**General Experimental**

Thin Layer Chromatography (TLC) was carried out using aluminium plates coated with 60 F254 silica gel. Plates were visualised using UV light (254 or 365 nm) unless otherwise stated. Automated flash chromatography was carried out on a Biotage Isolera One flash column chromatography system (LPLC), using Biotage® SNAP KP-Sil cartridges (unless otherwise state).

NMR spectra were recorded using a Bruker Avance 400 MHz spectrometer using the indicated deuterated solvent. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the residual solvent peak. Multiplicities are denoted as s- singlet, d- doublet, t- triplet and q- quartet, and derivatives thereof. Coupling constants are recorded in Hz and rounded to the nearest 0.1 Hz. Two-dimensional NMR experiments (COSY, HSQC) were used to aid the assignment of 1H and 13C spectra. Atom numbering in structures is purely for the purposes of assignment and does not reflect IUPAC numbering conventions.



**Scheme 1;** Full synthesis of VinSpinIn and VinSpinIC.

**2-(4-(Benzyloxy)-3-methoxyphenyl)-2-methylpropanenitrile (1);**



A solution of the 2-(4-(benzyloxy)-3-methoxyphenyl)acetonitrile (1.387 g, 5.48 mmol, 1 eq) and sodium hydroxide (aq. 50 wt%, 1.752 g, 21.90 mmol, 4 eq) in DMSO (10 mL) were cooled to 0 ᵒC. Iodomethane (1.364 ml, 21.90 mmol, 4 eq) was added dropwise and the mixture was stirred at room temperature for 1 h after the addition.

The mixture was diluted with water (100 mL) and the product was extracted with toluene (3 x 30 mL), dried (Na2SO4) and evaporated to give the title compound (1.508 g, 5.36 mmol, 98%) as a yellow oil.

1H NMR (400 MHz, CDCl3) δ 7.45-7.29 (m, 5H, Ph), 7.01 (d, *J* = 2.2 Hz, 1H, Ar-*H*), 6.92 (dd, *J* = 8.4, 2.2 Hz, 1H, Ar-*H*), 6.87 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 5.15 (s, 2H, PhC*H*2), 3.92 (s, 3H, OC*H*3), 1.70 (s, 6H, 2C*H*3); 13C NMR (100 MHz, CDCl3) δ 149.8, 147.7, 136.9, 134.5 (4 x Ar-*C*), 128.6, 127.9, 127.2 (3 x Ph-*C*H), 124.7 (*C*), 117.1, 113.9, 109.4 (3 x Ar-*C*H), 71.1 (Ph-*C*H2), 56.2 (O*C*H3), 36.8 (*C*), 29.3 (2*C*H3).

**2-(4-(Benzyloxy)-5-methoxy-2-nitrophenyl)-2-methylpropanenitrile (2);**



A solution of 2-(4-(benzyloxy)-3-methoxyphenyl)-2-methylpropanenitrile (1.500 g, 5.33 mmol, 1 eq), in 1:1 acetic acid:acetic anhydride (5 mL), was added dropwise to a solution of glacial acetic acid (5 mL), acetic anhydride (5 mL) and nitric acid (70%, 5 mL), maintaining the internal temperature of the reaction between 0 and -5°C. The mixture was stirred at 0 °C for approx. 30 min after the addition. The reaction mixture was poured over crushed ice and stirred vigorously for approx. 10 mins. The product was isolated by filtration and rinsed thoroughly with cold water to give the title compound (1.517 g, 4.65 mmol, 87%) as a pale yellow solid.

1H NMR (400 MHz, CDCl3) δ 7.45-7.31 (m, 6H, Ar-*H*), 7.06 (s, 1H, Ar-*H*), 5.17 (s, 2H, PhC*H*2), 3.98 (s, 3H, OC*H*3), 1.89 (s, 6H, 2C*H*3); 13C NMR (100 MHz, CDCl3) δ 152.5, 147.4, 142.2, 135.4 (4 x Ar-*C*), 128.8, 128.5 (2 x Ph-*C*H), 127.8 (*C*), 127.5 (Ph-*C*H), 123.0 (*C*), 111.1, 110.2 (2 x Ar-*C*H), 71.4 (Ph-*C*H2), 56.5 (O*C*H3), 36.4 (*C*), 28.4 (2*C*H3).

**2-(4-(Benzyloxy)-5-hydroxy-2-nitrophenyl)-2-methylpropanenitrile (3);**



Dodecane-1-thiol (2.64 ml, 11.03 mmol, 2.4 eq) was added to a solution of potassium *tert*-butoxide (1.289 g, 11.49 mmol, 2.5 eq) in dry DMF (10 mL) under N2, which resulted in a heavy white precipitate. The mixture was cooled in an ice bath and a solution of 2-(4-(benzyloxy)-5-methoxy-2-nitrophenyl)-2-methylpropanenitrile (1.5 g, 4.60 mmol, 1 eq) in dry DMF (10 mL) was added dropwise maintaining the temperature at 0 °C. After the addition, the mixture was heated to 50 °C for approx. 2 hours and monitored by TLC.

Solid sodium hydrogen sulfate (2.207 g, 18.39 mmol, 4 eq) was added to the cooled reaction mixture and the solvent was evaporated. The residue was purified by automated flash chromatography using 50-100% DCM in cyclohexane as eluent, to give the title compound (1.129 g, 3.61 mmol, 79%) as a yellow oil.

1H NMR (400 MHz, CDCl3) δ 7.51 (s, 1H, Ar-*H*), 7.47-7.36 (m, 5H, Ph), 7.12 (s, 1H, Ar-*H*), 5.17 (s, 2H, PhC*H*2), 1.87 (s, 6H, 2C*H*3); 13C NMR (100 MHz, CDCl3) δ 149.6, 144.7, 141.9, 134.6, 129.2 (5 x Ar-*C*), 129.1, 129.0, 128.2, (3 x Ph-*C*H), 122.6 (*C*), 113.5, 110.3 (2 x Ar-*C*H), 71.9 (Ph-*C*H2), 36.4 (*C*), 28.8 (2*C*H3).

**2-(4-(Benzyloxy)-5-(cyclopropylmethoxy)-2-nitrophenyl)-2-methylpropanenitrile (4);**



2-(4-(Benzyloxy)-5-hydroxy-2-nitrophenyl)-2-methylpropanenitrile (1.118 g, 3.58 mmol, 1 eq), potassium carbonate (0.989 g, 7.16 mmol, 2 eq) and (bromomethyl)cyclopropane (0.521 ml, 5.37 mmol, 1.5 eq) were heated in acetonitrile (ACN, 25 mL) at 80 °C overnight. The cooled reaction mixture was evaporated and the residue was purified by automated flash chromatography using a gradient elution of 50-100% DCM in cyclohexane, to give the title compound (1.206 g, 3.29 mmol, 92%) as a yellow solid.

1H NMR (400 MHz, CDCl3) δ 7.46-7.31 (m, 6H, Ar-*H*), 7.07 (s, 1H, Ar-*H*), 5.18 (s, 2H, PhC*H*2), 3.98 (d, *J* = 6.9 Hz, 2H, OC*H*2), 1.87 (s, 6H, 2C*H*3), 1.37-1.28 (m, 1H, C*H*), 0.71-0.66 (m, 2H, C*H*H-C*H*H), 0.42-0.38 (m, 2H, CH*H*-CH*H*); 13C NMR (100 MHz, CDCl3) δ 152.3, 147.8, 142.3, 135.7 (4 x Ar-*C*), 128.7, 128.4 (2 x Ph-*C*H), 127.9 (*C*), 127.3 (Ph-*C*H), 123.0 (*C*), 112.4, 112.0 (2 x Ar-*C*H), 74.6 (O*C*H2), 71.5 (Ph-*C*H2), 36.3 (*C*), 28.4 (2*C*H3), 10.1 (*C*H), 3.5 (*C*H2*C*H2).

**2-(5-(Cyclopropylmethoxy)-4-hydroxy-2-nitrophenyl)-2-methylpropanenitrile (5);**



Palladium (10% on carbon (50% wet), 200 mg) was added to a solution of 2-(4-(benzyloxy)-5-(cyclopropylmethoxy)-2-nitrophenyl)-2-methylpropanenitrile (0.971 g, 2.65 mmol, 1 eq) in 9:1 EtOAc:EtOH (50 mL). The system was flushed with N2, followed by H2 and the mixture was stirred at room temperature under H2. The reaction was monitored closely by TLC and was complete in approximately 30 min. The catalyst was removed by filtration through a bed of celite and the solvent was evaporated. The residue was purified by automated flash chromatography using a gradient elution of 0-10% MeOH in DCM, to give the title compound (0.699 g, 2.53 mmol, 95%) as a yellow oil.

1H NMR (400 MHz, CDCl3) δ 7.36 (s, 1H, Ar-*H*), 7.02 (s, 1H, Ar-*H*), 3.98 (d, *J* = 7.2 Hz, 2H, OC*H*2), 1.86 (s, 6H, 2C*H*3), 1.36-1.24 (m, 1H, C*H*), 0.74-0.70 (m, 2H, C*H*H-C*H*H), 0.42-0.39 (m, 2H, CH*H*-CH*H*); 13C NMR (100 MHz, CDCl3) δ 148.8, 145.4, 142.9, 126.3, 123.2 (5 x *C*), 112.4, 110.4 (2 x Ar-*C*H), 74.7 (O*C*H2), 36.6 (*C*), 28.3 (2*C*H3), 10.0 (*C*H), 3.5 (*C*H2*C*H2).

**2-(4-(3-Chloropropoxy)-5-(cyclopropylmethoxy)-2-nitrophenyl)-2-methylpropanenitrile (6);**



2-(5-(Cyclopropylmethoxy)-4-hydroxy-2-nitrophenyl)-2-methylpropanenitrile (0.783 g, 2.83 mmol, 1 eq), potassium carbonate (0.783 g, 5.67 mmol, 2 eq) and 1-bromo-3-chloropropane (0.419 ml, 4.25 mmol, 1.5 eq) were heated in ACN (25 mL) at 80 °C overnight. The cooled reaction mixture was evaporated and the residue was purified by automated flash chromatography using a gradient elution of 50-100% DCM in cyclohexane, to give the title compound (0.985 g, 2.79 mmol, 99%) as a yellow solid.

1H NMR (400 MHz, CDCl3) δ 7.37 (s, 1H, Ar-*H*), 7.03 (s, 1H, Ar-*H*), 4.20 (t, *J* = 5.8 Hz, 2H, ClCH2CH2C*H*2O-), 3.94 (d, *J* = 6.8 Hz, 2H, OC*H*2), 3.77 (t, *J* = 6.2 Hz, 2H, ClC*H*2CH2CH2O-), 2.32-2.26 (m, 2H, ClCH2C*H*2CH2O-), 1.86 (s, 6H, 2C*H*3), 1.34-1.23 (m, 1H, C*H*), 0.69-0.65 (m, 2H, C*H*H-C*H*H), 0.40-0.36 (m, 2H, CH*H*-CH*H*); 13C NMR (100 MHz, CDCl3) δ 152.2, 147.9, 142.3, 127.9, 123.0 (5 x *C*), 112.2, 111.3 (2 x Ar-*C*H), 74.4 (O*C*H2), 66.2 (ClCH2CH2*C*H2O-), 41.2 (Cl*C*H2CH2CH2O-), 36.2 (*C*), 31.9 (ClCH2*C*H2CH2O-), 28.5 (2*C*H3), 10.1 (*C*H), 3.4 (*C*H2*C*H2).

**2-(4-(4-Chlorobutoxy)-5-(cyclopropylmethoxy)-2-nitrophenyl)-2-methylpropanenitrile (7);**



2-(5-(Cyclopropylmethoxy)-4-hydroxy-2-nitrophenyl)-2-methylpropanenitrile (0.754 g, 2.73 mmol, 1 eq), potassium carbonate (0.754 g, 5.46 mmol, 2 eq) and 1-bromo-4-chlorobutane (0.472 ml, 4.09 mmol, 1.5 eq) were heated in ACN (25 mL) at 80 °C overnight. The cooled reaction mixture was evaporated and the residue was purified by automated flash chromatography using a gradient elution of 50-100% DCM in cyclohexane, to give the title compound (0.997 g, 2.72 mmol, 100%) as a yellow solid.

1H NMR (400 MHz, CDCl3) δ 7.33 (s, 1H, Ar-*H*), 7.03 (s, 1H, Ar-*H*), 4.09 (t, *J* = 5.8 Hz, 2H, ClCH2CH2CH2C*H*2O-), 3.94 (d, *J* = 6.9 Hz, 2H, OC*H*2), 3.66 (t, *J* = 6.3 Hz, 2H, ClC*H*2CH2CH2CH2O-), 2.03-1.98 (m, 4H, ClCH2C*H*2C*H*2CH2O-), 1.87 (s, 6H, 2C*H*3), 1.35-1.25 (m, 1H, C*H*), 0.71-0.65 (m, 2H, C*H*H-C*H*H), 0.41-0.36 (m, 2H, CH*H*-CH*H*); 13C NMR (100 MHz, CDCl3) δ 152.0, 148.1, 141.3, 127.6, 123.0 (5 x *C*), 112.1, 110.9 (2 x Ar-*C*H), 74.4 (O*C*H2), 69.0 (ClCH2CH2CH2*C*H2O-), 44.6 (Cl*C*H2CH2CH2CH2O-), 36.3 (*C*), 29.4 (ClCH2CH2*C*H2CH2O-), 28.4 (2*C*H3), 26.3 (ClCH2*C*H2CH2CH2O-), 10.1 (*C*H), 3.4 (*C*H2*C*H2).

**5-(But-3-yn-1-yloxy)isoindolines (8);**



But-3-yn-1-ol (0.386 ml, 5.10 mmol, 1.2 eq) was added to a solution of *tert*-butyl 5-hydroxyisoindoline-2-carboxylate (1.000 g, 4.25 mmol, 1 eq) and triphenylphosphine (1.115 g, 4.25 mmol, 1 eq) in dry THF (20 mL) under N2. The solution was cooled to 0 °C and diethyl azodicarboxylate (DEAD, 0.669 ml, 4.25 mmol, 1 eq) was added. The solution was heated at 60 °C for 5 h. The solvent was evaporated and the residue was purified by automated flash chromatography using a gradient elution of 50-100% DCM in cyclohexane (and using Seebach’s stain to visualise the product) to give the Boc protected intermediate (0.509 g, 1.77 mmol, 42%) as a colourless oil.

Trifluoroacetic acid (TFA, 2 mL) was added to a solution of the Boc protected intermediate in dry DCM (20 mL) and the reaction was stirred at room temperature for approximately 2 h. The solvent was evaporated and the residue was purified by automated flash chromatography using a gradient elution of 0-10% of {7 N NH3 in MeOH} in DCM (and using ninhydrin stain to visualise the product) to give the title compound (0.302 g, 1.61 mmol, 91% (38% overall)) as a brown solid.

1H NMR (400 MHz, CDCl3) δ 7.13 (d, *J* = 8.2 Hz, 1H, Ar-*H*), 6.83-6.72 (m, 2H, Ar-*H*), 4.2 (s, 2H, C*H*2NCH2), 4.18 (s, 2H, CH2NC*H*2), 4.08 (t, *J* = 7.0 Hz, 2H, OC*H*2CH2CCH), 2.67 (td, *J* = 7.0, 2.7 Hz, 2H, OCH2C*H*2CCH), 2.04 (t, *J* = 2.7 Hz, 1H, OCH2CH2CC*H*); 13C NMR (100 MHz, CDCl3) δ 157.9, 143.3, 134.1 (3 x Ar-*C*), 122.9, 113.6, 108.7 (3 x Ar-*C*H), 80.5 (OCH2CH2*C*CH), 69.9 (OCH2CH2C*C*H), 66.3 (O*C*H2CH2CCH), 53.1, 52.3 (*C*H2N*C*H2), 19.6 (OCH2*C*H2CCH).

**5-(Prop-2-yn-1-yloxy)isoindolines (9);**



Propargyl bromide (80 wt% in toluene, 0.302 ml, 2.81 mmol, 1.1 eq) was added to a stirring mixture of tert-butyl 5-hydroxyisoindoline-2-carboxylate (0.600 g, 2.55 mmol, 1 eq) and potassium carbonate (0.705 g, 5.10 mmol, 2 eq) in ACN, and the mixture was stirred at 40 °C overnight. The solvent was evaporated and the residue was purified by automated flash chromatography using a gradient elution of 0-5% MeOH in DCM (and using Seebach’s stain to visualise the product) to give the Boc protected intermediate (0.630 g, 2.30 mmol, 90%) as a colourless oil.

TFA (2 mL) was added to a solution of the Boc protected intermediate in dry DCM (20 mL) and the reaction was stirred at room temperature for approximately 2 h. The solvent was evaporated and the residue was purified by automated flash chromatography using a gradient elution of 0-10% of {7 N NH3 in MeOH} in DCM (and using ninhydrin stain to visualise the product) to give the title compound (0.413 g, 2.38 mmol, 93% (84% overall)) as a brown solid.

1H NMR (400 MHz, CDCl3) δ 7.15 (d, *J* = 8.2 Hz, 1H, Ar-*H*), 6.90-6.79 (m, 2H, Ar-*H*), 4.68 (d, *J* = 2.4 Hz, 2H, OC*H*2CCH), 4.22 (s, 2H, C*H*2NCH2), 4.19 (s, 2H, CH2NC*H*2), 2.51 (t, *J* = 2.4 Hz, 1H, OCH2CC*H*); 13C NMR (100 MHz, CDCl3) δ 157.0, 143.2, 134.5 (3 x Ar-*C*), 122.9, 113.9, 109.0 (3 x Ar-*C*H), 78.7 (OCH2*C*CH), 75.5 (OCH2C*C*H), 56.1 (O*C*H2CCH), 53.0, 52.3 (*C*H2N*C*H2).

**2-(4-(3-(5-(But-3-yn-1-yloxy)isoindolin-2-yl)propoxy)-5-(cyclopropylmethoxy)-2-nitrophenyl)-2-methylpropanenitrile (10);**



2-(4-(3-Chloropropoxy)-5-(cyclopropylmethoxy)-2-nitrophenyl)-2-methylpropanenitrile (0.315 g, 0.89 mmol, 1 eq), potassium iodide (0.297 g, 1.79 mmol, 2 eq), potassium carbonate (0.371 g, 2.68 mmol, 3 eq), and 5-(but-3-yn-1-yloxy)isoindoline (0.251 g, 1.34 mmol, 1.5 eq) were heated in ACN (20 mL) at 80 °C for 48 h. The cooled reaction mixture was evaporated and the residue was purified by automated flash chromatography using a gradient elution of 0-5% MeOH in DCM, to give the title compound (0.442 g, 0.89 mmol, 98%) as a brown oil.

1H NMR (400 MHz, CDCl3) δ 7.38 (s, 1H, Ar-*H*), 7.10 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.03 (s, 1H, Ar-*H*), 6.79-6.74 (m, 2H, Ar-*H*), 4.19 (t, *J* = 6.4 Hz, 2H, NCH2CH2C*H*2O), 4.07 (t, *J* = 7.1 Hz, 2H, OC*H*2CH2CCH), 3.98-3.90 (m, 6H, OC*H*2, C*H*2NC*H*2), 2.94 (t, *J* = 7.0 Hz, 2H, NC*H*2CH2CH2O), 2.66 (td, *J* = 7.0, 2.7 Hz, 2H, OCH2C*H*2CCH), 2.17-2.11 (m, 2H, NCH2C*H*2CH2O), 2.03 (t, J = 2.7 Hz, 1H, OCH2CH2CC*H*), 1.87 (s, 6H, 2C*H*3), 1.36-1.25 (m, 1H, C*H*), 0.70-0.65 (m, 2H, C*H*H-C*H*H), 0.42-0.38 (m, 2H, CH*H*-CH*H*); 13C NMR (100 MHz, CDCl3) δ 157.9, 151.9, 148.3, 142.5, 141.0, 132.1, 127.3, 123.1 (7 x Ar-*C*), 123.0, 113.6, 112.5, 111.0, 109.0 (5 x Ar-*C*H), 80.4 (OCH2CH2*C*CH), 74.5 (O*C*H2), 69.9 (OCH2CH2C*C*H), 67.7 (NCH2CH2*C*H2O), 66.4 (O*C*H2CH2CCH), 59.3, 58.5 (*C*H2N*C*H2), 52.5 (N*C*H2CH2CH2O), 36.3 (*C*), 28.4 (2*C*H3), 28.2 (NCH2*C*H2CH2O), 19.5 (OCH2*C*H2CCH), 10.1 (*C*H), 3.4 (*C*H2*C*H2).

**2-(5-(Cyclopropylmethoxy)-2-nitro-4-(4-(5-(prop-2-yn-1-yloxy)isoindolin-2-yl)butoxy)phenyl)-2-methylpropanenitrile (11);**



2-(4-(4-Chlorobutoxy)-5-(cyclopropylmethoxy)-2-nitrophenyl)-2-methylpropanenitrile (0.997 g, 2.72 mmol, 1 eq), potassium iodide (0.902 g, 5.44 mmol 2 eq), potassium carbonate (1.127 g, 8.15 mmol, 3 eq) and 5-(prop-2-yn-1-yloxy)isoindoline (0.706 g, 4.08 mmol, 1.5) were heated in ACN (20 mL) at 80 °C for 48 h. The cooled reaction mixture was evaporated and the residue was purified by automated flash chromatography using a gradient elution of 0-5% MeOH in DCM, to give the title compound (0.767 g, 1.52 mmol, 56%) as a brown oil.

1H NMR (400 MHz, CDCl3) δ 7.34 (s, 1H, Ar-*H*), 7.11 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.03 (s, 1H, Ar-*H*), 6.86-6.78 (m, 2H, Ar-*H*), 4.67 (d, *J* = 2.4 Hz, 2H, OC*H*2CCH), 410 (t, *J* = 6.4 Hz, 2 H, NCH2CH2CH2C*H*2O), 3.98-3.85 (m, 6H, OC*H*2, C*H*2NC*H*2), 2.81 (t, *J* = 7.2 Hz, 2H, NC*H*2CH2CH2CH2O), 2.50 (t, *J* = 2.4 Hz, 1H, OCH2CC*H*), 2.0-1.94 (m, 2H, NCH2CH2C*H*2CH2O), 1.87 (s, 6H, 2C*H*3), 1.82-1.74 (m, 2H, NCH2C*H*2CH2CH2O), 1.36-1.26 (m, 1H, C*H*), 0.70-0.63 (m, 2H, C*H*H-C*H*H), 0.42-0.38 (m, 2H, CH*H*-CH*H*); 13C NMR (100 MHz, CDCl3) δ 156.9, 151.9, 148.3, 142.4, 141.4, 133.0, 127.2, 123.1 (7 x Ar-*C*), 123.0, 113.7, 112.3, 110.7, 109.2 (5 x Ar-*C*H), 79.0 (OCH2*C*CH), 75.4 (OCH2C*C*H), 74.4 (O*C*H2), 69.4 (NCH2CH2*C*H2O), 59.2, 58.4 (*C*H2N*C*H2), 56.1 (OCH2C*C*H), 55.6 (N*C*H2CH2CH2CH2O), 36.3 (*C*), 28.4 (2*C*H3), 26.7, 25.2 (NCH2*C*H2*C*H2CH2O), 10.2 (*C*H), 3.4 (*C*H2*C*H2).

**2-Azido-1-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)ethan-1-one (12);**



2-Azidoacetic acid (0.23 ml, 3.03 mmol, 1.3 eq) was added to a stirring solution of *p*-toluenesulfonyl chloride (0.489 g, 2.57 mmol, 1.1 eq) and resin bound DIPEA (3 mmol/g, 2.333 g, 3 eq) in dry DCM (20 mL), and the mixture was stirred a room temperature for 1 h. 4-(2-(Pyrrolidin-1-yl)ethyl)piperidine (0.425 g, 2.333 mmol, 1 eq) was added and the mixture was stirred for a further 1 h. The mixture was filtered, and the filtrate was washed with Na2CO3 (1 M, 50 mL) and dried (Na2SO4) to give the title compound (0.5217 g, 1.966 mmol, 84%) as a yellow solid.

1H NMR (400 MHz, CDCl3) δ 4.55 (d, *J* = 13.3 Hz, 1H, 6 or 4-C*H*H), 3.92 (s, 2H, 15-C*H*2), 3.61 (d, *J* = 13.5 Hz, 1H, 6 or 4-C*H*H), 3.02 (td, *J* = 13.0, 2.8 Hz, 1H, 6 or 4-CH*H*), 2.62 (td, *J* = 12.9, 2.9 Hz, 1H, 6 or 4-CH*H*), 2.55-2.40 (m, 6H, 10,13-C*H*2, 8-C*H*2), 1.84-1.71 (m, 6H, 11,12-C*H*2, 1 or 3-C*H*2), 1.65-1.45 (m, 3H, 2-C*H*, 7-C*H*2), 1.22-1.08 (m, 2H, 1 or 3-C*H*2); 13C NMR (100 MHz, CDCl3) δ 165.3 (14-*C*O), 54.3 (10,13-*C*H2), 53.8 (8-*C*H2), 50.8 (15-*C*H2), 45.4, 42.5 (6-*C*H2, 4-*C*H2), 35.4 (7-*C*H2), 34.3 (2-*C*H), 32.8, 31.8 (1-*C*H2, 3-*C*H2), 23.4 (11,12-*C*H2).

**VinSpinIn (13);**

**2-(4-(2-((2-(3-((2-Amino-5-(cyclopropylmethoxy)-3,3-dimethyl-3H-indol-6-yl)oxy)propyl)isoindolin-5-yl)oxy)ethyl)-1H-1,2,3-triazol-1-yl)-1-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)ethan-1-one;**



2-(4-(3-(5-(But-3-yn-1-yloxy)isoindolin-2-yl)propoxy)-5-(cyclopropylmethoxy)-2-nitrophenyl)-2-methylpropanenitrile (86 mg, 0.17 mmol, 1 eq), 2-azido-1-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)ethan-1-one (91 mg, 0.34 mmol, 2 eq) and copper powder (271 mg, 4.27 mmol, 25 eq) were heated in DMF (4 mL) at 60 °C, under N2, until all the alkyne starting material had been consumed (approx. 2 h). The cooled reaction mixture was evaporated and the residue was purified by automated flash chromatography using a gradient elution of 0-10% of {7 N NH3 in MeOH} in DCM to give the triazole nitro intermediate (47 mg, 0.06 mmol, 36%) as a colourless oil.

Zinc (112 mg, 1.71 mmol, 10 eq) was added to the triazole nitro intermediate and the mixture was stirred vigorously in glacial acetic acid (4 mL) at 110 °C for 2 h. The acetic acid was evaporated and the residue was dissolved in DCM (2 mL). Solid potassium carbonate (0.236 g, 1.71 mmol, 10 eq) was added and the mixture was stirred vigorously until CO2 was no longer liberated. The mixture was directly loaded onto a Biotage® SNAP KP-NH column and the product was eluted with an eluent of 0-10% MeOH in DCM, to give the title compound (33 mg, 0.05 mmol, 73% (26% overall)) as a colourless oil which solidified on standing.

1H NMR (400 MHz, CDCl3) δ 7.62 (s, 1H, Ar-*H*), 7.06 (d, *J* = 6.5 Hz, 1H, Ar-*H*), 6.82 (s, 1H, Ar-*H*), 6.78-6.70 (m, 3H, Ar-*H*), 5.24-5.14 (m, 2H, 33-C*H*2), 4.51 (d, *J* = 13.4 Hz, 1H, 37 or 41-CH*H*), 4.22 (t, *J* = 6.5 Hz, 2H, 26-C*H*2), 4.11 (t, *J* = 6.3 Hz, 2H, 13-C*H*2), 3.93-3.76 (m, 7H, 17-C*H*2, 20-C*H*2, 9-C*H*2, 37 or 41-C*H*H), 3.21 (t, *J* = 6.5 Hz, 2H, 27-C*H*2), 3.09 (td, *J* = 13.2, 2.5 Hz, 1H, 37 or 41-C*H*H), 2.91 (t, *J* = 7.3 Hz, 2H, 15-C*H*2), 2.63 (td, *J* = 12.9, 2.6 Hz, 1H, 37 or 41-CH*H*), 2.53-2.41 (m, 6H, 45,48-C*H*2, 43-C*H*2), 2.13-2.03 (m, 2H, 14-C*H*2), 1.84-1.70 (m, 6H, 46,47-C*H*2, 38 or 40-C*H*2), 1.66-1.53 (m, 1H, 39-C*H*), 1.52-1.42 (m, 2H, 42-CH2), 1.35-1.21 (m, 7H, 53,52-CH3, 10-C*H*), 1.19-1.04 (m, 2H, 38 or 40-CH2), 0.62-0.54 (m, 2H, 11,12-C*H*H), 0.36-0.27 (m, 2H, 11,12-CH*H*); 13C NMR (100 MHz, CDCl3) δ 179.3 (50-C), 163.2, 158.0, 150.0, 148.3, 144.9, 144.2, 141.7, 133.3, 132.5, (9 x *C*), 123.5, 122.9, 113.2, 111.4, 108.8, 103.6 (6 x Ar-*C*H), 76.3 (9-*C*H2), 67.6 (13-*C*H2), 67.0 (26-*C*H2), 59.4, 58.6 (17,20-*C*H2), 54.3 (45,48-*C*H2), 53.7 (43-*C*H2), 53.0 (15-*C*H2), 51.1 (33-*C*H2), 48.7 (51-*C*), 45.7, 42.7 (37,41-*C*H2), 35.3 (42-*C*H2), 34.2 (39-*C*H), 32.6, 31.7 (38,40-*C*H2), 29.0 (14-*C*H2), 26.4 (27-*C*H2), 25.1 (52,53-*C*H3), 23.4 (46,47-*C*H2), 10.8 (10-*C*H), 3.2 (11,12-CH2).

**VinSpinIC (14);**

**2-(4-(((2-(4-((2-Amino-5-(cyclopropylmethoxy)-3,3-dimethyl-3H-indol-6-yl)oxy)butyl)isoindolin-5-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-1-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)ethan-1-one;**



2-(5-(Cyclopropylmethoxy)-2-nitro-4-(4-(5-(prop-2-yn-1-yloxy)isoindolin-2-yl)butoxy)phenyl)-2-methylpropanenitrile (64 mg, 0.13 mmol, 1 eq), 2-azido-1-(4-(2-(pyrrolidin-1-yl)ethyl)piperidin-1-yl)ethan-1-one (67.4 mg, 0.25 mmol, 2 eq) and copper powder (202 mg, 3.18 mmol, 25 eq) were heated in DMF (4 mL) at 60 °C, under N2, until all the alkyne starting material had been consumed (approx. 2 h). The cooled reaction mixture was evaporated and the residue was purified by automated flash chromatography using a gradient elution of 0-10% of {7 N NH3 in MeOH} in DCM to give the triazole nitro intermediate (70 mg, 0.09 mmol, 71%) as a colourless oil.

Zinc (83 mg, 1.27 mmol, 10 eq) was added to the triazole nitro intermediate and the mixture was stirred vigorously in glacial acetic acid (4 mL) at 110 °C for 2 h. The acetic acid was evaporated and the residue was dissolved in DCM (2 mL). Solid potassium carbonate (0.176 g, 1.27 mmol, 10 eq) was added and the mixture was stirred vigorously until CO2 was no longer liberated. The mixture was directly loaded onto a Biotage® SNAP KP-NH column and the product was eluted with an eluent of 0-10% MeOH in DCM, to give the title compound (51 mg, 0.07 mmol, 76% (54% overall)) as a colourless oil which solidified on standing.

1H NMR (400 MHz, CDCl3) δ 7.78 (s, 1H, Ar-*H*), 7.07 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.83-6.76 (m, 4H, Ar-*H*), 5.26-5.16 (m, 4H, 33-C*H*2, 26-C*H*2), 4.51 (d, *J* = 13.4 Hz, 1H, 37 or 41-CH*H*), 4.05 (t, *J* = 6.3 Hz, 2H, 13-C*H*2), 3.91-3.77 (m, 7H, 18-C*H*2, 21-C*H*2, 9-C*H*2, 37 or 41-C*H*H), 3.11 (td, *J* = 13.0, 2.8 Hz, 1H, 37 or 41-C*H*H), 2.76 (t, *J* = 7.2 Hz, 2H, 16-C*H*2), 2.65 (td, *J* = 12.9, 2.9 Hz, 1H, 37 or 41-CH*H*), 2.56-2.43 (m, 6H, 45,48-C*H*2, 43-C*H*2), 1.96-1.86 (m, 2H, 14-C*H*2), 1.86-1.70 (m, 8H, 46,47-C*H*2, 15-C*H*2, 38 or 40-C*H*2), 1.67-1.54 (m, 1H, 39-C*H*), 1.54-1.45 (m, 2H, 42-C*H*2), 1.36-1.22 (m, 7H, 53,52-CH3, 10-C*H*), 1.22-1.07 (m, 2H, 38 or 40-CH2), 0.62-0.54 (m, 2H, 11,12-C*H*H), 0.36-0.27 (m, 2H, 11,12-CH*H*); 13C NMR (100 MHz, CDCl3) δ 179.2 (50-C), 162.9, 157.5, 150.1, 147.9, 144.5, 144.3, 141.7, 133.0, 132.9, (9 x *C*), 124.5, 122.9, 113.5, 111.4, 109.1, 103.5 (6 x Ar-*C*H), 76.3 (9-*C*H2), 69.1 (13-*C*H2), 62.3 (26-*C*H2), 59.3, 58.5 (18,21-*C*H2), 55.8 (16-*C*H2), 54.3 (45,48-*C*H2), 53.7 (43-*C*H2), 51.1 (33-*C*H2), 48.7 (51-*C*), 45.7, 42.8 (37,41-*C*H2), 35.2 (42-*C*H2), 34.2 (39-*C*H), 32.6, 31.7 (38,40-*C*H2), 27.3 (14-*C*H2), 25.5 (15-*C*H2), 25.1 (52,53-*C*H3), 23.4 (46,47-*C*H2), 10.8 (10-*C*H), 3.2 (11,12-CH2).