A Core Switching Strategy to Pyrrolo[2,3-*b*]quinolines and Diazocino[1,2-*a*]indolinones

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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.[1] In particular, rearrangements that give difficult to access ring sizes and ring fusions are much sought after.[2] 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.[3] 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)[4] and PGP-4008 (as a selective P-glycoprotein (P-gp) mediated drug release (MDR) modulator).[5] The diazocino and fused diazocino scaffold can be found in natural products such as the sperimidine derived alkaloids,[6] peptidomimetic scaffolds,[7] in SM-406/AT-406 (Figure 1A) an inhibitor of proteins involved in apoptosis[8] and small-molecule mimetics of second mitochondria-derived activator of caspases (Smac).[9] The α-hydroxyindolinone unit is present in the natural products matemone[10] and melochicorine.[11] 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*.

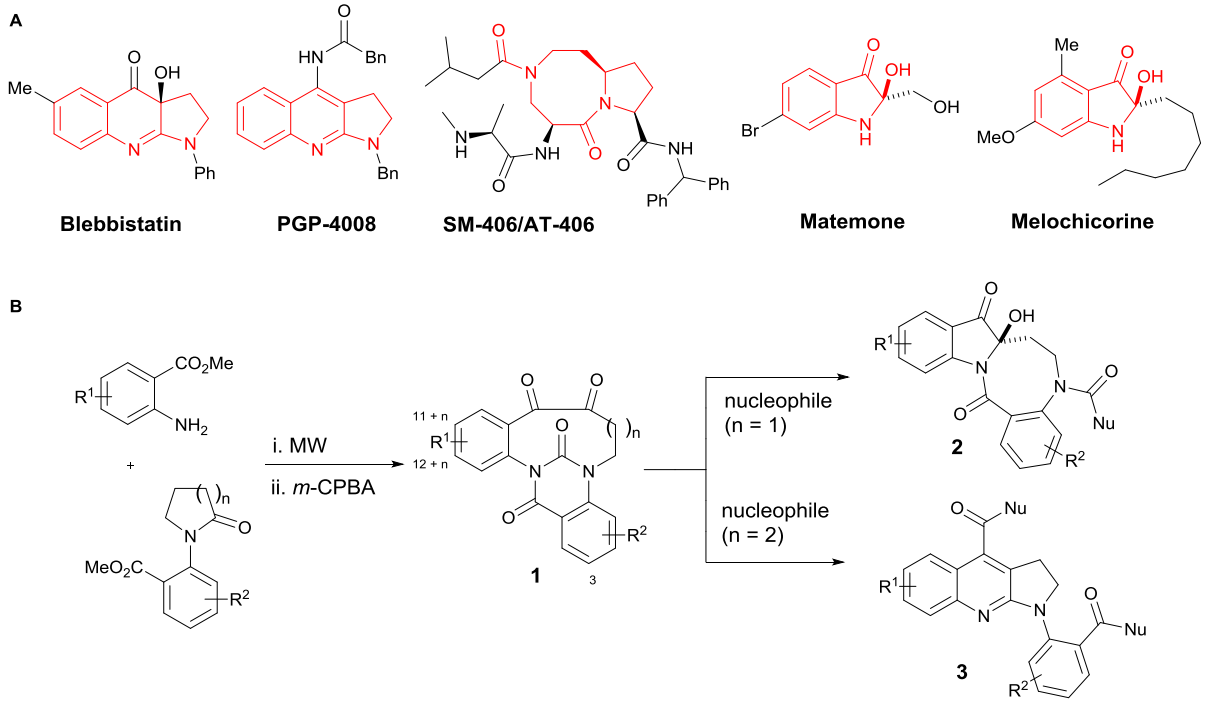
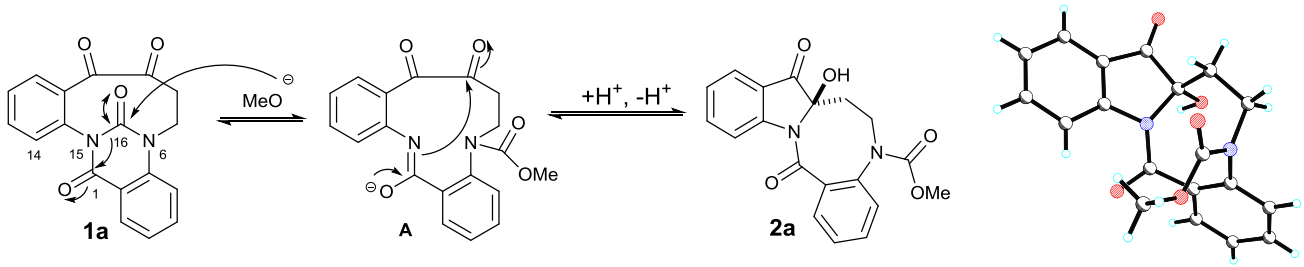


Figure 1A Representative bioactive small molecules containing motifs present in **2** and **3**. **1B** The rearrangement of **1** to diazocino[1,2-*a*]indolinone **2** and pyrrolo[2,3-*b*]quinoline **3**.

Our recent studies with compounds related to type **1**[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[13] followed by *m*-CPBA mediated Grob fragmentation.[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**,[14] it was found that **1a** in d_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).[15,16]



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 ^{o}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).[14] The key dihedral angle for **1a** C(14a)-N(15)-C(16)-O(16) is +25^{o}. 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[17] 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).[15] A screen of nucleophiles that could potentially replicate this transformation was also carried out (Table **S1**).[15] 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**).[15]

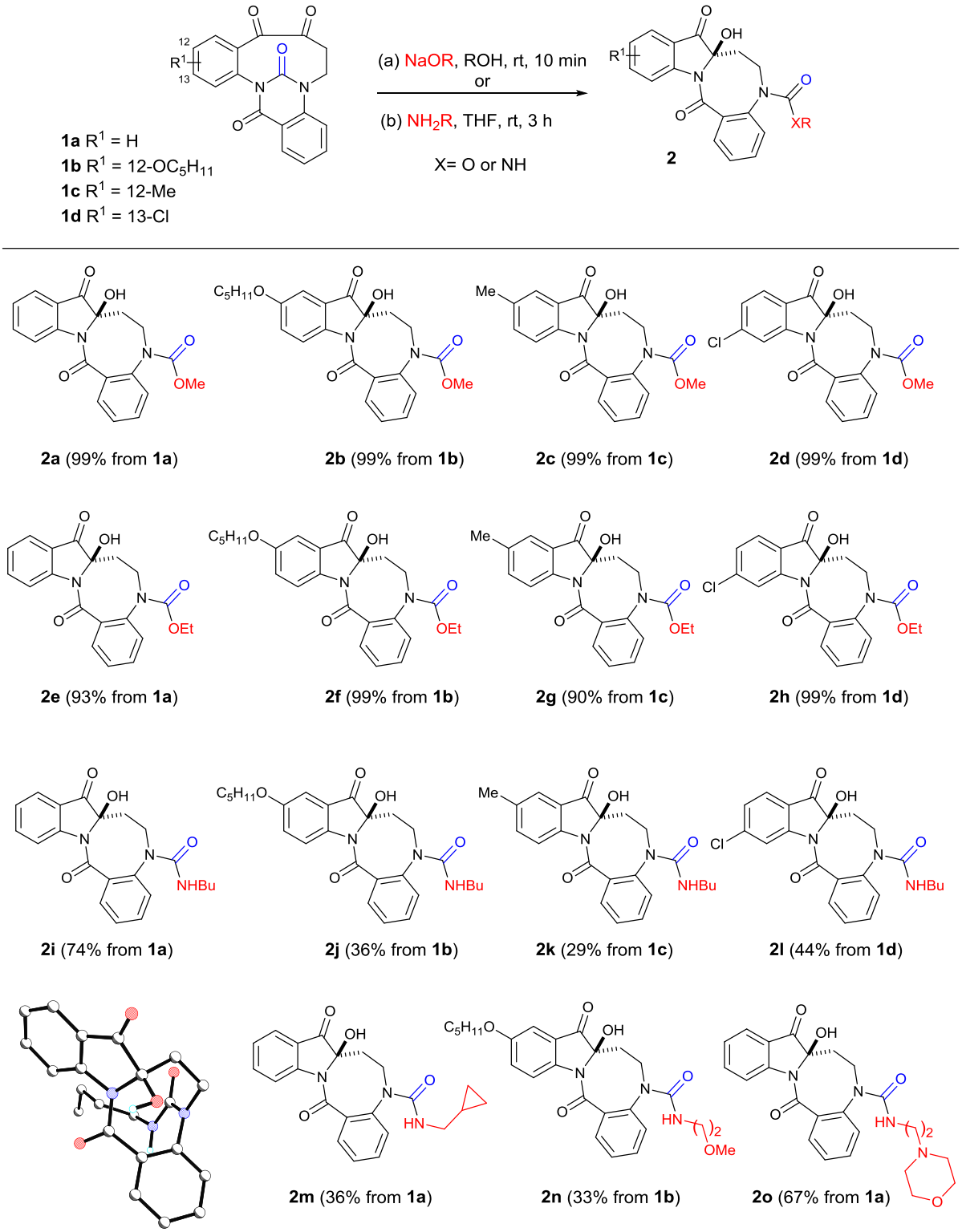


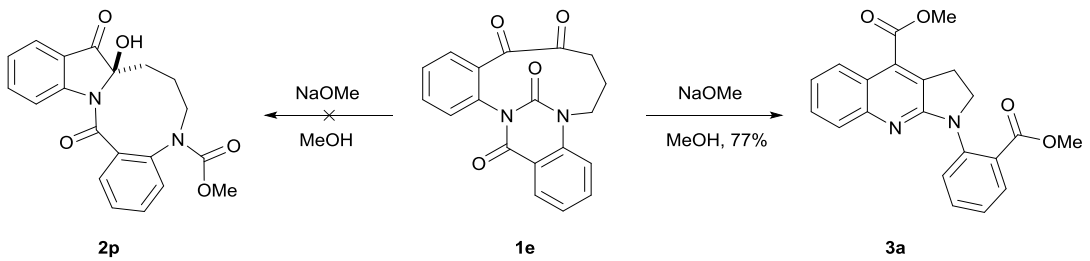
Table 1. Examples of *O* and *N*-centred nucleophile-induced rearrangement of the nine-membered ring system to (±)-**2** and a representation of the small molecule X-ray crystallographic analysis of **2i**. [a]Reaction conditions: **1** (0.06 mmol), NaOR (0.13

mmol), ROH (2 mL), 25 ^{o}C, 10 min. [b]Reaction conditions: **1** (0.06 mmol), RNH_2 (0.06 mmol), THF (3 mL), 25 ^{o}C, 3h. [c]All isolated yields.

It was observed that the alkoxide-induced rearrangement was general on a selection of nine-membered substrates (**1a**-**1d**).[14] Almost all alkoxide-induced rearrangments 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 ^{1}H NMR analysis of the crude reaction mixture.[15] 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).[15,16]

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**[14] 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**.

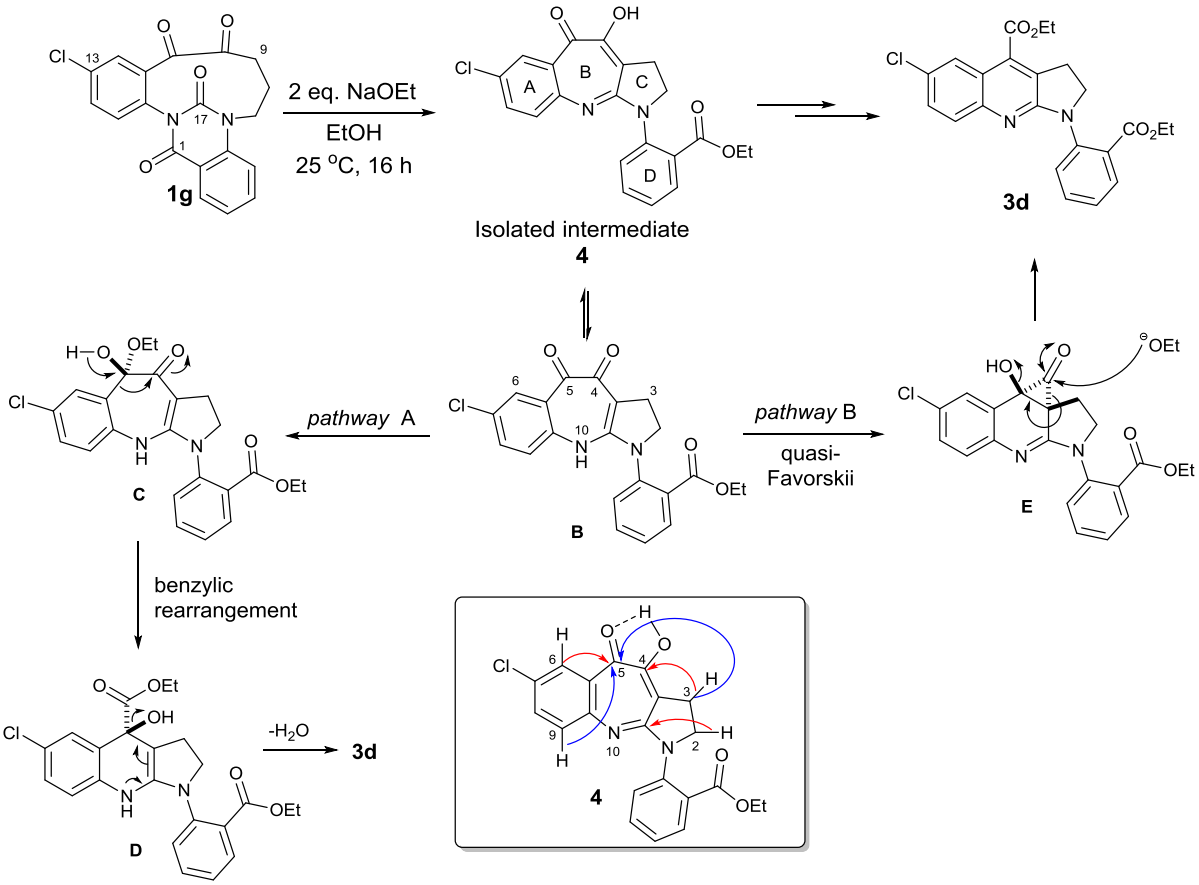
It is proposed that enolisation of the α-diketone in **1e** with sodium methoxide acting as a base would lead to the formation of products containing a pyrrolidine ring system in **3** from attack of the C9 enolate at the C(17) carbonyl group (see Scheme 3 for mechanistic discussion in the context of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

The small molecule X-ray crystallographic analysis of **1e** also provided interesting information.[14] The key dihedral angle (C(15a)-N(16)-C(17)-O(17)) was closer to planarity in the ten-membered **1e** at +14^{o} [18] (*c.f.* +25^{o} 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).[15] The tabulated ^{1}H and ^{13}C NMR assignments relating to **4** are shown in Table **S4**.[15]

Key points in the structural determination of **4** included the signals corresponding to the C2-$\underline{H}_2$ and C3-$\underline{H}_2$ 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.* O$\underline{H}$ or N$\underline{H}$ 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.[19] 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 (δ 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-Favorksii rearrangement[21] proceeding *via* cyclisation of the N(10) enamine onto the C(5) carbonyl group will form a strained

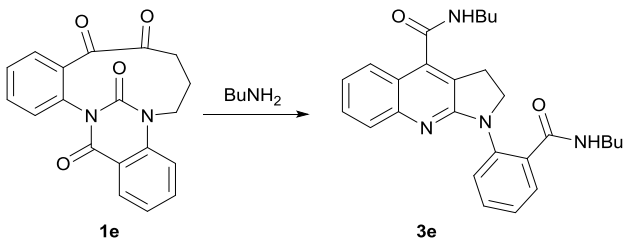
cyclopropanone (intermediate **E**). The cyclopropanone **E** will be labile to attack by alkoxide and in doing so the ring strain will be relieved. Elimination of hydroxide from **E** will generate an aromatic quinoline ring (*c.f.* Camps quinolinol synthesis[22]). In favour of pathway B is recent work by Karimi[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.[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 ^{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**).[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%.



1e 3e

Entry	Nucleophile (eq.)	Solvent	Temperature (°C)	Time (h)	% Conversion
1	2	DCM	25	48	<10
2	10	DCM	25	168	31 (20[a])
3	2	THF	25	48	<10
4	10	THF	66	48	54 (36[a])
5	10	DCE	84	48	80 (48[a])
6	10	No solvent	80 (100 W)	10 min	50
7	10	No solvent	80 (200 W)	10 min	Degradation
8	10	No solvent	80 (150 W)	10 min	95 (58[a])
9	10	No solvent	80 (150 W)	5 min	95 (58[a])

Table 2. Optimisation Studies on the Synthesis of **3e** from **1e**.[a]Indicates 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.

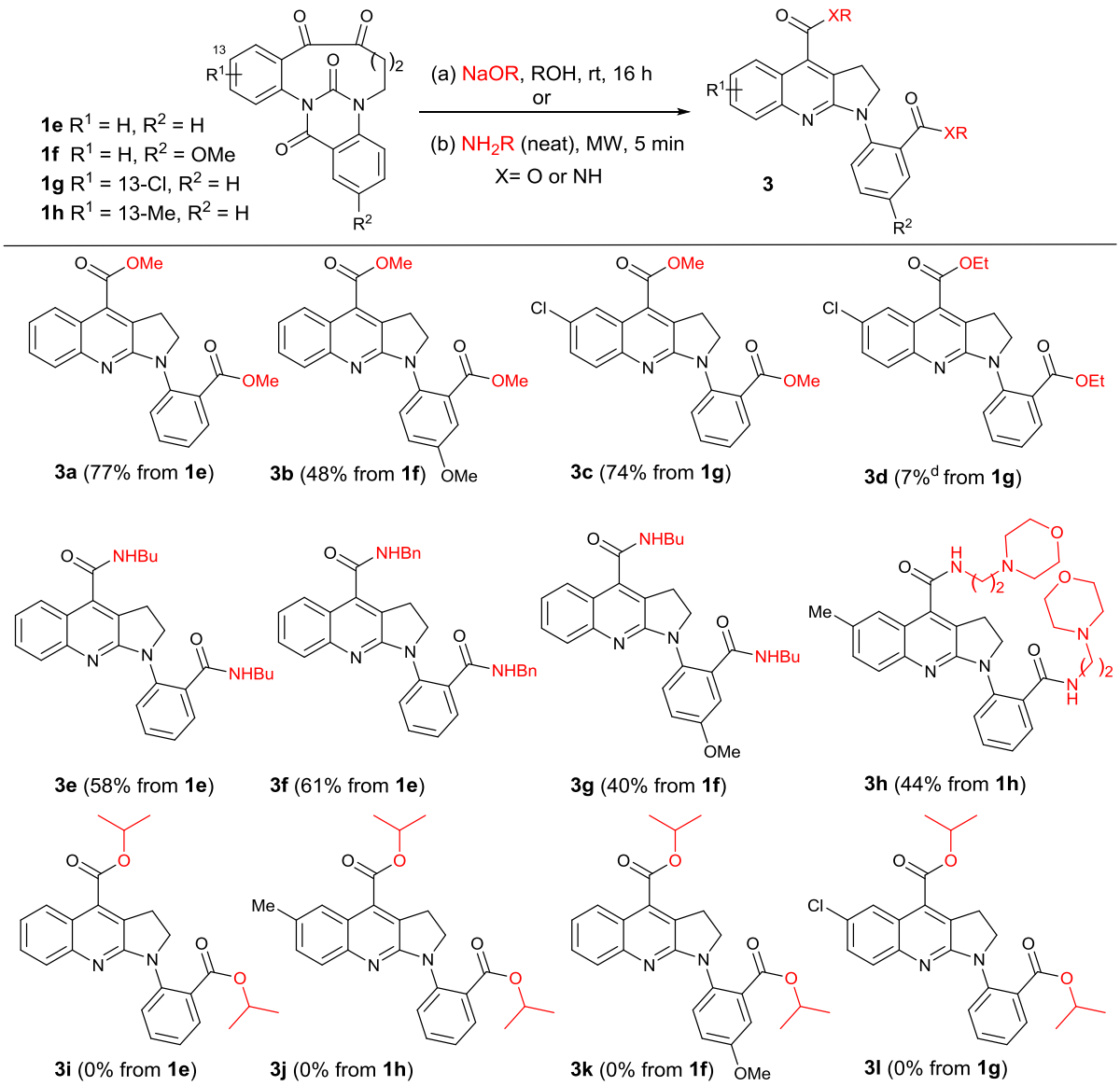


Table 3. Examples of *O* and *N*-centred nucleophile-induced rearrangement of the ten-membered ring system. [a]Reaction conditions: **1** (0.06 mmol), NaOR (0.12 mmol), ROH (2 mL), 25 ^{o}C, 16 h. [b]Reaction conditions: **1** (0.06 mmol), RNH_2 (0.6 mmol), mw 80 ^{o}C (150 W), 5 min. [c] All isolated yields. [d]Concomitant 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 *iso*propoxide) 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 tri*iso*propylamine 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 ^{o}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^{TM} 4.0.Global. Separations were performed using a Waters Xterra^{TM} RP_{18} (5µm, 3.0 x 50 mm) HPLC column. Nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (^{1}H, 300.1 MHz; ^{13}C, 75.5 MHz), Bruker Avance 400 (^{1}H, 400 MHz; ^{13}C, 100.1 MHz) or a Bruker Avance 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) spectrometer and in the deuterated solvent stated. ^{13}C 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 diethylazodicarboxylate (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 ($MgSO_4$), 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. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, ^4J = 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, NH_2), 3.89 (t, ^3J = 6.5 Hz, 2H, OCH_2) 3.87 (s, 3H, CO_2CH_3), 1.82-1.70 (m, 2H, OCH_2CH_2), 1.49-1.32 (m, 4H, $CH_2CH_2CH_3$), 0.93 (t, ^3J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.7 (CO_2Me), 150.4 (C5), 145.5 (C2), 124.2 (C4), 118.6 (C3), 114.7 (C6), 111.1 (C1), 69.2 (OCH_2), 52.0 (CO_2CH_3), 29.5 (OCH_2CH_2), 28.6 ($CH_2CH_2CH_3$), 22.9 ($CH_2CH_2CH_3$), 14.4 (CH_3); IR (KBr): ν_{max} = 3478 (m) (NH_2), 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 $C_{13}H_{19}NO_3Na$ $[M+Na]^+$: 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 ^{o}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 ^{o}C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$): 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, ^{4}J = 1.0 Hz, 1H, C2-H), 7.15 (dd, ^{3}J = 9.5 Hz, ^{4}J = 3.0 Hz, 1H, C11-H), 6.93 (d, ^{3}J = 8.0 Hz, 1H, C4-H), 4.28 (t, ^{3}J = 9.0 Hz, 2H, C6-H_2), 4.05 (t, ^{3}J = 6.5 Hz, 2H, OCH_2), 3.36 (t, ^{3}J = 9.0 Hz, 2H, C7-H_2), 1.89-1.78 (m, 2H, OCH_2CH_2), 1.54-1.37 (m, 4H, $CH_2CH_2CH_3$), 0.96 (t, ^{3}J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 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 (OCH_2), 47.3 (C6), 28.9 (OCH_2CH_2), 28.2 ($CH_2CH_2CH_3$), 23.4 (C7), 22.5 ($CH_2CH_2CH_3$), 14.0 (CH_3); IR (KBr): ν_{max} = 2953 (s) (OCH_2), 2933 (s) (OCH_2), 2870 (s) (OCH_2), 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 $C_{23}H_{23}N_2O_3$ $[M+H]^{+}$: 375.1709; found 375.1706. Using the Büchi Syncore parallel reaction apparatus the following procedure was performed.[14] 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-tetrone*,**1b** (0.17 g, 0.41 mmol, 41%) was afforded as a pale grey powder. Mp 58-59 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (dd, ^{3}J = 8.0 Hz, ^{4}J = 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, OCH_2),

3.85-3.76 (m, 1H, C8-$\underline{H}_a$), 2.93-2.85 (m, 1H, C8-$\underline{H}_b$), 1.88-1.78 (m, 2H, $OCH_2C\underline{H}_2$), 1.51-1.35 (m, 4H, $C\underline{H}_2C\underline{H}_2CH_3$), 0.95 (t, ^3J = 7.0 Hz, 3H, $C\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 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 ($O\underline{C}H_2$), 44.8 (C7), 35.9 (C8), 28.9 ($OCH_2\underline{C}H_2$), 28.2 ($\underline{C}H_2CH_2CH_3$), 22.5 ($CH_2\underline{C}H_2CH_3$), 14.5 ($\underline{C}H_3$); IR (KBr): ν_{max} = 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 $C_{23}H_{22}N_2O_5Na$ $[M+Na]^+$: 429.1426; found 429.1424.

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 $NaHCO_{3(aq.)}$ (2 x 2.0 mL). The mixtures were passed through an Isolute^{TM} phase separator and the organic layer was dried (Na_2SO_4 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-(2-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**)[15,16]: white powder (22 mg, 99%), mp 226-227 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (d, ^{3}J = 8.5 Hz, 1H, C1-H), 7.77-7.71 (m, 2H, C2-H, C4-H), 7.58-7.51 (m, 2H, C12-H, C10-H), 7.45-7.39 (m, 1H, C11-H), 7.30-7.19 (m, 2H, C3-H, C9-H), 4.23 (dt, ^{2}J = 14.0 Hz, ^{3}J = 4.0 Hz, 1H, C7-H_a), 3.59 (s, 3H, CO_2CH_3), 3.65-3.51 (m, 1H, C7-H_b), 2.38-2.27 (m, 1H, C6-H_a), 1.75 (dt, ^{2}J = 14.0 Hz, ^{3}J = 4.0 Hz, 1H, C6-H_b); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 199.1 (C5), 166.5 (C13), 155.4 (CO_2Me), 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): ν_{max} = 3285 (s), 2994 (m), 2957 (m), 1732 (s), 1674 (s), 1601 (m), 1468 (m), 1371 (m), 1027 (m), 759 (m) cm^{-1}; LRMS (ES^{+}): *m/z* (%) 374.97 (100) [M+Na]$^{+}$; HRMS (ES^{+}): *m/z* calcd for $C_{19}H_{16}N_2O_5Na$ [M+Na]$^{+}$: 375.0957; found 375.0946; An analytical sample of **2a** was prepared by recrystallisation from EtOAc/hexane; Anal. calcd for $C_{19}H_{16}N_2O_5$: 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, ^{3}J = 9.0 Hz, 1H, C1-H), 7.51 (ddd, ^{3}J = 7.7 Hz, ^{3}J = 7.7 Hz, ^{4}J =

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, ^{3}J = 9.0 Hz, ^{4}J = 3.0 Hz, 1H, C2-H), 7.18 (d, ^{3}J = 7.7 Hz, 1H, C9-H), 7.02 (d, ^{4}J = 3.0 Hz, 1H, C4-H), 4.21 (dt, ^{2}J = 14.0 Hz, ^{3}J = 4.0 Hz, 1H, C7-H_a), 3.96 (t, ^{3}J = 6.5 Hz, 2H, OCH_2), 3.56 (s, 3H, OCH_3), 3.47 (ddd, ^{2}J = 13.0 Hz, ^{3}J = 12.0 Hz, ^{3}J = 4.0 Hz, 1H, C7-H_b), 2.26 (ddd, ^{2}J = 13.0 Hz, ^{3}J = 12.0 Hz, ^{3}J = 4.0 Hz, 1H, C6-H_a), 1.82 (qt, ^{3}J = 6.5 Hz, ^{3}J = 6.5 Hz, 2H, OCH_2CH_2), 1.72 (dt, ^{2}J = 14.0 Hz, ^{3}J = 4.0 Hz, 1H, C6-H_b), 1.52-1.35 (m, 4H, $CH_2CH_2CH_3$), 0.97 (t, ^{3}J = 6.5 Hz, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 199.6 (C5), 166.0 (C13), 156.8 (C3), 155.5 (CO_2Me), 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 (OCH_2R), 53.3 (OCH_3), 45.1 (C7), 34.3 (C6), 28.9 (OCH_2CH_2R), 28.3 ($OCH_2CH_2CH_2$R), 22.6 (CH_2CH_3), 14.2 (CH_2CH_3); IR (NaCl): ν_{max} = 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 $C_{24}H_{26}N_2O_6Na$ [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 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, ^{3}J = 9.0 Hz, 1H, C1-H), 7.61-7.52 (m, 4H, C4-H, C10-H, C12-H, C2-H), 7.45 (ddd, ^{3}J = 7.5 Hz, ^{4}J = 1.5 Hz, 1H, C11-H), 7.24-7.19 (m, 1H, C9-H), 4.32-4.22 (m, 1H, C7-H_a), 3.61 (s, 3H, CO_2CH_3), 3.55-3.45 (m, 1H, C7-H_b), 2.42 (s, 3H, Ar-CH_3), 2.41-2.31 (m, 1H, C6-H_a), 1.80-1.72 (m, 1H, C6-H_b); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 199.5 (C5), 166.4 (C13), 155.4 (CO_2Me), 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 (OCH_3), 45.0 (C7), 34.0 (C6), 21.0 (ArCH_3); IR (KBr): ν_{max} = 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* calcd for $C_{20}H_{18}N_2O_5Na$ $[M+Na]^+$: 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 ^oC; ^1H NMR (300 MHz, $CDCl_3$): 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-H_a), 3.61 (s, 3H, CO_2CH_3), 3.54-3.44 (m, 1H, C7-H_b), 2.41-2.30 (m, 1H, C6-H_a), 1.75 (dt, ^2J = 14.0 Hz, ^3J = 3.9 Hz, 1H, C6-H_b); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 197.9 (C5), 166.6 (C13), 152.4 (CO_2Me), 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 (CH_3), 44.9 (C6), 34.3 (C7); IR (KBr): ν_{max} = 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* calcd for $C_{19}H_{15}N_2O_5NaCl$ $[M+Na]^+$: 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 ^oC; ^1H NMR (300 MHz, $CDCl_3$): 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-H_a), 4.14-4.04 (m, 1H, $CH_{2(a)}CH_3$), 3.98-3.86 (m, 1H, $CH_{2(b)}CH_3$), 3.82 (br s, 1H, OH), 3.45 (ddd, ^2J = 14.0 Hz, ^3J = 12.0 Hz, ^3J = 4.0 Hz, 1H, C7-H_b), 2.27 (ddd, ^2J = 14.0 Hz, ^3J = 12.0 Hz, ^3J = 4.0 Hz, 1H, C6-H_a), 1.69 (dt, ^2J = 14.0 Hz, ^3J = 4.0 Hz, 1H, C6-H_b), 1.10 (t, ^3J = 7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 199.3 (C5), 166.5 (C13), 155.0 (CO_2Me), 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 ($O\underline{C}H_2CH_3$), 44.9 (C7), 34.0 (C6), 14.7 ($OCH_2\underline{C}H_3$); IR (KBr): ν_{max} = 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) $[M+H_2O]^+$; HRMS (ES^+): *m/z* calcd for $C_{20}H_{18}N_2O_5Na$ $[M+Na]^+$: 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%), ^{1}H NMR (300 MHz, $CDCl_3$): 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, ^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-H_a), 4.18-4.06 (m, 1H, $OCH_{2(a)}CH_3$), 4.00-3.88 (m, 1H, $OCH_{2(b)}CH_3$), 3.96 (t, ^3J = 6.5 Hz, 2H, OCH_2), 3.69 (br s, 1H, OH), 3.47 (ddd, ^2J = 13.3 Hz, ^3J = 12.0 Hz, ^3J = 3.0 Hz, 1H, C7-H_b), 2.31 (ddd, ^2J = 13.3 Hz, ^3J = 12.0 Hz, ^3J = 4.0 Hz, 1H, C6-H_a), 1.82 (qt, ^3J = 6.5 Hz, ^3J = 6.5 Hz, 2H, OCH_2CH_2), 1.72 (dt, ^2J = 14.0 Hz, ^3J = 4.0 Hz, 1H, C6-H_b), 1.52-1.34 (m, 4H, $CH_2CH_2CH_3$), 1.12 (t, ^3J = 7.0 Hz, 3H, OCH_2CH_3), 0.96 (t, ^3J = 6.5 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 199.5 (C5), 165.9 (C13), 156.6 (C3), 154.8 ($\underline{C}O_2Me$), 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 ($O\underline{C}H_2R$), 61.9 ($O\underline{C}H_2CH_3$), 44.9 (C7), 34.0 (C6), 29.7 ($OCH_2\underline{C}H_2R$), 28.7 ($OCH_2CH_2\underline{C}H_2R$), 22.4 ($\underline{C}H_2CH_3$), 14.7 ($CH_2\underline{C}H_3$) 14.2 ($OCH_2\underline{C}H_3$); IR (NaCl): ν_{max} = 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) $[M+H_2O]^+$; HRMS (ES^+): *m/z* calcd for $C_{25}H_{28}N_2O_6Na$ $[M+Na]^+$: 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 ^{o}C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (d, ^{3}J = 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, ^{3}J = 7.3 Hz, ^{3}J = 7.3 Hz, ^{4}J = 1.2 Hz, 1H, C11-H), 7.19 (d, ^{3}J = 7.3 Hz, 1H, C9-H), 4.20 (dt, ^{2}J = 14.0 Hz, ^{3}J = 4.0 Hz, 1H, C7-H_a), 4.15-4.06 (m, 1H, OC$H_{2(a)}$), 3.97-3.88 (m, 1H, OC$H_{2(b)}$), 3.78 (br s, 1H, OH), 3.46 (ddd, ^{2}J = 12.8 Hz, ^{3}J = 12.8 Hz, ^{3}J = 3.4 Hz, 1H, C7-H_b), 2.39 (s, 3H, ArCH_3), 2.28 (ddd, ^{2}J = 12.8 Hz, ^{3}J = 12.8 Hz, ^{3}J = 4.0 Hz, 1H, C6-H_a), 1.70 (dt, ^{2}J = 14.0 Hz, ^{3}J = 4.0 Hz, 1H, C6-H_b), 1.10 (t, ^{3}J = 7.1 Hz, 3H, OCH_2CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 199.5 (C5), 166.3 (C13), 154.9 (CO_2Me), 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 (OCH_2CH_3), 44.9 (C7), 34.0 (C6), 21.0 ($ArCH_3$), 14.7 (OCH_2CH_3); IR (KBr): ν_{max} = 3286 (s), 1735 (s) (C=O), 1708 (s) (C=O), 1648 (s) (C=O), 1489 (m), 1389 (m), 1266 (m) 764 (m) (Ar-H) cm^{-1}; LCMS (ES^{+}): (purity 98%) *m/z* (%) 380.90 (100) $[M+H]^{+}$, 397.82 (70) $[M+H_2O]^{+}$; HRMS (ES^{+}): *m/z* calcd for $C_{21}H_{20}N_2O_5Na$ $[M+Na]^{+}$: 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 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (d, ^{4}J = 1.5 Hz, 1H, C1-H), 7.66 (d, ^{3}J = 8.2 Hz, 1H, C4-H), 7.58-7.52 (m, 2H, C10-H, C12-H), 7.43 (ddd, ^{3}J = 7.8 Hz, ^{3}J = 7.8 Hz, ^{4}J = 1.3 Hz, 1H, C11-H), 7.25 (dd, ^{3}J = 8.2 Hz, ^{4}J = 1.5 Hz, 1H, C3-H), 7.21 (d, ^{3}J = 7.8 Hz, 1H, C9-H), 4.21 (dt, ^{2}J = 14.0 Hz, ^{3}J = 4.0 Hz, 1H, C7-H_a), 4.16-4.07 (m, 1H, OC$H_{2(a)}CH_3$), 4.02-3.93 (m, 1H, OC$H_{2(b)}CH_3$), 3.53 (br s, 1H, OH), 3.47 (ddd, ^{2}J = 13.0 Hz, ^{3}J = 12.0 Hz, ^{3}J = 4.0 Hz, 1H, C7-H_b), 2.33 (ddd, ^{2}J = 13.0 Hz, ^{3}J = 11.8 Hz, ^{3}J = 4.0 Hz, 1H, C6-H_a), 1.73 (dt, ^{2}J = 14.0 Hz, ^{3}J = 3.9 Hz, 1H, C6-H_b), 1.12 (t, ^{3}J = 7.0 Hz, 3H, OCH_2CH_3);

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 198.2 (C5), 166.6 (C13), 155.0 (<u>C</u>O_2Me), 152.4 (C14a), 144.9 (C2), 138.3 (C8a), 136.4 (C12a), 132.5 (C10), 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 (O<u>C</u>H_2CH_3), 44.8 (C6), 34.1 (C7), 14.7 (OCH_2<u>C</u>H_3); IR (KBr): ν_{max} = 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) $[M+H_2O]^+$; HRMS (ES^+): *m/z* calcd for $C_{20}H_{17}N_2O_5NaCl$ $[M+Na]^+$: 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 ^oC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, ^3J = 8.5 Hz, 1H, C1-<u>H</u>), 7.70-7.62 (m, 2H, C2-<u>H</u>, C4-<u>H</u>), 7.52 (ddd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, ^4J = 1.7 Hz, C10-<u>H</u>), 7.44-7.40 (m, 1H, C12-<u>H</u>), 7.37-7.32 (m, 1H, C11-<u>H</u>), 7.24-7.18 (m, 2H, C3-<u>H</u>, C9-<u>H</u>), 4.82 (br s, 1H, O<u>H</u>), 4.19 (dt, ^2J = 14.0 Hz, ^3J = 4.0 Hz, 1H, C7-<u>H</u>$_a$), 4.06 (t, ^3J = 6.0 Hz, 1H, N<u>H</u>), 3.26 (ddd, ^2J = 12.0 Hz, ^3J = 11.5 Hz, ^3J = 3.0 Hz, 1H, C7-<u>H</u>$_b$), 3.06-2.96 (m, 1H, NHC<u>H</u>$_{(a)}$), 2.88-2.79 (m, 1H, NHC<u>H</u>$_{(b)}$), 2.07 (ddd, ^2J = 12.0 Hz, ^3J = 10.2 Hz, ^3J = 3.0 Hz, 1H, C6-<u>H</u>$_a$), 1.59 (dt, ^2J = 14.0 Hz, ^3J = 3.0 Hz, 1H, C6-<u>H</u>$_b$), 1.29-1.20 (m, 2H, $NHCH_2$C<u>H</u>$_2$), 1.19-1.10 (m, 2H, $NHCH_2CH_2$C<u>H</u>$_2$), 0.82 (t, ^3J = 7.5 Hz, 3H, C<u>H</u>$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 199.4 (C5), 166.3 (C13), 156.2 (N<u>C</u>ONH), 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 (NH<u>C</u>H_2), 35.0 (C6), 32.4 ($NHCH_2$<u>C</u>H_2), 20.0 ($NHCH_2CH_2$<u>C</u>H_2), 13.9 (CH_3); IR (KBr): ν_{max} = 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 $C_{22}H_{23}N_3O_4Na$ $[M+Na]^+$: 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%), ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, ^{3}J = 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, ^{3}J = 9.0 Hz, ^{4}J = 2.9 Hz, 1H, C2-H), 7.29-7.25 (m, 1H, C9-H), 7.12 (d, ^{4}J = 2.9 Hz, 1H, C4-H), 4.44 (dt, ^{2}J = 14.0 Hz, ^{3}J = 4.0 Hz, 1H, C7-H_a), 4.11 (t, ^{3}J = 5.8 Hz, 1H, NH), 3.98 (t, ^{3}J = 6.7 Hz, 2H, OCH_2), 3.36 (ddd, ^{2}J = 13.3 Hz, ^{3}J = 11.7 Hz, ^{3}J = 2.9 Hz, 1H, C7-H_b), 3.22-3.10 (m, 1H, $NHCH_{2(a)}$), 3.04-2.92 (m, 1H, $NHCH_{2(b)}$), 2.30 (ddd, ^{2}J = 13.3 Hz, ^{3}J = 11.7 Hz, ^{3}J = 4.0 Hz, 1H, C6-H_a), 1.87-1.77 (m, 2H, OCH_2CH_2), 1.72 (dt, ^{2}J = 14.0 Hz, ^{3}J = 4.0 Hz, 1H, C6-H_b), 1.50-1.30 (m, 4H, $OC_2H_4CH_2CH_2CH_3$), 1.29-1.15 (m, 4H, $NHCH_2CH_2CH_2CH_3$), 0.96 (t, ^{3}J = 7.0 Hz, 3H, $OC_4H_8CH_3$), 0.87 (t, ^{3}J = 7.2 Hz, 3H, $NHC_3H_6CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): 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 (OCH_2), 44.0 (C7), 40.7 ($NCONHCH_2$), 35.3 (C6), 32.6 ($NCONHCH_2CH_2$) 28.9 ($OCH_2CH_2CH_2CH_2CH_3$), 28.3 ($OCH_2CH_2CH_2CH_2CH_3$), 22.6 ($OCH_2CH_2CH_2CH_2CH_3$), 20.0 ($NCONHCH_2CH_2CH_2$), 14.2 ($OCH_2CH_2CH_2CH_2CH_3$), 14.0 ($NCONHCH_2CH_2CH_2CH_3$); IR (NaCl): ν_{max} = 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 $C_{27}H_{33}N_3O_5Na$ $[M+Na]^+$: 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 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, ^{3}J = 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, ^{2}J = 14.0 Hz, ^{3}J = 4.0 Hz, 1H, C7-H_a), 4.08 (t, ^{3}J = 5.9 Hz, 1H, NH), 3.66 (br s, 1H, OH), 3.33 (ddd, ^{2}J = 13.0 Hz, ^{3}J =

11.8 Hz, ^{3}J = 4.0 Hz, 1H, C7-$\underline{H}_b$), 3.18-3.06 (m, 1H, NHC$\underline{H}_{(a)}$), 3.00-2.88 (m, 1H, NHC$\underline{H}_{(b)}$), 2.40 (s, 3H, ArC$\underline{H}_3$), 2.24 (ddd, ^{2}J = 13.0 Hz, ^{3}J = 11.8 Hz, ^{3}J = 4.0 Hz, 1H, C6-$\underline{H}_a$), 1.67 (dt, ^{2}J = 14.0 Hz, ^{3}J = 4.0 Hz, 1H, C6-$\underline{H}_b$), 1.37-1.14 (m, 4H, NHCH$_2$C$\underline{H}_2$C$\underline{H}_2$), 0.86 (t, ^{3}J = 7.3 Hz, 3H, CH$_2$C$\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 199.4 (C5), 166.1 (C13), 156.4 (N$\underline{C}$ON), 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 (NH$\underline{C}$H$_2$), 35.1 (C6), 32.5 (NHCH$_2$$\underline{C}H_2$), 21.0 (Ar$\underline{C}H_3$), 20.0 (NHCH$_2CH_2$$\underline{C}H_2$), 13.9 (NHCH$_2CH_2CH_2$$\underline{C}H_3$); IR (KBr): ν_{max} = 3236 (s), 1722 (s) (C=O), 1638 (s) (C=O), 1525 (m), 1490 (w), 1152 (w), 742 (m) cm^{-1}; LRMS (ES$^+$): *m/z* (%) 430.04 (100) [M+Na]$^+$; HRMS (ES$^+$): *m/z* calcd for $C_{23}H_{25}N_3O_4Na$ [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 (**2l**): White powder (10 mg, 44%), mp 211-212 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (d, ^{4}J = 1.8 Hz, 1H, C1-$\underline{H}$), 7.66 (d, ^{3}J = 8.0 Hz, 1H, C4-$\underline{H}$), 7.63-7.45 (m, 3H, C10-$\underline{H}$, C12-$\underline{H}$, C11-$\underline{H}$), 7.29-7.23 (m, 2H, C3-$\underline{H}$, C9-$\underline{H}$), 4.33 (dt, ^{2}J = 14.0 Hz, ^{3}J = 3.8 Hz, 1H, C7-$\underline{H}_a$), 4.07 (t, ^{3}J = 5.6 Hz, 1H, N$\underline{H}$), 3.86 (br s, 1H, O$\underline{H}$), 3.34 (ddd, ^{2}J = 12.8 Hz, ^{3}J = 11.6 Hz, ^{3}J = 3.8 Hz, 1H, C7-$\underline{H}_b$), 3.19-3.07 (m, 1H, NHC$\underline{H}_{2(a)}$), 2.98-2.86 (m, 1H, NHC$\underline{H}_{2(b)}$), 2.25 (ddd, ^{2}J = 13.0 Hz, ^{3}J = 10.7 Hz, ^{3}J = 4.0 Hz, 1H, C6-$\underline{H}_a$), 1.68 (dt, ^{2}J = 14.0 Hz, ^{3}J = 3.9 Hz, 1H, C6-$\underline{H}_b$), 1.37-1.14 (m, 4H, NHCH$_2$C$\underline{H}_2$C$\underline{H}_2$), 0.89 (t, ^{3}J = 7.0 Hz, 3H, CH$_2$C$\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 192.5 (C5), 161.5 (C13), 156.2 (N$\underline{C}$ON), 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 (NH$\underline{C}$H$_2$), 35.0 (C6), 32.6 (NHCH$_2$$\underline{C}H_2$), 19.9 (NHCH$_2CH_2$$\underline{C}H_2$), 13.9 (NHCH$_2CH_2CH_2$$\underline{C}H_3$); IR (KBr): ν_{max} = 3416 (m), 1741 (s) (C=O), 1655 (s) (C=O), 1599 (m), 1458 (w), 1367 (w), 1019 (m) cm^{-1}; LRMS (ES$^+$):

m/z (%) 449.99 (100) $[M+Na]^+$; HRMS (ES^+): *m/z* calcd for $C_{22}H_{22}N_3O_4NaCl$ $[M+Na]^+$: 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 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 8.43 (d, ^3J = 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, NHCH_2), 2.40-2.30 (m, 1H, C6-H_a), 1.78-1.70 (m, 1H, C6-H_b), 0.89-0.79 (m, 1H, $NHCH_2CH$), 0.42-0.36 (m, 2H, cyclopropane CH_2), 0.10-0.04 (m, 2H, cyclopropane CH_2); ^{13}C NMR (300 MHz, d_6-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_2CH), 3.0 (cyclopropane CH_2), 2.8 (cyclopropane CH_2); IR (KBr): ν_{max} = 3366 (s), 3240 (s), 1736 (s) (C=O), 1649 (s) (C=O), 1630 (s), 1601 (m), 1536 (m), 1464 (m), 764 (w) cm^{-1}; LRMS (ES^+): *m/z* (%) 414.02 (100) $[M+Na]^+$; HRMS (ES^+): *m/z* calcd for $C_{22}H_{21}N_3O_4Na$ $[M+Na]^+$: 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 ^oC; ^1H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, ^3J = 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, ^3J = 9.0 Hz, ^4J = 2.9 Hz, 1H, C2-H), 7.27-7.23 (m, 1H, C9-H), 7.08 (d, ^4J = 2.9 Hz, 1H, C4-H), 4.45-4.33 (m, 2H, C7-H_a, NH), 3.98 (t, ^3J = 6.6 Hz, 2H, OCH_2), 3.41-3.19 (m, 8H, C7-H_b, $NHC_2H_4OCH_3$), 2.26 (ddd, ^2J = 13.0 Hz, ^3J = 10.5 Hz, ^3J = 4.0 Hz, 1H, C6-H_a), 1.82 (quintet, ^3J = 7.3 Hz,

2H, $OCH_2C\underline{H}_2$), 1.70 (dt, ^2J = 14.0 Hz, ^3J = 4.0 Hz, 1H, C6-$\underline{H}_b$), 1.53-1.34 (m, 4H, $OCH_2CH_2C\underline{H}_2C\underline{H}_2CH_3$), 0.96 (t, ^3J = 6.9 Hz, 3H, $OCH_2CH_2CH_2CH_2C\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 198.9 (C5), 166.7 (N$\underline{C}$ONHR), 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 ($NCONHCH_2\underline{C}H_2OCH_3$), 68.9 ($O\underline{C}H_2$), 58.9 ($O\underline{C}H_3$), 44.0 (C7), 40.5 ($NCONH\underline{C}H_2CH_2OCH_3$), 35.2 (C6), 29.0 ($OCH_2\underline{C}H_2CH_2CH_2CH_3$), 28.3 ($OCH_2CH_2\underline{C}H_2CH_2CH_3$), 22.7 ($OCH_2CH_2CH_2\underline{C}H_2CH_3$), 14.2 ($CH_2\underline{C}H_3$); IR (KBr): ν_{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 $C_{25}H_{30}N_3O_6$ $[M+H]^+$: 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 ^oC; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (d, ^3J = 8.7 Hz, 1H, C1-$\underline{H}$), 7.72-7.66 (m, 2H, C2-$\underline{H}$, C4-$\underline{H}$), 7.55 (ddd, ^3J = 7.9 Hz, ^3J = 7.9 Hz, ^4J = 1.7 Hz, 1H, C10-$\underline{H}$), 7.49 (dd, ^3J = 7.9 Hz, ^4J = 1.7 Hz, 1H, C12-$\underline{H}$), 7.41 (ddd, ^3J = 7.9 Hz, ^3J = 7.9 Hz, ^4J = 1.7 Hz, 1H, C11-$\underline{H}$), 7.26-7.19 (m, 2H, C3-$\underline{H}$, C9-$\underline{H}$), 4.80 (t, ^3J = 4.9 Hz, 1H, N$\underline{H}$), 4.23 (dt, ^2J = 14.0 Hz, ^3J = 3.9 Hz, 1H, C7-$\underline{H}_a$), 3.49-3.40 (m, 4H, morpholine 2x $C\underline{H}_2O$), 3.33 (ddd, ^2J = 13.0 Hz, ^3J = 11.8 Hz, ^3J = 3.9 Hz, 1H, C7-$\underline{H}_b$), 3.13-2.97 (m, 2H, $CONHC\underline{H}_2$), 2.35-2.22 (m, 6H, $CONHCH_2C\underline{H}_2N(C\underline{H}_2CH_2)_2O$), 2.14 (ddd, ^2J = 14.0 Hz, ^3J = 11.8 Hz, ^3J = 4.0 Hz, 1H, C6-$\underline{H}_a$), 1.66 (dt, ^2J = 14.0 Hz, ^3J = 4.0 Hz, 1H, C6-$\underline{H}_b$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 199.6 (C5), 166.2 (C13), 156.2 (N$\underline{C}$ONH), 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 ($CONHCH_2CH_2N(CH_2\underline{C}H_2)_2O$), 56.8 ($CONHCH_2\underline{C}H_2$), 52.9 ($CONHCH_2CH_2N(\underline{C}H_2CH_2)_2O$), 43.6 (C7), 36.7

(CONH<u>C</u>H$_2$CH$_2$), 35.1 (C6); IR (KBr): ν_{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 $C_{24}H_{26}N_4O_5Na$ [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^{TM} phase separator and the organic layer was then dried (Na_2SO_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 ^{o}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^{TM} phase separator. The organic layer was dried (Na_2SO_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**) [15,16]: Yellow powder (17 mg, 77%), mp 149-150 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 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-H_2), 4.04 (s, 3H, $PyCO_2CH_3$), 3.55-3.47 (m, 5H, C3-H_2, $ArCO_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.0 ($ArCO_2CH_3$), 166.8 ($PyCO_2CH_3$), 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 ($PyCO_2CH_3$), 51.9 ($ArCO_2CH_3$), 50.3 (C2), 26.9 (C3); IR (KBr): ν_{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 $C_{21}H_{19}N_2O_4$ $[M+H]^{+}$: 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 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 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, ^{4}J = 3.0 Hz, 1H, C5'-H), 4.07 (t, ^{3}J = 7.6 Hz, 2H, C2-H_2), 3.96 (s, 3H, $PyCO_2CH_3$), 3.80 (s, 3H, $ArOCH_3$), 3.45-3.39 (m, 5H, C3-H_2, $ArCO_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.3 ($ArCO_2Me$), 167.5 ($PyCO_2Me$), 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 ($PyCO_2CH_3$), 52.1 ($ArCO_2CH_3$), 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 ^oC; ^1H NMR (300 MHz, $CDCl_3$): 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-H_2), 4.05 (s, 3H, $PyCO_2CH_3$), 3.56-3.51 (m, 5H, C3-H_2, $ArCO_2CH_3$); ^{13}C NMR (75.5 MHz, d_6-DMSO): δ 167.1 ($ArCO_2CH_3$), 165.6 ($PyCO_2CH_3$), 158.5 (C9a), 145.7 (C8a), 138.6 (C1'), 132.6 (C5'), 130.9 (C4), 130.1 (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 ($PyCO_2CH_3$), 51.6 ($ArCO_2CH_3$), 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 ^oC; ^1H NMR (300 MHz, $CDCl_3$): 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, ^3J = 7.7 Hz, ^4J = 1.6 Hz, 1H, C5'-H), 7.51 (d, ^3J = 8.9 Hz, 1H, C8-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, $PyCO_2CH_2CH_3$), 4.20 (t, ^3J = 7.6 Hz, 2H, C2-H_2), 3.93 (q, ^3J = 7.2 Hz, 2H,

$ArCO_2C\underline{H}_2CH_3$), 3.53 (t, ^3J = 7.6 Hz, 2H, C3-$\underline{H}_2$), 1.48 (t, ^3J = 7.2 Hz, 3H, $PyCO_2CH_2C\underline{H}_3$), 1.03 (t, ^3J = 7.2 Hz, 3H, $ArCO_2CH_2C\underline{H}_3$); ^{13}C NMR (300 MHz, $CDCl_3$): δ 167.4 ($Ar\underline{C}O_2R$), 165.9 ($Py\underline{C}O_2R$), 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 ($PyCO_2\underline{C}H_2CH_3$), 61.0 ($ArCO_2\underline{C}H_2CH_3$), 50.7 (C2), 27.2 (C3), 14.5 ($PyCO_2CH_2\underline{C}H_3$), 14.0 ($ArCO_2CH_2\underline{C}H_3$); IR (KBr): ν_{max} = 2986 (m) (CH_2), 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 $C_{23}H_{22}N_2O_4Cl$ $[M+H]^+$: 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 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (dd, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 1H, C5-$\underline{H}$), 7.67 (dd, ^3J = 8.1 Hz, ^4J = 1.8 Hz, 1H, C3'-$\underline{H}$), 7.58-7.53 (m, 1H, C6'-$\underline{H}$), 7.52-7.48 (m, 1H, C5'-$\underline{H}$), 7.47-7.41 (m, 1H, C7-$\underline{H}$), 7.39-7.33 (m, 2H, C8-$\underline{H}$, C6-$\underline{H}$), 7.27-7.22 (m, 1H, C4'-$\underline{H}$), 7.04 (t, ^3J = 5.2 Hz, 1H, $N\underline{H}_b$), 6.01 (t, ^3J = 5.5 Hz, 1H, $N\underline{H}_a$), 4.09 (t, ^3J = 7.7 Hz, 2H, C2-$\underline{H}_2$), 3.57 (q, ^3J = 5.5 Hz, 2H, C(a1)-$\underline{H}_2$), 3.32 (t, ^3J = 7.7 Hz, 2H, C3-$\underline{H}_2$), 3.13 (q, ^3J = 5.2 Hz, 2H, C(b1)-$\underline{H}_2$), 1.73-1.62 (m, 2H, C(a2)-$\underline{H}_2$), 1.54-1.41 (m, 2H, C(a3)-$\underline{H}_2$), 1.22-1.07 (m, 4H, C(b2)-$\underline{H}_2$, C(b3)-$\underline{H}_2$), 1.01 (t, ^3J = 7.3 Hz, 3H, C(a4)-$\underline{H}_3$), 0.69 (t, ^3J = 7.1 Hz, 3H, C(b4)-$\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 168.3 ($\underline{C}ONH_b$), 166.8 ($\underline{C}ONH_a$), 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): ν_{max} = 1647 (br s) (C=O), 1485 (m) 1265 (s), 741 (s) cm^{-1}; LRMS (ES^+): *m/z* (%) 467.09 (100) $[M+Na]^+$, 445.14

(25) $[M+H]^+$, 911.20 (25) $[2M+Na]^+$; HRMS (ES^+): *m/z* calcd for $C_{27}H_{32}N_4O_2Na$ $[M+Na]^+$: 467.2423; found 467.2426.

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.) ^oC; ^1H NMR (300 MHz, d_6-DMSO): δ 9.24 (t, ^3J = 6.0 Hz, ^3J = 6.0 Hz, 1H, N$\underline{H}_a$), 8.81 (t, ^3J = 6.0 Hz, ^3J = 6.0 Hz, 1H, N$\underline{H}_b$), 7.63 (d, ^3J = 8.1 Hz, 1H, C5-$\underline{H}$), 7.60 (d, ^3J = 7.5 Hz, 1H, C3'-$\underline{H}$), 7.56-7.51 (m, 2H, C5'-$\underline{H}$, C8-$\underline{H}$), 7.46-7.43 (m, 2H, C7-$\underline{H}$, C4'-$\underline{H}$), 7.42 (m, 4H, benzyl C-$\underline{H}$), 7.38-7.33 (m, 1H, C6'-$\underline{H}$), 7.33 (m, 1H, C*p*-$\underline{H}$), 7.24-7.19 (m, 1H, C6-$\underline{H}$), 7.14-7.10 (m, 5H, benzyl C-$\underline{H}$), 4.57 (d, ^3J = 6.0 Hz, 2H, benzyl C$\underline{H}_{2a}$), 4.21 (d, ^3J = 6.0 Hz, 2H, benzyl C$\underline{H}_{2b}$), 4.03 (t, ^3J = 7.7 Hz, 2H, C2-$\underline{H}_2$), 3.14 (t, ^3J = 7.7 Hz, 2H, C3-$\underline{H}_2$); ^{13}C NMR (75.5 MHz, d_6-DMSO): δ 167.8 (Ar$\underline{C}$ONH), 165.8 (Py$\underline{C}$ONH), 159.2 (C9a), 147.2 (C8a), 139.3 (C*i* x 2), 138.6 (C1'), 137.3 (C4), 133.8 (C2'), 130.5 (C5'), 128.9 (C3'), 128.5 (C7 & benzyl $\underline{C}$H), 128.4 (benzyl $\underline{C}$H x 2), 128.1 (benzyl $\underline{C}$H x 2), 127.4 (benzyl $\underline{C}$H x 2), 127.0 (benzyl $\underline{C}$H x 2), 126.5 (C*p*), 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 $\underline{C}H_2$), 42.4 (benzyl $\underline{C}H_2$), 24.5 (C3); IR (KBr): ν_{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 $C_{33}H_{29}N_4O_2$ $[M+H]^+$: 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 ^oC; ^1H NMR (300 MHz, d_6-DMSO): δ 7.73 (dd, ^3J = 8.2 Hz, ^4J = 1.2 Hz, 1H, C5-$\underline{H}$), 7.57 (dd, ^3J = 8.2 Hz, ^4J = 1.2 Hz, 1H, C8-$\underline{H}$), 7.45 (ddd, ^3J = 8.2 Hz, ^3J = 8.2 Hz, ^4J = 1.2 Hz, 1H, C7-$\underline{H}$), 7.36 (t, ^3J = 5.9 Hz, 1H, N$\underline{H}_b$), 7.26-7.21 (m, 3H, C3'-$\underline{H}$, C6'-$\underline{H}$, C6-$\underline{H}$), 7.03

(dd, ^{3}J = 8.7 Hz, ^{4}J = 3.0 Hz, 1H, C5'-H), 5.97 (t, ^{3}J = 5.8 Hz, 1H, NH_a), 4.02 (t, ^{3}J = 7.9 Hz, 2H, C2-H_2), 3.86 (s, 3H, ArOCH_3), 3.58 (q, ^{3}J = 6.0 Hz, 2H, C(a1)-H_2), 3.31 (t, ^{3}J = 7.9 Hz, 2H, C3-H_2), 3.14 (q, ^{3}J = 5.7 Hz, 2H, C(b1)-H_2), 1.73-1.62 (m, 2H, C(a2)-H_2R), 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, ^{3}J = 7.2 Hz, 3H, C(a4)-H_3), 0.65 (t, ^{3}J = 7.2 Hz, 3H, C(b4)-H_3); ^{13}C NMR (75.5 MHz, d_6-DMSO): δ 167.0 (CONH$_b$), 165.6 (CONH$_a$), 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 $C_{28}H_{34}N_4O_3Na$ [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 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (dd, ^{3}J = 7.6 Hz, ^{4}J = 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, ^{3}J = 8.7 Hz, ^{3}J = 8.7 Hz, ^{4}J = 1.9 Hz, 1H, C7-H), 7.20 (t, ^{3}J = 5.0 Hz, 1H, ArCONH), 6.61 (t, ^{3}J = 5.1 Hz, 1H, PyCONH), 4.06 (t, ^{3}J = 7.8 Hz, 2H, C2-H_2), 3.34-3.69 (m, 4H, 2xCH_2(d)), 3.67 (q, ^{3}J = 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, ^{3}J = 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 (2x<u>C</u>H$_2$(h)), 57.2 (<u>C</u>H$_2$(b)), 57.1 (<u>C</u>H$_2$(f)), 53.5 (2x<u>C</u>H$_2$(c)), 53.4 (2x<u>C</u>H$_2$(g)), 52.2 (C2), 36.2 (<u>C</u>H$_2$(e)), 36.0 (<u>C</u>H$_2$(a)), 25.4 (C3), 21.6 (Ar<u>C</u>H$_3$); IR (KBr): ν_{max} = 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 $C_{32}H_{41}N_6O_4$ [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 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (br s, 1H, O<u>H</u>), 8.42 (d, ^4J = 2.6 Hz, 1H, C6-<u>H</u>), 7.90 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, C3'-<u>H</u>), 7.58 (ddd, ^3J = 7.7 Hz, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, C5'-<u>H</u>), 7.41 (dd, ^3J = 8.9 Hz, ^4J = 2.6 Hz, 1H, C8-<u>H</u>), 7.37 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, C4'-<u>H</u>), 7.32 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, C6'-<u>H</u>), 7.28 (d, ^3J = 8.9 Hz, 1H, C9-<u>H</u>), 4.19 (t, ^3J = 7.5 Hz, 2H, C2-<u>H</u>$_2$), 3.96 (q, ^3J = 7.2 Hz, 2H, C<u>H</u>$_2$CH$_3$), 3.36 (t, ^3J = 7.5 Hz, 2H, C3-<u>H</u>$_2$), 1.06 (t, 3H, ^3J = 7.2 Hz, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (300 MHz, $CDCl_3$): δ 178.3 (C5), 167.0 (CO_2R), 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 (CO_2<u>C</u>H$_2$CH$_3$), 49.8 (C2), 25.3 (C3), 14.1 (CO_2CH_2<u>C</u>H$_3$); IR (KBr): ν_{max} = 3449 (m) (OH), 2977 (m) (CH_2), 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 $C_{21}H_{17}N_2O_4NaCl$ [M+H]$^+$: 419.0775; found 419.0781; An analytical sample was prepared by recrystallisation from toluene; Anal. calcd for $C_{21}H_{17}ClN_2O_4$: 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.

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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.

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