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Synthesis and derivatisation of a novel spiro[1-benzofuran-2,4′-piperidin]-3-one scaffold

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The synthesis of a novel spiro[1-benzofuran-2,4′-piperidin]-3-one scaffold **6** has been achieved in five steps with an overall yield of 47%. The versatility of the spiropiperidine scaffold in the context of library synthesis is exemplified by selective and sequential derivatisation of the amino and aryl bromide functional groups, including the development of multi-step telescope reaction matrices.

Introduction

Since the generalisation of high throughput screening in drug discovery, there has been significant interest in the design of chemical libraries with the goal of identifying new lead compounds for further development.[1–3] Libraries based on privileged structures are considered by many to provide an ideal source of new leads.[4–9] The molecular framework identified is often capable of binding to several diverse biological receptors with good affinity, such that single libraries derived from scaffolds containing these structures may provide promising compounds in diverse therapeutic areas.[4–6] Empirical guidelines for desirable properties of molecular scaffolds have been formulated in order to increase the likelihood of identifying lead compounds with drug-like properties from their libraries.[5] An attractive scaffold should exhibit a balanced polarity profile with a molecular weight in the range of 100–300, depending on the number of available positions for diversification. Obviously the scaffold should be synthetically attainable on a multi-gram scale, and it should carry 1–3 sites with orthogonal reactivity amenable to rapid derivatisation.[5]

Frameworks incorporating spiropiperidine motifs have been labelled as privileged structures,[5–7] and many important examples have been discovered including the well-known painkiller morphine, growth hormone secretagogues (*e.g.* **1** and **5**),[10] NK-2 antagonists (*e.g.* **2**),[11] chemokine receptor antagonists (*e.g.* **3**),[12] and antihypertensive agents (*e.g.* **4**) (Fig. 1).[13] The spirocyclic ring system may be particularly important since its rigidity serves to position the required functional groups appropriately in 3-dimensional space, whilst minimising the number of rotatable bonds and thus increasing the potential for oral bioavailability.[5,14] With this in mind, we reasoned that the furan-3-one containing spiropiperidine **6** would provide an attractive conformationally constrained scaffold possessing a capacity for selective single, double, or triple substitution with appropriate reagents to provide a host of derivatised spirocycles (Fig. 2).

In this paper, we describe a convenient synthesis of the spiropiperidine scaffold **6** and go on to demonstrate its facile elaboration by selective reactions of the amino, aryl bromide and carbonyl functionalities.

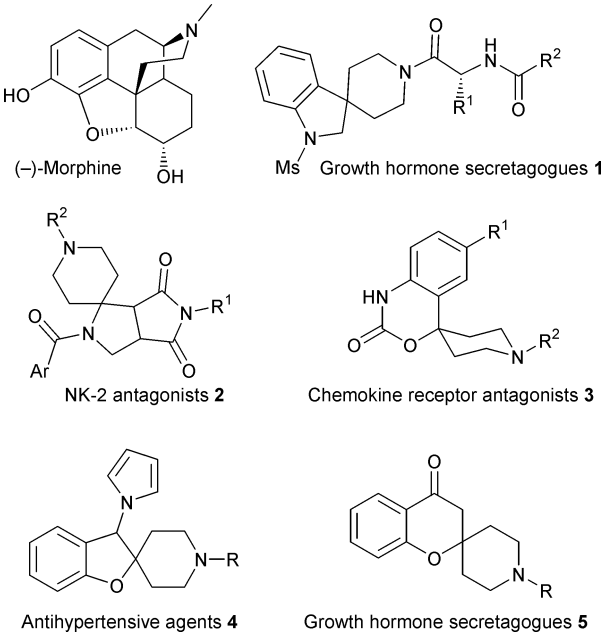


Fig. 1 Biologically active spiropiperidines.

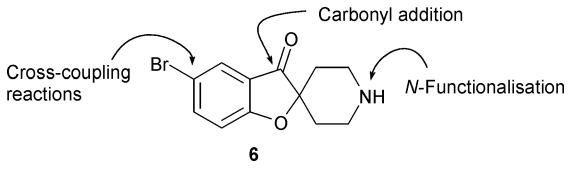
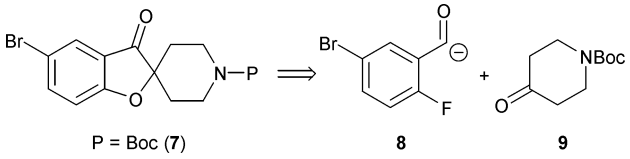


Fig. 2 Spiro[1-benzofuran-2,4′-piperidin]-3-one scaffold.



Scheme 1 Synthetic approach to spiropiperidine scaffold.

Results and discussion

Our analysis of the *N*-protected spiropiperidine scaffold **7** led us to consider a synthetic approach involving the use of an acyl anion equivalent to form the benzylic C–C bond (Scheme 1). Closure of the dihydrofuran ring could then be achieved *via* an intramolecular S_NAr reaction. Following this general strategy, the synthesis of **6** was achieved in five steps with an overall yield of 47% (Scheme 2). Thus 5-bromo-2-fluorobenzaldehyde was first converted to its corresponding dithiane **10** to facilitate formation of an acyl anion equivalent. The formation of the dithiane anion deserves some discussion as deprotonation of **10** at −78 °C using LDA led to metallation of the aromatic

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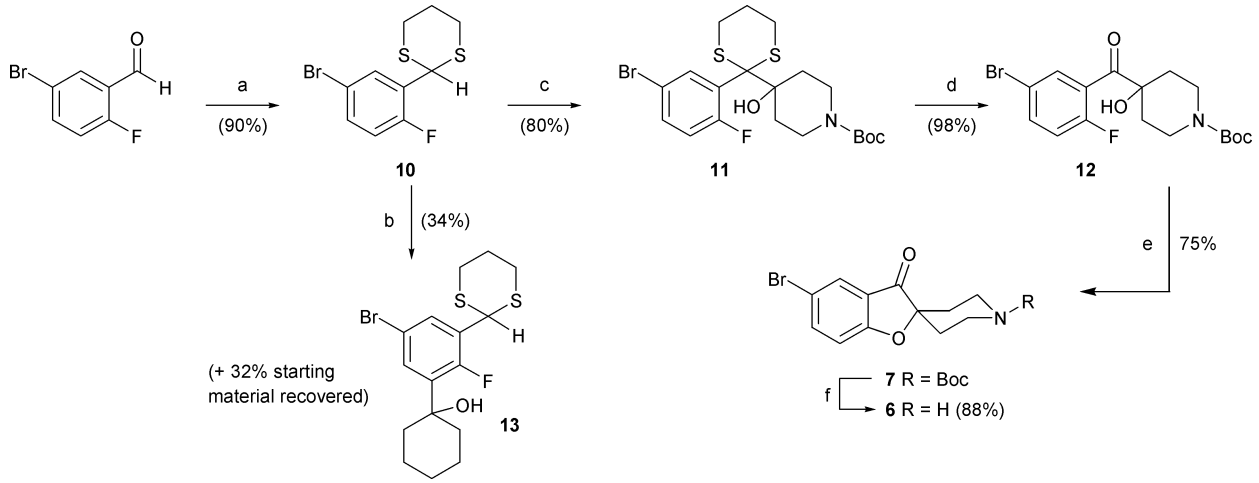
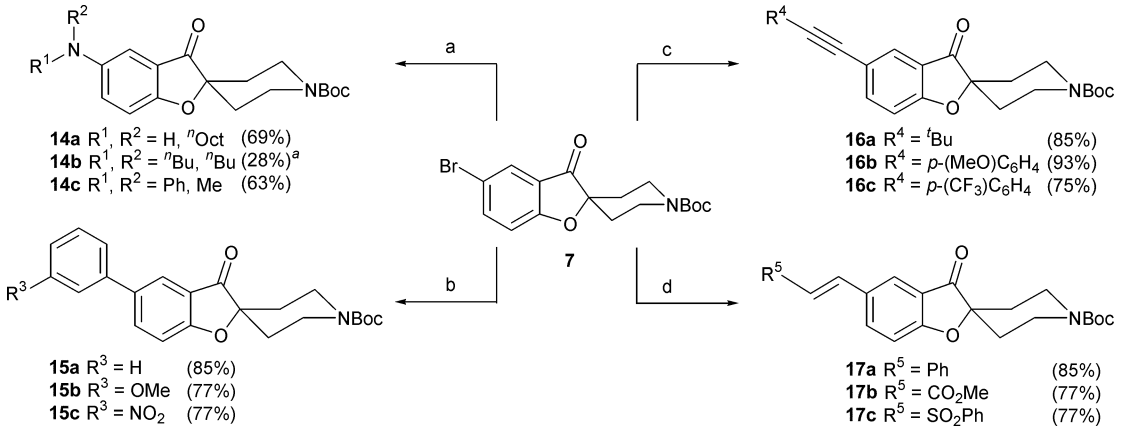


Scheme 2 *Reagents and conditions*: a) 1,3-propanedithiol, 0.03 eq I_2, $CHCl_3$; b) LDA, −78 °C, cyclohexanone, THF; c) LDA, −20 °C, **9**, THF; d) $C_5H_5N{\cdot}HBr{\cdot}Br_2$, pyridine, TBAB, H_2O, DCM; e) ^{t}BuOK, THF, 70 °C, 5 min (μw); f) TFA, DCM, 140 °C, 20 min, (μw).



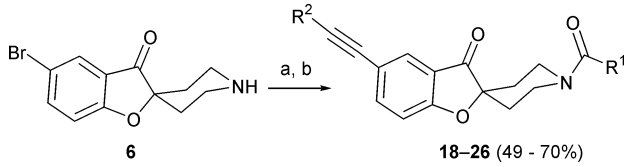
Scheme 3 *Reagents and conditions*: a) HNR_1R_2, $Pd_2(dba)_3$, BINAP, ^{t}BuOK, PhMe, 100 °C, 1 h, (μw); b) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, PhMe/EtOH/H_2O (5 : 5 : 2), 110 °C, 10 min, (μw); c) R_4CCH, $Pd(PPh_3)_2Cl_2$, CuI, NEt_3, 120 °C, 20 min (μw); d) R_5CHCH_2, $Pd(OAc)_2$, P(*o*-tol)$_3$, NEt_3, DMF, 100 °C, 18 h. [a](42% Debrominated starting material recovered).

ring adjacent to the fluorine substituent.[15] On warming the reaction mixture to −20 °C, the aryl lithium intermediate underwent equilibration to the thermodynamically preferred dithiane anion. Evidence for kinetic *ortho*-lithiation came from the isolation of 1-aryl-1-cyclohexanol **13** when the lithiation was carried out at −78 °C prior to the addition of cyclohexanone at the same temperature. The required lithiated dithiane anion was ultimately reacted with *N*-Boc-4-piperidone (**9**) to afford the tricycle **11**, which on treatment with pyridinium tribromide unmasked the carbonyl group to give ketone **12** in excellent yield.[16] The synthesis of the *N*-Boc protected scaffold **7** was completed by an extremely facile intramolecular ring closure through nucleophilic aromatic substitution of the fluoro group. In contrast, attempted cyclisation of the protected ketone **11** in the presence of ^{t}BuOK at elevated temperature led to expulsion of the dithiane anion, returning compounds **9** and **10**. The deprotected scaffold **6** was obtained in good yield following removal of the *N*-Boc group from **7** using TFA at 140 °C. The deprotection could be carried at room temperature, but was found to be rather sluggish.

With a scalable multi-gram synthesis of spiropiperidine **6** completed, attention turned to elaboration of the scaffold by derivatisation at each of three functional groups (the aryl bromide, ketone, and amine). A variety of palladium-catalysed C–C bond-forming reactions (Suzuki, Sonogashira, Heck) of the aryl bromide functionality were found to proceed readily under microwave irradiation, affording substituted spirocycles in good to excellent yield (Scheme 3).[17] Palladium-catalysed amination proved to be more challenging, but was ultimately effective using the $Pd_2(dba)_3$/BINAP/NaO^{t}Bu system to secure the desired anilines **14a–c**, even with the problematic 2° amine ^{n}Bu$_2$NH.[18,19] In the latter case reduction of the aryl bromide was observed as a significant side reaction.

Confident that the piperidine nitrogen could be acylated without problems, we chose to combine the *N*-functionalisation chemistry with a Sonogashira cross-coupling reaction in order to develop a one-pot sequential derivatisation of the spiropiperidine scaffold **6**. This technique of "telescoping" would provide quick and efficient access to a collection of potential drug candidates, and would constitute a valuable asset to library synthesis.

We elected to carry out three separate *N*-acylation reactions first, employing a slight excess of the appropriate acid chloride in THF (Scheme 4). After a short period *N*-methylpiperazine was added, which served a dual role, acting as a scavenger for any unreacted acylating reagent and by providing the base for the subsequent Sonogashira reaction. It is worth noting that *N*-methyl piperazine was chosen for this role in preference to piperidine due to its extra *N*-methyl group, which would ultimately facilitate removal of the polar scavenged by-products. At this stage each of the three crude reaction mixtures were divided into three equal portions and submitted to Sonogashira reaction conditions with three different alkynes. As can be seen by the results of the matrix (Table 1), a series of sequential derivatisations were executed to give the nine products in good overall yield (49–70% over 2 steps) after chromatography. The nine compounds prepared in the reaction matrix display physical characteristics consistent with the Lipinski "rule of 5" and contain 7 or fewer rotatable bonds,[5,14,20] vindicating the use of the scaffold **6** as a starting



Scheme 4 *Reagents and conditions*: a) R^1COCl, NEt_3, THF, RT; b) R^2CCH, $Pd(PPh_3)_2Cl_2$, CuI, *N*-methylpiperazine, THF, 120 °C, (μw).

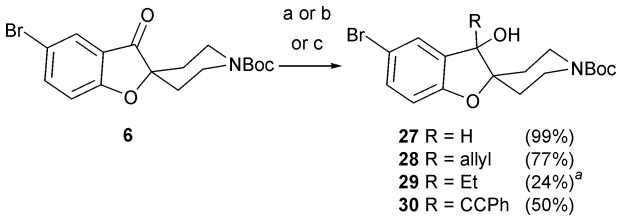
Table 1 3 × 3 Matrix for sequential derivatisation of **6** (see Scheme 4)

	Yield[a] (compound number)		
	$R^2 = p$-$MeOC_6H_4$	$R^2 = {}^t$Bu	$R^2 = m$-FC_6H_4
R^1 = Ph	66% (**18**)	69% (**19**)	53% (**20**)
$R^1 = {}^n$Pr	59% (**21**)	70% (**22**)	50% (**23**)
R^1 = 2-furyl	59% (**24**)	64% (**25**)	49% (**26**)

[a] Yields are reported for isolated purified compounds.

point to synthesise libraries of compounds with sound drug-like properties.

Derivatisation of the carbonyl group present in scaffold **6** was also explored, although it proved to be more restricted in terms of scope due to steric congestion. Additions of small nucleophiles (*e.g.* $NaBH_4$, allylMgBr, PhCCLi) proceeded in good to excellent yields, whereas reaction with EtMgBr gave the desired product **29** alongside the reduction product **27** (Scheme 5). Larger nucleophiles such as ^{i}PrMgCl and PhMgCl failed to react.



Scheme 5 *Reagents and conditions*: a) $NaBH_4$, EtOH; b) RMgBr, THF; c) PhCCH, ^{n}BuLi, THF. [a]Compound **27** (56%) was also obtained as a major by-product.

In summary, an efficient approach has been developed to access a novel spiropiperidine scaffold **6** that is capable of undergoing efficient selective modification at two sites. Both the aryl bromide and amine functional groups present in **6** can be readily built on to provide a host of novel chemical entities for screening purposes. This has been exemplified both in single chemoselective reactions, and later in the composition of multi-step telescope reaction matrices. In the latter case, the 9 compounds synthesised exhibit physical characteristics consistent with guidelines for sound drug-like properties.

Experimental

General

Melting points were obtained using an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet Impact 400 spectrometer. ^{1}H-NMR and ^{13}C-NMR were recorded in $CDCl_3$ solution using a Bruker DPX400 (400 and 100 MHz respectively) unless otherwise stated. Chemical shifts are reported in δ units with $CHCl_3$ being used as an internal standard. Coupling constants (J) are reported in Hz. Mass spectra acquired using an electrospray technique (ES+) were recorded on a Fisons VG platform single quadrupole mass spectrometer in electron spray ionisation mode. Those obtained using an electron (EIMS) or chemical ionisation technique (CIMS) were recorded on a Thermoquest trace GC-MS with combined EI/CI source using a Macherey-Nagel Optima Delta-3 column-0.25 μm (30 m × 0.25 mm). Microwave irradiation was carried out in a Biotage Smith Synthesiser™.

2-(5-Bromo-2-fluorophenyl)-[1,3]dithiane (10). To a stirred solution of 5-bromo-2-fluorobenzaldehyde (20.0 g, 98.5 mmol) and 1,3-propanedithiol (9.82 mL, 97.5 mmol) in $CHCl_3$ (350 mL) was added iodine (750 mg, 2.96 mmol). After stirring at room temperature for 18 h the orange solution was poured into $Na_2S_2O_3$ solution (0.4 M, 180 mL) and a 40% solution of NaOH was added (150 mL). The organic phase was separated and the aqueous extracted with a further portion of $CHCl_3$ (300 mL). The combined organic fractions were washed with water (400 mL), brine (400 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow solid (32.1 g). Recrystallisation from DCM–hexane afforded the title compound **10** as a white solid (26.0 g, 90%); Mp 51–53 °C (DCM–hexane); IR: ν_{max} ($CDCl_3$ film) 1484 cm^{-1}; NMR: δ_H 7.74 (1H, dd, J 6.3, 2.5, H_{ar}), 7.39 (1H, ddd, J 8.8, 4.5, 2.5, H_{ar}), 6.95 (1H, t, J 9.0, H_{ar}), 5.47 (1H, s, S_2CH), 3.10 (2H, ddd, J 14.8, 12.6, 2.5, SCH_{ax}), 2.92 (2H, ddd, J 14.8, 4.3, 3.0, SCH_{eq}), 2.18 (1H, dtt, J 13.8, 4.3, 2.5, CH_{eq}), 1.94 (1H, dtt, J 14.0, 12.6, 3.0, CH_{ax}); δ_C 158.2 (d, J 247.3, $C_{ar}F$), 133.0 (d, J 8.7, $C_{ar}H$), 132.7 (d, J 2.9, $C_{ar}H$), 128.6 (d, J 15.4, C_{ar}), 117.4 (d, J 24.2, $C_{ar}H$), 117.3 (C_{ar}), 42.6 (d, J 4.5, CH), 32.2 (2 × CH_2S), 25.1 (CH_2); (EI) m/z (%): 292, 294 ([M]$^{+\bullet}$, 39), 217, 219 (51), 74 (100); Elemental analysis: Found: C, 40.98; H, 3.56. $C_{10}H_{10}BrFS_2$ requires: C, 40.96; H, 3.44%.

1-(5-Bromo-3-[1,3]dithian-2-yl-2-fluorophenyl)-cyclohexanol (13). To a degassed and stirred solution of diisopropylamine (105 μL, 0.75 mmol) in THF (2 mL) at −78 °C was added ^{n}BuLi (2.31 M solution in hexanes, 325 μL, 0.75 mmol) dropwise. The solution was then stirred at −78 °C for 10 min, 0 °C for 10 min and then cooled back to −78 °C. To the stirred solution of LDA was added a solution of **10** (200 mg, 0.68 mmol) in THF (3 mL) and the reaction stirred at −78 °C for 30 min. Cyclohexanone (106 μL, 0.75 mmol) was added dropwise and the reaction stirred at −78 °C for 30 min. TLC showed incomplete conversion. A further portion of cyclohexanone was added (106 μL, 0.75 mmol) and the reaction stirred for a further hour, after which no further progress was observed. The reaction was poured into sat. NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic fractions were washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), filtered and evaporated to give a yellow oil (307 mg). This was purified by column chromatography (5% EtOAc–hexane) to give the title compound **13** as a white solid (91 mg, 34%); Mp 118–119 °C (EtOAc–hexane). Starting material **10** was also recovered from the reaction (64 mg, 32%). IR: ν_{max} ($CDCl_3$ film) 3442, 1446 cm^{-1}; NMR: δ_H 7.69 (1H, dd, J 7.0, 2.8, H_{ar}), 7.64 (1H, dd, J 5.8, 2.8, H_{ar}), 5.48 (1H, s, S_2CH), 3.10 (2H, ddd, J 14.3, 12.6, 2.5, SCH_{ax}), 2.93 (2H, dt, J 14.3, 3.3, SCH_{eq}), 2.34–1.64 (12H, m, CH_2 + OH), 1.35–1.28 (1H, m, H_{cyc}); δ_C 155.5 (d, J 247.3, $C_{ar}F$), 138.3 (d, J 14.5, C_{ar}), 131.2 (d, J 2.9, $C_{ar}H$), 130.4 (d, J 4.9, $C_{ar}H$), 129.1 (d, J 17.5, C_{ar}), 117.5 (d, J 2.9, C_{ar}), 73.0 (d, J 3.9, COH), 43.0 (d, J 5.8, CS_2), 36.6 (d, J 3.9, 2 × CH_2), 32.4 (2 × CH_2S), 25.3, 25.2 (CH_2), 21.9 (2 × CH_2); (EI) m/z (%): 390, 392 ([M]$^{+\bullet}$, 47), 372, 374 (36), 105 (78), 45 (100); Elemental analysis: Found: C, 48.73; H, 5.20. $C_{16}H_{20}BrFOS_2$ requires: C, 49.11; H, 5.15%.

4-[2-(5-Bromo-2-fluoro-phenyl)-[1,3]dithian-2-yl]-4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (11). Compound **10** (21.8 g, 74.4 mmol) was added to a solution of LDA (1 eq) in THF (300 mL) following the procedure for compound **13**. The reaction mixture was then allowed to warm to −20 °C for 30 min before being cooled back to −78 °C and a solution of *N*-Boc-4-piperidone (**9**, 15.1 g, 75.8 mmol) in THF (150 mL) added. Work-up and purification (20–40% EtOAc–hexane) gave the title compound **11** as a pale yellow solid (29.3 g, 80%); Mp 111–112 °C (hexane); IR: ν_{max} ($CDCl_3$ film) 3428, 1673 cm^{-1}; NMR: δ_H 8.21 (1H, dd, J 7.5, 2.5, H_{ar}), 7.44 (1H, ddd, J 8.5,

3.5, 2.5, H_{ar}), 6.99 (1H, dd, J 12.0, 8.5, H_{ar}), 3.93 (2H, br s, CH_{eq}N), 2.99 (2H, br t, J 11.6, CH_{ax}N), 2.86 (2H, dt, 14.6, 4.5, SCH_{eq}), 2.64 (2H, ddd, J 14.6, 9.8, 5.0, SCH_{ax}), 2.46 (1H, br s, OH), 1.92–1.85 (2H, m, CH_2), 1.84–1.73 (4H, m, CH_2COH), 1.43 (9H, s, (CH_3)$_3$); δ_C 161.0 (d, J 252.1, C_{ar}F), 154.9 (C=O), 137.6 (C_{ar}H), 133.3 (d, J 9.7 Hz, C_{ar}H), 127.4 (d, J 8.7, C_{ar}), 119.7 (d, J 28.0, C_{ar}H), 116.9 (d, J 2.9 Hz, C_{ar}), 79.6 (O–CMe$_3$), 77.0 (COH), 69.6 (d, J 6.8, CS$_2$), 39.7 (2 × CH$_2$N), 32.6 (2 × CH$_2$COH), 28.6 ((CH$_3$)$_3$), 27.84 (2 × CH$_2$), 24.3 (CH$_2$); (ES$^+$) m/z: 1005, 1007, 1009 ([2M + Na]$^+$); Elemental analysis: Found: C, 48.91; H, 5.69; N, 2.69. $C_{20}H_{27}BrFOS_2$ requires: C, 48.78; H, 5.53; N, 2.84%.

4-(5-Bromo-2-fluoro-benzoyl)-4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (12). Following a procedure described by Bates and O'Doherty,[16] to a stirred solution of **11** (4.15 g, 8.43 mmol) and pyridine (1.02 mL, 12.6 mmol) in DCM (50 mL) and water (10 mL) was added pyridine tribromide (4.04 g, 12.6 mmol) followed by TBAB (272 mg, 0.84 mmol). The resulting mixture was stirred at room temperature for 24 h. The reaction was then poured into water (120 mL) and extracted with DCM (3 × 160 mL). The combined organic fractions were washed with water (400 mL), brine (400 mL), dried (Na_2SO_4), filtered and evaporated to give a cream residue (4.33 g). This was absorbed onto silica and purified by column chromatography (0–20% EtOAc–hexane) to give the title compound **12** as a pale yellow oil (3.32 g, 98%); IR: ν_{max} ($CDCl_3$ film) 3413, 1664 cm^{-1}; NMR: δ_H 7.54 (1H, ddd, J 8.6, 4.5, 2.5, H_{ar}), 7.49 (1H, dd, J 5.8, 2.5, H_{ar}), 7.01 (1H, t, J 8.8, H_{ar}), 3.96 (2H, br d, J 9.4, CH_{eq}N), 3.47 (1H, br s, OH), 3.13 (2H, br t, J 10.6, CH_{ax}N), 1.96 (2H, td, J 12.8, 4.8, CH_{ax}COH), 1.65 (2H, br d, J 13.0, CH_{eq}COH), 1.43 (9H, s, (CH_3)$_3$); δ_C 205.0 (d, J 1.9, Ar–C=O), 158.0 (d, J 247.3, C_{ar}F), 154.8 (CO$_2$^{t}Bu), 135.4 (d, J 8.7, C_{ar}H), 131.5 (d, J 3.9, C_{ar}H), 128.1 (d, J 19.3, C_{ar}), 118.1 (d, J 24.1, C_{ar}H), 117.0 (d, J 2.9, C_{ar}), 80.0 (O–CMe$_3$), 77.8 (COH), 39.1 (2 × CH$_2$N), 33.3 (2 × CH$_2$COH), 28.5 ((CH$_3$)$_3$); (ES$^+$) m/z: 402, 404 ([M + H]$^+$); HR(ES$^+$) m/z: [2M + Na]$^{+\bullet}$: 825.1174. $C_{34}H_{42}Br_2F_2N_2O_8Na$ requires 825.1168.

***tert*-Butyl 5-bromo-spiro[1-benzofuran-2,4′-piperidine]-3-one-1′-carboxylate (7).** To a solution of **12** (190 mg, 0.47 mmol) in THF (2 mL) was added ^{t}BuOK (80 mg, 0.71 mmol) and the mixture reacted in the microwave at 70 °C for 5 min (heating may also be conducted thermally). The reaction was then poured into water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with water (30 mL), brine (30 mL), dried (Na_2SO_4), filtered and evaporated to give a pale yellow oil (97 mg). Purification by column chromatography (20% EtOAc–hexane) gave the title compound **7** as a yellow crystalline solid (135 mg, 75%). On a 4.08 mmol scale, this reaction was performed in 3 microwave vials (5 mL each) to afford **7** in 72% yield; Mp 124–126 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 2978, 1706, 1678 cm^{-1}; NMR: δ_H 7.79 (1H, dd, J 2.3, 0.5, H_{ar}), 7.71 (1H, dd, J 8.8, 2.3, H_{ar}), 7.04 (1H, dd, J 8.8, 0.5, H_{ar}), 4.15 (2H, br s, CH_{eq}N), 3.22 (2H, br t, J 12.1, CH_{ax}N), 1.94 (2H, ddd, J 13.8, 12.3, 5.0, CH_{ax}COAr), 1.59 (2H, br d, J 13.6, CH_{eq}COAr), 1.49 (9H, s, (CH_3)$_3$); δ_C 201.1 (Ar–C=O), 169.8 (C_{ar}), 154.7 (CO$_2$^{t}Bu), 140.9, 127.6 (C_{ar}H), 122.0 (C_{ar}), 115.7 (C_{ar}H), 114.7 (C_{ar}), 88.4 (C–OAr), 80.2 (O–CMe$_3$), 39.8 (2 × CH$_2$N), 31.4 (2 × CH$_2$COH), 28.6 ((CH$_3$)$_3$); (ES$^+$) m/z: 785, 787, 789 ([2M + Na]$^+$); Elemental analysis: Found: C, 53.47; H, 5.34; N, 3.62. $C_{17}H_{20}BrNO_4$ requires: C, 53.42; H, 5.27; N, 3.66%.

5-Bromo-spiro[1-benzofuran-2,4′-piperidin]-3-one (6). To a solution of **7** (100 mg, 0.26 mmol) in THF (1 mL) was added TFA (0.10 mL, 1.31 mmol) dropwise and the reaction heated in the microwave for 20 min at 140 °C. The reaction was then evaporated to dryness and chromatographed on silica (0–10% MeOH–DCM, 1% NH_3) to afford the title compound **6** as a white solid (65 mg, 0.23 mmol, 88% yield); Mp 171–173 °C (dec.). On a 2.62 mmol scale, this reaction was refluxed in 15 mL of DCM for 4 h to afford **6** in 74% yield; IR: ν_{max} ($CDCl_3$ film) 1720, 1677 cm^{-1}; NMR: δ_H 7.79 (1H, d, J 2.2, H_{ar}), 7.73 (1H, dd, J 8.8, 2.2, H_{ar}), 7.06 (1H, d, J 8.8, H_{ar}), 6.75 (1H, br s, NH), 3.44 (2H, dt, J 12.9, 3.9, CH_{eq}N), 2.27 (2H, td, J 12.8, 3.2, CH_{ax}N), 2.17 (2H, ddd, J 13.9, 12.8, 4.6, CH_{ax}COAr), 1.78 (2H, d, J 13.8 Hz, CH_{eq}COAr); δ_C 200.1 (C=O), 169.7 (C_{ar}), 141.2 (C_{ar}H), 127.7 (C_{ar}H), 121.7 (C_{ar}), 115.7 (C_{ar}H), 115.1 (C_{ar}), 86.4 (C–OAr), 40.8 (2 × CH$_2$N), 30.1 (2 × CH$_2$COAr); (EI) m/z: 281, 283 ([M$^{+\bullet}$], 81), 238, 240 (18), 56 (100); HR(EI) m/z: [M$^{+\bullet}$]: 281.0036. $C_{12}H_{12}BrNO_2$ requires 281.0051.

***tert*-Butyl 5-(octylamino)-spiro[1-benzofuran-2,4′-piperidine]-3-one-1′-carboxylate (14a).** To a stirred mixture of BINAP (9.8 mg, 15.7 μmol) in toluene (1.3 mL) was added $Pd_2(dba)_3$ (4.8 mg, 5.2 μmol) and the reaction stirred at room temperature for 5 min. To this solution was added **7** (100 mg, 0.26 mmol), octylamine (56 μL, 0.34 mmol), and ^{t}BuONa (35 mg, 0.37 mmol) in that order. The orange solution was heated in the microwave for 1 h at 100 °C. The reaction was then filtered, washing with ether (15 mL), concentrated to a brown oil (113 mg) and purified by column chromatography (1–4% EtOAc–DCM) to afford the title compound **14a** as a bright yellow oil (78 mg, 69%); IR: ν_{max} ($CDCl_3$ film) 2922, 1701, 1678 cm^{-1}; NMR: δ_H 6.99 (1H, dd, J 8.8, 2.2, H_{ar}), 6.95 (1H, d, J 8.8, H_{ar}), 6.73 (1H, d, J 2.0, H_{ar}), 4.13 (2H, br s, CH_{eq}N), 3.63 (1H, br s, NH), 3.25–3.18 (2H, m, CH_{ax}N), 3.07 (2H, t, J 7.0, ArNHCH_2), 1.42 (2H, td, J 13.6, 4.8, CH_{ax}COAr), 1.61 (2H, t, J 7.0, CH_2), 1.55 (2H, d, J 13.4 Hz, CH_{eq}COAr), 1.48 (9H, s, C(CH_3)$_3$), 1.44–1.21 (10H, m, 5 × CH_2), 0.89 (3H, t, J 7.0, CH_3); δ_C 203.3 (Ar–C=O), 164.9 (C_{ar}), 154.8 (CO$_2$^{t}Bu), 144.2 (C_{ar}), 126.9 (C_{ar}H), 120.3 (C_{ar}), 114.3, 103.3 (C_{ar}H), 87.2 (C–OAr), 79.9 (O–CMe$_3$), 44.8 (CH$_2$NH), 40.1 (2 × CH$_2$N), 32.0, 32.0, 31.6, 29.5, 29.5, 29.4 (CH$_2$), 28.6 ((CH$_3$)$_3$), 27.3, 22.8 (CH$_2$), 14.2 (CH$_3$); (ES$^+$) m/z: 883 ([2M + Na]$^+$), 431 ([M + H]$^+$); HR(ES$^+$) m/z: 431.2904. $C_{25}H_{39}N_2O_4$ requires 431.2901.

***tert*-Butyl 5-(dibutylamino)-spiro[1-benzofuran-2,4′-piperidine]-3-one-1′-carboxylate (14b).** Following the procedure described for the synthesis of **14a**, **7** (100 mg, 0.26 mmol) was coupled with dibutylamine (62 μL, 0.37 mmol). Column chromatography of the crude product (10% EtOAc–hexane) afforded the title compound **14b** as a bright yellow oil (31 mg, 28%). The resulting product of scaffold debromination was also recovered from the reaction (33 mg, 42%); IR: ν_{max} ($CDCl_3$ film) 1696 cm^{-1}; NMR: δ_H 7.11 (1H, dd, J 9.0, 2.8, H_{ar}), 7.01 (1H, d, J 9.0, H_{ar}), 6.79 (1H, d, J 2.8, H_{ar}), 4.15 (2H, br s, CH_{eq}N), 3.22 (2H, br s, CH_{ax}N), 3.22 (4H, t, J 7.5, ArN(CH_2)$_2$), 1.93 (2H, td, J 12.8, 4.8, CH_{ax}COAr), 1.56–1.49 (6H, m, CH_2), 1.49 (9H, s, C(CH_3)$_3$), 1.33 (4H, sext, J 7.3, CH_2), 0.94 (6H, t, J 7.3, CH_3); δ_C 203.6 (Ar–C=O), 163.7 (C_{ar}), 154.8 (CO$_2$^{t}Bu), 144.5 (C_{ar}), 125.6 (C_{ar}H), 120.3 (C_{ar}), 114.3, 104.7 (C_{ar}H), 87.1 (C–OAr), 79.9 (O–CMe$_3$), 51.7 (2 × CH$_2$N), 40.4, 39.6 (CH$_2$N), 31.6, 29.4 (4 × CH$_2$), 28.6 ((CH$_3$)$_3$), 20.5 (2 × CH$_2$), 14.2 (2 × CH$_3$); (ES$^+$) m/z: 431 ([M + H]$^+$); HR(ES$^+$) m/z: 431.2899. $C_{25}H_{39}N_2O_4$ requires 431.2904.

***tert*-Butyl 5-[methyl(phenyl)amino]-spiro[1-benzofuran-2,4′-piperidine]-3-one-1′-carboxylate (14c).** Following the procedure described for the synthesis of **14a**, **7** (100 mg, 0.26 mmol) was coupled with *N*-methylaniline (62 μL, 0.37 mmol). Column chromatography of the crude product (10% EtOAc–hexane afforded the title compound **14c** as a bright yellow oil (67 mg, 63%); IR: ν_{max} ($CDCl_3$ film) 2969, 1697 cm^{-1}; NMR: δ_H 7.40 (1H, dd, J 8.8, 2.5, H_{ar}), 7.30 (1H, d, J 2.5, H_{ar}), 7.26 (2H, dd, J 8.0, 7.0, H_{ar}), 7.05 (1H, d, J 8.8, H_{ar}), 6.94 (1H, t, J 7.0, H_{ar}), 6.93 (2H, d, J 8.0, H_{ar}), 4.15 (2H, br s, CH_{eq}N), 3.29 (3H, s, NCH_3), 3.27–3.21 (2H, m, CH_{ax}N), 1.96 (2H, td, J 13.6, 4.8, CH_{ax}COAr), 1.61 (2H, d, J 13.3, CH_{eq}COAr), 1.50 (9H, s, (CH_3)$_3$); δ_C 202.5 (Ar–C=O), 167.1 (C_{ar}), 154.8 (CO$_2$^{t}Bu), 149.2, 144.4 (C_{ar}), 134.0, 129.5, 129.5, 121.3 (C_{ar}H), 120.7 (C_{ar}), 119.4, 119.4, 115.7, 114.4 (C_{ar}H), 87.9 (C–OAr), 80.0 (O–CMe$_3$), 40.9

(NCH_3), 39.9 (2 × CH_2N), 33.6 (2 × CH_2COAr), 28.6 (($CH_3)_3$); (ES$^+$) *m/z*: 409 ([M + H]$^+$), 426 ([M + NH_4]$^+$); HR(ES$^+$) *m/z*: 409.2127. $C_{24}H_{29}N_2O_4$ requires 409.2122.

***tert*-Butyl 5-phenyl-spiro[1-benzofuran-2,4′-piperidine]-3-one-1′-carboxylate (15a).** To a stirred biphasic mixture of **7** (400 mg, 1.05 mmol) and phenyl boronic acid (191 mg, 1.57 mmol) in toluene (1 mL), ethanol (1 mL) and 2M Na_2CO_3 (1 mL) was added $Pd(PPh_3)_4$ (60 mg, 0.05 mmol) and the reactions heated in the microwave for 10 min at 110 °C. The reaction was poured into water (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic fractions were washed with water (70 mL), brine (70 mL), dried (Na_2SO_4), filtered and evaporated to give a brown residue (672 mg). This was purified by column chromatography (10% EtOAc–hexane) to afford the title compound **15a** as a white solid (337 mg, 85%); Mp 134–135 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 1716, 1678 cm^{-1}; NMR: δ_H 7.90 (1H, dd, *J* 8.3, 1.8, H_{ar}), 7.79 (1H, s, H_{ar}), 7.56 (2H, d, *J* 7.5, H_{ar}), 7.45 (2H, t, *J* 7.3, H_{ar}), 7.37 (1H, t, *J* 7.3, H_{ar}), 7.21 (1H, d, *J* 8.3, H_{ar}), 4.18 (2H, br s, $CH_{eq}N$), 3.27 (2H, br t, *J* 12.8, $CH_{ax}N$), 1.99 (2H, td, *J* 12.6, 4.8, $CH_{ax}CO$), 1.63 (2H, br d, *J* 12.0 Hz, $CH_{eq}CO$), 1.51 (9H, s, $(CH_3)_3$); δ_C 202.6 (Ar–*C*=O), 170.6 (C_{ar}), 154.8 ($CO_2{}^tBu$), 139.8 (C_{ar}), 137.7 ($C_{ar}H$), 135.9 (C_{ar}), 129.2 (2 × C_{ar}), 127.7 ($C_{ar}H$), 129.2 (2 × C_{ar}), 122.9 ($C_{ar}H$), 120.7 (C_{ar}), 114.2 ($C_{ar}H$), 88.0 (*C*–OAr), 80.1 (O–$C(CH_3)_3$), 39.8 (2 × CH_2N) 31.5 (2 × CH_2COAr) 28.6 (($CH_3)_3$); (ES$^+$) *m/z*: 781 ([2M + Na]$^+$); Elemental analysis: Found: C, 72.84; H, 6.68; N, 3.63. $C_{23}H_{25}NO_4$ requires: C, 72.80; H, 6.64; N, 3.69%.

***tert*-Butyl 5-(3-methoxyphenyl)-spiro[1-benzofuran-2,4′-piperidine]-3-one-1′-carboxylate (15b).** Following the procedure described for the synthesis of **15a**, **7** (100 mg, 0.26 mmol) was coupled with 3-methoxyphenyl boronic acid (60 mg, 0.39 mmol) to afford the title compound **15b** as a pale yellow solid (83 mg, 77%); Mp 141–142 °C (hexane); IR: ν_{max} ($CDCl_3$ film) 1715, 1692 cm^{-1}; NMR: δ_H 7.89 (1H, dd, *J* 8.3, 2.0, H_{ar}), 7.88 (1H, br s, H_{ar}), 7.36 (1H, t, *J* 8.0, H_{ar}), 7.20 (1H, dd, *J* 8.3, 1.3, H_{ar}), 7.14 (1H, ddd, *J* 7.8, 1.5, 0.8, H_{ar}), 7.08 (1H, t, *J* 1.8, H_{ar}), 6.91 (1H, ddd, *J* 8.3, 2.5, 0.8, H_{ar}), 4.17 (2H, br s, $CH_{eq}N$), 3.87 (3H, s, OCH_3), 3.27 (2H, br t, *J* = 13.7 Hz, $CH_{ax}N$), 1.98 (2H, td, *J* 13.8, 4.8, $CH_{ax}CO$), 1.63 (2H, br d, *J* 13.6 Hz, $CH_{eq}CO$), 1.51 (9H, s, $C(CH_3)_3$); δ_C 202.6 (Ar–*C*=O), 170.6 (C_{ar}), 160.3 (C_{ar}), 154.8 ($CO_2{}^tBu$), 141.2 (C_{ar}), 137.7 ($C_{ar}H$), 135.6 (C_{ar}), 130.2, 123.0 ($C_{ar}H$), 120.6 (C_{ar}), 119.5, 114.1, 113.2, 112.8 ($C_{ar}H$), 88.1 (*C*–OAr), 80.1 (O–CMe_3), 55.5 (OCH_3), 40.0 (2 × CH_2N), 31.5 (2 × CH_2COAr) 28.6 ($C(CH_3)_3$); (ES$^+$) *m/z*: 841 ([2M + Na]$^+$); Elemental analysis: Found: C, 69.99; H, 6.70; N, 3.33. $C_{24}H_{27}NO_5$ requires: C, 70.40; H, 6.65; N, 3.42%.

***tert*-Butyl 5-(3-nitrophenyl)-spiro[1-benzofuran-2,4′-piperidine]-3-one-1′-carboxylate (15c).** Following the procedure described for the synthesis of **15a**, **7** (100 mg, 0.26 mmol) was coupled with 3-nitrophenyl boronic acid (66 mg, 0.39 mmol) to afford the title compound **15c** as a pale yellow solid (85 mg, 77%); Mp 175–176 °C (hexane); IR: ν_{max} ($CDCl_3$ film) 1720, 1692 cm^{-1}; NMR: δ_H 8.42 (1H, t, *J* 2.0, H_{ar}), 8.22 (1H, ddd, *J* 8.3, 2.3, 1.0, H_{ar}), 7.94 (1H, dd, *J* 9.2, 2.0, H_{ar}), 7.92 (1H, d, 2.0 H_{ar}), 7.88 (1H, ddd, *J* 7.8, 1.8, 1.0, H_{ar}), 7.63 (1H, t, *J* 8.0, H_{ar}), 7.28 (1H, t, *J* 9.3, H_{ar}), 4.17 (2H, br s, $CH_{eq}N$), 3.27 (2H, br t, *J* 11.3 Hz, $CH_{ax}N$), 1.99 (2H, td, *J* 12.3, 5.0 Hz, $CH_{ax}CO$), 1.64 (2H, br d, *J* 12.8 Hz, $CH_{eq}CO$), 1.50 (9H, s, $(CH_3)_3$); δ_C 202.1 (Ar–*C*=O), 171.1 (C_{ar}), 154.8 ($CO_2{}^tBu$), 149.0 (C_{ar}), 141.4 (C_{ar}), 137.3 ($C_{ar}H$), 133.2 (C_{ar}), 132.8, 130.2, 123.4, 122.4, 121.8 ($C_{ar}H$), 121.0 (C_{ar}), 114.8 ($C_{ar}H$), 88.5 (*C*–OAr), 80.2 (O–CMe_3), 39.8 (2 × CH_2N) 31.5 (2 × CH_2COAr) 28.6 (($CH_3)_3$); (ES$^+$) *m/z*: 871 ([2M + Na]$^+$); Elemental analysis: Found: C, 64.84; H, 5.78; N, 6.53. $C_{23}H_{24}N_2O_6$ requires: C, 65.08; H, 5.70; N, 6.60%.

***tert*-Butyl 5-(3,3-dimethylbut-1-yn-1-yl)-3-oxo-spiro[1-benzofuran-2,4′-piperidine]-1′-carboxylate (16a).** To a degassed solution of **7** (100 mg, 0.26 mmol), and 3,3-dimethylbutyne (97 μL, 0.78 mmol) in NEt_3 (2 mL) was added $Pd(PPh_3)_2Cl_2$ (9.2 mg, 13.1 μmol) followed by CuI (2.5 mg, 13.1 μmol). The reaction was purged with N_2 before being heated in the microwave for 15 min at 100 °C. The reaction was concentrated to give an orange solid (158 mg), which was purified by column chromatography (5% EtOAc–hexane) to afford to title compound **16a** as a pale orange solid (85 mg, 85%); Mp 51–53 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 1711, 1682 cm^{-1}; NMR: δ_H 7.69 (1H, d, *J* 1.5, H_{ar}), 7.63 (1H, dd, *J* 8.6, 1.7, H_{ar}), 7.04 (1H, d, *J* 8.6, H_{ar}), 4.13 (2H, br s, $CH_{eq}N$), 3.22 (2H, br t, *J* 12.0 Hz, $CH_{ax}N$), 1.94 (2H, td, *J* 12.5, 4.8 Hz, $CH_{ax}CO$), 1.57 (2H, br d, *J* 13.6 Hz, $CH_{eq}CO$), 1.49 (9H, s, $OC(CH_3)_3$), 1.49 (9H, s, $CC(CH_3)_3$); δ_C 201.8 (Ar–*C*=O), 170.0 (C_{ar}), 154.8 ($CO_2{}^tBu$), 141.5, 128.0 (2 × $C_{ar}H$), 120.2 (C_{ar}), 118.6 (C_{ar}), 113.7 ($C_{ar}H$), 98.7 (C_{alkyne}), 88.0 (*C*–OAr), 80.1 (O–CMe_3), 77.7 (C_{alkyne}), 40.1 (2 × CH_2N), 31.5 (2 × CH_2COAr), 31.1 ($OC(CH_3)_3$), 28.6 ($CC(CH_3)_3$), 28.1 ($CCMe_3$); (EI) *m/z*: 383 ([M$^{+\bullet}$], 36), 310 (57), 56 (100); HR(EI) *m/z*: [M$^{+\bullet}$]: 383.2077. $C_{23}H_{29}NO_4$ requires 383.2097.

***tert*-Butyl 5-[(4-methoxyphenyl)ethynyl]-3-oxo-spiro[1-benzofuran-2,4′-piperidine]-1′-carboxylate (16b).** Following the procedure described for the synthesis of **16a**, **7** (100 mg, 0.26 mmol) was coupled with 1-ethynyl-4-methoxybenzene (104 mg, 0.78 mmol) in piperidine (2 mL) to afford the title compound **16b** as a pale yellow coloured solid (105 mg, 93%); Mp 144–145 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 1725, 1682 cm^{-1}; NMR: δ_H 7.81 (1H, d, *J* 2.0, H_{ar}), 7.76 (1H, dd, *J* 8.6, 2.0, H_{ar}), 7.46 (2H, d, *J* 8.8, H_{ar}), 7.11 (1H, d, *J* 8.6, H_{ar}), 6.89 (2H, d, *J* 9.0, H_{ar}), 4.15 (2H, br s, $CH_{eq}N$), 3.84 (3H, s, OCH_3), 3.25 (2H, br t, *J* 12.4 Hz, $CH_{ax}N$), 1.96 (2H, td, *J* 12.5, 4.8 Hz, $CH_{ax}CO$), 1.61 (2H, br d, *J* 12.8, $CH_{eq}CO$), 1.51 (9H, s, $C(CH_3)_3$); δ_C 201.6 (Ar–*C*=O), 170.3 (C_{ar}), 160.0 (C_{ar}), 154.8 ($CO_2{}^tBu$), 141.3 ($C_{ar}H$), 133.2 (2 × $C_{ar}H$), 127.9 ($C_{ar}H$), 120.4 (C_{ar}), 118.1, 115.2 (C_{ar}), 114.3 (2 × $C_{ar}H$), 114.1 ($C_{ar}H$), 89.6 (C_{alkyne}), 88.2 (*C*–OAr), 86.7 (C_{alkyne}), 80.1 (O–CMe_3), 55.5 (OCH_3), 40.2 (2 × CH_2N) 31.5 (2 × CH_2COAr) 28.6 ($C(CH_3)_3$); (ES$^+$) *m/z*: 378 ([M + H–C_4H_8]$^+$), 334 ([M + H–C_4H_8OCO]$^+$); HR(ES$^+$) *m/z* [M + H–C_4H_8OCO]$^+$: 334.1454. $C_{21}H_{20}NO_3$ requires 334.1443.

***tert*-Butyl 3-oxo-5-{[4-(trifluoromethyl)phenyl]ethynyl}-spiro[1-benzofuran-2,4′-piperidine]-1′-carboxylate (16c).** Following the procedure described for the synthesis of **16a**, **7** (100 mg, 0.26 mmol) was coupled with 4-ethynyl-α,α,α-trifluorotoluene (109 μL, 0.78 mmol) in piperidine (2 mL) to afford the title compound **16c** as a cream solid (92 mg, 75%); Mp 177–178 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 1721, 1682 cm^{-1}; NMR: δ_H 7.88 (1H, d, *J* 1.8, H_{ar}), 7.81 (1H, dd, *J* 8.6, 1.8, H_{ar}), 7.68–7.61 (4H, m, H_{ar}), 7.15 (1H, d, *J* 8.7, H_{ar}), 4.16 (2H, br s, $CH_{eq}N$), 3.26 (2H, br t, *J* 11.8, $CH_{ax}N$), 1.88 (2H, td, *J* 13.4, 5.0, $CH_{ax}CO$), 1.62 (2H, br d, *J* 14.0, $CH_{eq}CO$), 1.50 (9H, s, $C(CH_3)_3$); δ_C 201.4 (Ar–*C*=O), 170.7 (C_{ar}), 154.8 ($CO_2{}^tBu$), 141.4 ($C_{ar}H$), 132.0 (2 × $C_{ar}H$), 130.3 (q, *J* 32.9, $C_{ar}CF_3$), 128.6 ($C_{ar}H$), 127.0 (C_{ar}), 123.1 (q, *J* 272.0, CF_3), 125.6 (q, *J* 3.8, 2 × $C_{ar}H$), 120.6 (C_{ar}), 117.0 (C_{ar}), 114.3 ($C_{ar}H$), 90.4 (C_{alkyne}), 88.4 (*C*–OAr), 88.1 (C_{alkyne}), 80.2 (O–CMe_3), 39.8 (2 × CH_2N), 31.4 (2 × CH_2COAr) 28.6 ($C(CH_3)_3$); ^{19}F NMR (376 MHz): δ_F 63.2 (CF_3); (ES$^+$) *m/z*: 416 ([M + H–C_4H_8]$^+$), 372 ([M + H–C_4H_8OCO]$^+$); HR(EI) *m/z*: [M + H–C_4H_8OCO]$^+$: 372.1216 $C_{21}H_{17}NO_2F_3$ requires 372.1211.

***tert*-Butyl 3-oxo-5-[(*E*)-2-phenylvinyl]-spiro[1-benzofuran-2,4′-piperidine]-1′-carboxylate (17a).** To a stirred solution of $Pd(OAc)_2$ (1.8 mg, 7.85 μmol) and P(*o*-tol)$_3$ (7.3 mg, 23.54 μmol) in DMF (1 mL) was added **7** (100 mg, 0.26 mmol), styrene (36 μL, 0.31 mmol), and triethylamine (55 μL, 0.39 mmol). The reaction mixture was purged with nitrogen before being heated at 100 °C for 2 days. The reaction was then poured into water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic fractions were washed with water (30 mL) and brine

(30 mL), dried (Na_2SO_4), filtered and evaporated to give an orange oil (160 mg). This was purified by column chromatography (20% EtOAc–hexane) to afford the title compound **17a** as a pale yellow solid (101 mg, 95%); Mp 193–194 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 1706, 1677 cm^{-1}; NMR: δ_H 7.84 (1H, dd, *J* 8.5, 2.0, H_{ar}), 7.79 (1H, d, *J* 1.8, H_{ar}), 7.50 (2H, d, *J* 7.5, H_{ar}), 7.38 (2H, t, *J* 7.5, H_{ar}), 7.29 (1H, t, *J* 7.4, H_{ar}), 7.14 (1H, d, *J* 8.5, H_{ar}), 7.10 (1H, d, *J* 16.3, H_{alkene}), 7.05 (1H, d, *J* 16.3, H_{alkene}), 4.17 (2H, br s, $CH_{eq}N$), 3.26 (2H, br t, *J* 10.8, $CH_{ax}N$), 1.97 (2H, td, *J* 12.6, 5.0, $CH_{ax}COAr$), 1.61 (2H, br d, *J* 12.8, $CH_{eq}COAr$), 1.51 (9H, s, $(CH_3)_3$); δ_C 202.4 (Ar–*C*=O), 170.6 (C_{ar}), 154.8 ($CO_2{}^tBu$), 137.1 (C_{ar}), 136.7 ($C_{ar}H$), 132.3 (C_{ar}), 129.1, 128.9, 128.9 ($C_{ar}H$), 128.0, 127.0 (C_{alkene}), 126.7, 126.7, 122.2 ($C_{ar}H$), 120.6 (C_{ar}), 114.1 ($C_{ar}H$), 88.1 (*C*–OAr), 80.1 (O–*C*Me_3), 40.0 (2 × CH_2N), 31.5 (2 × CH_2COAr), 28.6 ($(CH_3)_3$); (ES$^+$) *m*/*z*: 833 ([2M + Na]$^+$); Elemental analysis: Found: C, 73.99; H, 6.54; N, 3.36. $C_{25}H_{27}NO_4$ requires: C, 74.05; H, 6.71; N, 3.45%.

***tert*-Butyl 5-[(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]-3-oxo-spiro[1-benzofuran-2,4′-piperidine]-1′-carboxylate (17b).** Following the procedure described for the synthesis of **17a**, **7** (100 mg, 0.26 mmol) was coupled with methyl acrylate (28 µL, 0.31 mmol) to afford the title compound **17b** as a pale yellow solid (85 mg, 77%); Mp 165–166 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 1711, 1678, 1616 cm^{-1}; NMR: δ_H 7.83 (1H, d, *J* 2.0 H_{ar}), 7.82 (1H, dd, *J* 9.3, 2.0, H_{ar}), 7.67 (1H, d, *J* 16.1, H_{alkene}), 7.16 (1H, d, *J* 9.3, H_{ar}), 6.38 (1H, d, *J* 16.1, H_{alkene}), 4.15 (2H, br s, $CH_{eq}N$), 3.81 (3H, s, OCH_3), 3.24 (2H, br t, *J* 12.3, $CH_{ax}N$), 1.96 (2H, td, *J* 13.1, 4.8, $CH_{ax}COAr$), 1.60 (2H, br d, *J* 13.3, $CH_{eq}COAr$), 1.49 (9H, s, $(CH_3)_3$); δ_C 201.7 (Ar–*C*=O), 172.0 (C_{ar}), 167.3 (CO_2Me), 154.7 ($CO_2{}^tBu$), 143.2 (C_{alkene}), 137.7 ($C_{ar}H$), 129.1 (C_{ar}), 124.8 ($C_{ar}H$), 120.8 (C_{ar}), 117.9 (C_{alkene}), 114.6 ($C_{ar}H$), 88.6 (*C*–OAr), 80.2 (O–*C*Me_3), 51.9 (OCH_3), 39.8 (2 × CH_2N) 31.4 (2 × CH_2COAr), 28.6 ($(CH_3)3$); (ES$^+$) *m*/*z*: 797 ([2M + Na]$^+$); Elemental analysis: Found: C, 64.96; H, 6.33; N, 3.41. $C_{21}H_{25}NO_6$ requires: C, 65.10; H, 6.50; N, 3.61%.

***tert*-Butyl 3-oxo-5[(*E*)-2-(phenylsulfonyl)vinyl]-spiro[1-benzofuran-2,4′-piperidine]-1′-carboxylate (17c).** Following the procedure described for the synthesis of **17a**, **7** (100 mg, 0.26 mmol) was coupled with phenylvinyl sulfone (53 mg, 0.39 mmol) to afford the title compound **17c** as a white solid (95 mg, 77%); Mp 168–170 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 1716, 1682, 1163 cm^{-1}; NMR: δ_H 7.94 (2H, d, *J* 7.0, H_{ar}), 7.79 (1H, d, *J* 2.0, H_{ar}), 7.76 (1H, dd, *J* 8.5, 2.0, H_{ar}), 7.66 (1H, d, *J* 15.3, H_{alkene}), 7.62 (1H, t, *J* 7.2, H_{ar}), 7.55 (2H, t, *J* 7.0, H_{ar}), 7.16 (1H, d, *J* 8.5, H_{ar}), 6.82 (1H, d, *J* 15.3, H_{alkene}), 4.13 (2H, br s, $CH_{eq}N$), 3.22 (2H, br t, *J* 12.5, $CH_{ax}N$), 1.93 (2H, td, *J* 13.8, 4.8, $CH_{ax}COAr$), 1.58 (2H, br d, *J* 13.6, $CH_{eq}COAr$), 1.49 (9H, s, $(CH_3)_3$); δ_C 201.3 (Ar–*C*=O), 172.3 (C_{ar}), 154.7 ($CO_2{}^tBu$), 140.7 (C_{ar}), 140.6 (C_{alkene}), 138.1, 133.6, 129.5, 129.5, 127.8, 127.8 ($C_{ar}H$), 127.4 (C_{alkene}), 127.0 (C_{ar}), 125.5 ($C_{ar}H$), 120.9 (C_{ar}), 114.8 ($C_{ar}H$), 88.9 (*C*–OAr), 80.2 (O–*C*Me_3), 39.7 (2 × CH_2N) 31.3 (2 × CH_2COAr), 28.6 ($(CH_3)_3$); (ES$^+$) *m*/*z*: 961 ([2M + Na]$^+$); Elemental analysis: Found: C, 63.62; H, 5.61; N, 2.72. $C_{25}H_{27}NO_6S$ requires: C, 63.95; H, 5.80; N, 2.98%.

REACTION MATRIX: Compounds 18–20

To a solution of **6** (150 mg, 0.53 mmol) and NEt_3 (0.1 mL) in THF (5.7 mL) was added benzoyl chloride (74 µL, 0.64 mmol). A white precipitate formed immediately. The reaction was stirred at room temperature for 5 minutes, after which LCMS revealed complete conversion to the amide intermediate (ES$^+$) *m*/*z*: 388, 386 ([M + H]$^+$). *N*-Methylpiperazine was added (0.2 mL), the reaction mixture was stirred for a further 5 minutes and then separated into 3 equal portions. To the 3 reaction mixtures were added 1-ethynyl-4-methoxybenzene (91 mg, 0.71 mmol), 3,3-dimethylbutyne (87 µL, 0.71 mmol), and 1-ethynyl-3-fluorobenzene (82 µL, 0.71 mmol) respectively. The reactions were then purged with nitrogen before addition of $Pd(PPh_3)_2Cl_2$ (6.2 mg, 8.7 µmol) and copper iodide (1.7 mg, 8.9 µmol). A second nitrogen purge was carried out and the reactions then heated in the microwave at 120 °C for 20 minutes (or 1 h for the 1-ethynyl-3-fluorobenzene substrates). On completion of coupling, the reaction mixtures were concentrated to give brown residues, which were purified by column chromatography (0–30% EtOAc–hexane) to afford the following products:

1′-Benzoyl-5-[(4-methoxyphenyl)ethynyl]-spiro[1-benzofuran-2,4′-piperidin]-3-one (18). Yield: 51 mg, 66%. Mp 164–165 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 1716, 1617 cm^{-1}; NMR (500 MHz, DMSO, 100 °C): δ_H 7.85 (1H, dd, *J* 8.7, 1.9, H_{ar}), 7.75 (1H, dd, *J* 1.8, 0.5, H_{ar}), 7.48–7.46 (7H, m, H_{ar}), 7.31 (1H, dd, *J* 8.5, 0.6, H_{ar}), 6.98 (2H, dd, *J* 6.8, 2.1, H_{ar}), 4.07 (2H, br d, *J* 12.0, $CH_{eq}N$), 3.82 (3H, s, OCH_3), 3.43 (2H, td, *J* 12.0, 3.5, $CH_{ax}N$), 1.90 (2H, td, *J* 11.2, 4.7, $CH_{ax}COAr$), 1.76 (2H, br d, *J* 10.9, $CH_{eq}COAr$); δ_C 199.8 (Ar–*C*=O), 169.1 (C_{ar}), 169.0 (N–*C*=O), 159.3 (C_{ar}), 140.6 ($C_{ar}H$), 135.6 (C_{ar}), 132.3 (2 × $C_{ar}H$), 128.9 ($C_{ar}H$), 127.8 (2 × $C_{ar}H$), 126.3 ($C_{ar}H$), 126.1 (2 × $C_{ar}H$), 119.4 (C_{ar}), 116.7, 113.8 (C_{ar}), 114.0 (2 × $C_{ar}H$), 113.7 ($C_{ar}H$), 88.8 (C_{alkyne}), 87.1 (*C*–OAr), 86.1 (C_{alkyne}), 54.9 (OCH_3), 39.0 (2 × CH_2N) 30.5 (2 × CH_2COAr); (ES$^+$) *m*/*z*: 438 ([M + H]$^+$); HR(ES$^+$) *m*/*z*: [M + H]$^+$: 438.1725. $C_{28}H_{24}NO_4$ requires 438.1705.

1′-Benzoyl-5-(3,3-dimethylbut-1-yn-1-yl)-spiro[1-benzofuran-2,4′-piperidin]-3-one (19). Yield: 47 mg, 69%. Mp 209–210 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 1715, 1616 cm^{-1}; NMR: δ_H 7.70 (1H, s, H_{ar}), 7.65 (1H, d, *J* 8.6, H_{ar}), 7.47–7.42 (5H, m, H_{ar}), 7.06 (1H, d, *J* 8.6, H_{ar}), 4.72 (1H, br s, $CH_{eq}N$), 3.86 (1H, br s, $CH_{eq}N$), 3.43 (2H, br s, $CH_{ax}N$), 2.02 (2H, br s, $CH_{ax}COAr$), 1.67 (2H, br s, $CH_{eq}COAr$), 1.31 (9H, s, $(CH_3)_3$); δ_C 201.3 (Ar–*C*=O), 170.8 (C_{ar}), 169.9 (N–*C*=O), 141.7 ($C_{ar}H$), 135.9 (C_{ar}), 130.0 ($C_{ar}H$), 128.8 (2 × $C_{ar}H$), 128.0 ($C_{ar}H$), 127.1 (2 × $C_{ar}H$), 120.1 (C_{ar}), 118.8 (C_{ar}), 113.8 ($C_{ar}H$), 98.9 (C_{alkyne}), 87.7 (*C*–OAr), 77.6 (C_{alkyne}), 32.0 (2 × CH_2N), 31.1 ($(CH_3)_3$), 31.1 (2 × CH_2COAr), 28.1 (*C*Me_3); (EI) *m*/*z*: 387 ([M]$^{+\bullet}$, 42), 282 (11), 240 (85), 105 (100); HR(EI) *m*/*z*: [M$^{+\bullet}$]: 387.1851. $C_{25}H_{25}NO_3$ requires 387.1834.

1′-Benzoyl-5-[(3-fluorophenyl)ethynyl]-spiro[1-benzofuran-xsxs2,4′-piperidin]-3-one (20). Yield: 40 mg, 53%, oil; IR: ν_{max} ($CDCl_3$ film) 1717, 1604 cm^{-1}; NMR: δ_H 7.81 (1H, dd, *J* 1.8, 0.5, H_{ar}), 7.85 (1H, dd, *J* 8.8, 1.8, H_{ar}), 7.48–7.42 (5H, m, H_{ar}), 7.35–7.29 (2H, m, H_{ar}), 7.21 (1H, d, *J* 9.2, H_{ar}), 7.15 (1H, d, *J* 8.8, H_{ar}), 7.09–7.04 (1H, m, H_{ar}), 4.73 (1H, br s, $CH_{eq}N$), 3.88 (1H, br s, $CH_{eq}N$), 3.45 (2H, br s, $CH_{ax}N$), 2.05 (2H, br s, $CH_{ax}COAr$), 1.71 (2H, br s, $CH_{eq}COAr$); δ_C 201.0 (Ar–*C*=O), 170.8 (C_{ar}), 170.6 (N–*C*=O), 162.6 (d, *J* 245.4, $C_{ar}F$), 141.6 ($C_{ar}H$), 135.9 (C_{ar}), 130.2 (d, *J* 8.7, $C_{ar}H$), 130.1 ($C_{ar}H$), 128.8 (2 × $C_{ar}H$), 128.4 ($C_{ar}H$), 127.7 ($C_{ar}H$), 127.1 (2 × $C_{ar}H$), 124.9 (d, *J* 9.7, C_{ar}), 120.4 (C_{ar}), 118.5 (d, *J* 23.2, $C_{ar}H$), 117.5 (C_{ar}), 116.0 (d, *J* 21.3, $C_{ar}H$), 114.3 ($C_{ar}H$), 88.7, 88.4 (C_{alkyne}), 88.0 (*C*–OAr), 38.5 (2 × CH_2N), 31.8 (2 × CH_2COAr); (ES$^+$) *m*/*z*: 448 ([M + Na]$^+$); HR(ES$^+$) *m*/*z*: [M + Na]$^+$: 448.1323. $C_{27}H_{20}NO_3Na$ requires 448.1319.

Compounds 21–23

Following the procedure described for the synthesis of **18** to **20**, **6** (150 mg, 0.53 mmol) was coupled with butyryl chloride (66 µL, 0.64 mmol) to afford the required acylated intermediate as identified by LCMS (ES$^+$) *m*/*z*: 354, 352 ([M + H]$^+$). Again the reaction mixture was divided into 3 portions and the intermediate bromide coupled with 1-ethynyl-4-methoxybenzene (91 mg, 0.71 mmol), 3,3-dimethylbutyne (87 µL, 0.71 mmol), and 1-ethynyl-3-fluorobenzene (82 µL, 0.71 mmol) respectively. The crude reaction mixtures were concentrated and purified by column chromatography (0–30% EtOAc–hexane) to afford the following products:

1′-Butyryl-5-[(4-methoxyphenyl)ethynyl]-spiro[1-benzofuran-2,4′-piperidin]-3-one (21). Yield: 42 mg, 59%, oil; IR: ν_{max} ($CDCl_3$ film) 1720, 1620 cm^{-1}; NMR: δ_H 7.81 (1H, d, *J* 1.8, H_{ar}), 7.77 (1H, dd, *J* 8.6, 1.8, H_{ar}), 7.46 (2H, d, *J* 9.0, H_{ar}), 7.12 (1H, d, *J* 8.8, H_{ar}), 6.89 (2H, d, *J* 9.0, H_{ar}), 4.64 (1H, br d, *J* 13.1, CH_{eq}N), 3.94 (1H, br d, *J* 14.0, CH_{eq}N), 3.84 (3H, s, OCH_3), 3.53 (1H, td, *J* 14.2, 3.1, CH_{ax}N), 3.15 (1H, td, *J* 12.8, 2.4, CH_{ax}N), 2.37 (2H, t, *J* 7.5, C(O)CH_2), 1.98 (1H, td, *J* 13.1, 4.8, CH_{ax}COAr), 1.94 (1H, td, *J* 13.8, 5.5, CH_{ax}COAr), 1.71 (2H, sext, *J* 7.5, CH_2CH_3), 1.73–1.66 (2H, m, CH_{eq}COAr), 1.01 (3H, t, *J* 7.5, CH_3); δ_C 201.3 (Ar–*C*=O), 171.7 (C_{ar}), 170.2 (N–*C*=O), 160.0 (C_{ar}), 141.5 (C_{ar}H), 133.2 (2 × C_{ar}H), 127.9 (C_{ar}H), 120.4 (C_{ar}), 115.1, 114.3 (C_{ar}), 114.3 (2 × C_{ar}H), 114.1 (C_{ar}H), 89.7 (C_{alkyne}), 87.9 (*C*–OAr), 86.6 (C_{alkyne}), 55.5 (OCH_3), 41.8, 37.7 (CH_2N), 35.5, 32.2, 31.5, 18.9 (CH_2), 14.2 (CH_3); (EI) *m*/*z*: 403 ([M]$^{+\bullet}$, 33), 333 (9), 290 (100); HR(EI) *m*/*z*: [$M^{+\bullet}$]: 403.1791. $C_{25}H_{25}NO_4$ requires 403.1784.

1′-Butyryl-5-(3,3-dimethylbut-1-yn-1-yl)-spiro[1-benzofuran-2,4′-piperidin]-3-one (22). Yield: 44 mg, 70%. Mp 147–148 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 1725, 1611 cm^{-1}. NMR: δ_H 7.69 (1H, dd, *J* 1.8, 0.4, H_{ar}), 7.64 (1H, dd, *J* 8.6, 1.8, H_{ar}), 7.05 (1H, dd, *J* 8.6, 0.6, H_{ar}), 4.63 (1H, br d, *J* 13.4, CH_{eq}N), 3.93 (1H, br d, *J* 13.5, CH_{eq}N), 3.51 (1H, td, *J* 13.6, 2.9, CH_{ax}N), 3.13 (1H, td, *J* 13.4, 2.9, CH_{ax}N), 2.36 (2H, t, *J* 7.5, C(O)CH_2), 1.96 (1H, td, *J* 13.4, 4.6, CH_{ax}COAr), 1.92 (1H, td, *J* 13.6, 4.8, CH_{ax}COAr), 1.71 (2H, sext, *J* 7.5, CH_2CH_3), 1.66 (2H, br d, *J* 13.2, CH_{eq}COAr), 1.31 (9H, s, $(CH_3)_3$), 1.00 (3H, t, *J* 7.5, CH_3); δ_C 201.4 (Ar–*C*=O), 171.7 (C_{ar}), 170.0 (N–*C*=O), 141.6 (C_{ar}H), 128.0 (C_{ar}H), 120.1 (C_{ar}), 118.8 (C_{ar}), 113.7 (C_{ar}H), 98.8 (C_{alkyne}), 87.7 (*C*–OAr), 77.6 (C_{alkyne}), 41.8, 37.7 (CH_2N), 35.5, 32.1, 31.5 (CH_2), 31.1 ($(CH_3)_3$), 28.1 (*C*Me$_3$), 19.0 (CH_2), 14.2 (CH_3); (EI) *m*/*z*: 353 ([M]$^{+\bullet}$, 18), 283 (15), 240 (100); HR(EI) *m*/*z*: [$M^{+\bullet}$]: 353.1981. $C_{22}H_{27}NO_3$ requires 353.1991.

1′-Butyryl-5-[(3-fluorophenyl)ethynyl]-spiro[1-benzofuran-2,4′-piperidin]-3-one (23). Yield: 35 mg, 50%, oil; IR: ν_{max} ($CDCl_3$ film) 1717, 1605 cm^{-1}; NMR: δ_H 7.84 (1H, d, *J* 1.8, H_{ar}), 7.79 (1H, dd, *J* 8.5, 1.8, H_{ar}), 7.35–7.29 (2H, m, H_{ar}), 7.22 (1H, d, *J* 9.5, H_{ar}), 7.15 (1H, d, *J* 8.5, H_{ar}), 7.09–7.04 (1H, m, H_{ar}), 4.66 (1H, br d, *J* 12.2, CH_{eq}N), 3.95 (1H, br d, *J* 10.8, CH_{eq}N), 3.53 (1H, t, *J* 11.0, CH_{ax}N), 3.16 (1H, t, *J* 12.0, CH_{ax}N), 2.37 (2H, t, *J* 7.7, C(O)CH_2), 1.97 (2H, br s, CH_{ax}COAr), 1.70 (2H, sext, *J* 7.6, CH_2CH_3), 1.72–1.66 (2H, m, CH_{eq}COAr), 1.01 (3H, t, *J* 7.5, CH_3); δ_C 201.1 (Ar–*C*=O), 171.7 (C_{ar}), 170.6 (N–*C*=O), 162.6 (d, *J* 245.4, C_{ar}F), 141.6 (C_{ar}H), 130.2 (d, *J* 8.7, C_{ar}H), 128.4 (C_{ar}H), 127.7 (C_{ar}H), 124.9 (d, *J* 9.7, C_{ar}), 120.5 (C_{ar}), 118.5 (d, *J* 23.1, C_{ar}H), 117.4 (C_{ar}), 116.0 (d, *J* 21.3, C_{ar}H), 114.2 (C_{ar}H), 88.8, 88.4 (C_{alkyne}), 88.1 (*C*–OAr), 41.8, 37.7 (CH_2N), 35.5, 32.2, 31.5, 19.0, (CH_2), 14.2 (CH_3); (ES$^+$) *m*/*z*: 414 ([M + Na]$^+$); HR(ES$^+$) *m*/*z*: [M + Na]$^+$: 414.1482. $C_{24}H_{22}NO_3Na$ requires 414.1476.

Compounds 24–26

Following the procedure described for the synthesis of **18** to **20**, **6** (150 mg, 0.53 mmol) was coupled with 2-furoyl chloride (63 μL, 0.64 mmol) to afford the required acylated intermediate as identified by LCMS (ES$^+$) *m*/*z*: 378, 376 ([M + H]$^+$). Again the reaction mixture was divided into 3 portions and the intermediate bromide coupled with 1-ethynyl-4-methoxybenzene (91 mg, 0.71 mmol), 3,3-dimethylbutyne (87 μL, 0.71 mmol), and 1-ethynyl-3-fluorobenzene (82 μL, 0.71 mmol) respectively. The crude reaction mixtures were concentrated and purified by column chromatography (0–30% EtOAc–hexane) to afford the following products:

1′-(2-Furoyl)-5-[(4-methoxyphenyl)ethynyl]-spiro[1-benzofuran-2,4′-piperidin]-3-one (24). Yield: 45 mg, 59%. Mp 155–156 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 1715, 1616 cm^{-1}; NMR: δ_H 7.82 (1H, d, *J* 1.8, H_{ar}), 7.78 (1H, dd, *J* 8.6, 1.8, H_{ar}), 7.50 (1H, d, *J* 1.8, H_{ar}), 7.46 (2H, d, *J* 8.8, H_{ar}), 7.14 (1H, d, *J* 8.6, H_{ar}), 7.05 (1H, d, *J* 3.5, H_{ar}), 6.89 (2H, d, *J* 8.8, H_{ar}), 6.51 (1H, dd, *J* 3.5, 1.8, H_{ar}), 4.60 (2H, br d, *J* 13.2, CH_{eq}N), 3.84 (3H, s, OCH_3), 3.55–3.44 (2H, m, CH_{ax}N), 2.10 (2H, ddd, *J* 13.8, 12.3, 4.8, CH_{ax}COAr), 1.74 (2H, br d, *J* 13.6, CH_{eq}COAr); δ_C 201.1 (Ar–*C*=O), 170.2 (C_{ar}), 160.0 (N–*C*=O), 159.4 (C_{ar}), 148.1 (C_{ar}), 143.9 (C_{ar}H), 141.5 (C_{ar}H), 133.2 (2 × C_{ar}H), 127.9 (C_{ar}H), 120.4 (C_{ar}), 118.3 (C_{ar}), 116.7 (C_{ar}H), 115.1 (C_{ar}), 114.3 (2 × C_{ar}H), 114.1, 111.6 (C_{ar}H), 89.7 (C_{alkyne}), 88.0 (*C*–OAr), 86.6 (C_{alkyne}), 55.5 (OCH_3), 41.0 (2 × CH_2N), 32.0 (2 × CH_2COAr); (EI) *m*/*z*: 427 ([M]$^{+\bullet}$, 52), 290 (99), 95 (100); HR(EI) *m*/*z*: [$M^{+\bullet}$]: 427.1407. $C_{26}H_{21}NO_5$ requires 427.1420.

5-(3,3-Dimethylbut-1-yn-1-yl)-1′-(2-furoyl)-spiro[1-benzofuran-2,4′-piperidin]-3-one (25). Yield: 43 mg, 64%. Mp 120–121 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 1715, 1616 cm^{-1}; NMR: δ_H 7.70 (1H, d, *J* 1.8, H_{ar}), 7.65 (1H, dd, *J* 8.6, 1.8, H_{ar}), 7.49 (1H, d, *J* 1.8, H_{ar}), 7.07 (1H, d, *J* 8.8, H_{ar}), 7.04 (1H, d, *J* 3.5, H_{ar}), 6.50 (1H, dd, *J* 3.5, 1.8, H_{ar}), 4.58 (2H, br d, *J* 13.2, CH_{eq}N), 3.53–3.43 (2H, m, CH_{ax}N), 2.07 (2H, td, *J* 14.1, 4.8, CH_{ax}COAr), 1.70 (2H, br d, *J* 14.3, CH_{eq}COAr), 1.31 (9H, s, $(CH_3)_3$); δ_C 201.2 (Ar–*C*=O), 169.9 (C_{ar}), 159.4 (N–*C*=O), 148.1 (C_{ar}), 143.9, 141.6, 128.0 (C_{ar}H), 120.1, 118.8 (C_{ar}), 116.7, 113.8, 111.5 (C_{ar}H), 98.8 (C_{alkyne}), 87.8 (*C*–OAr), 77.6 (C_{alkyne}), 40.0 (2 × CH_2N), 32.0 (2 × CH_2COAr), 31.1 ($(CH_3)_3$), 28.1 (*C*Me$_3$); (EI) *m*/*z*: 377 ([M]$^{+\bullet}$, 14), 240 (52), 95 (100); HR(EI) *m*/*z*: [$M^{+\bullet}$]: 377.1619. $C_{23}H_{23}NO_4$ requires 377.1627.

1′-(2-Furoyl)-5-[(3-fluorophenyl)ethynyl]-spiro[1-benzofuran-2,4′-piperidin]-3-one (26). Yield: 35 mg, 49%, oil; IR: ν_{max} ($CDCl_3$ film) 1713, 1603 cm^{-1}; NMR: δ_H 7.86 (1H, d, *J* 1.8, H_{ar}), 7.80 (1H, dd, *J* 8.5, 1.8, H_{ar}), 7.51 (1H, dd, *J* 1.8, 0.8, H_{ar}), 7.36–7.28 (2H, m, H_{ar}), 7.22 (1 H, dd, *J* 9.0, 0.8, H_{ar}), 7.16 (1H, d, *J* 8.7, H_{ar}), 7.09–7.04 (1H, m, H_{ar}), 7.06 (1H, dd, *J* 3.5, 0.8, H_{ar}), 6.51 (1H, dd, *J* 3.5, 1.8, H_{ar}), 4.60 (2H, br d, *J* 13.0, CH_{eq}N), 3.52 (2H, br s, CH_{ax}N), 2.11 (2H, td, *J* 14.0, 4.8, CH_{ax}COAr), 1.75 (2H, br d, *J* 13.5, CH_{eq}COAr); δ_C 201.0 (Ar–*C*=O), 170.6 (C_{ar}), 162.6 (d, *J* 245.4, C_{ar}F), 159.5 (N–*C*=O), 148.1 (C_{ar}), 143.9, 141.6 (C_{ar}H), 130.2 (d, *J* 8.7, C_{ar}H), 128.4 (C_{ar}H), 127.7 (C_{ar}H), 124.9 (d, *J* 9.7, C_{ar}), 120.5 (C_{ar}), 118.5 (d, *J* 23.1, C_{ar}H), 117.4 (C_{ar}), 116.8 (C_{ar}H), 116.0 (d, *J* 21.2, C_{ar}H), 114.2 (C_{ar}H), 111.6 (C_{ar}H), 88.8, 88.4 (C_{alkyne}), 88.2 (*C*–OAr), 40.0 (2 × CH_2N), 32.0 (2 × CH_2COAr); (ES$^+$) *m*/*z*: 438 ([M + Na]$^+$); HR(ES$^+$) *m*/*z*: [M + Na]$^+$: 438.1114. $C_{25}H_{18}NO_4Na$ requires 438.1112.

***tert*-Butyl 5-bromo-3-hydroxy-spiro[1-benzofuran-2,4′-piperidine]-1′-carboxylate (27).** To a solution of **7** (50 mg, 0.13 mmol) in ethanol (2 mL) was added $NaBH_4$ (6 mg, 0.15 mmol) and the reaction stirred at room temperature for 5 minutes. Acetic acid was then added (0.1 mL) and the reaction concentrated to a white residue (80 mg). The residue was purified by column chromatography (10–20% EtOAc–hexane) to afford the title compound **27** as a white powder (50 mg, 0.13 mmol, 99%); Mp 142–143 °C (EtOAc–hexane); IR: ν_{max} ($CDCl_3$ film) 3385, 1668 cm^{-1}; NMR: δ_H 7.51 (1H, d, *J* 2.2, H_{ar}), 7.36 (1H, dd, *J* 8.6, 2.2, H_{ar}), 6.73 (1H, d, *J* 8.6, H_{ar}), 4.79 (1H, s, *J* 5.3, C*H*OH), 3.91 (1H, br d, *J* 13.4, CH_{eq}N), 3.80 (1H, br d, *J* 13.1, CH_{eq}N), 3.58–3.31 (2H, m, CH_{ax}N), 1.92–1.90 (2H, m, CH_{ax}COAr), 1.65–1.58 (2H, m, CH_{eq}COAr), 1.48 (9H, s, $(CH_3)_3$), (O*H* not observed); δ_C 157.8 (C_{ar}), 155.0 ($CO_2{}^tBu$), 133.8 (C_{ar}H), 130.7 (C_{ar}), 129.4, 112.8 (C_{ar}H), 112.6 (C_{ar}), 89.3 (*C*–OAr), 80.0 (O–*C*Me$_3$), 77.5 (Ar–*C*OH), 40.7 (2 × CH_2N) 34.5, 29.6 (CH_2COAr) 28.6 ($(CH_3)_3$). (EI) *m*/*z*: 383, 385 ([M]$^{+\bullet}$, 32), 327, 329 ([M–C_4H_8]$^+$, 76), 223, 225 (78), 57 ($C_4H_9{}^+$, 100); HRMS (EI) *m*/*z*: [$M^{+\bullet}$]: 383.0732. $C_{17}H_{22}BrNO_4$ requires 383.0730.

***tert*-Butyl 3-allyl-5-bromo-3-hydroxy-spiro[1-benzofuran-2,4′-piperidine]-1′-carboxylate (28).** To a solution of **7** (100 mg, 0.26 mmol) in THF (2 mL) at 0 °C was added allylMgBr (0.39 mL, 0.39 mmol) and the reaction stirred at this temperature

for 10 min. Sat. NH_4Cl solution was then added (2 mL) and the resulting biphasic mixture extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated to an orange residue (136 mg). The residue was purified by column chromatography (5–10% EtOAc–hexane) to afford the title compound **28** as a white solid (85 mg, 0.20 mmol, 77%); Mp 82–83 °C (EtOAc–hexane); IR: ν_{max} (film) 3404, 1659 cm^{-1}; NMR: δ_H 7.40 (1H, d, *J* 2.0, H_{ar}), 7.33 (1H, dd, *J* 8.3, 2.0, H_{ar}), 6.73 (1H, d, *J* 8.5, H_{ar}), 6.02 (1H, ddt, *J* 17.3, 10.0, 7.3, CH_2=C*H*), 5.29 (1H, d, J_{cis} 10.0, CH_2=CH), 5.25 (1H, d, J_{trans} 17.3, CH_2=CH), 4.09 (2H, br s, CH_{eq}N), 3.10 (2H, br s, CH_{ax}N), 2.68 (1H, dd, *J* 14.3, 7.3, CH_2=CHCH_2), 2.51 (1H, dd, *J* 14.3, 7.3, CH_2=CHCH_2), 1.97 (1H, dd, *J* 14.0, 1.8, CH_{eq}COAr), 1.71 (2H, td, *J* 13.8, 4.8, CH_{ax}COAr), 1.58 (1H, dd, *J* 14.0, 1.8, CH_{eq}COAr), 1.47 (9H, s, (CH_3)$_3$), (O*H* not observed); δ_C 156.9 (C_{ar}), 155.0 (*C*O$_2$^{t}Bu), 134.5 (C_{ar}), 133.2 (C_{ar}H), 132.1 (CH_2=*C*H), 127.6 (C_{ar}H), 120.5 (*C*H$_2$=CH), 113.0 (C_{ar}H), 112.6 (C_{ar}), 91.6 (*C*–OAr), 80.9 (Ar–*C*OH), 79.8 (O–*C*Me$_3$), 40.4 (2 × *C*H$_2$N), 39.5 (CH_2=CH*C*H$_2$), 30.8, 29.8 (*C*H$_2$COAr), 28.6 ((*C*H$_3$)$_3$). (ES$^+$) *m*/*z*: 424, 426 ([M + H]$^+$); Elemental analysis: Found: C, 56.26; H, 6.05; N, 3.16. $C_{20}H_{26}BrNO_4$ requires: C, 56.61; H, 6.18; N, 3.30%.

***tert*-Butyl 5-bromo-3-ethyl-3-hydroxy-spiro[1-benzofuran-2,4′-piperidine]-1′-carboxylate (29).** To a solution of **7** (100 mg, 0.26 mmol) in THF (2 mL) at 0 °C was added EtMgBr (0.39 mL, 0.39 mmol) and the reaction stirred at this temperature for 30 min. Sat. NH_4Cl solution was then added (2 mL) and the resulting biphasic mixture extracted with EtOAc (3 × 5 mL). The combined organic fractions were concentrated to an orange residue (136 mg). The residue was purified by column chromatography (10–20% EtOAc–hexane) to afford the title compound **29** as a white powder (26 mg, 63 μmol, 24%). The reduced product **27** was also recovered from the reaction (56 mg, 0.15 mmol, 56%); Mp 81–82 °C (EtOAc–hexane); IR: ν_{max} (film) 3153, 1663 cm^{-1}; NMR: δ_H 7.39 (1H, d, *J* 2.2, H_{ar}), 7.33 (1H, dd, *J* 8.5, 2.2, H_{ar}), 6.72 (1H, d, *J* 8.3, H_{ar}), 4.08 (2H, br s, CH_{eq}N), 3.11 (2H, br s, CH_{ax}N), 1.97 (2H, br d, *J* 14.5, CH_{eq}COAr), 1.79 (2H, q, *J* 7.5, CH_2CH$_3$), 1.67–1.61 (2H, m, CH_{ax}COAr), 1.48 (9H, s, (CH_3)$_3$), 1.09 (3H, t, *J* 7.5, CH$_2$CH_3), (O*H* not observed); δ_C 156.8 (C_{ar}), 155.0 (*C*O$_2$^{t}Bu), 135.1 (C_{ar}), 133.1, 127.4, 113.0 (C_{ar}H), 112.6 (C_{ar}), 91.7 (*C*–OAr), 82.0 (Ar–*C*OH), 79.8 (O–*C*Me$_3$), 40.4 (2 × *C*H$_2$N), 30.7, 30.1 (*C*H$_2$COH) 28.6 ((*C*H$_3$)$_3$), 27.7 (*C*H$_2$CH$_3$), 7.8 (CH$_2$*C*H$_3$); (ES$^+$) *m*/*z*: 312, 314 ([M + H–C$_4$H$_8$OCO]$^+$); HRMS (EI) *m*/*z*: [M–H$_2$O$^{+\bullet}$]: Found 393.0941. $C_{19}H_{24}BrNO_3$ requires 393.0940.

***tert*-Butyl 5-bromo-3-hydroxy-3-(2-phenylethynyl)-spiro[1-benzofuran-2,4′-piperidine]-1′-carboxylate (30).** To a solution of phenylacetylene (30 μL, 0.27 mmol) in THF (1 mL) at −78 °C was added ^{n}BuLi (2.31 M solution in hexanes, 119 μL, 0.27 mmol) and the reaction stirred at this temperature for 15 min. The anion formed was then added dropwise to a solution of **7** (100 mg, 0.26 mmol) in THF (2 mL) at −78 °C and the reaction warmed to −20 °C to be stirred at this temperature for 1 h. The reaction was later poured into sat. NH_4Cl solution and extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with water (20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated to an orange residue (120 mg). The residue was purified by column chromatography (10% EtOAc–hexane) to afford the title compound **30** as a white solid (63 mg, 0.13 mmol, 50%); Mp 217–218 °C (EtOAc–hexane); IR: ν_{max} (film) 3350, 1660 cm^{-1}; NMR: δ_H 7.64 (1H, d, *J* 2.3, H_{ar}), 7.48 (2H, dd, *J* 7.8, 1.8, H_{ar}), 7.39 (1H, dd, *J* 8.5, 2.1, H_{ar}), 7.37–7.33 (3H, m, H_{ar}), 6.77 (1H, d, *J* 8.5, H_{ar}), 4.18 (1H, br s, CH_{eq}N), 4.07 (1H, br s, CH_{eq}N), 3.18–3.09 (2H, br m, CH_{ax}N), 2.59 (1H, s, O*H*), 2.15 (1H, dd, *J* 14.0, 2.3, CH_{eq}COAr), 2.03 (1H, td, *J* 13.3, 4.3, CH_{ax}COAr), 1.92 (1H, td, *J* 13.6, 5.0, CH_{ax}COAr), 1.72 (1H, dd, *J* 13.8, 2.0, CH_{eq}COAr), 1.48 (9H, s, (CH_3)$_3$); δ_C 157.2 (C_{ar}), 155.0 (*C*O$_2$^{t}Bu), 134.1 (C_{ar}H), 133.3 (C_{ar}), 132.0 (2 × C_{ar}H), 129.3 (C_{ar}H), 128.6 (2 × C_{ar}H), 127.9 (C_{ar}H), 111.8 (C_{ar}), 113.2 (C_{ar}H), 113.1 (C_{ar}), 92.4 (*C*–OAr), 88.9, 85.6 (C_{alkyne}), 79.9 (Ar–*C*OH), 78.1 (O–*C*Me$_3$), 40.5 (2 × *C*H$_2$N), 33.0 (2 × *C*H$_2$COAr), 28.6 ((*C*H$_3$)$_3$); (ES$^-$) *m*/*z*: 482, 484 ([M–H]$^-$); Elemental analysis: Found: C, 56.26; H, 6.05; N, 3.16. $C_{25}H_{26}BrNO_4$ requires: C, 56.61; H, 6.18; N, 3.30%.

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