**Total Syntheses of the 3*H*-Pyrrolo[2,3-*c*]quinolone-containing Alkaloids
Marinoquinolines A-F, K and Aplidiopsamine A Using a Palladium-catalysed
Ullmann Cross-coupling/Reductive Cyclization Pathway**

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Compounds **1-6** and **11** representing key members of the marinoquinoline family of natural products, together with the related marine alkaloid aplidiopsamine A (**12**), have been synthesized using various combinations of palladium-catalyzed Ullmann cross-coupling and reductive cyclization processes involving a C3-arylated pyrrole as the common intermediate. These natural products have been characterized by single-crystal X-ray analyses and evaluated as inhibitors of acetylcholine esterase (AChE) with congener **2** proving to be the most active.

Introduction

Marinoquinolines A-K (**1-11**, respectively) (Figure 1) are the currently known members of a family of natural products that embody the 3*H*-pyrrolo[2,3-*c*]quinoline ring system. They have been isolated from a range of bacterial sources. Thus, marinoquinoline A (MQ-A or **1**) was first isolated by Plubrukarn and co-workers from *Rapidiithrix thailandica* TISTR 1742, a gliding bacterium associated with seaweed collected from Yong Ling beach on the coast of Southern Thailand.¹ Its structure was established by single-crystal X-ray analysis.² Subsequently, marinoquinoline A (**1**) together with congeners B-F (**2-6**, respectively), that only differ in the nature of the substituent at C4, were isolated by Müller and co-workers from the gliding bacterium *Ohtaekwangia kribbensis* (PWU 25) obtained from a soil sample collected in the Northern Indian state of Uttar Pradesh.³ More recently, Fenical has reported the isolation of congeners **7-11** (*viz.* marinoquinolines G-K, respectively) from cultures of

the marine bacterium *Mooreia alkaloidigena* (CNX-216^T).⁴ On the other hand, the structurally related alkaloid aplidiopsamine A (**12**), that features a methylene-linked adenine residue attached at C4 of the above-mentioned heterocyclic ring system, was obtained from the ascidian *Aplidiopsis confluenta* found in temperate Australian waters. Its structure was proposed based on analyses of the derived mass and NMR spectral data.⁵

Figure 1: The structures of currently known members, A-K (**1-11**), of the marinoquinoline family of natural products and the related 3*H*-pyrrolo[2,3-*c*]quinolone aplidiopsamine A (**12**)

The biological evaluation of alkaloids **1-12** has been the subject of a number of reports, the first of these¹ identifying MQ-A (**1**) as an inhibitor ($IC_{50} = 4.9 \mu M$) of *Torpedo californica*-derived acetylcholinesterase (AChE).⁶ The IC_{50} of the positive control galanthamine tested in the same assay was $0.6 \mu M$. Furthermore, MQ-A as well as congeners **2-6** were shown to be weak anti-bacterial and anti-fungal agents and proved to be modestly cytotoxic against the mammalian cells L929, MCF-7, KB-3-1 and HUVEC (IC_{50} s ranging from 0.3 to $8.0 \mu g/mL$ vs 1.2 to 18×10^{-3} for epothilon and vinblastine).³ More interestingly, MQs A-F (*viz.* compounds **1-6**) displayed significant activity against the malarial parasite *Plasmodium falciparum* K1 (IC_{50} s

ranging from 1.7 to 15 μM),³ while aplidiopsamine A (**12**) showed values of 1.47 to 1.65 μM against chloroquine-sensitive and -resistant strains, respectively, while only completely inhibiting the growth of the normal cell line HEK-293 at the highest tested dose of 120 μM .⁵ More recently,⁴ MQ-A, MQ-B and MQ-C have been shown to display antibiotic activity against *Pontibacillus* sp. (strain CNJ-912). Aplidiopsamine A (**12**) is also a highly selective PDE4 inhibitor⁷ and may thus serve as a lead for the development of new treatments for depression and various forms of psychosis. Neuroprotective agents based on compound **12** have also been proposed.⁷

The biosynthetic origins of compounds **1-12** have been the subject of various studies and proposals^{5,8} while the significant range of biological activities attributed to these natural products have prompted a number of synthetic efforts. The parent ring system **11** (also now known as MQ-K) was first prepared in 1961⁹ and then again in 1978¹⁰ and 2009¹¹ with the last approach, involving a domino condensation-Heck reaction, providing material for evaluation that revealed it possessed anti-protozoal and cytotoxic effects.¹¹ Various targeted syntheses of certain of the marinoquinolines and of aplidiopsamine A have been reported with several of these^{7,12,13,14} involving biomimetic C3a-C4 bond formation (see structure **1** in Figure 1 for atom numbering) including *via* cyclodehydration of a C3-arylated pyrrole bearing an acetamido residue at the *ortho*-position of the benzenoid ring. In another approach,¹⁵ and during the course of synthesizing marinoquinolines C and E, Sperry and his co-worker employed the Bartoli indolization protocol to annulate the required pyrrole ring to 2-chloro-3-nitroquinoline. Mhaske and co-workers¹⁶ were able to effect the palladium-catalyzed cyclisation of a iodinated imine derived from the Schiff base condensation of *o*-iodoaniline with a C2-acylated pyrrole and thereby generating, *via* C9a-C9b bond formation, the required ring system and then elaborating this to targets **1** and **12**. Our own synthesis of marinoquinoline A (**1**)¹⁷ involved a reversal of the sequence of steps employed by Mhaske and used a palladium-catalyzed Ullmann cross-coupling reaction¹⁸ of *o*-bromonitrobenzene with a 3-iodopyrrole-2-carboxaldehyde and thus forming what would become the C9a-C9b bond within the developing 3*H*-pyrrolo[2,3-*c*]quinolone framework. Subsequent reactions, including a reductive cyclisation step resulting in formation of the C4-N5 bond, then provided the target natural product **1**. Various of these studies and certain others^{19,20,21,22,23} have been extended to analogues of the marinoquinolines including ones displaying superior activities.^{19,23} Taken together these studies have led to total syntheses of marinoquinolines A, B, C and E (**1**,

2, **3** and **5**, respectively) as well as aplidiopsamine A (**12**). However, the structures assigned to marinoquinolines D (**4**) and F (**6**) have yet to be prepared by any of the methods just described. Accordingly, we report herein total syntheses of all six of these members of the marinoquinoline class of natural product, as well as the parent system **11** and congener **12**, using a divergent approach from a common precursor.

Results and Discussion

Chemical Synthesis Studies

(i) *Initial Approach*

In our initial efforts to identify a late-stage precursor to all of the marinoquinolines and following the approach¹⁷ used in our synthesis of congener **1**, the 3-iodopyrrole-2-carboxaldehyde **13**²⁴ (Scheme 1) was subjected to a palladium-catalyzed Ullmann cross-coupling reaction with *o*-bromonitrobenzene (**14**) to give the previously reported¹⁷ product **15** (74%). However, when compound **15** was treated with *iso*-butylmagnesium bromide [in an effort to establish a route to MQ-B (**2**)] the *iso*-butylated aromatics **16** (25%) and **17** were obtained rather than the anticipated secondary alcohol arising from addition of the Grignard reagent to the aldehyde moiety within the substrate. Presumably product **16** arises from nucleophilic addition of the organometallic reagent to the electron-deficient aromatic ring of nitroarene **15** at the position (C5') remote from the nitro-group and the adduct so-produced, or a protonated form derived from this, is then oxidized (perhaps on work-up) to re-establish the aromatic character of the benzenoid ring. Alcohol **17**, on the other hand, probably results from initial addition of the Grignard reagent to the unsubstituted position (C3') of the benzenoid ring adjacent to the nitro-group within compound **15** and with the resulting stabilized carbanion adding to the pendant aldehyde moiety to afford a cyclopentanol. Elimination of the elements of nitrous acid from within this last species and accompanying re-aromatization of the six-membered ring would then afford product **17**. Since compound **17** could not be purified very readily, it was oxidized, using the Dess-Martin periodinane (DMP), to the corresponding ketone **18** and upon hydrogenation of this under conventional conditions it was converted into the crystalline pyrrolidine **19** (20% from **15**) for which a single-crystal X-ray analysis could be carried out (see the Experimental Section and Supporting Information – SI – for details).

Scheme 1: Initial Attempts to Establish a Synthesis of MQ-B (**2**)

(ii) **Synthesis of Marinoquinoline K (11) and a Late-Stage Precursor to Others**

In light of the outcomes detailed immediately above, reductive cyclisation of compound **15** (Scheme 2) was undertaken in order to both remove the nitro-group and establish the target 3*H*-pyrrolo[2,3-*c*]quinoline ring system bearing functionality allowing for introduction of the required C4 substituent. When such a cyclization reaction was carried out using hydrogen gas in the presence of W-7 Raney nickel then (Scheme 2) complete reduction took place to give, via *N*-oxide **20**, compound **21** (80%). The structures of both of these products were confirmed by single-crystal X-ray analysis. Treatment of compound **21** with *m*-chloroperbenzoic acid (*m*-CPBA) allowed for its ready conversion into *N*-oxide **20** (83%) but this was a thermally sensitive material and on heating in moist DMSO at 80°C for relatively short periods of time it isomerized to the previously unreported lactam **22** (91%). In anticipation of the necessary removal of the sulfonamide group at the conclusion of the syntheses of the target marinoquinolines, it was established that when compound **21** was treated with

freshly prepared sodium methoxide in methanol then the parent 3*H*-pyrrolo[2,3-*c*]quinolone (**11**) (a.k.a. MQ-K) could be obtained in 95% yield. Once again the structure of this material was confirmed by a single-crystal X-ray analysis. All of the other spectral data acquired on the bulk material, and involving the use of (CD₃)₂CO as the solvent for acquiring NMR spectra, were also entirely consistent with the assigned structure. We were unable to dissolve the synthetically-derived sample of compound **11** in CD₃OD, the NMR solvent used in characterizing the natural product MQ-K⁴ so completely “legitimate” comparisons (see SI) of the two ¹³C NMR data sets could not be made. However, these do suggest they are one and the same compound.

Scheme 2: Synthesis of Marinoquinoline K (**11**) and 3,5-Dihydro-4*H*-pyrrolo[2,3-*c*]quinolin-4-one **22**

(iii) Synthesis of Marinoquinolines A, B and C from the N-oxide **20**

With a concise and reliable route to the *N*-oxide **20** established, efforts were focused on the capacity to engage this compound in a nucleophilic addition at C4 with the relevant Grignard reagent. In the event, reaction of compound **20** with methylmagnesium bromide (**Scheme 3**) gave a product (presumed to be alcohol **23** or the corresponding conjugate base) that upon treatment with sodium methoxide in methanol afforded marinoquinoline A (**1**) in 57% yield. The spectral data obtained on this product were completely consistent with the assigned structure and in good agreement with those derived from sample of marinoquinoline A obtained by our earlier route¹⁷ (and for which a single-crystal analysis had been obtained). A comparison of the ¹³C NMR data recorded for compound **1** obtained by the present route with those reported for the natural product revealed good agreement (see SI) but it should be noted that minor variations in the water content and/or the pH of the

medium used in acquiring such spectra can impact significantly on the chemical shifts of some resonances.

Extensions of this synthesis of marinoquinoline A to congeners B (**2**) and C (**3**) proved straightforward. Thus, treatment of compound **20** with either iso-butylmagnesium bromide or its benzyl counterpart and then with sodium methoxide gave, presumably via intermediates **24** or **25**, marinoquinolines B (**2**) (69%) and C (**3**) (55%), respectively. While all the spectral data obtained on these products were in complete accord with the assigned structures, final confirmation of these followed from single-crystal X-ray analyses, details of which are presented in the Experimental Section and the SI. In addition the acquired NMR, IR and mass spectral data matched those reported³ for the natural products, especially when account is taken, as mentioned above, of the impacts of the water content and pH of the medium used in acquiring NMR spectra.

Scheme 3: Syntheses of Marinoquinolines **1**, **2** and **3** from *N*-Oxide **20**

(iv) *Synthesis of Marinoquinoline D*

The reaction sequence used to produce compound **4**, the structure assigned to the hitherto previously unsynthesized marinoquinoline D, is shown in **Scheme 4**. Thus, as before, the *N*-oxide **20** was treated with the relevant Grignard reagent (in this case *p*-methoxybenzylmagnesium bromide). ¹H NMR and mass spectral analysis of an aliquot of the reaction mixture suggested that the major component of this initial reaction was the C4 substituted *N*-oxide **26**, presumably arising from re-oxidation of the initially formed adduct (analogous to compounds **23-25** shown in Scheme 3). Accordingly, the mixture was exposed to dihydrogen in the presence of 5% palladium on carbon in methanol. Under such conditions both the *N*-oxide and tosyl residues were cleaved and thus affording, in 68% yield, the *O*-methyl ether derivative **27** of target **4**. Finally, reaction of compound **27** with boron tribromide in dichloromethane at 0 to 22 °C resulted in the required demethylation and formation of compound **4** which was

obtained in 89% yield. All the spectral data acquired on this material were consistent with the assigned structure but final confirmation of this also followed from a single-crystal X-ray analysis. Significantly, the ^1H and ^{13}C NMR spectra of compound **4** recorded in CD_3OD did not match those reported³ for marinoquinoline D until a drop of acetic acid was added to the sample being analyzed and then the matches between the relevant data sets were very good (see SI). It should be noted that over the time needed to acquire ^{13}C NMR spectra data on the synthetically-derived compound **4** decomposition of the acetic acid-treated sample became evident.

Scheme 4: The Total Synthesis of MQ-D (**4**)

(v) *Synthesis of Marinoquinoline E*

In order to exploit indole as the nucleophilic species that would become attached at C4 of the 3*H*-pyrrolo[2,3-*c*]quinolone framework [and thus producing marinoquinoline E (**5**)], the pivotal *N*-oxide **20** was activated (Scheme 5) by in situ treatment with *p*-toluenesulfonic anhydride. The resulting sulfonate was then treated with indole followed by sodium methoxide and so producing target **5** in 73% yield. All the spectral data recorded on adduct **5** were in accord with the assigned structure which was confirmed by a single-crystal X-ray analysis. In addition these spectral data proved to be an excellent match with those reported for the natural product marinoquinoline E (see SI for a tabular comparison of the two sets of ^{13}C NMR spectral data). In the ^{13}C NMR spectrum, the doubling-up or fine splitting of the resonances due to those carbons adjacent to the linkage between the indole and 3*H*-pyrrolo[2,3-*c*]quinolone

subunits of compound **5** suggests that, on the NMR time-scale, there may be some restricted rotation between them.

Scheme 5: The Synthesis of Marinoquinoline E (**5**).

(vi) *Synthesis of Marinoquinoline F*

In an initial attempt to prepare the structure, **6**, assigned to marinoquinoline F the pivotal *N*-oxide **20** was treated (Scheme 6) with ClCONMe_2 and TMS-CN^{25} and thereby affording, via a modified Reissert-Henze reaction, the 2-cyano-substituted 3*H*-pyrrolo[2,3-*c*]quinolone **28** (82%). While the success of this conversion was evident from the spectral data obtained on the product final confirmation of its structure followed from a single-crystal X-ray analysis (see Experimental Section and SI for details). Compound **28** was itself treated with indole in the presence SnCl_4 , conditions defined by Ottoni²⁶ for C3-acylation (of indoles), but rather than obtaining the hoped-for target MQ-F (**6**) only CN group cleavage was observed. As such a new approach to this natural product was pursued.

Scheme 6: The Synthesis of Nitrile **28**.

The ultimately successful but non-regioselective route to MQ-F established during the course of the present study is shown in Scheme 7. This involved treating the *N*-oxide **20** with POBr_3 and thereby providing bromide **29** (81%), the structure of which was

established by single-crystal X-ray analysis. Treatment of this last compound with *n*-BuLi, with the intention of forming the halogen-for-lithium exchange product **30**, then quenching the reaction mixture with the readily prepared indole-3-carboxaldehyde **31**²⁷ afforded, after aqueous work-up and chromatographic purification, the anticipated adduct **32** (52%) together with its separable regio-isomer **33** (24%). The latter product presumably arises through reaction of the C2-lithiated isomer of compound **30** with the added electrophile. Separate treatment of each of alcohols **32** and **33** with activated manganese dioxide in dichloromethane afforded the corresponding ketones, **34** (99%) and **35** (93%), respectively and independent treatment of each of these with sodium methoxide in methanol resulted in cleavage of the associated tosyl residues and the formation of corresponding free pyrroles **36** (85%) and **6** (85%). The spectral data derived from compounds **6** and **36** were entirely consistent with assigned structures but confirmation of these followed from single-crystal X-ray analyses on each of them (see Experimental Section and SI for details). Furthermore, a comparison of the spectral data derived from compound **6** with those reported³ for MQ-F (see SI) revealed a good match. As appeared to be the case with congener **5**, in the ¹³C NMR spectrum the doubling-up or fine splitting of the resonances due to those carbons involved in or adjacent to the carbonyl-linked indole and 3*H*-pyrrolo[2,3-*c*]quinolone subunits of compound **6** suggests there may be some restricted rotation between them.

Scheme 7: The Synthesis of MQ-F (6).

On one occasion, after oxidation of compound **32** with manganese dioxide then the mono-tosylate **37** (21%) was obtained alongside the previously observed bis-tosylate **35** and so suggesting that the sulfonamide residue attached to the 3*H*-pyrrolo[2,3-*c*]quinolone framework is more labile than its counterpart associated with the indole moiety.

(vii) *Synthesis of Aplidiopsamine A*

The adaptation of the synthetic sequences described above to the preparation of aplidiopsamine A (**12**) is shown in Scheme 8. Thus, the initial step involves the same one as employed earlier, namely the palladium-catalyzed Ullmann cross-coupling of iodopyrrole **13** with bromobenzene **14** to afford product **15**. However, at this point rather than effecting reductive cyclization of the last compound this was, instead, reacted with methyl lithium and the product alcohol immediately oxidized with

manganese dioxide and so producing the previously reported¹⁷ and crystalline methyl ketone **38** (42% over two steps). Interestingly, reactions analogous to those observed on treating compound **15** with *iso*-butylmagnesium bromide (see Scheme 1), and wherein nucleophilic addition to the nitroaromatic takes place, were not observed on reaction of the same substrate with methyl lithium.

The conversion of compound **38** into the corresponding mono-bromide **39** (that would serve as the electrophile in a reaction with adenine) proved challenging due to the co-production of its di-bromo derivative. Eventually, it was established that copper(II) bromide was the most effective reagent for this purpose²⁸ and the ca. 10% of contaminating di-bromide could be removed by treating the brominated mixture with diethyl phosphite and so providing compound **39** in 94% yield after purification by flash chromatography. Treatment of a 1:1 mixture of the last compound and adenine with sodium hydride and using DMF as the solvent then afforded adduct **40** (84%) in which the *N*-tosyl moiety associated with substrate **39** had been cleaved. The structure of compound **40** was confirmed by single-crystal X-ray analysis. Exposure of a THF solution of this adduct to an atmosphere of dihydrogen in the presence of Raney nickel for 24 h effected a reductive cyclization to afford the *N*-oxide **41** (33%), a rather intractable compound that proved difficult to fully dissolve in a range of standard solvents. By using Raney cobalt as the catalyst, ethyl acetate as the solvent and heating the reaction under reflux for 60 h then complete conversion of substrate **40** into target **12** (92%) could be realized. Product **12** proved much more tractable than congener **41** and its structure was confirmed by single-crystal X-ray analysis of the dihydrate of its bis-hydrochloride salt. A comparison (see SI) of the ¹³C NMR spectroscopic data recorded on this synthetically-derived material with the corresponding data reported⁵ for the natural product aplidiopsamine A clearly established that they are one and the same compound.

Scheme 8: A Total Synthesis of Aplidiopsamine A (12)

Biological Evaluation and Docking Studies

The evaluation of compounds **1-6** and **11** together with synthetically-derived aplidiopsamine A (**12**) as inhibitors of acetylcholine esterase (AChE) was undertaken using the same protocols¹ as employed by those researchers who identified and evaluated the naturally-derived marinoquinoline A (**1**). Lactam **22** and compound **36**, the regioisomer of marinoquinoline F (**6**), were also evaluated in the same assay. As shown in Table 1, the most active of all these heterocyclic compounds was MQ-B (**2**) while congeners **1**, **3** and **5** also displayed notable inhibitory properties. The significantly less potent activities of MQ-D (**4**) and the “parent” heterocycle (viz. MQ-K or **11**) as well as the lack of any inhibitory effects of compounds **6**, **12**, **22** and **36** clearly demonstrate that the precise nature of the C4 substituent on the 3*H*-pyrrolo[2,3-*c*]quinolone framework plays a major role in determining activity.

Table 1: Results of Testing Compounds **1-6**, **11**, **12**, **22** and **36** as AChE Inhibitors^a

Entry	Compound	IC ₅₀ (μM)	Entry	Compound	IC ₅₀ (μM)
1	1	5.5 (± 0.8) ^b	6	6	No inhib.
2	2	3.6 (±1.8)	7	11	42.7 (±3.4)
3	3	8.1 (±1.5)	8	12	No inhib.
4	4	31.8 (±3.1)	9	22	No inhib.
5	5	5.8 (±01.8)	10	36	No inhib.

a: see experimental section for details of the assay employed; b Sangnoi *et al* report¹ an IC₅₀ of 4.9 μM for compound **1**.

In an effort to understand how such substituent effects might be arising, the structure of the active marinoquinoline B (**2**) was docked into that of human acetylcholinesterase (**4BDT**) using Autodock Vina²⁹ with tacrine removed from the active site gorge of this enzyme. As revealed in Figure 2, the 3*H*-pyrrolo[2,3-*c*]quinolone framework of compound **2** participates, on its opposite faces, in π -stacking interactions with the aromatic residues of tyrosine Y337 and tryptophan W86 and in an orientation that allows the C4 *iso*-butyl group to insert into a nearby pocket and so enhancing binding, presumably through van der Waals interactions.

Figure 2: Marinoquinoline B (**2**) docked into the structure of human acetylcholinesterase (**4BDT**) showing the main interactions between W86, Y337 and this inhibitor.

Conclusions

The chemical synthesis studies detailed herein serve to confirm the structures of a significant fraction of the currently known members of the marinoquinoline family of natural products, most notably congeners **4** and **6** that have not been the subject of previous such efforts. This work, when considered alongside the outcomes of the evaluation of these compounds and certain analogues as inhibitors of AChE, should form the basis for the development of even more potent compounds that may, themselves, allow for the development of useful new therapeutic agents. Work directed towards such ends is now underway in our laboratories, including through various efforts to find analogues with enhanced lipophilic properties that address the solubility issues that are otherwise likely to compromise the development of the title compounds in medical settings.

Experimental Section

Chemical Synthesis Studies

(i) General Experimental Procedures

Unless otherwise specified, proton (^1H) and proton-decoupled carbon [$^{13}\text{C}\{^1\text{H}\}$] NMR spectra were recorded at 18 °C in base-filtered CDCl_3 on a Varian spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For ^1H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^1H NMR data are recorded as follows: chemical shift (δ [ppm] multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual CHCl_3 appearing at δ_{H} 7.26 and the central resonance of the CDCl_3 “triplet” appearing at δ_{C} 77.0 were used to reference ^1H and ^{13}C NMR spectra, respectively. Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer 1800 Series FTIR Spectrometer. Samples were analyzed as thin films on KBr plates. A VG Fisons AutoSpec mass spectrometer was used to obtain low- and high-resolution electron impact (EI) mass spectra. Low- and high-resolution electrospray (ESI) mass spectra were obtained on a VG Quattro II triple-quadrupole MS instrument operating in positive ionization mode. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F₂₅₄ plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al.*³⁰ with silica gel 60 (40-63 μm) as the stationary phase.

HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma-Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF), methanol and dichloromethane (DCM) were dried using a Glass Contour solvent purification system that is based upon a technology originally described by

Grubbs *et al.*³¹ Where necessary, reactions were performed under an argon atmosphere.

(ii) Specific Experimental Procedures and Product Characterization

3-(5-Isobutyl-2-nitrophenyl)-1-tosyl-1*H*-pyrrole-2-carbaldehyde (16) and 7-Isobutyl-1-tosyl-1,8-dihydroindeno[2,1-*b*]pyrrol-8-ol (17). A magnetically stirred solution of compound **15**¹⁷ (248 mg, 0.67 mmol) in THF (7 mL) was cooled to –78 °C and while being maintained under nitrogen was treated, dropwise, with *i*-BuMgBr (370 µL of a 2.0 M solution in diethyl ether, 0.74 mmol) and the ensuing mixture warmed to 0 °C over 2 h. The reaction mixture was then quenched with NH₄Cl (10 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were washed with water (2 × 50 mL) before being dried (MgSO₄), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) and so giving two fractions, A and B.

Concentration of fraction A (*R*_f = 0.4) gave compound **16** (73 mg, 25%) as an amorphous, yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 9.84 (s, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 3.2 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.28 (dd, *J* = 8.3 and 1.9 Hz, 1H), 7.09 (d, *J* = 1.9 Hz, 1H), 6.39 (d, *J* = 3.2 Hz, 1H), 2.53 (d, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 1.88 (m, 1H), 0.90 (d, *J* = 6.7 Hz, 6H). ¹³C{¹H}NMR (100 MHz, CDCl₃) δ 178.8, 147.7, 146.8, 146.0, 136.3, 135.2, 132.9, 130.2, 129.9, 128.5, 128.3, 128.2, 127.4, 124.6, 113.9, 44.9, 30.0, 22.2, 21.7. IR ν_{max} 2958, 1674, 1612, 1586, 1549, 1522, 1446, 1375, 1178, 1089, 1027, 966, 910 cm⁻¹. MS (ESI, +ve) 449 [(M+Na)⁺, 100%], 427 [(M+H)⁺, 35]; HRMS (ESI, +ve) [M+H]⁺ calcd. for C₂₂H₂₃N₂O₅³²S 427.1328, found 427.1327.

Concentration of fraction B (*R*_f = 0.35) afforded a brown oil presumed to contain compound **17**. This material was subjected, without further purification, to the transformation detailed immediately below.

(rel-3a*S*,8a*S*)-7-Isobutyl-1-tosyl-2,3,3a,8a-tetrahydroindeno[2,1-*b*]pyrrol-8(1*H*)-one (19). The oil presumed to contain alcohol **17** (and obtained as detailed immediately above) was dissolved in dichloromethane (10 mL). While being maintained at 22 °C under nitrogen, the resulting and magnetically stirred solution was treated with the Dess-Martin periodinane³² (106 mg, 0.25 mmol). After a further 1 h the reaction mixture was concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 9:1 v/v 40-60 petroleum spirits/ethyl acetate

elution). Concentration of the relevant fractions ($R_f = 0.5$) gave a clear, yellow oil (44 mg) presumed to contain compound **18**. This oil was dissolved in methanol (4 mL) and the resulting solution treated with Pd/C (10 mg of 10% w/w material) then stirred magnetically under an atmosphere of hydrogen at 22 °C for 16 h. The reaction mixture was then filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v hexane/ethyl acetate elution) to afford, after concentration of the appropriate fractions ($R_f = 0.35$), the title compound **19** (36 mg, 20% over 3 steps) as a white, crystalline solid, no melting point, slow decomposition above ca. 100 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.85 (d, $J = 8.3$ Hz, 2H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.32 (d, $J = 7.7$ Hz, 2H), 7.22 (m, 1H), 7.11 (d, $J = 7.4$ Hz, 1H), 4.62 (d, $J = 7.2$ Hz, 1H), 3.81 (m, 1H), 3.71 (m, 1H), 2.96-2.87 (complex m, 2H), 2.80 (dd, $J = 12.5$ and 7.3 Hz, 1H), 2.44 (s, 3H), 1.97 (m, 1H), 1.85-1.74 (complex m, 2H), 0.87 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.6$ Hz, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 201.1, 155.3, 143.7, 143.5, 136.6, 135.0, 132.8, 130.4, 129.7, 127.6, 123.4, 66.3, 47.9, 42.4, 40.5, 32.6, 29.8, 22.4, 22.3, 21.6. IR ν_{max} (neat) 2955, 1717, 1593, 1350, 1161, 1091, 966, 717, 661 cm^{-1} . MS (EI, 70 eV) 383 (M^+ , 50%), 228 (100), 210 (25), 199 (40), 185 (30), 91 (38). HRMS (EI, 70 eV) M^+ calcd. for $\text{C}_{22}\text{H}_{25}\text{NO}_3^{32}\text{S}$, 383.1555, found 383.1554.

3-Tosyl-3H-pyrrolo[2,3-*c*]quinolone (21). A magnetically stirred a solution of compound **15**¹⁷ (4.33 g, 11.7 mmol) in THF (35 mL) maintained at 22 °C was treated with W-7 Raney-nickel³³ (430 mg of 10% w/w material) and the resulting suspension stirred vigorously under an atmosphere of hydrogen for 4 h. The ensuing mixture was concentrated under reduced pressure and the residue subjected to flash chromatography (silica, 9:1 v/v dichloromethane/diethyl ether then 9:1 v/v dichloromethane/methanol elution) to yield, after concentration of the appropriate fractions ($R_f = 0.5$ in 7:2:1 v/v/v dichloromethane/40-60-petroleum spirit/diethyl ether elution) compound **21** (1.20 g, 80%) as an amorphous yellow solid. A fraction of this solid was crystallized (dichloromethane) to give a spectroscopically pure sample of compound **21** as yellow crystals, m.p. = 215-216 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 9.58 (s, 1H), 8.19 (d, $J = 8.3$ Hz, 1H), 8.09 (dd, $J = 8.0$ and 1.5 Hz, 1H), 7.83 (d, $J = 8.4$ Hz, 2H), 7.79 (d, $J = 3.5$ Hz, 1H), 7.66 (m, 1H), 7.59 (m, 1H), 7.22 (d, $J = 8.4$ Hz, 2H), 7.16 (d, $J = 3.5$ Hz, 1H), 2.31 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ 145.8, 143.7, 137.8, 134.9, 132.6, 130.2, 129.7, 128.6, 127.9, 127.8, 127.0, 126.9, 123.1, 122.5, 106.5, 21.5. IR ν_{max} (thin film) 3129, 3041, 1592, 1511, 1493, 1375, 1362,

1164, 1136, 1086, 939, 671, 586 cm^{-1} . MS (ESI, +ve) 323 $[(\text{M} + \text{H})^+, 100\%]$. HRMS (EI, 70 eV) $\text{M}^{+\bullet}$ calcd. for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_2^{32}\text{S}$, 322.0776, found 322.0776.

3-Tosyl-3*H*-pyrrolo[2,3-*c*]quinoline 5-oxide (20). A solution of compound **21** (1.42 g, 4.4 mmol) in dichloromethane (15 mL) was treated with *m*-CPBA (1.30 g of 70% w/w peracid material, 5.3 mmol) and the resulting solution stirred magnetically at 22 °C for 2 h. After this time flash chromatography-grade silica (5 g) was added to the reaction mixture before it was concentrated under reduced pressure. Then resulting free-flowing solid was subjected to flash chromatography (silica, 9:1 v/v dichloromethane/methanol elution) to give, after concentration of the appropriate fractions ($R_f = 0.2$ in 4:1 v/v dichloromethane/acetone), compound **20** (1.23 g, 83%) as a light-brown amorphous solid. Crystallization of a fraction of this material (from warm DMSO) gave yellow crystals, no melting point, slow decomposition between 80 and 300 °C. ^1H NMR (CDCl_3 , 400 MHz) δ 9.37 (s, 1H), 8.86-8.79 (complex m, 1H), 8.11-8.08 (complex m, 1H), 7.83 (d, $J = 8.4$ Hz, 2H), 7.77 (m, 1H), 7.76-7.68 (complex m, 2H), 7.28 (d, $J = 8.4$ Hz, 2H), 7.11 (m, 1H), 2.36 (s, 3H). ^1H NMR (acetone- D_6 , 400 MHz) δ 9.15 (s, 1H), 8.72-8.67 (complex m, 1H), 8.38-8.33 (complex m, 1H), 8.03 (d, $J = 8.4$ Hz, 2H), 7.98 (d, $J = 3.5$ Hz, 1H), 7.82-7.75 (complex m, 2H), 7.49-7.43 (complex m, 3H), 2.38 (s, 3H). IR ν_{max} 3048, 1593, 1424, 1376, 1211, 1170, 1129, 936, 668 cm^{-1} . MS (EI, 70 eV) 338 ($\text{M}^{+\bullet}$, 30%) 322 $[(\text{M}-\text{O}\bullet)^+, 100]$. HRMS (EI, 70 eV) $\text{M}^{+\bullet}$ calcd. for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_3^{32}\text{S}$ 338.0725, found 338.0730. Due to its limited solubility in all commonly available deuterated solvents a ^{13}C NMR spectrum of this compound could not be obtained.

3-Tosyl-3,5-dihydro-4*H*-pyrrolo[2,3-*c*]quinolin-4-one (22). In an attempt to dissolve it, a suspension of compound **20** (34 mg, 0.1 mmol) in DMSO- D_6 (0.5 mL containing traces of water) was heated to 80 °C for 0.25 h. The cooled mixture was concentrated overnight under a stream of nitrogen and the residue subjected to flash chromatography (silica, 4:1 v/v dichloromethane/ethyl acetate elution) to afford, after concentration of the appropriate fractions ($R_f = 0.4$), a pale-brown, amorphous solid, crystallization (dichloromethane/methanol) of which gave lactam **22** (30.9 mg, 91%) bright-yellow crystals, m.p. = 265-266 °C. ^1H NMR (400 MHz, CDCl_3) δ 11.07 (broad s, 1H), 8.06-8.00 (complex m, 3H), 7.85 (d, $J = 7.9$ Hz, 1H), 7.47 (m, 1H), 7.38 (m, 1H), 7.30-7.25 (complex m, 3H), 6.96 (d, $J = 3.4$ Hz, 1H), 2.37 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 145.2, 135.9, 135.7, 135.1, 131.2, 129.7, 129.5, 128.7(1), 128.6(5), 126.4, 123.5, 122.8, 116.1, 116.1, 104.7, 21.7. IR ν_{max} 1600, 1593, 1417, 1373, 1360, 1170, 1121, 1084, 1008, 807, 783, 731, 748, 736, 666, 603 cm^{-1} . MS

(ESI, +ve) 699 [(2M + Na)⁺, 80%], 361 [(M + Na)⁺, 100], 339 [(M + H)⁺, 20]. HRMS (ESI, +ve) (M+Na)⁺ calcd. for C₁₈H₁₄N₂O₃³²S²³Na 361.0623, found 361.0624.

3H-Pyrrolo[2,3-*c*]quinoline (11). A magnetically stirred solution of compound **21** (100 mg, 0.31 mmol) in methanol (5 mL) maintained at 22 °C was treated with sodium methoxide (30 mg, 0.62 mmol) and the resulting mixture heated under reflux for 2 h. Flash chromatography-grade silica gel (1.0 g) was then added to the cooled reaction mixture that was then concentrated under reduced pressure. The resulting free-flowing solid was subjected to flash chromatography (silica, 95:5 v/v dichloromethane/methanol elution) to give, after concentration of the appropriate fractions (*R*_f = 0.2), a yellow solid that upon recrystallization (acetone) gave compound **11** (49.7 mg, 95%) as pale-yellow crystals, m.p. = 226-227 °C. ¹H NMR (400 MHz, acetone-D₆) δ 11.22 (broad s, 1H), 9.09 (s, 1H), 8.29 (m, 1H), 8.09 (m, 1H), 7.65 (d, *J* = 2.8 Hz, 1H), 7.56 (m, 2H), 7.15 (d, *J* = 2.8 Hz, 1H). ¹³C NMR (100 MHz, acetone-D₆) δ 143.7, 139.0, 130.6, 128.6, 127.8, 127.7, 126.4, 126.1, 124.7, 123.9, 101.5. IR ν_{max} 2812, 1590, 1483, 1366, 1347, 793, 750 cm⁻¹. MS (ESI, +ve) 169 [(M + H)⁺, 100%]. HRMS (ESI, +ve) (M + H)⁺ calcd. for C₁₁H₉N₂ 169.0766, found 169.0766.

4-Methyl-3H-pyrrolo[2,3-*c*]quinoline (1). Methylmagnesium bromide (750 μL of a 2.0 M solution in THF, 1.5 mmol) was added, dropwise, to a magnetically stirred solution of compound **20** (100 mg, 0.3 mmol) in THF (3 mL) maintained at 0 °C and the ensuing mixture was then allowed to warm to 22 °C. After 6 h the reaction mixture was quenched with NH₄Cl (10 mL of a saturated solution) then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with brine (1 × 30 mL) before being dried (MgSO₄), filtered and concentrated under reduced pressure. The residue thus obtained, and presumed to contain compound **23**, was dissolved in methanol (10 mL) and the ensuing solution treated with sodium methoxide (32 mg, 0.6 mmol) then heated under reflux for 16 h. reflux overnight. The cooled reaction mixture was concentrated under reduced pressure and the residue so obtained subjected to flash chromatography (silica, 9:1 v/v dichloromethane/methanol elution) to afford, after concentration of the relevant fractions (*R*_f = 0.4), compound **1** (31 mg, 57%) as a pale-yellow and amorphous solid. ¹H NMR (400 MHz, acetone-D₆) δ 11.39 (broad s, 1H), 8.24 (m, 1H), 8.05 (m, 1H), 7.63 (d, *J* = 3.0 Hz, 1H), 7.52 (m, 2H), 7.14 (d, *J* = 2.9 Hz, 1H), 2.87 (s, 3H). ¹³C{¹H} NMR (100 MHz, acetone-D₆) δ 146.8, 143.0, 129.6, 129.2, 128.7, 127.8, 126.3, 125.9, 124.0, 123.8, 102.1, 20.9. IR ν_{max} 3119, 3082, 2952,

2795, 1587, 1533, 1481, 1364, 1198, 1137, 751 cm^{-1} . MS (ESI, +ve) 183 $[(M + H)^+]$, 100%]. HRMS (ESI, +ve) $(M + H)^+$, calcd. for $\text{C}_{12}\text{H}_{11}\text{N}_2$ 183.0922, found 183.0922.

4-Isobutyl-3H-pyrrolo[2,3-c]quinoline (2). *iso*-Butylmagnesium bromide (750 μL of a 2.0 M solution in Et_2O , 1.5 mmol) was added, dropwise, to a magnetically stirred solution of compound **20** (100 mg, 0.3 mmol) in THF (3 mL) maintained at 0 $^\circ\text{C}$. The ensuing mixture was then allowed to warm to 22 $^\circ\text{C}$ and after 24 h treated with methanol (1 mL) before being concentrated under reduced pressure. The residue thus obtained, and presumed to contain compound **24**, was dissolved in methanol (10 mL) and the ensuing solution treated with sodium methoxide (32 mg, 0.6 mmol) before being heated under reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the resulting brown solid subjected to flash chromatography (silica, 19:1 v/v dichloromethane/methanol elution) to afford, after concentration of the relevant fractions ($R_f = 0.3$), an amorphous white solid. Crystallization (acetone) of this material gave compound **2** (48 mg, 69%) as a colorless crystals, m.p. = 189-191 $^\circ\text{C}$. ^1H NMR (400 MHz, acetone- D_6) δ 11.20 (broad s, 1H), 8.24 (m, 1H), 8.04 (m, 1H), 7.57 (d, $J = 3.0$ Hz, 1H), 7.55-7.46 (complex m, 2H), 7.13 (d, $J = 3.0$ Hz, 1H), 3.08 (d, $J = 7.3$ Hz, 2H), 2.45 (m, 1H), 0.99 (d, $J = 6.6$ Hz, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, acetone- D_6) δ 150.0, 143.7, 130.1, 128.6, 127.0, 126.8, 126.0, 125.6, 124.1, 123.7, 101.9, 44.1, 29.0, 23.0. IR ν_{max} 3080, 2957, 2794, 1586, 1481, 1361, 1195, 1139, 876, 846, 751 cm^{-1} . MS (ESI, +ve) 225 $[(M + H)^+]$, 100%]. HRMS (ESI, +ve) $(M + H)^+$ calcd. for $\text{C}_{15}\text{H}_{17}\text{N}_2$ 225.1392, found 225.1392.

4-Benzyl-3H-pyrrolo[2,3-c]quinoline (3). Benzylmagnesium bromide (750 μL of a 2.0 M solution in THF, 1.5 mmol) was added, dropwise, to a magnetically stirred solution of compound **20** (100 mg, 0.3 mmol) in THF (3 mL) maintained at 0 $^\circ\text{C}$ and the ensuing mixture then allowed to warm to 22 $^\circ\text{C}$. After 24 h methanol (1 mL) was added to the reaction mixture that was then concentrated under reduced pressure. The ensuing residue, presumed to contain compound **25**, was dissolved in methanol (10 mL) and the solution so-formed treated with sodium methoxide (32 mg, 0.6 mmol) then heated under reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure and resulting brown solid subjected to flash chromatography (silica, 19:1 v/v dichloromethane/methanol elution). Concentration of the relevant fractions ($R_f = 0.3$) gave a light-yellow and amorphous solid that upon crystallization (acetone) gave compound **3** (42 mg, 55%) as yellow crystals, m.p. = 176-178 $^\circ\text{C}$. ^1H NMR (400 MHz, acetone- D_6) δ 11.19 (broad s, 1H), 8.25 (dd, $J = 7.8$ and 1.9 Hz, 1H), 8.10 (dd, $J = 7.4$ and 2.2 Hz, 1H), 7.58 (d, $J = 3.0$ Hz, 1H), 7.54 (m, 2H), 7.44 (d, $J = 7.6$ Hz,

2H), 7.23 (m, 2H), 7.15 (m, 2H), 4.60 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, acetone- D_6) δ 148.8, 143.3, 139.8, 129.7(7), 129.7(5), 129.5, 129.2, 127.9 (broadened), 127.1, 126.4, 126.1, 124.1, 123.8, 102.2, 41.3 (one signal obscured or overlapping). IR ν_{max} 3429, 3059, 2924, 2853, 1646, 1479, 1361, 878, 748 cm^{-1} . MS (EI, 70 eV) 258 ($\text{M}^{+\bullet}$, 60%), 257 [$(\text{M} - \text{H}\bullet)^+$, 100]. HRMS (EI, 70 eV) $\text{M}^{+\bullet}$ calcd. for $\text{C}_{18}\text{H}_{14}\text{N}_2$ 258.1157, found 258.1158; [$(\text{M} - \text{H}\bullet)^+$ calcd. for $\text{C}_{18}\text{H}_{13}\text{N}_2$ 257.1079, found 257.1067.

4-(4-methoxybenzyl)-3H-pyrrolo[2,3-*c*]quinolone (27). *p*-Methoxybenzyl-magnesium bromide (6.0 mL of a 0.25 M solution in THF, 1.5 mmol) was added, dropwise, to a magnetically stirred solution of compound **20** (101 mg, 0.3 mmol) in THF (3 mL) maintained at 22 °C under nitrogen and then the ensuing mixture heated under reflux for 16 h. After this time, methanol (1 mL) was added to the cooled reaction mixture that was then concentrated under reduced pressure. ^1H NMR and mass spectral analysis of the ensuing residue suggested the presence of significant quantities of oxide **26** and so it (the residue) was dissolved in methanol (10 mL) and the resulting solution treated with Pd/C (100 mg of 5% w/w material) and the suspension so-formed stirred at 22 °C under an atmosphere of hydrogen for 16 h. The reaction mixture was then filtered through a short pad of TLC-grade silica that was itself washed with methanol (15 mL). The combined filtrates were concentrated under reduced pressure and the resulting brown oil subjected to flash chromatography (silica, 4:1 v/v dichloromethane/ethyl acetate elution) to afford, after concentration of the relevant fractions ($R_f = 0.3$), compound **27** (58 mg, 68%) as a white, amorphous solid. ^1H NMR (400 MHz, CD_3OD) δ 8.33 (broad s, 1H), 8.18 (dd, $J = 7.3$ and 2.0 Hz, 2H), 7.64-7.53 (complex m, 2H), 7.27 (d, $J = 8.3$ Hz, 2H), 7.23 (m, 1H), 7.00 (m, 1H), 6.86 (d, $J = 8.6$ Hz, 2H), 4.54 (s, 2H), 3.78 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CD_3OD) δ 160.0, 149.1, 140.9, 131.9, 131.4, 130.7, 130.6, 128.9, 127.9, 127.2, 126.7, 124.5, 124.2, 115.1, 102.9, 55.6, 39.3. MS (EI, 70 eV) 288 ($\text{M}^{+\bullet}$, 98%), 287 [$(\text{M} - \text{H}\bullet)^+$, 100], 273 [$(\text{M} - \text{Me}\bullet)^+$, 80]. HRMS (EI, 70 eV) $\text{M}^{+\bullet}$ calcd. for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$ 288.1263, found 288.1262; ($\text{M} - \text{H}\bullet$) calcd. for $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}$ 287.1184, found 287.1188.

4-((3H-Pyrrolo[2,3-*c*]quinolin-4-yl)methyl)phenol (4). Boron tribromide (500 μL of a 1 M solution in dichloromethane, 0.5 mmol) was added, dropwise, to a magnetically stirred solution of compound **27** (60 mg, 0.2 mmol) in dichloromethane, maintained at 0 °C. After 1 h the reaction mixture was allowed to warm to 22 °C over 2 h then treated with NaHCO_3 (20 mL of a saturated aqueous solution). The ensuing biphasic mixture was stirred for an additional 1 h then diluted with water (30 mL) and extracted with dichloromethane (3×30 mL). The combined organic phases were washed with

water (1 × 50 mL) before being dried (MgSO₄), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v dichloromethane/methanol elution) to afford, after evaporation of the appropriate fractions (*R*_f = 0.3), compound **4** (51 mg, 89%) as a white, crystalline solid, no melting point, degradation above 180 °C. ¹H NMR (400 MHz, CD₃OD with a trace of AcOH) δ 8.37 (m, 1H), 8.09 (m, 1H), 7.84 (dd, *J* = 2.9 and 1.2 Hz, 1H), 7.75-7.65 (complex m, 2H), 7.28 (d, *J* = 2.9 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 4.57 (s, 2H) (signals due to NH and OH group protons not observed). ¹³C{¹H} NMR (100 MHz, CD₃OD) δ 157.1, 150.0, 142.7, 130.8, 130.6, 130.2, 129.3, 128.2, 127.1, 126.6, 124.5, 124.2, 116.3, 102.3, 40.1 (one signal obscured or overlapping). ¹³C NMR (100 MHz, CD₃OD with a trace of AcOH) δ 157.7, 148.5, 138.4, 134.1, 133.3, 130.6, 129.0, 128.4, 128.0, 124.9, 124.6, 123.7, 116.7, 103.7, 38.2. IR ν_{max} 3438, 3223, 2926, 1586, 1513, 1480, 1360, 1250, 750 cm⁻¹. MS (ESI, +ve) 275 [(M + H)⁺, 100%]. HRMS (ESI, +ve) (M + H)⁺ calcd. for C₁₈H₁₅N₂O 275.1184, found 275.1183.

4-(1*H*-Indol-3-yl)-3*H*-pyrrolo[2,3-*c*]quinoline (5). A magnetically stirred solution of compound **20** (101 mg, 0.3 mmol), tosic anhydride (108 mg, 0.36 mmol) and indole (70 mg, 0.6 mmol) in THF (10 mL) was maintained at 22 °C under nitrogen for 1 h then heated under reflux for 12 h. The cooled reaction mixture was treated with methanol (10 mL) then sodium methoxide (32 mg, 0.6 mmol) and the resulting mixture heated under reflux for a further 2 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue partitioned between NH₄Cl (20 mL of a saturated aqueous solution) and ethyl acetate (20 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 20 mL) then the combined organic layers were dried (MgSO₄), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 19:1 v/v dichloromethane/methanol elution) to afford, after concentration of the appropriate fractions (*R*_f = 0.2), a yellow and amorphous solid, crystallization (acetone) of which gave compound **5** (61 mg, 73%) as bright-yellow crystals, m.p. = 251-252 °C. ¹H NMR (400 MHz, acetone-D₆) δ 10.96 (broad s, 1H), 10.79 (broad s, 1H), 8.79 (d, *J* = 7.7 Hz, 1H), 8.27 (m, 2H), 8.16 (dd, *J* = 8.1 and 1.1 Hz, 1H), 7.60 (d, *J* = 3.1 Hz, 1H), 7.59-7.48 (compound m, 3H), 7.28-7.18 (compound m, 3H). ¹³C{¹H} NMR (100 MHz, acetone-D₆) δ 144.5, 144.0, 137.9, 130.0, 129.5, 128.1, 127.8, 127.4, 126.9, 126.3, 125.5, 123.6(4), 123.5(9), 123.5(6), 123.3, 121.0, 115.2, 112.3, 102.1. IR ν_{max}

3401, 3167, 2920, 2850, 1703, 1581, 1452, 1380, 1241, 1116, 886 cm^{-1} . MS (ESI, +ve) 284 $[(\text{M} + \text{H})^+, 100\%]$. HRMS (ESI, +ve) $(\text{M} + \text{H})^+$, calcd. for $\text{C}_{19}\text{H}_{14}\text{N}_3$ 284.1188, found: 284.1183.

3-Tosyl-3H-pyrrolo[2,3-c]quinoline-4-carbonitrile (28). A magnetically stirred solution of compound **20** (338 mg, 1.0 mmol) in dichloromethane (10 mL) maintained under nitrogen at 10 °C was treated with dimethylaminocarbamoyl chloride (110 μL , 1.2 mmol) then TMSCN (150 μL , 1.2 mmol). The resulting mixture was stirred at 10 °C for 48 h and after this time treated with K_2CO_3 (10 mL of a saturated aqueous solution) then stirred vigorously for 1 h before the separated aqueous phase was extracted with dichloromethane (2×20 mL). The combined organic phases were dried (MgSO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 2:1 v/v 40-60 petroleum spirit/ethyl acetate elution) to afford, after concentration of the appropriate fractions ($R_f = 0.5$ in dichloromethane), a white amorphous solid, crystallization (acetone) of which gave compound **28** (82 mg, 82%) as white, crystalline masses, m.p. = 194-196 °C. ^1H NMR (400 MHz, acetone- D_6) δ 8.47 (m, 1H), 8.36 (d, $J = 3.6$ Hz, 1H), 8.17 (m, 1H), 8.07 (d, $J = 8.5$ Hz, 2H), 7.88-7.82 (complex m, 2H), 7.70 (d, $J = 3.6$ Hz, 1H), 7.49 (d, $J = 8.5$ Hz, 2H), 2.41 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, acetone- D_6) δ 147.4, 144.1, 137.0, 135.7, 133.6, 131.3, 130.8, 130.6, 130.2, 128.8, 126.6, 124.5, 124.3, 121.2, 116.7, 107.2, 21.6. IR ν_{max} 3148, 2925, 2235, 1512, 1493, 1380, 1175, 1135, 672, 600 cm^{-1} . MS (ESI, +ve) 717 $[(2\text{M} + \text{Na})^+, 40\%]$, 370 $[(\text{M} + \text{Na})^+, 50]$, 348 $[(\text{M} + \text{H})^+, 100]$. HRMS (ESI, +ve) $(\text{M} + \text{Na})^+$ calcd. for $\text{C}_{19}\text{H}_{13}\text{N}_3\text{O}_2^{32}\text{S}^{23}\text{Na}$ 370.0626, found 370.0627.

4-Bromo-3-tosyl-3H-pyrrolo[2,3-c]quinoline (29). A magnetically stirred solution of compound **15** (1.02 g, 3.0 mmol) in THF/dichloromethane (20 mL of a 1:1 v/v mixture) maintained at 22 °C under a nitrogen atmosphere was treated with phosphorus oxytribromide (1.29 g, 4.5 mmol) and the ensuing mixture stirred for 16 h then treated with NH_4OH (20 mL of a 10% w/w aqueous solution) before being extracted with dichloromethane (3×20 mL). The combined organic phases were dried (Na_2SO_4), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, dichloromethane elution) and gave, after concentration of the appropriate fractions ($R_f = 0.5$), an off-white solid, recrystallization (dichloromethane) of which gave compound **29** (970 mg, 81%) as white, crystalline masses, m.p. = 146-151 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.22 (d, J

= 3.6 Hz, 1H), 8.14 (m, 1H), 8.06 (m, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.70-7.61 (complex m, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 3.6 Hz, 1H), 2.41 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 145.4, 143.6, 136.8, 136.6, 133.2, 129.9, 128.8, 128.6, 127.5, 127.3(1), 127.2(8), 126.0, 123.1, 121.9, 104.7, 21.7. IR ν_{max} 3153, 1562, 1481, 1369, 1324, 1193, 1170, 1122, 1088, 942 cm^{-1} . MS (ESI, +ve) 403 and 401 [(M + H) $^+$, 95 and 100%]. HRMS (ESI, +ve) (M + H) $^+$ calcd. for $\text{C}_{18}\text{H}_{14}^{81}\text{BrN}_2\text{O}_2\text{S}$ 402.9939, found 402.9940; calcd. for $\text{C}_{18}\text{H}_{14}^{79}\text{BrN}_2\text{O}_2\text{S}$ 400.9959, found 400.9960.

(1-Tosyl-1*H*-indol-3-yl)(3-tosyl-3*H*-pyrrolo[2,3-*c*]quinolin-4-yl)methanol (32) and (1-Tosyl-1*H*-indol-3-yl)(3-tosyl-3*H*-pyrrolo[2,3-*c*]quinolin-2-yl)methanol (33). A magnetically stirred solution of compound **29** (555 mg, 1.38 mmol) in diethyl ether (14 mL) maintained at $-78\text{ }^\circ\text{C}$ under a nitrogen atmosphere was treated rapidly with *n*-BuLi (1.1 mL of a 1.31 M solution in hexanes, 1.45 mmol) and the ensuing mixture stirred for a further 0.25 h then a solution of *N*-tosylindole-3-carboxaldehyde (**31**)²⁷ (495 mg, 1.66 mmol) in THF (10 mL) added in one portion. The reaction mixture thus formed was stirred at $-78\text{ }^\circ\text{C}$ for an additional 1 h, quenched with NH_4Cl (10 mL of a saturated aqueous solution) then allowed to warm to $22\text{ }^\circ\text{C}$ before being extracted with ethyl acetate ($3 \times 30\text{ mL}$). The combined organic phases were washed with brine ($1 \times 50\text{ mL}$) then dried (MgSO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v dichloromethane/diethyl ether elution) and so affording two fractions, A and B.

Concentration of fraction A gave (R_f = 0.3) gave a pale-yellow solid, recrystallization (dichloromethane) of which gave compound **32** (444 mg, 52%) as pale-yellow crystals, m.p. = $179\text{--}181\text{ }^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3) δ 8.15 (broad s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.95 (m, 1H), 7.83-7.63 (complex m, 3H), 7.60 (t, J = 7.5 Hz, 1H), 7.47 (d, J = 7.9 Hz, 2H), 7.25 (m, 1H), 7.22-7.09 (complex m, 3H), 7.07-7.00 (complex m, 4H), 6.76 (d, J = 8.0 Hz, 2H), 6.33 (s, 1H), 5.80 (broad s, 1H), 2.20 (s, 3H), 2.14 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 148.0, 145.5, 144.8, 141.4, 136.8, 135.1, 135.0, 134.6, 133.8, 129.9, 129.8, 128.8, 128.4, 127.4, 126.7, 125.9, 125.6, 125.3, 124.7, 123.9, 123.3, 123.2, 122.4, 120.9, 113.2, 106.7, 65.3, 21.5(2), 21.4(7) (one signal obscured or overlapping). IR ν_{max} 3339, 1595, 1447, 1370, 1321, 1189, 1174, 1121, 1094, 1019, 990, 965, 811 cm^{-1} ; MS (ESI, +ve) 685 [(M + Na + MeCN) $^+$, 20%], 644 [(M + Na) $^+$ 10], 622 [(M + H) $^+$, 100]. HRMS (ESI, +ve) (M + H) $^+$ calcd. for $\text{C}_{34}\text{H}_{28}\text{N}_3\text{O}_5\text{S}_2$ 622.1470, found 622.1472.

Concentration of fraction B (R_f = 0.2) gave a light-brown solid, recrystallization (dichloromethane) of which gave compound **33** (204 mg, 24%) as

white, crystalline masses, m.p. = 234-236 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.69 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.85 (dd, *J* = 8.2 and 1.4 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.66-7.60 (complex m, 4H), 7.51 (m, 1H), 7.28 (m, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.13-7.02 (complex m, 4H), 6.89 (s, 1H), 6.73 (s, 1H), 4.25 (broad s, 1H), 2.34 (s, 3H), 2.31 (s, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 146.0, 145.1, 144.7, 143.4, 138.3, 135.3, 135.0(9), 135.0(6), 130.9, 130.4, 130.2, 129.9, 129.2, 128.5, 128.2, 127.1, 126.9, 126.4, 124.9, 123.3, 123.2, 122.4, 122.3, 122.0, 120.0, 113.8, 108.5, 63.1, 21.6 (one signal obscured or overlapping). IR ν_{max} 3116, 1710, 1364, 1169, 669, 570 cm⁻¹. MS (ESI, +ve) 644 [(M + Na)⁺, 20%], 622 [(M + H)⁺, 100]. HRMS (ESI, +ve) (M + H)⁺ calcd. for C₃₄H₂₈N₃O₅³²S₂ 622.1470, found 622.1470.

(1-Tosyl-1*H*-indol-3-yl)(3-tosyl-3*H*-pyrrolo[2,3-*c*]quinolin-2-yl)methanone (34). A magnetically stirred solution of compound **33** (404 mg, 0.65 mmol) in dichloromethane (10 mL) maintained under nitrogen at 22 °C was treated with activated MnO₂³⁴ (1.13 g, 13.0 mmol). The resulting suspension was stirred for 2 h then filtered through a pad of diatomaceous earth and the solids so-retained washed with dichloromethane (2 × 10 mL). The combined filtrates were concentrated under reduced pressure and the residue subjected to flash chromatography (silica, dichloromethane elution) to afford, after concentration of the appropriate fractions (*R*_f = 0.5), compound **34** (398 mg, 99%) as a bright-yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.78 (s, 1H), 8.41 (dd, *J* = 6.6 and 2.2 Hz, 1H), 8.34 (d, *J* = 8.4 Hz, 1H), 8.18 (s, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 2H), 8.02-7.96 (complex m, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.77 (m, 1H), 7.69 (m, 1H), 7.47 (s, 1H), 7.47-7.40 (complex m, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 2.40 (s, 3H), 2.38 (s, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 181.2, 146.3, 146.2, 142.9, 140.1, 138.3, 135.4, 135.1, 134.6, 134.1, 131.0, 130.4, 130.1, 129.9, 129.2, 128.7, 128.1, 127.9, 127.5, 127.3, 126.3, 125.2, 123.2, 123.0, 122.3, 121.8, 113.3, 110.9, 21.7(0), 21.6(5). IR ν_{max} 1650, 1532, 1381, 1190, 1176, 1131, 1086, 662, 570 cm⁻¹. MS (ESI, +ve) 683 [(M + Na + MeCN)⁺ 25%], 642 [(M + Na)⁺, 25], 620 [(M + H)⁺, 100]. HRMS (ESI, +ve) (M + H)⁺ calcd. for C₃₄H₂₆N₃O₅³²S₂ 620.1314, found 620.1315.

(1-Tosyl-1*H*-indol-3-yl)(3-tosyl-3*H*-pyrrolo[2,3-*c*]quinolin-4-yl)methanone (35) and (3*H*-Pyrrolo[2,3-*c*]quinolin-4-yl)(1-tosyl-1*H*-indol-3-yl)methanone (37). A magnetically stirred solution of compound **32** (879 mg, 1.41 mmol) in dichloromethane (20 mL) maintained at 22 °C under a nitrogen atmosphere was treated with activated MnO₂ (2.45 g, 28.2 mmol) and the resulting suspension stirred

for 1 h then filtered through a pad of diatomaceous earth and the solids thus retained washed with dichloromethane (2 × 20 mL). The combined filtrates were concentrated under reduced pressure and the residue subjected to flash chromatography (silica, dichloromethane elution). Concentration of the appropriate fractions ($R_f = 0.85$) gave a pale-orange solid, recrystallization (dichloromethane/diethyl ether/acetone) of which afforded compound **35** (816 mg (93%)), as yellow, crystalline masses, m.p. = 237-239 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.49-8.43 (complex m, 1H), 8.25-8.19 (complex m, 2H), 8.07 (s, 1H), 8.00-7.93 (complex m, 2H), 7.79 (d, $J = 8.2$ Hz, 2H), 7.77-7.67 (complex m, 4H), 7.45-7.38 (complex m, 2H), 7.35 (d, $J = 3.6$ Hz, 1H), 7.27 (d, $J = 8.1$ Hz, 4H), 2.39 (s, 3H), 2.35 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 187.5, 145.8, 145.5, 145.4, 142.1, 135.7, 135.4, 135.0(4), 135.0(2), 134.5, 131.6, 130.2, 129.8, 129.7, 128.5, 128.4, 127.9, 127.4, 127.2, 125.7, 124.9, 124.7, 123.1(0), 123.0(8), 123.0, 120.4, 113.2, 106.8, 21.7, 21.6. IR ν_{max} 3139, 3057, 1661, 1538, 1445, 1377, 1326, 1190, 1177, 1135, 1088, 962, 816, 750, 666, 572 cm^{-1} . MS (ESI, +ve) 700 [(M + Na + acetone) $^+$, 50%], 683 [(M + Na + MeCN) $^+$, 15], 642 [(M + Na) $^+$, 10], 620 [(M + H) $^+$, 100]. HRMS (ESI, +ve) (M + Na) $^+$ calcd. for $\text{C}_{34}\text{H}_{25}\text{N}_3\text{O}_5^{32}\text{S}_2^{23}\text{Na}$ 642.1133, found 642.1133.

On one occasion during the preparation of compound **35** small amounts of congener **37** were obtained as a brown oil, $R_f = 0.4$ (in 3:2 v/v dichloromethane 40-60 petroleum spirit). ^1H NMR (400 MHz, CDCl_3) δ 10.73 (broad s, 1H), 9.92 (s, 1H), 8.55 (m, 1H), 8.40 (dd, $J = 6.3$ and 3.4 Hz, 1H), 8.26 (dd, $J = 6.3$ and 3.4 Hz, 1H), 8.04 (m, 1H), 7.96 (d, $J = 8.2$ Hz, 2H), 7.70 (dd, $J = 6.3$ and 3.4 Hz, 2H), 7.55 (m, 1H), 7.40 (m, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 7.11 (m, 1H), 2.23 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ 188.9, 145.7, 141.3, 140.2, 138.0, 134.8, 134.2, 130.9, 130.7, 130.2, 129.2, 128.3, 128.2, 127.6, 127.3, 126.6, 125.4, 125.0, 124.8, 123.0, 123.0, 118.4, 113.1, 101.1, 21.6. IR ν_{max} 3437, 1626, 1525, 1377, 1176, 1134, 1103, 979, 797, 747, 665, 574 cm^{-1} . MS (ESI, +ve) 488 [(M + Na) $^+$, 21%], 466 [(M + H) $^+$, 31], 102 (100). HRMS (ESI, +ve) (M + H) $^+$ calcd. for $\text{C}_{27}\text{H}_{20}\text{N}_3\text{O}_3\text{S}$ 466.1225, found 466.1226.

(1*H*-Indol-3-yl)(3*H*-pyrrolo[2,3-*c*]quinolin-2-yl)methanone (36). A magnetically stirred solution of compound **34** (390 mg, 0.63 mmol) in methanol (10 mL) maintained at 22 °C under a nitrogen atmosphere was treated with sodium methoxide (78 mg, 1.44 mmol) and the resulting mixture heated under reflux for 1 h then cooled to 22 °C and treated with flash chromatography-grade silica (2 g) before being concentrated under reduced pressure. The resulting free-flowing solid was subjected to flash chromatography (silica, 19:1 v/v dichloromethane/methanol elution) and

concentration of the appropriate fractions ($R_f = 0.35$) gave compound **36** (166 mg, 85%) as a yellow, crystalline solid, no melting point, decomposition above ca. 150 °C. ^1H NMR (400 MHz, DMSO- D_6) δ 11.72 (broad s, 1H), 11.29 (broad s, 1H), 9.25 (s, 1H), 8.67 (m, 1H), 8.50-8.34 (complex m, 2H), 8.12 (m, 1H), 8.04 (s, 1H), 7.68-7.52 (complex m, 3H), 7.33-7.24 (complex m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- D_6) δ 179.9, 142.2, 139.5, 137.4, 136.6, 134.7, 130.2, 129.5, 126.8, 126.4(3), 126.4(1), 126.0, 123.8, 123.5, 123.3, 122.0, 121.6, 114.9, 112.3, 105.5. IR ν_{max} 3127, 2925, 2854, 1708, 1604, 1519, 1426, 1374, 1244, 1189, 854 cm^{-1} . MS (ESI, +ve) 334 [(M + Na) $^+$, 30%], 312 [(M + H) $^+$, 55], 169 (100). HRMS (ESI, +ve) (M + H) $^+$ calcd. for $\text{C}_{20}\text{H}_{14}\text{N}_3\text{O}$ 312.1137, found 312.1137.

(1*H*-Indol-3-yl)(3*H*-pyrrolo[2,3-*c*]quinolin-4-yl)methanone (6). A magnetically stirred solution of compound **35** (328 mg, 0.52 mmol) in methanol (10 mL) maintained at 22 °C under a nitrogen atmosphere was treated with sodium methoxide (115 mg, 2.1 mmol) and the resulting mixture heated under reflux for 16 h. The cooled reaction was concentrated under reduced pressure and the resulting yellow solid subjected to flash chromatography (silica, 99:1 v/v dichloromethane/diethyl ether elution) to afford, after concentration of the relevant fractions ($R_f = 0.55$), a bright-yellow, amorphous solid that was crystallized (dichloromethane) to give compound **6** (140 mg, 85%) yellow crystals, m.p. = 225-228 °C. ^1H NMR (400 MHz, acetone- D_6) δ 11.61 (broad s, 1H), 11.23 (broad s, 1H), 9.72 (s, 1H), 8.67 (d, $J = 6.7$ Hz, 1H), 8.38 (m, 1H), 8.31 (m, 1H), 7.79 (broad s, 1H), 7.72-7.64 (complex m, 2H), 7.60 (m, 1H), 7.35-7.25 (complex m, 2H), 7.24 (broad s, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, acetone- D_6) δ 189.0, 143.1, 142.3, 139.3, 137.2, 131.5, 131.4, 129.3, 129.0, 128.6, 128.3, 126.9, 125.8, 124.0, 123.9(5), 123.2, 123.1, 115.9, 112.8, 101.3. IR ν_{max} 3418, 3238, 1589, 1553, 1507, 1439, 1382, 1365, 1235, 1160, 1097, 1076, 866 cm^{-1} . MS (ESI, +ve) 645 [(2M + Na) $^+$, 5%], 334 [(M + Na) $^+$, 20], 312 [(M + H) $^+$, 100]. HRMS (ESI, +ve) (M + H) $^+$ calcd. for $\text{C}_{20}\text{H}_{14}\text{N}_3\text{O}$ 312.1137, found 312.1138.

1-(3-(2-Nitrophenyl)-1-tosyl-1*H*-pyrrol-2-yl)ethan-1-one (38). This compound was prepared according to a previously reported procedure¹⁷ and after chromatographic purification and recrystallization (diethyl ether) obtained, in 42% yield from compound **15**, as a light-yellow, crystalline solid, m.p. = 114-116 °C (lit.¹⁷ m.p. = 111-113 °C). ^1H NMR (400 MHz, CDCl_3) δ 8.00 (dd, $J = 8.0$ and 2.0 Hz, 1H), 7.89-7.80 (complex m, 2H), 7.68 (d, $J = 4.0$ Hz, 1H), 7.65-7.50 (complex m, 2H), 7.40-7.30 (complex m, 3H), 6.25 (d, $J = 4.0$ Hz, 1H), 2.44 (s, 3H), 1.96 (s, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR

(100 MHz, CDCl₃) δ 189.2, 148.9, 145.0, 136.1, 132.7, 132.4, 131.2, 131.0, 129.6, 129.5, 129.3, 127.8, 127.6, 124.5, 113.0, 29.9, 21.7. IR $\nu_{\max}$ 1675, 1527, 1402, 1354, 1175, 1137, 674, 578 cm⁻¹. MS (ESI, +ve) 791 [(2M + Na)⁺, 11%], 407 [(M + Na)⁺, 100], 385 [(M + H)⁺, 20]. HRMS (ESI, +ve) (M + Na)⁺ calcd. for C₁₉H₁₆N₂O₅S²³Na 407.0678, found: 407.0678.

2-Bromo-1-(3-(2-nitrophenyl)-1-tosyl-1H-pyrrol-2-yl)ethan-1-one (39). A magnetically stirred solution of compound **38**¹⁷ (1.35 g, 3.5 mmol) in ethyl acetate/chloroform (30 mL of a 1:1 v/v mixture) maintained under nitrogen at 22 °C was treated CuBr₂ (1.73 g, 7.7 mmol) and the ensuing mixture heated under reflux for 16 h. The cooled reaction mixture was filtered through a pad of diatomaceous earth, the solids thus retained washed with dichloromethane (2 × 25 mL) and the combined filtrates concentrated under reduced pressure. ¹H NMR spectroscopic analysis of the solid thus obtained suggested this was comprised of a ca. 9:1 mixture of the target monobromide **39** and its dibrominated-counterpart. Accordingly, the solid was dissolved in dry THF (20 mL) and the resulting solution was treated, while being maintained at 0 °C under a nitrogen atmosphere, with Et₃N (1 mL) and diethylphosphite (100 μ L, 0.8 mmol). The ensuing mixture was warmed to 22 °C over 1 h then concentrated under reduced pressure and the residue so formed subjected to flash chromatography (silica, 12:6:1 v/v/v 40-60 petroleum spirit/dichloromethane/diethyl ether elution). Concentration of the relevant fractions (*R*_f = 0.3) gave compound **39** (1.27 g, 94%) as a pale-yellow and amorphous solid. ¹H NMR (400 MHz, CDCl₃) δ 8.22 (dd, *J* = 7.9 and 1.6 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.62 (td, *J* = 7.4 and 1.6 Hz, 1H), 7.60-7.55 (complex m, 2H), 7.38-7.33 (complex m, 3H), 6.27 (d, *J* = 3.2 Hz, 1H), 3.96 (s, 2H), 2.44 (s, 3H). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 184.3, 148.9, 145.6, 135.2, 132.8, 132.4, 131.9, 129.9, 129.8, 128.4, 127.8(9), 127.8(5), 127.7, 124.6, 114.2, 34.4, 21.7. IR $\nu_{\max}$ 1683, 1528, 1402, 1371, 1350, 1191, 1175, 1141, 673, 575 cm⁻¹. MS (ESI, +ve) 487 and 485 [(M + Na)⁺, 100 and 95%], 465 and 463 [(M + H)⁺, 52 and 50]. HRMS (ESI, +ve) (M + Na)⁺ calcd. for C₁₉H₁₅⁸¹BrN₂O₅³²S²³Na 486.9762, found 486.9759; calcd. for C₁₉H₁₅⁷⁹BrN₂O₅³²S²³Na 484.9783, found 484.9794.

2-(6-Amino-9H-purin-9-yl)-1-(3-(2-nitrophenyl)-1H-pyrrol-2-yl)ethan-1-one (40). A magnetically stirred solution of compound **39** (1.27 g, 2.7 mmol) and adenine (910 mg, 6.8 mmol) in DMF (32 mL) maintained at 0 °C under a nitrogen atmosphere was treated, in portions, with NaH (220 mg, of a 60% suspension in mineral oil, 5.4 mmol). The ensuing mixture was allowed to warm to 22 °C and then stirred at this temperature or 24 h before being quenched with NH₄Cl (50 mL of a saturated aqueous

solution) (CAUTION: POSSIBILITY OF HYDROGEN GENERATION) then extracted with dichloromethane (4 × 50 mL). The combined organic phases were washed with brine (1 × 75 mL) then dried (MgSO₄), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash chromatography (silica, 9:1 v/v dichloromethane/methanol elution) and so affording, after concentration of the appropriate fractions (*R_f* = 0.45), compound **40** (839 mg, 84%) as a clear, orange oil. ¹H NMR (400 MHz, acetone-D₆) δ 11.74 (broad s, 1H), 8.16 (s, 1H), 8.01 (dd, *J* = 8.1 and 1.3 Hz, 1H), 7.98 (s, 1H), 7.74 (m, 1H), 7.68-7.60 (complex m, 2H), 7.27 (t, *J* = 2.8 Hz, 1H), 7.08 (broad s, 2H), 6.30 (t, *J* = 2.3 Hz, 1H), 5.19 (s, 2H). ¹³C{¹H} NMR (100 MHz, acetone-D₆) δ 182.7, 156.9, 153.4, 151.1, 150.7, 142.7, 133.8, 133.5, 131.3, 130.1, 128.1, 127.7, 125.7, 124.8, 119.5, 113.4, 49.6. IR ν_{max} 3327, 3169, 1706, 1649, 1599, 1525, 1397, 1420, 1355, 753 cm⁻¹. MS (ESI, +ve) 749 [(2M + Na)⁺, 60%], 386 [(M + Na)⁺, 100], 364 [(M + H)⁺, 40]. HRMS (ESI, +ve) (M + Na)⁺ calcd. for C₁₇H₁₃N₇O₃²³Na 386.0978, found 386.0975. On standing a small sample of this material crystallized and one of the crystals thus obtained was subjected to single-crystal X-ray analysis.

4-((6-Amino-9H-purin-9-yl)methyl)-3H-5λ⁴-pyrrolo[2,3-*c*]quinolin-5-ol (41). A magnetically stirred suspension of compound **40** (145 mg, 0.4 mmol) and W-7 Raney nickel (45 mg, 31% w/w wrt **40**) in THF (10 mL) maintained at 22 °C was placed under an atmosphere of hydrogen for 24 h. The reaction mixture was then concentrated under reduced pressure and the residue so obtained subjected to flash chromatography (silica, 4:1 v/v dichloromethane/methanol elution). Concentration of the appropriate fractions (*R_f* = 0.2) gave a brown solid, recrystallization (DMSO) of which gave compound **41** (33 mg, 33%) as dark-brown crystals, m.p. = 262-263 °C. ¹H NMR (400 MHz, DMSO-D₆) δ 12.32 (broad s, 1H), 8.56 (dd, *J* = 8.5 and 1.4 Hz, 1H), 8.37 (dd, *J* = 8.1 and 1.4 Hz, 1H), 8.29 (s, 1H), 8.08 (s, 1H), 7.79 (d, *J* = 2.9 Hz, 1H), 7.72 (m, 1H), 7.64 (m, 1H), 7.22 (d, *J* = 2.9 Hz, 1H), 7.19 (broad s, 2H), 5.96 (s, 2H). IR ν_{max} 3292, 3152, 1686, 1645, 1603, 1424, 1229, 1029 cm⁻¹. MS (ESI, +ve) 354 [(M + Na)⁺, 85%], 332 [(M + H)⁺, 100]. Due to its limited solubility in all commonly available deuterated solvents, a satisfactory ¹³C NMR spectrum of this compound could not be obtained.

9-((3H-Pyrrolo[2,3-*c*]quinolin-4-yl)methyl)-9H-purin-6-amine (12). A magnetically stirred suspension of compound **40** (145 mg, 0.4 mmol) and Raney cobalt (430 mg, 300% w/w wrt **40**) in ethyl acetate (20 mL) maintained under an atmosphere of

hydrogen was heated under reflux for 60 h. The cooled reaction mixture was concentrated reduced pressure and the residue thus obtained subjected to flash chromatography (silica, 9:1 v/v dichloromethane/methanol elution). Concentration of the appropriate fractions ($R_f = 0.55$) gave yellow solid that was recrystallized (methanol/1 M aqueous HCl) to give compound **12** (122 mg, 92%) as its dihydrochloride salt and as bright-yellow crystals, m.p. = 263-264 °C. ^1H NMR (400 MHz, DMSO- D_6) δ 12.38 (broad s, 1H), 8.32 (s, 1H), 8.27 (dd, $J = 7.9$ and 1.6 Hz, 1H), 8.07 (s, 1H), 7.78-7.73 (complex m, 2H), 7.52 (ddd, $J = 8.1$, 7.0 and 1.5 Hz, 1H), 7.47 (ddd, $J = 8.4$, 6.9 and 1.6 Hz, 1H), 7.24 (broad s, 2H), 7.21 (dd, $J = 2.9$ and 1.2 Hz, 1H), 5.94 (s, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- D_6) δ 155.9, 152.4, 149.8, 143.3, 142.1, 141.4, 128.9, 128.1, 127.8, 126.7, 125.6, 125.5, 123.1, 123.1, 118.4, 101.3, 44.5. IR ν_{max} 3109, 1687, 1608, 1479, 1338, 1295, 738 cm^{-1} . MS (ESI, +ve) 338 $[(\text{M} + \text{Na})^+, 50\%]$, 316 $[(\text{M} + \text{H})^+, 100]$. HRMS (ESI, +ve) $(\text{M} + \text{H})^+$ calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_7$ 316.1311, found 316.1316.

(iii) Crystallographic Studies

Crystallographic Data for Compound 2

$\text{C}_{15}\text{H}_{16}\text{N}_2$, $M = 224.31$, $T = 200$ K, tetragonal, space group $P-42_1c$, $Z = 8$, $a = 17.2396(2)$, $c = 8.5097(2)$ Å; $V = 2529.11(7)$ Å³, $D_x = 1.178$ g cm⁻³, 1627 unique data ($2\theta_{\text{max}} = 55^\circ$), $R = 0.033$ [for 1504 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.084$ (all data), $S = 1.00$.

Crystallographic Data for Compound 3

$\text{C}_{18}\text{H}_{14}\text{N}_2$, $M = 258.32$, $T = 200$ K, monoclinic, space group $P2_1/n$, $Z = 12$, $a = 14.0236(2)$, $b = 15.8376(2)$, $c = 19.3464(2)$ Å; $\beta = 107.4595(7)$; $V = 4098.88(9)$ Å³, $D_x = 1.256$ g cm⁻³, 9397 unique data ($2\theta_{\text{max}} = 55^\circ$), $R = 0.038$ [for 7461 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.096$ (all data), $S = 0.97$.

Crystallographic Data for Compound 4

$\text{C}_{18}\text{H}_{14}\text{N}_2\text{O} \cdot \text{CH}_4\text{O}$, $M = 306.36$, $T = 200$ K, monoclinic, space group $P2_1/n$, $Z = 4$, $a = 9.5218(2)$, $b = 8.2073(2)$, $c = 20.3649(3)$ Å; $\beta = 96.7633(13)$; $V = 1580.41(6)$ Å³, $D_x = 1.288$ g cm⁻³, 3631 unique data ($2\theta_{\text{max}} = 55^\circ$), $R = 0.044$ [for 2616 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.116$ (all data), $S = 0.95$.

Crystallographic Data for Compound 5

$\text{C}_{19}\text{H}_{13}\text{N}_3$, $M = 283.33$, $T = 200$ K, orthorhombic, space group $Pbca$, $Z = 8$, $a = 16.1616(6)$, $b = 9.5535(3)$, $c = 18.6080(9)$ Å; $V = 2873.07(17)$ Å³, $D_x = 1.310$ g cm⁻³,

3296 unique data ($2\theta_{\max} = 55^\circ$), $R = 0.046$ [for 2286 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.119$ (all data), $S = 0.99$.

Crystallographic Data for Compound 6

$C_{20}H_{13}N_3O$, $M = 311.34$, $T = 150$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 3.8360(1)$, $b = 11.6306(4)$, $c = 32.4071(11)$ Å; $\beta = 91.612(3)$; $V = 1445.27(17)$ Å³, $D_x = 1.431$ g cm⁻³, 2852 unique data ($2\theta_{\max} = 144.6^\circ$), $R = 0.048$ [for 2601 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.135$ (all data), $S = 1.00$.

Crystallographic Data for Compound 11

$C_{11}H_8N_2$, $M = 168.20$, $T = 150$ K, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 5.8450(1)$, $b = 10.0578(2)$, $c = 14.2170(3)$ Å; $V = 835.79(3)$ Å³, $D_x = 1.337$ g cm⁻³, 1311 unique data ($2\theta_{\max} = 55^\circ$), $R = 0.043$ [for 1076 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.091$ (all data), $S = 1.02$.

Crystallographic Data for Compound 12

$(C_{17}H_{15}N_7^{2+})(Cl^-)_2 \cdot 2H_2O$, $M = 424.29$, $T = 150$ K, triclinic, space group $P-1$ (No. 2), $Z = 2$, $a = 7.1854(5)$, $b = 10.7930(8)$, $c = 12.3568(7)$ Å; $\alpha = 81.329(6)$, $\beta = 88.911(5)$, $\gamma = 79.292(6)$; $V = 930.81(11)$ Å³, $D_x = 1.514$ g cm⁻³, 3523 unique data ($2\theta_{\max} = 144.4^\circ$), $R = 0.075$ [for 2838 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.201$ (all data), $S = 1.00$.

Crystallographic Data for Compound 19

$C_{22}H_{25}NO_3S$, $M = 383.51$, $T = 200$ K, triclinic, space group $P-1$ (No. 2), $Z = 4$, $a = 9.8349(2)$, $b = 11.6854(3)$, $c = 17.3039(3)$ Å; $\alpha = 87.6157(12)$, $\beta = 86.7426(14)$, $\gamma = 86.4995(11)$; $V = 1980.28(7)$ Å³, $D_x = 1.286$ g cm⁻³, 9073 unique data ($2\theta_{\max} = 55^\circ$), $R = 0.045$ [for 6845 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.109$ (all data), $S = 0.98$.

Crystallographic Data for Compound 20

$C_{18}H_{14}N_2O_3S$, $M = 338.39$, $T = 200$ K, triclinic, space group $P-1$ (No. 2), $Z = 2$, $a = 8.0748(2)$, $b = 8.0842(1)$, $c = 12.4871(3)$ Å; $\alpha = 82.5503(12)$, $\beta = 87.7791(10)$, $\gamma = 67.7136(12)$; $V = 747.83(3)$ Å³, $D_x = 1.503$ g cm⁻³, 4382 unique data ($2\theta_{\max} = 60^\circ$), $R = 0.036$ [for 3938 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.100$ (all data), $S = 0.99$.

Crystallographic Data for Compound 21

$C_{18}H_{14}N_2O_2S$, $M = 322.39$, $T = 200$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 7.9602(2)$, $b = 15.4039(4)$, $c = 12.2247(3)$ Å; $\beta = 98.6554(15)$; $V = 1481.90(7)$ Å³, $D_x = 1.445$ g cm⁻³, 4333 unique data ($2\theta_{\max} = 60^\circ$), $R = 0.046$ [for 3434 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.110$ (all data), $S = 0.99$.

Crystallographic Data for Compound 28

$C_{19}H_{13}N_3O_2S$, $M = 347.40$, $T = 200$ K, monoclinic, space group $P2_1/n$, $Z = 4$, $a = 13.1847(2)$, $b = 7.5178(1)$, $c = 16.1336(2)$ Å; $\beta = 98.2249(8)^\circ$; $V = 1582.71(4)$ Å³, $D_x = 1.458$ g cm⁻³, 4637 unique data ($2\theta_{\max} = 60^\circ$), $R = 0.036$ [for 4094 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.099$ (all data), $S = 0.99$.

Crystallographic Data for Compound 29

$C_{18}H_{13}BrN_2O_2S$, $M = 401.28$, $T = 150$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 15.3482(6)$, $b = 5.9203(2)$, $c = 17.8258(7)$ Å; $\beta = 90.310(3)^\circ$; $V = 1619.73(11)$ Å³, $D_x = 1.645$ g cm⁻³, 3688 unique data ($2\theta_{\max} = 57^\circ$), $R = 0.034$ [for 3253 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.091$ (all data), $S = 1.01$.

Crystallographic Data for Compound 36

$C_{20}H_{13}N_3O$, $M = 311.34$, $T = 150$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 13.4569(2)$, $b = 6.5269(1)$, $c = 17.6639(2)$ Å; $\beta = 109.2474(16)^\circ$; $V = 1464.73(4)$ Å³, $D_x = 1.412$ g cm⁻³, 2875 unique data ($2\theta_{\max} = 144.6^\circ$), $R = 0.032$ [for 2678 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.081$ (all data), $S = 0.99$.

Crystallographic Data for Compound 38

$C_{19}H_{16}N_2O_5S$, $M = 384.41$, $T = 150$ K, orthorhombic, space group $Pbca$, $Z = 8$, $a = 6.4446(1)$, $b = 14.5466(2)$, $c = 37.4103(4)$ Å; $V = 3507.10$ (8) Å³, $D_x = 1.456$ g cm⁻³, 3428 unique data ($2\theta_{\max} = 144^\circ$), $R = 0.045$ [for 3233 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.104$ (all data), $S = 1.04$.

Crystallographic Data for Compound 40

$C_{24}H_{19}N_7O_5S$, $M = 517.52$, $T = 150$ K, monoclinic, space group $C2/c$, $Z = 16$, $a = 63.464(2)$, $b = 6.8824(1)$, $c = 30.4144(12)$ Å; $\beta = 129.298$ (6) $^\circ$; $V = 10280.4(10)$ Å³, $D_x = 1.337$ g cm⁻³, 10061 unique data ($2\theta_{\max} = 144^\circ$), $R = 0.040$ [for 8743 reflections with $I > 2.0\sigma(I)$]; $R_w = 0.105$ (all data), $S = 0.98$.

Structure Determination

Images for compounds **2-5**, **19-21** and **28** were measured on a Nonius Kappa CCD diffractometer (MoK α , graphite monochromator, $\lambda = 0.71073$ Å) and data extracted using the DENZO package.³⁶ Images for compounds **6**, **12**, **29**, **36**, **38** and **40** were measured on an Agilent SuperNova (CuK α , graphite monochromator, $\lambda = 1.54184$ Å) while that for compound **11** was measured on a Rigaku Xcalibur CCD diffractometer (Mo K α , graphite monochromator, $\lambda = 0.71073$ Å). In both instances data were extracted using CrysAlisPro.³⁷ Structure solution was by direct methods (SIR92).³⁸ The structures of all compounds were refined using the CRYSTALS program package.³⁹ Atomic coordinates, bond lengths and angles, and displacement parameters

have been deposited at the Cambridge Crystallographic Data Centre (CCDC numbers 1955252-1955266). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

(iv) Evaluation of Compounds 1-6, 11, 12, 22 and 36 as AChE Inhibitors

The title compounds were tested for inhibition against AChE as described previously by Sangnoi et al.¹ Thus, the compounds were dissolved in DMSO and made up to concentrations ranging from 5 mM to 3.05 μ M by half dilutions. 2.5 μ l of each compound was added to a solution consisting of 125 μ l 5,5'-dithiobis-(2-nitrobenzoic acid) (1.5 mM), 72.5 μ l Tris buffer (15 mM, pH 8.0) and 25 μ l acetylthiocholine iodide (150 μ M). Enzyme activity was followed after the addition of 25 μ l AChE at 0.03 μ M (*Electrophorus electricus*, Type V-S, EC 3.1.1.7) measuring at 412 nm using the Epoch microplate spectrophotometer (BioTek). The assays were repeated in triplicates and the rate was calculated using the first two minutes. Prism v5 (GraphPad Software Inc.) was used to calculate IC₅₀ values.

(v) Molecular Docking Simulation Between AChE and Marinoquinoline B

The molecular docking of marinoquinoline B was conducted with Autodock vina v1.1.2 using the crystal structure of human acetylcholinesterase complexed with tacrine (PDB code 4BDT).²⁹ The crystal structure was retrieved from RCSB Protein Data Bank (<http://www.rcsb.org>) and prepared by the removal of tacrine and water molecules. The three-dimensional coordinates of marinoquinoline B were generated using the PRODRG server (<http://davapc1.bioch.dundee.ac.uk/cgi-bin/prodrg>).⁴⁰ The Autodock tools program was used to prepare the crystal structure and marinoquinoline B for docking and the grid box was placed on the center of the active site pocket.²⁹ Default values were used for simulations with 10 independent docking runs resulting in the lowest binding energy conformation being taken as the representative. Visualization of the docking was carried out in PyMOL Molecular Graphic System (<http://www.pymol.org>).

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Notes

The authors declare no competing financial interest.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free-of-charge on the ACS Publications website at DOI: 10.1021/acs.joc.XXXXXX.

Experimental procedures and characterization data for all new compounds (PDF)

X-ray crystallographic data compound **2** (CIF)
X-ray crystallographic data compound **3** (CIF)
X-ray crystallographic data compound **4** (CIF)
X-ray crystallographic data for compound **5** (CIF)
X-ray crystallographic data for compound **6** (CIF)
X-ray crystallographic data for compound **11** (CIF)
X-ray crystallographic data for compound **12** (CIF)
X-ray crystallographic data for compound **19** (CIF)
X-ray crystallographic data for compound **20** (CIF)
X-ray crystallographic data for compound **21** (CIF)
X-ray crystallographic data for compound **28** (CIF)
X-ray crystallographic data for compound **29** (CIF)
X-ray crystallographic data for compound **36** (CIF)
X-ray crystallographic data for compound **38** (CIF)
X-ray crystallographic data for compound **40** (CIF)

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