6.96 (d, J = 7.9 Hz, 1 H), 7.04 (td, J = 7.5, 0.8 Hz, 1 H), 7.12 (dd, J = 7.5, 1.0 Hz, 1 H), 7.32–7.41 (m, 2 H), 8.17–8.23 (m, 1 H), 8.51 (ddd, J = 9.8, 7.6, 1.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.3, 26.7, 28.9, 40.8, 64.0 (d, J = 6.3 Hz), 109.3, 119.9 (d, J = 26.8 Hz), 121.7 (d, J = 4.3 Hz), 123.4, 124.5 (d, J = 1.1 Hz), 129.6, 130.7, 140.7 (d, J = 3.2 Hz), 142.4, 147.9 (d, J = 15.2 Hz), 159.0 (d, J = 240.3 Hz), 172.1 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2952, 2933, 2867, 1709, 1609, 1602, 1489, 1466, 1421, 1369, 1356, 1296, 1240, 1162, 1144, 1094, 1025, 924, 902, 826, 812, 758, 742, 727, 711 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{18}ClFN_2O$ $[M + H]^+$ 333.1164; found 333.1162.

General Method to Prepare Compounds 8 and 9: Compound **6** (3.82 g, 10 mmol) or **7** (3.33 g, 10 mmol) was dissolved in tetrahydrofuran (70 mL) and acetic acid (30 mL), and zinc dust (3.27 g, 50 mmol) was added. The reaction mixture was stirred at ambient temperature for 3 h and filtered. The filtrate was concentrated in vacuo to dryness. The residue was dissolved in ethyl acetate, washed with saturated aqueous ammonium chloride solution and brine, dried with anhydrous sodium sulfate, filtered, and concentrated in vacuo to dryness to afford pure compound **8** or **9**, each in quantitative yield.

3-(2-Fluoropyridin-3-yl)-1-(4-methoxybenzyl)indolin-2-one (8): M.p. 133 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.81 (s, 3 H), 4.88 (d, J = 15.5 Hz, 1 H), 4.91 (s, 1 H), 5.02 (d, J = 15.3 Hz, 1 H), 6.85 (d, J = 7.8 Hz, 1 H), 6.89 (d, J = 8.6 Hz, 2 H), 7.02 (t, J = 7.5 Hz, 1 H), 7.13 (d, J = 7.2 Hz, 1 H), 7.18–7.26 (m, 2 H), 7.32 (d, J = 8.6 Hz, 2 H), 7.59 (ddd, J = 9.4, 7.4, 1.9 Hz, 1 H), 8.20 (d, J = 5.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 34.6, 46.5 (d, J = 2.7 Hz), 55.3, 109.5, 114.2 (2×CH), 119.7 (d, J = 30.3 Hz), 121.8 (d, J = 4.3 Hz), 123.0, 124.4, 127.4, 127.6, 128.7, 128.8 (2×CH), 140.9 (d, J = 4.8 Hz), 143.3, 146.9 (d, J = 14.7 Hz), 159.2, 161.9 (d, J = 239.8 Hz), 174.5 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2913, 1184, 2050, 1980, 1710, 1612, 1603, 1511, 1491, 1437, 1303, 1244, 1173, 1120, 1104, 1028, 928, 825, 787, 760, 727, 687 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{17}FN_2O_2$ $[M + H]^+$ 349.1347; found 349.1346.

3-(2-Fluoropyridin-3-yl)-1-pentylindolin-2-one (9): M.p. 85 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (t, J = 7.1 Hz, 3 H), 1.32–1.46 (m, 4 H), 1.68–1.81 (m, 2 H), 3.71–3.89 (m, 2 H), 4.82 (s, 1 H), 6.94 (d, J = 7.9 Hz, 1 H), 7.04 (td, J = 7.5, 0.8 Hz, 1 H), 7.14 (d, J = 7.4 Hz, 1 H), 7.18 (ddd, J = 7.2, 4.9, 1.7 Hz, 1 H), 7.33 (ddd, J = 7.9, 2.0, 1.0 Hz, 1 H), 7.56 (ddd, J = 9.4, 7.4, 1.9 Hz, 1 H), 8.18 (ddd, J = 4.9, 1.8, 1.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.3, 27.0, 29.0, 40.4, 46.5 (d, J = 2.7 Hz), 108.7, 119.8 (d, J = 30.3 Hz), 121.8 (d, J = 4.3 Hz), 122.7, 124.5 (d, J = 1.0 Hz), 127.6, 128.7, 140.8 (d, J = 4.9 Hz), 143.8, 146.8 (d, J = 14.7 Hz), 161.9 (d, J = 239.7 Hz), 174.34 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2923, 2859, 1712, 1600, 1488, 1466, 1432, 1260, 1239, 1183, 1105, 994, 900, 875, 866, 849, 789, 752, 732, 670 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{19}FN_2O$ $[M + H]^+$ 299.1554; found 299.1553.

General Method to Prepare Compounds 10–13: A solution of **8** or **9** (2 mmol) and a dihaloalkane (4 mmol) in DMF (4 mL) was degassed and bubbled with argon under ice-cooling. Powdered KOH

(4 mmol) was added to the solution in one portion, and the reaction mixture was stirred at room temperature for 2 h, diluted with H_2O, and extracted with ethyl acetate. The organic layer was washed with H_2O and brine and dried with Na_2SO_4, and the solvents were evaporated. The residue was purified on a silica gel column (petroleum ether/EtOAc, 9:1 to 7:3) to give compounds **10**–**13** in good to excellent yields.

3-(2-Fluoropyridin-3-yl)-3-(iodomethyl)-1-(4-methoxybenzyl)indolin-2-one (10): Yellow oil; yield 95%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.80 (s, 3 H), 3.95 (d, J = 9.7 Hz, 1 H), 4.15 (d, J = 9.7 Hz, 1 H), 4.94 (d, J = 15.4 Hz, 1 H), 5.03 (d, J = 15.4 Hz, 1 H), 6.86–6.90 (m, 3 H), 7.08 (td, J = 7.6, 1.0 Hz, 1 H), 7.22 (ddd, J = 7.5, 4.8, 1.8 Hz, 1 H), 7.23–7.32 (m, 1 H), 7.33 (dd, J = 7.6, 1.3 Hz, 1 H), 7.38 (d, J = 8.6 Hz, 2 H), 7.85 (ddd, J = 9.7, 7.6, 1.8 Hz, 1 H), 8.17 (dt, J = 4.8, 1.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 7.2 (d, J = 4.6 Hz), 44.0, 53.9 (d, J = 5.4 Hz), 55.3, 109.8, 114.2 (2 CH), 121.1 (d, J = 27.9 Hz), 121.8 (d, J = 4.3 Hz), 123.2, 124.0 (d, J = 5.4 Hz), 127.3 (d, J = 1.6 Hz), 129.1 (2 CH), 129.4, 130.4 (d, J = 2.0 Hz), 139.5 (d, J = 4.5 Hz), 143.0, 147.0 (d, J = 15.4 Hz), 159.2, 160.9 (d, J = 240.2 Hz), 175.0 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2931, 2836, 1711, 1610, 1573, 1512, 1486, 1466, 1432, 1303, 1246, 1177, 1103, 910, 835, 789, 748, 728, 694, 648 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{18}FIN_2O_2$ [M + H]$^+$ 489.0470; found 489.0468.

3-(2-Bromoethyl)-3-(2-fluoropyridin-3-yl)-1-(4-methoxybenzyl)-indolin-2-one (11): Yellow oil; yield 75%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.79–2.88 (m, 1 H), 2.95–3.09 (m, 2 H), 3.22–3.15 (m, 1 H), 3.81 (s, 3 H), 4.90 (d, J = 15.3 Hz, 1 H), 5.02 (d, J = 15.3 Hz, 1 H), 5.02 (d, J = 15.3 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 2 H), 7.03 (t, J = 7.3 Hz, 1 H), 7.12 (d, J = 6.9 Hz, 1 H), 7.22–7.28 (m, 2 H), 7.33 (d, J = 8.6 Hz, 2 H), 7.93 (ddd, J = 9.7, 7.6, 1.8 Hz, 1 H), 8.17 (dd, J = 3.5, 1.3 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.0, 38.9, 43.9, 53.5 (d, J = 4.7 Hz), 55.3, 109.7, 114.3 (2 CH), 121.7 (d, J = 4.2 Hz), 122.2 (d, J = 27.8 Hz), 123.3, 123.5 (d, J = 3.3 Hz), 127.4, 128.9 (2 CH), 129.0, 130.1, 138.9 (d, J = 4.6 Hz), 142.7, 146.7 (d, J = 15.5 Hz), 159.3, 160.9 (d, J = 240.8 Hz), 176.1 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3299, 2932, 1740, 1587, 1507, 1468, 1455, 1430, 1366, 1325, 1263, 1194, 1178, 1061, 968, 823, 809, 798, 785 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{20}FN_2O_2$ [M + H]$^+$ 455.0765; found 455.0761.

3-(3-Bromopropyl)-3-(2-fluoropyridin-3-yl)-1-(4-methoxybenzyl)-indolin-2-one (12): Yellow oil; yield 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.41–1.56 (m, 1 H), 1.67–1.79 (m, 1 H), 2.46–2.58 (m, 2 H), 3.30–3.39 (m, 2 H), 3.80 (s, 3 H), 4.94 (d, J = 15.3 Hz, 1 H), 4.99 (d, J = 15.3 Hz, 1 H), 6.87 (d, J = 7.9 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 2 H), 6.99–7.07 (m, 2 H), 7.19–7.30 (m, 2 H), 7.34 (d, J = 8.6 Hz, 2 H), 8.00 (ddd, J = 9.7, 7.6, 1.8 Hz, 1 H), 8.14 (ddd, J = 4.9, 1.8, 1.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.7, 33.1, 34.4, 43.8, 52.5 (d, J = 4.6 Hz), 55.3, 109.4, 114.2 (2 CH), 121.6 (d, J = 4.2 Hz), 123.1 (d, J = 27.7 Hz), 123.1, 123.3 (d, J = 2.7 Hz), 127.7, 128.7, 129.0 (2 CH), 131.0, 139.0 (d, J = 4.8 Hz), 142.9, 146.4 (d, J = 15.4 Hz), 159.2, 160.9 (d, J = 241.0 Hz), 177.0 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2932, 1708, 1610, 1574, 1512, 1486, 1465, 1429, 1303, 1245, 1176, 1103, 1031, 806, 748, 645, 631 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{22}BrFN_2O_2$ [M + H]$^+$ 471.0974; found 471.0901.

3-(Bromomethyl)-3-(2-fluoropyridin-3-yl)-1-pentylindolin-2-one (13): Yellow oil; yield 90%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (t, J = 6.9 Hz, 3 H), 1.50–1.31 (m, 4 H), 1.74–1.81 (m, 2 H), 3.78–3.85 (m, 2 H), 4.04 (d, J = 10.0 Hz, 1 H), 4.32 (d, J = 10.0 Hz, 1 H), 6.96 (dd, J = 8.1, 1.0 Hz, 1 H), 7.10 (td, J = 7.6, 1.0 Hz, 1 H), 7.21 (ddd, J = 7.6, 4.8, 1.9 Hz, 1 H), 7.32–7.43 (m, 2 H), 7.82 (ddd, J = 9.7, 7.6, 1.8 Hz, 1 H), 8.16 (dt, J = 4.8, 1.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.3, 27.0, 29.1, 40.6, 54.4, (d, J = 5.4 Hz), 67.1, 108.8, 121.0 (d, J = 28.0 Hz), 121.7 (d, J = 4.3 Hz), 123.0, 124.3 (d, J = 5.2 Hz), 129.4, 129.6, 139.7 (d, J = 4.6 Hz), 143.4, 147.0 (d, J = 15.6 Hz), 161.0 (d, J = 240.2 Hz), 174.4 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2930, 2860, 1710, 1611, 1488, 1433, 1363, 1255, 1122, 1103, 909, 873, 812, 749, 729, 694, 673 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{20}BrFN_2O$ [M + H]$^+$ 391.0816; found 391.0815.

General Method to Prepare Compounds 14–19: In a 5 mL microwave reaction vial, compound **10**, **11**, **12**, or **13** (0.30 mmol, 1 equiv.) was dissolved in 1,4-dioxane (1.8 mL), and the appropriate amine (10 equiv.) was then added, after which the vial was sealed. The reaction mixture was subjected to microwave irradiation with stirring at 200 °C for 3 h. After the system had cooled down to room temperature, 1,4-dioxane was removed under reduced pressure. The residue was then purified by column chromatography on silica gel (petroleum ether/EtOAc, 9:1 to 7:3) to provide the expected products.

1′-Butyl-1-(4-methoxybenzyl)-1′,2′-dihydrospiro[indoline-3,3′-pyrrolo[2,3-*b*]pyridin]-2-one (14): Yellow oil; yield 85%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.01 (t, J = 7.4 Hz, 3 H), 1.49 (dq, J = 14.6, 7.3 Hz, 2 H), 1.63–1.75 (m, 2 H), 3.36–3.46 (m, 1 H), 3.63–3.70 (m, 1 H), 3.77 (d, J = 9.3 Hz, 1 H), 3.82 (s, 3 H), 4.01 (d, J = 9.3 Hz, 1 H), 4.81 (d, J = 15.3 Hz, 1 H), 5.05 (d, J = 15.3 Hz, 1 H), 6.39 (dd, J = 7.1, 5.3 Hz, 1 H), 6.77 (dd, J = 7.2, 1.5 Hz, 1 H), 6.85 (d, J = 7.8 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 2 H), 7.01 (td, J = 7.6, 0.9 Hz, 1 H), 7.17 (dd, J = 7.4, 0.7 Hz, 1 H), 7.22 (td, J = 7.7, 1.2 Hz, 1 H), 7.31 (d, J = 8.7 Hz, 2 H), 7.98 (dd, J = 5.3, 1.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 20.3, 29.6, 43.6, 45.1, 54.0, 55.3, 59.3, 109.3, 112.5, 114.3 (2×CH), 123.3, 123.4, 124.7, 127.9, 128.6, 128.8 (2×CH), 130.1, 133.8, 141.9, 147.9, 159.2, 162.6, 177.7 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2956, 2929, 2858, 1713, 1608, 1574, 1512, 1486, 1465, 1302, 1273, 1246, 1175, 1106, 1061, 924, 838, 748, 656 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{27}N_3O_2$ [M + H]$^+$ 414.2176; found 414.2180.

1′-Butyl-1-(4-methoxybenzyl)-2′,3′-dihydro-1′*H*-spiro[indoline-3,4′-[1,8]naphthyridin]-2-one (15): Yellow oil; yield = 90%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.02 (t, J = 7.3 Hz, 3 H), 1.42–1.52 (m, 2 H), 1.70–1.78 (m, 2 H), 2.14–2.19 (m, 2 H), 3.49–3.55 (m, 1 H), 3.65–3.75 (m, 1 H), 3.80 (s, 3 H), 3.81–3.85 (m, 1 H), 4.04–4.11 (m, 1 H), 4.91 (q, J = 15.4 Hz, 2 H), 6.34 (dd, J = 7.4, 4.9 Hz, 1 H), 6.62 (dd, J = 7.4, 1.8 Hz, 1 H), 6.85 (d, J = 7.9 Hz, 1 H), 6.88 (d, J = 8.7 Hz, 2 H), 7.01–7.09 (m, 2 H), 7.22 (td, J = 7.7, 1.5 Hz, 1 H), 7.27 (d, J = 8.7 Hz, 2 H), 7.27 (d, J = 8.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2, 20.4, 29.3, 30.7, 42.8, 43.2, 48.7, 50.2, 55.3, 109.2, 111.3, 114.2 (2 CH), 115.2, 123.0, 124.0, 128.0, 128.2, 128.6 (2 CH), 134.5, 135.0, 142.4, 147.4, 155.4, 159.1, 179.1 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2928, 2870, 2323, 1709, 1609, 1593, 1488, 1464, 1351, 1304, 1279, 1196, 1178, 1165, 1140, 930, 919, 900, 871, 764, 750, 694 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{29}N_3O_2$ [M + H]$^+$ 428.2333; found 428.2337.

9′-Butyl-1-(4-methoxybenzyl)-6′,7′,8′,9′-tetrahydrospiro[indoline-3,5′-pyrido[2,3-*b*]azepin]-2-one (16): Yellow oil; yield 68%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.02 (t, J = 7.4 Hz, 3 H), 1.41–1.56 (m, 2 H), 1.65–1.85 (m, 2 H), 1.94–2.04 (m, 2 H), 2.08–2.15 (m, 1 H), 2.19–2.30 (m, 1 H), 3.45–3.54 (m, 2 H), 3.73–3.89 (m, 2 H), 3.80 (s, 3 H), 4.94 (s, 2 H), 6.49 (dd, J = 7.6, 4.6 Hz, 1 H), 6.74 (dd, J = 7.6, 1.7 Hz, 1 H), 6.84 (d, J = 7.7 Hz, 1 H), 6.88 (d, J = 8.6 Hz, 2 H), 6.97 (t, J = 7.4 Hz, 1 H), 7.12–7.21 (m, 2 H), 7.30 (d, J = 8.9 Hz, 2 H), 8.03 (dd, J = 4.6, 1.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.2, 20.7, 24.8, 30.7, 33.5, 43.3, 50.6, 51.9, 55.3, 55.9, 109.1, 114.2, 114.3, 121.6, 122.8, 124.5, 127.7, 128.2,

128.7 (2 CH), 137.4, 139.0, 141.2, 145.2, 159.1, 161.7, 179.3 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2928, 2857, 1704, 1608, 1557, 1512, 1483, 1465, 1434, 1372, 1246, 1223, 1196, 1174, 1032, 953, 879, 797, 763, 745, 670, 667 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{31}N_3O_2$ $[M + H]^+$ 442.2489; found 442.2489.

1′-Butyl-1-pentyl-1′,2′-dihydrospiro[indoline-3,3′-pyrrolo[2,3-*b*]pyridin]-2-one (17): Yellow oil; yield 80%. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (t, J = 6.9 Hz, 3 H), 0.99 (t, J = 7.3 Hz, 3 H), 1.33–1.43 (m, 4 H), 1.44–1.52 (m, 2 H), 1.64–1.71 (m, 2 H), 1.72–1.81 (m, 2 H), 3.35–3.42 (m, 1 H), 3.60–3.76 (m, 2 H), 3.73 (d, J = 9.3 Hz, 1 H), 3.81–3.88 (m, 1 H), 3.95 (d, J = 9.3 Hz, 1 H), 6.37 (dd, J = 7.1, 5.3 Hz, 1 H), 6.76 (dd, J = 7.2, 1.6 Hz, 1 H), 6.92 (d, J = 7.8 Hz, 1 H), 7.03 (td, J = 7.6, 0.8 Hz, 1 H), 7.17 (dd, J = 7.4, 0.8 Hz, 1 H), 7.28–7.32 (m, 1 H), 7.95 (dd, J = 5.3, 1.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0 (2 CH_3), 20.2, 22.3, 27.1, 29.0, 29.6, 40.3, 45.1, 53.9, 59.3, 108.5, 112.4, 123.1, 123.4, 124.7, 128.6, 130.0, 134.0, 142.2, 147.8, 162.6, 177.4 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2955, 2929, 2859, 1713, 1606, 1487, 1464, 1354, 1324, 1281, 1137, 1098, 750, 686, 648 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{29}N_3O$ $[M + H]^+$ 364.2383; found 364.2386.

1,1′-Bis(4-methoxybenzyl)-1′,2′-dihydrospiro[indoline-3,3′-pyrrolo-[2,3-*b*]pyridin]-2-one (18): Yellow oil; yield 75%. ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.61 (d, J = 9.4 Hz, 1 H), 3.80 (s, 3 H), 3.81 (s, 3 H), 3.91 (d, J = 9.4 Hz, 1 H), 4.51 (d, J = 14.9 Hz, 1 H), 4.79 (d, J = 15.3 Hz, 1 H), 4.91 (d, J = 14.8 Hz, 1 H), 5.01 (d, J = 15.3 Hz, 1 H), 6.46 (dd, J = 7.2, 5.2 Hz, 1 H), 6.79–6.83 (m, 2 H), 6.89 (dd, J = 8.6, 6.7 Hz, 4 H), 6.98 (td, J = 7.6, 1.0 Hz, 1 H), 7.10 (dd, J = 7.5, 1.4 Hz, 1 H), 7.19 (td, J = 7.7, 1.3 Hz, 1 H), 7.28 (d, J = 8.5 Hz, 2 H), 7.34 (d, J = 8.5 Hz, 2 H), 8.03 (dd, J = 5.3, 1.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 43.6, 48.7, 53.8, 55.3 (2 CH_3), 58.8, 109.3, 113.0, 114.0 (2 CH), 114.3 (2 × CH), 123.3, 123.5, 124.6, 127.8, 128.6, 128.7 (2 CH), 129.3 (2 CH), 129.3, 130.5, 133.6, 141.9, 147.9, 158.9, 159.2, 162.4, 177.6 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2930, 2835, 1713, 1608, 1575, 1511, 1486, 1464, 1379, 1307, 1273, 1244, 1178, 1031, 917, 749, 643 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{27}N_3O_3$ $[M + H]^+$ 478.2125; found 478.2127.

1,1′-Bis(4-methoxybenzyl)-2′,3′-dihydro-1′*H*-spiro[indoline-3,4′-[1,8]naphthyridin]-2-one (19): Yellow oil; yield 78%. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.08–2.23 (m, 2 H), 3.42–3.48 (m, 1 H), 3.80 (s, 3 H), 3.83 (s, 3 H), 3.86–4.40 (m, 1 H), 4.88 (d, J = 15.4 Hz, 1 H), 4.95 (d, J = 15.3 Hz, 1 H), 5.09 (d, J = 15.2 Hz, 1 H), 6.41 (dd, J = 7.4, 4.9 Hz, 1 H), 6.69 (dd, J = 7.4, 1.8 Hz, 1 H), 6.85 (d, J = 8.0 Hz, 1 H), 6.88 (d, J = 8.6 Hz, 2 H), 6.91 (d, J = 8.6 Hz, 2 H), 6.98–7.09 (m, 2 H), 7.22 (td, J = 7.6, 1.9 Hz, 1 H), 7.26 (d, J = 8.6 Hz, 2 H), 7.34 (d, J = 8.6 Hz, 2 H), 8.08 (dd, J = 4.9, 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$ 100 MHz): δ = 30.7, 42.0, 43.3, 50.3, 50.8, 55.3 (2 CH_3), 109.2, 112.0, 113.9 (2 CH), 114.2 (2 × CH), 115.3, 123.0, 124.0, 128.0, 128.2, 128.6 (2 CH), 128.7, 128.9 (2 CH), 130.8, 134.4, 135.2, 142.3, 147.4, 155.5, 158.7, 159.1, 178.9 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2930, 2834, 1706, 1610, 1563, 1510, 1487 1380, 1352, 1301, 1279, 1245, 1173, 1032, 952, 808, 750, 674, 644, 621 cm^{-1}. HRMS (ESI): calcd. for $C_{31}H_{29}N_2O_3$ $[M + H]^+$ 492.2282; found 492.2284.

Preparation of 1′-Butyl-2′,3′-dihydro-1′*H*-spiro[indoline-3,4′-[1,8]naphthyridin]-2-one (20): Trifluoromethanesulfonic acid (0.22 mL, 2.5 mmol) was added to a stirred solution of **15** (0.1 g, 0.25 mmol) in dichloromethane (2 mL) and trifluoroacetic acid (2 mL). The reaction mixture was stirred at ambient temperature for 12 h and concentrated in vacuo. The residue was basified with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The organic phase was washed with water and brine, dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (EtOAc). Yellow oil; yield 90%. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.01 (t, J = 7.3 Hz, 3 H), 1.38–1.57 (m, 2 H), 1.63–1.94 (m, 2 H), 2.09–2.16 (m, 1 H), 2.18–2.24 (m, 1 H), 3.50–3.56 (m, 1 H), 3.67–3.85 (m, 2 H), 3.97–4.04 (m, 1 H), 6.36 (dd, J = 7.4, 4.9 Hz, 1 H), 6.74 (dd, J = 7.4, 1.7 Hz, 1 H), 6.96 (d, J = 7.8 Hz, 1 H), 7.00–7.12 (m, 2 H), 7.19–7.27 (m, 1 H), 8.05 (dd, J = 4.9, 1.8 Hz, 1 H), 9.09 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$ 100 MHz): δ = 14.1, 20.4, 29.3, 30.6, 42.8, 48.7, 50.8, 110.1, 111.3, 115.0, 123.0, 124.2, 128.3, 135.0, 135.3, 140.5, 147.1, 155.2, 181.7 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3180, 3077, 2956, 2926, 2871, 1699, 1616, 1502, 1470, 1427, 1387, 1353, 1294, 1191, 1169, 1041, 798, 786, 729, 684, 666 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{21}N_3O_2$ $[M + H]^+$ 308.1757; found 308.1754.

General Method to Prepare Compounds 21–22: In a 5 mL microwave reaction vial, compound **18** or **19** (0.40 mmol, 1 equiv.) was dissolved in trifluoroacetic acid (2 mL). The reaction mixture was subjected to microwave irradiation with stirring at 100 °C for 30 min. After the system had cooled down to room temperature, trifluoroacetic acid was removed under reduced pressure. The residue was then purified by column chromatography on silica gel (petroleum ether/EtOAc/Et_3N 7:3:1 to 0:10:1) to provide the expected product in excellent yield.

1-(4-Methoxybenzyl)-1′,2′-dihydrospiro[indoline-3,3′-pyrrolo[2,3-*b*]-pyridin]-2-one (21): M.p. 176 °C; yield 95%. ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.81 (s, 3 H), 3.85 (d, J = 9.3 Hz, 1 H), 4.21 (d, J = 9.3 Hz, 1 H), 4.81 (d, J = 15.3 Hz, 1 H), 4.98 (s, 1 H), 5.04 (d, J = 15.3 Hz, 1 H), 6.51 (dd, J = 7.3, 5.2 Hz, 1 H), 6.82–6.90 (m, 2 H), 6.90 (d, J = 8.6 Hz, 2 H), 7.02 (td, J = 7.5, 1.0 Hz, 1 H), 7.22 (td, J = 7.6, 1.2 Hz, 2 H), 7.31 (d, J = 8.6 Hz, 2 H), 7.96 (dd, J = 5.2, 1.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 43.6, 54.4, 55.3, 55.8, 109.3, 114.1, 114.3 (2 CH), 123.4, 123.6, 123.6, 127.9, 128.7, 128.8 (2 CH), 130.9, 133.5, 141.9, 148.0, 159.2, 164.1, 177.6 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3151, 2915, 1708, 1608, 1592, 1508, 1486, 1463, 1441, 1379, 1362, 1250, 1121, 1108, 944, 930, 907, 809, 776, 760, 674 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{19}N_3O_2$ $[M + H]^+$ 358.1550; found 358.1554.

1-(4-Methoxybenzyl)-2′,3′-dihydro-1′*H*-spiro[indoline-3,4′-[1,8]-naphthyridin]-2-one (22): M.p. 193 °C; yield 98%. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.11–2.27 (m, 2 H), 3.58–3.69 (m, 1 H), 3.80 (s, 3 H), 4.09–4.15 (m,1 H), 4.88 (d, J = 15.4 Hz, 1 H), 4.93 (d, J = 15.3 Hz, 1 H), 6.46 (dd, J = 7.4, 5.3 Hz, 1 H), 6.78 (dd, J = 7.4, 1.7 Hz, 1 H), 6.84–6.92 (m, 3 H), 6.98 (s, 1 H), 7.09 (ddd, J = 14.0, 7.5, 1.3 Hz, 2 H), 7.21–7.31 (m, 3 H), 7.86 (dd, J = 5.3, 1.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 30.3, 26.6, 43.4, 49.2, 55.3, 109.5, 112.4, 114.3 (2 CH), 116.5, 123.2, 123.9, 127.8, 128.7 (2 CH), 133.4, 137.1, 142.4, 143.9, 154.8, 159.2, 178.3 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3150, 2928, 1706, 1610, 1593, 1512, 1486, 1464, 1414, 1349, 1295, 1250, 1200, 1171, 1123, 1067, 944, 931, 905, 817, 761, 744, 721, 674, 647 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{21}N_3O_2$ $[M + H]^+$ 372.1707; found 372.1709.

Preparation of 3-(2-Fluoropyridin-3-yl)-3-(hydroxymethyl)-1-(4-methoxybenzyl)indolin-2-one (23): Paraformaldehyde (2.00 g, 67 mmol) and diisopropylamine (3.77 mL, 26.8 mmol) were added at 0 °C to a solution of 3-(2-fluoropyridin-3-yl)-1-(4-methoxybenzyl)indolin-2-one (**8**; 2.53 g, 6.70 mmol) in THF (20.0 mL). The reaction mixture was stirred at room temperature for 12 h, followed by the addition of ammonium chloride solution (10.0 mL) and ethyl acetate (100 mL). The organic layer was washed with water and brine, dried with Na_2SO_4, and filtered. The filtrate was concentrated to dryness in vacuo to give the title compound after purification by column chromatography (petroleum ether/EtOAc,

5:5). M.p. 110 °C; yield 99%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.12 (d, J = 7.9 Hz, 1 H), 3.79 (s, 3 H), 4.05–4.17 (m, 1 H), 4.35–4.46 (m, 1 H), 4.95 (d, J = 15.4 Hz, 1 H), 5.02 (d, J = 15.4 Hz, 1 H), 6.85 (d, J = 7.9 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 2 H), 6.95–7.05 (m, 1 H), 7.03–7.06 (m, 1 H), 7.22 (td, J = 7.7, 1.4 Hz, 1 H), 7.25–7.29 (m, 1 H), 7.32 (d, J = 8.6 Hz, 2 H), 8.07–8.33 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 43.7, 54.6 (d, J = 4.5 Hz), 55.3, 65.0, 109.8, 114.1, 114.3 (2 CH), 120.6 (d, J = 28.3 Hz), 121.6 (d, J = 4.1 Hz), 123.1, 123.7 (d, J = 2.0 Hz), 127.4, 128.7 (2 CH), 128.9, 129.1, 140.5 (d, J = 4.7 Hz), 142.9, 146.6 (d, J = 15.3 Hz), 159.2, 161.3 (d, J = 240.3 Hz), 177.2 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3300, 2931, 1708, 1610, 1574, 1513, 1487, 1466, 1432, 1304, 1246, 1177, 1120, 908, 723, 695 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{19}FN_2O_3$ [M + H]$^+$ 379.1452; found 379.1451.

General Method to Prepare Compounds 25 and 26: Compound **4** or **5** (8.97 mmol) was added to a solution of sodium methoxide (8.0 mL, 35.9 mmol, 4.0 equiv., 25% in methanol) in methanol (60 mL). The reaction mixture was heated at reflux under argon for 12 h and then diluted with ethyl acetate and water. The organic layer was washed with water and brine and dried with sodium sulfate. The solvent was removed at reduced pressure to give **25** or **26** after purification by column chromatography (petroleum ether/EtOAc, 7:3).

3-Hydroxy-1-(4-methoxybenzyl)-3-(2-methoxypyridin-3-yl)indolin-2-one (25): M.p. 152 °C; yield 95%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.59 (s, 3 H), 3.81 (s, 3 H), 3.86 (br. s, 1 H), 4.77 (d, J = 15.3 Hz, 1 H), 5.03 (d, J = 15.3 Hz, 1 H), 6.85 (d, J = 7.8 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 2 H), 6.95–7.01 (m, 2 H), 7.07 (d, J = 7.2 Hz, 1 H), 7.25 (td, J = 7.8, 1.1 Hz, 1 H), 7.37 (d, J = 8.7 Hz, 2 H), 8.08 (dd, J = 7.4, 1.8 Hz, 1 H), 8.12 (dd, J = 4.9, 1.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 43.6, 53.4, 55.3, 75.5, 109.2, 114.4 (2 CH), 116.9, 122.8, 123.0, 124.2, 127.8, 129.1 (2 CH), 129.8, 130.0, 135.8, 143.6, 145.5, 159.2, 160.1, 176.7 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3319, 3015, 2952, 1702, 1611, 1518, 1489, 1468, 1436, 1406, 1315, 1248, 1186, 1176, 1028, 1007, 972, 957, 821, 788, 758, 742, 709, 666, 629 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{20}N_2O_4$ [M + H]$^+$ 377.1496; found 377.1493.

3-Hydroxy-3-(2-methoxypyridin-3-yl)-1-pentylindolin-2-one (26): M.p. 104 °C; yield 96%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (t, J = 7.0 Hz, 3 H), 1.32–1.51 (m, 4 H), 1.62–1.83 (m, 2 H), 3.58–3.69 (m, 1 H), 3.73 (s, 3 H), 3.79–3.91 (m, 1 H), 3.85 (s, 1 H), 6.90 (d, J = 7.8 Hz, 1 H), 6.98 (ddd, J = 12.5, 7.5, 2.9 Hz, 2 H), 7.08 (dd, J = 7.3, 0.9 Hz, 1 H), 7.32 (td, J = 7.7, 1.3 Hz, 1 H), 8.05 (dd, J = 7.4, 1.9 Hz, 1 H), 8.10 (dd, J = 5.0, 1.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.4, 27.2, 29.1, 40.3, 53.3, 75.5, 108.4, 116.9, 122.8, 123.0, 124.3, 129.8, 130.1, 135.8, 143.9, 145.4, 160.0, 176.5 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3302, 3063, 2930, 2870, 1699, 1611, 1588, 1490, 1463, 1449, 1402, 1359, 1210, 1179, 1119, 1065, 1013, 962, 948, 787, 772, 749, 685 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{22}N_2O_3$ [M + H]$^+$ 327.1703; found 327.1702.

General Method to Prepare Compounds 27 and 28: See general method to prepare compounds **6** and **7**.

3-Chloro-1-(4-methoxybenzyl)-3-(2-methoxypyridin-3-yl)indolin-2-one (27): Yellow oil; yield 75%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.48 (s, 3 H), 3.82 (s, 3 H), 4.90 (d, J = 15.3 Hz, 1 H), 5.03 (d, J = 15.4 Hz, 1 H), 6.86 (d, J = 7.8 Hz, 1 H), 6.92 (d, J = 8.7 Hz, 2 H), 6.96–7.01 (m, 2 H), 7.08 (dd, J = 7.5, 5.0 Hz, 1 H), 7.25 (ddd, J = 7.8, 7.0, 2.1 Hz, 1 H), 7.41 (d, J = 8.6 Hz, 2 H), 8.17 (dd, J = 5.0, 1.8 Hz, 1 H), 8.41 (dd, J = 7.5, 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 43.9, 53.4, 55.3, 65.9, 109.3, 114.2 (2 CH), 116.9, 119.3, 123.0, 123.7, 127.7, 129.2 (2 CH), 129.9, 130.5, 138.4, 142.4, 147.2, 159.3, 159.4, 173.4 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2951, 2836, 1728, 1610, 1513, 1487, 1464, 1401, 1304, 1246, 1177, 1163, 1031, 925, 881, 813, 773, 747, 709, 684, 662, 640 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{19}ClN_2O_3$ [M + H]$^+$ 395.1157; found 395.1156.

3-Chloro-3-(2-methoxypyridin-3-yl)-1-pentylindolin-2-one (28): Yellow oil; yield 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.96 (t, J = 7.1 Hz, 3 H), 1.37–1.55 (m, 4 H), 1.74–1.85 (m, 2 H), 3.65 (s, 3 H), 3.69–3.80 (m, 1 H), 3.82–3.93 (m, 1 H), 6.91 (d, J = 7.9 Hz, 1 H), 6.99 (dd, J = 5.4, 1.6 Hz, 2 H), 7.06 (dd, J = 7.5, 5.0 Hz, 1 H), 7.33 (ddd, J = 7.9, 6.4, 2.6 Hz, 1 H), 8.16 (dd, J = 5.0, 1.8 Hz, 1 H), 8.38 (dd, J = 7.5, 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.4, 27.1, 29.0, 40.6, 53.3, 65.8, 108.5, 116.9, 119.5, 122.8, 123.9, 130.0, 130.5, 138.3, 142.7, 147.2, 159.3, 173.2 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2953, 2930, 2870, 1728, 1610, 1583, 1487, 1464, 1428, 1401, 1354, 1258, 1157, 1139, 1114, 1014, 945, 793, 773, 749, 707, 685, 660 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{21}ClN_2O_2$ [M + H]$^+$ 345.1364; found 345.1361.

General Method to Prepare Compounds 29 and 30: See general method to prepare compounds **8** and **9**.

1-(4-Methoxybenzyl)-3-(2-methoxypyridin-3-yl)indolin-2-one (29): M.p. 135 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.81 (s, 3 H), 3.82 (s, 3 H), 4.82 (d, J = 15.4 Hz, 1 H), 4.85 (s, 1 H), 5.08 (d, J = 15.3 Hz, 1 H), 6.83 (d, J = 7.8 Hz, 1 H), 6.87–6.92 (m, 3 H), 6.97 (td, J = 7.5, 0.7 Hz, 1 H), 7.06 (d, J = 7.4 Hz, 1 H), 7.20 (t, J = 7.7 Hz, 1 H), 7.35 (d, J = 8.7 Hz, 2 H), 7.44 (dd, J = 7.3, 1.8 Hz, 1 H), 8.14 (dd, J = 5.0, 1.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 43.5, 47.9, 53.5, 55.3, 108.9, 114.1 (2 CH), 116.9, 120.1, 122.5, 124.0, 128.0, 128.1, 128.7, 129.0 (2 CH), 138.8, 143.4, 145.2, 159.1, 161.9, 175.8 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2953, 1707, 1610, 1585, 1513, 1487, 1465, 1438, 1412, 1348, 1304, 1273, 1246, 1177, 1111, 1028, 906, 874, 749, 726, 655 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{20}N_2O_3$ [M + H]$^+$ 361.1547; found 361.1546.

3-(2-Methoxypyridin-3-yl)-1-pentylindolin-2-one (30): M.p. 87 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (t, J = 7.0 Hz, 3 H), 1.37–1.47 (m, 4 H), 1.72–1.80 (m, 2 H), 3.64–3.77 (m, 1 H), 3.80–3.90 (m, 1 H), 3.88 (s, 3 H), 4.78 (s, 1 H), 6.84–6.92 (m, 2 H), 6.99 (t, J = 7.5 Hz, 1 H), 7.08 (d, J = 7.4 Hz, 1 H), 7.29 (t, J = 7.7 Hz, 1 H), 7.40 (dd, J = 7.3, 1.7 Hz, 1 H), 8.12 (dd, J = 5.0, 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.4, 27.2, 29.1, 40.2, 47.7, 53.5, 108.2, 116.9, 120.4, 122.3, 124.1, 128.1, 128.9, 138.5, 143.7, 146.0, 161.9, 175.6 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2953, 2930, 1709, 1610, 1586, 1487, 1464, 1411, 1355, 1306, 1186, 1155, 1092, 1019, 897, 780, 748, 727, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{22}N_2O_2$ [M + H]$^+$ 311.1754; found 311.1752.

General Method to Prepare Compounds 31 and 32: Aqueous HCl solution (3 M, 20 mL) was added to a solution of **29** or **30** (5.3 mmol) in 1,4-dioxane (20 mL). The reaction mixture was heated at 80 °C overnight. The solution was basified to pH = 8 with NaOH solution (1 N) and extracted with ethyl acetate. The combined organic layers were dried with $MgSO_4$ and concentrated to yield **31** or **32**, each as a white solid, after purification by column chromatography (CH_2Cl_2/MeOH, 95:5).

1-(4-Methoxybenzyl)-3-(2-oxo-1,2-dihydropyridin-3-yl)indolin-2-one (31): M.p. 210 °C; yield 65%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.77 (s, 3 H), 4.83 (d, J = 15.5 Hz, 1 H), 4.82 (s, 1 H), 5.11 (d, J = 15.6 Hz, 1 H), 6.21 (t, J = 6.7 Hz, 1 H), 6.75 (d, J = 7.6 Hz, 1 H), 6.86 (d, J = 8.6 Hz, 2 H), 6.97 (t, J = 7.4 Hz, 1 H), 7.09 (dd, J = 6.5, 1.9 Hz, 1 H), 7.15–7.21 (m, 2 H), 7.38 (dd, J = 7.8, 4.2 Hz, 3 H), 12.73 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 43.4, 48.2, 55.2, 106.4, 109.0, 114.1 (2 CH), 122.4, 123.9, 128.0, 128.1, 128.4, 128.7, 128.8 (2 CH), 134.0, 140.4, 143.6, 159.0, 163.7, 175.7 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2918, 1980, 1702, 1642, 1610, 1513, 1486, 1351, 1318, 1253, 1221, 1175, 1052, 1031, 953, 922,

794, 764, 698, 657, 646 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{18}N_2O_3$ [M + H]$^+$ 347.1390; found 347.1387.

3-(2-Oxo-1,2-dihydropyridin-3-yl)-1-pentylindolin-2-one (32): M.p. 130 °C; yield 70%. ^{1}H NMR ($CDCl_3$ 400 MHz): δ = 0.93 (t, J = 7.0 Hz, 3 H), 1.31–1.48 (m, 4 H), 1.70–1.85 (m, 2 H), 3.33–4.11 (m, 2 H), 4.83 (s, 1 H), 6.23 (t, J = 6.7 Hz, 1 H), 6.89 (d, J = 7.8 Hz, 1 H), 7.00 (t, J = 7.5 Hz, 1 H), 7.19–7.25 (m, 2 H), 7.28–7.33 (m, 2 H), 12.81 (s, NH) ppm. ^{13}C NMR ($CDCl_3$ 100 MHz): δ = 14.0, 22.4, 27.0, 29.1, 40.2, 47.6, 106.5, 108.2, 122.3, 124.2, 128.0, 128.8, 129.0, 133.8, 139.9, 143.9, 164.0, 175.6 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2960, 2924, 2855, 1714, 1644, 1621, 1607, 1567, 1488, 1463, 1351, 1309, 1254, 1197, 1179, 1165, 1091, 955, 929, 920, 810, 797, 764, 754, 733, 724, 696, 640 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{20}N_2O_2$ [M + H]$^+$ 297.1598; found 297.1594.

General Method to Prepare Compounds 24 and 33: Cs_2CO_3 (1.3 g, 4 mmol) and chloroiodomethane (2.22 mL, 3 mmol) was added to a solution of **31** or **32** (2 mmol) in DMF (5 mL). The reaction mixture was stirred at room temperature overnight and then diluted with ethyl acetate and water. After decantation, the aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with water and brine and dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue, after purification by column chromatography (petroleum ether/EtOAc, 8:2 to 5:5), afforded **24** or **33**, each as a white solid.

1′-(4-Methoxybenzyl)-2*H*-spiro[furo[2,3-*b*]pyridine-3,3′-indolin]-2′-one (24): M.p. 80 °C; yield 80%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.81 (s, 3 H), 4.76 (d, J = 9.1 Hz, 1 H), 4.81 (d, J = 15.3 Hz, 1 H), 5.03 (d, J = 15.3 Hz, 1 H), 5.04 (d, J = 9.1 Hz, 1 H), 6.81 (dd, J = 7.3, 5.1 Hz, 1 H), 6.87–6.93 (m, 3 H), 7.02–7.10 (m, 2 H), 7.14 (dd, J = 7.4, 0.8 Hz, 1 H), 7.24–7.29 (m, 1 H), 7.31 (d, J = 8.7 Hz, 2 H), 8.15 (dd, J = 5.1, 1.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 43.8, 53.4, 55.3, 56.5, 77.4, 109.6, 114.3 (2 CH), 117.4, 122.1, 123.6, 123.8, 127.6, 128.8 (2 CH), 129.3, 131.9, 132.8, 142.1, 148.7, 159.3, 169.6, 176.6 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2913, 2323, 2162, 2050, 1709, 1660, 1612, 1558, 1514, 1492, 1426, 1274, 1247, 1206, 1172, 1121, 1027, 931, 905, 867, 827, 788, 760, 748, 672, 659, 629 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{18}N_2O_3$ [M + H]$^+$ 359.1390; found 359.1394.

1′-Pentyl-2*H*-spiro[furo[2,3-*b*]pyridine-3,3′-indolin]-2′-one (33): M.p. 109 °C; yield 81%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (t, J = 7.0 Hz, 3 H), 1.32–1.47 (m, 4 H), 1.72–1.79 (m, 2 H), 3.69–3.89 (m, 2 H), 4.72 (d, J = 9.1 Hz, 1 H), 4.98 (d, J = 9.1 Hz, 1 H), 6.80 (dd, J = 7.4, 5.1 Hz, 1 H), 6.96 (d, J = 7.9 Hz, 1 H), 7.08 (ddd, J = 8.7, 5.2, 1.3 Hz, 2 H), 7.15 (dd, J = 7.4, 0.9 Hz, 1 H), 7.35 (td, J = 7.7, 1.3 Hz, 1 H), 8.12 (dd, J = 5.1, 1.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.3, 27.1, 29.0, 40.5, 56.4, 77.4, 108.8, 117.3, 122.1, 123.9, 123.9, 129.3, 132.1, 132.7, 142.5, 148.6, 168.6, 176.3 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3059, 2955, 2930, 2858, 1694, 1610, 1599, 1490, 1465, 1422, 1355, 1315, 1228, 1183, 1160, 1115, 1102, 1088, 994, 948, 867, 789, 754, 724, 711, 685, 654 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{20}N_2O_2$ [M + H]$^+$ 309.1598; found 309.1602.

Preparation of 2*H*-Spiro[furo[2,3-*b*]pyridine-3,3′-indolin]-2′-one (34): Trifluoromethanesulfonic acid (1.24 mL, 10 equiv.) was added to a stirred solution of 1′-(4-methoxybenzyl)-2*H*-spiro[furo[2,3-*b*]-pyridine-3,3′-indolin]-2′-one (**32**; 0.50 g, 1.4 mmol) in dichloromethane (5 mL) and trifluoroacetic acid (5 mL). The reaction mixture was stirred at ambient temperature for 12 h and concentrated in vacuo. The residue was basified with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The organic phase was washed with water and brine, dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/EtOAc 3:7). M.p. 246 °C; yield 87%. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 4.72 (d, J = 9.4 Hz, 1 H), 4.85 (d, J = 9.4 Hz, 1 H), 6.88 (dd, J = 7.3, 5.1 Hz, 1 H), 6.96 (d, J = 7.8 Hz, 1 H), 7.00 (td, J = 7.6, 1.0 Hz, 1 H), 7.19 (dd, J = 7.5, 1.2 Hz, 1 H), 7.23 (dd, J = 7.3, 1.7 Hz, 1 H), 7.28 (td, J = 7.7, 1.3 Hz, 1 H), 8.07 (dd, J = 5.1, 1.7 Hz, 1 H), 10.70 (s, 1 H) ppm. ^{13}C NMR ([D$_6$]DMSO, 100 MHz): δ = 56.6, 77.1, 110.4, 118.0, 122.9 (2 C), 124.5, 129.6, 132.3, 133.4, 142.5, 148.3, 168.6, 178.2 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3068, 3023, 2796, 1711, 1618, 1471, 1458, 1366, 1235, 1213, 1149, 1096, 1014, 981, 929, 866, 852, 810, 742, 731, 718, 698, 642, 603 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{10}N_2O_2$ [M + H]$^+$ 239.0815; found 239.0819.

General Method To Prepare Compounds 35 and 36: A solution of 3-(2-fluoropyridin-3-yl)-1-(4-methoxybenzyl)indolin-2-one (**8**; 1.00 g, 3.10 mmol) and either methyl bromoacetate (0.44 mL, 4.60 mmol) or methyl bromopropionate (4.60 mmol) in THF (20.0 mL) was degassed by bubbling argon through it. Sodium hydride (0.19 g, 4.60 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 2 h and quenched with ammonium chloride solution. The mixture was poured into water (150 mL) and extracted with ethyl acetate (200 mL). The organic layer was washed with water, dried with sodium sulfate, and filtered. The filtrate was concentrated in vacuo to dryness. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 8:2) to afford **35** or **36**.

Methyl 2-[3-(2-Fluoropyridin-3-yl)-1-(4-methoxybenzyl)-2-oxoindolin-3-yl]acetate (35): White oil; yield 98%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.41 (d, J = 16.2 Hz, 1 H), 3.49 (s, 3 H), 3.66 (d, J = 16.2 Hz, 1 H), 3.81 (s, 3 H), 4.90 (d, J = 15.5 Hz, 1 H), 5.08 (d, J = 15.5 Hz, 1 H), 6.83 (d, J = 7.9 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 2 H), 7.03 (td, J = 7.6, 0.8 Hz, 1 H), 7.17 (ddd, J = 7.5, 4.8, 1.8 Hz, 1 H), 7.22 (td, J = 7.8, 1.1 Hz, 1 H), 7.35 (d, J = 8.6 Hz, 2 H), 7.38 (d, J = 7.5 Hz, 1 H), 7.71 (ddd, J = 9.8, 7.7, 1.8 Hz, 1 H), 8.14 (dt, J = 4.8, 1.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 39.2 (d, J = 5.1 Hz), 44.0, 51.5 (d, J = 5.6 Hz), 51.8, 55.3, 109.6, 114.2 (2 CH), 121.7 (d, J = 4.3 Hz), 122.2 (d, J = 27.4 Hz), 123.0, 124.0 (d, J = 5.8 Hz), 127.7 (2 CH), 128.8, 128.9, 130.3, 139.2 (d, J = 4.7 Hz), 143.3, 146.6 (d, J = 15.6 Hz), 159.1, 161.2 (d, J = 240.3 Hz), 169.6, 176.5 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2952, 2837, 1713, 1610, 1574, 1513, 1487, 1466, 1431, 1352, 1294, 1246, 1199, 1177, 1127, 11031, 1014, 886, 827, 750, 731, 695, 648 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{21}FN_2O_4$ [M + H]$^+$ 421.1558; found 421.1558.

Methyl 3-[3-(2-Fluoropyridin-3-yl)-1-(4-methoxybenzyl)-2-oxoindolin-3-yl]propanoate (36): White oil; yield 80%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.96–2.06 (m, 1 H), 2.19–2.27 (m, 1 H), 2.64–2.77 (m, 2 H), 3.59 (s, 3 H), 3.80 (s, 3 H), 4.89 (d, J = 15.3 Hz, 1 H), 5.04 (d, J = 15.3 Hz, 1 H), 6.86 (d, J = 7.9 Hz, 1 H), 6.90 (d, J = 8.6 Hz, 2 H), 6.97–7.04 (m, 2 H), 7.21 (td, J = 7.8, 1.5 Hz, 1 H), 7.25–7.27 (m, 1 H), 7.35 (d, J = 8.6 Hz, 2 H), 8.03 (ddd, J = 9.5, 7.7, 1.6 Hz, 1 H), 8.14 (d, J = 4.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.4, 30.6, 43.8, 51.7, 52.2 (d, J = 4.5 Hz), 55.2, 109.5, 114.2 (2 CH), 121.6 (d, J = 4.2 Hz), 122.9 (d, J = 27.8 Hz), 123.1, 123.5 (d, J = 2.5 Hz), 127.6, 128.8, 128.9 (2 CH), 130.4, 139.0 (d, J = 4.7 Hz), 143.0, 146.5 (d, J = 15.4 Hz), 159.2, 160.9 (d, J = 241.0 Hz), 172.8, 176.7 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2951, 2837, 1709, 1610, 1574, 1513, 1486, 1466, 1430, 1349, 1302, 246, 1175, 1102, 1029, 022, 906, 827, 805, 750, 730, 693, 646, 632 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{23}FIN_2O_4$ [M + H]$^+$ 435.1715; found 435.1713.

General Method To Prepare Compounds 37 and 38: NaOH (2 N, 2 mL) was added to a mixture of **35** or **36** (1 mmol) in MeOH (15 mL). The solution was stirred at room temperature for 12 h,

and then the solvent was removed. The residue was dissolved in H_2O (10 mL), and the mixture was acidified to pH = 1 with aqueous HCl (10%). Extractions were performed with CH_2Cl_2 (3× 20 mL), and the combined organic layers were concentrated in vacuo to give **37** or **38** in quantitative yield.

2-[3-(2-Fluoropyridin-3-yl)-1-(4-methoxybenzyl)-2-oxoindolin-3-yl]-acetic Acid (37): White oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.50 (s, 2 H), 3.81 (s, 3 H), 4.93 (d, J = 15.5 Hz, 1 H), 5.02 (d, J = 15.4 Hz, 1 H), 6.84 (d, J = 7.8 Hz, 1 H), 6.89 (d, J = 8.6 Hz, 2 H), 7.04 (t, J = 7.6 Hz, 1 H), 7.21 (dt, J = 6.9, 4.2 Hz, 2 H), 7.32 (d, J = 8.5 Hz, 3 H), 7.77 (ddd, J = 9.6, 7.7, 1.6 Hz, 1 H), 8.16 (d, J = 4.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 39.5, 44.1, 51.1 (d, J = 5.2 Hz), 55.3, 110.0, 114.3 (2 CH), 121.8, 121.9, 123.5, 123.9 (d, J = 4.9 Hz), 127.1, 128.8 (2 CH), 129.2, 130.1, 139.0 (d, J = 4.4 Hz), 142.7, 146.9 (d, J = 14.7 Hz), 159.2, 160.9 (d, J = 240.8 Hz), 172.0, 177.5 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2939, 2835, 1722, 1611, 1467, 1247, 1196, 1115, 1020, 983, 930, 813, 757, 664 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{19}FN_2O_4$ [M + H]$^+$ 407.1402; found 407.1399.

3-[3-(2-Fluoropyridin-3-yl)-1-(4-methoxybenzyl)-2-oxoindolin-3-yl]-propanoic Acid (38): M.p. 133 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.93–2.08 (m, 1 H), 2.24 (ddd, J = 16.5, 11.1, 5.2 Hz, 1 H), 2.68 (dtd, J = 24.3, 13.2, 5.1 Hz, 2 H), 3.79 (s, 3 H), 4.89 (d, J = 15.3 Hz, 1 H), 5.03 (d, J = 15.3 Hz, 1 H), 6.86–6.91 (m, 2 H), 6.95–7.05 (m, 2 H), 7.15–7.30 (m, 2 H), 7.34 (d, J = 8.5 Hz, 2 H), 8.02 (t, J = 8.0 Hz, 1 H), 8.15 (d, J = 4.7 Hz, 1 H), 9.05 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.3, 30.3, 43.9, 52.1 (d, J = 4.5 Hz), 55.7, 109.6, 114.3 (2 CH), 121.7 (2 C), 122.8 (d, J = 27.5 Hz), 123.5 (d, J = 2.2 Hz), 127.5, 128.9, 129.0 (2 CH), 130.3, 139.1 (d, J = 4.6 Hz), 142.9, 146.5 (d, J = 15.1 Hz), 159.2, 160.86 (d, J = 241.5 Hz), 176.8, 177.4 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2914, 1730, 1709, 1610, 1431, 1342, 1306, 1246, 1222, 1201, 1186, 1177, 1167, 1127, 950, 938, 803, 787, 760, 752, 697, 659, 649, 633 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{21}FN_2O_4$ [M + H]$^+$ 421.1558; found 421.1558.

General Method To Prepare Compounds 39 and 40: Triethylamine (0.58 mmol, 1.2 equiv.) was added to a solution of **37** or **38** (0.48 mmol) in THF (8 mL). The mixture was cooled to –10 °C. Ethyl chloroformate (0.53 mmol, 1.1 equiv.) was added, and the solution was stirred at the same temperature for 0.5 h. The precipitate was filtered off and washed with THF (2× 2 mL). The combined filtrates were concentrated in vacuo to give a crude oil, which was used for further experiments without any purification. $NaBH_4$ (20 mg, 0.53 mmol) was added at room temperature to a stirred solution of the mixed anhydride (0.48 mmol) in dry EtOH (5 mL). The resulting solution was stirred overnight. TLC (petroleum ether/EtOAc, 5:5) indicated the reaction was complete. The reaction mixture was concentrated in vacuo to give a residue, which was extracted with EtOAc (3× 10 mL), washed with brine (3× 5 mL), dried with sodium sulfate, and concentrated in vacuo to give a residue, which was purified by column chromatography (petroleum ether/EtOAc, 5:5) to give **39** or **40**.

3-(2-Fluoropyridin-3-yl)-3-(2-hydroxyethyl)-1-(4-methoxybenzyl)-indolin-2-one (39): M.p. 180 °C; yield 80%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.20 (s, 1 H), 2.39–2.59 (m, 1 H), 2.76–2.83 (m, 1 H), 3.50–3.65 (m, 2 H), 3.80 (s, 3 H), 4.97 (q, J = 15.4 Hz, 2 H), 6.85 (d, J = 7.8 Hz, 1 H), 6.90 (d, J = 8.7 Hz, 2 H), 7.01 (td, J = 7.6, 0.9 Hz, 1 H), 7.15 (d, J = 7.4 Hz, 1 H), 7.15–7.27 (m, 2 H), 7.34 (d, J = 8.7 Hz, 2 H), 7.93 (ddd, J = 9.7, 7.7, 1.8 Hz, 1 H), 8.11–8.17 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 38.1, 43.9, 52.30 (d, J = 4.8 Hz), 55.3, 58.8, 109.6, 114.2 (2 CH), 121.69 (d, J = 4.2 Hz), 122.8 (d, J = 27.7 Hz), 123.2, 123.5 (d, J = 4.0 Hz), 127.5, 128.7, 128.9 (2 CH), 131.3, 139.3 (d, J = 4.8 Hz), 142.5, 146.45 (d, J = 15.5 Hz), 159.2, 161.1 (d, J = 240.7 Hz), 178.0 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2923, 1730, 1709, 1610, 1431, 1414, 1579, 1514, 1486, 1379, 1342, 1246, 1221, 1201, 1177, 1103, 1068, 953, 938, 895, 803, 787, 752, 744, 696, 659, 648, 633 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{21}FN_2O_3$ [M + H]$^+$ 393.1609; found 393.1607.

3-(2-Fluoropyridin-3-yl)-3-(3-hydroxypropyl)-1-(4-methoxybenzyl)-indolin-2-one (40): White oil; yield 75%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.16–1.25 (m, 1 H), 1.34 (s, 1 H), 1.39–1.47 (m, 1 H), 2.36–2.55 (m, 2 H), 3.58–3.62 (m, 2 H), 3.81 (s, 3 H), 4.90 (d, J = 15.3 Hz, 1 H), 5.03 (d, J = 15.3 Hz, 1 H), 6.85 (d, J = 7.8 Hz, 1 H), 6.89 (d, J = 8.6 Hz, 2 H), 6.97–7.07 (m, 2 H), 7.20 (dd, J = 7.6, 1.6 Hz, 1 H), 7.22–7.28 (m, 1 H), 7.35 (d, J = 8.6 Hz, 2 H), 8.02 (ddd, J = 9.7, 7.6, 1.9 Hz, 1 H), 8.14 (dt, J = 4.9, 1.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.7, 32.1, 43.8, 52.8 (d, J = 4.4 Hz), 55.3, 62.4, 109.4, 114.2 (2 CH), 121.6 (d, J = 4.2 Hz), 123.0, 123.3 (t, J = 2.8 Hz), 123.6, 127.7, 128.5, 129.0 (2 CH), 131.3, 139.1 (d, J = 4.9 Hz), 143.1, 146.3 (d, J = 15.4 Hz), 159.1, 160.97 (d, J = 241.2 Hz), 177.3 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3429, 2933, 1708, 1609, 1575, 1513, 1486, 1466, 1428, 1348, 1302, 1244, 1177, 1124, 807, 749, 645 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{23}FN_2O_3$ [M + H]$^+$ 407.1765; found 407.1766.

General Method To Prepare Compounds 41 and 42: In a 5 mL microwave reaction vial, compound **39** or **40** (0.30 mmol, 1 equiv.) was dissolved in THF (2 mL), NaH (1.1 equiv.) was then added, degassing was performed, and the vial was sealed. The reaction mixture was subjected to microwave irradiation with stirring at 150 °C for 2 h. After the system had cooled down to room temperature, the THF was removed under reduced pressure. The residue was then purified by column chromatography on silica gel (petroleum ether/EtOAc, 8:2 to 5:5) to provide the expected product.

1-(4-Methoxybenzyl)-2′,3′-dihydrospiro[indoline-3,4′-pyrano[2,3-*b*]-pyridin]-2-one (41): White oil; yield 78%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.23–2.38 (m, 2 H), 3.81 (s, 3 H), 4.54–4.61 (m, 1 H), 4.87 (d, J = 15.3 Hz, 1 H), 4.96 (d, J = 15.3 Hz, 1 H), 5.18–5.03 (m, 1 H), 6.78 (dd, J = 7.5, 4.7 Hz, 1 H), 6.84–6.93 (m, 4 H), 7.01–7.10 (m, 2 H), 7.20–7.35 (m, 3 H), 8.18 (dd, J = 4.7, 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 31.8, 43.4, 48.1, 55.3, 62.7, 109.4, 114.3 (2 CH), 116.8, 117.7, 123.3, 123.8, 127.8, 128.7, 128.8 (2 CH), 133.7, 137.8, 142.6, 148.1, 159.2, 161.3, 178.5 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2921, 2361, 2323, 1705, 1610, 1577, 1513, 1487, 1466, 1434, 1378, 1353, 1273, 1244, 1170, 1103, 1051, 1030, 963, 920, 839, 798, 774, 750, 694, 673, 646 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{20}N_3O_3$ [M + H]$^+$ 373.1547; found 373.1548.

1-(4-Methoxybenzyl)-3′,4′-dihydro-2′*H*-spiro[indoline-3,5′-oxepino-[2,3-*b*]pyridin]-2-one (42): M.p. 120 °C; yield 90%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.99–2.20 (m, 2 H), 2.24–2.38 (m, 1 H), 2.39–2.64 (m, 1 H), 3.80 (s, 3 H), 4.16–4.32 (m, 1 H), 4.67–4.77 (m, 1 H), 4.94 (d, J = 15.3 Hz, 1 H), 5.02 (d, J = 15.3 Hz, 1 H), 6.85 (d, J = 7.8 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 2 H), 6.95 (dd, J = 7.7, 4.7 Hz, 1 H), 7.00 (td, J = 7.6, 0.9 Hz, 1 H), 7.19 (td, J = 7.8, 1.1 Hz, 1 H), 7.29 (d, J = 8.2 Hz, 2 H), 7.36 (dd, J = 7.7, 1.9 Hz, 1 H), 7.74 (dd, J = 7.5, 0.6 Hz, 1 H), 8.16 (dd, J = 4.7, 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.5, 37.4, 43.3, 55.3, 55.7, 72.0, 109.4, 114.3 (2 CH), 120.1, 122.9, 126.0, 127.2, 127.8, 128.2, 128.7 (2 CH), 133.2, 139.4, 141.2, 146.9, 159.2, 165.8, 178.4 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2917, 1702, 1607, 1515, 1485, 1440, 1297, 1280, 1250, 1199, 1178, 1109, 1041, 1028, 905, 870, 818, 757, 745, 677, 642, 633 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{22}N_2O_3$ [M + H]$^+$ 387.1703; found 387.1708.

3a-(2-Fluoropyridin-3-yl)-8-(4-methoxybenzyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (43): $LiAlH_4$ (9 mg, 0.238 mmol) was added to a cold (0 °C) solution of **35** (0.2 g, 0.476 mmol) in THF (10 mL).

The mixture was stirred at 0 °C for 1 h and then treated with brine cautiously until the evolution of H_2 had ceased. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 8:2) to give **43**. M.p. 102 °C; yield 65%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.52–2.57 (m, 1 H), 2.73–2.80 (m, 1 H), 3.68 (ddd, J = 11.4, 8.7, 4.7 Hz, 1 H), 3.82 (s, 3 H), 4.19 (t, J = 7.8 Hz, 1 H), 4.51 (d, J = 15.4 Hz, 1 H), 4.56 (d, J = 15.4 Hz, 1 H), 5.69 (s, 1 H), 6.46 (d, J = 7.8 Hz, 1 H), 6.73 (t, J = 7.4 Hz, 1 H), 6.89 (d, J = 8.6 Hz, 2 H), 7.07–7.17 (m, 3 H), 7.32 (d, J = 8.5 Hz, 2 H), 7.69 (ddd, J = 9.7, 7.6, 1.8 Hz, 1 H), 8.11 (d, J = 4.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 39.9 (d, J = 3.8 Hz), 48.3, 55.3, 57.7 (d, J = 5.8 Hz), 67.3, 101.9 (d, J = 3.2 Hz), 106.3, 114.0 (2 CH), 118.0, 121.5 (d, J = 4.2 Hz), 142.4, 126.0 (d, J = 27.5 Hz), 128.8 (2 CH), 129.0, 129.9, 130.5, 138.8 (d, J = 5.3 Hz), 145.8 (d, J = 15.1 Hz), 150.3, 158.8, 161.1 (d, J = 240.6 Hz) ppm. IR (ATR diamond): $\tilde{\nu}$ = 2993, 2953, 2858, 2831, 1980, 1601, 1575, 1486, 1420, 1384, 1354, 1227, 1078, 958, 94, 924, 876, 863, 849, 823, 804, 761, 752, 671, 644, 622 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{21}FN_3O_2$ [M + H]$^+$ 377.1660; found 377.1655.

Further elution furnished compound **39** (20% yield).

General Method To Prepare 44 and 45: In a 5 mL microwave reaction vial, compound **8** or **9** (0.60 mmol, 1 equiv.) was dissolved in 1,4-dioxane (2 mL). The appropriate amine (10 equiv.) was then added, after which the vial was sealed. The reaction mixture was subjected to microwave irradiation with stirring at 180 °C for 3 h. After the system had cooled down to room temperature, 1,4-dioxane was removed under reduced pressure. The residue was then purified by column chromatography on silica gel (petroleum ether/EtOAc, 9:1 to 7:3) to give **44** or **45**.

3-[2-(Butylamino)pyridin-3-yl]-1-(4-methoxybenzyl)indolin-2-one (44): Yellow oil; yield 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.96 (t, J = 7.3 Hz, 3 H), 1.34–1.51 (m, 2 H), 1.52–1.72 (m, 2 H), 3.27–3.55 (m, 2 H), 3.79 (s, 3 H), 4.80 (d, J = 15.4 Hz, 1 H), 4.81 (s, 1 H), 4.95 (d, J = 15.4 Hz, 1 H), 5.73 (s, 1 H), 6.53 (dd, J = 7.4, 5.0 Hz, 1 H), 6.82–6.94 (m, 3 H), 7.02 (dd, J = 7.4, 1.3 Hz, 1 H), 7.11 (td, J = 7.5, 0.7 Hz, 1 H), 7.19 (d, J = 7.4 Hz, 1 H), 7.18–1.31 (m, 3 H), 8.14 (dd, J = 5.0, 1.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 20.3, 31.7, 41.8, 43.4, 47.9, 55.2, 109.6, 112.5, 114.2 (2 CH), 116.8, 123.0, 125.6, 126.4, 127.5, 128.7, 128.8 (2 CH), 135.6, 143.7, 147.0, 158.2, 159.2, 176.2 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3344, 2955, 2929, 2869, 1695, 1610, 1578, 1512, 1488, 1465, 1438, 1303, 1342, 1280, 1246, 1176, 1031, 900, 797, 749, 730, 657, 605 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{27}N_3O_2$ [M + H]$^+$ 402.2176; found 402.2176.

3-[2-(4-Methoxybenzylamino)pyridin-3-yl]-1-pentylindolin-2-one (45): Yellow oil; yield 65%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (t, J = 6.9 Hz, 3 H), 1.27–1.39 (m, 4 H), 1.55–1.68 (m, 2 H), 3.57–3.75 (m, 2 H), 3.82 (s, 3 H), 4.56 (dd, J = 14.0, 3.9 Hz, 1 H), 4.64 (dd, J = 14.0, 6.4 Hz, 1 H), 4.75 (s, 1 H), 6.01 (s, 1 H), 6.57 (dd, J = 7.4, 5.0 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 2 H), 6.92 (d, J = 7.9 Hz, 1 H), 7.05 (dd, J = 7.4, 1.4 Hz, 1 H), 7.13 (td, J = 7.5, 0.8 Hz, 1 H), 7.21 (d, J = 7.4 Hz, 1 H), 7.33 (d, J = 8.6 Hz, 2 H), 7.37 (t, J = 7.7 Hz, 1 H), 8.15 (dd, J = 5.0, 1.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.3, 27.0, 29.0, 40.2, 45.7, 47.8, 55.3, 108.9, 113.0, 113.9 (2 CH), 117.2, 122.8, 125.6, 126.4, 128.7, 129.1 (2 CH), 131.9, 135.6, 144.0, 145.9, 157.8, 158.6, 175.9 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3337, 2929, 2859, 1694, 1611, 1592, 1508, 1465, 1412, 1361, 1301, 1277, 1244, 1198, 1173, 1154, 1094, 933, 869, 750, 728, 697, 673 cm^{-1}. HRMS (ESI): calcd. for $C_{26}H_{29}N_3O_2$ [M + H]$^+$ 416.2333; found 416.2331.

General Method To Prepare 46, 47, and 48: A solution of **44** or **45** (0.3 mmol) and either methyl bromoacetate (0.6 mmol) or methyl bromopropionate (0.6 mmol) in THF (2 mL) was degassed by bubbling argon through it. Sodium hydride (25 mg, 0.6 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 2 h and quenched with ammonium chloride solution. The mixture was poured into water (15 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with water, dried with sodium sulfate, and filtered. The filtrate was concentrated in vacuo to dryness. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc, 9:1 to 7:3) to afford compounds **46**–**48**.

Methyl 2-{3-[2-(Butylamino)pyridin-3-yl]-1-(4-methoxybenzyl)-2-oxoindolin-3-yl}acetate (46): Yellow oil; yield 50%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.99 (t, J = 7.3 Hz, 3 H), 1.41–1.56 (m, 2 H), 1.65–1.74 (m, 2 H), 3.00 (d, J = 16.9 Hz, 1 H), 3.38–3.53 (m, 2 H), 3.43 (s, 3 H), 3.78 (s, 3 H), 4.47 (d, J = 16.9 Hz, 1 H), 4.86 (d, J = 15.6 Hz, 1 H), 4.92 (d, J = 15.6 Hz, 1 H), 6.41 (dd, J = 7.7, 4.8 Hz, 1 H), 6.78–6.88 (m, 3 H), 6.95 (dd, J = 7.7, 1.7 Hz, 1 H), 7.14 (t, J = 7.4 Hz, 1 H), 7.20 (dd, J = 7.3, 1.0 Hz, 1 H), 7.24–7.33 (m, 3 H), 7.39 (s, 1 H), 8.08 (dd, J = 4.8, 1.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 20.6, 31.6, 36.7, 41.9, 43.8, 51.7, 53.6, 55.2, 110.0, 111.9, 114.1 (2 CH), 116.9, 122.7, 125.1, 127.5, 128.7 (2 CH), 128.9, 129.8, 136.0, 143.2, 147.2, 157.8, 159.1, 170.8, 178.7 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3306, 2955, 2930, 2871, 1738, 1691, 1610, 1587, 1513, 1488, 1466, 1420, 1347, 1303, 1247, 1197, 1175, 1032, 1000, 881, 761, 748, 730, 685 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{31}N_3O_4$ [M + H]$^+$ 474.2387; found 474.2389.

Methyl 3-[2-(4-Methoxybenzylamino)pyridin-3-yl]-2-oxo-1-pentylindoline-3-carboxylate (47): Yellow oil; yield = 50%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.92 (t, J = 6.9 Hz, 3 H), 1.32–1.43 (m, 4 H), 1.78–1.91 (m, 2 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 4.05 (t, J = 7.4 Hz, 2 H), 4.61 (d, J = 5.7 Hz, 2 H), 4.92 (s, 1 H), 6.68 (dd, J = 7.2, 5.1 Hz, 1 H), 6.82 (d, J = 8.7 Hz, 2 H), 7.15 (t, J = 7.0 Hz, 1 H), 7.21–7.31 (m, 3 H), 7.36 (d, J = 8.2 Hz, 1 H), 7.45 (dd, J = 7.2, 1.9 Hz, 2 H), 8.20 (dd, J = 5.0, 1.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.2, 29.0, 29.3, 42.7, 44.8, 55.2, 56.2, 98.1, 109.7, 112.2, 112.4, 113.7 (2 CH), 120.0, 120.4, 122.2, 124.8, 128.8 (2 CH), 132.1, 132.2, 138.6, 139.3, 147.1, 152.7, 156.7, 158.5 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3430, 2955, 1776, 1611, 1582, 1566, 1465, 1440, 1420, 1301, 1235, 1205, 1175, 1115, 1092, 931, 770, 734 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{31}N_3O_4$ [M + H]$^+$ 474.2387; found 474.2390.

Methyl 2-{3-[2-(4-Methoxybenzylamino)pyridin-3-yl]-2-oxo-1-pentylindolin-3-yl}acetate (48): Yellow oil; yield 55%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89 (t, J = 6.9 Hz, 3 H), 1.27–1.42 (m, 3 H), 1.56–1.75 (m, 2 H), 3.02 (d, J = 16.7 Hz, 1 H), 3.44 (s, 3 H), 3.62–3.71 (m, 2 H), 3.83 (s, 3 H), 4.36 (d, J = 16.7 Hz, 1 H), 4.52 (dd, J = 14.3, 4.1 Hz, 1 H), 4.69 (dd, J = 14.3, 5.9 Hz, 1 H), 6.46 (dd, J = 7.7, 4.8 Hz, 1 H), 6.87–6.94 (m, 3 H), 7.02 (dd, J = 7.7, 1.7 Hz, 1 H), 7.16 (td, J = 7.4, 0.6 Hz, 1 H), 7.21 (dd, J = 7.4, 1.2 Hz, 1 H), 7.34 (d, J = 8.6 Hz, 2 H), 7.38 (td, J = 7.7, 1.4 Hz, 1 H), 7.64 (s, 1 H), 8.08 (dd, J = 4.8, 1.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.3, 26.6, 29.0, 37.0, 40.5, 45.5, 51.6, 53.4, 55.3, 109.1, 112.4, 113.8 (2 CH), 117.2, 122.5, 125.3, 128.0 (2 CH), 130.0, 132.2, 136.0, 143.4, 147.1, 157.3, 158.5, 170.6, 178.3 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3299, 2953, 2870, 1740, 1670, 1610, 1586, 1586, 1509, 1491, 1466, 1365, 1303, 1244, 1196, 1174, 1174, 1153, 1138, 1036, 927, 909, 771, 755, 730, 648, 605 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{33}N_3O_4$ [M + H]$^+$ 488.2544; found 488.2544.

General Method To Prepare 49, 51, and 52: In a 5 mL microwave reaction vial, compound **46**, **47**, or **48** (0.30 mmol, 1 equiv.) was dissolved in methanol (2 mL) in the presence of Et_3N (0.5 mL). The reaction mixture was subjected to microwave irradiation with

stirring at 100 °C for 2 h. After the system had cooled down to room temperature, the solvent was removed under reduced pressure. The residue was then purified by column chromatography on silica gel (petroleum ether/EtOAc, 8:2 to 7:3) to give **49**, **51**, or **52**.

1′-Butyl-1-(4-methoxybenzyl)-1′*H*-spiro[indoline-3,4′-[1,8]naphthyridine]-2,2′(3′*H*)-dione (49): Yellow oil; yield 95%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.03 (t, J = 7.4 Hz, 3 H), 1.45–1.55 (m, 2 H), 1.73–1.87 (m, 2 H), 2.94 (d, J = 15.9 Hz, 1 H), 3.13 (d, J = 15.9 Hz, 1 H), 3.81 (s, 3 H), 4.21–4.46 (m, 2 H), 4.91 (s, 2 H), 6.80–6.92 (m, 4 H), 7.01 (dd, J = 7.6, 1.7 Hz, 1 H), 7.05 (dd, J = 7.5, 0.7 Hz, 1 H), 7.14 (d, J = 6.7 Hz, 1 H), 7.22–7.28 (m, 3 H), 8.32 (dd, J = 4.8, 1.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 20.4, 30.0, 39.7, 40.9, 43.5, 49.5, 55.3, 109.9, 114.3 (2 CH), 118.5, 120.8, 123.4, 127.4, 128.7 (2 CH), 129.2, 130.9, 134.5, 142.0, 147.6, 152.2, 159.2, 167.2, 176.5 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2956, 2931, 2871, 1713, 1679, 1610, 1585, 1487, 1465, 1446, 1378, 1359, 1271, 1247, 1221, 1032, 1013, 913, 874, 780, 747, 730, 685, 662, 641 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{27}N_3O_3$ [M + H]$^+$ 442.2125; found 442.2127.

1′-(4-Methoxybenzyl)-1-pentylspiro[indoline-3,3′-pyrrolo[2,3-*b*]pyridine]-2,2′(1′*H*)-dione (51): Yellow oil; yield 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (t, J = 7.1 Hz, 3 H), 1.32–1.47 (m, 4 H), 1.75–1.80 (m, 2 H), 3.69–3.88 (m, 2 H), 3.80 (s, 3 H), 5.04 (s, 2 H), 6.82 (dd, J = 7.4, 0.7 Hz, 1 H), 6.88 (d, J = 8.7 Hz, 2 H), 6.93 (dd, J = 7.3, 5.3 Hz, 1 H), 6.93 (dd, J = 7.3, 5.3 Hz, 1 H), 7.03 (dd, J = 7.6, 0.8 Hz, 1 H), 7.15 (dd, J = 7.3, 1.6 Hz, 1 H), 7.38 (td, J = 7.8, 1.2 Hz, 1 H), 7.44 (d, J = 8.7 Hz, 2 H), 8.27 (dd, J = 5.3, 1.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.3, 27.0, 28.8, 40.8, 42.8, 55.2, 61.6, 109.3, 114.0 (2 CH), 118.8, 122.9, 123.2, 123.8, 127.1, 128.4, 129.4 (2 CH), 129.8, 131.3, 144.8, 148.4, 158.2, 159.0, 171.3, 171.7 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2931, 2870, 1732, 1708, 1607, 1593, 1513, 1487, 1464, 1450, 1336, 1303, 1256, 1175, 1137, 1106, 1092, 946, 931, 783, 805, 752, 694, 640 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{27}N_3O_3$ [M + H]$^+$ 442.2125; found 442.2128.

1′-(4-Methoxybenzyl)-1-pentyl-1′*H*-spiro[indoline-3,4′-[1,8]naphthyridine]-2,2′(3′*H*)-dione (52): Yellow oil; yield 85%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (t, J = 6.9 Hz, 3 H), 1.32–1.45 (m, 4 H), 1.63–1.85 (m, 2 H), 2.86 (d, J = 15.8 Hz, 1 H), 3.18 (d, J = 15.8 Hz, 1 H), 3.71–3.85 (m, 2 H), 3.81 (s, 3 H), 5.44 (d, J = 13.9 Hz, 1 H), 5.54 (d, J = 13.9 Hz, 1 H), 6.80 (d, J = 6.8 Hz, 1 H), 6.91–6.85 (m, 4 H), 6.92 (d, J = 7.9 Hz, 1 H), 7.03 (dd, J = 7.6, 1.7 Hz, 1 H), 7.29 (td, J = 7.8, 1.2 Hz, 1 H), 7.56 (d, J = 8.7 Hz, 2 H), 8.33 (dd, J = 4.9, 1.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.3, 27.1, 29.0, 39.8, 40.4, 43.2, 49.6, 55.2, 109.1, 113.6 (2 CH), 118.8, 121.1, 123.2, 123.5, 129.1, 130.1, 130.4 (2 CH), 131.1, 134.6, 141.9, 147.4, 151.7, 158.8, 167.4, 176.2 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2931, 2871, 2248, 1711, 1682, 1609, 1585, 1511, 1487, 1465, 1444, 1378, 1359, 1321, 1245, 1175, 1033, 909, 891, 848, 810, 780, 753, 77, 685, 646, 632 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{29}N_3O_3$ [M + H]$^+$ 456.2282; found 456.2284.

Preparation of 1′-Butyl-1′*H*-spiro[indoline-3,4′-[1,8]naphthyridine]-2,2′(3′*H*)-dione (50): Trifluoromethanesulfonic acid (0.22 mL, 2.5 mmol) was added to a stirred solution of **49** (0.1 g, 0.23 mmol) in dichloromethane (2 mL) and trifluoroacetic acid (2 mL). The reaction mixture was stirred at ambient temperature for 12 h and concentrated in vacuo. The residue was basified with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The organic phase was washed with water and brine, dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated in vacuo. The residue was purified by column chromatography (EtOAc) to give **50**. Yellow oil; yield 97%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.02 (t, J = 7.3 Hz, 3 H), 1.44–1.62 (m, 2 H), 1.70–1.92 (m, 2 H), 2.98 (d, J = 15.9 Hz, 1 H), 3.11 (d, J = 15.9 Hz, 1 H), 4.31 (t, J = 7.6 Hz, 2 H), 6.87 (dd, J = 7.5, 4.9 Hz, 1 H), 6.98 (d, J = 7.8 Hz, 1 H), 7.04–7.13 (m, 3 H), 7.29 (td, J = 7.7, 1.2 Hz, 1 H), 8.32 (dd, J = 4.8, 1.7 Hz, 1 H), 9.06 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 20.4, 29.9, 39.4, 40.8, 50.0, 110.7, 118.5, 120.5, 123.4, 123.7, 129.4, 131.2, 134.7, 140.3, 147.6, 152.1, 167.4, 178.9 ppm. IR (ATR diamond): $\tilde{\nu}$ = 2918, 1710, 1609, 1513, 1487, 1466, 1431, 1304, 1247, 1176, 1029, 1014, 1029, 1014, 957, 801, 750, 730, 648, 632 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{19}N_3O_2$ [M + H]$^+$ 322.1550; found 322.1550.

Preparation of 3-(2-Aminopyridin-3-yl)-1-pentylindolin-2-one (53): In a 5 mL microwave reaction vial, compound **45** (0.4 g, 0.96 mmol, 1 equiv.) was dissolved in trifluoroacetic acid (2.5 mL). The reaction mixture was subjected to microwave irradiation with stirring at 100 °C for 30 min. After the system had cooled down to room temperature, trifluoroacetic acid was removed under reduced pressure. The residue was then purified by column chromatography on silica gel (petroleum ether/EtOAc 5:5) to give **53** in excellent yield. M.p. 157 °C; yield 98%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (t, J = 6.8 Hz, 3 H), 1.32–1.41 (m, 4 H), 1.67–1.75 (m, 2 H), 3.68–3.80 (m, 2 H), 4.78 (s, 1 H), 6.75 (dd, J = 7.5, 6.1 Hz, 1 H), 7.01 (d, J = 8.0 Hz, 1 H), 7.15–7.26 (m, 2 H), 7.43–7.53 (m, 2 H), 7.77 (dd, J = 6.1, 1.6 Hz, 1 H), 8.46 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.3, 27.0, 28.9, 40.6, 47.2, 109.7, 112.3, 121.7, 123.4, 123.7, 125.6, 129.9, 135.5, 141.5, 144.0, 155.8, 173.9 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3393, 3100, 2933, 1709, 1660, 1610, 1490, 1467, 1361, 1195, 1176, 1133, 1095, 799, 778, 752, 721, 698, 631 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{21}N_3O$ [M + H]$^+$ 296.1757; found 296.1755.

General Method To Prepare 54 and 55: Either methyl bromoacetate (2.53 mmol) or methyl bromopropionate (2.53 mmol) was added to a solution of compound **53** (0.5 g, 1.69 mmol) and Et_3N (1 mL) in THF (9 mL). The reaction solution was stirred at room temperature for 12 h. The solvent was removed in vacuo to give a crude oil. The crude oil was dissolved in methanol (5 mL) in the presence of triethylamine (0.5 mL). The reaction mixture was subjected to microwave irradiation with stirring at 100 °C for 1 h. After the system had cooled down to room temperature, the solvent was removed under reduced pressure. The residue was then purified by column chromatography on silica gel (petroleum ether/EtOAc, 4:6) to give **54** or **55** in good yield.

1-Pentylspiro[indoline-3,3′-pyrrolo[2,3-*b*]pyridine]-2,2′(1′*H*)-dione (54): M.p. 190 °C; yield 60%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (t, J = 7.0 Hz, 3 H), 1.35–1.45 (m, 4 H), 1.71–1.84 (m, 2 H), 3.81 (t, J = 7.4 Hz, 2 H), 6.89–7.04 (m, 3 H), 7.07 (t, J = 7.9 Hz, 1 H), 7.21 (dd, J = 7.5, 1.6 Hz, 1 H), 7.40 (td, J = 7.7, 1.4 Hz, 1 H), 8.28 (dd, J = 5.3, 1.6 Hz, 1 H), 10.90 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 14.0, 22.3, 27.0, 28.8, 40.8, 62.3, 109.3, 118.7, 123.3, 123.6, 124.0, 126.8, 129.9, 132.3, 144.7, 147.7, 158.2, 171.1, 172.6 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3207, 2927, 2859, 1740, 1682, 1599, 1482, 1462, 1429, 1306, 1255, 1202, 1172, 1150, 1125, 976, 952, 804, 786, 760, 666, 644, 628 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{19}N_3O_2$ [M + H]$^+$ 322.1550; found 322.1554.

1-Pentyl-1′*H*-spiro[indoline-3,4′-[1,8]naphthyridine]-2,2′(3′*H*)-dione (55): M.p. 220 °C; yield 70%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.93 (t, J = 6.9 Hz, 3 H), 1.27–1.50 (m, 4 H), 1.64–2.01 (m, 2 H), 2.85 (d, J = 16.3 Hz, 1 H), 3.12 (d, J = 16.3 Hz, 1 H), 3.68–3.93 (m, 2 H), 6.91 (dd, J = 7.6, 5.0 Hz, 1 H), 6.97 (d, J = 7.8 Hz, 1 H), 7.11–7.04 (m, 2 H), 7.29 (d, J = 5.9 Hz, 1 H), 7.36 (td, J = 7.8, 1.1 Hz, 1 H), 8.39 (dd, J = 5.0, 1.6 Hz, 1 H), 10.33 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 22.3, 27.1, 29.0, 39.1,

40.4, 50.1, 109.2, 119.1, 119.1, 123.4, 123.6, 129.4, 131.3, 135.0, 142.1, 147.8, 151.5, 168.2, 176.3 ppm. IR (ATR diamond): $\tilde{\nu}$ = 3047, 2959, 2898, 1697, 1608, 1589, 1500, 1452, 1430, 1406, 1332, 1276, 1231, 1189, 1136, 1124, 1097, 998, 971, 945, 860, 794, 780, 755, 693, 658, 645 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{21}N_3O_2$ [M + H]$^+$ 336.1707; found 336.1710.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra.

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Received: October 2, 2014
Published Online: ■

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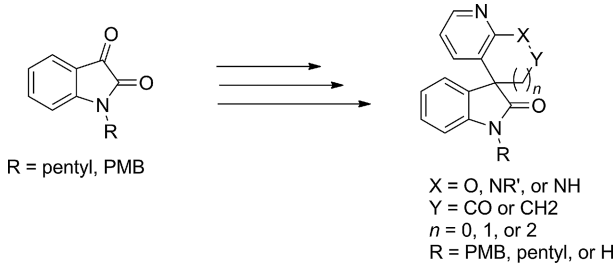
Spiro Compounds



Tetracyclic spirooxindoles were easily prepared from *N*-protected isatins and 2-fluoropyridine, leading to fused C-3 oxindole heterocycles in good yields.

Keywords: Anionic condensation / Reduction / Cyclization / Selective deprotection / Tetracyclic spirooxindole / Spiro compounds

