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Palladium-catalyzed domino Heck/cyanation: synthesis of 3-cyanomethyloxindoles and their conversion to spirooxoindoles

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ABSTRACT

3′-Alkyl-3-cyanomethyloxindoles, prepared by a palladium-catalyzed domino Heck/cyanation, were efficiently converted to spiropyrrolidinyl-, spiropiperidinyl- and spirocyclopropyl-oxindoles. The so-obtained spirooxindoles bearing three diversity points were further functionalized via selective N-acylation, N-alkylation, N-sulfonylation, S_NAr reaction and Buchwald–Hartwig N-arylation reaction to reach diverse set of heterocycles.

1. Introduction

The 3,3′-spirocyclooxindole skeleton is found in a growing number of natural or synthetic products presenting various biological activities.[1] In particular, the spiropyrrolidinyloxindole, due to its presence in a large number of bioactive alkaloids, such as spirotryprostatin A[2] (**1**) and horsfiline[3] (**2**, Fig. 1), to just name a few, is being considered as a privileged structure in medicinal chemistry. The intense research work has led to the development of promising anticancer drug candidates.[4] In addition, the potential of synthetic spiropiperidinyl- or spirocyclopropyl-oxindoles as leads in the development of effective pharmaceuticals and agrochemicals has also been recognized. For example, cyclopropyloxindole **3** was reported to exhibit potent antiviral activity,[5] whereas compound **4** or **5** have been reported to behave as pain killer[6] or to have insecticidal activities,[7] respectively.

We have been interested in the synthesis of oxindoles featuring a key palladium-catalyzed cyclization processes.[8] One such reaction that we developed is the intramolecular domino Heck/cyanation sequence allowing ready access to diversely functionalized 3-alkyl-3-cyanomethyl-2-oxindoles **6**.[9–11] As a continuation of this work, we describe herein the synthesis of spiropyrrolidinyl-, spiropiperidinyl- and spirocyclopropyl-oxindoles using **6** as common starting materials.

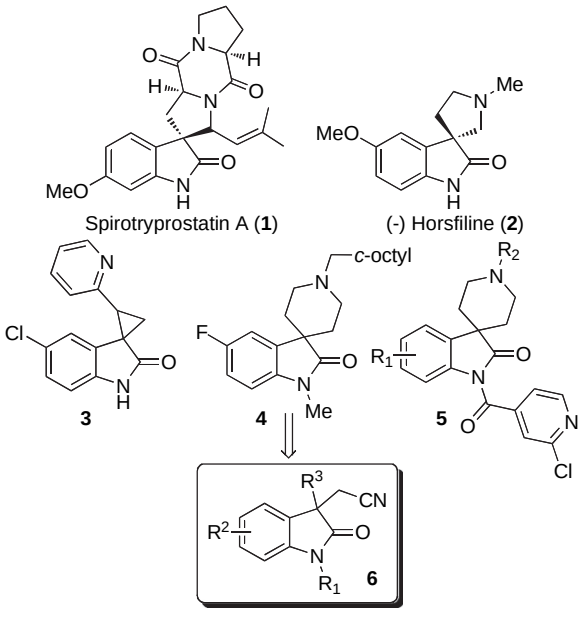

Fig. 1. Natural and synthetic 3,3′-spirooxindoles.

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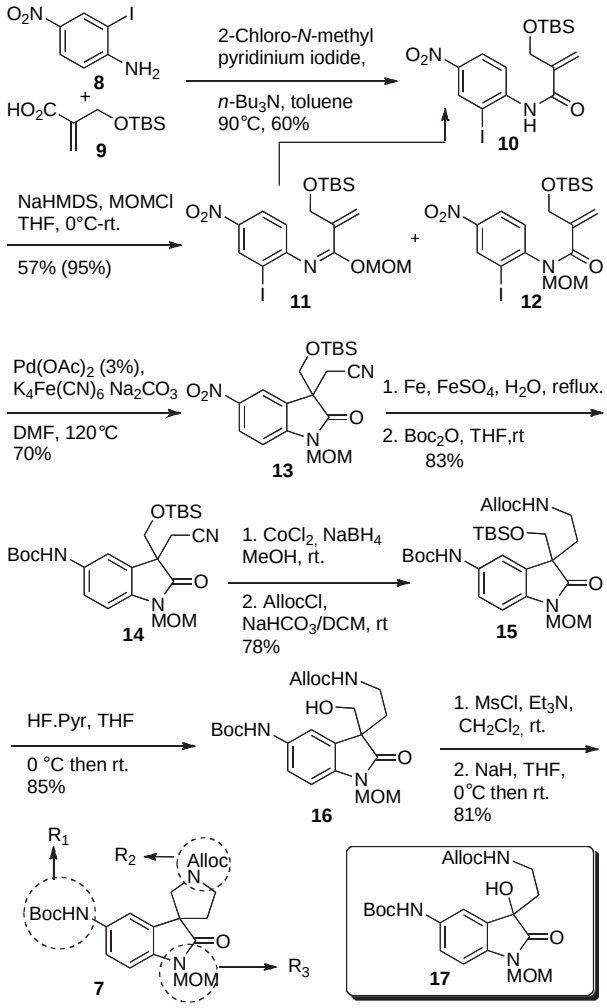
2. Results and discussion

2.1. Preparation of spiropyrrolidinyloxindoles

Among all 3,3′-spirocyclooxindoles known in literature, the spiropyrrolidinyloxindoles have attracted the most attention and considerable efforts are continuously being made to prepare them. Having recently successfully synthesized horsfiline[9b] and in a view of biological evaluation of this class of spirocycle, we decided to prepare more analogues using the same methodology. Orthogonally protected 5-amino-spiro[3,3′-pyrrolidin]-oxindole **7** (Scheme 1) was targeted as convenient platform as the three nitrogen present in this heterocycle could be used as diversity entries for parallel synthesis.



Scheme 1. Synthesis of 5-amino-spiro[3,3′-pyrrolidin]-oxindole platform **7**.

Our synthesis began with the coupling of 4-nitro-2-iodoaniline[12] **8** with carboxylic acid **9**[9b] under Mukaiyama's conditions.[13] Protection of the amide proved to be rather difficult because the *para* nitro group strongly reduced the nucleophilicity of the nitrogen. However, deprotonation of **10** with NaHMDS in THF followed by addition of MOMCl furnished a clean mixture of *N*-alkylated and *O*-alkylated products in a 1.3/1 ratio. The *O*-alkylated compound was unstable on silica during flash chromatography and was hydrolyzed back to the starting material **10**. Thus, the *N*-MOM intermediate **12** was obtained in a 95% yield based on recovered starting material (Scheme 1).

The properly functionalized amide was submitted to our previously established Heck/cyanation reaction conditions [$Pd(OAc)_2$ (3 mol %), $K_4[Fe(CN)_6]$ (0.22 equiv), Na_2CO_3 (1.0 equiv), DMF, 120 °C] to give key intermediate **13** in 70% yield. At this stage, all attempts to selectively reduce the nitrile group without affecting the nitro function failed.[14] On the contrary, selective reduction of the nitro group was easily achieved using iron in refluxing water and the newly formed aniline was protected as a *tert*-butylcarbamate furnishing compound **14** in 83% yield over two steps. Reduction of the nitrile group ($NaBH_4/CoCl_2\cdot 6H_2O$)[15] followed by protection of the resulting primary amine as an allylcarbamate provided **15**. O-deprotection of compound **15** was best achieved using HF·Pyr leading to alcohol **16** in 85% yield. The same reaction performed in the presence of TBAF provided **16** (38%) together with a significant amount of tertiary alcohol **17** (20%). The formation of **17** can be account for by the retro-aldol followed by oxidation of enolate by residual oxygen in the solvent.[16] Pyrrolidine ring closure was finally achieved in two steps: treatment of **16** with methanesulfonyl chloride (MsCl, Et_3N, CH_2Cl_2) afforded the corresponding mesylate, which without purification, was cyclized upon treatment with NaH in THF to afford the spirooxindole **17** in 81% yield.

Selective removal of three *N*-protective groups in spirooxindole **7** was next evaluated (Fig. 2). Treatment of **7** under mild acidic conditions (TFA, CH_2Cl_2, rt) afforded the aniline **18** in 84% yield. *N*-Allyloxy carbamate was selectively cleaved under Guibe's conditions (*n*-Bu_3SnH, $Pd(PPh_3)_4$ cat.)[17] affording compound **19** in excellent yield (95%). On the other hand, heating a solution of **7** in

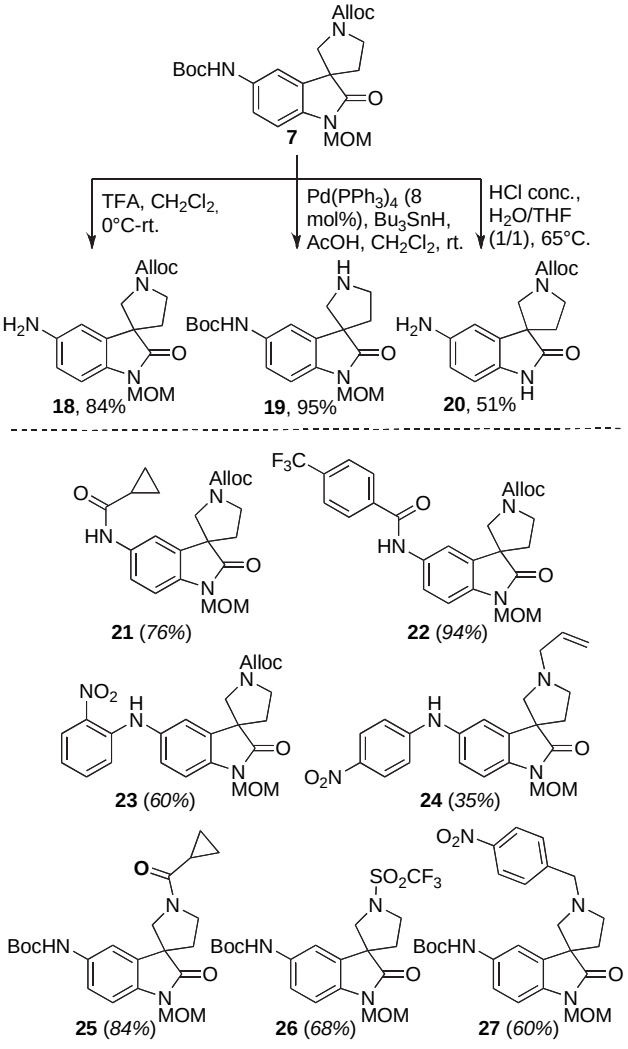


Fig. 2. Functionalized spiropyrrolidinyloxindoles.

a mixed solvent H_2O/THF (v/v=1/1) in the presence of concd HCl at 65 °C afforded double *N*-deprotected oxindole **20**.

Various derivatives prepared from compound **18** and **19** are given in Fig. 2. Acylation, sulfonylation [RCOCl or RSO_2Cl, Et_3N, DCM, rt] or alkylation [*p*-NO_2–BnBr, TBAI, Cs_2CO_3, DMF, rt] of **18** and **19** under classic conditions furnished compound **21**, **22**, and **25**–**27** in good to excellent yields. The S_NAr reaction between **18** and 1-fluoro-2-nitrobenzene (*t*-BuOK, DMSO) provided compounds **23** in moderate yield. Palladium-catalyzed N-arylation of **18** with with 1-bromo-4-nitrobenzene [$Pd(OAc)_2$ (10 mol %), BINAP (20 mol %), Cs_2CO_3 Toluene, 90 °C][18] afforded compound **24** in which the alloc group was converted to allyl group.[19]

2.2. Preparation of spiropiperidinyloxindoles

In order to expand the structural diversity of our analogues, we envisaged the construction of spiropiperidinyloxindoles. Classical route to spiropiperidinyloxindoles involves treatment of oxindole with bis(2-chloroethylmethylamine) under basic conditions followed by a three step protection/deprotection procedure.[20] Recent alternative strategies rely on intramolecular α-arylation of amides as initially reported by Hartwig[21] or dearomatization of *N*-arylisonicotinamides[22]

In analogy to the pyrrolidine series, we thought that the construction of spiropiperidinyloxindoles could be achieved starting from a 3-functionalized-3-cyanomethyl-oxindole (Fig. 3). Direct reductive cyclization of ω-oxo nitrile derivative **28b** seemed to be an attractive route even if, to the best of our knowledge, such cyclization starting from a 3,3′-disubstituted oxindole has not been reported so far.

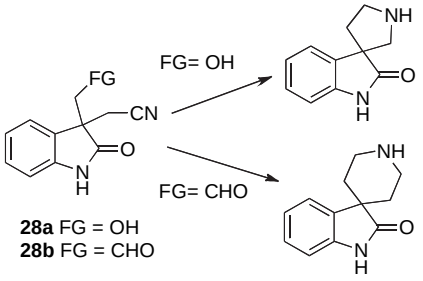
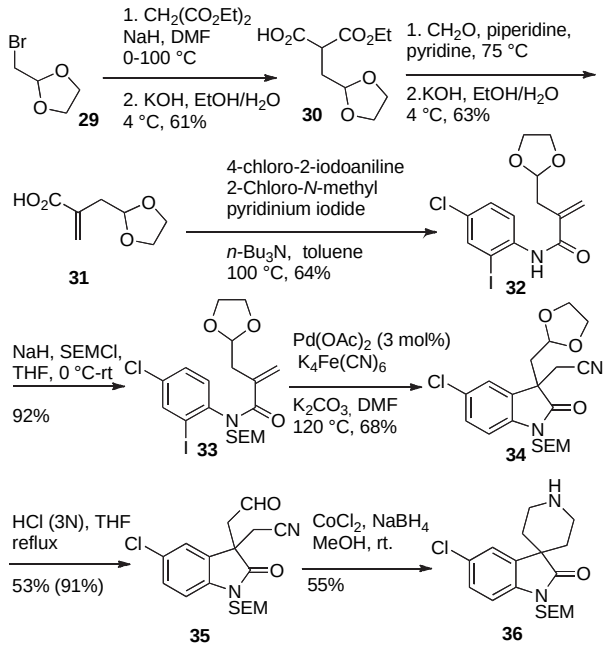


Fig. 3. 3-Functionalized-3-cyanomethyl-oxindoles as precursor of spiropyrrolidinyl- and spiropiperidinyl-oxindoles.

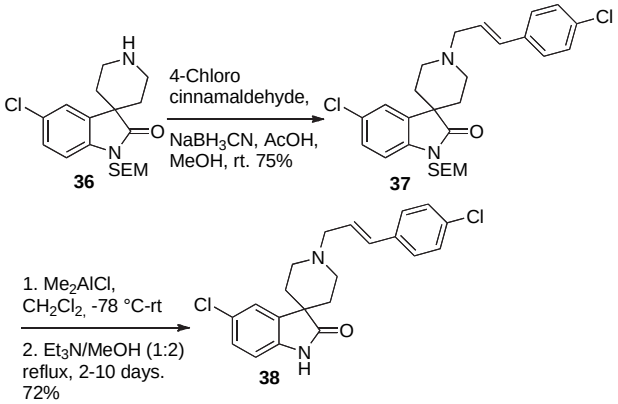
The synthesis of 5-chloro-spiro[3,4′-piperidin]-oxindole **36**, presenting again three points of diversity, is depicted in Scheme 2. The carboxylic acid **31** was prepared in four steps from diethyl malonate and bromomethyldioxolane **29** in 41% overall yield. Thus monoalkylation of diethyl malonate with **29** followed by saponification gave mono acid **30**.[23] Subsequent Knoevenagel condensation between **30** and formaldehyde gave, after hydrolysis of the ethyl ester, the carboxylic acid **31**. Coupling between this acid and the 4-chloro-2-iodoaniline[24] was best realized here again in the presence of Mukaiyama's reagent to afford the amide **32**. N-protection of **32** under standard conditions (NaH, SEMCl, 0 °C then rt) furnished the tertiary amide **33** in a 92% yield. As expected, Palladium-catalyzed domino Heck/cyanation provided uneventfully the key oxindole **34** in a 68% yield. Piperidine ring formation was next evaluated. Reduction of nitrile to primary amine proceeded smoothly. However, attempts to realize the intramolecular reductive aminoalkylation of the resulting amino acetal under a variety of acidic conditions failed to afford the desired spiropiperidinyl oxindole.[25] The acetal function was found to be noticeably stable in this case. Alternatively, heating to reflux a THF solution of **34** in the presence of HCl (3 N) afforded aldehyde **35** in 91% yield (based on conversion) without touching the *N*-SEM function. Gratefully, treatment of a methanol



Scheme 2. Synthesis of the spiropiperidinyloxindole **36**.

solution of **35** with $NaBH_4/CoCl_2\cdot 6H_2O$ provided directly the spiropiperidine **36** in a 55% yield. Under these conditions, a sequence of reduction of nitrile to primary amine, intramolecular condensation of aldehyde and amine to iminium salt and its reduction occurred to deliver the desired compound. It is also noteworthy that under these conditions, reduction of nitrile function went faster than that of aldehyde, a pre-condition in order for the present reductive cyclization process to proceed effectively.

For the derivatization of **36**, we decided to focus our efforts in the introduction of diversity on the nitrogen of the oxindole. Compound **36** was first reductively alkylated with 4-chloro-cinnamaldehyde[26] to give compound **37** in a 75% yield. The SEM group was next cleaved in two steps: treatment of **37** with dimethylaluminium chloride furnished the *N*-hydroxymethylated intermediate that was hydrolyzed to **38** under basic conditions (MeOH, Et_3N, reflux, Scheme 3). Diverse substituents were then introduced on the oxindole nitrogen of **38** (Fig. 4). Acylation [RCOCl, Et_3N, DCM, rt] provided rather unstable imide **39a**–**b** prone to deacylation in deuterated chloroform. Alkylation under classic conditions [RBr, NaH, THF, rt] furnished compound **39c**–**g**. The thiooxindole **39h** was prepared from **38** by its reaction with Lawesson's reagent in refluxing xylene in a moderate 25% yield.[27] We also applied an N-cyclopropylation method recently developed in our group [Cu $(OAc)_2$/BiPy, Na_2CO_3, DCE, 70 °C, air] and obtained compound **39i** in



Scheme 3. Synthesis of oxindole **38**.

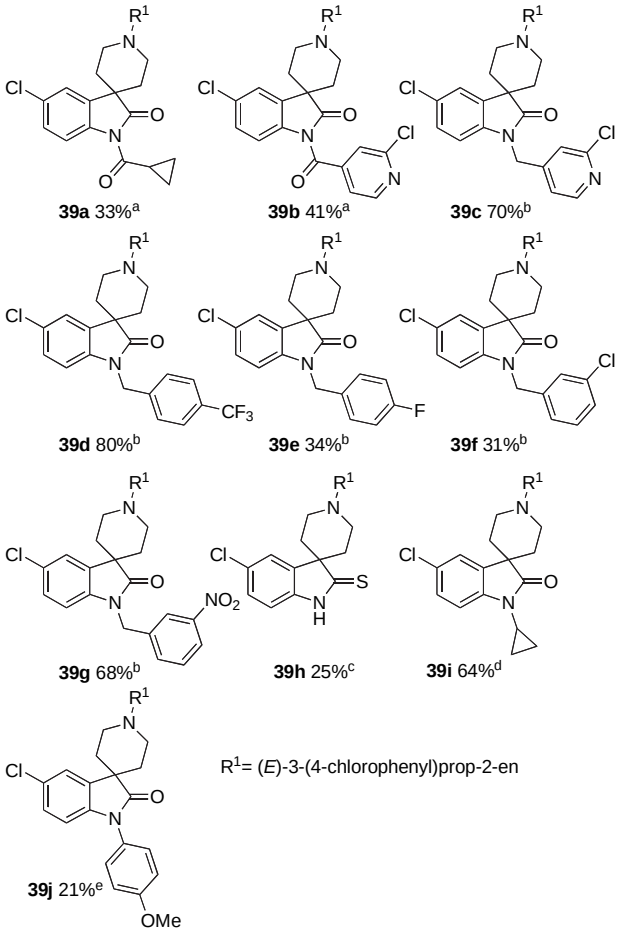


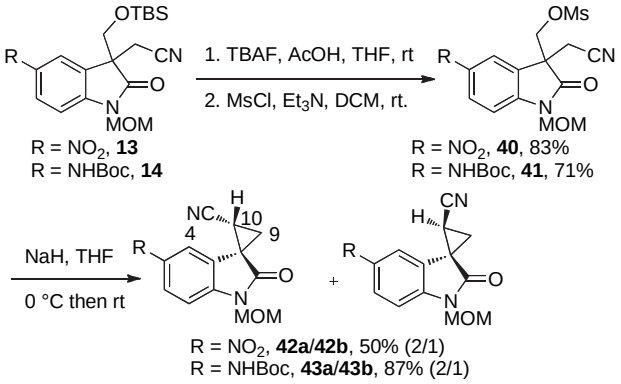
Fig. 4. Synthesized spiropiperidinyloxindoles **39**. [a]Condition: **38** (1.0 equiv), RCOCl (1.2 equiv), Et_3N (1.2 equiv), CH_2Cl_2, rt. [b]Condition: **38** (1.0 equiv), RX (2.0 equiv), NaH 60% (2.0 equiv), THF, 0 °C. [c]Condition: **38** (1.0 equiv), Lawesson's reagent (1.2 equiv), xylene, 140 °C. [d]Condition: **38** (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), bipyridine (1.0 equiv), cyclopropyl boronic acid (2.5 equiv), Na_2CO_3 (2.0 equiv), DCE, air, 70 °C. [e]Condition: **38** (1.0 equiv), *p*-methoxyiodobenzene (1.0 equiv), K_2CO_3 (2 equiv), CuI (0.1 equiv), *N*,*N*-dimethylenediamine (0.2 equiv), CH_3CN, reflux.

64% yield.[28a] Finally, a copper-catalyzed N-arylation[29] [4-iodo-anisole, CuI, *N*,*N*-dimethylethylenediamine, K_2CO_3, CH_3CN, refux][30a] afforded compound **39j**.

2.3. Spirocyclopropyloxindoles

Different strategies to access spirocyclopropyloxindoles have been developed including alkylation of oxindole enolate with dibromoethane.[5b,31] Based on this process, 3-cyanomethyloxindole has recently been converted to spirocyclopropyl oxindole through a one-pot double alkylation process.[32] This result prompted us to apply such alkylation strategy starting from the already available intermediates **13** and **14**.

In the event, oxindoles **13** and **14** were *O*-deprotected and converted to their mesylated derivatives **40** and **41** in 83 and 71% overall yields, respectively (Scheme 4). Simple treatment of intermediate **40** with sodium hydride provided diastereomeric spirocyclopropyloxindoles **42a** and **42b** in a 2:1 diastereomeric ratio in 50% yield. Reaction was much cleaner with the NHBoc derivative **41** leading to spirocyclopropyloxindoles **43a** and **43b** (dr=2:1) in 87% yield. In both cases, diastereoisomers were separated by flash chromatography on silica gel. The unambiguous attribution of their relative configuration was based on anisotropic effects of the nitrile and carbonyl groups on the chemical shifts of H_4 and H_{10}, respectively, and by comparison with literature data of known spirocyclopropyloxindoles.[32,33]



Scheme 4. Synthesis of spirocyclopropyloxindoles.

3. Conclusion

In conclusion, we demonstrated that 3-alkyl-3-cyanomethyloxindole, easily accessible through a palladium-catalyzed domino intramolecular Heck/cyanation sequence, is a versatile intermediate for the elaboration of spirocyclooxindoles. The so-obtained spiropyrrolidinyl-, spiropiperidinyl-, or spirocyclopropyloxindoles bearing three diversity points were further functionalized via N-acylation, N-alkylation, N-sulfonylation, S_NAr reaction and the Buchwald–Hartwig N-arylation to reach diverse set of spirooxindoles. Evaluation of their bioactivities, especially as agrochemicals, is ongoing.

4. Experimental section

4.1. General

Proton NMR (^1H NMR) spectra were recorded at 500 MHz on a Bruker AC-500 spectrometer. Carbon NMR (^{13}C NMR) spectra were recorded at 75 MHz on a Bruker AC-300 spectrometer. ^1H NMR and ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent signals in $CDCl_3$ (δ=7.26, 77.16). Melting points (mp) were recorded using Büchi B-540 melting point apparatus. Infrared spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. Mass spectra were obtained from an AEI MS-9 spectrometer using positive electron spray (ES^+). Flash chromatography was performed using SDS silica gel 60 (35–70 μm). Preparative thin layer chromatography (preparative TLC) was carried out on 20×20 cm glass support plates with a layer thickness of 0.5 mm (SDS Silica gel 60 F_{254}). All reagents were obtained from commercial suppliers. Organic solvents were routinely dried and/or distilled prior to use. When needed, solvents were degazed using freeze-drying. All reactions were performed under an argon atmosphere unless otherwise stated.

4.2. Spiropyrrolidinyloxindoles synthesis

*4.2.1. 2-((tert-Butyldimethylsilyloxy)methyl)-N-(2-iodo-4-nitro-phenyl)acrylamide (**10**).* To a solution of 2-chloro-1-methylpyridinium iodide (13.94 g, 54.5 mmol, 2.4 equiv) in toluene (45 mL) were added 2-((*tert*-butyldimethylsilyloxy)methyl)acrylic acid **9** (9.83 g, 45.4 mmol, 2.0 equiv), *n*-Bu_3N (26.0 mL, 109.0 mmol, 4.8 equiv) and 2-iodo-4-nitroaniline (6.0 g, 22.7 mmol, 1.0 equiv). After being stirred at 100 °C under argon atmosphere for 16 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4). The crude was concentrated under reduced pressure, dissolved in THF/H_2O (8/1) (40 mL) and LiOH (1.0 g, 23.8 mmol) was added. The mixture was stirred at room temperature for 6 h, diluted with EtOAc and extracted. The combined

organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, Heptane/EtOAc: 100/0 to 100/5) to give the corresponding anilide **10** (6.31 g, 60%) as a yellow solid. Mp 89–91 °C. IR ($CHCl_3$, cm^{-1}) ν 3386, 3082, 2953, 2928, 2884, 1686, 1530, 1496, 1348, 1096. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.96 (br s, 1H), 8.68 (d, J=2.6 Hz, 1H), 8.59 (d, J=9.2 Hz, 1H), 8.24 (dd, J=2.6, 9.2 Hz, 1H), 6.25 (s, 1H), 5.77 (s, 1H), 4.55 (s, 2H), 0.93 (s, 9H), 0.15 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.9, 144.4, 143.6, 142.0, 134.4, 124.7, 124.1, 120.7, 87.7, 63.2, 26.0, 18.0, −4.9. HRMS (m/z, ESI^+) calcd for $C_{16}H_{23}N_2O_4NaSiI$: 485.0370, found 485.0370.

*4.2.2. 2-((tert-Butyldimethylsilyloxy)methyl)-N-(2-iodo-4-nitrophenyl)-N-(methoxymethyl)acrylamide (**12**).* To a solution of anilide **10** (5.0 g, 10.8 mmol, 1.0 equiv) in THF (100 mL) at 0 °C, was added dropwise a 0.5 M solution of NaHMDS in THF (43.2 mL, 21.6 mmol, 2.0 equiv). The reaction mixture turned dark and was further stirred for 30 min at 0 °C. MOMCl (2.46 mL, 32.4 mmol, 3.0 equiv) was added dropwise at 0 °C before reaction was allowed to reach room temperature. After being stirred for an additional 1 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, Heptane/EtOAc: 100/0 to 100/5) to give starting material **10** (2.0 g, 40%) and compound **12** (3.12 g, 57%) as a yellow oil. IR ($CHCl_3$, cm^{-1}) ν 3093, 2950, 2928, 2855, 1671, 1524, 1256, 1110, 1086. ^1H NMR ($CDCl_3$, 500 MHz) (rotamers) δ 8.72 (d, J=2.3 Hz, 1H), 8.21 (m, 1H), 7.46 (d, J=7.7 Hz, 1H), 5.83–5.00 (m, 3H), 4.62 (d, J=9.0 Hz, 1H), 4.48 (d, J=9.0 Hz, 1H), 4.26 (br s, 1H), 3.40 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H). Due to the sever presence of rotamers the ^{13}C NMR was poorly resolved. HRMS (m/z, ESI^+) calcd for $C_{18}H_{27}N_2O_5NaSiI$: 529.0632, found 529.0616.

*4.2.3. 2-(3-((tert-Butyldimethylsilyloxy)methyl)-1-(methoxymethyl)-5-nitro-2-oxoindolin-3-yl)acetonitrile (**13**).* To a degassed solution of iodoanilide **12** (3.10 g, 6.12 mmol, 1.0 equiv) in DMF (30 mL) were added $K_4Fe(CN)_6\cdot 3H_2O$ (0.57 g, 1.35 mmol, 0.22 equiv), Na_2CO_3 (0.65 g, 6.12 mmol, 1.0 equiv) and $Pd(OAc)_2$ (41.0 mg, 0.18 mmol, 0.03 equiv). After being stirred at 120 °C under argon atmosphere for 4 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, Heptane/EtOAc: 10/0 to 10/2) to give oxindole **13** (1.73 g, 70%) as a yellow oil. IR ($CHCl_3$, cm^{-1}) ν 2950, 2930, 2885, 1736, 1617, 1523, 1488, 1336, 1098. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.35–8.33 (m, 2H), 7.22 (d, J=8.9 Hz, 1H), 5.22 (d, J=11.1 Hz, 1H), 5.16 (d, J=11.1 Hz, 1H), 3.96 (d, J=9.7 Hz, 1H), 3.80 (d, J=9.7 Hz, 1H), 3.35 (s, 3H), 3.08 (d, J=16.8 Hz, 1H), 2.91 (d, J=16.8 Hz, 1H), 0.80 (s, 9H), −0.02 (2s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.8, 147.7, 144.0, 128.8, 126.5, 120.1, 115.5, 110.1, 71.8, 66.4, 56.7, 52.1, 25.6, 21.6, 18.1, −5.6. HRMS (m/z, ESI^+) calcd for $C_{19}H_{27}N_3O_5NaSi$: 428.1618, found 428.1607.

*4.2.4. tert-Butyl 3-((tert-butyldimethylsilyloxy)methyl)-3-(cyanomethyl)-1-(methoxymethyl)-2-oxoindolin-5-ylcarbamate (**14**).* To a suspension of compound **13** (1.50 g, 3.70 mmol, 1.0 equiv) in water (37 mL) were added iron (2.10 g, 37 mmol, 10.0 equiv), $FeSO_4\cdot 7H_2O$ (1.03 g, 3.70 mmol, 1.0 equiv) and the reaction was heated at reflux for 14 h. The reaction mixture was cooled to room temperature, filtered on Celite and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, Heptane/EtOAc: 9/1 to 7/3) to give the corresponding aniline (1.30 g, 94%). To a solution of this aniline (1.30 g, 3.46 mmol, 1.0 equiv) in THF (35 mL) was added Boc_2O (0.91 g, 4.16 mmol, 1.2 equiv) and the reaction was stirred at room temperature for 15 h. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, Heptane/EtOAc: 9/1 to 4/1) to give the compound **14** (1.46 g, 88%) as white solid. Mp 127–129 °C. IR ($CHCl_3$, cm^{-1}) ν 3338, 2931, 2857, 1714, 1540, 1497, 1367, 1338, 1229, 1161, 1104. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.60 (d, J=2.0 Hz, 1H), 7.25 (dd, J=2.0, 8.5 Hz, 1H), 6.99 (d, J=8.5 Hz, 1H), 6.49 (s, 1H), 5.13 (d, J=11.0 Hz, 1H), 5.09 (d, J=11.0 Hz, 1H), 3.91 (d, J=9.6 Hz, 1H), 3.80 (d, J=9.6 Hz, 1H), 3.32 (s, 3H), 2.97 (d, J=16.7 Hz, 1H), 2.81 (d, J=16.7 Hz, 1H), 1.51 (s, 9H), 0.80 (s, 9H), 0.00 (2 s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.8, 152.7, 137.5, 134.6, 128.4, 119.8, 116.2, 115.6, 110.1, 80.6, 71.5, 66.7, 56.3, 52.0, 28.3 25.6, 21.7, 18.1, −5.6. HRMS (m/z, ESI^+) calcd for $C_{24}H_{37}N_3O_5NaSi$ ($[M+Na]^+$): 498,2400, found 498,2402.

*4.2.5. tert-Butyl 3-(2-(allyloxycarbonylamino)ethyl)-3-((tert-butyldimethylsilyloxy)methyl)-1-(methoxymethyl)-2-oxoindolin-5-ylcarbamate (**15**).* To a solution of oxindole **14** (1.45 g, 3.05 mmol, 1.0 equiv) in MeOH (30 mL) were added $CoCl_2\cdot 6H_2O$ (1.44 g, 6.10 mmol, 2.0 equiv) and portion wise $NaBH_4$ (1.15 g, 30.0 mmol, 10.0 equiv) over 45 min. After being further stirred for 1 h, the reaction mixture was quenched by slow addition of HCl (2 N, 50 mL) and washed with EtOAc. The aqueous phase was basified with NaOH (2 N) and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was taken in a 1/1 mixture of CH_2Cl_2/$NaHCO_3$ saturated (30 mL) and AllocCl (0.36 mL, 3.37 mmol, 1.1 equiv) was added. After being stirred at room temperature overnight, the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, Heptane/EtOAc: 9/1 to 7/3) to give the compound **15** (1.34 g, 78%) as a white foam. IR ($CHCl_3$, cm^{-1}) ν 3327, 2930, 2856, 1703, 1610, 1537, 1495, 1450, 1137, 1233, 1162, 1114. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.42 (m, 1H), 7.16 (d, J=8.4 Hz, 1H), 6.92 (d, J=8.4 Hz, 1H), 6.44 (br s, 1H), 5.89–5.81 (m, 1H), 5.24 (d, J=17.2 Hz, 1H), 5.17 (dd, J=1.2, 10.4 Hz, 1H), 5.07 (AB, J=10.9 Hz, 2H), 4.71 (br s, 1H), 4.45 (d, J=5.4 Hz, 2H), 3.81 (s, 2H), 3.30 (s, 3H), 3.05–2.90 (m, 2H), 2.12–2.04 (m, 2H), 1.51 (s, 9H), 0.72 (s, 9H), −0.10 (2s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.8, 155.8, 152.8, 138.0, 134.2, 132.9, 130.5, 118.5, 117.5, 115.3, 109.5, 80.4, 71.4, 68.2, 65.4, 56.3, 54.5, 37.1, 32.4, 28.4, 25.6, 18.1, −5.6. HRMS (m/z, ESI^+) calcd for $C_{28}H_{45}N_3O_7NaSi$: 586.2924, found 586.2928.

*4.2.6. tert-Butyl 3-(2-(allyloxycarbonylamino)ethyl)-3-(hydroxymethyl)-1-(methoxymethyl)-2-oxoindolin-5-ylcarbamate (**16**).* To a solution of compound **15** (1.0 g, 1.77 mmol, 1.0 equiv) in THF (35 mL) at 0 °C was added dropwise HF·Pyr (2.5 mL). The reaction was stirred at room temperature for 12 h and poured into Et_2O/$NaHCO_3$ saturated at 0 °C, and extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, Heptane/EtOAc: 2/1 to 1/1) to give the compound **16** (0.68 g, 85%) as white solid. Mp 125–127 °C. IR ($CHCl_3$, cm^{-1}) ν 3323, 3015, 2976, 2933, 1702, 167, 1537, 1494, 1335, 1235, 1216, 1156, 1062. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.45 (s, 1H), 7.15 (d, J=8.4 Hz, 1H), 6.94 (d, J=8.4 Hz, 1H), 6.75 (s, 1H), 5.88–5.80 (m, 1H), 5.23 (d, J=17.1 Hz, 1H) 5.16 (d, J=10.4 Hz, 1H), 5.07 (AB, J=10.9 Hz, 2H), 4.81 (br s, 1H), 4.44 (d, J=4.6 Hz, 2H), 3.78 (m, 2H), 3.28 (s, 3H), 3.02–2.88 (m, 2H), 2.71 (br s, 1H), 2.20 (m, 1H), 2.04 (m, 1H), 1.50 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.2, 155.9, 153.1, 137.8, 134.5, 132.8, 129.6, 119.3, 117.6, 115.1, 110.0, 80.6, 71.3, 67.4, 65.5, 56.2, 54.2, 37.0, 32.6, 28.4. HRMS (m/z, ESI^+) calcd for $C_{22}H_{31}N_3O_7Na$: 472.2060, found 472.2079.

*4.2.7. Allyl 5-(tert-butoxycarbonylamino)-1-(methoxymethyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (**7**).* To a solution of compound **16** (0.65 g, 1.45 mmol, 1.0 equiv) in CH_2Cl_2 (29 mL) at 0 °C were added Et_3N (0.81 mL, 5.82 mmol, 4.0 equiv) and MsCl (0.45 mL, 5.82 mmol, 4.0 equiv). After being stirred at room temperature for

16 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to furnish crude mesylated compound. The crude was taken in THF (25 mL) and NaH 60% (116 mg, 2.9 mmol, 2.0 equiv) was added in small portion at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was carefully quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, Heptane/EtOAc: 2/1 to 1/1) to give the compound **7** (0.51 g, 81%) as white foam. IR ($CHCl_3$, cm^{-1}) ν 3315, 2978, 2935, 1702, 1697, 1571, 1498, 1445, 1334, 1231, 1158, 1086. ^1H NMR ($CDCl_3$, 500 MHz) (rotamers) δ 7.41 and 7.32 (2m, 1H), 7.25 and 7.15 (2d, J=7.9 Hz, 1H) 6.95 and 6.93 (2d, J=7.9 Hz, 1H), 6.71 (br s, 1H), 6.01–5.85 (m, 1H), 5.33 and 5.22 (2d, J=17.2 Hz, 1H), 5.25 and 5.15 (2d, J=10.4 Hz, 1H), 5.09 (s, 2H), 4.64 and 4.59 (2d, J=4.9 Hz, 2H), 3.93–3.77 (m, 2H), 3.80 (m, 1H), 3.64 (m, 1H), 3.29 (s, 3H), 2.40–2.34 (m, 1H), 2.19–2.07 (m, 1H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) (rotamers) δ 178.4 and 178.1, 154.6 and 154.5, 153.05 and 153.00, 136.65 and 136.60, 134.7, 133.0 and 132.9, 131.9 and 131.5, 119.4 and 119.2, 117.4, 114.5, 109.9, 80.6, 71.5, 66.0, 56.2, 54.6 and 54.2, 53.3 and 52.3, 45.7 and 45.3, 36.5 and 35.8, 28.3. HRMS (m/z, ESI^+) calcd for $C_{22}H_{29}N_3O_6Na$: 454.1954, found 454.1960.

*4.2.8. Allyl 5-amino-1-(methoxymethyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (**18**).* To a solution of compound **7** (150.0 mg, 0.35 mmol, 1.0 equiv) in CH_2Cl_2 (3.5 mL) at 0 °C, was added TFA (0.26 mL, 3.5 mmol, 10.0 equiv). After being stirred at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH: 9/1) to give the compound **18** (98 mg, 84%) as yellow oil. IR ($CHCl_3$, cm^{-1}) ν 3356, 2942, 1702, 1697, 1497, 1410, 1349, 1229, 1133, 1085. ^1H NMR ($CDCl_3$, 500 MHz) (rotamers) δ 6.85 (d, J=8.1 Hz, 1H), 6.63 (dd, J=2.1, 8.1 Hz, 1H) 6.59 (m, 1H), 6.01–5.87 (m, 1H), 5.35 and 5.27 (2d, J=17.1 Hz, 1H), 5.24 and 5.18 (2d, J=10.4 Hz, 1H), 5.08 (s, 2H), 4.65 and 4.61 (2 m, 2H), 3.92–3.87 (m, 1H), 3.81–3.75 (m, 2H), 3.64 (m, 1H), 3.30 (s, 3H), 2.46–2.38 (m, 1H), 2.12–2.02 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) (rotamers) δ 177.4, 154.6, 142.7, 133.0 and 132.9, 132.8, 132.4, 117.4, 114.8 and 114.7, 110.5, 110.4, 71.5, 65.9, 56.1, 54.6 and 54.3, 53.3 and 52.3, 45.7 and 45.2, 36.6 and 35.7. HRMS (m/z, ESI^+) calcd for $C_{17}H_{21}N_3O_4Na$: 354.1430, found 354.1430.

*4.2.9. tert-Butyl 1-(methoxymethyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-5-ylcarbamate (**19**).* To a solution of compound **7** (100.0 mg, 0.23 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL) were added AcOH (0.060 mL, 1.03 mmol, 4.5 equiv), $Pd(PPh_3)_4$ (21.4 mg, 0.018 mmol, 0.08 equiv) and dropwise n-Bu_3SnH (135 μL, 0.46 mmol, 2.0 equiv). After being stirred at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH: 100/1) to give the compound **19** (77 mg, 95%) as yellow oil. IR ($CHCl_3$, cm^{-1}) ν 3308, 2933, 1711, 1608, 1539, 1498, 1367, 1338, 1238, 1161, 1099, 1077. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.47 (d, J=2.2 Hz, 1H), 7.14 (dd, J=2.2, 8.3 Hz, 1H), 6.91 (d, J=8.3 Hz, 1H), 6.90 (br s, 1H), 5.10 (s, 2H), 3.50–3.41 (m, 2H), 3.35 (d, J=12.0 Hz, 1H), 3.29 (s, 3H), 3.08 (d, J=12.0 Hz, 1H), 2.35–2.25 (m, 1H), 2.17–2.11 (m, 1H), 1.49 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.5, 153.1, 136.9, 134.7, 132.9, 118.6, 114.2, 109.6, 80.5, 71.3, 59.3, 56.2, 54.8, 48.4, 39.0, 28.4. HRMS (m/z, ESI^+) calcd for $C_{18}H_{26}N_3O_4$: 348.1923, found 348.1933.

*4.2.10. Allyl 5-amino-2-oxospiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (**20**).* To a solution of compound **7** (25.0 mg, 0.075 mmol, 1.0 equiv) in THF/H_2O (1/1) (4 mL) was added three drops of concd HCl. After being stirred at reflux overnight, the reaction mixture was quenched with NaOH 2 N and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH: 100/8) to give the compound **20** (11 mg, 51%) as light yellow oil. IR ($CHCl_3$, cm^{-1}) ν 3231, 2935, 1692, 1494, 1433, 1410, 1323, 1214, 1130. ^1H NMR ($CDCl_3$, 500 MHz) (rotamers) δ 8.55 (dl, 1H), 6.72 (d, J=8.2 Hz, 1H), 6.58–6.56 (m, 2H), 6.01–5.88 (m, 1H), 5.38–5.10 (m, 2H), 4.66–4.60 (m, 2H), 3.90–3.86 (m, 1H), 3.81–3.75 (m, 2H), 3.65–3.61 (m, 1H), 2.45–2.39 (m, 1H), 2.09–2.04 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) (rotamers) δ 179.7 and 179.2, 154.7 and 154.6, 142.4 and 142.2, 134.1 and 133.7, 133.1 and 132.9, 132.1 and 131.8, 117.4, 114.7 and 114.6, 110.7 (2C), 66.0, 54.3 and 54.1, 53.6 and 52.6, 45.6 and 45.2, 36.3 and 35.4. HRMS (m/z, ESI^+) calcd for $C_{15}H_{17}N_3O_3Na$: 310.1168, found 310.1178.

4.3. Spiropiperidinyloxindoles synthesis

*4.3.1. 2-((1,3-Dioxolan-2-yl)methyl)-N-(4-chloro-2-iodophenyl)acrylamide (**32**).* Following the same procedure as for the synthesis of compound **10**, using compound **31** and 4-chloro-2-iodoaniline, furnished compound **32** (64%) as white solid. Mp 58–60 °C. IR ($CHCl_3$, cm^{-1}) ν 3386, 3298, 2956, 2884, 1679, 1626, 1568, 1504, 1376, 1288, 1127, 1030. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.26 (br s, 1H), 8.18 (d, J=8.9 Hz, 1H), 7.77 (d, J=2.3 Hz, 1H), 7.32 (dd, J=2.3, 8.9 Hz, 1H), 6.10 (s, 1H), 5.65 (s, 1H), 5.08 (t, J=4.5 Hz, 1H), 4.02 (m, 2H), 3.88 (m, 2H), 2.82 (d, J=4.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.3, 139.6, 137.9, 137.4, 130.0, 129.1, 124.2, 122.9, 103.2, 90.0, 65.1, 36.9. HRMS (m/z, ESI^+) calcd for $C_{13}H_{13}NO_3{}^{35}ClINa$: 415.9526, found 415.9532.

*4.3.2. 2-[(1,3-Dioxolan-2-yl)methyl]-N-(4-chloro-2-iodophenyl)-N-[(2-(trimethylsilyl)ethoxy)methyl]-acrylamide (**33**).* Following the same procedure as for the synthesis of compound **11**, using compound **32** and SEMCl, furnished compound **33** (92%) as colourless oil. IR ($CHCl_3$, cm^{-1}) ν 3015, 2952, 2888, 1660, 1627, 1468, 1248, 1217, 1066, 1031, 834, 749. ^1H NMR ($CDCl_3$, 500 MHz) (rotamers) δ 7.87 (m, 1H), 7.33 (m, 1H), 7.22 (d, J=8.4 Hz, 1H), 5.93–4.97 (m, 4H), 4.55 (m, 1H), 3.98 (s, 2H), 3.85 (s, 2H), 3.77–3.32 (m, 2H), 2.76–2.36 (m, 2H), 0.89 (m, 2H), 0.01 (s, 9H). Due to the presence of sever rotamers the ^{13}C NMR was poorly resolved. HRMS (m/z, ESI^+) calcd for $C_{19}H_{27}NO_4Si^{35}ClNa$: 546.0340, found 546.0317.

*4.3.3. 2-[3-((1,3-Dioxolan-2-yl)methyl)-5-chloro-2-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)indolin-3-yl]acetonitrile (**34**).* Following the same procedure as for the synthesis of compound **12**, using compound **33** furnished compound **34** (68%) as white solid. Mp 67–69 °C. IR ($CHCl_3$, cm^{-1}) ν 2952, 2892, 2250, 1725, 1673, 1485, 1432, 1337, 1248, 1083, 858, 836. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.41 (d, J=1.9 Hz, 1H),7.32 (dd, J=1.9, 8.4 Hz, 1H), 7.07 (d, J=8.4 Hz, 1H), 5.14 (s, 2H), 4.77 (dd, J=3.4, 6.5 Hz, 1H), 3.78–3.67 (m, 4H), 3.60 (m, 2H), 2.88 (d, J=16.6 Hz, 1H), 2.65 (d, J=16.6 Hz, 1H), 2.35–2.26 (m, 2H), 0.91 (t, J=7.3 Hz, 2H), 0.03 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.6, 140.6, 129.6, 129.5, 128.8, 124.3, 115.7, 111.4, 100.7, 70.0, 66.4, 64.6, 47.1, 39.1, 26.6, 17.8, −1.4. HRMS (m/z, ESI^+) calcd for $C_{20}H_{27}N_2O_4Si^{35}ClNa$: 445.1326, found 445.1335.

*4.3.4. 2-[5-Chloro-2-oxo-3-(2-oxoethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)indolin-3-yl]acetonitrile (**35**).* A solution of compound **34** (2.0 g, 4.72 mmol, 1.0 equiv) in a 1/2 mixture of HCl 3 N/THF (24 mL) was heated at 65 °C overnight. The reaction was quenched with NaOH 2 N and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, Hept/AcOEt: 85/15) to give the compound **35** (0.95 g, 53%) as colourless oil. IR ($CHCl_3$, cm^{-1}) ν 3441, 3021, 2953, 1725, 1612, 1486, 1434, 1333,

1249, 1219, 1081, 860, 837, 756. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.53 (s, 1H), 7.37 (d, J=2.0 Hz, 1H), 7.35 (dd, J=2.0, 8.3 Hz, 1H), 7.11 (d, J=8.3 Hz, 1H), 5.22 (d, J=11.1 Hz, 1H), 5.17 (d, J=11.1 Hz, 1H), 3.69 (dt, J=8.3, 16.7 Hz, 1H), 3.60 (dt, J=8.3, 16.7 Hz, 1H), 3.37 (d, J=18.5 Hz, 1H) 3.17 (d, J=18.5 Hz, 1H), 2.90 (d, J=16.6 Hz, 1H), 2.60 (d, J=16.6 Hz, 1H), 0.94 (t, J=8.3 Hz, 2H), 0.02 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.8, 176.1, 140.8, 129.8, 129.5, 129.1, 123.5, 115.2, 111.7, 70.1, 66.5, 48.3, 45.8, 26.3, 17.8, −1.4. HRMS (m/z, ESI$^+$) calcd for $C_{18}H_{23}N_2O_3Si^{35}ClNa$: 401.1064, found 401.1076.

*4.3.5. 5-Chloro-1-((2-(trimethylsilyl)ethoxy)methyl)spiro[indoline-3,4′-piperidin]-2-one (**36**).* To a solution of oxindole **35** (800 mg, 2.12 mmol, 1.0 equiv) in MeOH (14 mL) were added $CoCl_2\cdot 6H_2O$ (1.0 g, 4.24 mmol, 2.0 equiv), and portion wise $NaBH_4$ (800 mg, 21.2 mmol, 10.0 equiv) over 45 min. After being further stirred for 30 min, the reaction mixture was quenched by slow addition of HCl (2 N, 20 mL) and washed with EtOAc. The aqueous phase was basified with NaOH (2 N) and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH: 10/0 to 10/1) to give the compound **36** (428 mg, 55%) as colourless oil. IR ($CHCl_3$, cm^{-1}) ν 3055, 2924, 1714, 1610, 1485, 1430, 1335, 1247, 1090. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (d, J=1.9 Hz, 1H), 7.24 (dd, J=1.9, 8.3 Hz, 1H), 6.97 (d, J=8.3 Hz, 1H), 5.12 (s, 2H), 3.52 (t, J=8.3 Hz, 2H), 3.37 (m, 2H), 3.06 (m, 2H), 2.22 (br s, 1H), 1.84 (m, 2H), 1.75 (m, 2H), 0.89 (t, J=8.2 Hz, 2H), −0.05 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.7, 139.6, 135.7, 128.1, 127.8, 124.0, 110.6, 69.1, 65.9, 46.0, 41.1, 33.4, 17.7, −1.4. HRMS (m/z, ESI$^+$) calcd for $C_{18}H_{28}N_2O_2Si^{35}Cl$: 367.1609, found 367.1596.

*4.3.6. (E)-5-Chloro-1′-(3-(4-chlorophenyl)allyl)-1-((2-(trimethylsilyl)ethoxy)methyl)spiro[indoline-3,4′-piperidin]-2-one (**37**).* To a solution of **36** (400 mg, 1.09 mmol, 1.0 equiv) and *p*-chlorocinammaldehyde (217 mg, 1.31 mmol, 1.2 equiv) in 7 mL dry MeOH was added 0.1 mL of acetic acid. After been stirred for 15 min at rt, $NaCNBH_3$ (82 mg, 1.31 mmol, 1.2 equiv) was added and reaction mixture was stirred for 15 h. Reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, Hept/acetone: 9/1) to give the compound **37** (423 mg, 75%) as white foam. IR ($CHCl_3$, cm^{-1}) ν 2948, 1714, 1609, 1486, 1332, 1248, 1214, 1086. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38–7.36 (m, 6H), 7.02 (d, J=8.3 Hz, 1H), 6.56 (d, J=15.9 Hz, 1H), 6.33 (td, J=6.7, 15.8 Hz, 1H), 5.15 (s, 2H), 3.55 (t, J=8.2 Hz, 2H), 3.34 (d, J=6.7 Hz, 2H), 3.01 (m, 2H), 2.80 (m, 2H), 1.96 (m, 4H), 0.92 (t, J=8.2 Hz, 2H), −0.03 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.8, 142.1, 139.6, 135.6, 135.4, 133.1, 131.8, 128.7, 128.1, 127.8, 127.5, 123.9, 110.6, 69.1, 65.9, 61.1, 48.4, 45.4, 33.3, 17.7, −1.5. HRMS (m/z, ESI$^+$) calcd for $C_{27}H_{35}N_2O_2Si^{35}Cl_2Na$: 517.1845, found 517.1848.

*4.3.7. (E)-5-Chloro-1′-(3-(4-chlorophenyl)allyl)spiro[indoline-3,4′-piperidin]-2-one (**38**).* To a solution of **37** (150 mg, 0.29 mmol, 1 equiv) in 6 mL dry CH_2Cl_2 at −78 °C was added dropwise Me_2AlCl 1 M in hexane (1.75 mL, 1.75 mmol, 6 equiv). After being stirred at −78 °C for 1 h, the reaction mixture was allowed to reach rt. After being further stirred for 2 h, reaction was cautiously quenched at 0 °C with saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2. After vigorous stirring for 1 h, reaction was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The crude residue was dissolved in 3 mL Et_3N/MeOH (ratio 1:2) and heated at reflux for 5 days. Solvents were concentrated and residue was purified by preparative TLC (SiO_2, Hept/acetone: 2/1) to give **38** (81 mg, 72%) as a pale yellow solid. Mp 75–77 °C. IR ($CHCl_3$, cm^{-1}) ν 3192, 2825, 1706, 1621, 1479, 1327, 1215, 1090. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.75 (br s, 1H), 7.36 (d, J=1.9 Hz, 1H), 7.34 (d, J=8.7 Hz, 2H), 7.30 (d, J=8.7 Hz, 2H), 7.20 (dd, J=2.0, 8.2 Hz, 1H), 6.85 (d, J=8.2 Hz, 1H), 6.56 (d, J=15.9 Hz, 1H), 6.33 (td, J=6.6, 15.9 Hz, 1H), 3.35 (d, J=6.6 Hz, 2H), 3.00 (m, 2H), 2.78 (m, 2H), 2.01 (m, 2H), 1.94 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 181.8, 138.5, 136.7, 135.4, 133.1, 132.0, 128.7, 127.7, 127.5, 127.3, 124.2, 110.5, 61.1, 48.4, 45.7, 33.0. HRMS (m/z, ESI$^+$) calcd for $C_{21}H_{21}N_2O^{35}Cl_2$: 387.1017, found 387.1026.

4.4. Spirocyclopropyloxindoles synthesis

4.4.1. 2-(3-(Hydroxymethyl)-1-(methoxymethyl)-5-nitro-2-oxoindolin-3-yl)acetonitrile. To a solution of compound **13** (250 mg, 0.62 mmol, 1.0 equiv) in THF (6 mL) and AcOH (0.8 mL) at 0 °C was slowly added TBAF (1 M in THF) (0.80 mL, 0.81 mmol, 1.3 equiv). After being stirred at room temperature overnight, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, Hept/AcOEt: 4/1 to 1/1) to give the 2-(3-(hydroxymethyl)-1-(methoxymethyl)-5-nitro-2-oxoindolin-3-yl)acetonitrile (154 mg, 85%) as sticky yellow solid. IR ($CHCl_3$, cm^{-1}) ν 3479, 2927, 1730, 1617, 1522, 1487, 1337, 1276, 1101, 1080. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.33 (m, 2H), 7.26 (d, J=9.3 Hz, 1H), 5.22 (AB, J=11.1 Hz, 2H), 4.00 (d, J=10.9 Hz, 1H), 3.94 (d, J=10.9 Hz, 1H), 3.36 (s, 3H), 3.10 (d, J=16.9 Hz, 1H), 2.99 (d, J=16.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.3, 147.7, 144.1, 128.0, 126.7, 119.8, 115.4, 110.4, 71.8, 65.4, 56.6, 51.6, 21.5. HRMS (m/z, ESI$^+$) calcd for $C_{13}H_{13}N_3O_5Na$: 314.0753, found 314.0755.

*4.4.2. [3-(Cyanomethyl)-1-(methoxymethyl)-5-nitro-2-oxoindolin-3-yl]methyl methanesulfonate (**40**).* To a solution of 2-(3-(hydroxymethyl)-1-(methoxymethyl)-5-nitro-2-oxoindolin-3-yl)acetonitrile (100 mg, 0.34 mmol, 1.0 equiv) in CH_2Cl_2 (7 mL) at 0 °C were added Et_3N (100 μL, 0.68 mmol, 2.0 equiv) and MsCl (48 μL, 0.61 mmol, 1.8 equiv). After being stirred at room temperature overnight, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, Hept/AcOEt: 1/2) to give the compound **40** (122 mg, 97%) as yellow oil. IR ($CHCl_3$, cm^{-1}) ν 2919, 1737, 1618, 1524, 1488, 1338, 1176. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.38 (m, 2H), 7.29 (d, J=9.3 Hz, 1H), 5.22 (s, 3H), 4.62 (d, J=10.2 Hz, 1H), 3.94 (d, J=10.2 Hz, 1H), 3.36 (s, 3H), 3.10 (d, J=16.8 Hz, 1H), 3.00 (s, 3H), 2.99 (d, J=16.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.0, 147.5, 144.3, 127.3, 126.2, 120.2, 114.4, 110.8, 72.1, 69.4, 56.7, 49.7, 37.7, 22.3. HRMS (m/z, ESI$^+$) calcd for $C_{14}H_{15}N_3O_7NaS$: 392.0528, found 392.0534.

*4.4.3. 1′-(Methoxymethyl)-5′-nitro-2′-oxospiro(cyclopropane-1,3′-indoline)-2-carbonitrile (**42a**/**42b**).* To a solution of compound **40** (60 mg, 0.16 mmol, 1.0 equiv) in THF (3 mL) was added NaH (60% in mineral oil) (13 mg, 0.32 mmol, 2.0 equiv). After being stirred at room temperature overnight, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by preparative TLC (SiO_2, Hept/AcOEt: 1/1) to give the compound **42a** (15 mg, 34%) as colourless oil and the compound **42b** (7 mg, 16%) as white solid.

Data for compound **42a**: IR ($CHCl_3$, cm^{-1}) ν 2935, 1736, 1619, 1523, 1488, 1378, 1340, 1277, 1231, 1187, 1103. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.36 (dd, J=2.1, 8.8 Hz, 1H), 8.12 (d, J=2.1 Hz, 1H), 7.29 (d, J=8.8 Hz, 1H), 5.25 (s, 2H), 3.40 (s, 3H), 2.63 (dd, 1H, J=7.2, 9.5 Hz, 1H), 2.30 (dd, J=5.4, 9.5 Hz, 1H), 2.14 (dd, J=5.4, 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.5, 147.8, 144.1, 125.8, 124.9, 117.0, 115.8, 110.1, 72.2, 56.9, 31.6, 22.2, 16.3. HRMS (m/z, ESI$^+$) calcd for $C_{13}H_{11}N_3O_4Na$: 296.0647, found 296.0610.

Data for compound **42b**: Mp 157–159 °C. IR ($CHCl_3$, cm^{-1}) ν 2935, 1736, 1619, 1523, 1488, 1378, 1340, 1277, 1231, 1187, 1103. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.32 (dd, J=2.0, 8.7 Hz, 1H), 7.79 (d, J=2.0 Hz, 1H), 7.26 (d, J=8.7 Hz, 1H), 5.28 (AB, J=11.0 Hz, 2H), 3.40 (s, 3H), 2.53 (dd, J=7.7, 9.1 Hz, 1H), 2.35 (dd, J=5.6, 7.7 Hz, 1H), 2.21 (dd, J=5.6, 9.1 Hz, 1H). ^{13}C NMR ($(CD_3)_2CO$, 75 MHz) δ 172.3, 148.2, 143.7, 127.7, 125.0, 116.2, 115.5, 109.8, 71.7, 55.8, 31.7, 22.0, 15.8. HRMS (m/z, ESI^+) calcd for.$C_{13}H_{11}N_3O_4Na$: 296.0647, found 296.0641.

*4.4.4. tert-Butyl-2-cyano-1′-(methoxymethyl)-2′-oxospiro[cyclopropane-1,3′-indoline]-5′-ylcarbamate (**43a**/**43b**).* Following the same procedure as for the synthesis of compound **42a**/**42b** using compound **41** (80 mg, 0.18 mmol) furnished compound **43a** (36 mg, 58%) as white solid and compound **43b** (18 mg, 29%) as colourless oil.

Data for compound **43a**: Mp>200 °C. IR ($CHCl_3$, cm^{-1}) ν 3330, 2934, 1714, 1606, 1537, 1495, 1455, 1367, 1336, 1238, 1160. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.47 (dd, J=1.9, 8.3 Hz, 1H), 7.15 (d, J=1.9 Hz, 1H), 7.07 (d, J=8.3 Hz, 1H), 6.54 (br s, 1H), 5.15 (s, 2H), 3.34 (s, 3H), 2.47 (dd, J=7.1, 9.4 Hz, 1H), 2.14 (dd, J=5.1, 9.4 Hz, 1H), 1.92 (dd, J=5.1, 6.9 Hz, 1H), 1.5 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.4, 152.7, 137.8, 134.3, 124.1, 119.6, 116.4, 112.6, 110.2, 80.6, 71.8, 56.3, 37.8, 28.2, 21.6, 15.2. HRMS (m/z, ESI^+) calcd for $C_{18}H_{21}N_3O_4Na$: 366.1430, found 366.1427.

Data for compound **43b**: Mp 157–159 °C. IR ($CHCl_3$, cm^{-1}) ν 3330, 2934, 1714, 1606, 1537, 1495, 1455, 1367, 1336, 1238, 1160. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.33 (br s, 1H), 7.03 (d, J=8.4 Hz, 1H), 6.96 (dd, J=1.8, 8.4 Hz, 1H), 6.52 (d, J=1.8 Hz, 1H), 5.19 (AB, J=10.9 Hz, 2H), 3.36 (s, 3H), 2.38 (dd, J=7.7, 9.0 Hz, 1H), 2.20 (dd, J=5.1, 7.7 Hz, 1H), 2.05 (dd, J=5.1, 9.0 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.0, 152.8, 137.7, 134.5, 126.3, 118.9, 115.6, 110.5, 110.3, 80.9, 71.9, 56.5, 32.3, 28.8, 21.6, 15.7. HRMS (m/z, ESI^+) calcd for $C_{18}H_{21}N_3O_4Na$: 366.1430, found 366.1424.

4.5. Functionalization of spiropyrrolidinyloxindoles and spiropiperidinyloxindoles

4.5.1. General procedure A, acylation/sulfonylation. To a solution of the amine containing oxindole (1.0 equiv) and Et_3N (1.2 equiv) in dry CH_2Cl_2 (0.1 M) was added dropwise at 0 °C the corresponding acyl chloride or sulfonyl chloride (1.2 equiv). Reaction mixture was stirred at 0 °C or rt until full conversion of the starting amine. Reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 or EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated.

4.5.2. General procedure B, alkylation. To a solution of the amine (1.0 equiv) in dry THF (0.1 M) at 0 °C was added portion wise NaH 60% (2.0 equiv). After being stirred at 0 °C for 10 min, the corresponding halogenated compound (2.0 equiv) was added and reaction stirred at rt until complete conversion. Reaction was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 or EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated.

*4.5.3. Allyl 5-(cyclopropanecarboxamido)-1-(methoxymethyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (**21**).* Prepared following general procedure A. Colourless oil. IR ($CHCl_3$, cm^{-1}) ν 3312, 3010, 2940, 2887, 1702, 1682, 1609, 1548, 1493, 1445, 1407, 1331, 1227, 1187, 1086. ^1H NMR ($CDCl_3$, 500 MHz). *Rotamer* 1: δ 7.69 (br s, 1H), 7.57 (m, 1H), 7.31 (d, J=7.9 Hz, 1H), 6.97 (d, J=7.9 Hz, 1H), 6.00–5.93 (m, 1H), 5.35 (d, J=17.3 Hz, 1H), 5.24 (d, J=11.1 Hz, 1H), 5.10 (s, 2H), 4.66–4.63 (m, 2H), 3.95–3.88 (m, 1H), 3.83–3.77 (m, 2H), 3.65 (d, J=10.9 Hz, 1H), 3.31 (s, 3H), 2.44–2.37 (m, 1H), 2.19–2.07 (m, 1H), 1.53–1.48 (m, 1H), 1.09–1.04 (m, 2H), 0.85–0.83 (m, 2H).

Rotamer 2: δ 7.69 (br s, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.41 (m, 1H), 6.99 (d, J=7.8 Hz, 1H), 5.93–5.86 (m, 1H), 5.26 (d, J=17.9 Hz, 1H), 5.17 (d, J=10.4 Hz, 1H), 5.10 (s, 2H), 4.63–4.58 (m, 2H), 3.95–3.88 (m, 1H), 3.83–3.77 (m, 2H), 3.65 (d, J=10.9 Hz, 1H), 3.31 (s, 3H), 2.44–2.37 (m, 1H), 2.19–2.07 (m, 1H), 1.53–1.48 (m, 1H), 1.09–1.04 (m, 2H), 0.85–0.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz). *Rotamer* 1: δ 178.3, 171.9, 154.6, 137.2, 134.4, 132.9, 131.9, 120.5, 117.4, 115.5, 109.8, 71.5, 66.0, 56.2, 54.6, 53.2, 45.7, 36.5, 15.5, 7.9. *Rotamer* 2:δ 177.9, 171.9, 154.6, 137.2, 134.4, 132.8, 131.5, 120.2, 117.4, 115.3, 109.8, 71.5, 66.0, 56.2, 54.2, 52.2, 45.2, 35.7, 15.5, 7.9. HRMS (m/z, ESI^+) calcd for $C_{21}H_{25}F_3N_3O_5Na$: 422.1692, found 422.1678.

*4.5.4. Allyl 1-(methoxymethyl)-2-oxo-5-(4-(trifluoromethyl)benzamido)spiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (**22**).* Prepared following general procedure A. Colourless oil. IR ($CHCl_3$, cm^{-1}) ν 3311, 2937, 1703, 1673, 1547, 1494, 1444, 1408, 1324, 1167, 1126, 1065, 1017. ^1H NMR ($CDCl_3$, 500 MHz) *Rotamer* 1: δ 8.39 (br s, 1H), 7.98 (d, J=7.8 Hz, 2H), 7.72 (d, J=7.8 Hz, 2H), 7.68 (d, J=8.4 Hz, 1H), 7.54 (s, 1H), 7.05 (d, J=8.4 Hz, 1H), 5.98–5.90 (m, 1H), 5.32 (d, J=17.1 Hz, 1H), 5.20 (d, J=10.6 Hz, 1H), 5.11 (s, 2H), 4.62–4.57 (m, 2H), 3.95–3.86 (m, 1H), 3.82–3.77 (m, 2H), 3.65 (d, J=11.3 Hz, 1H), 3.32 (s, 3H), 2.44–2.39 (m, 1H), 2.21–2.14 (m, 1H). *Rotamer* 2: δ 8.39 (br s, 1H), 7.98 (d, J=7.8 Hz, 2H), 7.72 (d, J=7.8 Hz, 2H), 7.66 (s, 1H), 7.51 (d, J=8.5 Hz, 1H), 7.03 (d, J=8.5 Hz, 1H), 5.90–5.84 (m, 1H), 5.24 (d, J=17.4 Hz, 1H), 5.15 (d, J=10.6 Hz, 1H), 5.09 (s, 2H), 4.57–4.53 (m, 2H), 3.95–3.86 (m, 1H), 3.82–3.77 (m, 2H), 3.65 (d, J=11.3 Hz, 1H), 3.31 (s, 3H), 2.44–2.39 (m, 1H), 2.14–2.05 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz). *Rotamer* 1: δ 178.1, 164.6, 154.6, 138.1, 138.0, 133.9, 133.7, 132.8, 131.8 (d, J=35 Hz), 127.6, 125.7 (d, J=4 Hz), 123.5 (d, J=272 Hz), 121.2, 117.5, 116.1, 110.0, 71.5, 66.0, 56.3, 54.6, 53.2, 45.7, 36.5. *Rotamer* 2: δ 177.7, 164.6, 154.6, 138.1, 138.0, 133.8, 133.2, 132.6, 131.8 (d, J=35 Hz), 127.6, 125.7 (d, J=4 Hz), 123.5 (d, J=272 Hz), 121.2, 117.5, 115.9, 110.0, 71.5, 66.0, 56.3, 54.2, 52.2, 45.2, 35.7. HRMS (m/z, ESI^+) calcd for $C_{25}H_{24}N_3O_5F_3Na$: 526.1566, found 526.1570.

*4.5.5. Allyl 1-(methoxymethyl)-5-(2-nitrophenylamino)-2-oxospiro[indoline-3,3′-pyrrolidine]-1′-carboxylate (**23**).* To a solution of **18** (20.0 mg, 0.06 mmol, 1.0 equiv) in 0.3 mL DMSO were added 2-nitrofluorobenzene (6.5 μL, 0.06 mmol, 1.0 equiv) and *t*-BuOK (14.9 mg, 0.13 mmol, 2.0 equiv). After stirring at rt overnight, reaction mixture was diluted and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by preparative TLC (Hept/EtOAc: 1/2) to afford compound **27** (16.4 mg, 60%) as a bright orange oil. IR ($CHCl_3$, cm^{-1}) ν 3345, 2938, 1720, 1702, 1613, 1573, 1494, 1407, 1341, 1259, 1225, 1188, 1145, 1079. ^1H NMR ($CDCl_3$, 500 MHz) (rotamers) δ 9.42 (br s, 1H), 8.21 (d, J=8.5 Hz, 1H), 7.35 (m, 1H), 7.24 (m, 1H), 7.14–7.10 (m, 2H), 7.05–7.02 (m, 1H), 6.77 (dd, J=7.5 Hz, 1H), 6.00–5.88 (m, 1H), 5.33–5.25 (m, 1H), 5.21–5.14 (m, 1H), 5.16 (s, 2H), 4.66–4.57 (m, 2H), 3.97–3.90 (m, 1H), 3.87–3.75 (m, 2H), 3.73–3.66 (m, 1H), 3.36 (s, 3H), 2.51–2.46 (m, 1H), 2.20–2.12 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) (rotamers) δ 177.9 and 177.7, 154.5 and 154.4, 143.6, 139.2 and 139.1, 135.9 and 135.8, 134.6 and 134.5, 133.3, 133.0 and 132.8, 126.7, 125.9, 120.3 and 120.2, 117.5; 117.4, 115.6 and 115.5, 110.7, 71.6, 66.1, 56.4, 54.7 and 54.3, 53.3 and 52.3, 45.7 and 45.1, 36.5 and 35.8. HRMS (m/z, ESI^+) calcd for $C_{23}H_{24}N_4O_6Na$: 475.1594, found 475.1591.

*4.5.6. 1′-Allyl-1-(methoxymethyl)-5-(4-nitrophenylamino)spiro[indoline-3,3′-pyrrolidin]-2-one (**24**).* To a solution of **18** (20.0 mg, 0.06 mmol, 1.2 equiv) in 0.6 mL dry toluene were added *p*-nitrobromobenzene (10.2 mg, 0.05 mmol, 1.0 equiv), Cs_2CO_3 (23.0 mg, 0.07 mmol, 1.4 equiv), $Pd(OAc)_2$ (1.4 mg, 0.006 mmol, 0.1 equiv) and BINAP (7.5 mg, 0.012 mmol, 0.2 equiv) and reaction mixture was heated at 90 °C for 3 h. After cooling, water was added and reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The

residue was purified by preparative TLC (CH_2Cl_2/MeOH: 9/1) to afford compound **24** (8.6 mg, 35%) as an orange solid. Mp 106–108 °C. IR ($CHCl_3$, cm^{-1}) ν 3323, 2936, 1715, 1590, 1488, 1321, 1307, 1182, 1100. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.10 (d, J=9.1 Hz, 2H), 7.46 (d, J=1.9 Hz, 1H), 7.15 (dd, J=1.9, 8.2 Hz, 1H), 7.02 (d, J=8.2 Hz, 1H), 6.83 (d, J=9.1 Hz, 2H), 6.26 (br s, 1H), 5.99–5.91 (m, 1H), 5.26 (d, J=17.2 Hz, 1H), 5.16 (d, J=10.2 Hz, 1H), 5.13 (s, 2H), 3.35 (s, 3H), 3.35–3.32 (m, 1H), 3.27–3.22 (m, 2H), 3.15–3.08 (m, 1H), 2.88–2.78 (m, 2H), 2.44–2.39 (m, 1H), 2.21–2.13 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.2, 150.9, 139.6, 138.3, 135.3, 134.5, 126.3, 123.0, 119.3, 118.1, 113.0, 110.0, 71.6, 63.6, 58.1, 56.4, 53.9, 53.1, 37.5. ESI (+) m/z 409.1 [M+H].

*4.5.7. tert-Butyl 1′-(cyclopropanecarbonyl)-1-(methoxymethyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-5-ylcarbamate (**25**).* Prepared following general procedure A. Colourless oil. IR ($CHCl_3$, cm^{-1}) ν 3292, 2933, 1714, 1609, 1540, 1499, 1454, 1366, 1339, 1236, 1159, 1092. ^1H NMR ($CDCl_3$, 500 MHz). *Rotamer* 1: δ 7.47 (d, J=1.6 Hz, 2H), 7.11 (dd, J=1.6, 8.5 Hz, 1H), 6.95 (d, J=8.5 Hz, 1H), 6.61 (br s, 1H), 5.12 (s, 2H), 4.20–4.15 (m, 1H), 4.07–4.02 (m, 2H), 3.91–3.86 (m, 1H), 3.32 (s, 3H), 2.50–2.45 (m, 1H), 2.33–2.27 (m, 1H), 1.76–1.71 (m, 1H), 1.50 (s, 9H), 1.07–1.03 (m, 2H), 0.85–0.82 (m, 2H). *Rotamer* 2: δ 7.33 (m, 1H), 7.25 (d, J=1.4 Hz, 1H), 7.00 (d, J=8.3 Hz, 1H), 6.57(br s, 1H), 5.12 (s, 2H), 4.00–3.95 (m, 1H), 3.91–3.86 (m, 2H), 3.77 (m, 1H), 3.30 (s, 3H), 2.44–2.39 (m, 1H), 2.12–2.07 (m, 1H), 1.54–1.47 (m, 1H), 1.50 (s, 9H), 1.07–1.03 (m, 2H), 0.78–0.75 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz). *Rotamer* 1: δ 178.6, 172.4, 153.1, 136.7, 134.8, 132.1, 119.6, 114.6, 110.0, 80.7, 71.6, 56.3, 54.8, 53.6, 45.8, 36.6, 28.4, 12.7, 7.9. *Rotamer* 2: δ 177.7, 172.3, 153.0, 136.5, 134.7, 131.3, 119.3, 114.5, 109.9, 80.6, 71.4, 56.2, 54.3, 51.8, 45.5, 35.3, 28.4, 12.6, 7.7. HRMS (m/z, ESI^+) calcd for $C_{22}H_{29}N_3O_5Na$: 438.2029, found 438.2026.

*4.5.8. tert-Butyl 1-(methoxymethyl)-2-oxo-1′-(trifluoromethylsulfonyl)spiro[indoline-3,3′-pyrrolidine]-5-ylcarbamate (**26**).* Prepared following general procedure A. Colourless oil. IR ($CHCl_3$, cm^{-1}) ν 3329, 2977, 2936, 1720, 1713, 1698, 1537, 1500, 1450, 1389, 1367, 1337, 1225, 1158, 1093, 1051. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.46 (d, J=2.0 Hz, 1H), 7.22 (dd, J=2.0, 8.4 Hz, 1H), 6.99 (d, J=8.4 Hz, 1H), 6.50 (br s, 1H), 5.10 (AB, J=10.9 Hz, 2H), 4.11–4.07 (m, 1H), 3.98–3.93 (m, 1H), 3.89 (d, J=10.4 Hz, 1H), 3.77 (d, J=10.4 Hz, 1H), 3.32 (s, 3H), 2.50–2.43 (m, 1H), 2.37–2.30 (m, 1H), 1.52 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.2, 152.9, 136.7, 134.9, 129.6, 119.8, 114.4, 110.3, 80.9, 71.6, 56.3, 56.2, 52.9, 48.2, 36.7, 28.3. HRMS (m/z, ESI^+) calcd for $C_{19}H_{24}N_3O_6NaSF_3$: 502.1236, found 502.1253.

*4.5.9. tert-Butyl 1-(methoxymethyl)-1′-(4-nitrobenzyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-5-ylcarbamate (**27**).* Prepared following general procedure B. Yellow oil. IR ($CHCl_3$, cm^{-1}) ν 3320, 2933, 1712, 1606, 1519, 1493, 1343, 1232, 1159, 1092. ^1H NMR ($CDCl_3$, 500 MHz) (rotamers) δ 8.21 (m, 2H), 7.81 (m, 1H), 7.66 (m, 2H), 7.05 (m, 1H), 6.91 (d, J=8.0 Hz, 1H), 6.48 (br s, 1H), 5.09 (s, 2H), 3.95–3.78 (m, 2H), 3.29 (s, 3H), 3.25–3.17 (m, 1H), 2.97–2.70 (m, 3H), 2.44–2.40 (m, 1H), 2.17–2.13 (m, 1H), 1.55 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) (rotamers) δ 180.1, 152.9, 147.2, 136.4, 134.7, 129.3, 123.8, 118.6, 115.2, 109.5, 80.6, 71.6, 64.0, 58.5, 56.2, 54.1, 53.3, 37.3, 28.4. HRMS (m/z, ESI^+) calcd for $C_{25}H_{31}N_4O_6$: 483.2244, found 483.2239.

*4.5.10. (E)-5-Chloro-1′-(3-(4-chlorophenyl)allyl)-1-(cyclopropanecarbonyl)spiro[indoline-3,4′-piperidin]-2-one (**39a**).* Prepared following general procedure A. Colourless oil. IR ($CHCl_3$, cm^{-1}) ν 2938, 2823, 2358, 2340, 1748, 1697, 1474, 1389, 1318, 1290, 1252, 1143, 1103. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.08 (d, J=8.7 Hz, 1H), 7.34–7.25 (m, 6H), 6.55 (d, J=15.8 Hz, 1H), 6.34 (td, J=6.6, 15.8 Hz, 1H), 3.36 (d, J=6.6 Hz, 2H), 3.14 (m, 1H), 2.96 (m, 2H), 2.87 (m, 2H), 2.02 (m, 4H), 1.27 (m, 2H), 1.10 (m, 2H, H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.1, 175.2, 137.7, 135.3, 135.1, 133.2, 132.1, 130.4, 128.8, 128.2, 127.6 (2C), 123.2, 117.5, 61.1, 48.2, 45.3, 33.9, 15.2, 11.5. HRMS (m/z, ESI^+) calcd for $C_{25}H_{25}N_2O_2{}^{35}Cl_2$: 455.1293, found 455.1315.

*4.5.11. (E)-5-Chloro-1-(2-chloroisonicotinoyl)-1′-(3-(4-chlorophenyl)allyl)spiro[indoline-3,4′-piperidin]-2-one (**39b**).* Prepared following general procedure A. Title compound rapidly decomposed. Colourless oil. IR ($CHCl_3$, cm^{-1}) ν 2927, 2822, 1761, 1704, 1478, 1371, 1338, 1296, 1264, 1148, 1104. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.54 (d, J=5.0 Hz, 1H), 7.99 (d, J=8.6 Hz, 1H), 7.38 (d, J=1.8 Hz, 1H), 7.36 (dd, J=1.8, 8.6 Hz, 1H), 7.31–7.27 (m, 6H), 6.51 (d, J=15.6 Hz, 1H), 6.27 (m, 1H), 3.27 (d, J=5.2 Hz, 1H), 2.83 (m, 2H), 2.76 (m, 2H), 2.00 (m, 4H).

*4.5.12. (E)-5-Chloro-1′-(3-(4-chlorophenyl)allyl)-1-((2-chloropyridin-4-yl)methyl)spiro[indoline-3,4′-piperidin]-2-one (**39c**).* Prepared following general procedure B. Colourless oil. IR ($CHCl_3$, cm^{-1}) ν 2921, 2823, 1710, 1594, 1487, 1427, 1351, 1169, 1086. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.32 (d, J=5.1 Hz, 1H), 7.40 (d, J=2.0 Hz, 1H), 7.33 (d, J=8.5 Hz, 2H), 7.28 (d, J=8.5 Hz, 2H), 7.18 (dd, J=2.0, 8.3 Hz, 1H), 7.16 (s, 1H), 7.04 (d, J=5.1 Hz, 1H), 6.56 (d, J=17.4 Hz, 1H), 6.55 (d, J=8.3 Hz, 1H), 6.35 (m, 1H), 4.85 (s, 2H), 3.38 (m, 2H), 3.06 (m, 2H), 2.86 (m, 2H), 2.07 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.4, 152.3, 150.2, 148.0, 139.5, 135.7, 135.1, 133.3, 132.0, 128.7, 128.6, 128.0, 127.6 (2C), 124.4, 122.3, 120.5, 109.3, 61.0, 48.3, 45.1, 42.1, 33.0. HRMS (m/z, ESI^+) calcd for $C_{27}H_{25}N_3O^{35}Cl_3$: 512.1063, found 512.1043 and calcd for $C_{27}H_{25}N_3O^{35}Cl_2{}^{37}Cl$: 514.1034, found 514.1030.

*4.5.13. (E)-5-Chloro-1′-(3-(4-chlorophenyl)allyl)-1-(4-(trifluoromethyl)benzyl)spiro[indoline-3,4′-piperidin]-2-one (**39d**).* Prepared following general procedure B. Colourless oil. IR ($CHCl_3$, cm^{-1}) ν 2938, 2821, 1707, 1608, 1486, 1322, 1166, 1124, 1110, 1066. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.57 (d, J=8.1 Hz, 2H), 7.37–7.27 (m, 7H), 7.14 (dd, J=2.0, 8.3 Hz, 1H), 6.58 (d, J=8.2 Hz, 1H), 6.55 (d, J=15.9 Hz, 1H), 6.33 (td, J=6.7, 15.8 Hz, 1H), 4.92 (s, 2H), 3.34 (d, J=6.7 Hz, 2H), 3.02 (m, 2H), 2.80 (m, 2H), 1.98 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.5, 140.0, 139.7, 136.0, 135.4, 133.2, 132.1, 130.2 (d, J=32 Hz), 128.7, 128.1, 127.8, 127.6, 127.4, 127.1, 126.0 (d, J=4 Hz), 124.2, 123.9 (d, J=270 Hz), 109.6, 61.1, 48.5, 45.2, 43.1, 33.2. HRMS (m/z, ESI^+) calcd for $C_{29}H_{26}N_2OF_3{}^{35}Cl_2$: 545.1374, found 543.1379 and calcd for $C_{29}H_{26}N_2OF_3{}^{35}Cl^{37}Cl$: 547.1345, found 547.1378.

*4.5.14. (E)-5-Chloro-1′-(3-(4-chlorophenyl)allyl)-1-(4-fluorobenzyl)spiro[indoline-3,4′-piperidin]-2-one (**39e**).* Prepared following general procedure B. Colourless oil. IR ($CHCl_3$, cm^{-1}) ν 3044, 2919, 2825, 1709, 1608, 1510, 1486, 1427, 1342, 1223, 1197. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34 (d, J=1.7 Hz, 1H), 7.32 (d, J=8.6 Hz, 2H), 7.28 (d, J=8.6 Hz, 2H), 7.20 (dd, J=5.3, 8.5 Hz, 2H), 7.14 (dd, J=1.7, 8.2 Hz, 1H), 7.00 (dd, J=8.6 Hz, 2H), 6.61 (d, J=8.2 Hz, 1H), 6.55 (d, J=15.9 Hz, 1H), 6.33 (td, J=6.6, 15.9 Hz, 1H), 4.84 (s, 2H), 3.35 (m, 2H), 3.03 (m, 2H), 2.80 (m, 2H), 1.98 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.1, 162.6 (d, J=246 Hz), 140.2, 136.0, 135.4, 133.2, 132.0, 131.4, 128.8 (d, J=22 Hz), 128.7, 127.9, 127.7, 127.6 (2C), 124.1, 115.8 (d, J=8 Hz), 109.2, 61.1, 48.4, 45.2, 42.8, 33.1. HRMS (m/z, ESI^+) calcd for $C_{28}H_{26}N_2OF^{35}Cl_2$: 495.1406, found 495.1396 and calcd for $C_{28}H_{26}N_2OF^{35}Cl^{37}Cl$: 497.1377, found 497.1398.

*4.5.15. (E)-5-Chloro-1-(4-chlorobenzyl)-1′-(3-(4-chlorophenyl)allyl)spiro[indoline-3,4′-piperidin]-2-one (**39f**).* Prepared following general procedure B. Colourless oil. IR ($CHCl_3$, cm^{-1}) ν 2930, 2822, 1709, 1608, 1486, 1427, 1340, 1170, 909. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36 (d, J=1.7 Hz, 1H), 7.33 (d, J=8.5 Hz, 2H), 7.28 (d, J=8.5 Hz, 2H), 7.24 (m, 2H), 7.21 (s, 1H), 7.15 (dd, J=2.0, 8.3 Hz, 1H), 7.10 (m, 1H), 6.60 (d, J=8.3 Hz, 1H), 6.56 (d, J=15.9 Hz, 1H), 6.34 (dt, J=6.6, 15.9 Hz, 1H), 4.84 (s, 2H), 3.35 (d, J=6.6 Hz, 2H), 3.04 (m, 2H), 2.82 (m, 2H), 2.00 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.5, 140.1, 137.7, 136.0, 135.4, 134.8, 133.2, 132.1, 130.2, 128.7, 128.0, 127.8, 127.6, 127.2, 125.1, 124.1, 109.7, 61.1, 48.4, 45.2, 43.0, 33.1. HRMS

(m/z, ESI^+) calcd for $C_{28}H_{26}N_2O^{35}Cl_3$: 511.1111, found 511.1127 and calcd for $C_{28}H_{26}N_2O^{35}Cl_2{}^{37}Cl$: 513.1128, found 513.1103.

*4.5.16. (E)-5-Chloro-1′-(3-(4-chlorophenyl)allyl)-1-(4-nitrobenzyl) spiro[indoline-3,4′-piperidin]-2-one (**39g**).* Prepared following general procedure B. Colourless oil. IR ($CHCl_3$, cm^{-1}) ν 2936, 2822, 1709, 1068, 1530, 1486, 1427, 1348, 1170, 1088. ^1H NMR ($CDCl_3$, 500 MHz) δ 8.14 (d, J=8.1 Hz, 1H), 8.09 (s, 1H), 7.56 (d, J=7.8 Hz, 1H), 7.51 (dd, J=7.8, 8.1 Hz, 1H), 7.38 (d, J=2.0 Hz, 1H), 7.33 (d, J=8.5 Hz, 2H), 7.28 (d, J=8.5 Hz, 2H), 7.16 (dd, J=2.0, 8.3 Hz, 1H), 6.59 (d, J=8.3 Hz, 1H), 6.55 (d, J=15.9 Hz, 1H), 6.34 (dt, J=6.2, 15.9 Hz, 1H), 4.97 (s, 2H), 3.35 (d, 2J=6.2 Hz, 2H), 3.04 (m, 2H), 2.82 (m, 2H), 2.01 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.5, 148.6, 139.6, 137.8, 136.0, 135.3, 133.2, 133.0, 132.1, 130.1, 128.7, 128.3, 127.8, 127.6 (2C), 124.3, 122.9, 121.9, 109.4, 61.1, 48.4, 45.2, 42.8, 33.2. HRMS (m/z, ESI^+) calcd for $C_{28}H_{26}N_3O_3{}^{35}Cl_2$: 522.1351, found 522.1359 and calcd for $C_{28}H_{26}N_3O_3{}^{35}Cl^{37}Cl$: 524.1322, found 524.1348.

*4.5.17. (E)-5-Chloro-1′-(3-(4-chlorophenyl)allyl)spiro [indoline-3,4′-piperidine]-2-thione (**39h**).* To a solution of compound **38** (20.0 mg, 0.052 mmol, 1.0 equiv) in 0.5 mL xylene was added Lawesson's reagent (25 mg, 0.062 mmol, 1.2 equiv) and the reaction mixture was heated at 140 °C for 12 h. After solvent evaporation, crude residue was purified by flash chromatography (SiO_2, Hept/acetone: 9/1) to give the thioamide **39h** (5.2 mg, 25%) as a yellow glue. IR ($CHCl_3$, cm^{-1}) ν 3058, 2939, 2820, 1618, 1593, 1490, 1470, 1454, 1336, 1236, 1162. ^1H NMR ($CDCl_3$, 500 MHz) δ 9.68 (br s, 1H), 7.68 (m, 1H), 7.34–7.26 (m, 5H), 6.94 (d, J=8.3 Hz, 1H), 6.57 (d, J=15.7 Hz, 1H), 6.34 (m, 1H), 3.37 (d, J=6.6 Hz, 2H), 2.65 (m, 2H), 2.36 (m, 2H), 1.64 (m, 4H). HRMS (m/z, ESI^+) calcd for $C_{21}H_{21}N_2S^{35}Cl_2$: 403.0803, found 403.0802.

*4.5.18. (E)-5-Chloro-1′-(3-(4-chlorophenyl)allyl)-1-cyclopropylspiro [indoline-3,4′-piperidin]-2-one (**39i**).* A solution of $Cu(OAc)_2$ (11.7 mg, 0.064 mmol, 1.0 equiv) and bipyridine (10.0 mg, 0.064 mmol, 1.0 equiv) in 0.4 mL DCE was added to a solution of **38** (25 mg, 0.064 mmol, 1.0 equiv), cyclopropyl boronic acid (14.0 mg, 0.16 mmol, 2.5 equiv) and Na_2CO_3 (13.6 mg, 0.13 mmol, 2.0 equiv) in 0.2 mL DCE. Resulting reaction mixture was heated at 70 °C for 1 h 30 min. Reaction was quenched with water, acidified with dilute HCl and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH: 100/1) to give the compound **39i** (8.5 mg, 31%) as colourless oil and starting material **38** (12 mg, 48%) IR ($CHCl_3$, cm^{-1}) ν 2923, 2848, 2364, 1716, 1608, 1485, 1374, 1332. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.33–7.27 (m, 5H), 7.24 (dd, J=2.0, 8.3 Hz), 7.02 (d, J=8.3 Hz, 1H), 6.53 (d, J=15.9 Hz, 1H), 6.34 (m, 1H), 3.33 (m, 2H), 3.01 (m, 2H), 2.76 (m, 2H), 2.61 (m, 1H), 1.90 (m, 4H), 1.06 (m, 2H), 0.87 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.1, 141.7, 135.5, 135.3, 133.2, 132.1, 129.7, 128.7, 128.5, 127.65, 127.58, 123.7, 110.2, 61.0, 48.3, 44.8, 33.0, 22.1, 6.0. HRMS (m/z, ESI^+) calcd for $C_{24}H_{25}N_2O^{35}Cl_2$: 427.1344, found 427.1343.

*4.5.19. (E)-5-Chloro-1′-(3-(4-chlorophenyl)allyl)-1-(4-methoxyphenyl)spiro[indoline-3,4′-piperidin]-2-one (**39j**).* To a degassed solution of oxindole **38** (25 mg, 0.065 mmol, 1.0 equiv) and *p*-methoxyiodobenzene (15.0 mg, 0.065 mmol, 1 equiv) in 0.6 mL of acetonitrile were successively added K_2CO_3 (18 mg, 0.13 mmol, 2 equiv), CuI (1.2 mg, 0.0065 mmol, 0.1 equiv) and dimethylenediamine (1.5 μL, 0.013 mmol, 0.2 equiv) and the reaction mixture was heated at reflux for 20 h. After cooling, reaction was quenched with HCl 1 M and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH: 100/5) to give the compound **39j** (6.7 mg, 21%) as colourless oil. IR ($CHCl_3$, cm^{-1}) ν 2926, 2850, 1720, 1607, 1514, 1481, 1298, 1250, 1170. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38 (d, J=1.8 Hz, 1H), 7.32 (d, J=8.5 Hz, 2H), 7.28 (d, J=8.5 Hz, 2H), 7.26 (d, J=8.8 Hz, 2H), 7.17 (dd, J=1.8, 8.3 Hz, 1H), 7.02 (d, J=8.8 Hz, 2H), 6.69 (d, J=8.3 Hz, 1H), 6.55 (d, J=15.9 Hz, 1H), 6.35 (dt, J=6.6, 15.9 Hz, 1H), 3.85 (s, 3H), 3.35 (d, J=6.6 Hz, 2H), 3.08 (m, 2H), 2.85 (m, 2H), 2.06 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.9, 159.2, 141.6, 135.6, 135.2, 133.3, 128.7, 128.0, 127.8 (2C), 127.7, 127.6, 126.6, 124.0, 114.9, 110.2, 61.0, 55.6, 48.2, 44.9, 33.1. HRMS (m/z, ESI^+) calcd for $C_{28}H_{27}N_2O_2{}^{35}Cl_2$: 493.1450, found 493.1435.

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Supplementary data

Copies of NMR spectra. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.09.056. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

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