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Tetrahedron 63 (2007) 5579–5586
Tetrahedron

Synthesis of novel 3′-spirocyclic-oxindole derivatives and assessment of their cytostatic activities

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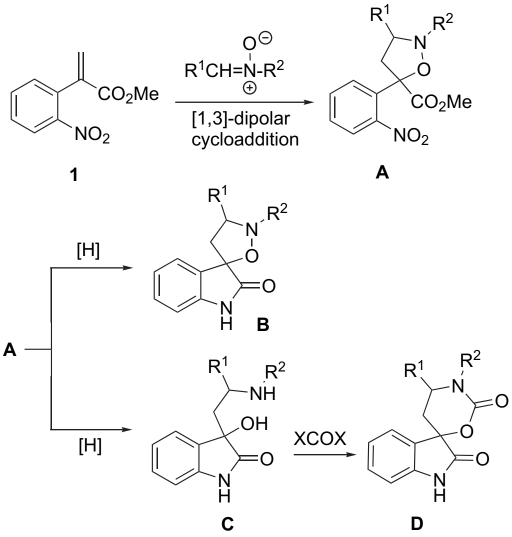
Received 17 January 2007; revised 15 March 2007; accepted 5 April 2007
Available online 14 April 2007

Abstract—The synthesis of some novel 3′-spirocyclic-oxindole compounds, based on the spiro[indole-3,5′-isoxazolidin]-2(1*H*)-one, the 2′*H*-spiro[indole-3,6′-[1,3]oxazinane]-2,2′(1*H*)-dione and the 2′*H*-spiro[indoline-3,3′-pyrrolo[1,2-*c*][1,3′]oxazine]-1′,2(1*H*)-dione heterocyclic structures, is described. These compounds were prepared from methyl α-(2-nitrophenyl)acrylate via [1,3]-dipolar cycloaddition reactions with two acyclic nitrones and one cyclic nitrone followed by reduction of the cycloadducts and then treatment with triphosgene. Two of these compounds showed significant cytostatic activity on three cancer cell lines with GI_{50} values of 2.6–4.1 μM on the human breast cancer cell line, MCF-7.

1. Introduction

3′-Spirocyclo-oxindoles, of synthetic or natural origin, have a range of biological activities.[1] As part of a medicinal chemistry project we have been focusing on the synthesis of novel 3′-spirocyclo-oxindoles as scaffolds for new drug discovery.[2,3] As an extension of this project we required the synthesis of the novel 3′-spirocyclic-oxindoles of the types **B** and **D**. These were planned to be accessed from the isoxazoline intermediate **A**, which in principle could be formed via a [1,3]-dipolar cycloaddition reaction between the acrylate **1**[2–4] and nitrones. Regioselective reduction of **A** would provide isoxazolidine spirocyclic oxindoles **B**, while further reduction would provide the amino-alcohol **C**, which upon treatment with phosgene, or its equivalent, was expected to provide oxazinane spirocyclic oxindoles of the type **D** (Scheme 1).



Scheme 1.

During the course of this project Parmar et al.[1f] reported the synthesis of isoxazolidine spirocyclic oxindoles, related to **B**, from the [1,3]-dipolar cycloaddition of the 3-methyleneindolone derivative **2a** (R=CO_2Et) with nitrones (Fig. 1), while Williams,[5] Wang[1a] and Schreiber[6] have earlier described [1,3]-dipolar cycloadditions of azomethine ylides to **2a** (R=CO_2Et, aryl and CO_2allyl) and their 5- and 6-substituted derivatives to provide novel spirocyclic structures. Some of these were found to be a new class of non-peptide, small molecule MDM2-p53 inhibitors, a relatively new target for cancer chemotherapy.[1a] In 1998, Melot[7] reported the synthesis of isoxazolidine spirocyclic isoindolines, compounds isomeric to **B**, using a nitrone cycloaddition reaction of 3-methyleneisoindolines **2b**.

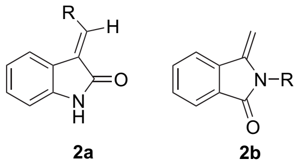


Figure 1.

Keywords: Isoxazolidine; Oxazinane; Oxindole; Nitrones; [1,3]-Dipolar cycloaddition; Spirocyclic compounds; Cytotoxic activity.

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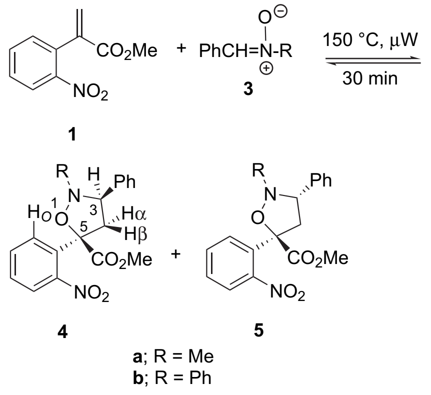
doi:10.1016/j.tet.2007.04.028

We report here our efforts for preparing novel spirocycles related to **B** and **D** and their stereochemistries and the cytostatic activities of some of these compounds against three cancer cell lines.

2. Results and discussion

Initial investigations on the [1,3]-dipolar cycloaddition of **1** with nitrones involved a study of the reaction of **1** and the nitrone **3a**. Heating a dichloromethane solution of **1** and **3a** (1.1 molar equiv) at 60 °C in a sealed tube for 4 d resulted in a mixture of **1**, **4a** and **5a**, from which pure samples of **4a** and **5a** could be isolated in yields of 26% and 20%, respectively, after purification by column chromatography (Scheme 2). Heating a mixture of **1** and **3a** (1.1–1.2 molar equiv) at 150 °C in a microwave reactor in toluene solution, or in the absence of solvent, for 30 min resulted in the isolation of pure samples of **1**, **4a** and **5a**, in yields of 29%, 15% and 30%, respectively. In each case unreacted dipolarophile (**1**) was isolated. When pure cycloadduct **4a** was heated at 150 °C in a microwave reactor without solvent for 30 min, a 42:30:28 mixture of **1**, **4a** and **5a**, respectively, was produced. This experiment clearly demonstrated the reversible nature of the cycloaddition reaction between **1** and **3a** and also helped to explain the lack of complete consumption of the dipolarophile in these reactions. We assume that the nitrone **3a** was also generated in this experiment but it could not be detected from ^{1}H NMR analysis of the crude reaction mixture. We suspect that **3a** was unstable to the thermal conditions. Heating a mixture of **1** and nitrone **3b** (1.3 molar equiv) at 150 °C in a microwave reactor in the absence of solvent resulted in ca. 20:60:20 mixture of **1**, **4b** and **5b**, respectively, from ^{1}H NMR analysis. Separation of this mixture by column chromatography gave pure samples of **1**, **4b** and **5b**, in yields of 11%, 58% and 6%, respectively, and a mixture of **1** and **5b** that was difficult to separate.



Scheme 2. Compounds **4** and **5** are racemic.

^{1}H NMR analysis clearly indicated that **4a**,**b** and **5a**,**b** were all 5-isoxazolidinecarboxylate regioisomers (with the expected three proton coupled spin system of H-3 and H-4α and H-4β clearly evident) and not the alternative 4-isoxazolidinecarboxylate regioisomers. The structure of **4a** was unequivocally determined by a single crystal X-ray structural determination (Fig. 2),[8] which indicated that **4a** was the 5-*exo* isomer and thus indicated that **5a** was the 5-*endo* isomer.

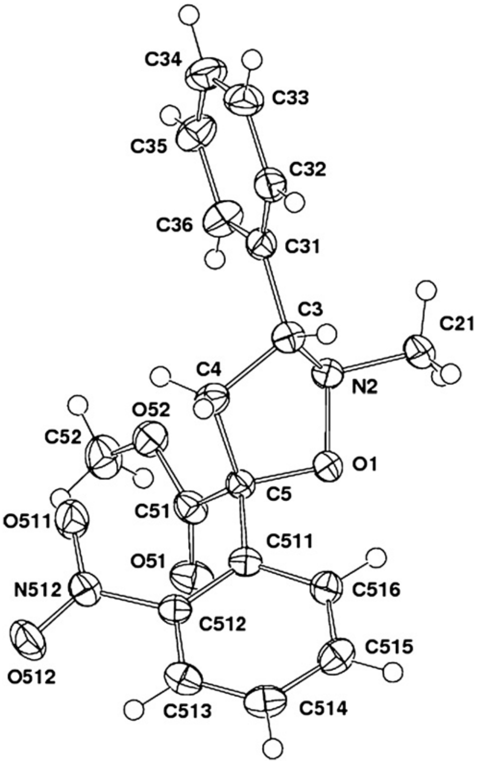
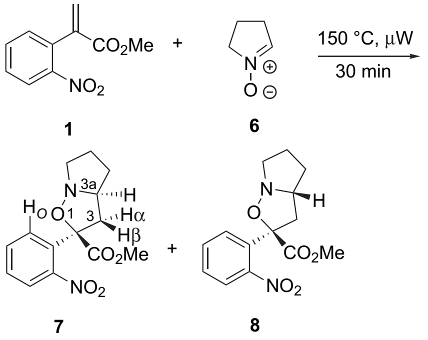


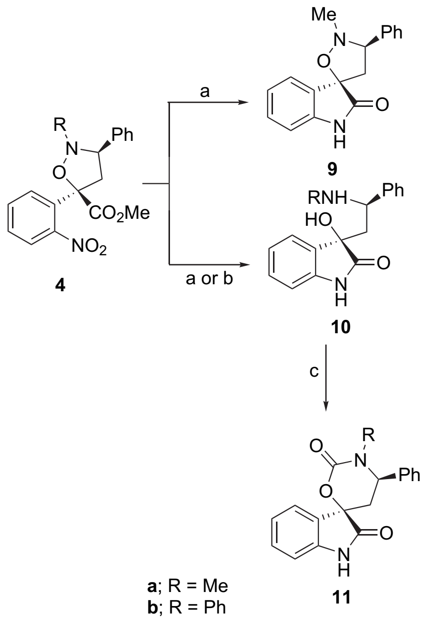
Figure 2. Molecular projection of **4a** (50% probability displacement amplitude ellipsoids for non-hydrogen atoms, hydrogen atoms having arbitrary radii of 0.1 Å/O(1)–N(2) is 1.472(3) Å.

Heating a toluene solution of a mixture of **1** and the cyclic nitrone **6** at 150 °C for 30 min in a microwave reactor gave a ca. 33:50:17 mixture of **1**, **7** and **8**, respectively (from ^{1}H NMR analysis) (Scheme 3). Separation of this mixture by column chromatography gave pure samples of **7** and **8**, in yields of 40% and 6%, respectively, and a mixture of **1** and **8** that was difficult to separate.



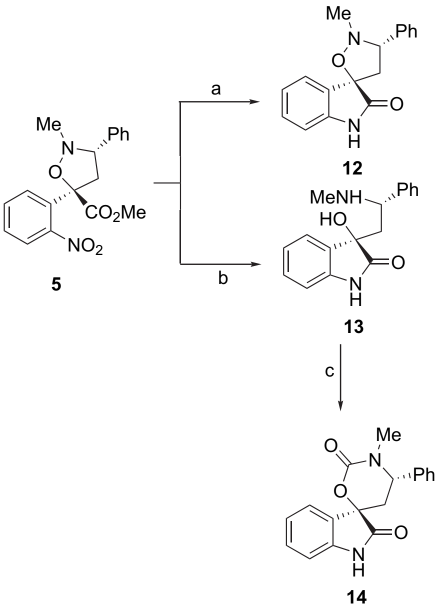
Scheme 3. Compounds **7** and **8** are racemic.

^{1}H NMR analysis clearly indicated that **7** and **8** were both pyrrolo[1,2-*b*]isoxazole-2-carboxylate regioisomers (with the expected three proton coupled spin system of H-3a and H-3α and H-3β clearly evident). The relative stereochemistry of these adducts was assigned based on NOESY studies. These studies showed cross-peaks between H$_O$ and the most upfield H-3 proton (H-3α) for both compounds **7** and **8** while cross-peaks were observed between H-3a and H-3α in **7** and between H-3a and H-3β (in C_6D_6) in **8**. This analysis indicated that **7** was the *endo*-isomer and **8** the *exo*-isomer.

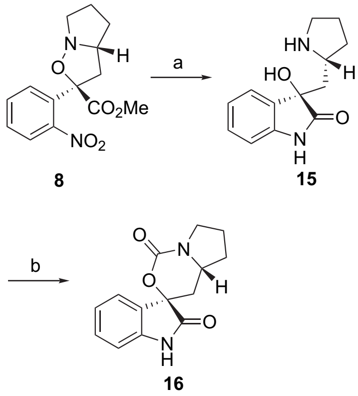


Scheme 4. Compounds **9–11** are racemic. *Reagents and conditions*: (a) 10% Pd/C, H_2 (1 atm), EtOAc, rt, 18 h, **9a** (24%), **10b** (55%); (b) Zn dust (10 equiv), HOAc, sonication, rt, 1 h, **10a** (58%), **10b** (90%); (c) triphosgene, Et_3N, THF, rt, **11a** (61%, 3 d), **11b** (68%, 2 d).

Treatment of **4a** over 10% Pd/C under a hydrogen atmosphere gave a mixture of the isoxazolidine spirocyclic oxindole **9a** and its further reduced product **10a** from which **9a** could be isolated in pure form in 24% yield (Scheme 4). The formation of the oxindole ring in **9a** was clearly evident from ^{13}C NMR analysis with a resonance at δ 179.4 for the oxindole carbonyl group. Treatment of **4b** under similar conditions gave **10b** in 55% yield. Treatment of **4a** or **4b** with activated zinc dust in glacial acetic acid under sonication conditions for 1 h provided **10a** and **10b**, in respective yields of 58% and 90% (Scheme 4). Treatment of these compounds with triphosgene under basic conditions (Et_3N) gave the oxazinane spirocyclic oxindoles **11a** and **11b** in respective yields of 61% and 68% (Scheme 4). The ^{13}C NMR spectra of these compounds clearly showed resonances for the oxindole (ca. δ 170) and oxazinanone (ca. δ 150) carbonyl groups.



Scheme 5. Compounds **12–14** are racemic. *Reagents and conditions*: (a) 10% Pd/C, H_2 (1 atm), EtOAc, rt, 18 h, 54%; (b) Zn dust (10 equiv), HOAc, sonication, rt, 1 h, 94%; (c) triphosgene, Et_3N, THF, rt, 2 d, 51%.



Scheme 6. Compounds **15** and **16** are racemic. *Reagents and conditions*: (a) $PdCl_2$, H_2 (1 atm), MeOH, rt, 3 h; (b) triphosgene, Et_3N, THF, rt, 2 d, 25% overall from **8**.

The compounds **12–16** were prepared in a similar fashion according to Schemes 5 and 6. All attempts at the hydrogenation of **7** or **8** over 10% Pd/C or the reduction of these compounds with zinc dust in glacial acetic acid under sonication conditions gave rise to complex reaction mixtures. However, hydrogenation/hydrogenolysis of **8** over $PdCl_2$ in methanol followed by treatment of the crude reaction mixture with triphosgene/Et_3N gave the desired tetracyclic spiro compound **16** in 25% overall yield (Scheme 6).

3. Cytostaticity studies

Cytostaticity studies against the cancer cell lines, H460 (human non small cell lung), MCF-7 (human breast) and SF-268 (human CNS) were performed at the Peter MacCallum Cancer Institute, Melbourne, Australia, using standard NCI protocols. Initially the percentage cell growth of cells incubated with 25 μM of compounds **4a**, **7**, **9**, **10b**, **11a**, **11b** and **14** was measured after 72 h. The results are presented in Table 1.

The initial screening indicated that only compounds **7** and **9** had an appreciable cytostatic activity against all three cell lines at 25 μM (Table 1, entries 2 and 3). The GI_{50} (concentration for 50% of growth inhibition) of these compounds on

Table 1. Cytostatic studies on cancer cell lines

Entry	Compound	Percentage cell growth		
		H460	MCF-7	SF-268
1	**4a**	64	97	78
2	**7**	2	7 (GI_{50}=4.1±0.2 μM)	18
3	**9**	0	1 (GI_{50}=2.6±0.1 μM)	14
4	**10b**	55	107	78
5	**11a**	63	79	77
6	**11b**	58	85	79
7	**14**	80	101	100

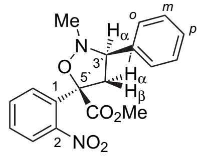
MCF-7 cells was 4.1 and 2.6 μM, respectively, as extrapolated from duplicate studies of growth inhibition over a drug concentration of 0–25 μM (see Supplementary data). It was observed that **9** had a much sharper GI curve (see Fig. A and B in Supplementary data) than **7** (see Fig. C and D in Supplementary data), which may suggest that it has a narrow therapeutic index, that is, there is a fineline between no activity and high toxicity. Furthermore at higher doses of **9**, cytotoxicity as opposed to cytostaticity was clearly demonstrated as fewer cells remained at the end of the assay than when at the beginning. Interestingly, while the isoxazolidine spirocyclic isoindoline **9** had the most cytostatic activity, its ring expanded analogues, **11a**,**b** having an oxazinane ring rather than an isoxazolidine showed little activity. This may be a function of the differences in ring size (five vs six) and/or the basicity of the respective nitrogen atoms.

In conclusion, the synthesis of some novel 3′-spirocyclic-oxindole compounds, based on the spiro[indole-3,5′-isoxazolidin]-2(1*H*)-one, the 2′*H*-spiro[indole-3,6′-[1,3]oxazinane]-2,2′(1*H*)-dione and the 2′*H*-spiro[indoline-3,3′-pyrrolo[1,2-*c*][1,3′]oxazine]-1′,2(1*H*)-dione heterocyclic structures has been achieved. These compounds were prepared from methyl α-(2-nitrophenyl)acrylate **1** via [1,3]-dipolar cycloaddition reactions with two acyclic nitrones and one cyclic nitrone followed by reduction of the cycloadducts and then treatment with triphosgene. Two of these compounds showed significant cytostatic activity on three cancer cell lines with GI_{50} values of 2.6–4.1 μM on the human breast cancer cell line, MCF-7.

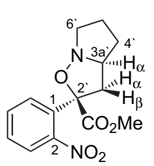
4. Experimental

4.1. General

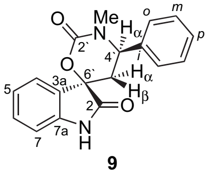
Petrol refers to the fraction of petroleum spirit with a boiling point of 40–60 °C. All ^{1}H NMR spectra were performed at 300 MHz and all ^{13}C NMR (DEPT) spectra at 75 MHz in $CDCl_3$ solution, unless otherwise noted. All spectra were referenced to $CDCl_3$ (^{1}H δ 7.26 ppm and ^{13}C NMR δ 77.00 ppm). ^{1}H NMR assignments were achieved with the aid of gCOSY, and in some cases NOESY and TOCSY experiments. ^{13}C NMR assignments were based upon DEPT, gHSQC and gHMBC experiments. All solvents were dried over anhydrous magnesium sulfate, unless stated otherwise. The atom numbering for compounds **4a** and **7** and **9** and their derivatives is as indicated below.



4a



7



9

4.1.1. Methyl (3′*R,5′*R**)-2′-methyl-5′-(2-nitrophenyl)-3′-phenylisoxazolidine-5′-carboxylate (4a) and methyl (3′*S**,5′*R**)-2′-methyl-5′-(2-nitrophenyl)-3′-phenylisoxazolidine-5′-carboxylate (5a).** The title compounds were prepared using two methods. *Method 1*: to a solution of **1** (110 mg, 5.3×10^{-4} mol) in anhydrous CH_2Cl_2 (1 mL), contained within a sealed tube was added nitrone **3a** (85.5 mg, 6.3×10^{-4} mol). The tube was sealed and the mixture was left stirring at 60 °C for 4 d. ^{1}H NMR analysis of the crude reaction mixture revealed the ratio of **4a**:**5a**:**1** was 59:33:8. The mixture was purified by column chromatography using 30% EtOAc/petrol as eluent to yield **4a** as a yellow oil (47.2 mg, 1.3×10^{-4} mol, 26%, R_f=0.37 in EtOAc/petrol (1:9)) and **5a** as a yellow oil (36.8 mg, 1.1×10^{-4} mol, 20%, R_f=0.16 in EtOAc/petrol (1:9)) and a mixture of **1** and **5a**. *Method 2*: a mixture of **1** (581.4 mg, 2.8 mmol) and nitrone **3a** (379 mg, 2.8 mmol) was placed in a sealed glass microwave reaction vessel. The mixture was subjected to microwave-assisted heating at 150 °C for 30 min (CEM microwave reactor with temperature and pressure control). ^{1}H NMR analysis of the crude reaction mixture revealed the ratio of **4a**:**5a**:**1** was 27:39:34. The mixture was purified by column chromatography using CH_2Cl_2/petrol/MeOH (1:4:0.1) as eluent to yield **4a** as off-white clear crystals (149.7 mg, 4.4×10^{-4} mol, 15%, mp 124–126 °C) and a mixture of **5a** and **1**. The mixture was further purified by column chromatography using 20% EtOAc/petrol as eluent to yield **5a** as a yellow oil (285 mg, 8.3×10^{-4} mol, 30%) and recovered **1** (168 mg, 8.0×10^{-4} mol, 29%).

Compound **4a**: MS (EI) *m/z* 342 (19%) [$M^{\bullet+}$], 296 (9%), 220 (11%), 134 (88%), 118 (5%), 104 (89%); HRMS (EI) calcd for $C_{18}H_{18}N_2O_5$ [$M^{\bullet+}$] 342.1216. Found 342.1217. ^{1}H NMR (500 MHz) δ 8.22 (d, *J* 7.5 Hz, 1H, ArC*H*-6); 8.14 (d, *J* 7.5 Hz, 1H, ArC*H*-3); 7.74 (t, *J* 7.5 Hz, 1H, ArC*H*-5); 7.53 (t, *J* 7.5 Hz, 1H, ArC*H*-4); 7.49 (d, *J* 7.3 Hz, 2H, ArC*H*-*o*); 7.36 (t, *J* 7.3 Hz, 2H, ArC*H*-*m*); 7.32 (t, *J* 7.3 Hz, 1H, ArC*H*-*p*); 3.88 (br t, *J* 11.7 Hz, 1H, $CH_\beta CH_\alpha$-4′); 3.75 (s, 3H, CO_2CH_3); 3.54 (br s, 1H, CH_α-3′); 2.73 (s, 3H, NCH_3); 2.62 (dd, *J* 13.5, 7.0 Hz, 1H, $CH_\alpha CH_\beta$-4′). ^{13}C NMR (125 MHz) δ 169.6 (*C*O_2); 146.3 (Ar*C*-2); 137.3 (Ar*C*-1); 136.9 (Ar*C*-*i*); 133.8 (Ar*C*H-5); 128.75 (Ar*C*H-4); 128.72 (Ar*C*H-*m*); 128.4 (Ar*C*H-*o*); 128.2 (Ar*C*H-*p*); 127.7 (Ar*C*H-6); 125.3 (Ar*C*H-3); 82.8 (*C*-5′); 73.4 (*C*H-3′); 53.0 (CO_2CH_3); 49.9 (CH_2-4′); 43.0 (NCH_3).

Compound **5a**: MS (EI) *m/z* 342 (13%) [$M^{\bullet+}$], 296 (4%), 220 (9%), 134 (89%); 118 (28%), 104 (72%); HRMS (EI) calcd for $C_{18}H_{18}N_2O_5$ [$M^{\bullet+}$] 342.1216. Found 342.1220. ^{1}H NMR (500 MHz) δ 8.29 (dd, *J* 8.0, 1.5 Hz, 1H, ArC*H*-6); 8.14 (dd, *J* 8.0, 1.5 Hz, 1H, ArC*H*-3); 7.77 (dt, *J* 8.0, 1.5 Hz, 1H, ArC*H*-5); 7.51 (dt, *J* 8.0, 1.5 Hz, 1H, ArC*H*-4); 7.30–7.23 (m, 5H, ArC*H*-*o*, ArC*H*-*m* and ArC*H*-*p*); 3.97 (t, *J* 9.0, 7.5 Hz, 1H, CH_β-3′); 3.92 (dd, *J* 12.7, 6.5 Hz, 1H, $CH_\beta CH_\alpha$-4′); 3.73 (s, 3H, CO_2CH_3); 2.72 (s, 3H, NCH_3); 2.39 (dd, *J* 13.0, 9.5 Hz, 1H, $CH_\alpha CH_\beta$-4′). ^{13}C NMR (125 MHz) δ 169.0 (*C*O_2); 146.3 (Ar*C*-2); 139.2 (Ar*C*-1); 137.1 (Ar*C*-*i*); 134.3 (Ar*C*H-5); 128.7 (Ar*C*H-*o*); 128.5 (Ar*C*H); 128.3 (Ar*C*H); 128.2 (Ar*C*H); 127.7 (Ar*C*H-*m*); 125.2 (Ar*C*H-3); 85.5 (*C*-5′); 74.1 (*C*H-3′); 53.0 (CO_2CH_3); 51.8 (CH_2-4′); 43.0 (NCH_3).

4.1.2. Methyl (3′*R,5′*R**)-5′-(2-nitrophenyl)-2′,3′-diphenylisoxazolidine-5′-carboxylate (4b) and methyl (3′*S**,5′*R**)-5′-(2-nitrophenyl)-2′,3′-diphenylisoxazolidine-5′-carboxylate (5b).** A mixture of **1** (133.7 mg, 6.5×10^{-4} mol) and nitrone **3b** (164.7 mg, 8.4×10^{-4} mol) was placed in a sealed glass microwave reaction vessel. The mixture was subjected to microwave-assisted heating at 150 °C for 30 min. ^{1}H NMR analysis of the crude reaction mixture revealed the ratio of **4b**:**5b**:**1** was 62:21:17. The mixture was purified by column chromatography using 0–10% EtOAc in petrol as eluent to yield **4b** as a bright yellow oil (151.3 mg, 3.7×10^{-4} mol, 58%, R_f=0.72 in EtOAc/petrol (1:9)) and a mixture of **5b** and **1**. The mixture was further purified using a Chromatotron® (0–2.5% EtOAc in petrol) to yield **5b** as a yellow oil (14.9 mg, 3.7×10^{-5} mol, 6%, R_f=0.31 in EtOAc/petrol (1:9)) and recovered **1** (15.3 mg, 7.4×10^{-5} mol, 11%) and a mixture of **5b** and **1** (43.6 mg).

Compound **4b**: MS (EI) *m/z* 404 (58%) [M$^{\bullet+}$], 345 (2%) [M^{+}−CO$_2$Me], 296 (7%), 220 (17%), 194 (21%), 180 (32%), 134 (26%), 104 (91%); HRMS (EI) calcd for $C_{23}H_{20}N_2O_5$ [M$^{\bullet+}$] 404.1372. Found 404.1357. ^{1}H NMR (500 MHz) δ 8.37 (dd, *J* 8.3, 1.3 Hz, 1H, ArC*H*-6); 8.14 (dd, *J* 8.3, 1.3 Hz, 1H, ArC*H*-3); 7.76 (dt, *J* 8.3, 1.3 Hz, 1H, ArC*H*-5); 7.52 (dt, 8.3, 1.3 Hz, 1H, ArC*H*-4); 7.31 (d, *J* 7.3 Hz, 2H, ArC*H-o*); 7.27 (t, *J* 7.3 Hz, 2H, ArC*H-m*); 7.24 (t, *J* 7.3 Hz, 1H, ArC*H-p*); 7.21 (t, *J* 8.0 Hz, 2H, ArC*H-m′*); 7.05 (d, *J* 8.0 Hz, 2H, ArC*H-o′*); 7.01 (t, *J* 8.0 Hz, 1H, ArC*H-p′*); 4.83 (dd, *J* 9.5, 7.5 Hz, 1H, CH_α-3′); 4.12 (dd, *J* 13.5, 7.5 Hz, 1H, CH_βCH_α-4′); 3.67 (s, 3H, CH_3); 2.54 (dd, *J* 13.5, 9.5 Hz, 1H, CH_αCH_β-4′). ^{13}C NMR (125 MHz) δ 168.6 (*C*O$_2$Me); 149.3 (Ar*C-i′*); 146.5 (Ar*C*-2); 139.3 (ArC-*i*); 137.9 (Ar*C*-1); 134.3 (Ar*C*H-5); 128.6 (Ar*C*H-*m′*); 128.84 (Ar*C*H-*m′*); 128.82 (Ar*C*H-4); 128.1 (Ar*C*H-6); 127.9 (Ar*C*H-*p*); 127.0 (Ar*C*H-*o*); 125.2 (Ar*C*H-3); 123.8 (Ar*C*H-*p′*); 117.7 (Ar*C*H-*o′*); 85.6 (*C*-5′); 71.0 (*C*H-3′); 52.9 (*C*H$_3$); 51.9 (*C*H$_2$-4′).

Compound **5b**: MS (EI) *m/z* 404 (52%) [M$^{\bullet+}$], 345 (2%) [M^{+}−CO$_2$Me], 296 (10%), 220 (18%), 194 (22%), 180 (39%), 134 (26%), 104 (92%); HRMS (EI) calcd for $C_{23}H_{20}N_2O_5$ [M$^{\bullet+}$] 404.1372. Found 404.1358. ^{1}H NMR δ 8.15 (dd, *J* 8.1, 1.2 Hz, 1H, ArC*H*-3); 8.12 (dd, *J* 7.8, 1.2 Hz, 1H, ArC*H*-6); 7.68 (dt, *J* 7.8, 1.2 Hz, 1H, ArC*H*-5); 7.53 (dt, *J* 8.1, 1.2 Hz, 1H, ArC*H*-4); 7.51 (d, *J* 6.9 Hz, 2H, ArC*H-o*); 7.36 (t, *J* 6.9 Hz, 2H, ArC*H-m*); 7.32 (t, *J* 6.9 Hz, 1H, ArC*H-p*); 7.20 (t, *J* 6.9 Hz, 2H, ArC*H-m′*); 7.02 (d, *J* 6.9 Hz, 2H, ArC*H-o′*); 7.02–6.98 (m, 1H, ArC*H-p′*); 4.37 (dd, *J* 9.3, 7.5 Hz, 1H, CH_β-3′); 3.93 (dd, *J* 13.5, 9.3 Hz, 1H, CH_βCH_α-4′); 3.78 (s, 3H, CH_3); 2.89 (dd, *J* 13.5, 7.5 Hz, 1H, CH_αCH_β-4′). ^{13}C NMR (125 MHz) δ 169.1 (CO$_2$Me); 148.5 (ArC-*i′*); 146.5 (ArC-2); 138.8 (ArC-*i*); 136.9 (Ar*C*-1); 133.8 (Ar*C*H-5); 128.95 (Ar*C*H-4); 128.89 (Ar*C*H-*m*); 128.5 (Ar*C*H-*m′*); 128.0 (Ar*C*H-*p*); 128.1 (Ar*C*H-6); 127.6 (Ar*C*H-*o*); 125.4 (Ar*C*H-3); 123.5 (Ar*C*H-*p′*); 118.0 (Ar*C*H-*o′*); 84.2 (*C*-5′); 69.0 (*C*H-3′); 53.1 (*C*H$_3$); 50.9 (*C*H$_2$-4′).

4.1.3. Methyl (2′*R,3a′*S**)-2′-(2-nitrophenyl)hexahydropyrrolo[1,2-*b*]isoxazole-2′-carboxylate (7) and methyl (2′*R**,3a′*R**)-2′-(2-nitrophenyl)hexahydropyrrolo[1,2-*b*]isoxazole-2′-carboxylate (8).** To **1** (87.7 mg, 4.2×10^{-4} mol) in a sealed glass microwave reaction vessel was added a solution of nitrone **6** (72 mg, 8.5×10^{-4} mol) in anhydrous toluene (0.4 mL). The mixture was subjected to microwave-assisted heating at 150 °C for 30 min. ^{1}H NMR analysis of the crude reaction mixture revealed the ratio of **7**:**8**:**1** was 49:18:33. The crude mixture was purified by column chromatography using 20–100% EtOAc/petrol as eluent to yield **7** as a light yellow crystalline solid (51.2 mg, 1.7×10^{-4} mol, 40%, R_f=0.54 in EtOAc/petrol (3:7)) and **8** as a light yellow semicrystalline oil (7.3 mg, 2.5×10^{-5} mol, 6%, R_f=0.22 in EtOAc/petrol (3:7)) and recovered **1** (35.6 mg, 1.7×10^{-4} mol, 40%).

Compound **7**: MS (EI) *m/z* 292 (33%) [M$^{\bullet+}$], 257 (34%), 244 (52%), 233 (85%), 104 (96%); HRMS (EI) calcd for $C_{14}H_{16}N_2O_5$ [M$^{\bullet+}$], 292.1059. Found 292.1051. ^{1}H NMR δ 8.20 (dd, *J* 8.1, 1.5 Hz, 1H, ArC*H*-6); 8.13 (dd, *J* 8.1, 1.5 Hz, ArC*H*-3); 7.71 (dt, *J* 7.2, 1.5 Hz, 1H, ArC*H*-5); 7.47 (dt, *J* 7.2, 1.5 Hz, 1H, ArC*H*-4); 3.66 (s, 3H, OCH_3); 3.63–3.55 (m, 2H, CH_ACH_B-6′ and CH_α-3a′); 3.50 (dd, *J* 13.2, 3.6 Hz, 1H, CH_βCH_α-3′); 3.05 (dt, *J* 13.5, 8.1 Hz, 1H, CH_BCH_A-6′); 2.58 (dd, *J* 13.2, 8.1 Hz, 1H, CH_αCH_β-3′); 2.21–2.01 (m, 2H, CH_ACH_B-4′ and CH_ACH_B-5′); 1.99–1.89 (m, 1H, CH_BCH_A-4′); 1.84–1.74 (m, 1H, CH_BCH_A-5′). ^{13}C NMR δ 168.9 (CO$_2$); 146.1 (ArC-2); 139.2 (ArC-1); 134.2 (Ar*C*H-5); 128.5 (Ar*C*H-4); 128.4 (Ar*C*H-6); 125.3 (Ar*C*H-3); 87.5 (*C*-2′); 66.7 (*C*H$_\alpha$-3a′); 56.8 (*C*H$_2$-6′); 53.0 (O*C*H$_3$); 47.9 (*C*H$_2$-3′); 29.9 (*C*H$_2$-4′); 23.7 (*C*H$_2$-5′). ^{13}C NMR (C_6D_6) 169.1 (*C*O$_2$); 147.0 (ArC-2); 140.1 (ArC-1); 133.7 (ArCH-5); 129.4 (ArCH-6); 128.0 (ArCH-4); 125.1 (ArCH-3); 87.9 (*C*-2′); 67.0 (*C*H-3a′); 57.0 (*C*H$_2$-6′); 52.5 (O*C*H$_3$); 48.5 (*C*H$_2$-3′); 30.2 (*C*H$_2$-4′); 24.1 (*C*H$_2$-5′).

Compound **8**: MS (EI) *m/z* 292 (12%) [M$^{\bullet+}$], 257 (18%), 244 (25%), 233 (39%), 104 (49%); HRMS (ESI+ve) calcd for $C_{14}H_{17}N_2O_5$ [MH^{+}] 293.1132. Found 293.1130. ^{1}H NMR (500 MHz) δ 8.06 (dd, *J* 8.0, 1.3 Hz, 1H, ArC*H*-3); 8.01 (dd, *J* 8.0, 1.3 Hz, 1H, ArC*H*-6), 7.67 (dt, *J* 8.0, 1.3 Hz, 1H, ArCH-5); 7.50 (dt, *J* 8.0, 1.3 Hz, 1H, ArCH-4); 4.02–3.96 (m, 1H, CH_β-3a′); 3.82 (dd, *J* 13.0, 8.0 Hz, 1H, CH_βCH_α-3′); 3.71 (s, 3H, OCH_3); 3.54 (ddd, *J* 13.8, 8.0, 4.0 Hz, 1H, CH_ACH_B-6′); 3.11 (dt, *J* 13.8, 8.0 Hz, 1H, CH_BCH_A-6′); 2.07 (dd, *J* 13.0, 4.0 Hz, 1H, CH_αCH_β-3′); 2.11–2.02 (m, 1H, CH_ACH_B-5′); 1.94 (dt, *J* 13.0, 8.0 Hz, 1H, CH_ACH_B-4′); 1.84–1.76 (m, 1H, CH_BCH_A-5′); 1.46 (ddt, *J* 13.0, 9.0, 4.0 Hz, 1H, CH_BCH_A-4′). ^{13}C NMR δ 169.7 (*C*O$_2$); 146.6 (Ar*C*-2); 136.9 (Ar*C*-1); 133.8 (Ar*C*H-5); 128.7 (Ar*C*H-4); 126.9 (Ar*C*H-6); 125.1 (Ar*C*H-3); 85.5 (*C*-2′); 66.9 (*C*H$_\beta$-3a′); 56.9 (*C*H$_2$-6′); 52.9 (O*C*H$_3$); 46.0 (*C*H$_2$-3′); 31.0 (*C*H$_2$-4′); 24.1 (*C*H$_2$-5′).

4.1.4. 2′-Methyl-(3′*S,5′*R**)-3′-phenylspiro[indole-3,5′-isoxazolidin]-2(1*H*)-one (9).** To a solution of **4a** (54 mg, 1.6×10^{-4} mol) in EtOAc (1 mL) under an atmosphere of N$_2$ was added 10% Pd/C (9 mg). The vessel was then flushed with H$_2$ and left stirring under an atmosphere of H$_2$ (balloon) for 18 h. The crude mixture was filtered through a bed of Celite, washed with EtOAc (3×50 mL) and the filtrate was evaporated in vacuo. The crude product was purified by column chromatography using 30–50% EtOAc in petrol as eluent to yield **9** as a yellow oil (10.6 mg, 3.8×10^{-5} mol, 24%, R_f=0.18 in EtOAc/petrol (3:7)). MS (EI) *m/z* 280 (10%) [M$^{\bullet+}$], 263 (15%), 145 (37%) [M^{+}−C$_6$H$_5$CHNCH$_3$O], 134

(92%), 117 (42%); HRMS (EI) calcd for $C_{17}H_{16}N_2O_2$ [M$^{•+}$] 280.1212. Found 280.1206. ^{1}H NMR (500 MHz) δ 8.79 (br s, 1H, N*H*); 7.57 (d, *J* 7.0 Hz, 2H, ArC*H*-*o*); 7.44 (d, *J* 7.5 Hz, 1H, ArC*H*-4); 7.39 (t, *J* 7.5 Hz, 2H, ArC*H*-*m*); 7.34 (d, *J* 7.5 Hz, 1H, ArC*H*-*p*); 7.28 (t, *J* 7.5 Hz, 1H, ArC*H*-6); 7.10 (t, *J* 7.5 Hz, 1H, ArC*H*-5); 6.94 (d, *J* 7.5 Hz, 1H, ArC*H*-7); 3.85 (br s, 1H, CH_{α}-3′); 3.01 (t, *J* 13.0 Hz, 1H, $CH_{\beta}CH_{\alpha}$-4′); 2.77 (dd, *J* 13.0, 6.5 Hz, 1H, $CH_{\alpha}CH_{\beta}$-4′); 2.71 (s, 3H, NCH_3). ^{13}C NMR (125 MHz) δ 179.4 (*C*-2); 141.1 (Ar*C*-7a); 137.0 (Ar*C*-*i*); 130.5 (Ar*C*-3a); 130.1 (Ar*C*H-6); 128.8 (Ar*C*H-*m*); 128.5 (Ar*C*H-*o*); 128.4 (Ar*C*H-*p*); 124.3 (Ar*C*H-4); 123.1 (Ar*C*H-5); 110.5 (Ar*C*H-7); 80.5 (*C*-3); 74.5 (*C*H-3′); 49.3 (CH_2-4′); 43.7 (N*C*H_3).

4.1.5. (2*R,3*R**)-3-Hydroxy-3-[2-(methylamino)-2-phenylethyl]-1,3-dihydro-2*H*-indol-2-one (10a).** To a solution of **4a** (78.4 mg, 2.3×10^{-4} mol) in glacial AcOH (9.2 mL) was added activated Zn dust (150 g, 2.3 mmol). The mixture was sonicated for 1 h. The crude mixture was then filtered through a bed of Celite and washed with EtOAc. The filtrate was washed with satd Na_2CO_3 solution and then H_2O, then dried, filtered and evaporated in vacuo. The crude was purified by column chromatography using 10–30% EtOAc in petrol as eluent to yield **10a** as a yellow oil (37.6 mg, 1.3×10^{-4} mol, 58%, R_f=0.16 in EtOAc/petrol (3:7)). MS (EI) *m*/*z* 282 (12%) [M$^{•+}$], 206 (6%), 146 (13%), 134 (21%), 120 (91%), 104 (12%); HRMS (EI) calcd for $C_{17}H_{18}N_2O_2$ [M$^{•+}$] 282.1368. Found 282.1365. ^{1}H NMR (500 MHz) δ 7.32 (t, *J* 7.3 Hz, 2H, ArC*H*-*m*); 7.30–7.26 (m, 1H, ArC*H*-*p*); 7.15–7.11 (m, 3H, ArC*H*-4 and ArC*H*-*o*); 7.08 (t, *J* 7.5 Hz, 1H Ar*C*H-6); 6.71 (t, *J* 7.3 Hz, 1H, Ar*C*H-5); 6.67 (d, *J* 7.5 Hz, 1H, Ar*C*H-7); 4.70 (dd, *J* 7.5, 6.0 Hz, 1H, C*H*); 2.98 (dd, *J* 14.0, 8.0 Hz, 1H, CH_ACH_B); 2.76 (s, 3H, $NHCH_3$); 2.48 (dd, *J* 14.0, 6.0 Hz, 1H, CH_BCH_A). ^{13}C NMR (125 MHz) δ 175.7 (C-2); 145.4 (ArC-7a); 139.7 (ArC-*i*); 129.2 (ArCH-6); 128.9 (ArCH-*m*); 128.1 (ArCH-*p*); 126.8 (Ar*C*H-*o*); 126.7 (Ar*C*-3a and Ar*C*H-4); 118.6 (ArCH-5); 118.4 (Ar*C*H-7); 79.4 (*C*-3); 61.8 (*C*H); 42.4 (CH_2); 28.8 ($NHCH_3$).

4.1.6. (2*R,3*S**)-3-(2-Anilino-2-phenylethyl)-3-hydroxy-1,3-dihydro-2*H*-indol-2-one (10b).** The title compound was prepared using two methods. *Method 1*: the title compound was prepared from **4b** (61 mg, 1.5×10^{-4} mol) using a similar method to that described for the preparation of **10a**. The crude product was purified by column chromatography using 20–40% EtOAc in petrol as eluent to yield **10b** as a yellow oil (28.6 mg, 8.3×10^{-5} mol, 55%, R_f= 0.66 in 40% EtOAc/petrol (2:3)). *Method 2*: the title compound was prepared from **4b** (72.7 mg, 1.8×10^{-4} mol) using a similar method to that described for the preparation of **10a**. After following the same workup procedure, the crude mixture was purified by column chromatography using 10–20% EtOAc in petrol as eluent to yield **10b** as a cream solid (55.5 mg, 1.6×10^{-4} mol, 90%) and purified further by recrystallisation to yield **10b** as a cream solid (29.8 mg, 8.7×10^{-5} mol, 48%). MS (EI) *m*/*z* 344 (15%) [M$^{•+}$], 148 (11%), 196 (46%), 120 (43%), 182 (92%), 104 (16%); HRMS (EI) calcd for $C_{22}H_{20}N_2O_2$ [M$^{•+}$] 344.1525. Found 344.1505. ^{1}H NMR (500 MHz) δ 7.36 (d, *J* 8.5 Hz, 2H, ArCH-*o*′); 7.27–7.21 (m, 6H, ArC*H*-*m*′, ArC*H*-*o* and ArC*H*-*m*); 7.20–7.15 (m, 2H, ArC*H*-*p* and ArC*H*-6); 7.09 (t, *J* 7.5 Hz, 1H, ArC*H*-*p*′); 6.94 (d, *J* 7.5 Hz, 1H, ArC*H*-4); 6.77 (d, *J* 7.5 Hz, 1H, ArC*H*-7); 6.71 (t, *J* 7.5 Hz, 1H, ArC*H*-5); 4.97 (dd, *J* 9.7, 6.0 Hz, 1H, CH_{α}); 4.66 (br s, 1H, N*H*); 3.34 (dd, *J* 13.0, 6.0 Hz, 1H, $CH_{\beta}CH_{\alpha}$); 2.42 (dd, *J* 13.0, 9.7 Hz, 1H, $CH_{\alpha}CH_{\beta}$). ^{13}C NMR (125 MHz) δ 175.3 (*C*-2); 146.0 (Ar*C*-7a); 139.1 (Ar*C*-*i*); 136.8 (Ar*C*-*i*′); 129.5 (Ar*C*H-6); 128.8 (Ar*C*H-*m*′); 128.7 (Ar*C*H-*m*); 128.0 (Ar*C*H-*p*); 127.0 (Ar*C*H-*o*); 125.9 (Ar*C*H-4); 125.8 (Ar*C*H-*p*′); 124.4 (Ar*C*-3a); 123.4 (Ar*C*H-*o*′); 118.3 (Ar*C*H-5); 118.0 (Ar*C*H-7); 79.8 (*C*-3); 60.1 (*C*HPh); 43.5 (CH_2).

4.1.7. 2′-Methyl-(3′*R,5′*R**)-3′-phenylspiro[indole-3,5′-isoxazolidin]-2(1*H*)-one (12).** The title compound was prepared from **5a** (78 mg, 2.3×10^{-4} mol) using a similar method to that described above for the preparation of **9**. However, the reaction was left for only 2 h. The crude product was purified by column chromatography using 30–50% EtOAc in petrol to yield **12** as a yellow oil (34.8 mg, 1.2×10^{-4} mol, 54%, R_f=0.16 in 30% EtOAc/petrol (3:7)). MS (EI) *m*/*z* 280 (13%) [M$^{•+}$], 263 (22%), 145 (58%), 134 (94%), 117 (63%); HRMS (ESI+ve) calcd for $C_{17}H_{17}N_2O_2$ [MH$^+$] 281.1285. Found 281.1293. ^{1}H NMR (500 MHz) δ 8.05 (br s, 1H, N*H*); 7.53 (d, *J* 7.5 Hz, 1H, ArC*H*-4); 7.50 (d, *J* 7.5 Hz, 2H, ArC*H*-*o*); 7.38 (d, *J* 7.5 Hz, 2H, ArC*H*-*m*); 7.33 (t, *J* 7.5 Hz, 1H, ArC*H*-*p*); 7.25 (t, *J* 7.5 Hz, 1H, ArC*H*-6); 7.08 (t, *J* 7.5 Hz, 1H, ArC*H*-5); 6.85 (d, *J* 7.5 Hz, 1H, ArC*H*-7); 4.23 (br m, 1H, CH_{β}-3′); 3.01 (dd, *J* 13.0, 6.0 Hz, 1H, $CH_{\beta}CH_{\alpha}$-4′); 2.79 (s, 3H, NCH_3); 2.74–2.70 (m, 1H, $CH_{\alpha}CH_{\beta}$-4′). ^{13}C NMR δ 178.2 (*C*-2); 140.7 (Ar*C*-7a); 137.7 (Ar*C*-*i*); 130.7 (ArC-3a); 129.7 (ArCH-6); 128.8 (ArCH-*m*); 128.1 (ArCH-*p*); 127.6 (ArCH-*o*); 124.7 (ArCH-4); 123.3 (Ar*C*H-5); 110.3 (Ar*C*H-7); 81.8 (*C*-3); 72.9 (*C*H-3′); 49.7 (CH_2-4′); 43.9 (NCH_3).

4.1.8. (2*R,3*S**)-3-Hydroxy-3-[2-(methylamino)-2-phenylethyl]-1,3-dihydro-2*H*-indol-2-one (13).** The title compound was prepared from **5a** (49 mg, 1.43×10^{-4} mol) using a similar method to that described above for the synthesis of **10a**. Compound **13** was obtained as a yellow oil, which required no further purification (38 mg, 1.35×10^{-4} mol, 94%, R_f=0.45 in EtOAc/petrol (3:7)). MS (EI) *m*/*z* 282 (31%) [M$^{•+}$], 146 (18%), 134 (26%), 120 (89%), 104 (13%); HRMS (EI) calcd for $C_{17}H_{18}N_2O_2$ [M$^{•+}$], 282.1368. Found 282.1366. ^{1}H NMR δ 7.39–7.34 (m, 3H, ArC*H*-*m* and ArC*H*-*p*); 7.26 (dd, *J* 7.0, 1.5 Hz, 2H, ArC*H*-*o*); 7.13 (dt, *J* 8.1, 1.5 Hz, 1H, ArC*H*-6); 6.89 (dd, *J* 8.1, 1.5 Hz, 1H, ArC*H*-4); 6.71 (t, 7.0 Hz, 2H, ArC*H*-5 and ArC*H*-7); 4.27 (dd, *J* 9.0, 6.0 Hz, 1H, C*H*); 3.15 (dd, *J* 13.2, 6.0 Hz, 1H, CH_ACH_B); 2.71 (s, 3H, $NHCH_3$); 2.34 (dd, *J* 13.2, 9.0 Hz, 1H, CH_BCH_A). ^{13}C NMR δ 176.1 (*C*-2); 146.0 (Ar*C*-7a); 138.7 (Ar*C*-*i*); 129.0 (Ar*C*H-*m*); 128.5 (Ar*C*H-*p*); 127.4 (ArCH-*o*); 129.2 (ArCH-6); 125.7 (ArCH-4); 124.8 (ArC-3a); 118.0 (ArCH-5); 117.8 (ArCH-7); 79.5 (*C*-3); 61.0 (*C*H); 43.5 (CH_2); 28.3 ($NHCH_3$).

4.1.9. 3′-Methyl-(4′*R,6′*R**)-4′-phenyl-2′*H*-spiro[indole-3,6′-[1,3]oxazinane]-2,2′(1*H*)-dione (11a).** To a solution of **10a** (68.2 mg, 2.4×10^{-4} mol) in anhydrous THF (2 mL) was added triphosgene (21.5 mg, 7.2×10^{-5} mol) and anhydrous NEt_3 (0.07 mL, 4.8×10^{-4} mol). The mixture was stirred under N_2 for 7 d. The reaction mixture was diluted with EtOAc and the solution was washed successively with H_2O, satd $NaHCO_3$ solution and brine and then dried and evaporated under reduced pressure. The crude product was purified by column chromatography using 30–100% EtOAc/petrol to yield **11a** as a white crystalline solid (45.9 mg, 1.5×10^{-4} mol, 61%, R_f=0.25 in EtOAc/petrol (1:1), mp 200–204 °C). MS (EI) *m/z* 308 (67%) [$M^{\bullet+}$], 309 (15%) [MH^+], 251 (91%) [$M^+-NMeCO$], 206 (84%), 146 (94%) [$M^+-CH_2C_6H_5CHNCH_3CO$], 130 (80%) [$M^+-CH_2C_6H_5CHNCH_3CO_2$], 118 (38%), 102 (43%); HRMS (EI) calcd for $C_{18}H_{16}N_2O_3$ [$M^{\bullet+}$] 308.1161. Found 308.1161. ^{1}H NMR (500 MHz) δ 9.02 (br s, 1H, N*H*); 7.45 (t, *J* 7.5 Hz, 2H, ArC*H*-*m*); 7.39 (t, *J* 7.5 Hz, 1H, ArC*H*-*p*); 7.29–7.25 (m, 3H, ArC*H*-*o* and ArC*H*-6); 7.09–7.05 (m, 2H, ArC*H*-4 and ArC*H*-5); 6.89 (d, *J* 7.5 Hz, 1H, ArC*H*-7); 4.88 (dd, *J* 7.5, 7.0 Hz, 1H, CH_α-4′); 3.09 (dd, *J* 15.0, 7.0 Hz, 1H, $CH_\beta CH_\alpha$-5′); 2.76 (s, 3H, NCH_3); 2.39 (dd, *J* 15.0, 7.0 Hz, 1H, $CH_\alpha CH_\beta$-5′). ^{13}C NMR (125 MHz) δ 169.9 (*C*-2); 150.8 (*C*-2′); 138.8 (Ar*C*-*i*); 135.6 (Ar*C*-7a); 130.0 (Ar*C*H-6); 129.3 (Ar*C*H-*m*); 128.7 (Ar*C*H-*p*); 126.7 (Ar*C*H-*o*); 124.4 (Ar*C*H-4); 123.6 (Ar*C*H-5); 118.4 (Ar*C*-3a); 115.0 (Ar*C*H-7); 86.1 (*C*-3); 60.8 (*C*H-4′); 43.6 (CH_2-5′); 29.0 (NCH_3).

4.1.10. 3′-Phenyl-(4′*R,6′*R**)-4′-phenyl-2′*H*-spiro[indole-3,6′-[1,3]oxazinane]-2,2′(1*H*)-dione (11b).** The title compound was prepared from **10b** (20.9 mg, 6.1×10^{-5} mol) using a similar method to that described above for the synthesis of **11a**. However, the reaction was left for only 2 d. The crude product was then purified by column chromatography using 30–100% EtOAc in petrol as eluent to yield **11b** as a white crystalline solid (15.4 mg, 4.2×10^{-5} mol, 68%, R_f=0.73 in MeOH/CHCl$_3$ (1:9), mp 256–258 °C). MS (EI) *m/z* 370 (21%) [$M^{\bullet+}$], 251 (65%) [$M^+-PhNCO$], 206 (46%), 180 (30%), 146 (89%), 130 (53%), 103 (32%); HRMS (EI) calcd for $C_{23}H_{18}N_2O_3$ [$M^{\bullet+}$] 370.1317. Found 370.1319. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.4 (s, 1H, N*H*); 7.50 (d, *J* 7.5 Hz, 1H, ArC*H*-4); 7.43 (d, *J* 7.5 Hz, 2H, ArC*H*-*o*′); 7.39 (d, *J* 7.5 Hz, 2H, ArC*H*-*o*); 7.33 (t, *J* 7.5 Hz, 1H, ArC*H*-6); 7.29 (t, *J* 7.5 Hz, 2H, ArCH-*m*); 7.26 (t, *J* 7.5 Hz, 2H, ArCH-*m*′); 7.20 (t, *J* 7.5 Hz, 1H, ArCH-*p*); 7.09 (t, *J* 7.5 Hz, 1H, ArC*H*-5); 7.08 (t, *J* 7.5 Hz, 1H, ArC*H*-*p*′); 6.91 (d, *J* 7.5 Hz, 1H, ArC*H*-7); 5.83 (dd, *J* 7.5, 7.0 Hz, 1H, CH_α-4′); 3.37–3.30 (m, 1H, $CH_\alpha CH_\beta$-5′); 2.40 (dd, *J* 14.3, 7.5 Hz, 1H, $CH_\alpha CH_\beta$-5′). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 169.5 (*C*-2); 149.1 (*C*-2′); 140.2 (Ar*C*-*i*); 136.6 (Ar*C*-*i*′); 135.9 (Ar*C*-7a); 130.0 (Ar*C*H-6); 128.8 (Ar*C*H-*m*); 128.6 (Ar*C*H-*m*′); 127.9 (Ar*C*H-*p*); 127.0 (Ar*C*H-*o*); 125.9 (ArCH-*p*′); 123.8 (Ar*C*H-4); 123.6 (Ar*C*H-*o*′); 122.9 (Ar*C*H-5); 119.7 (Ar*C*-3a); 114.4 (Ar*C*H-7); 84.2 (*C*-3); 58.8 (*C*H-4′); 42.5 (CH_2-5′).

4.1.11. 3′-Methyl-(4′*S,6′*R**)-4′-phenyl-2′*H*-spiro[indole-3,6′-[1,3]oxazinane]-2,2′(1*H*)-dione (14).** The title compound was prepared from **13** (41.8 mg, 1.5×10^{-4} mol) using a similar method to that described above for the synthesis of **11a**. However, the reaction was left for only 2 d. The crude product was purified by column chromatography using 30–100% EtOAc in petrol as eluent to yield **14** as a white crystalline solid (23.5 mg, 7.6×10^{-5} mol, 51%, R_f=0.39 in EtOAc/petrol (1:1), mp 244–248 °C). MS (EI) *m/z* 308 (43%) [$M^{\bullet+}$], 251 (72%), 206 (68%), 146 (94%), 130 (65%); HRMS (EI) calcd for $C_{18}H_{16}N_2O_3$ [$M^{\bullet+}$] 308.1161. Found 308.1166. ^{1}H NMR (500 MHz, (CD$_3$)$_2$CO) δ 9.27 (br s, 1H, N*H*); 7.49–7.48 (m, 4H, ArCH-*o* and ArCH-*m*); 7.43–7.40 (m, 1H, ArC*H*-*p*); 7.35 (d, *J* 7.5 Hz, 1H, ArC*H*-4); 7.32 (dt, *J* 7.5, 1.2 Hz, 1H, ArC*H*-6); 7.07 (dt, *J* 7.5, 1.2 Hz, 1H, ArC*H*-5); 7.03 (d, *J* 7.5 Hz, 1H, ArC*H*-7); 4.96 (dd, *J* 7.5, 7.0 Hz, 1H, CH_β-4′); 3.27 (dd, *J* 15.0, 7.5 Hz, 1H, $CH_\beta CH_\alpha$-5′); 2.64 (s, 3H, NCH_3); 2.47 (dd, *J* 15.0, 7.5 Hz, 1H, $CH_\alpha CH_\beta$-5′). ^{13}C NMR ((CD$_3$)$_2$CO) δ 171.0 (*C*-2); 150.2 (*C*-2′); 141.0 (Ar*C*-*i*); 137.4 (Ar*C*-7a); 130.6 (Ar*C*H-6); 129.9 (Ar*C*H-*m*), 129.3 (Ar*C*H-*p*); 128.1 (Ar*C*H-*o*); 124.5 (Ar*C*H-4); 123.6 (Ar*C*H-5); 121.7 (Ar*C*-3a); 115.1 (Ar*C*H-7); 85.0 (*C*-3); 61.4 (*C*H-4′); 43.9 (CH_2-5′); 28.6 (NCH_3).

4.1.12. (3*R,3*R**)-3-Hydroxy-3-(pyrrolidin-2-ylmethyl)-indol-2-one (15) and (3*R**,4a′*R**)-2′*H*-spiro[indoline-3,3′-pyrrolo[1,2-*c*][1,3′]oxazine]-1′,2(1*H*)-dione (16).** To a solution of **8** (41.3 mg, 1.4×10^{-4} mol) in anhydrous MeOH (2 mL) under an atmosphere of N$_2$ was added PdCl$_2$ (5.2 mg, 2.8×10^{-5} mol) and the vessel flushed with H$_2$ and left stirring for 3 h under an H$_2$ atmosphere (balloon). The crude mixture was then filtered through a bed of Celite and the solid was washed with MeOH (10 mL). The solvent was evaporated in vacuo. The crude product was purified by column chromatography using 50–100% EtOAc in petrol as eluent, to yield a material (**15**) that was impossible to analyse by NMR due to the broadening of all peaks, perhaps due to traces of palladium. To a solution of this material (28 mg, 1.2×10^{-4} mol) in anhydrous THF (1 mL) was added triphosgene (10.7 mg, 3.6×10^{-5} mol) and anhydrous NEt$_3$ (0.03 mL, 2.4×10^{-4} mol). The mixture was stirred under N$_2$ for 2 d. The crude was then washed with H$_2$O and extracted with EtOAc. The organic extracts were then successively washed with satd NaHCO$_3$ solution and brine, dried and evaporated under reduced pressure. The crude product was purified on a Chromatotron® (0–4% MeOH in CHCl$_3$) to yield **16** as a brown semicrystalline oil (9.2 mg, 3.6×10^{-5} mol, 25% over two steps).

Compound **15**: MS (EI) *m/z* 232 (10%) [$M^{\bullet+}$], 214 (6%) [M^+-H_2O], 149 (22%), 120 (34%), 86 (37%), 70 (77%), 43 (96%); HRMS (EI) calcd for $C_{13}H_{16}N_2O_2$ [$M^{\bullet+}$] 232.1212. Found 232.1206.

Compound **16**: MS (EI) *m/z* 258 (70%) [$M^{\bullet+}$], 259 (19%) [MH^+], 214 (32%), 186 (24%), 174 (94%), 146 (94%), 133 (50%), 117 (35%), 104 (29%); HRMS (EI) calcd for $C_{14}H_{14}N_2O_3$ [$M^{\bullet+}$] 258.1004. Found 258.0997. ^{1}H NMR δ 7.34–7.29 (m, 2H, ArC*H*-6 and ArC*H*-4); 7.10 (dt, *J* 7.5, 1.0 Hz, 1H, ArC*H*-5); 6.91 (dd, *J* 7.5, 1.0 Hz, 1H, ArC*H*-7); 4.11–4.01 (m, 1H, CH_β-4a′); 3.63–3.52 (m, 1H, $CH_A CH_B$-7′); 3.20–3.12 (m, 1H, $CH_B CH_A$-7′); 3.00 (dd, *J* 13.3, 6.0 Hz, 1H, $CH_\beta CH_\alpha$-4′); 2.36 (dd, *J* 13.3, 6.0 Hz, 1H, $CH_\alpha CH_\beta$-4′); 2.26–2.09 (m, 3H, $CH_A CH_B$-5′ and CH_2-6′); 1.53–1.47 (m, 1H, $CH_B CH_A$-5′). ^{13}C NMR δ 171.5 (*C*-2); 151.6 (*C*-1′); 136.6 (Ar*C*-7a); 121.5 (Ar*C*-3a); 90.6 (*C*-3′); 131.2 (Ar*C*H-6); 124.3 (Ar*C*H-4); 124.7 (Ar*C*H-5); 115.6 (Ar*C*H-7); 59.5 (CH_β-4a′); 42.5 (CH_2-7′); 43.1 (CH_2-4′); 33.5 (CH$_2$-5′); 27.1 (CH$_2$-6′).

Acknowledgements

We thank the University of Wollongong for financial support and the Australian Research Council for a Ph.D. scholarship to S.R.Y.

Supplementary data

Details of the X-ray crystal/refinement data and GI_{50} curves in duplicate for compounds **7** and **9** against an MCF-7 cell line (two pages). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.04.028.

References and notes

1. See for example, (a) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432–3435; (b) Kitajima, M.; Nakamura, T.; Kogure, N.; Ogawa, M.; Mitsuno, Y.; Ono, K.; Yano, S.; Aimi, N.; Takayama, H. *J. Nat. Prod.* **2006**, *69*, 715–718; (c) Bacher, N.; Tiefenthaler, M.; Sturm, S.; Stuppner, H.; Ausserlechner, M. J.; Kofler, R.; Konwalinka, G. *Br. J. Haematol.* **2006**, *132*, 615–622; (d) Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, *70*, 9430–9435; (e) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Qiu, S.; Ding, Y.; Gao, W.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Tomita, Y.; Parrish, D. A.; Deschamps, J. R.; Wang, S. *J. Am. Chem. Soc.* **2005**, *127*, 10130–10131; (f) Raunak; Kumar, V.; Mukherjee, S.; Poonam; Prasad, A. K.; Olsen, C. E.; Schaeffer, S. J. C.; Sharma, S. K.; Watterson, A. C.; Errington, W.; Parmar, V. S. *Tetrahedron* **2005**, *61*, 5687–5697; (g) Kang, T.-H.; Murakami, Y.; Matsumoto, K.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **2002**, *455*, 27–34; (h) Shimada, Y.; Goto, H.; Itoh, T.; Sakakibara, I.; Kubo, M.; Sasaki, H.; Terasawa, K. *J. Pharm. Pharmacol.* **1999**, *51*, 715–722; (i) Edmondson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155; (j) Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651–12666; (k) Kornet, M. J.; Thio, A. P. *J. Med. Chem.* **1976**, *19*, 892–898.
2. Yong, S. R.; Williams, M. C.; Pyne, S. G.; Ung, A. T.; Skelton, B. W.; White, A. H.; Turner, P. *Tetrahedron* **2005**, *61*, 8120–8129.
3. Yong, S. R.; Ung, A. T.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron* **2007**, *63*, 1191–1199.
4. Selvakumar, N.; Azhagan, A. M.; Srinivas, D.; Krishna, G. G. *Tetrahedron Lett.* **2002**, *43*, 9175–9178.
5. Sebahar, P. R.; Osada, H.; Usui, T.; Williams, R. M. *Tetrahedron* **2002**, *58*, 6311–6322.
6. Lo, M. M. C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077–16086.
7. Rigolet, S.; Goncalo, P.; Melot, J. M.; Vebrel, J. *J. Chem. Res.* **1998**, 686–687.
8. The CCDC deposition number for **4a** is 633506, see Supplementary data for crystal/refinement data.