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Application of copper(II)-mediated radical cross-dehydrogenative coupling to prepare spirocyclic oxindoles and to a formal total synthesis of Satavaptan‡

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| ARTICLE INFO | ABSTRACT |
| Article history:ReceivedReceived in revised formAcceptedAvailable online | Application of radical cross-dehydrogenative coupling (CDC) procedures to prepare a range of novel spirocyclic oxindoles and to a formal total synthesis of the vasopressin V2 receptor antagonist Satavaptan is reported. The key step involves a copper-mediated oxidative cyclisation of a simple linear anilide precursor to give the spirocyclic oxindole core. This synthetic approach was also used to prepare novel Satavaptan scaffolds and analogues.2009 Elsevier Ltd. All rights reserved. |
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1. Introduction

Hyponatremia, or low blood sodium levels, is a common complication in several diseases including congenital heart failure, cirrhosis of the liver, and syndrome of inappropriate antidiuretic hormone (SIADH);1 common diuretics typically used in the treatment of such diseases often lead to loss of essential sodium and potassium salts.2 Several vasopressin V2 receptor antagonists have been developed to address this problem (Figure 1). Selective vasopressin V2 receptor antagonists (e.g. **1**-**3**) work by blocking the production of vasopressin, an anti-diuretic hormone responsible for causing the kidneys to retain water. Thus, administration of Tolvaptan **2** alongside traditional diuretics has been shown to increase fluid excretion without causing hyponatremia in patients suffering from heart failure.3

Our interest concerned Satavaptan **1** and improved analogues. The synthesis of Satavaptan **1** was first reported by Sanofi in 1999 and involves formation of the oxindole core via a classical Fischer cyclisation under harsh conditions (180 °C reaction temperature), while tedious late-stage separation of the *syn*- and *anti*-stereoisomers was also required.4 These shortcomings were addressed in a subsequent synthesis by Liotta in 2001 (**Scheme 1**).5 Thus, in the Liotta synthesis, the key oxindole **6** was prepared via a Rh-catalysed annulation of diazo compound **5** at room temperature. Construction of the spirocyclic ketone **11** was



**Figure 1**. Examples of vasopressin V2 receptor antagonists.

achieved through subsequent double alkylation with dibromide **10**, itself prepared in 3 steps from methyl 3-



**Scheme 1**. Previous synthesis of Satavaptan and new approach via copper-mediated cross-dehydrogenative coupling

bromopropionate **7**. Crucially, conditions were established for the *syn*-selective reduction of ketone **12** using L-Selectride as the hydride source, obviating the need for separation of a mixture of isomers at a later stage in the synthesis. The origin of this selectivity was proposed to be trapping of the cyclohexane in the twist-boat conformation via coordination of both carbonyl oxygen atoms to the lithium cation, thus revealing the correct face for hydridic attack. Alkylation of the cyclohexanol and removal of the benzyl protecting group under Birch conditions gave N-H oxindole **14**, which was treated with arylsulfonyl chloride **15** to deliver Satavaptan **1**. Several other formal syntheses of Satavaptan have also been reported, invoking either a radical6 or hypervalent iodine-mediated7 spirocyclisation, or alkylation/Dieckmann condensation8 as the key step.

We have previously reported the synthesis of oxindoles **17** through the intramolecular Cu(II)-catalysed radical cross-dehydrogenative coupling (CDC) of simple anilides **16**, which proceeds via homolytic aromatic substitution of stabilised radical **18** (**Scheme 1**).9,10 A range of electron-withdrawing groups, including esters,9a lactams9b and ketones,9c-e were well tolerated

in this process. We now wish to report the application of this highly atom-economical approach to the preparation of Liotta’s key spirocyclic oxindole intermediate **12**, thus representing a new formal synthesis of Satavaptan. In our approach, the target molecule **12** would be derived by deoxygenation of selectively protected ketone **19**, produced by the radical CDC cyclisation of anilide **20**. This synthetic approach is also applied to prepare novel Satavaptan scaffolds and analogues (see later).

1. Results and Discussion

In order to establish the feasibility of preparing the key spirocyclic oxindole core of Satavaptan via our radical cross-dehydrogenative coupling procedure, initial studies focused on the cyclisation of simple anilides **21** (**Scheme 2**).9c In the event, treatment of linear precursors **21a-f** with inexpensive Cu(OAc)2·H2O in refluxing toluene under an atmosphere of O2 delivered a range of spirocyclic oxindoles **22a**-**f** featuring 5-, 6-, and 7-membered ring ketones. Crucially, several different removable *N*-protecting groups (including Bn, DMB and PMB) were well-tolerated in this process. Furthermore, groups allowing for further functionalisation such as an alkene (**22e**) or epoxide



**Scheme 2**. Substrate scope in the copper-mediated synthesis of spirocyclic oxindoles.

(**22f**) were also successfully incorporated into the spirocyclic products. With conditions for the oxindole spirocyclisation in hand, a simple model system was next examined to establish the viability of the deoxygenation required for the formal synthesis of Satavaptan (**Scheme 3**). Synthesis of the model system began with selectively protected ketoester **23**,11 which was saponified to acid **24** in a two-step procedure involving first transesterification to the benzyl ester followed by hydrogenolysis.12 Next, coupling of acid **24** with *N*-methylaniline in the presence of Mukaiyama’s reagent delivered linear precursor **25** primed for the cross-dehydrogenative coupling. Rapid cyclisation occurred on



**Scheme 3**. Model system for the deoxygenation of spirocyclic oxindoles.

treatment of anilide **25** with a catalytic quantity of Cu(OAc)2·2H2O in refluxing mesitylene to give spirocyclic oxindole **26** in 52% yield. To facilitate the carbonyl deoxygenation, ketone **26** was first reduced to the corresponding alcohol **27** in excellent yield. In the first instance, deoxygenation was successfully carried out using a classical Barton-McCombie reaction via the corresponding imidazole-1-thiocarbonyl derivative.13 However, an alternative route which negates the need for the use of highly toxic tin reagents was considered desirable. Thus, cleavage of the acetal and concomitant dehydration was achieved under acidic conditions to give enone **29**, which could be hydrogenated to give the desired ketone **30** in high yield.

Having successfully established protocols for the key oxindole spirocyclisation and deoxygenation reactions, attention finally turned to the formal synthesis of Satavaptan **1** (**Scheme 4**). Coupling of the appropriately substituted aniline **4** with ketoacid **24** was carried out in the presence of propylphosphonic anhydride (T3P)14 to give β-ketoamide **20**, which, on treatment with stoichiometric Cu(OAc)2·H2O in refluxing mesitylene or ethylene carbonate delivered the requisite spirocyclic keto-oxindole **19** in 58-62% yield. Ethylene carbonate has been shown to be an excellent green replacement for traditional organic solvents due to its low cost, ready availability, high flash point, low (eco)toxicity and excellent biodegradability.15 Pleasingly, in this instance, mesitylene was easily substituted for ethylene carbonate without a significant change in yield. Finally, deoxygenation was performed without incident via the 3-step sequence developed above to give Liotta’s spirocyclic oxindole **12**. This route therefore represents a new formal synthesis of Satavaptan, whilst removing the potentially dangerous diazo intermediates and costly rhodium salts used by Liotta et al.



**Scheme 4**. Formal total synthesis of Satavaptan.

In a final aspect to this work we wished to demonstrate the versatility of our route by applying it to the synthesis of a novel analogue of Satavaptan featuring a changed sulfonamide and a novel triazole side chain (**Scheme 5**). Mindful of the requirement to use the Birch reduction for cleavage of the benzyl protecting group used by Liotta, a different protecting group strategy was therefore adopted. In the event, the *para*-methoxybenzyl (PMB) group was chosen due to its potential removal under a wide variety of conditions (oxidation, acid, hydrogenolysis). In analogous fashion to the benzyl analogue above, amide formation (**32**→**33**), cross-dehydrogenative coupling using either



Scheme 5. Synthesis of a novel Satavaptan analogue.

Cu(OAc)2·H2O or Cu(2-ethylhexanoate)2 as catalyst (**33**→**34**), and deoxygenation (**34**→**36**) proceeded without incident. *Syn*-selective reduction of ketone **36** was accomplished under Liotta’s conditions (L-Selectride, THF, –78 °C) to give alcohol **37**, which was subjected to alkylation with propargyl bromide. Huisgen cycloaddition of the subsequent alkyne **38** with benzyl azide in the presence of CuI delivered triazole **39**. Contrary to the benzyl deprotection above, removal of the PMB group was achieved on simple reflux with TFA to give N-H oxindole **40** (57% yield over 2 steps from **38**). Finally, deprotonation of **40** followed by addition of the aryl sulfonyl chloride delivered the novel Satavaptan analogue **41**.

1. Conclusions

The highly atom-economical radical cross-dehydrogenative coupling (CDC) of simple linear β-ketoamides **21** to give spirocyclic oxindoles **22** bearing 5-, 6- and 7-membered ring ketones has been established (Schemes 2 and 3). This approach was subsequently employed in the formal total synthesis of the vasopressin V2 receptor antagonist Satavaptan (Scheme 4). CDC of linear anilide **20**, followed by deoxygenation in a three-step sequence involving reduction to the alcohol, dehydration, and hydrogenation delivered the key spirocyclic oxindole intermediate previously prepared by Liotta et al., and thus represents a new formal synthesis of Satavaptan. Finally, the versatility of this approach was demonstrated by the synthesis of a novel Satavaptan analogue **41**.

1. Experimental section
	1. General Methods

Except where stated, all reagents were purchased from commercial sources and used without further purification. 1H and 13C NMR spectra were recorded on a JEOL ECX400 or ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively. All spectral data was acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δH 7.27 and δC 77.0 for CDCl3 was used as a reference. Coupling constants (*J*) are reported in Hertz (Hz). The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a PerkinElmer UATR 2 spectrometer as a thin film dispersed from either CH2Cl2 or CDCl3. Mass-spectra (low and high-resolution) were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. Melting points were determined using a Gallenkamp apparatus. Thin layer chromatography was carried out on Merck silica gel 60F254 pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO2), 35–70 μm, 60 Å, under a light positive pressure, eluting with the specified solvent system.

* 1. Experimental procedures and compound characterisation
		1. Synthesis of spirocyclic oxindoles
			1. General procedure 1: Synthesis of linear anilides **21a**-**f**

The cyclic ketone (1 equiv) was added to a solution of magnesium methyl carbonate (2 M in DMF, 8 equiv). The reaction mixture was stirred at 130 °C for 6 h. After cooling to rt, 10% HCl solution was added until the pH became acidic. The aqueous phase was extracted with Et2O, and the combined organic layers washed with H2O and sat. brine, dried over MgSO4, filtered, and concentrated in vacuo to give the carboxylic acid.

To a solution of the crude acid in CH2Cl2 (0.06 M) at 0 °C was added the aniline (1.15 equiv), 2-chloro-1-methylpyridinium iodide (1.4 equiv) and Et3N (4.6 equiv). The reaction mixture was stirred at rt for 18 h, then quenched by the addition of 10% HCl. The layers were separated, and the aqueous phase extracted with CH2Cl2. The combined organic layers washed with H2O and sat. brine, dried over MgSO4, filtered, and concentrated in vacuo to give the crude product. Purification by column chromatography on silica gel (Hexane/EtOAc, 3:1 to 1:4) gave the title compound.

* + - 1. N-Benzyl-2-oxo-N-phenylcyclopentane-1-carboxamide (**21a**)

Following general procedure 1 from cyclopentanone (0.290 g, 2.26 mmol), methyl magnesium carbonate (2 M in DMF, 9.04 mL, 18.1 mmol) was obtained the carboxylic acid. Formation of the amide was carried out using N-benzylaniline (0.154 mL, 0.831 mmol), 2-chloro-1-methylpyridinium iodide (0.255 g, 0.997 mmol) and Et3N (0.462 mL, 3.32 mmol) to give the title compound **21a** (43 mg, 15%) as a colourless solid; mp. 97-99 ° C; νmax 2966, 1739, 1644, 1595, 1495, 1405, 700 cm-1; δH (400 MHz; CDCl3) 7.32-7.27 (3H, m), 7.27-7.23 (3H, m), 7.23-7.18 (2H, m), 7.13 (2H, br s), 5.01 (1H, d, *J* 14.4 Hz), 4.82 (1H, d, *J* 14.4 Hz), 3.08 (1H, dd, *J* 10.2, 9.2 Hz), 2.48-2.36 (1H, m), 2.35-2.24 (1H, m), 2.24-2.16 (1H, m), 2.14-2.03 (2H, m), 1.77-1.58 (1H, m); δC (100 MHz; CDCl3) 214.8 (C), 170.1 (C), 142.1 (C), 137.1 (C), 129.6 (CH), 128.7 (2 × CH), 128.5 (CH), 128.3 (CH), 127.4 (CH), 53.3 (CH2), 52.9 (CH), 38.6 (CH2), 28.4 (CH2), 21.1 (CH2); HRMS (ESI): MNa+, found 316.1297. C19H19NNaO2 requires 316.1308.

* + - 1. N-Methyl-2-oxo-N-phenylcyclohexane-1-carboxamide (**21b**)

Following general procedure 1 from cyclohexanone (0.21 mL, 2.04 mmol), methyl magnesium carbonate (2 M in DMF, 8.15 mL, 16.3 mmol) was obtained the carboxylic acid. Formation of the amide was carried out using N-methylaniline (0.254 mL, 2.34 mmol), 2-chloro-1-methylpyridinium iodide (0.720 g, 2.82 mmol) and Et3N (1.31 mL, 9.38 mmol) to give the title compound **21b** (65 mg, 30%) as a yellow oil; νmax 2941, 2865, 1710, 1652, 1595, 1495, 1450, 1421, 1382, 1126, 775, 702 cm-1; δH (400 MHz; CDCl3) 7.37-7.35 (2H, m), 7.34-7.31 (1H, m), 7.15 (2H, dd, *J* 8.2, 1.3 Hz), 3.28 (3H, s), 3.21 (1H, dd, *J* 11.7, 5.9 Hz), 2.44-2.37 (1H, m), 2.16 (1H, ddd, *J* 15.4, 12.9, 3.6 Hz), 2.04-1.94 (2H, m), 1.94-1.83 (2H, m), 1.78-1.64 (1H, m), 1.51-1.37 (1H, m); δC (100 MHz; CDCl3) 207.5 (C), 169.7 (C), 143.8 (C), 129.9 (CH), 128.2 (CH), 127.3 (CH), 55.3 (CH), 41.7 (CH2), 37.5 (Me), 30.5 (CH2), 26.9 (CH2), 23.8 (CH2); HRMS (ESI): MNa+, found 254.1149. C14H17NNaO2 requires 254.1151.

* + - 1. N-Methyl-2-oxo-N-phenylcycloheptanecarboxamide (**21c**)

A suspension of Pd/C (3 wt% on activated carbon, 84 mg) in EtOAc (10 mL) was thoroughly degassed three times while stirring. Benzyl 2-oxocycloheptanecarboxylate (0.247 g, 1.00 mmol) was added and the mixture stirred under an atmosphere of H2 for 1 h. The suspension was filtered through Celite®, washed with EtOAc, and concentrated in vacuo to give the crude acid as a colourless oil.

To a solution of the crude acid in CH2Cl2 (10 mL) at 0 °C was added *N*-methylaniline (0.062 mL, 0.570 mmol), 2-chloromethylpyridinium iodide (0.210 g, 0.812 mmol) and Et3N (0.400 mL, 2.64 mmol). The reaction was stirred at rt for 1 h, then quenched by the addition of 10% HCl (10 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over MgSO4, filtered and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by column chromatography on silica gel (Hexane/EtOAc, 6:1) gave the title compound **21c** (81 mg, 52%) as a colourless oil; νmax 2884, 1678, 1624, 1570, 1472, 1359, 1097 cm-1; δH (400 MHz; CDCl3) 7.45-7.29 (3H, m), 7.22-7.16 (2H, m), 3.45 (1H, dd, *J* 10.6, 3.9 Hz), 3.25 (3H, s), 2.55 (1H, ddd, *J* 14.6, 11.6, 3.3 Hz), 2.14-2.04 (1H, m), 2.02-1.92 (1H, m), 1.92-1.81 (2H, m), 1.80-1.71 (2H, m), 1.40-1.03 (3H, m); δC (100 MHz; CDCl3) 210.9 (C), 170.6 (C), 143.6 (C), 129.9 (CH), 128.2 (CH), 128.0 (CH), 56.6 (CH), 43.3 (CH2), 37.6 (Me), 29.6 (CH2), 28.6 (CH2), 28.4 (CH2), 24.60 (CH2); HRMS (ESI): MH+, found 246.1497. C15H20NO2 requires 246.1489.

* + - 1. N-(2,4-Dimethoxybenzyl)-2-oxo-N-phenylcycloheptanecarboxamide (**21d**)

A suspension of Pd/C (3 wt% on activated carbon, 0.403 g) in EtOAc (48 mL) was thoroughly degassed three times while stirring. Benzyl 2-oxocycloheptanecarboxylate (1.18 g, 4.80 mmol) was added and the mixture stirred under an atmosphere of H2 for 1 h. The suspension was filtered through Celite®, washed with EtOAc, and concentrated in vacuo to give the crude acid as a colourless oil.

To a solution of the crude acid in CH2Cl2 (48 mL) at 0 °C was added *N*-(2,4-dimethoxybenzyl)aniline (0.666 g, 2.74 mmol), 2-chloromethylpyridinium iodide (0.980 g, 3.84 mmol) and Et3N (1.76 mL, 12.6 mmol). The reaction was stirred at rt for 1 h, then quenched by the addition of 10% HCl (50 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over MgSO4, filtered and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by column chromatography on silica gel (Hexane/EtOAc, 6:1) gave the title compound **21d** (0.470 g, 45%) as a colourless solid; mp. 66-68 °C; νmax 1705, 1650, 1614, 1594, 1508, 1495, 1454, 1262, 1209, 1157, 1037, 702 cm-1; δH (400 MHz; CDCl3) 7.28-7.25 (3H, m), 7.26 (1H, d, *J* 8.3 Hz), 7.00 (2H, dd, *J* 7.6, 2.0 Hz), 6.42 (1H, dd, *J* 8.3, 2.4 Hz), 6.29 (1H, d, *J* 2.4 Hz), 4.90 (1H, d, *J* 14.5 Hz), 4.81 (1H, d, *J* 14.5 Hz), 3.76 (3H, s), 3.50 (3H, s), 3.44 (1H, dd, *J* 10.6, 3.9 Hz), 2.54 (1H, dd, *J* 8.8, 5.5 Hz), 2.10-1.95 (3H, m), 1.93-1.82 (2H, m), 1.75 (2H, dd, *J* 11.2, 4.6 Hz), 1.31-1.12 (2H, m); δC (100 MHz; CDCl3) 211.0 (C), 170.4 (C), 160.2 (C), 158.5 (C), 142.1 (C), 131.0 (CH), 129.3 (CH), 129.1 (CH), 127.9 (CH), 117.9 (C), 104.2 (CH), 98.3 (CH), 56.9 (CH), 55.4 (Me), 55.1 (Me), 47.1 (CH2), 43.4 (CH2), 29.6 (CH2), 28.7 (CH2), 28.5 (CH2), 24.6 (CH2); HRMS (ESI): MNa+, found 404.1831; C23H27NNaO4 requires 404.1832.

* + - 1. 5-(1-Hydroxypent-4-enylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione

A solution of DCC (4.74 g, 23.0 mmol) in CH2Cl2 (10 mL) was added slowly to a stirred solution of Meldrum’s acid (3.01 g, 20.9 mmol), 4-pentenoic acid (2.13 mL, 20.9 mmol), and 4-(dimethylamino)pyridine (2.81 g, 23.0 mmol) in CH2Cl2 (30 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 16 h. The suspension was filtered through Celite, and then washed with CH2Cl2 (50 mL). The filtrate was washed subsequently with 10% HCl (50 mL). The aqueous phase was extracted with CH2Cl2 (2 × 20 mL). The combined organic phases were washed with water (2 × 30 mL) and brine (2 × 30 mL), dried over MgSO4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc) to give the title compound (3.32 g, 70%) as a yellow oil; νmax 1739, 1665, 1574, 1408, 1282, 1154, 1031, 919 cm-1; δH (400 MHz; CDCl3) 5.84 (1H, ddt, *J* 16.9, 10.2, 6.6 Hz), 5.08 (1H, dtd, *J* 16.9, 1.4, 1.3 Hz), 5.02 (1H, dtd, *J* 10.2, 1.4, 1.3 Hz), 3.19 (2H, dd, *J* 7.7, 6.6 Hz), 2.48 (1H, ddd, *J* 6.6, 6.6, 1.4 Hz), 2.45 (1H, ddd, *J* 7.7, 6.6, 1.4 Hz), 1.72 (6H, s); δC (100 MHz; CDCl3) 197.2 (C), 170.6 (C), 160.3 (C), 136.1 (CH), 116.3 (CH2), 105.0 (C), 91.7 (C), 35.1 (CH2), 29.9 (CH2), 26.9 (2 x Me); HRMS (ESI): MNa+, found 249.0742. C11H14NaO5 requires 249.0733.

* + - 1. N-(4-Methoxybenzyl)-3-oxo-N-phenylhept-6-enamide

To a stirred solution of 5-(1-hydroxypent-4-enylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (2.16 g, 9.55 mmol) in 1,4-dioxane (14 mL) was added *N*-(4-methoxybenzyl)aniline (2.04 g, 9.55 mmol). The reaction mixture was stirred for 4 h at 110 °C, then the solvent was removed in vacuo and the residual oil was purified by column chromatography on silica gel (Hexane/EtOAc, 5:1) to give the title compound (2.81 g, 87%) as a yellow oil; νmax 1720, 1651, 1594, 1512, 1395, 1244, 1175, 1033, 821, 701 cm-1; δH (400 MHz; CDCl3) 7.32-7.28 (3H, m), 7.12 (2H, d, *J* 8.7 Hz), 6.94 (2H, dd, *J* 6.5, 3.1 Hz), 6.78 (2H, d, *J* 8.7 Hz), 5.70 (1H, ddt, *J* 16.8, 10.2, 6.6 Hz), 4.94 (1H, dd, *J* 16.8, 1.5 Hz), 4.91 (1H, dd, *J* 10.2, 1.5 Hz), 4.83 (2H, s), 3.76 (3H, s), 3.27 (2H, s), 2.41 (2H, t, *J* 7.1 Hz), 2.21 (2H, td, *J* 7.1, 6.6 Hz); δC (100 MHz; CDCl3) 203.7 (C), 166.7 (C), 159.0 (C), 141.9 (C), 136.8 (CH), 130.3 (CH), 129.7 (CH), 129.2 (C), 128.6 (CH), 128.5 (CH), 115.4 (CH2), 113.8 (CH), 55.3 (Me), 52.5 (CH2), 49.5 (CH2), 42.3 (CH2), 27.5 (CH2); HRMS (ESI): MNa+ found 360.1561. C21H23NNaO3 requires 360.1570.

* + - 1. N-(4-Methoxybenzyl)-2-(2-methylallyl)-3-oxo-N-phenylhept-6-enamide

To a stirred solution of NaH (60% in mineral oil, 0.336 g, 8.41 mmol) in DMF (100 mL) was added N-(4-Methoxybenzyl)-3-oxo-*N*-phenylhept-6-enamide (2.58 g, 7.65 mmol) at 0 °C. The reaction mixture was stirred for 15 min and allyl bromide (0.695 mL, 8.03 mmol) was added slowly. The resulting light green solution was stirred for 30 min and then allowed to warm to room temperature where it slowly turned yellow. The reaction mixture was stirred overnight and quenched with sat. NH4Cl (100 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with water (5 × 50 mL) and sat. brine (2 × 50 mL), dried over MgSO4, filtered and concentrated in vacuo. Purification by column chromatography on silica gel (Petrol/EtOAc, 6:1) gave the title compound (3.21 g, quant.) as a light yellow oil; νmax 1717, 1650, 1613, 1594, 1512, 1394, 1302, 1245, 1176, 1033, 916, 702 cm-1; δH (400 MHz; CDCl3) 7.34-7.29 (3H, m), 7.09 (2H, d, *J* 8.6 Hz), 6.90 (2H, dd, *J* 6.6, 3.1 Hz), 6.77 (2H, d, *J* 8.6 Hz), 5.75-5.58 (2H, m), 5.05-4.90 (4H, m), 4.82 (2H, s), 3.77 (3H, s), 3.35 (1H, dd, *J* 8.4, 5.9 Hz), 2.64 (1H, ddd, *J* 15.3, 8.4, 7.2 Hz), 2.47 (1H, ddd, *J* 15.3, 7.2, 5.9 Hz), 2.42-2.35 (1H, m), 2.29-2.21 (1H, m), 2.22-2.14 (2H, m); δC (100 MHz; CDCl3) 204.9 (C), 168.7 (C), 159.1 (C), 141.5 (C), 137.0 (CH), 135.1 (CH), 130.4 (CH), 129.8 (CH), 129.4 (C), 129.2 (CH), 128.5 (CH), 117.3 (CH2), 115.3 (CH2), 113.8 (CH), 56.9 (CH), 55.3 (Me), 52.8 (CH2), 40.3 (CH2), 33.6 (CH2), 27.4 (CH2); HRMS (ESI): MNa+, found 400.1878. C24H27NNaO3 requires 400.1883.

* + - 1. Z-N-(4-Methoxybenzyl)-7-oxo-N-phenylcyclohept-3-enecarboxamide (**21e**)

To a degassed solution of N-(4-methoxybenzyl)-2-(2-methylallyl)-3-oxo-N-phenylhept-6-enamide (0.493 g, 1.33 mmol) in CH2Cl2 (100 mL) was added Grubbs 2nd generation catalyst (52 mg, 0.067 mmol). The reaction mixture was stirred at 45 °C for 1 h. After cooling to rt, the solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (Petrol/EtOAc, 5:1 to 2:1) to give the title compound **21e** (0.264 g, 57%) as a colourless oil; νmax 1709, 1661, 1648, 1594, 1512, 1396, 1244, 1176, 1033, 702 cm-1; δH (400 MHz; CDCl3) 7.30-7.26 (3H, m), 7.12 (2H, d, *J* 8.7 Hz), 6.94 (2H, dd, *J* 5.8, 3.8 Hz), 6.77 (2H, d, *J* 8.7 Hz), 5.68-5.56 (2H, m), 4.88 (1H, d, *J* 14.2 Hz), 4.77 (1H, d, *J* = 14.2 Hz), 3.80 (1H, dd, *J* 11.9, 3.9 Hz), 3.75 (3H, s), 2.79-2.71 (1H, m), 2.67 (1H, dd, *J* 14.9, 7.3 Hz), 2.43-2.34 (1H, m), 2.08-2.02 (2H, m), 2.01-1.93 (1H, m); δC (100 MHz; CDCl3) 209.2 (C), 169.5 (C), 159.0 (C), 141.6 (C), 130.2 (CH), 129.6 (CH), 129.4 (C), 129.2 (CH), 129.1 (CH), 128.4 (CH), 128.2 (CH), 113.8 (CH), 55.3 (CH or Me), 55.2 (CH or Me), 52.5 (CH2), 42.2 (CH2), 28.4 (CH2), 23.9 (CH2); HRMS (ESI): MNa+, found 372.1573. C22H23NNaO3 requires 372.1570.

* + - 1. N-(4-Methoxybenzyl)-4-oxo-N-phenyl-8-oxabicyclo[5.1.0]octane-3-carboxamide (**21f**)

To a stirred solution of (*Z*)-*N*-(4-methoxybenzyl)-7-oxo-*N*-phenylcyclohept-3-enecarboxamide **21e** (0.122 g, 0.348 mmol) in acetone (2 mL) at 0 °C was added a solution of DMDO (0.06 M in acetone, 11.1 mL, 0.696 mmol). The reaction mixture was stirred at 0 °C for 1 h and allowed to warm to rt for a further 1 h. The solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/Petrol 2:1) to give the title compound **21f** (0.108 g, 85%) as a colourless oil and inseparable 1:1.5 mixture of diastereoisomers; νmax 1710, 1657, 1594, 1594, 1512, 1396, 1244, 1176, 1031, 730, 702 cm-1; δH (400 MHz; CDCl3) 7.31-7.26 (3H, m), 7.14-7.06 (2H, m), 6.92-6.84 (2H, m), 6.80-6.74 (2H, m), 4.84 (1H, d, *J* 14.3 Hz), 4.77 (0.4H, d, *J* 14.3 Hz), 4.75 (0.6H, d, *J* 14.3 Hz), 3.75 (3H, s), 3.66-3.58 (1H, m), 3.17 (1H, td, *J* 4.6, 1.7 Hz), 3.06-3.01 (1H, m), 2.54- 2.34 (2H, m), 2.09 (0.6H, ddd, *J* 12.1, 7.5, 4.4 Hz), 2.01-1.93 (2H, m), 1.82 (1.4H, ddd, *J* 12.1, 9.8, 4.4 Hz); δC (100 MHz; CDCl3) 209.3 and 207.4 (C), 168.9 and 168.7 (C), 159.0 (C), 141.3 and 141.2 (C), 130.2 and 130.1 (CH), 129.74 and 129.70 (CH), 129.4 (CH), 129.31 and 129.26 (C), 128.5 (CH), 113.8 (CH), 55.3 (Me), 54.4 (CH), 54.0 and 53.3 (CH), 52.6 and 52.5 (CH2), 51.7 and 51.4 (CH), 38.0 and 36.3 (CH2), 28.6 and 27.3 (CH2), 24.0 and 22.7 (CH2); HRMS (ESI): MNa+, found 388.1504. C22H23NNaO4 requires 388.1519.

* + - 1. General procedure 2: Copper(II)-mediated synthesis of spirocyclic oxindoles **22a**-**f**

To a stirred solution of linear amide **21** (1 equiv) in toluene (0.04 M) was added Cu(OAc)2∙H2O (10 mol%-1 equiv) under an O2 atmosphere. The reaction mixture was heated at 110 °C for 1.5 h then cooled to room temperature and the solvent was removed in vacuo. The residue was filtered through Celite®, washed with CH2Cl2 and concentrated in vacuo to give the crude product. Purification by column chromatography on silica gel (Hexane/EtOAc, 4:1) gave the title compound.

* + - 1. 1’-Benzyl-1’,2’-dihydrospiro[cyclopentane-1,3’-indole]-2’,5-dione (**22a**)

Following general procedure 2 from *N*-benzyl-2-oxo-*N*-phenylcyclopentane-1-carboxamide **21a** (11.0 mg, 0.037 mmol) was obtained the title compound **22a** (6.0 mg, 56%) as a colourless oil; νmax 2969, 1747, 1702, 1611, 1489, 1466, 1360, 1183, 1107, 754, 697 cm-1; δH (400 MHz; CDCl3) 7.34–7.24 (5H, m), 7.16 (1H, td, *J* 7.7, 1.3 Hz), 7.09 (1H, dd, *J* 7.2, 1.2 Hz), 7.00 (1H, td, *J* 7.6, 1.0 Hz), 6.69 (1H, d, *J* 7.9 Hz), 5.00 (1H, d, *J* 15.8 Hz), 4.80 (1H, d, *J* 15.8 Hz), 2.79–2.70 (1H, m), 2.70–2.61 (1H, m), 2.60–2.48 (2H, m), 2.46–2.37 (1H, m), 2.32–2.19 (1H, m); δC (100 MHz; CDCl3) 212.7 (C), 175.4 (C), 143.5 (C), 135.4 (C), 130.5 (C), 128.9 (CH), 128.7 (CH), 127.7 (CH), 127.1 (CH), 123.0 (CH), 122.6 (CH), 109.6 (CH), 63.1 (C), 43.9 (CH2), 38.4 (CH2), 34.2 (CH2), 20.4 (CH2); HRMS (ESI): MNa+, found 314.1154. C19H17NNaO2 requires 314.1151.

* + - 1. 1’-Methyl-1’-2’-dihydrospiro[cyclohexane-1,3’-indole]-2’,6-dione (**22b**)

Following general procedure 2 from *N*-methyl-2-oxo-*N*-phenylcyclohexane-1-carboxamide **21b** (0.016 g, 0.067 mmol) was obtained the title compound **22b** (0.010 g, 65%) as a colourless oil; νmax 2940, 2867, 1730, 1697, 1613, 1494, 1471, 1373, 1348, 1127, 754 cm-1; δH (400 MHz; CDCl3) 7.30 (1H, td, *J* 7.6, 1.1 Hz), 7.28 (1H, d, *J* 7.3 Hz), 7.09 (1H, td, *J* 7.5, 0.9 Hz), 6.83 (1H, d, *J* 7.8 Hz), 3.19 (3H, s), 3.05 (1H, ddd, *J* 14.2, 10.5, 5.5 Hz), 2.58 (1H, dt, *J* 14.2, 5.5 Hz), 2.41 (1H, dtt, *J* 14.2, 10.5, 4.0 Hz), 2.27–2.13 (2H, m), 2.08 (1H, ddd, *J* 14.2, 10.5, 4.0 Hz), 2.03–1.92 (1H, m), 1.90–1.81 (1H, m); δC (100 MHz; CDCl3) 205.4 (C), 174.4 (C), 143.3 (C), 129.5 (C), 128.8 (CH), 124.7 (CH), 122.8 (CH), 108.5 (CH), 63.8 (C), 39.9 (CH2), 37.4 (CH2), 27.0 (CH2), 26.6 (CH3), 20.4 (CH2); HRMS (ESI): MNa+, found 252.0998. C14H15NNaO2 requires 252.0995.

* + - 1. 1'-Methylspiro[cycloheptane-1,3'-indoline]-2,2'-dione (**22c**)

Following general procedure 2 from *N*-methyl-2-oxo-*N*-phenylcycloheptanecarboxamide **21c** (0.037 g, 0.152 mmol) was obtained the title compound **22c** (0.024 g, 66%) as a colourless oil; νmax 2889, 1703, 1668, 1585, 1471, 1447, 1352, 1325 cm-1; δH (400 MHz; CDCl3) 7.29 (1H, td, *J* 7.7, 1.2 Hz), 7.25 (1H, ddd, *J* 7.7, 1.2, 0.5 Hz), 7.06 (1H, td, *J* 7.7, 1.2 Hz), 6.83 (1H, d, *J* 7.7 Hz), 3.19 (3H, s), 3.09–3.01 (1H, m), 2.78–2.67 (1H, m), 2.31 (1H, dd, *J* 14.8, 9.1 Hz), 2.17–2.09 (1H, m), 2.07–1.95 (1H, m), 1.94–1.84 (1H, m), 1.84–1.73 (4H, m); δC (100 MHz; CDCl3) 207.6 (C), 175.3 (C), 143.5 (C), 130.8 (C), 128.7 (CH), 123.6 (CH), 122.7 (CH), 108.6 (CH), 65.6 (C), 42.3 (CH2), 34.8 (CH2), 30.9 (CH2), 26.8 (CH2), 26.5 (Me), 25.4 (CH2); HRMS (ESI): MH+, found244.1334. C15H18NO2 requires 244.1332.

* + - 1. 1'-(2,4-Dimethoxybenzyl)spiro[cycloheptane-1,3'-indoline]-2,2'-dione (**22d**)

Following general procedure 2 from *N*-(2,4-dimethoxybenzyl)-2-oxo-*N*-phenylcycloheptanecarboxamide **21d** (0.306 g, 0.798 mmol) was obtained the title compound **22d** (0.206 g, 68%) as a colourless solid; R*f* 0.40 (Hexane/EtOAc, 3:1); νmax 1716, 1692, 1609, 1590, 1508, 1465, 1361, 1208, 1156, 1035, 746 cm-1; δH (400 MHz; CDCl3) 7.24 (1H, dd, *J* 7.5, 1.0 Hz), 7.17 (1H, td, *J* 7.5, 1.0 Hz), 7.06 (1H, d, *J* 8.4 Hz), 7.01 (1H, td, *J* 7.5, 1.0 Hz), 6.77 (1H, d, *J* 7.5 Hz), 6.44 (1H, d, *J* 2.4 Hz), 6.38 (1H, dd, *J* 8.4, 2.4 Hz), 4.89 (1H, d, *J* 16.0 Hz), 4.80 (1H, d, *J* 16.0 Hz), 3.84 (3H, s), 3.75 (3H, s), 3.05 (1H, td, *J* 9.0, 2.1 Hz), 2.76 (1H, td, *J* 9.0, 2.1 Hz), 2.37 (1H, dd, *J* 14.7, 8.8 Hz), 2.22–2.12 (1H, m), 2.05 (1H, dd, *J* 14.7, 9.4 Hz), 1.97–1.73 (5H, m); δC (100 MHz; CDCl3) 207.7 (C), 175.7 (C), 160.4 (C), 158.1 (C), 143.0 (C), 130.7 (C), 129.1 (CH), 128.6 (CH), 123.4 (CH), 122.5 (CH), 116.0 (C), 109.8 (CH), 104.4 (CH), 98.5 (CH), 65.6 (C), 55.5 (Me), 55.4 (Me), 42.5 (CH2), 38.2 (CH2), 34.9 (CH2), 31.0 (CH2), 26.7 (CH2), 25.4 (CH2); HRMS (ESI): MNa+, found402.1665. C23H25NNaO4 requires 402.1676.

* + - 1. (Z)-1'-(4-Methoxybenzyl)spiro[cyclohept[3]ene-1,3'-indoline]-2',7-dione (**22e**)

Following general procedure 2 from (*Z*)-*N*-(4-methoxybenzyl)-7-oxo-*N*-phenylcyclohept-3-enecarboxamide **21e** (0.024 g, 0.068 mmol) at 100 °C was obtained the title compound **22e** (0.013 g, 55%) as a colourless solid; mp. 125-127 °C; νmax 1697, 1610, 1514, 1487, 1466, 1352, 1248, 1178, 1033, 750 cm-1; δH (400 MHz; CDCl3) 7.28 (1H, dd, *J* 7.6, 1.0 Hz), 7.20 (2H, d, *J* 8.7 Hz), 7.17 (1H, td, *J* 7.6, 1.0 Hz), 6.99 (1H, td, *J* 7.6, 1.0 Hz), 6.83 (2H, d, *J* 8.7 Hz), 6.72 (1H, d, *J* 7.6 Hz), 5.95–5.80 (2H, m), 4.88 (1H, d, *J* 15.5 Hz), 4.77 (1H, d, *J* 15.5 Hz), 3.76 (3H, s), 3.60 (1H, dd, *J* 14.2, 8.1 Hz), 3.41 (1H, ddd, *J* 15.4, 4.7, 2.2 Hz), 2.76–2.65 (2H, m), 2.63–2.50 (1H, m), 2.35 (1H, dd, *J* 15.4, 7.4 Hz); δC (100 MHz; CDCl3) 206.6 (C), 174.2 (C), 159.1 (C), 142.9 (C), 131.0 (CH), 130.6 (C), 128.8 (CH), 128.5 (CH), 127.5 (C), 125.6 (CH), 124.2 (CH), 122.8 (CH), 114.3 (CH), 109.6 (CH), 67.8 (C), 55.3 (Me), 43.4 (CH2), 39.0 (CH2), 31.4 (CH2), 27.7 (CH2); HRMS (ESI): MNa+ found 370.1410. C22H21NNaO3 requires 370.1414.

* + - 1. 1'-(4-Methoxybenzyl)-8-oxaspiro[bicyclo[5.1.0]octane-3,3'-indoline]-2',4-dione (**22f**)

Following general procedure 2 from *N*-(4-methoxybenzyl)-4-oxo-*N*-phenyl-8-oxabicyclo[5.1.0]octane-3-carboxamide (0.027 g, 0.073 mmol) was obtained the title compound **22f** (0.015 g, 62%) as a pale yellow oil; νmax 1698, 1611, 1514, 1488, 1466, 1362, 1248, 1178, 1033, 751 cm-1; δH (400 MHz; CDCl3) 7.55 (1H, dd, *J* 7.6, 1.0 Hz), 7.20 (1H, td, *J* 7.6, 1.0 Hz), 7.17 (2H, d, *J* 8.8 Hz), 7.08 (1H, td, *J* 7.6, 1.0 Hz), 6.83 (2H, d, *J* 8.8 Hz), 6.73 (1H, d, *J* 7.6 Hz), 4.87 (1H, d, *J* 15.6 Hz), 4.76 (1H, d, *J* 15.6 Hz), 3.75 (3H, s), 3.43 (1H, ddd, *J* 6.9, 3.9, 2.4 Hz), 3.31 (1H, dt, *J* 3.9, 2.8 Hz), 3.19 (1H, dd, *J* 8.4, 3.0 Hz), 3.13 (1H, dd, *J* 15.7, 2.4 Hz), 2.54–2.47 (3H, m), 2.41 (1H, dd, *J* 15.7, 6.9 Hz); δC (100 MHz; CDCl3) 204.0 (C), 173.9 (C), 159.2 (C), 142.9 (C), 130.3 (C), 128.8 (CH), 128.5 (CH), 127.4 (C), 125.6 (CH), 123.4 (CH), 114.3 (CH), 109.5 (CH), 63.8 (C), 55.3 (Me), 55.2 (CH), 54.3 (CH), 43.5 (CH2), 35.8 (CH2), 32.8 (CH2), 25.9 (CH2); HRMS (ESI): MNa+ found 386.1369. C22H21NNaO4 requires 386.1363.

* + 1. Synthesis of a Satavaptan model system
			1. N-Methyl-N-phenyl 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxamide (**25**)

A solution of benzyl 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxylate (2.07 g, 7.13 mmol) and 10% Pd/C (0.414 g) in EtOAc (71 mL) was evacuated and backfilled with H2 four times. The reaction mixture was stirred under an atmosphere of H2 (balloon) for 16 h, then filtered through a pad of Celite which was washed with EtOAc (3 × 15 mL). The combined organics were concentrated *in vacuo* to afford 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxylic acid **24** (1.40 g, 98%) as a colourless solid which was used directly in the next step without further purification.

To a solution of 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxylic acid **24** (1.40 g, 6.99 mmol) in CH2Cl2 (71 mL) at 0 °C was added *N*-methylaniline (0.93 mL, 8.56 mmol), 2-chloro-1-methylpyridinium iodide (2.73 g, 10.7 mmol) and Et3N (2.98 mL, 21.4 mmol). The reaction mixture was stirred at 0 °C for 30 min, then at rt for 19 h. H2O (150 mL) was then added, the organics separated, and the aqueous phase further extracted with CH2Cl2 (2 × 150 mL). The combined organics were washed with saturated NaHCO3 (150 mL), dried over MgSO4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/Hexane (1:1), afforded the title compound **25** (1.24 g, 60%) as a pale yellow solid; mp 105–107 °C; νmax 2918, 1715, 1656, 1595, 1489, 1421, 1385, 1307, 1237, 1131, 1091, 1032 cm-1; δH (400 MHz; CDCl3) 7.40-7.31 (3H, m), 7.18-7.16 (2H, m), 3.95-3.86 (4H, m), 3.29 (3H, s), 3.21 (1H, dd, *J* 10.2, 6.0 Hz), 2.70 (1H, dd, *J* 14.1, 2.1 Hz), 2.32 (1H, d, *J* 14.1 Hz), 2.27-2.17 (1H, m), 2.09-2.03 (1H, m), 1.92-1.84 (1H, m), 1.74-1.67 (1H, m).; δC (100 MHz; CDCl3) 203.0 (C), 168.8 (C), 143.4 (C), 129.7 (CH), 128.1 (CH), 127.1 (CH), 109.4 (C), 64.55 (CH2), 64.51 (CH2), 53.2 (CH), 51.0 (CH2), 37.3 (Me), 32.7 (CH2), 23.9 (CH2); HRMS (ESI): MNa+, found312.1196. C16H19NNaO4 requires 312.1206.

* + - 1. 1’’-Methyl-1’’,2’’-dihydrodispiro[1,3-dioxolane-2,1’-cyclohexane-4’,3’’-indole]-2’’,3’-dione (**26**)

A solution of *N*-methyl-*N*-phenyl 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxamide **25** (0.430 g, 1.49 mmol) and Cu(OAc)2·H2O (30.0 mg, 0.150 mmol) in mesitylene (30 mL) was heated at reflux for 15 min whilst compressed air (dried over H2SO4) was bubbled through the mixture. After cooling to rt, the reaction mixture was concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexane (1:9 to 1:4), afforded the title compound (0.222 g, 52%) as a colourless solid; mp 124–125 °C; νmax 2969, 1723, 1694, 1656, 1606, 1489, 1348, 1309, 1236, 1122, 1089, 1066 cm-1; δH (400 MHz; CDCl3) 7.32 (1H, td, *J* 7.7, 1.3 Hz), 7.24 (1H, dd, *J* 7.4, 0.7 Hz), 7.13 (1H, td, *J* 7.6, 0.9 Hz), 6.85 (1H, d, *J* 7.7 Hz), 4.06-4.00 (4H, m), 3.50 (1H, d, *J* 13.5 Hz), 3.20 (3H, s), 2.81 (1H, td, *J* 12.9, 4.9 Hz), 2.77 (1H, dd, *J* 13.5, 2.4 Hz), 2.26 (1H, td, *J* 12.5, 4.4 Hz), 2.10 (1H, dt, *J* 14.0, 4.1 Hz), 1.97-1.93 (1H, m); δC (100 MHz; CDCl3) 200.9 (C), 173.4 (C), 143.3 (C), 128.9 (CH), 128.8 (C), 125.1 (CH), 123.1 (CH), 110.0 (C), 108.5 (CH), 65.1 (CH2), 64.8 (CH2), 62.4 (C), 49.8 (CH2), 31.6 (CH2), 30.4 (CH2), 26.6 (Me); HRMS (ESI): MNa+, found310.1040. C16H17NNaO4 requires 310.1050.

* + - 1. 3’-Hydroxy-1’’-methyl-1’’,2’’-dihydrodispiro[1,3-dioxolane-2,1’-cyclohexane-4’,3’’-indole]-2’’-one (**27**)

To a solution of 1’’-methyl-1’’,2’’-dihydrodispiro[1,3-dioxolane-2,1’-cyclohexane-4’,3’’-indole]-2’’,3’-dione **26** (0.197 g, 0.686 mmol) in MeOH (6.9 mL) at 0 °C was added NaBH4 (39.0 mg, 1.03 mmol). Stirring was continued at 0 °C for 1 h, then saturated NH4Cl (20 mL) was added and the aqueous phase extracted with EtOAc (3 × 20 mL). The combined organics were dried over MgSO4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/Hexane (1:1), afforded the title compound (0.185 g, 93%) as a colourless solid; mp 169–171 °C; νmax 3394, 2896, 1673, 1609, 1491, 1470, 1417, 1377, 1358, 1238, 1126, 1095, 1070, 1039 cm-1; δH (400 MHz; CDCl3) 7.51 (1H, dd, *J* 7.5, 0.4 Hz), 7.31 (1H, td, *J* 7.8, 1.1 Hz), 7.06 (1H, td, *J* 7.6, 0.9 Hz), 6.86 (1H, d, *J* 7.7 Hz), 4.10-3.98 (5H, m), 3.21 (3H, s), 2.50-2.46 (1H, m), 2.20-2.17 (1H, m), 2.05-1.84 (4H, m); δC (100 MHz; CDCl3) 178.3 (C), 143.7 (C), 130.4 (C), 128.2 (CH), 125.6 (CH), 122.2 (CH), 108.8 (C), 107.9 (CH), 71.0 (CH), 64.5 (CH2), 64.4 (CH2), 52.7 (C), 37.9 (CH2), 30.0 (CH2), 28.1 (CH2), 26.3 (Me); HRMS (ESI): MNa+, found312.1212. C16H19NNaO4 requires 312.1206.

* + - 1. 1’-Methyl-1’,2’-dihydrospiro[cyclohexane-1,3’-indol]-2-ene-2’,4-dione (**29**)

To a solution of 3’-hydroxy-1’’-methyl-1’’,2’’-dihydrodispiro[1,3-dioxolane-2,1’-cyclohexane-4’,3’’-indole]-2’’-one **27** (29.0 mg, 0.100 mmol) in THF (0.5 mL) was added 10% aqueous HCl (0.2 mL). The reaction mixture was heated at reflux for 1 h, then cooled to rt and partitioned between saturated NaHCO3 (10 mL) and EtOAc (3 × 10 mL). The combined organics were dried over MgSO4, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexane (1:9 to 1:1), afforded the title compound as a colourless oil (16.9 mg, 74%); νmax 3056, 2934, 1704, 1674, 1607, 1491, 1469, 1418, 1383, 1370, 1344, 1301, 1267, 1255, 1237, 1189, 1126, 1089 cm-1; δH (400 MHz; CDCl3) 7.35 (1H, td, *J* 7.7, 1.2 Hz), 7.19 (1H, dd, *J* 7.4, 0.7 Hz), 7.09 (1H, td, *J* 7.6, 0.7 Hz), 6.90 (1H, d, *J* 7.7 Hz), 6.46 (1H, d, *J* 10.1 Hz), 6.24 (1H, d, *J* 10.1 Hz), 3.25 (3H, s), 3.11 (1H, ddd, *J* 17.2, 9.8, 5.3 Hz), 2.60 (1H, ddd, *J* 17.2, 9.8, 5.3 Hz), 2.43-2.36 (1H, m), 2.27 (1H, ddd, *J* 14.0, 9.8, 5.1 Hz); δC (100 MHz; CDCl3) 198.1 (C), 176.3 (C), 146.2 (CH), 143.1 (C), 131.5 (CH), 131.2 (C), 129.2 (CH), 123.7 (CH), 123.1 (CH), 108.7 (CH), 49.7 (C), 33.2 (CH2), 32.0 (CH2), 26.6 (Me); HRMS (ESI): MNa+, found250.0843. C14H13NNaO2 requires 250.0838.

* + - 1. 1’-Methyl-1’,2’-dihydrospiro[cyclohexane-1,3’-indole]-2’,4-dione (**30**)

A solution of 1’-methyl-1’,2’-dihydrospiro[cyclohexane-1,3’-indol]-2-ene-2’,4-dione **29** (16.9 mg, 0.074 mmol) and 10% Pd/C (3.4 mg) in EtOAc (1 mL) was evacuated and backfilled with H2 4 times. The reaction mixture was stirred under an atmosphere of H2 (balloon) for 16 h, then filtered through a pad of Celite which was washed with EtOAc (3 × 15 mL). The combined organics were concentrated in vacuo to afford the title compound as a colourless solid (16.0 mg, 94%); mp 128–130 °C; νmax 2927, 1700, 1609, 1493, 1467, 1443, 1377, 1347, 1330, 1301, 1228, 1186, 1131, 1085 cm-1; δH (400 MHz; CDCl3) 7.32 (1H, td, *J* 7.7, 1.0 Hz), 7.24 (1H, d, *J* 7.3 Hz), 7.09 (1H, td, *J* 7.6, 0.6 Hz), 6.89 (1H, d, *J* 7.8 Hz), 3.25 (3H, s), 3.17 (2H, ddd, *J* 16.1, 8.8, 8.8 Hz), 2.48 (2H, ddd, *J* 15.0, 5.4, 5.4 Hz), 2.15 (4H, dd, *J* 8.8, 5.4 Hz); δC (100 MHz; CDCl3) 210.9 (C), 179.3 (C), 142.9 (C), 133.3 (C), 128.4 (CH), 122.8 (CH), 122.6 (CH), 108.5 (CH), 45.6 (C), 37.0 (CH2), 33.7 (CH2), 26.3 (Me); HRMS (ESI): MNa+, found252.0983. C14H15NNaO2 requires 252.0995.

* + 1. Formal total synthesis of Satavaptan
			1. N-Benzyl-N-(4-ethoxyphenyl)-7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxamide (**20**)

To a stirred solution of ethyl 7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxylate **24** (0.577 g, 1.41 mmol), *N*-benzyl-4-ethoxyaniline **4** (0.141 g, 0.705 mmol) and DIPEA (311 µL, 1.83 mmol) in EtOAc (9 mL) at room temperature was added T3P (0.897 g, 1.41 mmol, 50% w/w solution in EtOAc). The reaction mixture was stirred at room temperature for 16 h. Saturated NaHCO3 (10 mL) was added and the aqueous phase extracted with EtOAc (10 × 5 mL). The combined organic extracts were washed with saturated NaHCO3 (10 mL), brine (10 mL), dried over MgSO4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane/EtOAc) afforded the title compound **20** (0.220 g, 76%) as a colourless oil; νmax2978, 1718, 1657, 1511, 1401, 1301, 1247 cm-1; δH (400 MHz; CDCl3): 7.28-7.16 (5H, m), 6.83 (2H, d, *J* 8.9 Hz), 6.73 (2H, d, *J* 8.9 Hz), 5.00 (1H, d, *J* 14.4 Hz), 4.73 (1H, d, *J* 14.4 Hz), 3.98-3.85 (6H, m), 3.21 (1H, dd, *J* 5.95, 4.12 Hz), 2.66 (1H, d, *J* 14.0 Hz), 2.31 (1H, d, *J* 14.0 Hz), 2.34-2.20 (1H, m), 2.07-2.20 (1H, m), 1.96-1.87 (1H, m), 1.72 (1H, td, *J* 12.8, 4.12 Hz), 1.37 (3H, t, *J* 6.9 Hz); δC (100 MHz, CDCl3): 203.3 (C), 169.4 (C), 158.7 (C), 137.4 (C), 134.3 (C), 129.5 (CH), 128.9 (CH), 128.4 (CH), 127.4 (CH), 115.1 (CH), 109.7 (C), 64.9 (CH2), 63.7 (CH2), 53.7 (CH), 53.3 (CH2), 51.4 (CH2), 33.1 (CH2), 24.1 (CH2), 14.8 (Me); HRMS [ESI]: MNa+, found 432.1776. C24H27NNaO5 requires 432.1781.

* + - 1. 1''-Benzyl-5''-ethoxy-2'H-dispiro[1,3-dioxolane-2,4'-cyclohexane-1',3''-indole]-2',2''(1''H)-dione (**19**)

*In mesitylene*: *N*-Benzyl-*N*-(4-ethoxyphenyl)-7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxamide **20** (80.0 mg, 0.196 mmol) and Cu(OAc)2∙H2O (3.9 mg, 10 mol%) in mesitylene (4 mL) was stirred at 165 °C with compressed air bubbled through for 30 min. Upon completion of the reaction, mesitylene was removed under reduced pressure and EtOAc (5 mL) was added. The organic phase was washed with 10% HCl solution (2 × 5 mL), 10% NH4OH solution (2 × 5 mL), brine (5 ml), dried over MgSO4, filtered and concentrated *in* *vacuo*. Purification by flash column chromatography (7:3 petrol/EtOAc) afforded the title compound **19** (46.0 mg, 58%) as a yellow oil.

*In ethylene carbonate*: *N*-Benzyl-*N*-(4-ethoxyphenyl)-7-oxo-1,4-dioxaspiro[4.5]decane-8-carboxamide **20** (55.0 mg, 0.134 mmol) and Cu(OAc)2∙H2O (26.8 mg, 0.134 mmol) in ethylene carbonate (3.3 mL) was stirred at 165 °C under an atmosphere of air for 1 h. The reaction mixture was removed from heat and allowed to cool to rt, then H2O (8 mL) and EtOAc (8 mL) were added and the reaction mixture allowed to cool to room temperature. The reaction mixture was transferred to a separating funnel to which EtOAc (15 mL) was added and the organic phase washed with H2O (5 × 10 mL), 10% aqueous NH4OH solution (3 × 5 mL), brine (5 mL), dried (MgSO4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound **19** (34.0 mg, 62%) as a yellow oil; νmax2978, 1718, 1698, 1496, 1455, 1352, 1300 cm-1; δH (400 MHz, CDCl3): 7.25-7.12 (5H, m), 6.77 (1H, d, *J* 2.3 Hz), 6.63 (1H, dd, *J* 8.4, 2.3 Hz), 6.51 (1H, d, *J* 8.4 Hz), 4.79 (2H, s), 4.01-3.83 (6H, m), 3.46 (1H, d, *J* 13.7 Hz), 2.77 (1H, td, *J* 12.9, 4.9 Hz), 2.72 (1H, d, *J* 13.7 Hz), 2.29-2.16 (1H, m), 2.09 (1H, dt, *J* 14.1, 4.6 Hz), 1.93-1.86 (1H, m), 1.30 (3H, t, *J* 6.9 Hz); δC (100 MHz, CDCl3): 200.8 (C), 173.2 (C), 155.5 (C), 135.54 (C), 135.47 (C), 129.9 (C), 128.8 (CH), 127.6 (CH), 127.0 (CH), 114.1 (CH), 113.9 (CH), 112.6 (CH), 109.8 (C), 65.0 (CH2), 64.7 (CH2), 64.0 (CH2), 62.6 (C), 49.8 (CH2), 43.9 (CH2), 31.8 (CH2), 30.4 (CH2), 14.8 (Me); HRMS [ESI]:MNa+, found 430.1620. C24H25NNaO5 requires 430.1625.

* + - 1. 1''-Benzyl-5''-ethoxy-3'-hydroxydispiro[1,3-dioxolane-2,1'-cyclohexane-4',3''-indol]-2''(1''H)-one (**31**)

To a stirred solution of 1''-benzyl-5''-ethoxy-2'*H*-dispiro[1,3-dioxolane-2,4'-cyclohexane-1',3''-indole]-2',2''(1''*H*)-dione **19** (0.355 g, 0.872 mmol) in MeOH (10.5 mL) at 0 °C was added NaBH4 (49.5 mg, 1.31 mmol) and stirred for 2 h. The reaction mixture was quenched with NH4Cl (10 mL) then the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried (MgSO4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane/EtOAc) afforded a single diastereoisomer of the title compound **31** (0.284 g, 80%) as a colourless powder; m.p. 174–175 °C; νmax3452, 2933, 1698, 1597, 1496, 1455, 1442, 1351 cm-1; δH (400 MHz, CDCl3): 7.31-7.19 (5H, m), 7.16 (1H, d, *J* 2.5 Hz), 6.68 (1H, dd, *J* 8.5, 2.5 Hz), 6.57 (1H, d, *J* 8.5 Hz), 4.98 (1H, d, *J* 16.0 Hz), 4.81 (1H, d, *J* 16.0 Hz), 4.20-3.91 (7H, m), 2.60-2.46 (1H, m), 2.25-2.13 (1H, m), 2.09-1.96 (3H, m), 1.94-1.86 (1H, m), 1.37 (3H, t, *J* 7.0 Hz); δC (100 MHz, CDCl3): 178.3 (C), 154.9 (C), 136.3 (C), 136.0 (C), 128.8 (CH), 127.5 (CH), 127.1 (C), 127.0 (CH), 114.5 (CH), 112.7 (CH), 109.3 (CH), 108.9 (C), 73.4 (CH), 71.3 (C), 64.6 (CH2), 64.5 (CH2), 64.1 (CH2), 43.7 (CH2), 38.1 (CH2), 30.1 (CH2), 28.4 (CH2), 15.0 (Me); HRMS [ESI]: MH+, found 410.1957. C24H28NO5 requires 410.1962.

* + - 1. 1'-Benzyl-5'-ethoxyspiro[cyclohex[2]ene-1,3'-indoline]-2',4-dione

To 1''-benzyl-5''-ethoxy-3'-hydroxydispiro[1,3-dioxolane-2,1'-cyclohexane-4',3''-indol]-2''(1''*H*)-one **31** (0.261 g, 0.638 mmol) was added THF (3 mL) and 10% aqueous HCl solution (1.2 mL) and the mixture stirred at 70 °C for 90 min. The reaction mixture was allowed to cool to room temperature then quenched with sat. NaHCO3 (6mL). The aqueous phase was extracted with EtOAc (2 × 5 mL). The combined organic phases were dried (MgSO4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound (0.188 g, 85%) as a colourless oil; νmax2979, 1705, 1675, 1560, 1495, 1453, 1384, 1341 cm-1; δH (400 MHz; CDCl3): 7.34-7.23 (5H, m), 6.80 (1H, d, *J* 2.4 Hz), 6.73 (1H, dd, *J* 8.4, 2.4 Hz), 6.67 (1H, d, *J* 8.4 Hz), 6.57 (1H, d, *J* 10.0 Hz), 6.27 (1H, d, *J* 10.0 Hz), 4.95 (1H, d, *J* 15.7 Hz), 4.85 (1H, d, *J* 15.7 Hz), 3.94 (2H, q, *J* 7.0 Hz), 3.16 (1H, ddd, *J* 17.2, 10.0, 5.3 Hz), 2.63 (1H, ddd, *J* 17.2, 6.9, 5.0 Hz), 2.51-2.42 (1H, m), 2.31 (1H, ddd, *J* 13.8, 10.0, 5.0 Hz), 1.36 (3H, t, *J* 7.0 Hz); δC (100 MHz, CDCl3): 198.0 (C), 176.0 (C), 155.6 (C), 146.2 (CH), 135.5 (C), 135.4 (C), 132.5 (C), 131.6 (CH), 128.9 (CH), 127.8 (CH), 127.2 (CH), 113.8 (CH), 111.8 (CH), 110.1 (CH), 64.1 (CH2), 50.1 (C), 44.1 (CH2), 33.2 (CH2), 32.3 (CH2), 14.9 (Me); HRMS [ESI]: MH+, found 348.1588. C22H22NO3 requires 348.1594.

* + - 1. 1'-Benzyl-5'-ethoxyspiro[cyclohexane-1,3'-indoline]-2',4-dione (**12**)

To a stirred solution of 1'-benzyl-5'-ethoxyspiro[cyclohex[2]ene-1,3'-indoline]-2',4-dione (0.166 g, 0.478 mmol) in EtOAc (6.5 mL) was added 10 wt% Pd/C (21.7 mg). The vessel was placed under vacuum and back-filled with H2 three times before being stirred at room temperature for 16 h under an atmosphere of H2 (balloon). The reaction mixture was filtered through celite. The celite was washed with EtOAc (3 × 5 mL) then the combined organics were concentrated *in vacuo*. Purification by flash column chromatography (7:3 hexane/EtOAc) afforded the title compound **12** (0.162 g, 97%) as a colourless powder; m.p. 140–143 °C (Lit.5 125–128 °C); νmax 3033, 2977, 2928, 1710, 1692, 1600, 1495, 1477, 1449, 1369, 1345 cm-1; δH (400 MHz; CDCl3): 7.32-7.21 (5H, m), 6.84 (1H, d, *J* 2.5 Hz), 6.68 (1H, d, *J* 8.6 Hz), 6.62 (1H, d, *J* 8.6 Hz), 4.90 (2H, s), 3.94 (2H, q, *J* 6.9 Hz), 3.25-3.14 (2H, m), 2.58-2.44 (2H, m), 2.25-2.09 (4H, m), 1.36 (3H, t, *J* 6.9 Hz); δC (100 MHz, CDCl3): 210.6 (C), 179.1 (C), 155.3 (C), 135.8 (C), 135.1 (C), 134.4 (C), 128.7 (CH), 127.6 (CH), 127.0 (CH), 112.5 (CH), 111.1 (CH), 109.6 (CH), 64.0 (CH2), 45.8 (C), 43.5 (CH2), 36.8 (CH2), 33.7 (CH2), 14.8 (Me); HRMS [ESI]: MH+, found 350.1741. C22H24NO3 requires 350.1751.

* + 1. Synthesis of a Satavaptan analogue
			1. N‐(4‐Ethoxyphenyl)‐N‐[(4‐methoxyphenyl)methyl]‐7‐oxo‐1,4‐dioxaspiro[4.5]decane‐8‐carboxamide (**33**)

To a solution of 4‐ethoxy‐*N*‐[(4‐methoxyphenyl)methyl]aniline **32** (1.99 g, 7.75 mmol) and 7‐oxo‐1,4‐dioxaspiro[4.5]decane‐8‐carboxylic acid **24** (3.10 g, 15.5 mmol) in EtOAc (77.5 mL) was added DIPEA (3.51 mL, 20.2 mmol) and T3P (50wt% in EtOAc, 9.86 g, 15.5 mmol). The reaction mixture was stirred at rt for 20 h, then diluted with EtOAc (50 mL), washed with H2O (2 × 50 mL) and sat. brine (50 mL), dried over MgSO4, filtered and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/hexane (1:4 to 1:1), afforded the title compound **33** (1.77 g, 52%) as a colourless solid; mp. 38–40 °C; νmax 2934, 2837, 1716, 1650, 1610, 1585, 1509, 1477, 1454, 1440, 1400, 1356, 1318, 1292, 1243, 1174, 1113, 1092, 1031 cm-1; δH (400 MHz; CDCl3) 7.15 (2H, d, *J* 8.7 Hz), 6.82-6.73 (6H, m), 4.94 (1H, d, *J* 14.2 Hz), 4.67 (1H, d, *J* 14.2 Hz), 3.97 (2H, q, *J* 6.9 Hz), 3.96-3.87 (4H, m), 3.77 (3H, s), 3.19 (1H, dd, *J* 10.5 and 6.0 Hz), 2.68 (1H, dd, *J* 14.2 and 2.3 Hz), 2.32 (1H, d, *J* 13.7 Hz), 2.31-2.21 (1H, m), 2.08-2.02 (1H, m), 1.94-1.87 (1H, m), 1.72 (1H, ddd, *J* 12.8, 12.8, 4.5 Hz), 1.39 (3H, t, *J* 6.9 Hz); δC (100 MHz; CDCl3) 203.2 (C), 169.1 (C), 158.8 (C), 158.5 (C), 134.1 (C), 130.1 (CH), 129.5 (CH), 115.0 (CH), 113.6 (CH), 109.6 (C), 64.7 (CH2), 64.6 (CH2), 63.6 (CH2), 55.2 (Me), 53.6 (CH), 52.5 (CH2), 51.3 (CH2), 33.0 (CH2), 24.0 (CH2), 14.7 (Me); HRMS (ESI): MNa+, found462.1874. C25H29NNaO6 requires 462.1887.

* + - 1. 5''‐Ethoxy‐1''‐[(4‐methoxyphenyl)methyl]‐1'',2''‐dihydrodispiro[1,3‐dioxolane‐2,1'‐cyclohexane‐4',3''‐indole]‐2'',5'‐dione (**34**)

*In mesitylene*: N‐(4‐Ethoxyphenyl)‐N‐[(4‐methoxyphenyl)methyl]‐7‐oxo‐1,4‐dioxaspiro[4.5]decane‐8‐carboxamide **33** (0.659 g, 1.50 mmol) and Cu(OAc)2·H2O (29.9 mg, 10 mol%) in mesitylene (30 mL) was stirred at 165 °C with compressed air bubbled through for 20 min. Upon completion of the reaction, the mesitylene was removed under reduced pressure. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:4 to 2:3) afforded the title compound **34** (0.341 g, 52%) as a colourless oil.

*In ethylene carbonate*: N‐(4‐Ethoxyphenyl)‐N‐[(4‐methoxyphenyl)methyl]‐7‐oxo‐1,4‐dioxaspiro[4.5]decane‐8‐carboxamide **33** (0.650 g, 1.48 mmol) and Cu(2-ethylhexanoate)2 (53.0 mg, 10 mol%) in ethylene carbonate (15 mL) was stirred at 165 °C with compressed air bubbled through for 20 min. The reaction mixture was cooled to rt, then sat. NH4Cl (30 mL) was added and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organics were washed with 10% NH4OH solution (30 mL), H2O (10 × 30 mL) and sat. brine (30 mL), dried over MgSO4, filtered and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:4 to 2:3) afforded the title compound **34** (0.265 g, 41%) as a colourless oil; mp 40–42 °C; νmax 2926, 1718, 1693, 1603, 1513, 1494, 1478, 1454, 1440, 1397, 1352, 1300, 1275, 1245, 1182, 1163, 1129, 1097, 1033, 1013 cm-1; δH (400 MHz; CDCl3) 7.15 (2H, d, *J* 8.7 Hz), 6.84-6.80 (3H, m), 6.71 (1H, dd, *J* 8.7, 2.3 Hz), 6.61 (1H, d, *J* 8.7 Hz), 4.79 (2H, s), 4.07-3.92 (6H, m), 3.76 (3H, s), 3.53 (1H d, *J* 13.7 Hz), 2.83 (1H, ddd, *J* 12.9, 12.8, 4.6 Hz), 2.78 (1H, dd, *J* 13.7, 1.8 Hz), 2.26 (1H, ddd, *J* 13.7, 13.7, 4.6 Hz), 2.14 (1H, ddd, *J* 13.7, 4.6, 4.6 Hz), 2.00-1.94 (1H, m), 1.37 (3H, t, *J* 6.9 Hz); δC (100 MHz; CDCl3) 200.8 (C), 173.1 (C), 159.0 (C), 155.4 (C), 135.6 (C), 129.9 (C), 128.4 (CH), 127.5 (C), 114.2 (CH), 113.9 (CH), 112.6 (CH), 109.7 (CH), 64.9 (CH2), 64.7 (CH2), 64.0 (CH2), 62.5 (C), 55.2 (Me), 49.7 (CH2), 43.3 (CH2), 31.7 (CH2), 30.4 (CH2), 14.8 (Me); HRMS (ESI): MNa+, found460.1732. C25H27NNaO6 requires 460.1731.

* + - 1. 5''‐Ethoxy‐5'‐hydroxy‐1''‐[(4‐methoxyphenyl)methyl]‐1'',2''‐dihydrodispiro[1,3‐dioxolane‐2,1'‐cyclohexane‐4',3''‐indol]‐2''‐one (**35**)

To a solution of 5''‐ethoxy‐1''‐[(4‐methoxyphenyl)methyl]‐1'',2''‐dihydrodispiro[1,3‐dioxolane‐2,1'‐cyclohexane‐4',3''‐indole]‐2'',5'‐dione **34** (0.260 g, 0.594 mmol) in MeOH (5.9 mL) at 0 °C was added NaBH4 (34.0 mg, 0.891 mmol) in one portion. The reaction mixture was stirred at 0 °C for 2 h, then quenched at the same temperature with sat. NH4Cl (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organics were dried over MgSO4, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:1) afforded the title compound **35** (0.231 g, 89%) as a colourless solid; mp 54–56 °C; νmax 3448, 2932, 2885, 1691, 1596, 1513, 1489, 1440, 1345, 1290, 1245, 1177, 1144, 1110, 1049 cm-1; δH (400 MHz; CDCl3) 7.17-7.14 (2H, m), 6.84-6.81 (3H, m), 6.71 (1H, dd, *J* 8.5, 2.5 Hz), 6.61 (1H, d, *J* 8.5 Hz), 4.79 (2H, s), 4.05-3.92 (6H, m), 3.76 (3H, s), 3.52 (1H, d, *J* 13.6 Hz), 2.83 (1H, td, *J* 12.9, 5.0 Hz), 2.79 (1H, dd, *J* 13.4, 1.9 Hz), 2.26 (1H, td, *J* 13.2, 4.4 Hz), 2.14 (1H, dt, *J* 13.8, 4.4 Hz), 1.99-1.94 (1H, m), 1.37 (3H, t, *J* 7.0 Hz); δC (100 MHz; CDCl3) 177.0 (C), 157.7 (C), 153.6 (C), 127.1 (CH), 126.8 (C), 113.2 (CH), 112.9 (CH), 111.4 (CH), 108.0 (CH), 107.6 (C), 70.0 (C), 63.3 (CH2), 63.2 (CH2), 62.8 (CH2), 54.0 (Me), 41.9 (CH2), 28.8 (CH2), 27.1 (CH2), 13.7 (Me); HRMS (ESI): MNa+, found462.1870. C25H29NNaO6 requires 462.1887.

* + - 1. 5''‐Ethoxy‐1''‐[(4‐methoxyphenyl)methyl]‐1'',2''‐dihydrodispiro[1,3‐dioxolane‐2,1'‐cyclohexane‐4',3''‐indol]‐2'‐en‐2''‐one

A solution of 5''‐ethoxy‐5'‐hydroxy‐1''‐[(4‐methoxyphenyl)methyl]‐1'',2''‐dihydrodispiro[1,3‐dioxolane‐2,1'‐cyclohexane‐4',3''‐indol]‐2''‐one **35** (0.210 g, 0.478 mmol) in THF (2.4 mL) and 10% HCl (0.96 mL) was heated at reflux for 2 h. After cooling to rt, the reaction mixture was partitioned between sat. NaHCO3 (25 mL) and EtOAc (3 × 25 mL). The combined organics were dried over MgSO4, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:4 to 1:3) afforded the title compound (0.156 g, 87%) as a colourless solid; mp 142–143 °C; νmax 2979, 2932, 1697, 1674, 1611, 1599, 1513, 1493, 1476, 1443, 1384, 1335, 1290, 1275, 1245, 1221, 1176, 1109, 1033 cm-1; δH (400 MHz; CDCl3) 7.22 (2H, d, *J* 8.7 Hz), 6.85 (2H, d, *J* 8.7 Hz), 6.80 (1H, d, *J* 2.8 Hz), 6.75 (1H, dd, *J* 8.2, 2.3 Hz), 6.70 (1H, d, *J* 8.2 Hz), 6.51 (1H, d, *J* 10.1 Hz), 6.28 (1H, d, *J* 10.1 Hz), 4.89 (1H, d, *J* 15.1 Hz), 4.79 (1H, d, *J* 15.1 Hz), 3.95 (2H, q, *J* 6.9 Hz), 3.78 (3H, s), 3.17 (1H, ddd, *J* 17.0, 10.1, 5.0 Hz), 2.63 (1H, ddd, *J* 17.4, 6.9, 5.0 Hz), 2.49-2.42 (1H, m), 2.30 (1H, ddd, *J* 14.6, 9.6, 5.0 Hz), 1.38 (3H, t, *J* 6.9 Hz); HRMS (ESI): MNa+, found400.1511. C23H23NNaO4 requires 400.1519.

* + - 1. 5''‐Ethoxy‐1''‐[(4‐methoxyphenyl)methyl]‐1'',2''‐dihydrodispiro[1,3‐dioxolane‐2,1'‐cyclohexane‐4',3''‐indol]‐2''‐one (**36**)

To a stirred solution of 5''‐ethoxy‐1''‐[(4‐methoxyphenyl)methyl]‐1'',2''‐dihydrodispiro[1,3‐dioxolane‐2,1'‐cyclohexane‐4',3''‐indol]‐2'‐en‐2''‐one (0.145 g, 0.384 mmol) in EtOAc (3.8 mL) was added 10% Pd/C (77 mg). The vessel was placed under vacuum and back-filled with H2 four times before being stirred at room temperature for 18 h under an atmosphere of H2. The reaction mixture was filtered through celite. The celite was washed with EtOAc (2 × 15 mL) then the combined organics concentrated in vacuo to afford the title compound **36** (0.143 g, 96%) as a colourless solid; mp 123–125 °C; νmax 2978, 2929, 1711, 1691, 1600, 1513, 1494, 1477, 1443, 1395, 1368, 1343, 1291, 1274, 1245, 1177, 1110, 1044, 1033. cm-1; δH (400 MHz; CDCl3) 7.21 (2H, d, *J* 8.7 Hz), 6.87-6.82 (3H, m), 6.70 (1H, dd, *J* 8.7, 1.8 Hz), 6.67 (1H, d, *J* 8.7 Hz), 4.85 (2H, s), 3.96 (2H, q, *J* 7.3 Hz), 3.77 (3H, s), 3.21 (2H, ddd, *J* 16.0, 10.5, 6.4 Hz), 2.50 (2H, ddd, *J* 14.7, 4.6, 4.6 Hz), 2.24-2.11 (4H, m), 1.38 (3H, t, *J* 6.9 Hz); δC (100 MHz; CDCl3) 210.7 (C), 178.9 (C), 159.1 (C), 155.3 (C), 135.2 (C), 134.5 (C), 128.5 (CH), 127.9 (C), 114.2 (CH), 112.6 (CH), 111.1 (CH), 109.6 (CH), 64.1 (CH2), 55.2 (Me), 45.8 (C), 43.0 (CH2), 36.9 (CH2), 33.7 (CH2), 14.8 (Me); HRMS (ESI): MNa+, found402.1680. C23H25NNaO4 requires 402.1676.

* + - 1. 5'‐Ethoxy‐4‐hydroxy‐1'‐[(4‐methoxyphenyl)methyl]‐1',2'‐dihydrospiro[cyclohexane‐1,3'‐indol]‐2'‐one (**37**)

To a solution of 5''‐ethoxy‐1''‐[(4‐methoxyphenyl)methyl]‐1'',2''‐dihydrodispiro[1,3‐dioxolane‐2,1'‐cyclohexane‐4',3''‐indol]‐2''‐one **36** (0.140 g, 0.369 mmol) in THF (2 mL) at –78 °C was added L-Selectride (1.0 M in THF, 0.55 mL, 0.550 mmol). The reaction mixture was stirred at –78 °C for 2 h, then quenched at the same temperature by the addition of H2O (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organics dried over MgSO4, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:1) afforded the title compound **37** (0.119 g, 84%) as a colourless oil; νmax 3406, 2925, 2855, 1688, 1612, 1598, 1513, 1495, 1476, 1442, 1393, 1365, 1341, 1289, 1273, 1245, 1177, 1109, 1050, 1035 cm-1; δH (400 MHz; CDCl3) 7.18 (2H, d, *J* 8.2 Hz), 6.85-6.81 (3H, m), 6.65 (1H, dd, *J* 8.7, 2.3 Hz), 6.59 (1H, d, *J* 8.2 Hz), 4.80 (2H, s), 3.95 (2H, q, *J* 6.9 Hz), 3.98-3.87 (1H, m), 3.76 (3H, s), 2.28-2.18 (2H, m), 2.05-1.94 (4H, m), 1.74-1.66 (2H, m), 1.37 (3H, t, *J* 6.9 Hz); δC (100 MHz; CDCl3) 179.7 (C), 158.8 (C), 155.0 (C), 135.9 (C), 135.1 (C), 128.4 (CH), 128.2 (C), 114.0 (CH), 112.0 (CH), 111.1 (CH), 109.1 (CH), 68.8 (CH), 64.0 (CH2), 55.1 (Me), 46.1 (C), 42.7 (CH2), 31.1 (CH2), 29.6 (CH2), 14.8 (Me); HRMS (ESI): MNa+, found404.1822. C23H27NNaO4 requires 404.1832.

* + - 1. 5'‐Ethoxy‐1'‐[(4‐methoxyphenyl)methyl]‐4‐(prop‐2‐yn‐1‐yloxy)‐1',2'‐dihydrospiro[cyclohexane‐1,3'‐indol]‐2'‐one (**38**)

To a solution of 5'‐ethoxy‐4‐hydroxy‐1'‐[(4‐methoxyphenyl)methyl]‐1',2'‐dihydrospiro[cyclohexane‐1,3'‐indol]‐2'‐one **37** (0.091 g, 0.239 mmol) in THF (3 mL) was added NaH (60% in mineral oil, 0.038 g, 0.956 mmol) in one portion. The reaction mixture was heated at reflux for 1 h before the addition of propargyl bromide (106 μL, 0.717 mmol). Stirring was maintained at reflux for a further 17 h. After cooling to rt, the reaction mixture was partitioned between sat. NH4Cl (20 mL) and EtOAc (3 × 20 mL). The combined organics were dried over MgSO4, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:9 to 1:1) afforded the title compound (0.077 g, 77%) as a colourless oil; νmax 3226, 2978, 2941, 2114, 1689, 1611, 1594, 1513, 1485, 1475, 1457, 1438, 1387, 1369, 1340, 1318, 1300, 1287, 1270, 1248, 1187, 1176, 1153, 1130, 1114, 1102, 1088, 1069, 1052, 1034, 1011 cm-1; δH (400 MHz; CDCl3) 7.18 (2H, d, *J* 8.7 Hz), 6.88 (1H, d, *J* 2.3 Hz), 6.83 (2H, d, *J* 8.7 Hz), 6.65 (1H, dd, *J* 8.7, 2.3 Hz), 6.59 (1H, d, *J* 8.7 Hz), 4.80 (2H, s), 4.26 (2H, d, *J* 2.3 Hz), 3.95 (2H, q, *J* 6.9 Hz), 3.87-3.79 (1H, m), 3.76 (3H, s), 2.43 (1H, t, *J* 2.3 Hz), 2.28-2.20 (2H, m), 2.06-1.95 (4H, m), 1.67-1.61 (2H, m), 1.38 (3H, t, *J* 6.9 Hz); δC (100 MHz; CDCl3) 179.8 (C), 159.0 (C), 155.0 (C), 136.1 (C), 135.4 (C), 128.6 (CH), 128.4 (C), 114.2 (CH), 112.0 (CH), 111.7 (CH), 109.2 (CH), 80.5 (C), 74.4 (CH), 74.0 (C), 64.1 (CH2), 55.3 (Me), 55.0 (CH2), 46.6 (C), 43.0 (CH2), 30.7 (CH2), 26.0 (CH2), 15.0 (Me); HRMS (ESI): MNa+, found442.1980. C26H29NNaO4 requires 442.1989.

* + - 1. 4-[(1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy]-5’-ethoxy-1’-[(4-methoxyphenyl)methyl]-1,2’-dihydrospiro[cyclohexane-1,3’-indole]-2’-one (**39**)

To a solution of 5'‐ethoxy‐1'‐[(4‐methoxyphenyl)methyl]‐4‐(prop‐2‐yn‐1‐yloxy)‐1',2'‐dihydrospiro[cyclohexane‐1,3'‐indol]‐2'‐one **38** (30.0 mg, 0.072 mmol) in THF (2 mL) was added benzyl azide (14 μL, 0.108 mmol), CuI (2.7 mg, 14.4 μmol) and DIPEA (25 μL, 0.144 mmol). The reaction mixture was stirred at rt for 22 h, then partitioned between H2O (20 mL) and EtOAc (3 × 20 mL). The combined organics were dried over MgSO4, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:4 to 2:3) afforded the title compound **39** (40.2 mg, quant.) as a colourless solid; mp 148–150 °C; νmax 2928, 2865, 1694, 1603, 1510, 1493, 1449, 1364, 1335, 1289, 1271, 1244, 1172, 1109, 1051, 1032 cm-1; δH (400 MHz; CDCl3) 7.54 (1H, s), 7.40-7.34 (3H, m), 7.30-7.28 (2H, m), 7.19-7.15 (2H, m), 6.86 (1H, d, *J* 2.4 Hz), 6.84-6.80 (2H, m), 6.64 (1H, dd, *J* 8.5, 2.4 Hz), 6.58 (1H, d, *J* 8.5 Hz), 5.52 (2H, s), 4.79 (2H, s), 4.72 (2H, s), 3.95 (2H, q, *J* 7.0 Hz), 3.75 (3H, s), 3.73-3.69 (1H, m), 2.27-2.18 (2H, m), 2.06-1.93 (4H, m), 1.65-1.60 (2H, m), 1.38 (3H, t, *J* 7.0 Hz); δC (100 MHz; CDCl3) 179.8 (C), 159.0 (C), 155.0 (C), 146.8 (C), 136.1 (C), 135.4 (C), 134.8 (C), 129.2 (CH), 128.8 (CH), 128.6 (CH), 128.4 (C), 128.2 (CH), 122.4 (CH), 114.2 (CH), 112.1 (CH), 111.6 (CH), 109.2 (CH), 75.5 (CH), 64.1 (CH2), 61.9 (CH2), 55.3 (Me), 54.2 (CH2), 46.6 (C), 42.9 (CH2), 30.8 (CH2), 26.3 (CH2), 15.0 (Me); HRMS (ESI): MNa+, found575.2612. C33H36N4NaO4 requires 575.2629.

* + - 1. 4‐[(1‐Benzyl‐1H‐1,2,3‐triazol‐4‐yl)methoxy]‐5'‐ethoxy‐1',2'‐dihydrospiro[cyclohexane‐1,3'‐indol]‐2'‐one (**40**)

A solution of 4-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-5’-ethoxy-1’-[(4-methoxyphenyl)methyl]-1,2’-dihydrospiro[cyclohexane-1,3’-indole]-2’-one **39** (33.7 mg, 0.061 mmol) in TFA (3 mL) was heated at reflux for 2 d. After cooling to rt, the reaction mixture was partitioned between sat. NaHCO3 (35 mL) and CH2Cl2 (3 × 35 mL). The combined organics were dried over MgSO4, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:1) afforded the title compound (23.5 mg, 89%) as a colourless solid; mp 70–72 °C; νmax 3211, 2925, 2854, 1697, 1603, 1494, 1456, 1392, 1364, 1328, 1307, 1245, 1196, 1112, 1081, 1047 cm-1; δH (400 MHz; CDCl3) 8.41 (1H, br s), 7.53 (1H, s), 7.38-7.34 (2H, m), 7.3-7.28 (2H, m), 6.83 (1H, d, *J* 2.4 Hz), 6.79 (1H, d, *J* 8.5 Hz), 6.70 (1H, dd, *J* 8.4, 2.5 Hz), 5.53 (2H, s), 4.72 (2H, s), 3.98 (2H, q, *J* 7.0 Hz), 3.72-3.66 (1H, m), 2.22-2.14 (2H, m), 2.03-1.94 (4H, m), 1.63-1.57 (2H, m), 1.40 (3H, t, *J* 7.0 Hz).; δC (100 MHz; CDCl3) 182.5 (C), 154.9 (C), 146.7 (C), 136.6 (C), 134.7 (C), 133.4 (C), 129.2 (CH), 128.8 (CH), 128.3 (CH), 122.5 (CH), 112.5 (CH), 111.5 (CH), 109.9 (CH), 75.5 (CH), 64.2 (CH2), 61.9 (CH2), 54.3 (CH2), 47.1 (C), 30.6 (CH2), 26.2 (CH2), 15.0 (Me); HRMS (ESI): MNa+, found455.2040. C25H28N4NaO3 requires 455.2054.

* + - 1. 4‐[(1‐benzyl‐1H‐1,2,3‐triazol‐4‐yl)methoxy]‐1'‐[2‐chloro‐4‐(trifluoromethyl)benzenesulfonyl]‐5'‐ethoxy‐1',2'‐dihydrospiro[cyclohexane‐1,3'‐indol]‐2'‐one (**41**)

To a solution of 4‐[(1‐benzyl‐1*H*‐1,2,3‐triazol‐4‐yl)methoxy]‐5'‐ethoxy‐1',2'‐dihydrospiro[cyclohexane‐1,3'‐indol]‐2'‐one **40** (20.6 mg, 0.048 mmol) in THF (1.5 mL) at 0 °C was added KO*t*-Bu (16.2 mg, 0.144 mmol). The reaction mixture was stirred at rt for 20 min before the addition of 2-chloro-4-(trifluoromethyl)benzenesulfonyl chloride (40.2 mg, 0.144 mmol). Stirring was continued at rt for 16 h, then sat. NH4Cl (15 mL) was added. The aqueous phase was extracted with EtOAc (3 × 15 mL), dried over MgSO4, filtered, and concentrated in vacuo. Purification by flash column chromatography, eluting with EtOAc/Hexanes (1:1) afforded the title compound **41** (17.4 mg, 54%) as a colourless solid; mp 56–58 °C; νmax 2980, 2933, 1746, 1690, 1594, 1487, 1471, 1393, 1371, 1321, 1289, 1247, 1228, 1177, 1142, 1116, 1080, 1043 cm-1; δH (400 MHz; CDCl3) 8.46 (1H, d, J 8.1 Hz), 7.78-7.73 (3H, m), 7.43 (1H, s), 7.39-7.34 (3H, m), 7.28-7.25 (2H, m), 6.83 (1H, dd, *J* 8.9, 2.6 Hz), 6.78 (1H, d, *J* 2.6 Hz), 5.50 (2H, s), 4.03 (2H, q, *J* 7.0 Hz), 3.61-3.55 (1H, m), 1.94-1.88 (6H, m), 1.67-1.59 (2H, m), 1.43 (3H, t, *J* 7.0 Hz); δC (100 MHz; CDCl3) 177.7 (C), 156.7 (C), 146.4 (C), 139.6 (C), 136.5 (C, q, *J* 34.0 Hz), 134.6 (C), 134.5 (C), 134.1 (CH), 133.4 (C), 131.4 (C), 129.2 (CH), 128.9 (CH), 128.8 (CH, q, *J* 3.9 Hz), 128.2 (CH), 124.2 (CH, q, *J* 3.7 Hz), 122.4 (C, q, *J* 272 Hz), 122.3 (CH) 115.1 (CH), 113.3 (CH), 110.4 (CH), 75.3 (CH), 64.0 (CH2), 61.7 (CH2), 54.3 (CH2), 46.4 (C), 31.8 (CH2), 26.1 (CH2), 14.9 (Me); HRMS (ESI): MNa+, found697.1477. C32H3035ClF3NNaO5S requires 697.1470.

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‡ Dedicated to Professor Léon Ghosez in recognition of his many contributions to science and to the Tetrahedron journals, and to acknowledge his friendship and advice. [↑](#footnote-ref-2)