This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
A Core Switching Strategy to Pyrrolo[2,3-b]quinolines and Diazocino[1,2-a]indolinones

Alan M. Jonesa+*, Stephen Pattersona, Magali M. Loriona, Alexandra M. Z. Slawina, and Nicholas J. Westwooda*

a School of Chemistry and Biomedical Sciences Research Complex, University of St Andrews, North Haugh, St Andrews, Fife, Scotland, KY16 9ST (UK)

+Current address: Division of Chemistry and Environmental Science, John Dalton Building, Manchester Metropolitan University, Manchester, England, M1 5GD (UK)

Corresponding Author Information

*E-mail: a.m.jones@mmu.ac.uk

*E-mail: njw3@st-andrews.ac.uk

Abstract

Two novel core-switching rearrangements to natural product-like privileged scaffolds that proceed in up to 99% yield have been developed. The deviation away from planarity of the central N-acyl urea carbonyl, caused by the structure of the medium-sized ring, dictates the exclusive reaction outcome. Proposed mechanisms and products for the reaction pathways are supported by small molecule X-ray crystallography and an isolated intermediate. Twenty-four novel rearrangement products are reported.

Keywords
Rearrangement, Medium-sized ring, Core-switching, Diversity-Oriented Synthesis

Privileged scaffold, Pyrrolo[2,3-b]quinoline, Diazocino[1,2-a]indolinone

Introduction

Rearrangements are of central importance in organic synthesis allowing remarkable and efficient transformations of simple starting materials to complex products in one pot. In particular, rearrangements that give difficult to access ring sizes and ring fusions are much sought after. As part of a discovery programme, we explored the reactivity and chemistry of nine and ten-membered N-acyl cyclic ureas towards nitrogen-containing heterocyclic rearrangement chemistry. Pyrrolo[2,3-b]quinolines and fused diazocines such as diazocino[1,2-a]indolinones are important nitrogen-containing heterocycles prevalent in natural products and pharmaceuticals. The pyrrolo[2,3-b]quinoline is a privileged scaffold found in biologically important molecules such as blebbistatin (a myosin II inhibitor, Figure 1A) and PGP-4008 (as a selective P-glycoprotein (P-gp) mediated drug release (MDR) modulator). The diazocino and fused diazocino scaffold can be found in natural products such as the sperimidine derived alkaloids, peptidomimetic scaffolds, in SM-406/AT-406 (Figure 1A) an inhibitor of proteins involved in apoptosis and small-molecule mimetics of second mitochondria-derived activator of caspases (Smac). The α-hydroxyindolinone unit is present in the natural products matemone and melochicorine. In particular, matemone inhibits cell division (IC$_{50}$ = 35 µg mL$^{-1}$) and showed moderate activity against three cancer cell lines (lung, pancreas and prostate) and antibacterial activity against S. Aureus.
Figure 1A Representative bioactive small molecules containing motifs present in 2 and 3. 1B The rearrangement of 1 to diazocino[1,2-a]indolinone 2 and pyrrolo[2,3-b]quinoline 3.

Our recent studies with compounds related to type 1\textsuperscript{12} (Figure 1B) have demonstrated the unusual properties associated with these atropisomeric medium-ring systems. Compounds of type 1 can be accessed rapidly via pentacyclic ring fusion from N-aryl lactams and anthranilates\textsuperscript{13} followed by \textit{m}-CPBA mediated Grob fragmentation.\textsuperscript{14} Herein, we report the rearrangement chemistry associated with 9 and 10-membered examples of 1 to access privileged diazocino[1,2-a]indolinones 2 and pyrrolo[2,3-b]quinolines 3.

Results and Discussion
During the detailed NMR spectroscopic experiments involved with understanding the atropisomeric nature of 1a,\textsuperscript{14} it was found that 1a in d\textsubscript{4}-methanol upon standing transformed quantitatively into a new product. This reaction could be replicated using sodium methoxide in methanol. X-ray crystallographic analysis of the crystals obtained revealed the structure as 2a (Scheme 1).\textsuperscript{15,16}

![Scheme 1](image)

**Scheme 1.** Plausible reaction pathway for the formation of 2a from 1a and a representation of the small molecule X-ray crystallographic analysis of 2a. Reaction conditions: NaOMe, MeOH, 25 °C, 10 min, 99%.

A proposed mechanism for the rearrangement of 1a is shown in Scheme 1. The key step in this transformation was attack of the nucleophile at the C(16) carbonyl group of 1a to afford A. It is proposed that cyclisation of A furnishes the more thermodynamically stable 2a. Ureas are typically quite poor electrophiles, so it was initially surprising that a reaction took place at this functionality. However, the C(16) carbonyl group is tilted out of the plane contains the two nitrogens (N(6) and N(15)) and the C(1) carbonyl group (the X-ray crystal structure of 1a can be found at CCDC-804714).\textsuperscript{14} The key dihedral angle for 1a C(14a)-N(15)-C(16)-O(16) is +25°. Therefore, the C(16) carbonyl group would be more reactive than expected to nucleophilic attack. The non-planarity of the urea has the effect of lessening the
electron donation into the π* orbital of the C(16) carbonyl group and hence increasing the electrophilicity of the urea carbonyl group. On simpler substrates there have been examples of oxidative cleavage and nucleophile induced rearrangement not driven by carbonyl group distortion. Consistent with the proposed mechanism, reaction of an optically-enriched sample of 1a with sodium methoxide gave a racemic sample of 2a (see Scheme S1 for a more detailed discussion). A screen of nucleophiles that could potentially replicate this transformation was also carried out (Table S1). The scope of this rearrangement was determined by screening a collection of nine-membered N-acyl cyclic ureas 1 (Table 1) with different alkoxides using optimised conditions (Table S2) and subsequently amines (optimised conditions detailed in Table S3).
Table 1. Examples of O and N-centred nucleophile-induced rearrangement of the nine-membered ring system to (±)-2 and a representation of the small molecule X-ray crystallographic analysis of 2i. aReaction conditions: 1 (0.06 mmol), NaOR (0.13
mmol), ROH (2 mL), 25 °C, 10 min. Reaction conditions: 1 (0.06 mmol), RNH₂ (0.06 mmol), THF (3 mL), 25 °C, 3 h. All isolated yields.

It was observed that the alkoxide-induced rearrangement was general on a selection of nine-membered substrates (1a-1d). Almost all alkoxide-induced rearrangements proceeded in nearly quantitative yield at ambient temperature and with short reaction times and the products could be easily purified either by column chromatography or recrystallisation.

The amine-induced rearrangements proceeded in similar high conversions as determined by ¹H NMR analysis of the crude reaction mixture. However, a significant reduction in isolated yield was observed across examples 2i-2o. This was due to the polar nature of the installed N, N'-substituted urea leading to difficulties in elution. Conclusive evidence that the amine-induced rearrangement afford the analogous 5,8-ring system was obtained via the small molecule X-ray crystallographic analysis of 2i (Table 1).

With the successful synthesis of the azepinoindole (5,8)-ring system 2 by rearrangement of the N-acyl cyclic ureas 1a-d (nine-membered), it was decided to investigate whether the ten-membered N-acyl cyclic ureas 1e-f would undergo a similar rearrangement to generate the azepinoindole (5,9)-ring system. Treatment of 1e with sodium methoxide in anhydrous methanol did not afford the expected 5,9-ring system (2p), instead a pyrrolo[2,3-b]quinoline 3a was obtained exclusively (Scheme 2).
Scheme 2. Formation of a pyrrolo[2,3-b]quinoline 3a from 1e and no observation of 2p.

It is proposed that enolisation of the α-diketone in 1e with sodium methoxide acting as a base would lead to the formation of products containing a pyrrolidine ring system in 3 from attack of the C9 enolate at the C(17) carbonyl group (see Scheme 3 for mechanistic discussion in the context of the reaction of 1g).

The small molecule X-ray crystallographic analysis of 1e also provided interesting information. The key dihedral angle (C(15a)-N(16)-C(17)-O(17)) was closer to planarity in the ten-membered 1e at +14° (c.f. +25° in the nine-membered 1a). This implies the C(17) carbonyl is less electrophilic and direct reaction with sodium methoxide leading to a ring-opened structure is less favoured. Enolisation at C8 (Scheme 1) could operate in the nine-membered ring system (such as 1a) but would be unproductive as a highly strained 4-membered ring would result from attack at the analogous C(16) carbonyl group.

The postulated mechanism for the formation of the pyrrolo[2,3-b]quinoline (Scheme 3) was supported when substrate 1g was used in this reaction. In this case it was found that only trace quantities of the now expected pyrrolo[2,3-b]quinoline 3d (Table 3) was isolated. Elucidation of the structure of the major isolated product 4 (Scheme 3) was
achieved by $^1$H, $^{13}$C and 2D-NMR experiments ($^1$H-$^{13}$C HSQC, $^1$H-$^{13}$C HMBC and $^1$H-$^{13}$C COSY NMR spectra). The tabulated $^1$H and $^{13}$C NMR assignments relating to 4 are shown in Table S4.

Key points in the structural determination of 4 included the signals corresponding to the C2-H$_2$ and C3-H$_2$ protons being observed as a pair of triplets indicating a five membered ring had formed as the C(9) protons in 1g had disappeared (Scheme 3). The $^1$H-$^{13}$C HMBC NMR spectrum of 4 was used to determine the location of the single ethyl ester, which indicated that it was connected to ring D. Furthermore, the $^1$H and $^{13}$C NMR shifts on the protons and carbons, in ring D of 4 were analogous with those present in 3d. A broad singlet in the $^1$H NMR spectra indicated that an exchangeable proton i.e. OH or NH existed. Due to the $^{13}$C chemical shifts of the C(9) (134.7 ppm) and C(9a) (148.6 ppm) carbons in 4 an NH motif was ruled out because, if present, this would have the effect of moving the chemical shifts in ring A upfield (which was not seen). Furthermore, infra-red spectroscopy indicated the presence of an intra-molecular H-bond at 2977 cm$^{-1}$. The enol form of the aza-tropinone in 4 is the preferred tautomer of the ring system and similar examples have been reported. The structure of ring B in 4 could now be assigned using a $^1$H-$^{13}$C HMBC NMR experiment (Scheme 3, inset). A correlation was observed between the C3, 6 and 9 protons with the C5 carbonyl carbon. Similarly, a correlation was observed between the C3 protons and the C4 carbon.
Scheme 3. Plausible reaction pathways a and b for the formation of 3d from 1g via isolated intermediate 4 and selected $^1$H-$^{13}$C HMBC NMR spectrum correlations of 4 that were used to determine the structure of ring B (red 3 bond, blue 4 bond correlations).

The structure 4 can be viewed as the intermediate immediately prior to the formation of intermediate C via pathway A or intermediate E via pathway B (Scheme 3). Pathway A, a benzylic rearrangement$^{20}$ of 4 is likely due to non-enolizable diketone functionality present and in particular, the highly electrophilic C5 carbonyl group ($\delta$ 178.3 ppm, $^{13}$C NMR). Therefore, attack of ethoxide at the C5 position of C could induce a ring contraction via D to 3d. Pathway B, a quasi-Favorskii rearrangement$^{21}$ proceeding via cyclisation of the N(10) enamine onto the C(5) carbonyl group will form a strained
cyclopropanone (intermediate E). The cyclopropanone E will be labile to attack by alkoxide and in doing so the ring strain will be relieved. Elimination of hydroxide from E will generate an aromatic quinoline ring (c.f. Camps quinolinol synthesis\textsuperscript{22}). In favour of pathway B is recent work by Karimi\textsuperscript{23} which details an oxidative Favorskii rearrangement of an aryl fused seven-membered ring which contracts invoking a cyclopropanone intermediate to a six-membered ring system. This type of ring contraction of seven to six-ring systems has previously been reported.\textsuperscript{24}

In this unexpected reaction of ten-membered examples of N-acyl cyclic ureas 1 (1e-1h) a series of steps occur in concert to generate a 2,3-dihydro-1H-pyrrolo[2,3-b]quinoline 3, the driving force being presumably the generation of an extended aromatic system. When 4 was re-submitted to the reaction conditions 3d was obtained. Intermediates of structural type 4 were not isolated and characterised from other alkoxide or amine-induced rearrangements to 3. Further evidence for the presence of intermediates analogous to 4 was provided by \textsuperscript{1}H NMR analysis of the NaOMe reaction with 1g which provided evidence of a similar intermediate (containing one methyl carboxylate group) but in insufficient quantity for a full assignment (trace < 5\%, data not shown).

The alkoxide-induced rearrangement of 1 to 3 required little optimization (Table S5).\textsuperscript{15} The initial reaction conditions proved robust, with good isolated yields after column chromatography. Attempts to push the reaction further by heating at reflux overnight led to a reduced yield alongside apparent degradation of the product. Addition of extra equivalents of alkoxide also failed to improve the reaction yield. Attempts to optimise the amine-induced rearrangement of 1e required more study (Table 2). The percentage conversion improved by refluxing the reaction mixture in higher boiling point solvents. It was also noted that using a 10-fold excess of the amine improved the
yield of the reaction but only modest improvements in conversion (and isolated yield) were observed.

Changing to microwave irradiation allowed for a dramatic reduction in reaction time. Low power usage using a commercially available microwave (100 W, entry 6) gave the first indication that the reaction conversion could be improved. Higher power usage (200 W, entry 7) led to degradation. A refinement of this approach allowed for the removal of the need for solvent. Instead, the addition of 10 equivalents of the amine to 1e formed a slurry which allowed the reaction to proceed. The percentage conversion measured by $^1$H NMR analysis of the crude reaction mixture indicated that almost complete consumption of the starting material had occurred when using 150 W (entries 8 and 9). After column chromatography the isolated yield for 3a was an acceptable 58%.
Table 2. Optimisation Studies on the Synthesis of 3e from 1e. aIndicates isolated yield obtained by flash column chromatography.

To explore if the pyrrolo[2,3-b]quinoline reaction was general, a series of ten-membered N-acyl cyclic ureas 1e-1h were subjected to alkoxide or amine-induced rearrangement using the optimised conditions in either a commercially available microwave reactor or a Radleys® Greenhouse parallel synthesiser. The results of these experiments are detailed in Table 3.
Table 3. Examples of O and N-centred nucleophile-induced rearrangement of the ten-membered ring system. aReaction conditions: 1 (0.06 mmol), NaOR (0.12 mmol), ROH (2 mL), 25 °C, 16 h. bReaction conditions: 1 (0.06 mmol), RNH₂ (0.6 mmol), mw 80 °C (150 W), 5 min. cAll isolated yields. dConcomitant isolation of 4 (40% isolated yield) from the same reaction as 3d.

The alkoxide-induced rearrangement proceeded in modest to good yields (3a-3c), the noticeable exception being 3d which was afforded in a 7% yield but delivered the isolated intermediate 4 in 40% yield and informed additional mechanistic
understanding of this reaction. A trend regarding the steric requirements of the alkoxides was identified. Using a secondary alkoxide (sodium isopropoxide) prevented the rearrangement occurring (3i-3l) and led to the recovery of the starting material (1e-1h).

Similarly, to the azepinoindole rearrangement in the nine-membered N-acyl cyclic urea series the incorporation of an amine-based nucleophile could be optimised for high conversions (Table 2) but the resulting isolated yield after column chromatography was reduced due to the polar character of the double amide-containing product that was formed (Table 3). Therefore, trends regarding amine nucleophiles were more difficult to rationalise due to the isolation method employed. Further examples of related structural analogues of the two rearrangements are in biological evaluation and will be reported in due course.

Conclusion

In summary, we have developed a selective, one-pot syntheses of diazocino[1,2-a]indolinones and pyrrolo[2,3-b]quinolines from readily accessed starting materials. Assignment of the products from these rearrangements was derived from X-ray crystal structure evidence and advanced NMR spectroscopic techniques. In the ring-enlarged N-acyl cyclic urea series a rearrangement was observed to afford pyrrolo[2,3-b]quinoline 3. The mechanism of the pyrrolo[2,3-b]quinoline reaction in the 10-membered N-acyl cyclic urea series was elucidated by the isolation of a reaction intermediate 4.
Experimental Section

General Methods. Unless otherwise noted, all the commercial reagents were used without further purification. All reactions involving moisture sensitive reagents were performed in oven dried glassware under a positive pressure of argon. Tetrahydrofuran (THF), dichloromethane (DCM) and toluene were obtained dry from a solvent purification system (MBraun, SPS-800). Alcohols used for the formation of alkoxides were dried either by standing over 4Å molecular sieves or by distillation from barium oxide under an argon atmosphere. N,N’-dimethylenediamine (DMED), triethylamine and triisopropylamine were all dried by distillation from KOH. Thin-layer chromatography was performed using glassplates coated with silica gel (with fluorescent indicator UV$_{254}$) (Aldrich). Developed plates were air-dried and analysed under a UV lamp. Flash column chromatography was performed using silica gel (40-63 μm) (Fluorochem). Melting points were recorded in open capillaries using an Electrothermal 9100 melting point apparatus. Values are quoted to the nearest 1 °C and are uncorrected. Elemental microanalyses were performed on a Carlo Erba CHNS analyser within the School of Chemistry at the University of St Andrews. Infrared spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer using either thin films on NaCl plates (NaCl) or KBr discs (KBr) as stated. Absorption maxima are reported as wavenumbers (cm$^{-1}$) and intensities are quoted as strong (s), medium (m), weak (w) and broad (br). Low resolution (LR) and high resolution (HR) electrospray mass spectral (ES-MS) analyses were acquired by electrospray ionisation (ESI), electron impact (EI) or chemical ionisation (CI) within the School of Chemistry, University of St Andrews. Low and high resolution ESI MS were carried out on a Micromass LCT spectrometer and low and high resolution CI MS were carried out on a Micromass GCT spectrometer recorded on a high performance orthogonal
acceleration reflecting TOF mass spectrometer, coupled to a Waters 2975 HPLC. Only the major peaks are reported and intensities are quoted as percentages of the base peak. The purity of compounds was measured using liquid chromatography mass spectrometry (LCMS). The LCMS system includes a Waters 2996 photodiode array detector, Waters 2795 Alliance HT Separations Module, Micromass LCT, Thinkcenter IBM running MassLynx™ 4.0. Global. Separations were performed using a Waters Xterra™ RP18 (5µm, 3.0 x 50 mm) HPLC column. Nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (1H, 300.1 MHz; 13C, 75.5 MHz), Bruker Avance 400 (1H, 400 MHz; 13C, 100.1 MHz) or a Bruker Avance 500 (1H, 500 MHz; 13C, 125 MHz) spectrometer and in the deuterated solvent stated. 13C NMR spectra were acquired using the PENDANT or DEPTQ pulse sequences. All NMR spectra were acquired using the deuterated solvent as the lock. Coupling constants (J) are quoted in Hz and are recorded to the nearest 0.1 Hz. The following abbreviations are used; s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublets of doublets; dt, doublet of triplets; t, triplet; m, multiplet; q, quartet; qt, quintet; and br, broad. Microwave assisted reactions were performed using a CEM Discover microwave operated in ‘powermax’ mode. The synthesis and characterisation of compounds 1a, 1c, 1d, 1e, 1f, 1g, 1h, 1i have been reported elsewhere.14

**Spectroscopic Data.**

12-Pentyloxy-7,8-dihydro-benzo[d]quinazolo[1,2,3-a,b][1,3]diazonane-1,9,10,16-tetrone (1b): 5-hydroxy methyl anthranilate (4.0 g, 23.9 mmol), 1-pentanol (3.9 mL, 35.9 mmol) and triphenylphosphine (9.4 g, 35.9 mmol) were dissolved in anhydrous tetrahydrofuran (40 mL) to which was added diethylzodicarboxylate (5.7 mL, 35.9 mmol) and stirred at room temperature for 72 h. The reaction mixture was washed with 2.0 M NaOH (2 x 50 mL), water (100 mL) and the aqueous layer extracted with ethyl
acetate (3 x 50 mL). The organic phase was dried (MgSO₄), filtered and concentrated in vacuo to give a brown oil which was purified by flash column chromatography on silica gel (1:10, ethyl acetate:hexane) to afford Methyl 2-amino-5-(pentyloxy)benzoate (5.62 g, 23.7 mmol, 99%) as a brown oil. ¹H NMR (300 MHz, CDCl₃): δ 7.35 (d, 3J = 3.0 Hz, 1H, C6-H), 6.95 (dd, 3J = 9.0 Hz, 4J = 3.0 Hz, 1H, C4-H), 6.62 (d, 3J = 9.0 Hz, 1H, C3-H), 5.39 (s, 2H, NH₂), 3.89 (t, 3J = 6.5 Hz, 2H, OCH₂) 3.87 (s, 3H, CO₂CH₃), 1.82-1.70 (m, 2H, OCH₂CH₂), 1.49-1.32 (m, 4H, CH₂CH₂CH₃), 0.93 (t, 3J = 7.0 Hz, 3H, CH₃); ¹³C NMR (75.5 MHz, CDCl₃): δ 168.7 (CO₂Me), 150.4 (C5), 145.5 (C2), 124.2 (C4), 118.6 (C3), 114.7 (C6), 111.1 (C1), 69.2 (OCH₂), 52.0 (CO₂CH₃), 29.5 (OCH₂CH₂), 28.6 (CH₂CH₂CH₃), 22.9 (CH₂CH₂CH₃), 14.4 (CH₃); IR (KBr): νmax = 3478 (m) (NH₂), 3370 (m), 2956 (s), 2872 (m), 1699 (s) (C=O), 1565 (m), 1497 (s), 1288 (s), 1221 (m), 1154 (w) (C-O), 1096 (w), 740 (m) (Ar-H) cm⁻¹; LRMS (ES⁺): m/z (%) 238.21 (100) [M+H]⁺, 260.17 (90) [M+Na]⁺; HRMS (ES⁺): m/z calcd for C₁₃H₁₉NO₃Na [M+Na]⁺: 260.1263; found 260.1268. 10-Pentyloxy-8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene (0.23 g, 0.63 mmol, 63%) was afforded as a yellow powder using the general procedure reported. ¹³ Briefly, A mixture of the methyl anthranilate (4.0 mmol, 4.0 eq.) and N-aryl lactam (1.0 mmol, 1.0 eq.) in a sealed glass microwave tube was heated to 190 °C, (maximum 275 W), with air flowing through the reaction chamber, for 30 minutes. Upon cooling the reaction mixture was added to diethyl ether (30 mL) and the resultant precipitate filtered. The precipitate was purified by flash column chromatography over silica gel (99:1, chloroform:methanol) to afford the title compound. An analytically pure sample was prepared by recrystallisation from acetic acid. Mp 264 °C (dec.); ¹H NMR (300 MHz, CDCl₃): δ 9.42 (d, 3J = 9.5 Hz, 1H, C12-H), 8.24 (dd, 3J = 8.0 Hz, 4J = 1.5 Hz, 1H, C1-H), 7.84 (d, 4J = 3.0 Hz, 1H, C9-H), 7.68 (ddd, 3J = 8.0 Hz, 3J = 8.0 Hz, 4J = 1.5 Hz, 1H, C3-H), 7.22 (ddd, 3J = 8.0 Hz, 3J = 8.0 Hz, 3J = 8.0 Hz, 1H, C8-H). 10-Pentyloxy-8,14-dioxo-6,7-dihydro-8H,14H-5,13-diazabenz[e]aceanthrylene (0.23 g, 0.63 mmol, 63%) was afforded as a yellow powder using the general procedure reported. ¹³ Briefly, A mixture of the methyl anthranilate (4.0 mmol, 4.0 eq.) and N-aryl lactam (1.0 mmol, 1.0 eq.) in a sealed glass microwave tube was heated to 190 °C, (maximum 275 W), with air flowing through the reaction chamber, for 30 minutes. Upon cooling the reaction mixture was added to diethyl ether (30 mL) and the resultant precipitate filtered. The precipitate was purified by flash column chromatography over silica gel (99:1, chloroform:methanol) to afford the title compound. An analytically pure sample was prepared by recrystallisation from acetic acid. Mp 264 °C (dec.); ¹H NMR (300 MHz, CDCl₃): δ 9.42 (d, 3J = 9.5 Hz, 1H, C12-H), 8.24 (dd, 3J = 8.0 Hz, 4J = 1.5 Hz, 1H, C1-H), 7.84 (d, 4J = 3.0 Hz, 1H, C9-H), 7.68 (ddd, 3J = 8.0 Hz, 3J = 8.0 Hz, 4J = 1.5 Hz, 1H, C3-H), 7.22 (ddd, 3J = 8.0 Hz, 3J = 8.0 Hz, 3J = 8.0 Hz, 1H, C8-H).
Hz, \(^4J = 1.0\) Hz, 1H, C2-H), 7.15 (dd, \(^3J = 9.5\) Hz, \(^4J = 3.0\) Hz, 1H, C11-H). 6.93 (d, \(^3J = 8.0\) Hz, 1H, C4-H), 4.28 (t, \(^3J = 9.0\) Hz, 2H, C6-H2), 4.05 (t, \(^3J = 6.5\) Hz, 2H, OCH2), 3.36 (t, \(^3J = 7.0\) Hz, 3H, CH3); \(^13^C\) NMR (75.5 MHz, CDCl3): \(\delta\) 172.1 (C8), 159.7 (C14), 157.3 (C10), 148.0 (C5a), 138.5 (C4a), 135.8 (C3), 130.1 (C12a), 129.9 (C1), 129.4 (C8a), 122.6 (C12), 122.4 (C2), 119.4 (C11), 114.5 (C14a), 112.1 (C4), 107.0 (C9), 101.9 (C7a), 68.3 (OCH2), 47.3 (C6), 28.9 (OCH2CH2), 28.2 (CH2CH2CH3), 23.4 (C7), 22.5 (CH2CH2CH3), 14.0 (CH3); IR (KBr): \(\nu_{max} = 2953\) (s) (OCH2), 2933 (s) (OCH2), 2870 (s) (OCH2), 1700 (s) (C=O), 1630 (s) (NHCO), 1585 (m), 1558 (m), 1351 (m), 1288 (s) (C-O), 1172 (m) cm\(^{-1}\); LRMS (ES\(^+\)): m/z (%) 375.17 (100) [M+H]\(^+\), 374.16 (45) [M]\(^+\); HRMS (ES\(^+\)): m/z calcd for C23H23N2O3 [M+H]\(^+\): 375.1709; found 375.1706. Using the Büchi Syncore parallel reaction apparatus the following procedure was performed.\(^1\) To a suspension of the diazabenz(e)aceanthrylene (1.0 mmol, 1.0 eq.) in anhydrous chloroform (15 mL) was added purified m-CPBA (2.5 mmol, 2.5 eq.) portion-wise. The reaction mixtures were shaken at room temperature for 16 hours and then added NaHCO\(_3\)(aq.) (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layer was dried (MgSO\(_4\)), filtered and concentrated in vacuo to give a solid which was purified by dry-flash column chromatography over silica gel (3:7, ethyl acetate:hexane) furnished the title compound. Recrystallisation from acetone afforded an analytically pure sample of 12-Pentyloxy-7,8-dihydro-benzo[d]quinazolo[1,2,3-a,b][1,3]diazonane-1,9,10,16-tetron,\(\text{1b}\) (0.17 g, 0.41 mmol, 41%) was afforded as a pale grey powder. Mp 58-59°C; \(^1^H\) NMR (300 MHz, CDCl3): \(\delta\) 8.20 (dd, \(^3J = 8.0\) Hz, \(^4J = 1.0\) Hz, 1H, C2-H), 7.76-7.71 (m, 1H, C4-H), 7.63-7.55 (m, 2H, C14-H, C11-H), 7.34-7.22 (m, 3H, C5-H, C3-H, C13-H), 4.84-4.76 (m, 1H, C7-H\(_a\)), 4.40-4.32 (m, 1H, C7-H\(_b\)), 4.10-3.98 (m, 2H, OCH2), 

3.85-3.76 (m, 1H, C8-Ha), 2.93-2.85 (m, 1H, C8-Hb), 1.88-1.78 (m, 2H, OCH2CH2), 
1.51-1.35 (m, 4H, CH2CH2CH3), 0.95 (t, 3J = 7.0 Hz, 3H, CH3); 13C NMR (75.5 MHz, 
CDCl3): δ 199.0 (C9), 190.9 (C10), 160.6 (C1), 159.1 (C12), 155.8 (C16), 141.5 (C5a), 
135.9 (C4), 131.2 (C10a), 130.9 (C14), 129.7 (C2), 129.1 (C14a), 124.4 (C5), 120.0 
(C13), 116.7 (C1a), 116.6 (C11), 115.9 (C3), 68.8 (OCH2), 44.8 (C7), 35.9 (C8), 28.9 
(OCH2CH2), 28.2 (CH2CH2CH3), 22.5 (CH2CH2CH3), 14.5 (CH3); IR (KBr): vmax = 2923 
(m), 1715 (s), 1669 (s), 1609 (s), 1575 (m), 1477 (m), 1386 (m), 1162 (m), 757 (m) cm−1; 
LRMS (ES+): m/z (%) 429.14 (100) [M+Na]+; HRMS (ES+): m/z calcd for 

Typical Procedure for the Synthesis of 2.

Alkoxide nucleophiles: Reactions were conducted in parallel using the Radleys 
Greenhouse Parallel synthesiser. To a solution of the N-acyl cyclic urea 1 (0.06 mmol, 
1.0 eq.) in the respective anhydrous alcohol (methanol or ethanol) (2 ml) was added 
the respective sodium alkoxide (sodium methoxide or sodium ethoxide) (0.13 mmol, 2 
eq). The reaction mixture was stirred at room temperature for 10 min and then 
evaporated in parallel, re-dissolved in dichloromethane (2 x 4.0 mL) and washed with 
NaHCO3(aq.) (2 x 2.0 mL). The mixtures were passed through an Isolute™ phase 
separator and the organic layer was dried (Na2SO4 cartridge) and concentrated in 
vacuo to give a solid which was purified by recrystallisation from ethyl acetate/hexane 
to afford the title compound.

Amine nucleophiles: Reactions were conducted in parallel using the Radleys 
Greenhouse Parallel synthesiser. To a solution of the N-acyl cyclic urea 1 (0.06 mmol, 
1.0 eq.) in anhydrous tetrahydrofuran (3 ml) was added the amine ((0.20 M n- 
butylamine, benzylamine used as received from Aldrich, 0.23 M
aminomethylcyclopropane, 0.23 M 2-methoxyethylamine, or 0.15 M 4(a)-aminoethyl)morpholine) from a freshly prepared stock solution in anhydrous tetrahydrofuran) (0.06 mmol, 1.0 eq.). The reaction mixture was stirred at room temperature for 3 h. The reaction mixtures were evaporated in parallel to give a solid which was purified by recrystallisation from ethyl acetate/hexane to afford the title compound.

8-Methyl carboxylate-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2a): white powder (22 mg, 99%), mp 226-227 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 8.37 (d, \(3J = 8.5 \text{ Hz}, 1\text{H}, C1-H\)), 7.77-7.71 (m, 2H, C2-H, C4-H), 7.58-7.51 (m, 2H, C12-H, C10-H), 7.45-7.47 (m, 2H, C11-H, C10-H), 7.45-7.49 (m, 2H, C12-H, C10-H), 7.30-7.27 (m, 2H, C3-H, C9-H), 4.23 (dt, \(2J = 14.0 \text{ Hz}, 3J = 4.0 \text{ Hz}, 1\text{H}, C7-H_a\)), 3.59 (s, 3H, CO\(_2\)C\(_3\)H\(_3\)), 3.65-3.51 (m, 1H, C7-H\(_b\)), 2.38-2.27 (m, 1H, C6-H\(_a\)); \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 199.1 (C5), 166.5 (C13), 155.4 (CO\(_2\)Me), 151.7 (C14a), 138.1 (C2), 138.0 (C8a), 136.6 (C12a), 132.0 (C10), 129.2 (C12), 128.4 (C11), 128.0 (C9), 125.2 (C3), 124.5 (C4), 121.2 (C4a), 120.2 (C1), 90.3 (C5a), 53.2 (CH\(_3\)) 44.9 (C7), 33.9 (C6); IR (KBr): \(\nu_{\max} = 3285 \text{ (s), 2994 \text{ (m), 2957 \text{ (m), 1732 \text{ (s), 1674 \text{ (s), 1601 \text{ (m), 1468 \text{ (m), 1371 \text{ (m), 1027 \text{ (m), 759 \text{ cm}^{-1}\). LRMS (ES\(^+\)): m/z (%) 374.97 (100) [M+Na]\(^+\); HRMS (ES\(^+\)): m/z calcd for C\(_{19}\)H\(_{18}\)N\(_2\)O\(_5\)Na [M+Na]\(^+\): 375.0957; found 375.0946; An analytical sample of 2a was prepared by recrystallisation from EtOAc/hexane; Anal. calcd for C\(_{19}\)H\(_{18}\)N\(_2\)O\(_5\): C, 64.77; H, 4.58; N, 7.95; found: C, 64.76; H, 4.24; N, 7.54.

8-(Methyl carboxylate)-3-pentyloxy-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2b): White powder (22 mg, 99%); \(^1\)H NMR (300 MHz, CDCl\(_3\)): δ 8.22 (d, \(3J = 9.0 \text{ Hz}, 1\text{H}, C1-H\)), 7.51 (ddd, \(3J = 7.7 \text{ Hz}, 3J = 7.7 \text{ Hz}, 4J =
1.4 Hz, 1H, C10-H), 7.48-7.43 (m, 1H, C12-H), 7.38-7.32 (m, 1H, C11-H), 7.27 (dd, 3J = 9.0 Hz, 4J = 3.0 Hz, 1H, C2-H), 7.18 (d, 3J = 7.7 Hz, 1H, C9-H), 7.02 (d, 4J = 3.0 Hz, 1H, C4-H), 4.21 (dt, 2J = 14.0 Hz, 3J = 4.0 Hz, 1H, C7-Ha), 3.96 (t, 3J = 6.5 Hz, 2H, OCH2), 3.56 (s, 3H, OCH3), 3.47 (dd, 2J = 13.0 Hz, 3J = 12.0 Hz, 3J = 4.0 Hz, 1H, C7-Hb), 2.26 (dd, 2J = 13.0 Hz, 3J = 12.0 Hz, 3J = 4.0 Hz, 1H, C6-Ha), 1.82 (qt, 3J = 6.5 Hz, 3J = 6.5 Hz, 2H, OCH2CH2), 1.72 (dt, 2J = 14.0 Hz, 3J = 4.0 Hz, 1H, C6-Hb), 1.52-1.35 (m, 4H, CH2CH2CH3), 0.97 (t, 3J = 6.5 Hz, 3H, CH2CH3); 13C NMR (75.5 MHz, CDCl3): δ 199.6 (C5), 166.0 (C13), 156.8 (C3), 155.5 (CO2Me), 146.3 (C14a), 138.3 (C8a), 136.8 (C12a), 132.0 (C10), 129.5 (C12), 128.6 (C11), 128.1 (C9), 127.6 (C2), 122.1 (C4a), 121.5 (C1), 105.9 (C4), 90.7 (C5a), 68.8 (OCH2R), 53.3 (OCH3), 45.1 (C7), 34.3 (C6), 28.9 (OCH2CH2R), 28.3 (OCH2CH2CH2R), 22.6 (CH2CH3), 14.2 (CH2CH3); IR (NaCl): νmax = 2956 (m), 2929 (m), 2858 (m), 1714 (s) (C=O), 1647 (s) (C=O), 1619 (m), 1489 (m), 1458 (m), 1029 (w), 766 (w) cm⁻¹; LRMS (ES⁺): m/z (%) 461.02 (100) [M+Na]+; HRMS (ES⁺): m/z calcd for C24H26N2O6Na [M+Na]+: 461.1689; found 461.1689.

3-Methyl-8-(methyl carboxylate)-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2c): White powder (22 mg, 99%), mp 99-100 °C; 1H NMR (300 MHz, CDCl3): δ 8.31 (d, 3J = 9.0 Hz, 1H, C1-H), 7.61-7.52 (m, 4H, C4-H, C10-H, C12-H, C2-H), 7.45 (dd, 3J = 7.5 Hz, 4J = 1.5 Hz, 1H, C11-H), 7.24-7.19 (m, 1H, C9-H), 4.32-4.22 (m, 1H, C7-Ha), 3.61 (s, 3H, CO2CH3), 3.55-3.45 (m, 1H, C7-Hb), 2.42 (s, 3H, Ar-CH3), 2.41-2.31 (m, 1H, C6-Ha), 1.80-1.72 (m, 1H, C6-Hb); 13C NMR (75.5 MHz, CDCl3): δ 199.5 (C5), 166.4 (C13), 155.4 (CO2Me), 149.7 (C14a), 139.3 (C2), 138.2 (C8a), 136.7 (C12a), 135.4 (C3), 132.0 (C10), 129.3 (C12), 128.5 (C11), 128.0 (C9), 124.1 (C4), 121.4 (C4a), 120.0 (C1), 90.8 (C5a), 53.2 (OCH3), 45.0 (C7), 34.0 (C6), 21.0 (ArCH3); IR (KBr): νmax = 3449 (br s), 1735 (s) (C=O), 1655 (s) (C=O), 1382 (m)
cm⁻¹; LRMS (ES⁺): m/z (%) 388.99 (100) [M+Na⁺]; HRMS (ES⁺): m/z calc'd for C₂₀H₁₈N₂O₅Na [M+Na⁺]: 389.1113; found 389.1110.

2-Chloro-8-(methyl carboxylate)-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2d): White powder (22 mg, 99%), mp 93-94 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.46 (d, ⁴J = 1.5 Hz, 1H, C1-H), 7.69 (d, ³J = 8.0 Hz, 1H, C4-H), 7.58-7.54 (m, 2H, C10-H, C12-H), 7.48-7.42 (m, 1H, C11-H), 7.28-7.20 (m, 2H, C3-H, C9-H), 4.23 (dt, ²J = 14.0 Hz, ³J = 4.0 Hz, 1H, C7-Hₐ), 3.61 (s, 3H, CO₂CH₃), 3.54-3.44 (m, 1H, C7-Hₐ); ¹³C NMR (75.5 MHz, CDCl₃): δ 197.9 (C5), 166.6 (C13), 152.4 (C2Me), 145.1 (C14a), 138.1 (C8a), 136.4 (C12a), 132.5 (C10), 130.6 (C2), 129.5 (C12), 128.8 (C11), 128.2 (C9), 126.2 (C3), 125.6 (C4), 120.6 (C1), 119.6 (C4a), 90.7 (C5a), 53.5 (CH₃), 44.9 (C6), 34.3 (C7); IR (KBr): νmax = 3423 (br s), 2925 (m), 1719 (s), 1655 (s), 1600 (m), 1426 (m), 1313 (m), 1061 (w), 766 (m) cm⁻¹; LRMS (ES⁺): m/z (%) 408.93 (100) [M+Na⁺]; HRMS (ES⁺): m/z calc'd for C₁₉H₁₅N₂O₅NaCl [M+Na⁺]: 409.0567; found 409.0560.

8-Ethyl carboxylate-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2e): White powder (21 mg, 93%), mp 191-192 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.30 (d, ³J = 8.4 Hz, 1H, C1-H), 7.74-7.66 (m, 2H, C2-H, C4-H), 7.56-7.48 (m, 2H, C12-H, C10-H), 7.41-7.34 (m, 1H, C11-H), 7.27-7.17 (m, 2H, C3-H, C9-H), 4.18 (dt, ²J = 14.0 Hz, ³J = 4.0 Hz, 1H, C7-Hₐ), 4.14-4.04 (m, 1H, CH₂(a)CH₃), 3.98-3.86 (m, 1H, CH₂(b)CH₃), 3.82 (br s, 1H, OH), 3.45 (ddd, ²J = 14.0 Hz, ³J = 12.0 Hz, ³J = 4.0 Hz, 1H, C6-Hₐ), 1.69 (dt, ²J = 14.0 Hz, ³J = 4.0 Hz, 1H, C6-Hₐ), 2.27 (ddd, ²J = 14.0 Hz, ³J = 12.0 Hz, ³J = 4.0 Hz, 1H, C6-Hₐ), 1.10 (t, ³J = 7.2 Hz, 3H, CH₃CH₂); ¹³C NMR (75.5 MHz, CDCl₃): δ 199.3 (C5), 166.5 (C13), 155.0 (CO₂Me), 151.9 (C14a),
138.3 (C8a), 138.2 (C2), 136.7 (C12a), 132.1 (C10), 129.4 (C12), 128.5 (C11), 128.1 (C9), 125.3 (C3), 124.7 (C4), 121.4 (C4a), 120.2 (C1), 90.5 (C5a), 62.1 (OCH2CH3), 44.9 (C7), 34.0 (C6), 14.7 (OCH2CH3); IR (KBr): νmax = 3286 (s), 2986 (m), 2956 (m), 1733 (s), 1673 (s), 1601 (m), 1458 (m), 1017 (m), 756 (m) cm⁻¹; LCMS (ES⁺): m/z (%) 366.88 (100) [M⁺], 383.90 (80) [M+H₂O⁺]; HRMS (ES⁺): m/z calcd for C20H18N2O5Na [M+Na⁺]: 389.1215; found 389.1204.

8-(Ethyl carboxylate)-3-pentyloxy-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2f): Brown oil (22 mg, 0.05 mmol, 99%), ¹H NMR (300 MHz, CDCl₃): δ = 8.23 (d, ³J = 9.0 Hz, 1H, C1-H), 7.55-7.48 (m, 2H, C10-H, C12-H), 7.38 (ddd, ³J = 7.5 Hz, ⁴J = 1.0 Hz, 1H, C11-H), 7.28 (dd, ³J = 9.0 Hz, ⁴J = 3.0 Hz, 1H, C2-H), 7.21-7.17 (m, 1H, C9-H), 7.05 (d, ⁴J = 3.0 Hz, 1H, C4-H), 4.23 (dt, ²J = 14.2 Hz, ³J = 4.0 Hz, 1H, C7-Ha), 4.18-4.06 (m, 1H, OCH2(a)CH3), 4.00-3.88 (m, 1H, OCH2(b)CH3), 3.96 (t, ³J = 6.5 Hz, 2H, OCH2), 3.69 (br s, 1H, O), 3.47 (dd, ²J = 13.3 Hz, ³J = 12.0 Hz, ⁴J = 3.0 Hz, 1H, C7-Hb), 2.31 (ddd, ²J = 13.3 Hz, ³J = 12.0 Hz, ⁴J = 4.0 Hz, 1H, C6-Ha), 1.82 (qt, ³J = 6.5 Hz, ³J = 6.5 Hz, 2H, OCH2CH2), 1.72 (dt, ²J = 14.0 Hz, ³J = 4.0 Hz, 1H, C6-Hb), 1.52-1.34 (m, 4H, CH2CH2CH3), 1.12 (t, ³J = 7.0 Hz, 3H, OCH2CH3), 0.96 (t, ³J = 6.5 Hz, 3H, CH2CH2CH3), ¹³C NMR (75.5 MHz, CDCl₃): δ 199.5 (C5), 165.9 (C13), 165.6 (C3), 154.8 (CO₂Me), 146.1 (C14a), 138.3 (C8a), 136.7 (C12a), 132.0 (C10), 129.4 (C12), 128.4 (C11), 127.9 (C9), 127.5 (C2), 122.1 (C4a), 121.5 (C1), 105.9 (C4), 90.8 (C5a), 68.7 (OCH2R), 61.9 (OCH2CH3), 44.9 (C7), 34.0 (C6), 29.7 (OCH2CH2R), 28.7 (OCH2CH2CH2R), 22.4 (CH2CH3), 14.7 (CH2CH3) 14.2 (OCH2CH3); IR (NaCl): νmax = 3422 (w), 2955 (m), 2928 (m), 2858 (m), 1719 (s) (C=O), 1650 (s) (C=O), 1620 (m), 1459 (m), 1265 (m), 741 (w) cm⁻¹; LCMS (ES⁺): (purity 99%) m/z (%) 452.91 (100) [M+H⁺], 469.93 (70) [M+H₂O⁺]; HRMS (ES⁺): m/z calcd for C25H28N2O6Na [M+Na⁺]: 475.1947; found 475.1948.
3-Methyl-8-(ethyl carboxylate)-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2g): White powder (21 mg, 90%), mp 196 °C (dec.); 1H NMR (300 MHz, CDCl3): δ 8.19 (d, 3J = 8.5 Hz, 1H, C1-H), 7.55-7.49 (m, 3H, C4-H, C10-H, C12-H), 7.45-7.43 (m, 1H, C2-H), 7.38 (ddd, 3J = 7.3 Hz, 3J = 7.3 Hz, 4J = 1.2 Hz, 1H, C11-H), 7.19 (d, 3J = 7.3 Hz, 1H, C9-H), 4.20 (dt, 2J = 14.0 Hz, 3J = 4.0 Hz, 1H, C7-Ha), 4.15-4.06 (m, 1H, OCH2(a)), 3.97-3.88 (m, 1H, OCH2(b)), 3.78 (br s, 1H, OH), 3.46 (ddd, 2J = 12.8 Hz, 3J = 12.8 Hz, 3J = 3.4 Hz, 1H, C1-H), 2.39 (s, 3H, ArCH3), 2.28 (ddd, 2J = 12.8 Hz, 3J = 12.8 Hz, 3J = 4.0 Hz, 1H, C6-Ha), 1.70 (dt, 2J = 14.0 Hz, 3J = 4.0 Hz, 1H, C6-Hb), 1.10 (t, 3J = 7.1 Hz, 3H, OCH2CH3); 13C NMR (75.5 MHz, CDCl3): δ 199.5 (C5), 166.3 (C13), 154.9 (CO2Me), 149.9 (C14a), 139.3 (C2), 138.4 (C8a), 136.8 (C12a), 135.4 (C3), 132.0 (C10), 129.4 (C12), 128.5 (C11), 128.1 (C9), 124.2 (C4), 121.4 (C4a), 120.0 (C1), 90.7 (C5a), 62.1 (OCH2CH3), 44.9 (C7), 34.0 (C6), 21.0 (ArCH3), 14.7 (OCH2CH3); IR (KBr): νmax = 3286 (s), 1735 (s) (C=O), 1708 (s) (C=O), 1648 (s) (C=O), 1489 (m), 1389 (m), 1266 (s) 764 (m) (Ar-H) cm⁻¹; LCMS (ES⁺): (purity 98%) m/z (%) 380.90 (100) [M+H]+, 397.82 (70) [M+H2O]+; HRMS (ES⁺): m/z calcd for C21H20N2O5Na [M+Na]+: 403.1371; found 403.1368.

2-Chloro-8-(ethyl carboxylate)-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2h): White powder (22 mg, 99%), mp 148-149 °C; 1H NMR (300 MHz, CDCl3): δ 8.41 (d, 4J = 1.5 Hz, 1H, C1-H), 7.66 (d, 3J = 8.2 Hz, 1H, C4-H), 7.58-7.52 (m, 2H, C10-H, C12-H), 7.43 (ddd, 3J = 7.8 Hz, 3J = 7.8 Hz, 4J = 1.3 Hz, 1H, C11-H), 7.25 (dd, 3J = 8.2 Hz, 4J = 1.5 Hz, 1H, C3-H), 7.21 (d, 3J = 7.8 Hz, 1H, C9-H), 4.21 (dt, 2J = 14.0 Hz, 3J = 4.0 Hz, 1H, C7-Ha), 4.16-4.07 (m, 1H, OCH2(a)CH3), 4.02-3.93 (m, 1H, OCH2(b)CH3), 3.53 (br s, 1H, OH), 3.47 (ddd, 2J = 13.0 Hz, 3J = 12.0 Hz, 3J = 4.0 Hz, 1H, C6-Ha), 2.33 (ddd, 2J = 13.0 Hz, 3J = 11.8 Hz, 3J = 4.0 Hz, 1H, C6-Ha), 1.73 (dt, 2J = 14.0 Hz, 3J = 3.9 Hz, 1H, C6-Ha), 1.12 (t, 3J = 7.0 Hz, 3H, OCH2CH3);
13C NMR (75.5 MHz, CDCl3): δ 198.2 (C5), 166.6 (C13), 155.0 (CO2Me), 152.4 (C14a), 144.9 (C2), 138.3 (C8a), 136.4 (C12a), 129.4 (C12), 128.3 (C11), 128.2 (C9), 126.1 (C3), 126.0 (C4), 120.5 (C1), 119.7 (C4a), 90.9 (C5a), 62.2 (OCH2CH3), 44.8 (C6), 34.1 (C7), 14.7 (OCH2C6H5); IR (KBr): νmax = 3420 (br s), 2927 (m), 1725 (s) (C=O), 1665 (s) (C=O), 1602 (m), 1458 (m), 1376 (m), 1260 (w), 767 (m) cm⁻¹; LCMS (ES⁺): (purity 99%) m/z (%) 400.86 (100) [M+H]+, 417.87 (80) [M+H2O]+; HRMS (ES⁺): m/z calcd for C20H17N2O5NaCl [M+Na]+: 423.0825; found 423.0818.

8-N-Butyl carboxamide-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2i)15,16: White powder (18 mg, 74%), mp 235-236 °C; 1H NMR (300 MHz, CDCl3): δ 8.31 (d, 3J = 8.5 Hz, 1H, C1-H), 7.70-7.62 (m, 2H, C2-H, C4-H), 7.52 (ddd, 3J = 7.6 Hz, 3J = 7.6 Hz, 4J = 1.7 Hz, C10-H), 7.44-7.40 (m, 1H, C12-H), 7.37-7.32 (m, 1H, C11-H), 7.24-7.18 (m, 2H, C3-H, C9-H), 4.82 (br s, 1H, OH), 4.19 (dt, 2J = 14.0 Hz, 3J = 4.0 Hz, 1H, C7-Ha), 4.06 (t, 3J = 6.0 Hz, 1H, NH), 3.26 (ddd, 2J = 12.0 Hz, 3J = 11.5 Hz, 3J = 3.0 Hz, 1H, C7-Hb), 3.06-2.96 (m, 1H, NHCH(a)), 2.88-2.79 (m, 1H, NHCH(b)), 2.07 (ddd, 2J = 12.0 Hz, 3J = 10.2 Hz, 3J = 3.0 Hz, 1H, C6-Ha), 1.59 (dt, 2J = 14.0 Hz, 3J = 3.0 Hz, 1H, C6-Hb), 1.29-1.20 (m, 2H, NHCH2CH2CH2), 0.82 (t, 3J = 7.5 Hz, 3H, CH3); 13C NMR (75.5 MHz, CDCl3): δ 199.4 (C5), 166.3 (C13), 156.2 (NCONH), 151.5 (C14a), 138.4 (C8a), 138.0 (C2), 137.6 (C12a), 132.7 (C10), 130.0 (C12), 129.3 (C11 & C9), 125.4 (C3), 124.5 (C4), 121.6 (C4a), 120.3 (C1), 90.7 (C5a), 43.8 (C7), 40.6 (NHCH2), 35.0 (C6), 32.4 (NHCH2CH2), 20.0 (NHCH2CH2CH2), 13.9 (CH3); IR (KBr): νmax = 3389 (s), 3246 (s), 2956 (m), 2872 (m), 1736 (s) (C=O), 1635 (s) (C=O), 1625 (m), 1535 (m), 1463 (m), 1381 (m), 764 (m) cm⁻¹; LRMS (ES⁺): m/z (%) 416.08 (100) [M+Na]+; HRMS (ES⁺): m/z calcd for C22H23N3O4Na [M+Na]+: 416.1586; found 416.1585.
8-(N-Butyl carboxamide)-3-pentyloxy-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2j): Yellow oil (8 mg, 36%), 1H NMR (300 MHz, CDCl3): δ 8.33 (d, 3J = 9.0 Hz, 1H, C1-H), 7.61-7.55 (m, 2H, C10-H, C12-H), 7.50-7.44 (m, 1H, C11-H), 7.31 (dd, 3J = 9.0 Hz, 4J = 2.9 Hz, 1H, C2-H), 7.29-7.25 (m, 1H, C9-H), 7.12 (d, 4J = 2.9 Hz, 1H, C4-H), 4.44 (dt, 2J = 14.0 Hz, 3J = 4.0 Hz, 1H, C7-Ha), 4.11 (t, 3J = 5.8 Hz, 1H, NH), 3.98 (t, 3J = 6.7 Hz, 2H, OCH2), 3.36 (ddd, 2J = 13.3 Hz, 3J = 11.7 Hz, 3J = 2.9 Hz, 1H, C7-Hb), 3.22-3.10 (m, 1H, NHCH2(a)), 3.04-2.92 (m, 1H, NHCH2(b)), 2.30 (ddd, 2J = 13.3 Hz, 3J = 11.7 Hz, 3J = 4.0 Hz, 1H, C6-Ha), 1.87-1.77 (m, 2H, OCH2CH2), 1.72 (dt, 2J = 14.0 Hz, 3J = 4.0 Hz, 1H, C6-Hb), 1.50-1.30 (m, 4H, OC2H4CH2CH2CH3), 1.29-1.15 (m, 4H, NHCH2CH2CH2CH3), 0.96 (t, 3J = 7.0 Hz, 3H, OC4H8CH3), 0.87 (t, 3J = 7.2 Hz, 3H, NH3H6CH3); 13C NMR (75.5 MHz, CDCl3): δ 199.4 (C5), 166.7 (C13), 156.8 (C3), 156.1 (NCONH), 146.1 (C14a), 138.5 (C8a), 137.8 (C12a), 132.7 (C10), 130.1 (C12), 129.4 (C11 & C9), 127.4 (C2), 122.4 (C4a), 121.6 (C1), 106.0 (C4), 90.9 (C5a), 68.8 (OCH2), 44.0 (C7), 40.7 (NCONHCH2), 35.3 (C6), 32.6 (NCONHCH2CH2) 28.9 (OCH2CH2CH2CH2CH3), 28.3 (OCH2CH2CH2CH2CH3), 22.6 (OCH2CH2CH2CH2CH3), 20.0 (NCONHCH2CH2CH2), 14.2 (OCH2CH2CH2CH2CH3), 14.0 (NCONHCH2CH2CH2CH3); IR (NaCl): vmax = 2957 (m), 2872 (m) 1728 (s) (C=O), 1637 (s), 1524 (m), 1488 (m), 1279 (m) cm⁻¹; LRMS (ES⁺): m/z (%) 502.13 (100) [M+Na]+; HRMS (ES⁺): m/z calcd for C27H33N3Os5Na [M+Na]+: 502.2318; found 502.2314.

3-Methyl-8-N-butyl carboxamide-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2k): White powder (7 mg, 29%), mp 204-205 °C; 1H NMR (300 MHz, CDCl3): δ 8.26 (d, 3J = 8.5 Hz, 1H, C1-H), 7.60-7.41 (m, 5H, C4-H, C10-H, C12-H, C2-H, C11-H), 7.27-7.23 (m, 1H, C9-H), 4.36 (dt, 2J = 14.0 Hz, 3J = 4.0 Hz, 1H, C7-Ha), 4.08 (t, 3J = 5.9 Hz, 1H, NH), 3.66 (br s, 1H, OCH3), 3.33 (ddd, 2J = 13.0 Hz, 3J =
11.8 Hz, $^{3}J = 4.0$ Hz, 1H, C7-Ha), 3.18-3.06 (m, 1H, NHCH$_{(a)}$), 3.00-2.88 (m, 1H, NHCH$_{(b)}$), 2.40 (s, 3H, ArCH$_{3}$), 2.24 (ddd, $^{2}J = 13.0$ Hz, $^{3}J = 11.8$ Hz, $^{3}J = 4.0$ Hz, 1H, C6-Ha), 1.67 (dt, $^{2}J = 14.0$ Hz, $^{3}J = 4.0$ Hz, 1H, C6-Hb), 1.37-1.14 (m, 4H, NHCH$_{2}$CH$_{2}$CH$_{2}$), 0.86 (t, $^{3}J = 7.3$ Hz, 3H, CH$_{2}$CH$_{3}$); $^{13}$C NMR (75.5 MHz, CDCl$_{3}$): δ 199.4 (C5), 166.1 (C13), 156.4 (NCON), 149.7 (C14a), 139.3 (C2), 138.4 (C8a), 137.7 (C12a), 135.5 (C3), 132.6 (C10), 130.0 (C12), 129.3 (C11 & C9), 124.2 (C4), 121.5 (C4a), 120.0 (C1), 90.7 (C5a), 43.8 (C7), 40.6 (NHCH$_{2}$), 35.1 (C6), 32.5 (NHCH$_{2}$CH$_{2}$), 21.0 (ArCH$_{3}$), 20.0 (NHCH$_{2}$CH$_{2}$), 13.9 (NHCH$_{2}$CH$_{2}$CH$_{2}$CH$_{3}$); IR (KBr): $\nu_{\text{max}} = 3236$ (s), 1722 (s) (C=O), 1638 (s) (C=O), 1525 (m), 1490 (w), 1152 (w), 742 (m) cm$^{-1}$; LRMS (ES$^+$): m/z (%) 430.04 (100) [M+Na]$^+$; HRMS (ES$^+$): m/z calcd for C$_{23}$H$_{25}$N$_{3}$O$_{4}$Na [M+Na]$^+$: 430.1743; found 430.1757.

2-Chloro-8-N-butyl carboxamide-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2I): White powder (10 mg, 44%), mp 211-212 °C; $^1$H NMR (300 MHz, CDCl$_{3}$): δ 8.44 (d, $^{4}J = 1.8$ Hz, 1H, C1-H), 7.66 (d, $^{3}J = 8.0$ Hz, 1H, C4-H), 7.63-7.45 (m, 3H, C10-H, C12-H, C11-H), 7.29-7.23 (m, 2H, C3-H, C9-H), 4.33 (dt, $^{2}J = 14.0$ Hz, $^{3}J = 3.8$ Hz, 1H, C7-Ha), 4.07 (t, $^{3}J = 5.6$ Hz, 1H, NH), 3.86 (br s, 1H, OH), 3.34 (ddd, $^{2}J = 12.8$ Hz, $^{3}J = 11.6$ Hz, $^{3}J = 3.8$ Hz, 1H, C7-Hb), 3.19-3.07 (m, 1H, NHCH$_{(a)}$), 2.98-2.86 (m, 1H, NHCH$_{(b)}$), 2.25 (ddd, $^{2}J = 13.0$ Hz, $^{3}J = 10.7$ Hz, $^{3}J = 4.0$ Hz, 1H, C6-Ha), 1.68 (dt, $^{2}J = 14.0$ Hz, $^{3}J = 3.9$ Hz, 1H, C6-Hb), 1.37-1.14 (m, 4H, NHCH$_{2}$CH$_{2}$CH$_{2}$), 0.89 (t, $^{3}J = 7.0$ Hz, 3H, CH$_{2}$CH$_{3}$); $^{13}$C NMR (75.5 MHz, CDCl$_{3}$): δ 192.5 (C5), 161.5 (C13), 156.2 (NCON), 152.4 (C14a), 144.9 (C2), 138.1 (C8a), 136.2 (C12a), 132.9 (C10), 130.0 (C12), 129.3 (C9), 129.0 (C11), 125.3 (C4), 121.1(C4a), 120.5 (C1), 90.9 (C5a), 43.7 (C7), 40.6 (NHCH$_{2}$), 35.0 (C6), 32.6 (NHCH$_{2}$CH$_{2}$), 19.9 (NHCH$_{2}$CH$_{2}$), 13.9 (NHCH$_{2}$CH$_{2}$CH$_{2}$CH$_{3}$); IR (KBr): $\nu_{\text{max}} = 3416$ (m), 1741 (s) (C=O), 1655 (s) (C=O), 1599 (m), 1458 (w), 1367 (w), 1019 (m) cm$^{-1}$; LRMS (ES$^+$):
m/z (%) 449.99 (100) [M+Na]+; HRMS (ES+): m/z calcd for C_{22}H_{22}N_{3}O_{4}NaCl [M+Na]+: 450.1197; found 450.1178.

8-(Cyclopropanemethyl)carboxamide-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2m): White powder (9 mg, 0.02 mmol, 36%), mp 236-237 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.43 (d, \(J = 8.3\) Hz, 1H, C1-H), 7.80-7.71 (m, 2H, C2-H, C4-H), 7.64-7.58 (m, 2H, C10-H, C12-H), 7.54-7.48 (m, 1H, C11-H), 7.32-7.26 (m, 2H, C3-H, C9-H), 4.51-4.42 (m, 1H, C7-H\(_a\)), 4.21-4.17 (m, 1H, NH), 3.44-3.33 (m, 1H, C7-H\(_b\)), 3.01-2.92 (m, 2H, NHC\(_3\)H), 2.40-2.30 (m, 1H, C6-H\(_a\)), 1.78-1.70 (m, 1H, C6-H\(_b\)), 0.89-0.79 (m, 1H, NHCH\(_2\)C\(_H\)), 0.42-0.36 (m, 2H, cyclopropane CH\(_2\)), 0.10-0.04 (m, 2H, cyclopropane CH\(_2\)); \(^{13}\)C NMR (300 MHz, de-DMSO): 199.1 (C5), 166.1 (C13), 155.7 (NCONH), 151.5 (C14a), 138.5 (C8a), 137.8 (C12a), 137.5 (C2), 132.1 (C10), 129.4 (C11 & C9), 128.1 (C12), 124.7 (C3), 124.0 (C4), 121.3 (C4a), 119.5 (C1), 90.3 (C5a), 43.9 (C7), 43.6 (NHCH\(_2\)), 33.9 (C6), 11.5 (NCH\(_2\)CH), 3.0 (cyclopropane CH\(_2\)), 2.8 (cyclopropane CH\(_2\)); IR (KBr): \(\nu_{\text{max}} = 3366\) (s), 3240 (s), 1736 (s) (C=O), 1649 (s) (C=O), 1630 (s), 1601 (m), 1536 (m), 1464 (m), 1386 (m), 764 (w) cm\(^{-1}\); LRMS (ES+): m/z (%) 414.02 (100) [M+Na]+; HRMS (ES+): m/z calcd for C_{22}H_{21}N_{3}O_{4}Na [M+Na]+: 414.1430; found 414.1412.

8-(2-Methoxyethyl carboxamide)-3-pentyloxy-6,7-dihydro-5a-hydroxy-indolin[1,2-a] benzo[c]-8,14-diazocin-5,13-dione (2n): White crystals (8 mg, 33%), mp 139-140 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.31 (d, \(J = 9.0\) Hz, 1H, C1-H), 7.59-7.53 (m, 2H, C10-H, C12-H), 7.47-7.41 (m, 1H, C11-H), 7.29 (dd, \(J = 9.0\) Hz, \(J = 2.9\) Hz, 1H, C2-H), 7.27-7.23 (m, 1H, C9-H), 7.08 (d, \(J = 2.9\) Hz, 1H, C4-H), 4.45-4.33 (m, 2H, C7-H\(_a\), NH), 3.98 (t, \(J = 6.6\) Hz, 2H, OCH\(_2\)), 3.41-3.19 (m, 8H, C7-H\(_b\), NHCH\(_2\)OCH\(_3\)), 2.26 (ddd, \(J = 13.0\) Hz, \(J = 10.5\) Hz, \(J = 4.0\) Hz, 1H, C6-H\(_a\)), 1.82 (quintet, \(J = 7.3\) Hz, \(J = 6.6\) Hz, 2H, OCH\(_2\)), 2.26 (ddd, \(J = 13.0\) Hz, \(J = 10.5\) Hz, \(J = 4.0\) Hz, 1H, C6-H\(_a\)), 1.82 (quintet, \(J = 7.3\) Hz,
2H, OCH₂CH₂), 1.70 (dt, 2J = 14.0 Hz, 3J = 4.0 Hz, 1H, C6-H₆), 1.53-1.34 (m, 4H, OCH₂CH₂CH₂CH₂CH₃), 0.96 (t, 3J = 6.9 Hz, 3H, OCH₂CH₂CH₂CH₂CH₃); ¹³C NMR (75.5 MHz, CDCl₃): δ 198.9 (C5), 166.7 (NCONH), 164.5 (C13), 156.4 (C3), 145.7 (C14a), 138.3 (C8a), 137.6 (C12a), 132.6 (C10), 130.1 (C12), 129.3 (C11), 129.2 (C9), 127.4 (C2), 122.3 (C4a), 121.6 (C1), 106.0 (C4), 90.8 (C5a), 71.8 (NCONHCH₂CH₂OCH₃), 68.9 (OCH₂), 58.9 (OCH₃), 44.0 (C7), 40.5 (NCONHCH₂CH₂OCH₃), 35.2 (C6), 29.0 (OCH₂CH₂CH₂CH₂CH₃), 28.3 (OCH₂CH₂CH₂CH₂CH₃), 22.7 (OCH₂CH₂CH₂CH₂CH₃), 14.2 (CH₂CH₃); IR (KBr): v_max = 3362 (s), 2936 (m), 1734 (s) (C=O), 1638 (s) (C=O), 1523 (w), 1489 (m), 1090 (w), 733 (m) cm⁻¹; LCMS (ES⁺): (purity 99%) m/z (%) 481.86 (100) [M+Na]⁺; HRMS (ES⁺): m/z calcd for C₂₅H₃₀N₃O₆ [M+H]⁺: 468.2135; found 468.2137.

8-(2-Morpholinoethyl)carboxamide-6,7-dihydro-5a-hydroxy-indolin[1,2-a]benzo[c]-8,14-diazocin-5,13-dione (2o): White powder (20 mg, 67%), mp 155-156 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.34 (d, 3J = 8.7 Hz, 1H, C1-H), 7.72-7.66 (m, 2H, C2-H, C4-H), 7.55 (ddd, 3J = 7.9 Hz, 3J = 7.9 Hz, 4J = 1.7 Hz, 1H, C10-H), 7.49 (dd, 3J = 7.9 Hz, 4J = 1.7 Hz, 1H, C11-H), 7.41 (ddd, 3J = 7.9 Hz, 3J = 7.9 Hz, 4J = 1.7 Hz, 1H, C12-H), 7.29-7.19 (m, 2H, C3-H, C9-H), 4.80 (t, 3J = 4.9 Hz, 1H, NH), 4.23 (dt, 2J = 14.0 Hz, 3J = 3.9 Hz, 1H, C7-Hₐ), 3.49-3.40 (m, 4H, morpholine 2x CH₂O), 3.33 (ddd, 2J = 13.0 Hz, 3J = 11.8 Hz, 3J = 3.9 Hz, 1H, C7-Hₐ), 3.13-2.97 (m, 2H, CONHCH₂), 2.35-2.22 (m, 6H, CONHCH₂CH₂N(CH₂CH₂)₂O), 2.14 (ddd, 2J = 14.0 Hz, 3J = 11.8 Hz, 3J = 4.0 Hz, 1H, C6-Hₐ), 1.66 (dt, 2J = 14.0 Hz, 3J = 4.0 Hz, 1H, C6-Hₐ); ¹³C NMR (75.5 MHz, CDCl₃): δ 199.6 (C5), 166.2 (C13), 156.2 (NCONH), 151.6 (C14a), 138.5 (C8a), 137.9 (C2), 137.8 (C12a), 132.4 (C10), 130.0 (C12), 129.2 (C11), 129.0 (C9), 125.2 (C3), 124.4 (C4), 121.7 (C4a), 120.3 (C1), 90.8 (C5a), 67.0 (CONHCH₂CH₂N(CH₂CH₂)₂O), 56.8 (CONHCH₂CH₂), 52.9 (CONHCH₂CH₂N(CH₂CH₂)₂O), 43.6 (C7), 36.7
(CONHCH_{2}CH_{2}), 35.1 (C6); IR (KBr): $\nu_{\text{max}} = 1735$ (s) (C=O), 1647 (s) (C=O), 1620 (m), 1524 (m), 1459 (m), 1300 (m), 1115 (m), 762 (m) cm$^{-1}$; LRMS (ES$^+$): $m/z$ (%) 473.03 (100) [M+Na]$^+$, 451.06 (75) [M+H]$^+$; HRMS (ES$^+$): $m/z$ calcd for C_{24}H_{26}N_{4}O_{5}Na [M+Na]$^+$: 473.1801; found 473.1779.

**Typical Procedure for the Synthesis of 3.**

**Alkoxide nucleophiles:** Reactions were conducted in parallel using the Radleys Greenhouse Parallel synthesiser. To a solution of the N-acyl cyclic urea 1 (0.06 mmol, 1.0 eq.) in anhydrous methanol or ethanol (2 mL) was added the sodium alkoxide (sodium methoxide or sodium ethoxide were added as powders (0.12 mmol, 2.0 eq.). The reaction mixture was stirred at room temperature for 16 h. The reaction mixtures were evaporated in parallel, re-dissolved in dichloromethane (2 x 4.0 mL) and washed with NaHCO$_3$(aq.) (2 x 2.0 mL). The mixtures were passed through an Isolute$^\text{TM}$ phase separator and the organic layer was then dried (Na$_2$SO$_4$ cartridge) and concentrated *in vacuo* to give a solid which was purified by recrystallisation from acetonitrile to afford the title compound.

**Amine nucleophiles:** N-acyl cyclic urea 1 (0.06 mmol, 1.0 eq.) in a glass microwave tube was added an excess of the relevant amine (n-butylamine, benzylamine, or 4-(2-aminoethyl)morpholine) (0.6 mmol, 10 eq.) forming a slurry. The reaction mixture was irradiated to 80 °C, (maximum 150 W), with air flowing through the reaction chamber, for 5 minutes. Upon cooling to room temperature the reaction mixture was added KHSO$_4$(aq.) (4.0 mL) and the organic material was extracted with dichloromethane (2 x 4.0 mL) using an Isolute$^\text{TM}$ phase separator. The organic layer was dried (Na$_2$SO$_4$ cartridge) and concentrated *in vacuo* to give a solid which was purified by recrystallisation from acetonitrile to afford the title compound.
**Methyl 1-(2-(methoxycarbonyl)phenyl)-2,3-dihydro-1H-pyrrolo[2,3-b]quinoline-4-carboxylate (3a)**: Yellow powder (17 mg, 77%), mp 149-150 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.18 (dd, $^3$J = 8.5 Hz, $^4$J = 1.0 Hz, 1H, C5-H), 7.88 (dd, $^3$J = 8.0 Hz, $^4$J = 1.5 Hz, 1H, C3′-H), 7.63-7.52 (m, 2H, C8-H, C5′-H), 7.49-7.42 (m, 1H, C7-H), 7.36-7.31 (m, 1H, C6′-H), 7.30-7.23 (m, 2H, C4′-H, C6-H), 4.20 (t, $^3$J = 8.0 Hz, 2H, C2-H2), 4.04 (s, 3H, PyCO$_2$CH$_3$), 3.55-3.47 (m, 5H, C3-H$_2$, ArCO$_2$CH$_3$); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 168.0 (ArCO$_2$CH$_3$), 166.8 (PyCO$_2$CH$_3$), 158.3 (C9a), 147.6 (C8a), 139.2 (C1′), 132.3 (C5′), 131.2 (C4), 130.7 (C3′), 128.9 (C7), 128.6 (C3a), 127.0 (C2′), 126.9 (C8), 124.9 (C5), 124.8 (C4′), 123.4 (C6), 122.9 (C6′), 120.9 (C4a), 52.3 (PyCO$_2$CH$_3$), 51.9 (ArCO$_2$CH$_3$), 50.3 (C2), 26.9 (C3); IR (KBr): $\nu_{max}$ = 2945 (m), 1725 (s) (C=O), 1717 (s) (C=O), 1617 (m), 1597 (m), 1483 (m), 1228 (w), 754 (w) cm$^{-1}$; LRMS (ES$^+$): m/z (%) 363.38 (100) [M+H]$^+$, 384.94 (65) [M+Na]$^+$; HRMS (ES$^+$): m/z calcd for C$_{21}$H$_{19}$N$_2$O$_4$ [M+H]$^+$: 363.1345; found 363.1340.

**Methyl 1-(4′-methoxy-2-(methoxycarbonyl)phenyl)-2,3-dihydro-1H-pyrrolo[2,3-b]quinoline-4-carboxylate (3b)**: Yellow powder (11 mg, 48%), mp 156-157 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.09 (dd, $^3$J = 8.2 Hz, $^4$J = 1.2 Hz, 1H, C5-H), 7.50 (dd, $^3$J = 8.2 Hz, $^4$J = 1.2 Hz, 1H, C8-H), 7.39-7.33 (m, 2H, C3′-H, C7-H), 7.23 (d, $^3$J = 8.8 Hz, 1H, C6′-H), 7.16 (ddd, $^3$J = 8.2 Hz, $^3$J = 8.2 Hz, $^4$J = 1.2 Hz, 1H, C6-H), 7.04 (dd, $^3$J = 8.8 Hz, 1H, C5′-H), 4.07 (t, $^3$J = 7.6 Hz, 2H, C2-H$_2$), 3.96 (s, 3H, PyCO$_2$CH$_3$), 3.80 (s, 3H, ArOCH$_3$), 3.45-3.39 (m, 5H, C3-H$_2$, ArCO$_2$CH$_3$); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 168.3 (ArCO$_2$Me), 167.5 (PyCO$_2$Me), 159.4 (C4′), 157.1 (C9a), 148.1 (C8a), 132.7 (C1′), 131.1 (C4), 128.9 (C7), 128.8 (C2′), 128.6 (C3a), 127.0 (C8), 126.3 (C5′), 125.0 (C5), 123.1 (C6), 120.8 (C4a), 118.9 (C3′), 115.4 (C6′), 55.9 (ArOCH$_3$), 52.3 (PyCO$_2$CH$_3$), 52.1 (ArCO$_2$CH$_3$), 51.1 (C2), 27.0 (C3); IR (KBr): 3422 (s), 2925 (m), 1719 (s), 1618 (s), 1500 (m), 1438 (m), 1220 (m), 768 (w) cm$^{-1}$; LRMS (ES$^+$): m/z (%)
415.07 (100) [M+Na]+, 393.09 (60) [M+H]+; HRMS (ES+): m/z calcd for C_{22}H_{21}N_2O_5 [M+H]+: 393.1450; found 393.1465.

6-Chloro methyl-1-(2-(methoxycarbonyl)phenyl)-2,3-dihydro-1H-pyrrolo[2,3-b]quinoline-4-carboxylate (3c): Yellow powder (16 mg, 74%); mp 164-165 °C; 1H NMR (300 MHz, CDCl3): δ 8.26 (d, 4J = 2.4 Hz, 1H, C5-H), 7.88 (dd, 3J = 7.7 Hz, 4J = 1.6 Hz, 1H, C3'-H), 7.60-7.51 (m, 2H, C8-H, C5'-H), 7.39 (dd, 3J = 8.9 Hz, 4J = 2.5 Hz, 1H, C7-H), 7.35-7.27 (m, 2H, C4'-H, C6'-H), 4.21 (t, 3J = 7.7 Hz, 2H, C2-H2), 4.05 (s, 3H, PyCO_2C,H_3), 3.56-3.51 (m, 5H, C3-H2, ArCO_2C,H_3); 13C NMR (75.5 MHz, d_6-DMSO): δ 167.1 (ArCO_2C,H_3), 165.6 (PyCO_2C,H_3), 158.5 (C9a), 145.7 (C8a), 138.6 (C1'), 132.6 (C5'), 130.9 (C4), 131.0 (C3'), 129.4 (C3a), 129.2 (C7), 127.8 (C8), 127.3 (C2'), 126.7 (C6), 125.1 (C5), 123.9 (C4'), 123.6 (C6'), 121.1 (C4a), 52.8 (PyCO_2C,H_3), 51.6 (ArCO_2C,H_3), 49.9 (C2), 26.5 (C3); IR (KBr): ν max = 2926 (m), 1715 (s) (C=O), 1602 (m), 1485 (m), 1265 (s), 743 (m) cm\(^{-1}\); LCMS (ES+): m/z (%) 396.75 (100) [M]+, 398.79 (70) [M+H]+; HRMS (ES+): m/z calcd for C_{21}H_{17}N_2O_4Cl [M+H]+: 397.0752; found 397.0724; An analytical sample of 171(1,2,5,1) was prepared by recrystallisation from DCM; Anal. calc’d for C_{21}H_{17}ClN_2O_4: C, 63.56; H, 4.32; N, 7.06; found: C, 63.64; H, 4.33; N, 7.23.

6-Chloro ethyl-1-(2-(ethoxycarbonyl)phenyl)-2,3-dihydro-1H-pyrrolo[2,3-b]quinoline-4-carboxylate (3d): Yellow solid (25 mg, 7%); mp 165-166 °C; 1H NMR (300 MHz, CDCl3): δ 8.27 (d, 4J = 2.3 Hz, 1H, C5-H), 7.91 (dd, 3J = 7.7 Hz, 4J = 1.6 Hz, 1H, C3'-H), 7.56 (ddd, 3J = 7.7 Hz, 4J = 1.6 Hz, 1H, C5'-H), 7.38 (dd, 3J = 8.9 Hz, 4J = 2.3 Hz, 1H, C7-H), 7.33 (dd, 3J = 7.7 Hz, 4J = 1.6 Hz, 1H, C4'-H), 7.28 (dd, 3J = 7.7 Hz, 4J = 1.6 Hz, 1H, C6'-H), 4.51 (q, 3J = 7.2 Hz, 2H, PyCO_2C,H_2CH_3), 4.20 (t, 3J = 7.6 Hz, 2H, C2-H2), 3.93 (q, 3J = 7.2 Hz, 2H,
ArCO₂CH₂CH₃), 3.53 (t, J = 7.6 Hz, 2H, C3-H₂), 1.48 (t, J = 7.2 Hz, 3H, PyCO₂CH₂CH₃), 1.03 (t, J = 7.2 Hz, 3H, ArCO₂CH₂CH₃); ¹³C NMR (300 MHz, CDCl₃): δ 167.4 (ArCO₂R), 165.9 (PyCO₂R), 159.1 (C9a), 146.5 (C8a), 139.2 (C1'), 132.6 (C5'), 131.1 (C3'), 130.4 (C4), 130.0 (C6), 129.4 (C7), 128.9 (C3a), 128.2 (C8), 127.7 (C2'), 125.5 (C6'), 124.4 (C5), 123.9 (C4'), 121.8 (C4a), 61.8 (PyCO₂C), 61.0 (ArCO₂CH₂CH₃), 50.7 (C2), 27.2 (C3), 14.5 (PyCO₂CH₂C), 14.0 (ArCO₂CH₂CH₃);

IR (KBr):  vmax = 2986 (m) (CH₂), 1725 (s) (C=O), 1675 (m) (C=O), 1219 (m), 746 (m) (Ar-H) cm⁻¹; LRMS (ES⁺): m/z (%) 424.90 (100) [M+H]⁺, 446.88 (30) [M+Na]⁺; HRMS (ES⁺): m/z calcd for C₂₃H₂₂N₂O₄Cl [M+H]⁺: 425.1268; found 425.1240.

N-butyl 1-[(2-butylcarbamoyl)phenyl]-2,3-dihydro-1H-pyrrolo[2,3-b]quinoline-4-carboxamide (3e): White powder (16 mg, 61%), mp 130-131 °C; ¹H NMR (300 MHz, CDCl₃): δ 7.73 (dd, J = 8.2 Hz, 4J = 1.1 Hz, 1H, C5-H), 7.67 (dd, J = 8.1 Hz, 4J = 1.8 Hz, 1H, C3'-H), 7.58-7.53 (m, 1H, C6'-H), 7.52-7.48 (m, 1H, C5'-H), 7.47-7.41 (m, 1H, C7-H), 7.39-7.33 (m, 2H, C8-H, C6-H), 7.27-7.22 (m, 1H, C4'-H), 7.04 (t, J = 5.2 Hz, 1H, NH₅), 6.01 (t, J = 5.5 Hz, 1H, NH₆), 4.09 (t, J = 7.7 Hz, 2H, C2'-H₂), 3.57 (q, J = 5.5 Hz, 2H, C(a1)-H₂), 3.32 (t, J = 7.7 Hz, 2H, C3'-H₂), 3.13 (q, J = 5.2 Hz, 2H, C(b1)-H₂), 1.73-1.62 (m, 2H, C(a2)-H₂), 1.54-1.41 (m, 2H, C(a3)-H₂), 1.22-1.07 (m, 4H, C(b2)-H₂, C(b3)-H₂), 1.01 (t, J = 7.3 Hz, 3H, C(a4)-H₃), 0.69 (t, J = 7.1 Hz, 3H, C(b4)-H₃); ¹³C NMR (75.5 MHz, CDCl₃): δ 168.3 (CONH₅), 166.8 (CONH₆), 160.3 (C9a), 147.4 (C8a), 138.3 (C4), 137.7 (C1'), 131.4 (C5'), 129.6 (C7), 129.3 (C3'), 127.3 (C6'), 126.7 (C6), 126.6 (C8), 124.6 (C5), 123.8 (C3a), 123.4 (C4'), 120.8 (C2'), 118.2 (C4a), 52.5 (C2), 39.7 (2 x height: C(a1), C(b1)), 31.9 (C(a2)), 31.3 (C(b2)), 25.2 (C3), 20.3 (C(b3)), 20.1 (C(a3)), 13.9 (C(a4)), 13.7 (C(b4)); IR (KBr):  vmax = 1647 (br s) (C=O), 1485 (m) 1265 (s), 741 (s) cm⁻¹; LRMS (ES⁺): m/z (%) 467.09 (100) [M+Na]⁺, 445.14

N-benzyl 1-(2-(benzylcarbamoyl)phenyl)-2,3-dihydro-1H-pyrrolo[2,3-b]quinoline-4-carboxamide (3f): White powder (19 mg, 61%), mp 190 (dec.) °C; 1H NMR (300 MHz, d6-DMSO): δ 9.24 (t, 3J = 6.0 Hz, 3J = 6.0 Hz, 1H, NHa), 8.81 (t, 3J = 6.0 Hz, 3J = 6.0 Hz, 1H, C3'-H), 7.56-7.51 (m, 2H, C5'-H, C8-H), 7.46-7.43 (m, 2H, C7-H, C4'-H), 7.42 (m, 4H, benzyl C-H), 7.38-7.33 (m, 1H, C6'-H), 7.33 (m, 1H, Cp-H), 7.24-7.19 (m, 1H, C6-H), 7.14-7.10 (m, 5H, benzyl C-H), 4.57 (d, 3J = 6.0 Hz, 2H, benzyl CH2a), 4.21 (d, 3J = 6.0 Hz, 2H, benzyl CH2b), 4.03 (t, 3J = 7.7 Hz, 2H, C2-H2), 3.14 (t, 3J = 7.7 Hz, 2H, C3-H2); 13C NMR (75.5 MHz, d6-DMSO): δ 167.8 (ArC-ONH), 165.8 (PyC-ONH), 159.2 (C9a), 147.2 (C8a), 139.3 (Ci x 2), 138.6 (C1'), 137.3 (C4), 133.8 (C2'), 130.5 (C5'), 128.9 (C3'), 128.5 (C7 & benzyl CH), 128.4 (benzyl CH x 2), 128.1 (benzyl CH x 2), 127.4 (benzyl CH x 2), 127.0 (benzyl CH x 2), 126.5 (Cp), 126.1 (C4'), 125.5 (C5 & C8), 124.5 (C6'), 123.5 (C3a), 122.3 (C6), 120.9 (C4a), 50.8 (C2), 42.5 (benzyl CH2), 42.4 (benzyl CH2), 24.5 (C3); IR (KBr): v_max = 2928 (m), 1648 (s) (C=O), 1598 (m), 1526 (m), 1480 (m), 1450 (m), 1327 (w), 759 (w) cm⁻¹; LRMS (ES+): m/z (%) 513.04 (100) [M+H]+, 535.01 (15) [M+Na]+; HRMS (ES+): m/z calcd for C33H29N4O2 [M+H]+: 513.2291; found 513.2293.

N-butyl 1-(4'-methoxy-2-(butylcarbamoyl)phenyl)-2,3-dihydro-1H-pyrrolo[2,3-b]quinoline-4-carboxamide (3g): Yellow powder (10 mg, 40%), mp 111-112 °C; 1H NMR (300 MHz, d6-DMSO): δ 7.73 (dd, 3J = 8.2 Hz, 4J = 1.2 Hz, 1H, C5-H), 7.57 (dd, 3J = 8.2 Hz, 4J = 1.2 Hz, 1H, C8-H), 7.45 (ddd, 3J = 8.2 Hz, 3J = 8.2 Hz, 4J = 1.2 Hz, 1H, C7-H), 7.36 (t, 3J = 5.9 Hz, 1H, NHb), 7.26-7.21 (m, 3H, C3'-H, C6'-H, C6-H), 7.03
(dd, $^3J = 8.7$ Hz, $^4J = 3.0$ Hz, 1H, C5'-H), 5.97 (t, $^3J = 5.8$ Hz, 1H, NH$_a$), 4.02 (t, $^3J = 7.9$ Hz, 2H, C2-H$_2$), 3.86 (s, 3H, ArOCH$_3$), 3.58 (q, $^3J = 6.0$ Hz, 2H, C(a1)-H$_2$), 3.31 (t, $^3J = 7.9$ Hz, 2H, C3-H$_2$), 3.14 (q, $^3J = 5.7$ Hz, 2H, C(b1)-H$_2$), 1.73-1.62 (m, 2H, C(a2)-H$_2$R), 1.54-1.41 (m, 2H, C(a3)-H$_2$), 1.14-1.05 (m, 4H, C(b2)-H$_2$, C(b3)-H$_2$), 1.01 (t, $^3J = 7.2$ Hz, 3H, C(a4)-H$_3$), 0.65 (t, $^3J = 7.2$ Hz, 3H, C(b4)-H$_3$); $^{13}$C NMR (75.5 MHz, $d_6$-DMSO): δ 167.0 (C ONH$_b$), 165.6 (C ONH$_a$), 159.8 (C4'), 157.0 (C9a), 147.3 (C8a), 136.3 (C1'), 132.1 (C2'), 131.4 (C4), 128.3 (C7), 128.0 (C8), 125.9 (C5'), 124.5 (C5), 123.1 (C3a), 122.0 (C6), 120.8 (C4a), 115.9 (C3'), 113.8 (C6'), 55.5 (ArOCH$_3$), 51.5 (C2), 38.7 (C(a1)), 38.4 (C(b1)), 31.2 (C(a2)), 30.9 (C(b2)), 24.4 (C3), 19.7 (C(b3)), 19.6 (C(a3)), 13.7 (C(a4)), 13.6 (C(b4)); IR (KBr): 3422 (s), 2925 (m), 1719 (s), 1618 (s), 1500 (m), 1438 (m), 1220 (m), 768 (w) cm$^{-1}$; LRMS (ES$^+$): m/z (%) 497.11 (100) [M+Na]$^+$; HRMS (ES$^+$): m/z calcd for C$_{28}$H$_{34}$N$_4$O$_3$Na [M+Na]$^+$: 497.2512; found 497.2517.

$N$-(2-morpholinoethyl)-1-(2-(2-morpholinoethylcarbamoyl)phenyl)-6-methyl-2,3-dihydro-1H-pyrrolo[2,3-b]quinoline-4-carboxamide (3h): Yellow solid (15 mg, 44%), mp 213-214 oC; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.74 (dd, $^3J = 7.6$ Hz, $^4J = 1.5$ Hz, 1H, C3'-H), 7.56-7.49 (m, 3H, C5-H, C5'-H, C8-H), 7.42-7.35 (m, 2H, C4'-H, C6'-H), 7.30 (ddd, $^3J = 8.7$ Hz, $^3J = 8.7$ Hz, $^4J = 1.9$ Hz, 1H, C7-H), 7.20 (t, $^3J = 5.0$ Hz, 1H, ArCONH), 6.61 (t, $^3J = 5.1$ Hz, 1H, PyCONH), 4.06 (t, $^3J = 7.8$ Hz, 2H, C2-H$_2$), 3.34-3.69 (m, 4H, 2xCH$_2$(d)), 3.67 (q, $^3J = 6.0$ Hz, 2H, NHCH$_2$(a)), 3.48-3.43 (m, 4H, 2xCH$_2$(h)), 3.33-3.26 (m, 4H, C3-H$_2$, NHCH$_2$(e)), 2.65 (t, $^3J = 6.0$ Hz, 2H, CH$_2$(b)), 2.57-2.51 (m, 4H, 2xCH$_2$(c)), 2.43 (s, 3H, ArCH$_3$), 2.29-2.22 (m, 6H, CH$_2$(f), 2xCH$_2$(g)); $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 168.4 (ArCO), 166.6 (PyCO), 159.7 (C9a), 146.0 (C8a), 138.8 (C1'), 137.4 (C4), 133.9 (C2'), 133.1 (C6), 131.5 (C5'), 131.0 (C7), 129.9 (C3'), 126.7 (C8 & C6'), 125.8 (C4'), 123.8 (C5), 123.6 (C3a), 120.9 (C4a), 67.0 (2xCH$_2$(d)),
66.9 (2xCH₂(h)), 57.2 (CH₂(b)), 57.1 (CH₂(f)), 53.5 (2xCH₂(c)), 53.4 (2xCH₂(g)), 52.2
(C2), 36.2 (CH₂(e)), 36.0 (CH₂(a)), 25.4 (C3), 21.6 (ArCH₃); IR (KBr): vₘₐₓ = 3339 (s),
3246 (s), 3073 (m), 2950 (m), 2858 (m), 2803 (m), 1671 (s) (C=O), 1641 (s) (C=O),
1599 (m), 1559 (w), 1475 (m), 1439 (m), 1327 (m), 1114 (m) cm⁻¹; LRMS (ES⁺): m/z
(%) 595.07 (100) [M+Na]⁺, 573.12 (10) [M+H]⁺; HRMS (ES⁺): m/z calcd for C₃₂H₄₁N₆O₄
[M+H]⁺: 573.3189; found 573.3187.

Ethyl 2-(7-chloro-4-hydroxy-5-oxo-2,3-dihydrobenzo[f]pyrrole[2,3-b]azepin-1(5H)-
yl)benzoate (4): Yellow solid (142 mg, 40%), mp 144-145 °C; ¹H NMR (300 MHz,
CDCl₃): δ 8.55 (br s, 1H, OH), 8.42 (d, 4J = 2.6 Hz, 1H, C₆-H), 7.90 (dd, 3J = 7.7 Hz,
4J = 1.5 Hz, 1H, C⁵'-H), 7.58 (ddd, 3J = 7.7 Hz, 3J = 7.7 Hz, 4J = 1.5 Hz, 1H, C⁵-H),
7.41 (dd, 3J = 8.9 Hz, 4J = 2.6 Hz, 1H, C⁸-H), 7.37 (dd, 3J = 7.7 Hz, 4J = 1.5 Hz, 1H,
C⁴'-H), 7.32 (dd, 3J = 7.7 Hz, 4J = 1.5 Hz, 1H, C⁶'-H), 7.28 (d, 3J = 8.9 Hz, 1H, C₉-H),
4.19 (t, 3J = 7.5 Hz, 2H, C₂-H₂), 3.96 (q, 3J = 7.2 Hz, 2H, CH₂CH₃), 3.36 (t, 3J = 7.5
Hz, 2H, C₃-H₂), 1.06 (t, 3J = 7.2 Hz, CH₂CH₃); ¹³C NMR (300 MHz, CDCl₃): δ 178.3
(C5), 167.0 (CO₂R), 157.8 (C10a), 153.1 (C4), 148.6 (C9a), 139.1 (C1’), 134.8 (C8),
134.7 (C9), 132.5 (C5’), 130.5 (C₃’), 129.6 (C7 & C2’), 129.1 (C6), 126.5 (C5a), 126.5
(C4’), 125.4 (C6’), 119.6 (C3a), 61.1 (CO₂CH₂CH₃), 49.8 (C2), 25.3 (C3), 14.1
(CO₂CH₂CH₃); IR (KBr): vₘₐₓ = 3449 (m) (OH), 2977 (m) (CH₂), 1717 (s) (C=O), 1675
(m) (C=O), 1612 (m), 1560 (m), 1459 (s), 1250 (m), 723 (m) (Ar-H) cm⁻¹; LCMS (ES⁺):
m/z (%) 419.02 (100) [M+Na]⁺; HRMS (ES⁺): m/z calcd for C₂₁H₁₇ClN₂O₄NaCl [M+H]⁺:
419.0775; found 419.0781; An analytical sample was prepared by recrystallisation
from toluene; Anal. calcd for C₂₁H₁₇ClN₂O₄: C, 63.56; H, 4.32; N, 7.06; found: C, 63.28;
H, 4.00; N, 6.83.

Associated Content
The Supporting Information is available free of charge

X-ray crystal structures of 2a, 2i (CIF)

Copies of \(^1\)H and \(^{13}\)C NMR spectra (PDF)

Notes

The authors declare no competing financial interest.

Acknowledgements

The authors gratefully acknowledge the Royal Society (N JW held a URF at the time this work was done), the BBSRC for PhD funding through the Doctoral Training Scheme (AMJ), the University of St Andrews and the EPSRC National Mass Spectrometry Service Centre, Swansea. Dr Ryan Mewis is thanked for helpful structural assignment discussions.

References


15. See supporting information for more details.

16. CCDC-1483760 (2a) and 1483761 (2i) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

18. see ESI associated with reference 14 or CCDC-804716 for further structural data associated with 1e.


