

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

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Received 24th May 2005, Accepted 13th July 2005

First published as an Advance Article on the web 3rd August 2005

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 spiro-piperidine 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 spiro-piperidine 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 spiro-piperidine **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 spiro-piperidine scaffold **6** and go on to demonstrate its facile elaboration by selective reactions of the amino, aryl bromide and carbonyl functionalities.

Results and discussion

Our analysis of the *N*-protected spiro-piperidine 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,

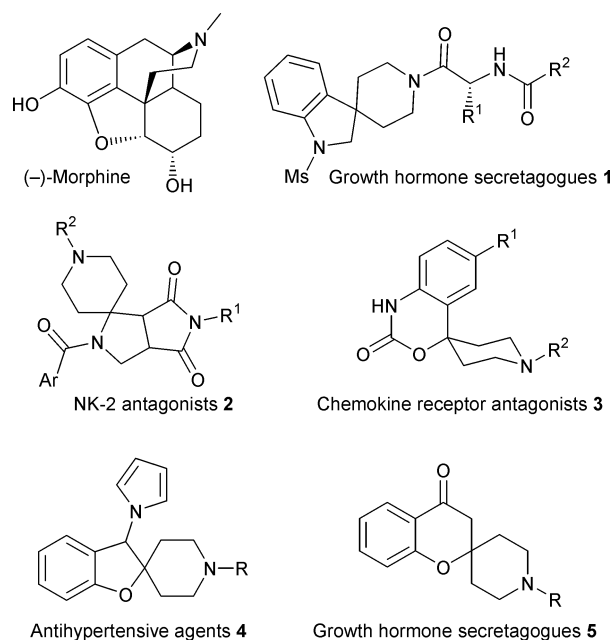


Fig. 1 Biologically active spiro-piperidines.

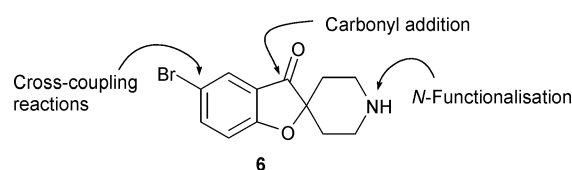
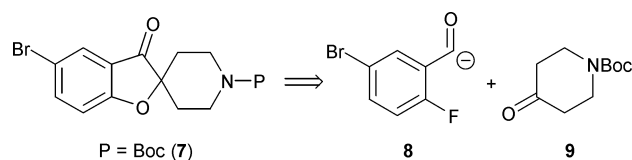
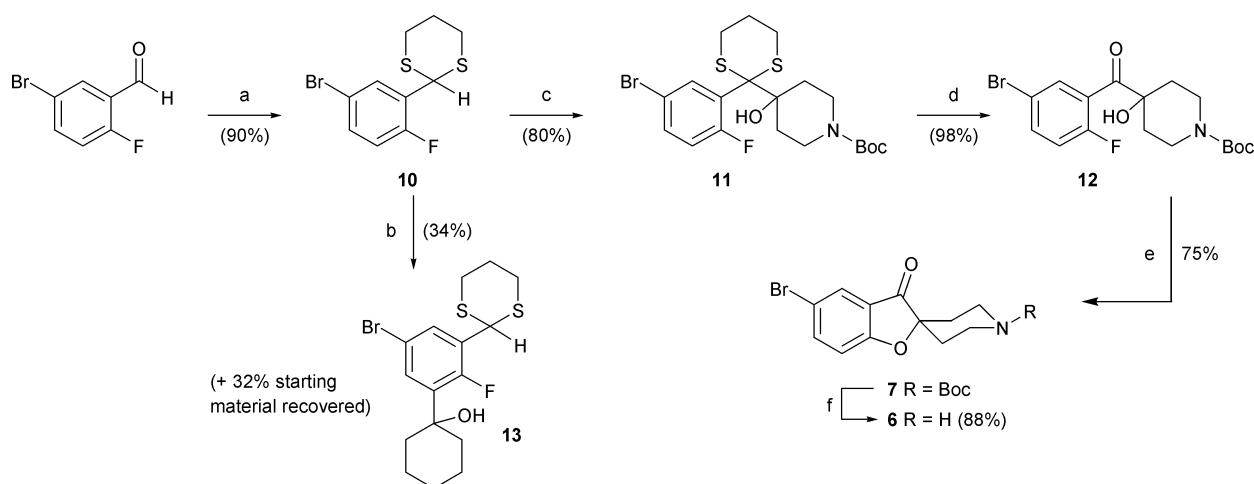


Fig. 2 Spiro[1-benzofuran-2,4'-piperidin]-3-one scaffold.

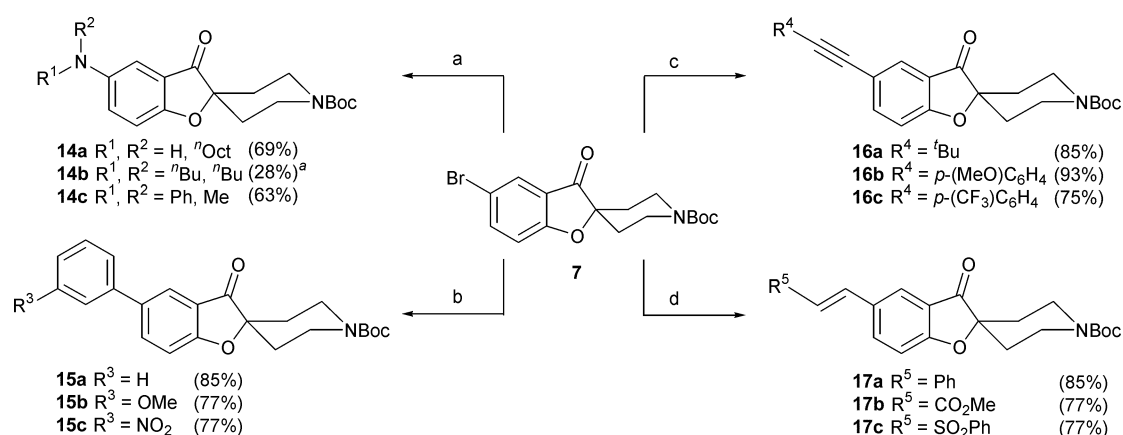


Scheme 1 Synthetic approach to spiro-piperidine scaffold.

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 $-78\text{ }^{\circ}\text{C}$ using LDA led to metallation of the aromatic



Scheme 2 Reagents and conditions: a) 1,3-propanedithiol, 0.03 eq I₂, CHCl₃; b) LDA, -78 °C, cyclohexanone, THF; c) LDA, -20 °C, **9**, THF; d) C₃H₅N·HBr·Br₂, pyridine, TBAB, H₂O, DCM; e) ^tBuOK, THF, 70 °C, 5 min (μw); f) TFA, DCM, 140 °C, 20 min, (μw).



Scheme 3 Reagents and conditions: a) HNR₁R₂, Pd₂(dba)₃, BINAP, ^tBuOK, PhMe, 100 °C, 1 h, (μw); b) ArB(OH)₂, Pd(PPh₃)₄, Na₂CO₃, PhMe/EtOH/H₂O (5 : 5 : 2), 110 °C, 10 min, (μw); c) R₄CCH, Pd(PPh₃)₂Cl₂, CuI, NEt₃, 120 °C, 20 min (μw); d) R₅CHCH₂, Pd(OAc)₂, P(*o*-tol), NEt₃, DMF, 100 °C, 18 h. ^a(42% Debrominated starting material recovered).

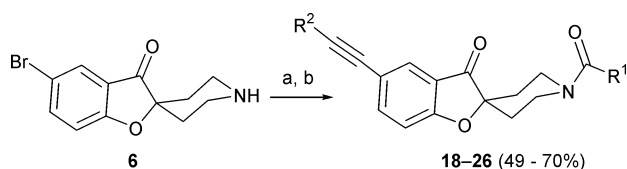
ring adjacent to the fluorine substituent.¹⁵ On warming the reaction mixture to -20 °C, the aryl lithium intermediate underwent equilibration to the thermodynamically preferred dithiane anion. Evidence for kinetic *ortho*-lithiation came from the isolation of 1-aryl-1-cyclohexanol **13** when the lithiation 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-piperidine (**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 ^tBuOK 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 spirocyclic scaffold **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 Pd₂(dba)₃/BINAP/Na^tBu system to secure

the desired anilines **14a–c**, even with the problematic 2° amine ⁿBu₂NH.^{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 spirocyclic 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) $R^1\text{COCl}$, NEt_3 , THF, RT; b) $R^2\text{CCH}$, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI , *N*-methylpiperazine, THF, 120°C , (μw).

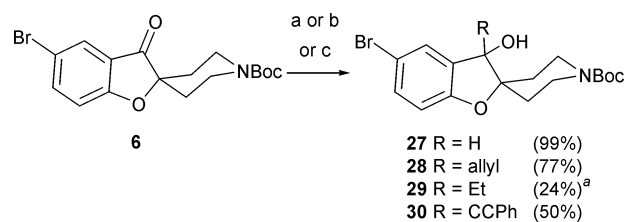
Table 1 3×3 Matrix for sequential derivatisation of **6** (see Scheme 4)

	Yield ^a (compound number)		
	$R^2 = p\text{-MeOC}_6\text{H}_4$	$R^2 = t\text{Bu}$	$R^2 = m\text{-FC}_6\text{H}_4$
$R^1 = \text{Ph}$	66% (18)	69% (19)	53% (20)
$R^1 = n\text{Pr}$	59% (21)	70% (22)	50% (23)
$R^1 = 2\text{-furyl}$	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 $t\text{PrMgCl}$ and PhMgCl failed to react.



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

In summary, an efficient approach has been developed to access a novel spirocyclic 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. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ 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- $0.25\ \mu\text{m}$ ($30\ \text{m} \times 0.25\ \text{mm}$). Microwave irradiation was carried out in a Biotage Smith SynthesiserTM.

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 $\text{Na}_2\text{S}_2\text{O}_3$ 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 $51\text{--}53^\circ\text{C}$ (DCM-hexane); IR: ν_{max} (CDCl_3 film) $1484\ \text{cm}^{-1}$; 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_{arF}), 133.0 (d, J 8.7, C_{arH}), 132.7 (d, J 2.9, C_{arH}), 128.6 (d, J 15.4, C_{ar}), 117.4 (d, J 24.2, C_{arH}), 117.3 (C_{ar}), 42.6 (d, J 4.5, CH), 32.2 ($2 \times \text{CH}_2\text{S}$), 25.1 (CH_2); (EI) m/z (%): 292, 294 ($[\text{M}]^+$, 39), 217, 219 (51), 74 (100); Elemental analysis: Found: C, 40.98; H, 3.56. $\text{C}_{10}\text{H}_{10}\text{BrFS}_2$ 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 $t\text{BuLi}$ (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 ($3 \times 15\ \text{mL}$). 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 $118\text{--}119^\circ\text{C}$ (EtOAc-hexane). Starting material **10** was also recovered from the reaction (64 mg, 32%). IR: ν_{max} (CDCl_3 film) $3442, 1446\ \text{cm}^{-1}$; 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, $\text{CH}_2 + \text{OH}$), 1.35–1.28 (1H, m, H_{cyc}); δ_{C} 155.5 (d, J 247.3, C_{arF}), 138.3 (d, J 14.5, C_{ar}), 131.2 (d, J 2.9, C_{arH}), 130.4 (d, J 4.9, C_{arH}), 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, $2 \times \text{CH}_2$), 32.4 ($2 \times \text{CH}_2\text{S}$), 25.3, 25.2 (CH_2), 21.9 ($2 \times \text{CH}_2$); (EI) m/z (%): 390, 392 ($[\text{M}]^+$, 47), 372, 374 (36), 105 (78), 45 (100); Elemental analysis: Found: C, 48.73; H, 5.20. $\text{C}_{16}\text{H}_{20}\text{BrFOS}_2$ 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 $111\text{--}112^\circ\text{C}$ (hexane); IR: ν_{max} (CDCl_3 film) $3428, 1673\ \text{cm}^{-1}$; 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– CM_e_3), 77.0 (COH), 69.6 (d, J 6.8, CS_2), 39.7 (2 \times CH_2N), 32.6 (2 \times CH_2COH), 28.6 ($(CH_3)_3$), 27.84 (2 \times 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. C₂₀H₂₇BrFOS₂ 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 \times 160 mL). The combined organic fractions were washed with water (400 mL), brine (400 mL), dried (Na₂SO₄), 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} (CDCl₃ 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 (CO₂^tBu), 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– CM_e_3), 77.8 (COH), 39.1 (2 \times CH_2N), 33.3 (2 \times CH_2COH), 28.5 ($(CH_3)_3$); (ES⁺) m/z : 402, 404 ([M + H]⁺); HR(ES⁺) m/z : [2M + Na]⁺: 825.1174. C₃₄H₄₂Br₂F₂N₂O₈Na 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 ^tBuOK (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 \times 10 mL). The combined organic fractions were washed with water (30 mL), brine (30 mL), dried (Na₂SO₄), 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} (CDCl₃ 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 (CO₂^tBu), 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– CM_e_3), 39.8 (2 \times CH_2N), 31.4 (2 \times CH_2COH), 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. C₁₇H₂₀BrNO₄ 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% NH₃) 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} (CDCl₃ 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 \times CH_2N), 30.1 (2 \times CH_2COAr); (EI) m/z : 281, 283 ([M⁺], 81), 238, 240 (18), 56 (100); HR(EI) m/z : [M⁺]: 281.0036. C₁₂H₁₂BrNO₂ 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 μ mol) in toluene (1.3 mL) was added Pd₂(dba)₃ (4.8 mg, 5.2 μ mol) and the reaction stirred at room temperature for 5 min. To this solution was added **7** (100 mg, 0.26 mmol), octylamine (56 μ L, 0.34 mmol), and ^tBuONa (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} (CDCl₃ 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, ArNHCH₂), 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(CH₃)₃), 1.44–1.21 (10H, m, 5 \times CH_2), 0.89 (3H, t, J 7.0, CH_3); δ_c 203.3 (Ar–C=O), 164.9 (C_{ar}), 154.8 (CO₂^tBu), 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– CM_e_3), 44.8 (CH₂NH), 40.1 (2 \times CH_2N), 32.0, 32.0, 31.6, 29.5, 29.5, 29.4 (CH₂), 28.6 ($(CH_3)_3$), 27.3, 22.8 (CH₂), 14.2 (CH₃); (ES⁺) m/z : 883 ([2M + Na]⁺), 431 ([M + H]⁺); HR(ES⁺) m/z : 431.2904. C₂₅H₃₉N₂O₄ 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 μ L, 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} (CDCl₃ 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(CH₂)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(CH₃)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 (CO₂^tBu), 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– CM_e_3), 51.7 (2 \times CH_2N), 40.4, 39.6 (CH₂N), 31.6, 29.4 (4 \times CH_2), 28.6 ($(CH_3)_3$), 20.5 (2 \times CH_2), 14.2 (2 \times CH_3); (ES⁺) m/z : 431 ([M + H]⁺); HR(ES⁺) m/z : 431.2899. C₂₅H₃₉N₂O₄ 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 μ L, 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} (CDCl₃ 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, NCH₃), 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 (CO₂^tBu), 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– CM_e_3), 40.9

(NCH₃), 39.9 (2 × CH₂N), 33.6 (2 × CH₂COAr), 28.6 ((CH₃)₃); (ES⁺) *m/z*: 409 ([M + H]⁺), 426 ([M + NH₄]⁺); HR(ES⁺) *m/z*: 409.2127. C₂₄H₂₉N₂O₄ 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 Na₂CO₃ (1 mL) was added Pd(PPh₃)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 (Na₂SO₄), 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} (CDCl₃ 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, (CH₃)₃); δ_{C} 202.6 (Ar–C=O), 170.6 (*C*_{ar}), 154.8 (CO₂'Bu), 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(CH₃)₃), 39.8 (2 × CH₂N) 31.5 (2 × CH₂COAr) 28.6 ((CH₃)₃); (ES⁺) *m/z*: 781 ([2M + Na]⁺); Elemental analysis: Found: C, 72.84; H, 6.68; N, 3.63. C₂₃H₂₅NO₄ 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} (CDCl₃ 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, OCH₃), 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(CH₃)₃); δ_{C} 202.6 (Ar–C=O), 170.6 (*C*_{ar}), 160.3 (*C*_{ar}), 154.8 (CO₂'Bu), 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–CMe₃), 55.5 (OCH₃), 40.0 (2 × CH₂N), 31.5 (2 × CH₂COAr) 28.6 (C(CH₃)₃); (ES⁺) *m/z*: 841 ([2M + Na]⁺); Elemental analysis: Found: C, 69.99; H, 6.70; N, 3.33. C₂₄H₂₇NO₅ 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} (CDCl₃ 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, (CH₃)₃); δ_{C} 202.1 (Ar–C=O), 171.1 (*C*_{ar}), 154.8 (CO₂'Bu), 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–CMe₃), 39.8 (2 × CH₂N) 31.5 (2 × CH₂COAr) 28.6 ((CH₃)₃); (ES⁺) *m/z*: 871 ([2M + Na]⁺); Elemental analysis: Found: C, 64.84; H, 5.78; N, 6.53. C₂₃H₂₄N₂O₆ 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 μ L, 0.78 mmol) in NEt₃ (2 mL) was added Pd(PPh₃)₂Cl₂ (9.2 mg, 13.1 μ mol) followed by CuI (2.5 mg, 13.1 μ mol). The reaction was purged with N₂ 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} (CDCl₃ 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(CH₃)₃), 1.49 (9H, s, CC(CH₃)₃); δ_{C} 201.8 (Ar–C=O), 170.0 (*C*_{ar}), 154.8 (CO₂'Bu), 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–CMe₃), 77.7 (*C*_{alkyne}), 40.1 (2 × CH₂N), 31.5 (2 × CH₂COAr), 31.1 (OC(CH₃)₃), 28.6 (CC(CH₃)₃), 28.1 (CCMe₃); (EI) *m/z*: 383 ([M⁺], 36), 310 (57), 56 (100); HR(EI) *m/z*: [M⁺]: 383.2077. C₂₃H₂₉NO₄ 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} (CDCl₃ 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, OCH₃), 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(CH₃)₃); δ_{C} 201.6 (Ar–C=O), 170.3 (*C*_{ar}), 160.0 (*C*_{ar}), 154.8 (CO₂'Bu), 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–CMe₃), 55.5 (OCH₃), 40.2 (2 × CH₂N) 31.5 (2 × CH₂COAr) 28.6 (C(CH₃)₃); (ES⁺) *m/z*: 378 ([M + H–C₄H₈]⁺), 334 ([M + H–C₄H₈OCO]⁺); HR(ES⁺) *m/z* [M + H–C₄H₈OCO]⁺: 334.1454. C₂₁H₂₀NO₃ 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 μ L, 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} (CDCl₃ 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(CH₃)₃); δ_{C} 201.4 (Ar–C=O), 170.7 (*C*_{ar}), 154.8 (CO₂'Bu), 141.4 (*C*_{ar}H), 132.0 (2 × *C*_{ar}H), 130.3 (q, *J* 32.9, *C*_{ar}CF₃), 128.6 (*C*_{ar}H), 127.0 (*C*_{ar}), 123.1 (q, *J* 272.0, CF₃), 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–CMe₃), 39.8 (2 × CH₂N), 31.4 (2 × CH₂COAr) 28.6 (C(CH₃)₃); ¹⁹F NMR (376 MHz): δ_{F} 63.2 (CF₃); (ES⁺) *m/z*: 416 ([M + H–C₄H₈]⁺), 372 ([M + H–C₄H₈OCO]⁺); HR(EI) *m/z*: [M + H–C₄H₈OCO]⁺: 372.1216 C₂₁H₁₇NO₂F₃ 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 μ mol) and P(*o*-tol)₃ (7.3 mg, 23.54 μ mol) in DMF (1 mL) was added **7** (100 mg, 0.26 mmol), styrene (36 μ L, 0.31 mmol), and triethylamine (55 μ L, 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 (Na₂SO₄), 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} (CDCl₃ 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, (CH₃)₃); δ_{C} 202.4 (Ar–C=O), 170.6 (*C*_{ar}), 154.8 (CO₂Bu), 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–CMe₃), 40.0 (2 × CH₂N), 31.5 (2 × CH₂COAr), 28.6 ((CH₃)₃); (ES⁺) *m/z*: 833 ([2M + Na]⁺); Elemental analysis: Found: C, 73.99; H, 6.54; N, 3.36. C₂₅H₂₇NO₄ requires: C, 74.05; H, 6.71; N, 3.45%.

tert-Butyl 5-[(1E)-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 μ L, 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} (CDCl₃ 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, OCH₃), 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, (CH₃)₃); δ_{C} 201.7 (Ar–C=O), 172.0 (*C*_{ar}), 167.3 (CO₂Me), 154.7 (CO₂Bu), 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–CMe₃), 51.9 (OCH₃), 39.8 (2 × CH₂N) 31.4 (2 × CH₂COAr), 28.6 ((CH₃)₃); (ES⁺) *m/z*: 797 ([2M + Na]⁺); Elemental analysis: Found: C, 64.96; H, 6.33; N, 3.41. C₂₁H₂₅NO₆ 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} (CDCl₃ 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, (CH₃)₃); δ_{C} 201.3 (Ar–C=O), 172.3 (*C*_{ar}), 154.7 (CO₂Bu), 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–CMe₃), 39.7 (2 × CH₂N) 31.3 (2 × CH₂COAr), 28.6 ((CH₃)₃); (ES⁺) *m/z*: 961 ([2M + Na]⁺); Elemental analysis: Found: C, 63.62; H, 5.61; N, 2.72. C₂₅H₂₇NO₆S 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 NEt₃ (0.1 mL) in THF (5.7 mL) was added benzoyl chloride (74 μ L, 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 μ L, 0.71 mmol), and 1-ethynyl-3-fluorobenzene (82 μ L, 0.71 mmol) respectively. The reactions were then purged with nitrogen before addition

of Pd(PPh₃)₂Cl₂ (6.2 mg, 8.7 μ mol) and copper iodide (1.7 mg, 8.9 μ mol). 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} (CDCl₃ 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, OCH₃), 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 (OCH₃), 39.0 (2 × CH₂N) 30.5 (2 × CH₂COAr); (ES⁺) *m/z*: 438 ([M + H]⁺); HR(ES⁺) *m/z*: [M + H]⁺: 438.1725. C₂₈H₂₄NO₄ 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} (CDCl₃ 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, (CH₃)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 × CH₂N), 31.1 ((CH₃)₃), 31.1 (2 × CH₂COAr), 28.1 (CMe₃); (EI) *m/z*: 387 ([M]⁺, 42), 282 (11), 240 (85), 105 (100); HR(EI) *m/z*: [M]⁺: 387.1851. C₂₅H₂₅NO₃ requires 387.1834.

1'-Benzoyl-5-[(3-fluorophenyl)ethynyl]-spiro[1-benzofuran-2,4'-piperidin]-3-one (20). Yield: 40 mg, 53%, oil; IR: ν_{\max} (CDCl₃ 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 × CH₂N), 31.8 (2 × CH₂COAr); (ES⁺) *m/z*: 448 ([M + Na]⁺); HR(ES⁺) *m/z*: [M + Na]⁺: 448.1323. C₂₇H₂₀NO₃Na 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 μ L, 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 μ L, 0.71 mmol), and 1-ethynyl-3-fluorobenzene (82 μ L, 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} (CDCl₃ 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, OCH₃), 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)CH₂), 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, CH₂CH₃), 1.73–1.66 (2H, m, *CH*_{eq}COAr), 1.01 (3H, t, *J* 7.5, CH₃); 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 (OCH₃), 41.8, 37.7 (CH₂N), 35.5, 32.2, 31.5, 18.9 (CH₂), 14.2 (CH₃); (EI) *m/z*: 403 ([M]⁺, 33), 333 (9), 290 (100); HR(EI) *m/z*: [M]⁺: 403.1791. C₂₅H₂₅NO₄ 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} (CDCl₃ 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)CH₂), 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, CH₂CH₃), 1.66 (2H, br d, *J* 13.2, *CH*_{eq}COAr), 1.31 (9H, s, (CH₃)₃), 1.00 (3H, t, *J* 7.5, CH₃); 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 (CH₂N), 35.5, 32.1, 31.5 (CH₂), 31.1 ((CH₃)₃), 28.1 (CMe₃), 19.0 (CH₂), 14.2 (CH₃); (EI) *m/z*: 353 ([M]⁺, 18), 283 (15), 240 (100); HR(EI) *m/z*: [M]⁺: 353.1981. C₂₂H₂₇NO₃ 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} (CDCl₃ 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)CH₂), 1.97 (2H, br s, *CH*_{ax}COAr), 1.70 (2H, sext, *J* 7.6, CH₂CH₃), 1.72–1.66 (2H, m, *CH*_{eq}COAr), 1.01 (3H, t, *J* 7.5, CH₃); 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}), 116.8 (*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}), 88.1 (C–OAr), 41.8, 37.7 (CH₂N), 35.5, 32.2, 31.5, 19.0, (CH₂), 14.2 (CH₃); (ES⁺) *m/z*: 414 ([M + Na]⁺); HR(ES⁺) *m/z*: [M + Na]⁺: 414.1482. C₂₄H₂₂NO₃Na 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 μ L, 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 μ L, 0.71 mmol), and 1-ethynyl-3-fluorobenzene (82 μ L, 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} (CDCl₃ 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, OCH₃), 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 (OCH₃), 41.0 (2 × CH₂N), 32.0 (2 × CH₂COAr); (EI) *m/z*: 427 ([M]⁺, 52), 290 (99), 95 (100); HR(EI) *m/z*: [M]⁺: 427.1407. C₂₆H₂₁NO₅ 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} (CDCl₃ 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, (CH₃)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 × CH₂N), 32.0 (2 × CH₂COAr), 31.1 ((CH₃)₃), 28.1 (CMe₃); (EI) *m/z*: 377 ([M]⁺, 14), 240 (52), 95 (100); HR(EI) *m/z*: [M]⁺: 377.1619. C₂₃H₂₃NO₄ 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} (CDCl₃ 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 (1H, 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 × CH₂N), 32.0 (2 × CH₂COAr); (ES⁺) *m/z*: 438 ([M + Na]⁺); HR(ES⁺) *m/z*: [M + Na]⁺: 438.1114. C₂₅H₁₈NO₄Na requires 438.1112.

tert-Butyl 5-bromo-3-hydroxy-spiro[1-benzofuran-2,4'-piperidin]-1'-carboxylate (27). To a solution of **7** (50 mg, 0.13 mmol) in ethanol (2 mL) was added NaBH₄ (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} (CDCl₃ 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, CHOH), 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, (CH₃)₃), (OH not observed); δ_{C} 157.8 (*C*_{ar}), 155.0 (CO₂t-Bu), 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–CMe₃), 77.5 (Ar–COH), 40.7 (2 × CH₂N) 34.5, 29.6 (CH₂COAr) 28.6 ((CH₃)₃). (EI) *m/z*: 383, 385 ([M]⁺, 32), 327, 329 ([M–C₄H₈]⁺, 76), 223, 225 (78), 57 (C₄H₉⁺, 100); HRMS (EI) *m/z*: [M]⁺: 383.0732. C₁₇H₂₀BrNO₄ requires 383.0730.

tert-Butyl 3-allyl-5-bromo-3-hydroxy-spiro[1-benzofuran-2,4'-piperidin]-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, $\text{CH}_2=\text{CH}$), 5.29 (1H, d, J_{cis} 10.0, $\text{CH}_2=\text{CH}$), 5.25 (1H, d, J_{trans} 17.3, $\text{CH}_2=\text{CH}$), 4.09 (2H, br s, $\text{CH}_{\text{eq}}\text{N}$), 3.10 (2H, br s, $\text{CH}_{\text{ax}}\text{N}$), 2.68 (1H, dd, J 14.3, 7.3, $\text{CH}_2=\text{CHCH}_2$), 2.51 (1H, dd, J 14.3, 7.3, $\text{CH}_2=\text{CHCH}_2$), 1.97 (1H, dd, J 14.0, 1.8, $\text{CH}_{\text{eq}}\text{COAr}$), 1.71 (2H, td, J 13.8, 4.8, $\text{CH}_{\text{ax}}\text{COAr}$), 1.58 (1H, dd, J 14.0, 1.8, $\text{CH}_{\text{eq}}\text{COAr}$), 1.47 (9H, s, $(\text{CH}_3)_3$), (OH not observed); δ_{C} 156.9 (C_{ar}), 155.0 (CO_2^tBu), 134.5 (C_{ar}), 133.2 ($C_{\text{ar}}\text{H}$), 132.1 ($\text{CH}_2=\text{CH}$), 127.6 ($C_{\text{ar}}\text{H}$), 120.5 ($\text{CH}_2=\text{CH}$), 113.0 ($C_{\text{ar}}\text{H}$), 112.6 (C_{ar}), 91.6 ($\text{C}-\text{OAr}$), 80.9 ($\text{Ar}-\text{COH}$), 79.8 ($\text{O}-\text{CMe}_3$), 40.4 ($2 \times \text{CH}_2\text{N}$), 39.5 ($\text{CH}_2=\text{CHCH}_2$), 30.8, 29.8 (CH_2COAr), 28.6 ($(\text{CH}_3)_3$). (ES^+) m/z : 424, 426 ($[\text{M} + \text{H}]^+$); Elemental analysis: Found: C, 56.26; H, 6.05; N, 3.16. $\text{C}_{20}\text{H}_{26}\text{BrNO}_4$ 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, $\text{CH}_{\text{eq}}\text{N}$), 3.11 (2H, br s, $\text{CH}_{\text{ax}}\text{N}$), 1.97 (2H, br d, J 14.5, $\text{CH}_{\text{eq}}\text{COAr}$), 1.79 (2H, q, J 7.5, CH_2CH_3), 1.67–1.61 (2H, m, $\text{CH}_{\text{ax}}\text{COAr}$), 1.48 (9H, s, $(\text{CH}_3)_3$), 1.09 (3H, t, J 7.5, CH_2CH_3), (OH not observed); δ_{C} 156.8 (C_{ar}), 155.0 (CO_2^tBu), 135.1 (C_{ar}), 133.1, 127.4, 113.0 ($C_{\text{ar}}\text{H}$), 112.6 (C_{ar}), 91.7 ($\text{C}-\text{OAr}$), 82.0 ($\text{Ar}-\text{COH}$), 79.8 ($\text{O}-\text{CMe}_3$), 40.4 ($2 \times \text{CH}_2\text{N}$), 30.7, 30.1 (CH_2COH) 28.6 ($(\text{CH}_3)_3$), 27.7 (CH_2CH_3), 7.8 (CH_2CH_3); (ES^+) m/z : 312, 314 ($[\text{M} + \text{H}-\text{C}_4\text{H}_8\text{OCO}]^+$); HRMS (EI) m/z : $[\text{M}-\text{H}_2\text{O}^+]$: Found 393.0941. $\text{C}_{19}\text{H}_{24}\text{BrNO}_3$ 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 $n\text{BuLi}$ (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, $\text{CH}_{\text{eq}}\text{N}$), 4.07 (1H, br s, $\text{CH}_{\text{eq}}\text{N}$), 3.18–3.09 (2H, br m, $\text{CH}_{\text{ax}}\text{N}$), 2.59 (1H, s, OH), 2.15 (1H, dd, J 14.0, 2.3, $\text{CH}_{\text{eq}}\text{COAr}$), 2.03 (1H, td, J 13.3, 4.3, $\text{CH}_{\text{ax}}\text{COAr}$), 1.92 (1H, td, J 13.6, 5.0, $\text{CH}_{\text{ax}}\text{COAr}$), 1.72 (1H, dd, J 13.8, 2.0, $\text{CH}_{\text{eq}}\text{COAr}$), 1.48 (9H, s, $(\text{CH}_3)_3$); δ_{C} 157.2 (C_{ar}), 155.0 (CO_2^tBu), 134.1 ($C_{\text{ar}}\text{H}$), 133.3 (C_{ar}), 132.0 ($2 \times C_{\text{ar}}\text{H}$), 129.3 ($C_{\text{ar}}\text{H}$), 128.6 ($2 \times C_{\text{ar}}\text{H}$), 127.9 ($C_{\text{ar}}\text{H}$), 111.8 (C_{ar}), 113.2 ($C_{\text{ar}}\text{H}$), 113.1 (C_{ar}), 92.4 ($\text{C}-\text{OAr}$), 88.9, 85.6 (C_{alkyne}), 79.9 ($\text{Ar}-\text{COH}$), 78.1 ($\text{O}-\text{CMe}_3$), 40.5 ($2 \times \text{CH}_2\text{N}$), 33.0 ($2 \times \text{CH}_2\text{COAr}$), 28.6 ($(\text{CH}_3)_3$); (ES^-) m/z : 482, 484 ($[\text{M}-\text{H}]^-$); Elemental analysis: Found: C, 56.26; H, 6.05; N, 3.16. $\text{C}_{25}\text{H}_{26}\text{BrNO}_4$ requires: C, 56.61; H, 6.18; N, 3.30%.

Acknowledgements

We thank AstraZeneca and the EPSRC for CASE studentship funding (RW) and The Royal Society for a University Research Fellowship (RCDB). We also gratefully acknowledge CEM and Biotage for the use of Explorer and Smith Synthesiser microwave reactors respectively.

References

- 1 J. S. Mason, I. Morize, P. R. Menard, D. L. Cheney, C. Hulme and R. F. Labaudiniere, *J. Med. Chem.*, 1999, **42**, 3251.
- 2 E. J. Martin and R. E. Critchlow, *J. Comb. Chem.*, 1999, **1**, 32.
- 3 G. W. Bemis and M. A. Murcko, *J. Med. Chem.*, 1996, **39**, 2887.
- 4 B. E. Evans, K. E. Rittle, M. G. Bock, R. M. Dipardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235.
- 5 R. W. DeSimone, K. S. Currie, S. A. Mitchell, J. W. Darrow and D. A. Pippin, *Comb. Chem. High Throughput Screening*, 2004, **7**, 473.
- 6 A. A. Patchett and R. P. Nargund, *Annu. Rep. Med. Chem.*, 2000, **35**, 289.
- 7 T. Klabunde and G. Hessler, *ChemBioChem*, 2002, **3**, 929.
- 8 D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893.
- 9 G. Müller, *Drug Discovery Today*, 2003, **8**, 681.
- 10 (a) A. A. Patchett, R. P. Nargund, J. R. Tata, M. H. Chen, K. J. Barakat, D. B. R. Johnston, K. Cheng, W. W. S. Chan, B. Butler, G. Hickey, T. Jacks, K. Schlein, S. S. Pong, L. Y. P. Chaung, H. Y. Chen, E. Frazier, K. H. Leung, S. H. L. Chiu and R. G. Smith, *Proc. Natl. Acad. Sci. USA*, 1995, **92**, 7001; (b) L. H. Yang, G. Morriello, K. Prendergast, K. Cheng, T. Jacks, W. W. S. Chan, P. D. Schlein, R. G. Smith and A. A. Patchett, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 107.
- 11 K. H. Bleicher, Y. Wuthrich, G. Adam, T. Hoffmann and A. J. Sleight, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3073.
- 12 T. Mirzadegan, F. Diehl, B. Ebi, S. Bhakta, I. Polsky, D. McCarley, M. Mulkins, G. S. Weatherhead, J. M. Lapierre, J. Dankwardt, D. Morgans, R. Wilhelm and K. Jarnagin, *J. Biol. Chem.*, 2000, **275**, 25562.
- 13 L. Davis, M. N. Agnew, R. C. Effland, J. T. Klein, J. M. Kitzen and M. A. Schwenkler, *J. Med. Chem.*, 1983, **26**, 1505.
- 14 D. F. Veber, S. R. Johnson, H. Y. Cheng, B. R. Smith, K. W. Ward and K. D. Kopple, *J. Med. Chem.*, 2002, **45**, 2615.
- 15 A. J. Bridges, A. Lee, E. C. Maduakor and C. E. Schwartz, *Tetrahedron Lett.*, 1992, **33**, 7495.
- 16 G. S. Bates and J. O'Doherty, *J. Org. Chem.*, 1981, **46**, 1745.
- 17 C. O. Kappe, *Angew. Chem., Int. Ed.*, 2004, **43**, 6250.
- 18 J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1144.
- 19 J. F. Hartwig, *Angew. Chem., Int. Ed.*, 1998, **37**, 2047.
- 20 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Delivery Rev.*, 1997, **23**, 3. Compounds **18–26** all have molecular weights of less than 500, CLog P values of less than 5, fewer than 5 H-bond donors and fewer than 10 H-bond acceptors.