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Strategies for the synthesis of *N*-(azacycloalkyl)bisindolylmaleimides: selective inhibitors of PKCβ

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Abstract—*N*-(Azacycloalkyl)bisindolylmaleimides **1** have been identified to be selective inhibitors of PKCβ. This manuscript will describe the synthetic approaches employed to prepare this class of compounds that resulted in development of efficient methods for preparation of *N*-(azacycloalkyl) indole **5**, indole-3-acetamide **8** and indole-3-glyoxylate ester **4** derivatives.

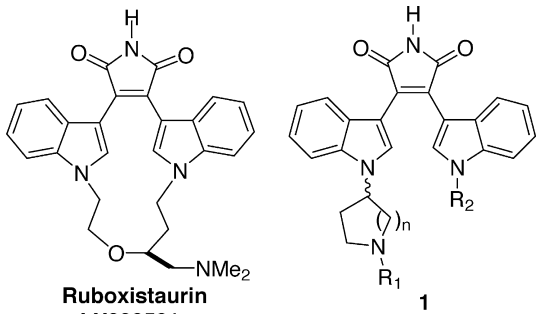
1. Introduction

Most solid tumors increase in mass through the proliferation of malignant and stromal cells, including endothelial cells, leading to formation of a tumor vasculature. Since active angiogenesis is a critical component of the mass expansion of most solid tumors, this process is a valid target for therapy. The most common and direct-acting angiogenic factor in cancer patients is the vascular endothelial growth factor (VEGF), and the up-regulation of VEGF receptors has been observed in tumor-associated endothelial cells. The signal transduction pathways of these receptors include downstream activation of PKC, and data from numerous assays indicate that PKC activation is directly responsible for the VEGF signaling that leads to neovascularization. Therefore, an inhibitor of PKC would be anticipated to block tumor angiogenesis. The macrocyclic bisindolylmaleimide ruboxistaurin (LY333531), a selective inhibitor of PKCβ is under evaluation in the clinic for treatment of retinopathy associated with diabetic complications (Chart 1). Ruboxistaurin has been shown to be effective in inhibiting tumor growth and metastasis in a variety of tumor models, presumably by preventing VEGF-driven angiogenesis.[1–3]

Rather than pursue ruboxistaurin in the clinic as an agent for treatment of malignant solid tumors, our goal was to evaluate a series of acyclic *N*-(azacycloalkyl)bisindolylmaleimides **1** for their ability to inhibit PKCβ (Chart 1). This manuscript will describe our efforts to develop a general method to prepare *N*-(azacycloalkyl)bisindolylmaleimides, that enabled rapid progression of the SAR and resulted in the selection of **1e** (LY317615) for clinical evaluation (Scheme 1).[4]

2. Results and discussion

Retrosynthetic analysis. We envisioned that the *N*-(azacycloalkyl)bisindolylmaleimides **1a-i** could be prepared either (i) by condensation of indole-3-acetamide (**2**) or *N*-methyl indole-3-acetamide (**3**) with substituted methyl indole-3-glyoxylates **4b-g** (strategy A, Scheme 1); or (ii) by condensation of indole-3-glyoxylate (**6**) or *N*-methyl



Ruboxistaurin
LY333531

1

Chart 1.

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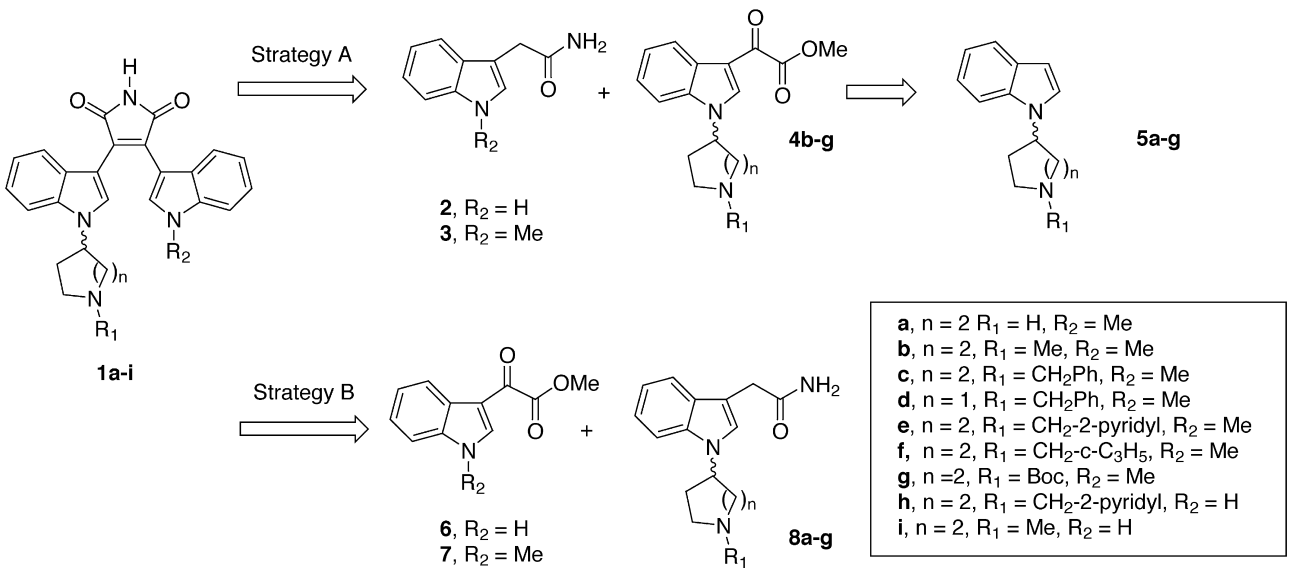
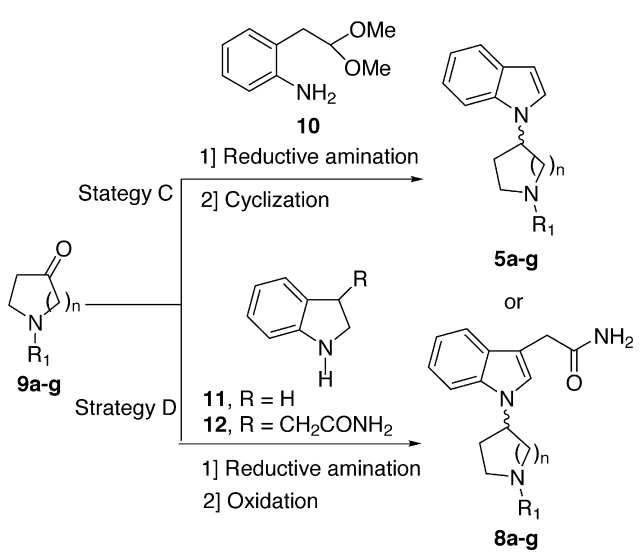


Scheme 1.

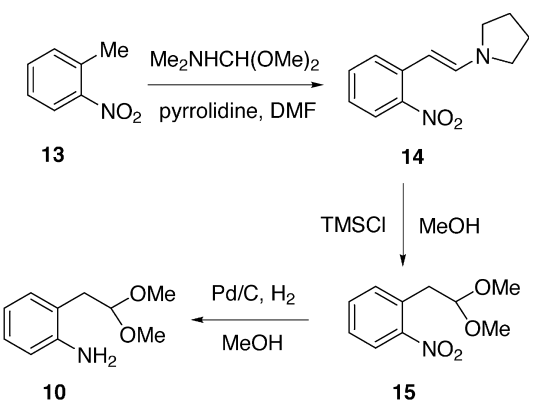
indole-3-glyoxylate (**7**) with substituted indole-3-acetamides **8b-g** (strategy B).[5] The key for each strategy was to develop a general method for the synthesis of functionalized *N*-(azacycloalkyl) indoles **5** and indole-3-acetamides **8**. In addition, the pyrrolidine derivative **1d** contains an asymmetric center and a route to both racemic and chiral versions of this compound was required. This manuscript will describe our synthetic efforts towards this class of compounds.

Synthesis of N-(azacyclo)alkyl indole and indole-3-acetamide derivatives. A number of approaches to the synthesis of *N*-(azacycloalkyl) indoles **5** have been reported.[6–9] A synthesis of the indole nucleus in two steps after reductive alkylation of 2-amino-α-chloroacetophenones with ketones has been described.[10–13] Coe has also reported a Leimgruber–Batcho synthesis of 6-carboxyester analogs **5b-d,g** by reductive amination of aniline (**10**) with the corresponding piperidones **9b-d,g**.[14] Presently, no methods for the synthesis of **5** or **8** by reductive amination on indoline (**11**) or 2,3-dihydro-1*H*-indole-3-acetamide (**12**) have been reported. Our goal was to develop general methodologies for the synthesis of **5** and **8** that would allow rapid access to a variety of *N*-(azacycloalkyl) bisindolylmaleimide derivatives for evaluation as PKCβ inhibitors.



Scheme 2.

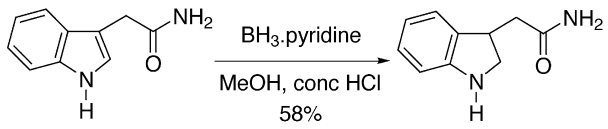
Our initial strategy was to develop a general convergent method for synthesis of these compounds by development of the reductive amination/cyclization chemistry (strategy C and D, Scheme 2). Aniline (**10**) was prepared from *ortho*-nitrotoluene (**13**) by a modification of the literature process (Scheme 3).[15] This improved procedure generated **10** via a more reactive pyrrolidine enamine **14** rather than dimethylenamine, which required temperatures of 130–150°C for reaction completion. The enhanced reactivity of **14** toward displacement resulted in a lower operating temperature (80°C) for the methanolysis step, alleviated safety concerns due to formation of nitroso intermediates and produced an overall cleaner purity profile. Purification by distillation afforded (**10**) in >70% overall yield from **13**.



Scheme 3.

A three step synthesis of **12** from indole-3-acetic ester has been reported.[16] However, we identified a one step method to prepare **12** in 58% yield by reduction of **2** with BH_3·pyridine in MeOH and concentrated HCl (Eq. (1)). Since indoline (**11**) is commercially available, we now had

access to anilines (**10**), (**11**) and (**12**) to evaluate the reductive amination chemistry.

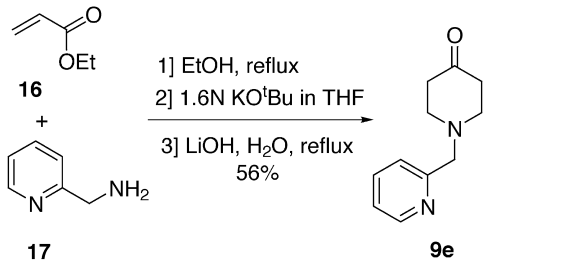


(1)

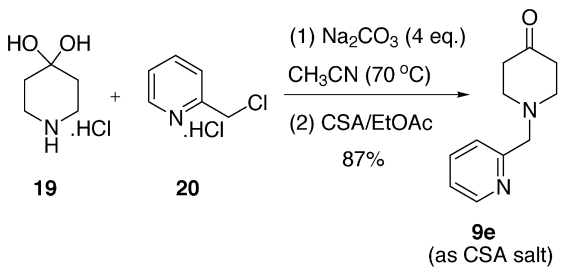
2 **12**

N-Alkyl piperidones and pyrrolidones **9b-d,g** are commercially available. Novel piperidones, e.g. *N*-(2-pyridinylmethyl)-4-piperidinone **9e** were prepared via the classical three step Dieckmann cyclization sequence (Eq. (2)).

Thus, bis Michael addition of 2 aminomethyl pyridine (**17**) to ethyl acrylate (**16**) and Dieckmann cyclization followed by base catalyzed decarboxylation generated **9e** in 56% overall yield.[17] Although this process worked well it required multiple steps and isolation of piperidone **9e** from aqueous media was difficult due to its high hydrophilicity. Therefore, a more efficient one step process for the synthesis of *N*-alkyl piperidones was developed that afforded an 87% yield of **9e** (as the CSA salt) by alkylation of 4-piperidone hydrochloride monohydrate **19** with picolyl chloride monohydrochloride **20** using Na_2CO_3 in refluxing acetonitrile (Eq. (3)).[18] This process also afforded a 67% yield of *N*-cyclopropylmethyl piperidone **9f** (Eq. (4)).[18]



(2)



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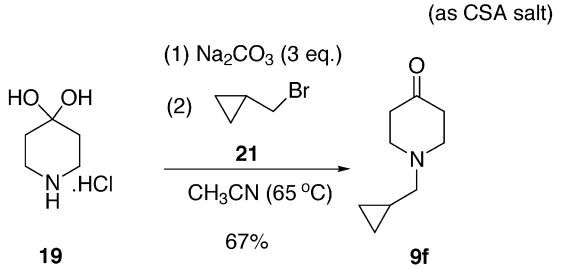
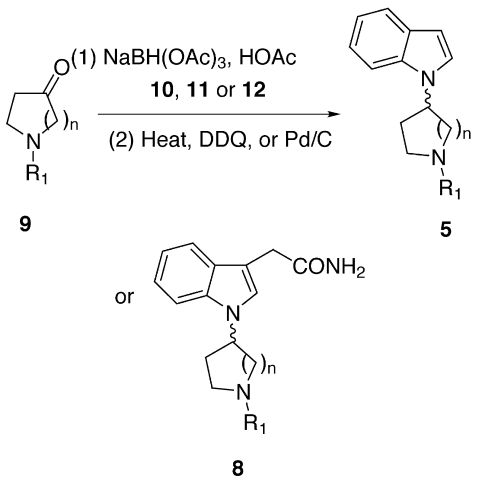


(4)

The reductive amination of piperidones **9** with (**10**), (**11**) and (**12**) was performed by addition of the reagents to a solution of $NaBH(OAc)_3$ (1.5 equiv.) in HOAc (Table 1, Eq. (5)). For reactions with (**10**), initial formation of the imine need to be performed at room temperature, otherwise significant amounts of indole and 1-acetyl indole were generated as by-products. However, heating to 50°C was required to effect cyclization of the intermediate imine to indole **5**. Using indolines (**11**) and (**12**), oxidation to **5** or **8** was effected with mild oxidizing agents such as DDQ or Pd/C.[19] Unfortunately, DDQ oxidation of the benzyl protected indolines derived from **9c** and **9d** was unsuccessful, presumably due to competitive oxidation at the benzylic position indicating that the choice of *N*-protecting group was important. Thus, synthesis of the *N*-benzyl protected acetamide **8c** was not achieved.



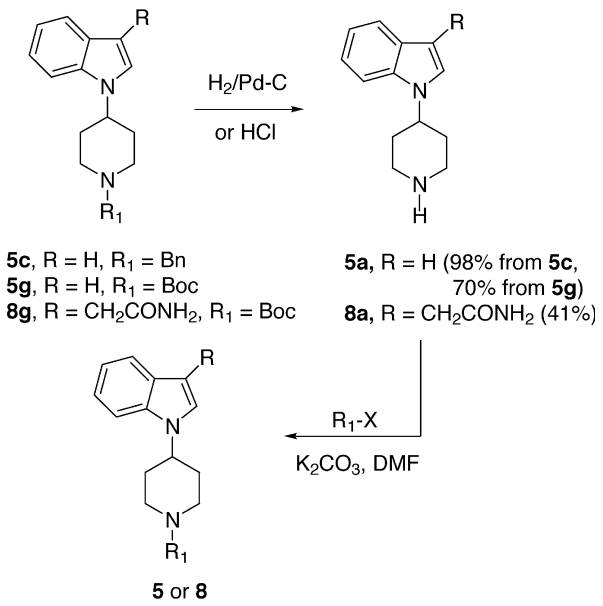
(5)

Table 1. Synthesis of *N*-(azacycloalkyl) indoles **5** and **8** via reductive amination (Eq. (5))

Entry	Aniline	*N*-Alkyl piperidone	Yield (%)	Product
1	**10**	**9b**	91	**5b**
2	**10**	**9c**	83	**5c**
3	**10**	**9d**	46	**5d**
4	**10**	**9e**	76	**5e**
5	**10**	**9f**	89	**5f**
6	**10**	**9g**	92	**5g**
7	**11**	**9e**	77 (2 steps)	**5e**
8	**11**	**9b**	79 (2 steps)	**5b**
9	**11**	**9f**	32 (2 steps)	**5f**
10	**11**	**9g**	87 (2 steps)	**5g**
11	**12**	**9b**	18 (2 steps)	**8b**
12	**12**	**9e**	50 (2 steps)	**8e**
13	**12**	**9f**	50 (2 steps)	**8f**
14	**12**	**9g**	42 (2 steps)	**8g**

Although this reductive amination strategy was successful, early commitment to the *N*-substituent required each product to be generated in a multi-step process. To enable a more rapid expansion of the SAR we needed a more direct approach to the synthesis of *N*-(azacycloalkyl) indoles **5** and indole-3-acetamides **8** wherein the alkyl group could be introduced later in the synthesis. Therefore, 4-(indol-1-yl) piperidine (**5a**) and 4-(indol-1-yl-3-acetamide) piperidine (**8a**) were identified as the key intermediates. Piperidine **5a** has been prepared in the patent literature by the reductive alkylation strategy of Sugasawa.[6,20] We identified a one step synthesis of **5a** in 98% yield by hydrogenation of the corresponding *N*-benzyl indole **5c**. The *N*-boc derivative **8g** was employed for preparation of **8a**, since preparation of the *N*-benzyl derivative was problematic during the oxidation

process. Alkylation of piperidines **5a** and **8a** then afforded access to a variety of *N*-(azacycloalkyl) indoles **5** or **8** in good yield (Table 2, Scheme 4), without the need to separately prepare the corresponding piperidones and perform the reductive amination chemistry. With these reagents available, the scope of the SAR of the *N*-(azacycloalkyl) bisindolylmaleimides was expanded.



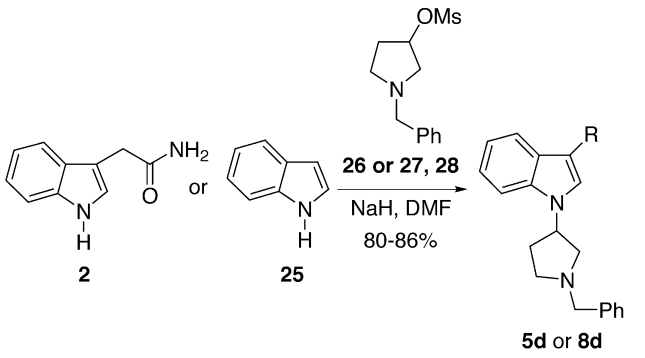
Scheme 4.

Table 2. Synthesis of *N*-(azacycloalkyl)-indoles **5** and **8** via alkylation (Scheme 4)

Entry	Reactant	R–X	Yield (%)	Product
1	**23**	MeI	49[a]	**5b**
2	**23**	*c*-$C_3H_5H_2Br$	86	**5f**
3	**23**	2-Pyr-CH_2Br	97	**5e**
4	**24**	MeI	55	**8b**
5	**24**	*c*-$C_3H_5CH_2Br$	69	**8f**
6	**24**	2-Pyr-CH_2Br	82	**8e**

[a] Problems with quaternary salt formation were observed for R=Me.

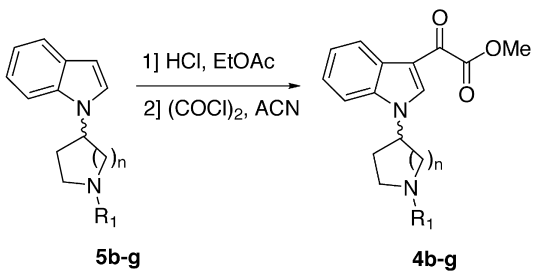
Although the reductive amination approach afforded access to the racemic *N*-benzyl pyrrolidine indole **5d**, we were interested in preparing the chiral variants of this compound. Literature reports indicate that most direct approach to these compounds via alkylation of indole with *N*-benzyl-3-chloropyrrolidinol affords primarily the elimination product.[6] However, due to the commercial availability of (*S*) and (*R*)-1-benzyl-3-hydroxypyrrolidines we sought to explore the application of these intermediates to the synthesis of chiral **1d** derivatives. To our delight alkylation of indole (**25**) or indole-3-acetamide (**2**) with the mesylates **26**, **27** or **28** derived from racemic or chiral (*S*) and (*R*)-1-hydroxypyrrolidines afforded an 80–86% yield of the corresponding chiral *N*-(azacycloalkyl) indole derivatives **5d** and **8d** (Eq. (6)). In addition, since the benzyl group can be removed and additional alkylating agents incorporated at the pyrrolidine nitrogen, this approach provided a valuable strategy for the synthesis of a variety of chiral *N*-alkyl pyrrolidine bisindolylmaleimides.



(6)

Synthesis of N-(azacyclo)alkyl indole-3-glyoxylyl derivatives. Methyl indole-3-glyoxylates **4** are prepared by reaction of indole with oxalyl chloride in an organic solvent, followed by quench of the intermediate glyoxylyl chloride with NaOMe or MeOH.[5] For the synthesis of **4b-g**, acetonitrile proved to be the optimal solvent.

Use of CH_2Cl_2 was avoided due to the known and observed ability of tertiary amines to react with this solvent.[21] In addition, for substrates **5b-g** the presence of a free tertiary amine was problematic with oxalyl chloride, presumably due to competing reactions at the tertiary nitrogen. Therefore, to successfully prepare glyoxylate esters of indoles **5b-g** containing tertiary amines initial formation of the monohydrochloride salts was required. Thus, treatment of **5b-g** with HCl at room temperature for 1 h generated the HCl salts. Although the HCl salts can be formed and isolated in quantitative yield, it was more convenient for them be prepared and used in situ. Subsequently, addition of oxalyl chloride at 0°C to a slurry of the HCl salt in acetonitrile resulted in rapid formation of the glyoxylyl chloride. After 2 h the reactions were quenched with MeOH and glyoxylate esters **4b-g** isolated in 65–94% yield (Table 3, Eq. (7)). Purification of **4** by chromatography or crystallization was necessary to remove residual dimethyloxalate (NMR singlet at 3.78 ppm), since this by-product can have a negative impact on the final condensation step to prepare **1**

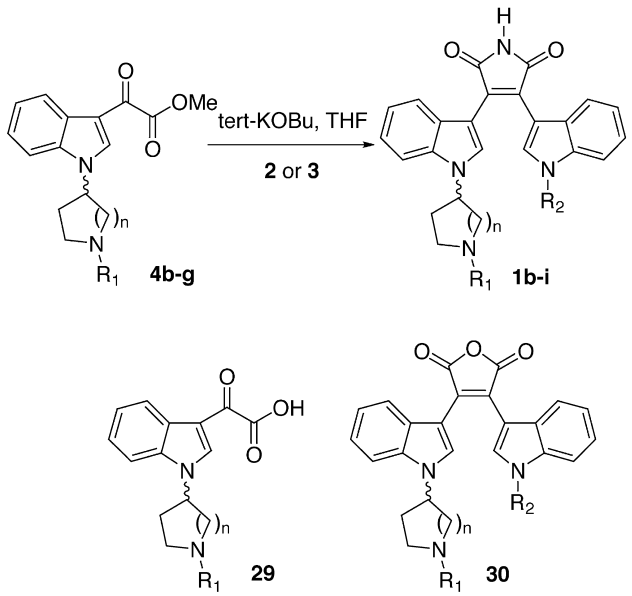


(7)

Table 3. Synthesis of *N*-(azacycloalkyl) indole glyoxylates **4** (Eq. (7))

Entry	Reactant	Yield (%)	Product
1	**5b**	83	**4b**
2	**5c**	94	**4c**
3	**5d**	69	**4d**
4	**5e**	86	**4e**
5	**5f**	92	**4f**
6	**5g**	67	**4g**

Synthesis of the bisindolylmaleimides strategy A. Reaction of *N*-(azacycloalkyl) indole glyoxylates **4b-g** with indole-3-acetamide (**2**) or (**3**) was performed in THF using *tert*-KOBu (2.2 equiv.) as base and afforded the corresponding bisindolylmaleimides **1** in 56–83% yield (Table 4, Eq. (8)). The *tert*-KOBu was added at −10°C to ensure that all the starting glyoxylate was consumed before elimination of the intermediate hydroximide, since this conversion generated 1 mol of water that competitively hydrolyzed **4** into their corresponding glyoxylic acids **29**. In addition, *tert*-KOBu can also pick up water and generate 1 mol of KOH and *tert*-butanol therefore, all reagents should be dried prior to performing this reaction. Upon completion the reaction was quenched with water, neutralized and cooled to 0°C. The bisindolylmaleimides precipitated from the reaction and were isolated by filtration. At this time any glyoxylic acid **29** formed during the process was removed. During the work-up procedure it was important to minimize exposure to basic pH, since competitive hydrolysis of **1** to the corresponding anhydride **30** was observed.

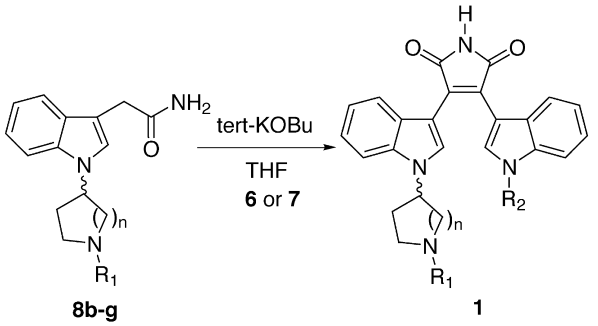


(8)

Table 4. Strategy A for synthesis of bisindolylmaleimides **1** (Eq. (8))

Entry	Acetamide	Glyoxylate	Yield (%)	Product
1	**3**	**4b**	83	**1b**
2	**2**	**4b**	72	**1i**
3	**3**	**4c**	73	**1c**
4	**3**	**4d**	71	**1d**
5	**3**	**4e**	75	**1e**
6	**2**	**4e**	61	**1h**
7	**3**	**4f**	56	**1f**
8	**3**	**4g**	62	**1g**

Synthesis of the bisindolylmaleimides strategy B. A synthesis of **1** was also successful by reaction of the indole-3-glyoxylate esters (**6**) and (**7**) with the corresponding *N*-(azacycloalkyl) indole-3-acetamides **8b-g**. The reactions were performed in analogy to the conditions outlined above and afforded **1** in 51–80% yield (Table 5, Eq. (9)). The unsubstituted bisindolylmaleimide **1a** was prepared in 70% yield by deprotection of **1g** with concentrated HCl.



(9)

Table 5. Strategy B for synthesis of bisindolylmaleimides **1** (Eq. (9))

Entry	Acetamide	Glyoxylate	Yield (%)	Product
1	**8b**	**7**	54	**1b**
2	**8c**	**7**	51	**1c**
3	**8d**	**7**	77	**1d**
4	**8e**	**7**	53	**1e**
5	**8g**	**7**	80	**1g**

3. Conclusion

Two comparable approaches to the synthesis of *N*-(azacycloalkyl)bisindolylmaleimides **1** have been identified. The first approach involves preparation of *N*-(azacycloalkyl) indoles **5b-g** in 2 steps by reductive amination/oxidation from indoline (**11**) or in 4 steps by reductive amination/cyclization of aniline (**10**). Although this multi-step sequence can be performed individually for each piperidone or pyrrolidinone **9**, we have found it more expedient to prepare the indolyl piperidine or pyrrolidinone **5a** and use this as the key intermediate to incorporate a variety of functional groups on the piperidine nitrogen. The *N*-(azacycloalkyl) indoles **5b-g** were then converted into glyoxylate esters **4b-g** and converted into the corresponding bisindolylmaleimides **1** in 8 steps by condensation with indole-3-acetamides (**2**) or (**3**).

In the second strategy, indole-3-acetamdes **8b-g** were generated by reductive amination/oxidation of indoline-3-acetamide (**12**) with piperidones or pyrrolidinones **9**. As with the previous route, the 4-(indol-1-yl 3-acetamide) piperidine **8a** can be generated from the corresponding *N*-boc analog and alkylated to expand the SAR around this position. *N*-(Azacycloalkyl) acetamides **8b-g** were treated with indole glyoxylates **6** and **7** to provide an alternative approach to bisindolylmaleimides **1** in 6 steps. These synthetic strategies allowed preparation of a variety of acyclic *N*-(azacycloalkyl)bisindolylmaleimides. From this series of compounds **1e** was identified as a potent inhibitor of PKC and is currently being evaluated in the clinic for the treatment of cancer.

4. Experimental

Reactions were run under an atmosphere of nitrogen. TLC was performed on Kieselgel 60 F254 plates (Merck) using reagent grade solvents. Flash chromatography was performed using E. M. Merck silica gel 60 (230–400

mesh). The Eli Lilly and Co. Physical Chemistry Department performed all physical chemistry analysis.

4.1. General methods for the synthesis of *N*-(azacycloalkyl) indoles (5)

4.1.1. (*E*)-1-[2-(2-Nitrophenyl)ethenyl-pyrrolidine (14). To a solution of 2-nitrotoluene (5.0 g, 36.5 mmol) in DMF (20 mL) was added pyrrolidine (3.1 g, 43.8 mmol) followed by dimethylformamide dimethylacetal (5.2 g, 43.8 mmol) and the resulting solution was heated to 60°C for 5 h, during which time the solution turned dark. NMR analysis ($CDCl_3$) of a reaction aliquot showed a 3:1 ratio of 2-nitrotoluene to desired product. The temperature was increased to 80°C and stirring continued for 17 h, after which time NMR analysis showed no 2-nitrotoluene remained. The solution was allowed to cool to rt and partitioned between MTBE (100 mL) and H_2O (100 mL). The aqueous layer was back-extracted with MTBE (50 mL) and the combined extracts were washed with aqueous saturated NaCl solution, dried ($MgSO_4$) and concentrated in vacuo to afford 7.45 g (94%) **14** as a dark red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (m, 4H), 3.32 (m, 4H), 5.83 (d, J=13.4 Hz, 1H), 6.93 (m, 1H), 7.23 (d, J=13.7 Hz, 1H), 7.31 (m, 1H), 7.44 (dd, J=8.2, 1.2 Hz, 1H), 7.83 (dd, J=8.2, 1.2 Hz, 1H).

4.1.2. 1-(2,2-Dimethoxyethyl)-2-nitrobenzene (15). Compound **14** (4.4 g, 20.2 mmol) was dissolved in MeOH (45 mL) and treated dropwise over 15 min with TMSCl (3.3 g, 3.8 mL, 30.2 mmol). An exotherm occurred during the addition and the dark red color mostly disappeared. The solution was heated to reflux for 22 h, after which time NMR analysis showed no starting material remained. The solution was allowed to cool to rt and concentrated to an orange-red residue. The residue was partitioned between EtOAc (75 mL) and 5% aqueous citric acid (75 mL). The aqueous layer was back-extracted with EtOAc (50 mL) and the combined organic layers were washed with aqueous saturated $NaHCO_3$, followed by aqueous saturated NaCl and concentrated in vacuo to afford 3.56 g (84%) **15** dark red oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25 (d, J=5.3 Hz, 2H), 3.38 (s, 6H), 4.60 (d, J=5.3 Hz, 1H), 7.42 (m, 2H), 7.56 (m, 1H), 7.92 (dd, J=7.9, 1.3 Hz, 1H).

4.1.3. 2-(2,2-Dimethoxyethyl)-benzenamine (10). A solution of compound **15** (20.9 kg, 98.8 mol, 1.0 equiv.) in cold MeOH (190 L) was stirred at rt under N_2. A slurry of 5% Pd/C (water wet, 2.05 kg) in cold MeOH (10 L) was charged to the reaction mixture and rinsed in with cold MeOH (2×5 L). The mixture was hydrogenated at rt under 25–50 psia H_2 for 2–4 h. The reaction mixture was filtered through hyflo and rinsed with MeOH (150 L). The filtrate was concentrated in vacuo to an oil that was dissolved in MTBE (25 L) and filtered through a 1μ cartridge filter. A potency assay of the product solution (49.3 kg) showed 35.8 wt% **10** that represented 5.7 bkg (100% yield).

4.2. Route 1 via reductive amination of aniline (10) and *N*-alkyl-4-piperidones or *N*-alkyl-3-pyrrolidinones

Aniline **10** (1.0 equiv.) was stirred as a solution in HOAc (50 mL) at rt under N_2. *N*-alkyl-4-piperidone or *N*-alkyl-3-pyrrolidinone (1.1 equiv.) was added in one portion; an exotherm to 35°C was observed. After cooling to rt, powdered $NaBH(OAc)_3$ (1.5 equiv.) was added in portions over 10–15 min, keeping the reaction temperature below 30°C; the $NaBH(OAc)_3$ was rinsed in with HOAc (5 mL). After stirring at rt for 1–4 h, the mixture was heated to 50–100°C until the cyclization to the indole was complete. The reaction was cooled to rt and diluted with deionized water and organic solvent. Aqueous concentrated NaOH was added dropwise to adjust the pH to 10–11, keeping the reaction temperature below 25°C. The layers were separated, and the aqueous layer extracted with an organic solvent. The combined organic layers were washed with aqueous saturated NaCl solution and dried ($MgSO_4$). The filtrate was concentrated in vacuo to afford the crude product that was purified by silica gel chromatography using the conditions described separately for each indole.

4.2.1. 1-(1-Methyl-piperidin-4-yl)-1*H*-indole (5b). Synthesis via route 1. Quantities employed **10** (10.0 g, 55.2 mmol), *N*-methyl-piperidone **9b** (7.5 mL, 61 mmol) and $NaBH(OAc)_3$ (17.5 g, 82.6 mmol) in HOAc (50 mL). Following addition of $NaBH(OAc)_3$ the reaction was stirred at rt for 1.5 h and 100°C for 1 h. Work-up employed deionized water (200 mL), aqueous concentrated NaOH (70 mL) and EtOAc as the extraction solvent. Purification using 300 g silica gel 60, 93:7 $MeCl_2$/MeOH afforded 10.7 g (91%) **5b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (dd, 2H, J=7.47 Hz), 7.46 (d, 1H, J=3.08 Hz), 7.10 (app. t, 1H, J=7.03 Hz), 6.99 (app. t, 1H, J=7.47 Hz), 6.43 (d, 1H, J=3.08 Hz), 4.30 (m, 1H), 2.90 (m, 2H), 2.23 (s, 3H), 2.13 (m, 2H), 1.98 (m, 2H), 1.89 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 135.0, 127.8, 124.7, 120.6, 120.2, 118.7, 109.6, 100.7, 54.6, 52.2, 45.8, 32.0; IR ($CHCl_3$) ν 3008, 2947, 2855, 2796, 2743, 1511, 1462, 1380, 1309, 1278, 1131 cm^{-1}. HRMS (ES+) *m/z* calculated for $C_{14}H_{18}N_2$ 215.1548 (M+1), found 215.1542 (M+1).

4.2.2. 1-(1-Benzyl-piperidin-4-yl)-1*H*-indole (5c). Synthesis via route 1. Quantities employed **10** (12.1 g, 66.7 mmol), *N*-benzyl piperidone **9c** (13.9 g, 73.4 mmol) and $NaBH(OAc)_3$ (22.3 g, 100 mmol) in HOAc (109 mL). Following addition of $NaBH(OAc)_3$ the reaction was stirred at rt for 4 h and 50°C for 15 h. Work-up employed deionized water (130 mL), aqueous 5N NaOH (115 mL) to pH 8 and extraction with CH_2Cl_2 (3×80 mL). Purification using 558 g of silica gel 60, 80:20 hexanes/EtOAc afforded 16.2 g (83%) **5c**. ^{1}H NMR ($CDCl_3$) δ 2.09 (m, 4H), 2.23 (m, 2H), 3.09 (m, 2H), 3.61 (s, 2H), 6.53 (d, 1H, J=3.3 Hz), 7.08–7.14 (m, 1H), 7.18–7.41 (m, 8H), 7.64 (d, 1H, J=8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 138.1, 135.6, 129.2, 128.9, 128.6, 128.3, 127.2, 124.1, 121.3, 121.1, 119.4, 109.3, 101.4, 63.0, 53.5, 53.1, 32.5; IR ($CHCl_3$) ν 2949, 2808, 2763, 1610, 1510, 1477, 1461 cm^{-1}. MS (ES^+) calculated for $C_{20}H_{22}N_2$ *m/z* 290, found 291 (M+1). Anal. calculated for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65, found: C, 82.63; H, 7.66; N, 9.66.

4.2.3. 1-(1-Methyl-piperidin-4-yl)-1*H*-indole (5d). Synthesis via route 1. Quantities employed **10** (1.0 g, 5.52 mmol), *N*-benzyl-3-pyrrolidinone **9c** (1.06 g, 6.05 mmol) and $NaBH(OAc)_3$ (1.75 g, 8.26 mmol) in HOAc (5 mL). Following addition of $NaBH(OAc)_3$ the reaction was stirred at rt for 1.5 h and 100°C for 2 h. Work-up employed deionized water (20 mL), EtOAc

(10 mL), aqueous concentrated NaOH to pH 10–11 and extraction with additional EtOAc. Purification using 50 g silica gel 60, CH_2Cl_2 to 98:2 CH_2Cl_2/MeOH afforded 0.70 g (46%) of **5d**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.58 (d, 1H, J=8.2 Hz), 7.49 (d, 2H, J=3.0 Hz), 7.36–7.20 (m, 5H), 7.09 (dt, 1H, J=8.2, 1.3 Hz), 6.99 (t, 1H, J=7.5 Hz), 6.42 (d, 1H, J=3.5 Hz), 5.13–5.08 (m, 1H), 3.65 (q, 2H, J=12.8 Hz), 2.98–2.93 (m, 1H), 2.76 (d, 2H, J=6.0 Hz), 2.49–2.38 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 139.3, 135.7, 128.8, 128.6, 128.5, 127.2, 126.2, 121.2, 120.7, 119.3, 110.4, 101.3, 60.0, 59.6, 54.2, 53.3, 32.2; IR ($CHCl_3$) ν 3009, 2798, 1611, 1511, 1480, 1461, 1348, 1311, 1230 cm^{-1}; HRMS (ES) m/z calculated for $C_{19}H_{20}N_2$ 277.1705 (M+1), found 277.1696. Anal. calculated for $C_{19}H_{20}N_2$ C, 67.92, H, 3.17, N, 8.80, found C, 67.86, H, 3.02, N, 8.74.

4.2.4. 1-(1-Pyridin-2-yl methyl-piperidin-4-yl)-1*H*-indole (5e). Synthesis via route 1. Quantities employed **10** (866 g, 4.78 mol), *N*-(2-pyridinylmethyl)-4-piperidinone **9e** (1.00 kg, 5.26 mol) and $NaBH(OAc)_3$ (1.52 kg, 7.71 mol) in HOAc (5 L). Following addition of $NaBH(OAc)_3$ the reaction was stirred at rt for 4 h and 50–60°C for 24–48 h. Work-up employed deionized water (20 L), EtOAc (8.5 L), aqueous 50% NaOH (6 L) to pH 9.5–10 and extraction with additional EtOAc (2×8 L). No chromatographic purification required. The organic layer was concentrated in vacuo to a thick oil. IPA (20 L) was added and the mixture was reconcentrated in vacuo to remove residual EtOAc. IPA (20 L) was added and the resulting slurry was concentrated in vacuo until crystallization began. The slurry was stirred at rt for 6–24 h, then cooled to 0–5°C for 2–3 h. The product was isolated by filtration, rinsed with cold IPA (2×1.5 L) and dried at 50°C to afford 1.06 kg (76%) **5e**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.50 (d, 1H, J=4.9 Hz), 7.78 (dt, 1H, J=7.5, 1.9 Hz), 7.54–7.43 (m, 4H), 7.26 (dt, 1H, J=4.9, 1.1 Hz), 7.12 (t, 1H, J=7.6 Hz), 6.98 (t, 1H, J=7.4 Hz), 6.44 (d, 1H, J=3.0 Hz), 4.41–4.30 (m, 1H), 3.68 (s, 2H), 2.98 (d, 2H, J=12.0 Hz), 2.32 (dt, 2H, J=11.5, 2.5 Hz), 2.08–1.90 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.6, 148.7, 136.4, 135.3, 128.0, 124.9, 122.7, 122.1, 120.8, 120.4, 118.9, 109.7, 100.8, 63.6, 52.5, 32.0; IR ($CHCl_3$) ν 2952, 2808, 1591, 1571, 1476, 1461, 1451, 1434, 1369, 1342, 1309, 1252, 1146, 1126, 997, 991 cm^{-1}; MS (FD) calculated for $C_{19}H_{21}N_3$ 291, found m/z (M+1) 292 (100%). Anal. calculated for $C_{19}H_{21}N_3$ C, 78.32, H, 7.26, N, 14.42, found C, 78.36, H, 7.19, N, 14.55.

4.2.5. 1-(1-Cyclopropylmethyl-piperidin-4-yl)-1*H*-indole (5f). Synthesis via route 1. Quantities employed **10** (805 mg, 4.44 mmol), *N*-cyclopropylmethyl-3-pyrrolidinone **9f** (750 mg, 4.89 mmol) and $NaBH(OAc)_3$ (1.42 g, 6.70 mmol) in HOAc (4 mL). Following addition of $NaBH(OAc)_3$ the reaction was stirred at rt for 1.5 h and 100°C for 1 h. Work-up employed deionized water (22 mL), EtOAc (6 mL), aqueous concentrated NaOH to pH 10–11, and extraction with additional EtOAc. Purification using 50 g silica gel 60, 95:5 CH_2Cl_2/MeOH afforded 1.01 g (89%) of **5f** as a red oil. ^{1}H NMR ($CDCl_3$) δ 0.15 (m, 2H), 0.57 (m, 2H), 0.94 (m, 1H), 2.15 (m, 6H), 2.35 (d, 2H, J=6.3 Hz), 3.27 (m, 2H), 4.25 (m, 1H), 6.53 (dd, 1H, J=0.6, 2.7 Hz), 7.10 (dt, 1H, J=0.9, 8.1 Hz), 7.20 (m, 1H), 7.26 (m, 1H), 7.40 (dd, 1H, J=0.6, 7.8 Hz), 7.64 (td, 1H, J=8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 135.6, 128.5, 124.0, 121.2, 121.0, 120.0, 119.4, 109.2, 101.4, 63.6, 53.4, 53.2, 53.1, 32.4, 8.4, 4.0; IR ($CHCl_3$) ν 3007, 2948, 2930, 2780, 1672, 1610, 1510, 1477, 1461, 1307 cm^{-1}. HRMS (ES) m/z calculated for $C_{17}H_{22}N_2$ 255.1861 (M+1), found 255.1850.

4.2.6. 4-Indol-1-yl-piperidine-1-carboxylic acid *tert*-butyl ester (5g). Synthesis via route 1. Quantities employed **10** (4.13 g, 22.8 mmol), *N*-(*tert*-butoxycarbonyl)-4-piperidone **9g** (5.00 g, 25.1 mmol) and $NaBH(OAc)_3$ (7.25 g, 34.2 mmol) in HOAc (38 mL). Following addition of $NaBH(OAc)_3$ the reaction was stirred at 50°C for 18 h. Work-up employed aqueous saturated $NaHCO_3$ (250 mL) and CH_2Cl_2 (3×50 mL). Purification by silica gel chromatography using 4:1 hexanes/EtOAc afforded 6.30 g (92%) **5g**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56–7.53 (m, 2H), 7.48 (d, 1H, J=3.3 Hz), 7.13, app. t, 1H, J=7 Hz), 7.02, app. t, 1H, J=8 Hz), 6.45 (d, 1H, J=3.3 Hz), 4.55 (m, 1H), 4.13 (bd, 1H, J=12.4 Hz), 2.95 (m, 3H), 1.90 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.8, 135.2, 127.9, 124.9, 120.8, 120.4, 119.0, 109.9, 100.9, 78.8, 52.2, 31.9, 28.1; IR ($CHCl_3$) ν 3009, 2981, 2862, 1685, 1477, 1462, 1453, 1427, 1368, 1311, 1245, 1165 cm^{-1}. MS (FD+) m/z calculated for $C_{18}H_{24}N_2O_2$ 300.4, found 300.4. Anal. calculated for $C_{18}H_{24}N_2O_2$ C, 71.9; H 8.05; N, 9.32, found: C, 72.2; H, 8.05; N, 9.29.

4.3. Route 2 via reductive amination of indoline (11) and 1-alkyl-4-piperidone

Indoline **11** (1.0 equiv.) was stirred as a solution in HOAc at rt under N_2; an exotherm to 34°C was observed. After cooling to rt, *N*-alkyl-4-piperidone (1.1 equiv.) was added in one portion; an exotherm to 35°C was observed. After cooling to rt, powdered $NaBH(OAc)_3$ (1.5 equiv.) was added in portions over 10–15 min, keeping the reaction temperature below 30°C; the $NaBH(OAc)_3$ was rinsed in with HOAc. After stirring for 1 h at rt, the reaction was diluted with deionized water and organic solvent. Aqueous concentrated NaOH was added dropwise to adjust the pH to 10–11, keeping the reaction temperature below 40°C. The layers were separated and the aqueous layer extracted. The combined organic layers were washed with aqueous saturated NaCl solution and dried ($MgSO_4$). The drying agent was removed by filtration and rinsed with EtOAc. The filtrate was concentrated in vacuo to afford the crude indoline intermediate.

A solution of the indoline in THF was stirred at 0–5°C under N_2. A solution of DDQ (1.0 equiv.) in THF was prepared and added dropwise to the reaction, keeping the temperature below 10°C. The dark, thick reaction was allowed to warm to rt and stirred overnight (21 h). Additional DDQ was added as needed in order to drive the reaction to completion. After stirring 1 h, the reaction mixture was diluted with an organic solvent and water. Aqueous 5N NaOH was added dropwise to adjust the pH to 10–11, keeping the reaction temperature below 25°C. The layers were separated and the aqueous layer extracted. The combined organic layers were washed with aqueous saturated NaCl solution and dried ($MgSO_4$). The drying agent was removed by filtration and rinsed. The filtrate was concentrated in vacuo to afford crude

product that was purified using the conditions specified for each indole.

4.3.1. 1-(1-Methyl-piperidin-4-yl)-1*H*-indole (5b). Synthesis via route 2. Indoline formation employed indoline **11** (2.50 mL, 22.3 mmol) in HOAc (13 mL), 1-methyl-4-piperidone (3.00 mL, 24.4 mmol) and $NaBH(OAc)_3$ (7.09 g, 33.5 mmol). Following addition of $NaBH(OAc)_3$ the reaction was stirred at rt for 1 h. Work-up employed deionized water (50 mL), EtOAc (10 mL) and aqueous concentrated NaOH to pH 10–11. The filtrate was concentrated in vacuo to afford 4.59 g (95%) crude indoline.

Indole formation employed indoline intermediate (4.20 g, 19.4 mmol) in THF (40 mL) and DDQ (4.41 g, 19.4 mmol) in THF (20 mL). Reaction was stirred at rt for 24 h. Additional DDQ (1.32 g, 5.81 mmol) was required to drive the reaction to completion. Work-up employed deionized water (50 mL), EtOAc (50 mL), aqueous 5N NaOH to pH 10–11 and additional EtOAc. Purification using 100 g silica gel 60, 95:5 CH_2Cl_2/MeOH→93:7 CH_2Cl_2/MeOH afforded 3.46 g (83%) of **5b**.

4.3.2. 1-(1-Pyridin-2-yl methyl-piperidin-4-yl)-1*H*-indole (5e). Synthesis via route 2. Indoline formation employed indoline **11** (1.50 g, 12.6 mmol), **9e** (2.63 g, 13.8 mmol) in HOAc (7.5 mL) and $NaBH(OAc)_3$ (4.01 g, 18.9 mmol). Following addition of $NaBH(OAc)_3$ the reaction was stirred at rt for 3 h. Work-up employed deionized water (40 mL), EtOAc (20 mL), aqueous concentrated NaOH to pH 10–11 and additional EtOAc (20 mL). The filtrate was concentrated in vacuo to afford crude indoline that was purified by silica gel chromatography (150 g silica 60, 88:12 EtOAc/MeOH) to afford 3.14 g (85%) of purified indoline.

Indole formation employed indoline intermediate (1.50 g, 5.11 mmol) in THF (15 mL) and DDQ (1.28 g, 5.64 mmol) in THF (7 mL). Reaction was stirred at 0–5°C for 1 h. Work-up employed aqueous $NaHCO_3$ (30 mL), EtOAc (30 mL), aqueous 5N NaOH to pH 10–11 and additional EtOAc. Purification using 50 g silica gel 60, 95:5 EtOAc/MeOH afforded 1.34 g (90%) of **5e**.

4.3.3. 1-(1-Cyclopropylmethyl-piperidin-4-yl)-1*H*-indole (5f). Synthesis via route 2. Indoline formation employed indoline **11** (0.79 g, 6.6 mmol), *N*-(cyclopropylmethyl)-4-piperidone **9f** (1.11 g, 7.24 mmol) in HOAc (5 mL) and $NaBH(OAc)_3$ (2.11 g, 9.96 mmol). Following addition of $NaBH(OAc)_3$ the reaction was stirred at rt for 1 h. Work-up employed deionized water (20 mL), EtOAc (10 mL), aqueous concentrated NaOH to pH 10–11 and additional EtOAc (20 mL). The filtrate was concentrated in vacuo to afford crude indoline. Purification using 50 g silica gel 60, 90:10 EtOAc/MeOH) to afford 1.54 g (90%) of purified indoline.

Indole formation employed indoline intermediate (1.00 g, 3.90 mmol) in THF (10 mL) and DDQ (974 mg, 4.29 mmol) in THF (5 mL). Reaction was stirred at rt for 24 h. Additional DDQ added (385 mg, 1.70 mmol) and reaction stirred for 1 h Work-up employed aqueous $NaHCO_3$ (15 mL), EtOAc (15 mL), aqueous 5N NaOH to pH 10–11 and additional EtOAc (10 mL). Purification using 150 g silica gel 60, CH_2Cl_2 to 95:5 CH_2Cl_2/MeOH afforded 0.35 g (35%) **5f**.

4.3.4. 4-Indol-1-yl-piperidine-1-carboxylic acid *tert*-butyl ester (5g). Synthesis via route 2. Indoline formation employed indoline **11** (11.9 g, 100 mmol), *N*-(*tert*-butoxycarbonyl)-4-piperidone **9g** (29.9 g, 150 mmol) in HOAc (150 mL) and $NaBH(OAc)_3$ (31.8 g, 150 mmol). Following addition of $NaBH(OAc)_3$ the reaction was stirred at rt for 1 h. Work-up employed aqueous 5N NaOH (500 mL) to pH 8 and EtOAc (500 mL). After re-extraction with EtOAc the filtrate was concentrated in vacuo to afford crude indoline that was purified by silica gel chromatography (7:1 hexanes/EtOAc) to afford 29.9 g (99%) of purified indoline.

Indole formation employed indoline intermediate (29.5 g, 97.4 mmol) in THF (300 mL) and DDQ (22.1 g, 97.4 mmol) in THF (100 mL). Reaction was stirred at 0–5°C for 45 min. Work-up employed aqueous $NaHCO_3$ (4×300 mL), EtOAc (700 mL) and aqueous saturated NaCl (2×300 mL). Purification using silica gel 60, 6:1 hexanes/EtOAc afforded 25.9 g (88%) **5g**.

4.4. Route 3 via alkylation of 1-(4-piperidinyl)-1*H*-indole (5a)

Indole **5a** (1.0 equiv.) and powdered K_2CO_3 (1.2 equiv.) were stirred as a slurry in DMF at rt under N_2-blanket. The alkylating agent (1.1 equiv.) was added in one portion. The reaction was allowed to cool gradually to rt and stirred overnight. The reaction mixture was partitioned between an organic solvent and water. The layers were separated and the aqueous layer was extracted with organic solvent. The combined organic layers were washed with aqueous saturated NaCl and dried ($MgSO_4$). The drying agent was removed by filtration and rinsed. The filtrate was concentrated in vacuo and the crude product was purified by silica gel chromatography using the conditions specified for each indole.

4.4.1. 1-(1-Methyl-piperidin-4-yl)-1*H*-indole (5b). Synthesis via route 3. Quantities employed indole **5a** (1.93 g, 9.64 mmol), powdered K_2CO_3 (1.60 g, 11.6 mmol) in DMF (14 mL) and dimethylsulfate (1.00 mL, 10.6 mmol). Work-up employed deionized water (20 mL) and EtOAc (20 mL). Purification using 50 g silica gel 60, 93:7 CH_2Cl_2/MeOH afforded 1.00 g (49%) **5b**, as an oil that crystallized upon standing.

4.4.2. 1-(1-Pyridin-2-yl methyl-piperidin-4-yl)-1*H*-indole (5e). Synthesis via route 3. Quantities employed indole **5a** (0.78 g, 3.89 mmol), powdered K_2CO_3 (1.18 g, 8.54 mmol) in DMF (5.5 mL) and 2-picolyl chloride monohydrochloride **20** (0.75 g, 4.3 mmol). Reaction was stirred at rt for 3 h and 50°C for 2 h. Work-up employed deionized water (24 mL) and CH_2Cl_2 (25 mL). Purification using 50 g silica gel 60, EtOAc to 95:5 EtOAc/MeOH afforded 1.10 g (97%) **5e**.

4.4.3. 1-(1-Cyclopropylmethyl-piperidin-4-yl)-1*H*-indole (5f). Synthesis via route 3. Quantities employed indole **5a** (3.4 g, 17 mmol), powdered K_2CO_3 (2.82 g, 20.4 mmol) in DMF (20 mL) and (bromomethyl)cyclopropane (1.82 mL,

18.8 mmol). The reaction was stirred at 60°C for 1 h. Work-up employed deionized water (50 mL) and Et_2O (3×30 mL). Purification using 189 g silica gel, 98:2 to 95:5 CH_2Cl_2/MeOH afforded 3.75 g (86% yield) **5f** as a yellow oil.

4.4.4. 1-Piperidin-4-yl-1*H*-indole (5a).[6] Route 1 from 1-[1-(phenylmethyl)-4-piperidinyl]-1*H*-indole (5c). Indole **5c** (5.00 g, 17.2 mmol) was dissolved in MeOH (80 mL) and added to a slurry of 10% Pd/C (0.4 g) in toluene (4 mL). The mixture was hydrogenated (50 psi) for 20 h. The catalyst was removed by filtration through hyflo and carefully rinsed with MeOH. The filtrate was concentrated in vacuo to afford 3.40 g (98%) **5a**. ^{1}H NMR ($CDCl_3$) δ 1.60 (br s, 1H), 1.88 (dd, 1H, J=4.2, 12.4 Hz), 1.97 (dd, 1H, J=3.9, 12.0 Hz), 2.10 (m, 2H), 2.84 (dt, 2H, J=2.4, 12.3 Hz), 3.27 (m, 2H), 4.35 (m, 1H), 6.53 (d, 1H, J=0.6, 3.3 Hz), 7.10 (m, 1H), 7.20 (m, 1H), 7.24 (m, 1H), 7.40, (dd, 1H, J=0.6, 8.1 Hz), 7.64 (td, 1H, J=0.9, 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 135.4, 128.6, 128.2, 124.0, 121.5, 121.2, 119.4, 109.3, 101.4, 53.7, 46.3, 33.8; IR ($CHCl_3$) ν 3008, 2953, 1602, 1510, 1477, 1461, 1319, 1309 cm^{-1}. HRMS (ES+) m/z calculated for $C_{13}H_{16}N_2$ 201.1391 (M+1), found 201.1393 (M+1).

4.5. Route 2 from 1,1-dimethylethyl ester 4-(1*H*-indol-1-yl)1-piperidinecarboxylic acid (5g)

Indole **5g** (30 g, 100 mmol) was stirred at rt as a solution in EtOAc (150 mL). Trifluoroacetic acid (38.5 mL, 500 mmol) was added dropwise over 10–15 min during which time an exotherm to 30°C was observed. The dark solution was heated to 60°C for 12 h, then allowed to cool to rt overnight. The solution was cooled to 10°C and water (150 mL) added. Aqueous 50% NaOH was added dropwise to adjust the pH to 10–11 keeping the temperature below 30°C. The aqueous layer was extracted with EtOAc and the combined organic layers dried ($MgSO_4$). The drying agent was removed by filtration, rinsed with EtOAc and the filtrate was concentrated to dryness to obtain 14 g (70%) **5a**.

4.6. Alternative procedure for the synthesis 1-(1-methyl-piperidin-4-yl)-1*H*-indole (5d) via alkylation of indole (25) with 1-benzyl-3-mesyloxy pyrrolidine (26)

NaH (300 mg, 7.63 mmol) was slurried in DMF (5 mL) and cooled to 0°C. Indole **25** (850 mg, 7.30 mmol) was added as a solution in DMF (5 mL) and the reaction was allowed to stir at rt for 1 h. The reaction was then cooled to 0°C. 1-Benzyl-3-mesyloxypyrrolidine **26**[22–24] (1.50 g, 5.87 mmol) in DMF (5 mL) was added dropwise and the reaction heated to 50°C for 20 h. After cooling to rt the reaction was diluted with EtOAc and washed with water (3×). The organic layer was washed with aqueous saturated NaCl, dried ($MgSO_4$) and the solvent was removed in vacuo to give an oil that was purified by silica gel chromatography (1:1:0.5 hexanes/CH_2Cl_2/EtOAc) to afford 1.30 g **5d** (80%) as a yellow oil.

4.7. Synthesis of glyoxylyl esters

4.7.1. [1-(1-Methyl-piperidin-4-yl)-1*H*-indol-3-yl]-oxo-acetic acid methyl ester (4b). To solution of **5b** (5.00 g, 23.3 mmol) in ACN (50 mL) and MTBE (50 mL) at rt was added 4 M HCl in dioxane (5.90 mL, 23.6 mmol, 1.0 equiv.) in one portion. The hydrochloride salt of **5b** precipitated. The very thick slurry was heated to 50°C for 5–10 min to then slowly cooled to −15 to −10°C, during which time the slurry remained thin and stirred well. Oxalyl chloride (3.10 mL, 35.5 mmol, 1.5 equiv.) was added dropwise, keeping the reaction temperature below −5°C for 1–2 h. The slurry became very thick and was diluted with ACN (50 mL) and allowed to warm to rt. After the reaction was complete the mixture was cooled to 0–5°C. MeOH (10 mL) was added dropwise, keeping the reaction temperature below 10°C. The resulting violet solution was allowed to warm to rt until the methanolysis reaction was complete, then it was cooled to 5–10°C. Aqueous 2N NaOH (60 mL) was added dropwise to adjust the pH to 9.5–10, keeping the reaction temperature below 25°C. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with aqueous saturated NaCl solution and dried ($MgSO_4$). The drying agent was removed by filtration and rinsed with EtOAc. The filtrate was concentrated in vacuo and the crude product purified using 200 g silica gel 60, 85:15:1 EtOAc/MeOH/c.NH_4OH) to afford 5.81 g (83%) **4b** as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.18 (app d, 1H), 7.74 (app d, 1H), 7.32 (m, 2H), 4.47 (m, 1H), 3.89 (s, 3H), 2.93 (app d, 2H), 2.24 (s, 3H), 2.17–1.93 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.2, 163.6, 137.0, 136.2, 125.8, 123.6, 123.1, 121.2, 121.2, 111.6, 111.4, 54.2, 53.6, 52.6, 45.7, 31.6; IR ($CHCl_3$) ν 3019, 2949, 2851, 2792, 2739, 1728, 1640, 1517, 1462, 1380, 1280, 1183, 1141 cm^{-1}. Anal. calculated for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33, found: C, 68.15, H, 6.72. N, 9.33. HRMS (ES) m/z (M+1) calculated for $C_{17}H_{20}N_2O_3$ 301.1552, found 301.1543.

4.7.2. [1-(1-Benzyl-piperidin-4-yl)-1*H*-indol-3-yl]-oxo-acetic acid methyl ester (4c). A mixture of **5c** (6.00 g, 20.7 mmol) in dry ACN (54 mL) was cooled to 0°C. 5.72 M HCl in ACN (3.8 mL, 21.73 mmol, 1.05 equiv.) was added and the reaction mixture stirred for 10 min at 0–10°C and 1 h at rt. After cooling to −10°C, oxalyl chloride (3.60 mL, 41.3 mmol. 2.00 equiv.) was added dropwise at −10 to 0°C over 15 min to obtain an orange mixture. The mixture was stirred for 1 h at 0°C. MeOH (12 mL) was added and the resulting red solution was stirred for 30 min at 0°C, then partitioned between cold water (100 mL) and EtOAc (80 mL). The pH was adjusted to 7 with 5N NaOH (22 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2×30 mL). The combined organic solution was washed with aqueous saturated NaCl (100 mL), dried (Na_2SO_4) and concentrated in vacuo to an oil. Purification using 180 g silica gel 60 (60:40 to 50:50 hexanes/EtOAc) followed by trituration with hexanes (2 mL) afforded 7.33 g (94%) **4c**. ^{1}H NMR ($CDCl_3$) δ 2.15–2.25 (m, 6H), 3.11 (m, 2H), 3.61 (s, 2H), 3.95 (s, 3H), 4.30 (m, 1H), 7.26–7.45 (m, 8H), 8.46 (m, 1H), 8.51 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 178.6, 164.0, 138.3, 137.2, 136.4, 128.7, 128.0, 127.8, 126.8, 125.9, 123.8, 123.3, 121.4, 111.8, 111.4, 61.8, 53.9, 52.5, 51.9, 31.6; IR ($CHCl_3$) ν 1729, 1643, 1517, 1462, 1281, 1267, 1192, 1142, 1062 cm^{-1}. MS (ES) m/z calculated for $C_{23}H_{24}N_2O_3$ 376, found 377 (M+1). Anal. calculated for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.42; 7.44, found: C, 73.09; H, 6.41; N, 7.36.

4.7.3. [1-(1-Benzyl-pyrrolidin-3-yl)-1*H*-indol-3-yl]-oxo-acetic acid methyl ester (4d). Indole **5d** (3.00 g, 10.9 mmol) was dissolved in Et_2O (30 mL) and 1 M solution of HCl, 1N in Et_2O (10.9 mL, 10.9 mmol) added dropwise, forming a slurry that was allowed to stir at rt for 1 h. The slurry was filtered and dried to afford 3.20 g (94%) of the HCl salt as an off-white solid. The HCl salt (3.00 g, 9.60 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0°C. Oxalyl chloride (1.68 mL, 19.2 mmol) was added dropwise, and the reaction allowed to come to rt and stirred for 1.5 h. It was then cooled to −60°C. A 25% solution of NaOMe in MeOH (11.0 mL, 48.0 mmol) was added dropwise and after 1.5 h at −60°C the reaction warmed to rt. Aqueous saturated NH_4Cl and CH_2Cl_2 were added and the layers separated. The combined organics were washed with aqueous saturated NaCl and dried ($MgSO_4$). The solvent was removed in vacuo to give a yellow oil that was purified through a silica gel filter pad (95:5 EtOAc/MeOH) to afford 2.40 g **4d** (69%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.18 (d, 1H, J=7.0 Hz), 7.84 (d, 1H, J=7.3 Hz), 7.46–7.19 (m, 7H), 5.26 (bs, 1H), 3.92 (s, 3H), 3.89–3.64 (m, 2H), 3.31–2.99 (m, 2H), 2.76–2.71 (m, 1H), 2.60–2.50 (m, 1H), 2.43–2.34 (m, 1H), 2.04–1.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 136.2, 128.5, 128.4, 127.2, 123.8, 123.4, 122.8, 110.3, 59.7, 59.5, 55.5, 53.0, 52.7, 35.6, 32.5; IR ($CHCl_3$) ν 2961, 2802, 1728, 1642, 1518, 1275, 1262, 1142, 1096, 1076, 1040, 1027, 1016, 809 cm^{-1}. HRMS (ES+) calculated for $C_{22}H_{23}N_2O_3$ 363.1708, found m/z (M+1) 363.1701 (100%).

4.7.4. Oxo-[1-(1-pyridin-2-ylmethyl-piperidin-4-yl)-1*H*-indol-3-yl]-acetic acid methyl ester (4e). Anhydrous HCl (130 g, 3.57 mol, 1.0 equiv.) was bubbled into a mixture of **5e** (1.05 kg, 3.60 mol, 1.0 equiv.) in ACN (9.3 L) at 0–20°C. The mixture was stirred for 30 min, then cooled to −10 to 0°C. Oxalyl chloride (914 g, 7.20 mol, 2.0 equiv.) was added dropwise to the reaction mixture at −10 to 0°C. The reaction was stirred at −10 to 0°C for 2 h. MeOH (2.1 L) was added dropwise at −10 to 0°C and the reaction stirred at that temperature for 1 h. The reaction mixture was slowly added to a mixture of cold (0–10°C) aqueous 5 wt% $NaHCO_3$ solution (20 L) and cold EtOAc (13 L). The pH of the mixture was adjusted to 7–8 with aqueous 2N NaOH (2 L). The layers were separated and the aqueous layer extracted with EtOAc (10 L). The combined organic layers were washed with dilute aqueous NaCl solution (10 L) and concentrated in vacuo. The concentrate was dissolved in EtOAc (7 L) and treated with **4e** seed crystals (0.5 g). After stirring 30–60 min to allow significant crystallization, heptane (10 L) was added dropwise over 60–90 min. The mixture was concentrated in vacuo to remove 5 L of solvent. The product slurry was stirred at 0–10°C for 1–2 h, filtered and rinsed with heptane (2×2.5 L), then dried in a vacuum oven at 50–60°C to yield 1.176 kg (86.5%) **4e**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.50 (dd, 1H, J=4.8, 1.6 Hz), 8.17 (dd, 1H, J=5.9, 1.7 Hz), 7.80–7.74 (m, 2H), 7.49 (d, 1H, J=7.7 Hz), 7.36–7.24 (m, 3H), 4.57–4.50 (m, 1H), 3.89 (s, 3H), 3.67 (s, 2H), 2.98 (bd, 2H, J=11.8 Hz), 2.33 (bt, 2H, J=9.1 Hz), 2.11–1.97 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.6, 164.0, 158.5, 148.7, 137.2, 136.4, 125.9, 124.8, 123.8, 123.3, 122.7, 122.1, 121.3, 111.8, 111.4, 63.4, 53.7, 52.5, 52.1, 31.6; IR ($CHCl_3$) ν 2954, 1728, 1642, 1517, 1462, 1436, 1280, 1268, 1255, 1192, 1142, 1062 cm^{-1}. MS (FD) calculated for $C_{22}H_{23}N_3O_3$ 377, found m/z (M+1) 378 (100%). Anal. calculated for $C_{22}H_{23}N_3O_3$ C, 70.01, H, 6.14, N, 11.13, found C, 69.71; H, 6.22; N, 11.21.

4.7.5. Methyl *N*-(1-(cyclopropylmethyl)-4-piperidinylindolyl)-3-glyoxylate (4f). A solution of **5f** (3.37 g, 13.3 mmol) in dry ACN (35 mL) was cooled to 0°C and treated with 3.42 M HCl in ACN (4.07 mL, 13.9 mmol, 1.05 equiv.). The solution was stirred for 10 min at 0°C and 1 h at rt. Upon cooling to −10°C, oxalyl chloride (2.30 mL, 26.4 mmol, 2.00 equiv.) was added dropwise over 10 min at 0°C. The resulting orange solution was stirred for 1 h at 0°C, then MeOH (7.7 mL) added. After 0.5 h the solution was poured into water (60 mL) and the pH adjusted to 8 with 5N NaOH (17 mL). The mixture was extracted with EtOAc (4×30 mL). The combined organic layers were washed with aqueous saturated NaCl (50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to an oil. Purification using 190 g silica gel 60 (98:2 to 95:5 CH_2Cl_2/MeOH) afforded 4.18 g (92%) **4f**. ^{1}H NMR ($CDCl_3$) δ 0.15 (m, 2H), 0.57 (m, 2H), 0.92 (m, 1H), 2.22 (m, 6H), 2.35 (d, 2H, J=6.9 Hz), 3.30 (m, 2H), 3.94 (s, 3H), 4.30 (m, 1H), 7.35 (m, 2H), 7.40 (m, 1H), 8.46 (m, 1H), 8.52 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 178.6, 164.0, 137.3, 136.4, 125.9, 123.8, 123.2, 121.4, 111.8, 111.4, 62.5, 54.0, 52.5, 52.0, 31.6, 8.4, 3.7; IR ($CHCl_3$) ν 1729, 1642, 1517, 1462, 1276, 1192, 1141 cm^{-1}. MS calculated for $C_{20}H_{24}N_2O_3$ 340, found (ES) m/z 340.20. Anal. calculated for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.10; N, 8.22, found C, 70.66; H, 7.09; N, 8.30.

4.7.6. 4-(3-Methoxyoxalyl-indol-1-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (4g). Oxalyl chloride (1.53 mL, 1.76 mmol, 1.06 equiv.) was added dropwise to a solution of **5g** (500 mg, 1.66 mmol) in Et_2O (22 mL) at 0°C. The reaction was stirred for 90 min at 0°C then cooled to −70°C. MeOH (0.169 mL, 4.16 mmol) was added and the resulting yellow slurry allowed to warm to rt. After stirring at rt for 3 h the mixture was concentrated in vacuo and the residue dissolved in CH_2Cl_2 (25 mL). The organic layer was washed with aqueous saturated $NaHCO_3$ (25 mL), aqueous saturated NaCl, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by silica gel chromatography (2:1 hexanes/EtOAc) afforded 430 mg (67%) **4g**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.20 (d, 1H, J=7.3 Hz), 7.79 (d, 1H, J=7.3 Hz), 7.41–7.26 (m, 2H), 4.79–4.63 (m, 1H), 4.16 (bd, 2H, J=11.0 Hz), 3.90 (s, 3H), 3.13–2.81 (m, 2H), 2.09–1.80 (m, 4H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.8, 164.0, 153.7, 137.3, 136.4, 125.8, 123.8, 123.4, 121.4, 111.4, 78.9, 53.5, 52.5, 31.5, 28.1; IR ($CHCl_3$) ν 3030, 2981, 2955, 2935, 2863, 1728, 1687, 1644 cm^{-1}. MS (ES+) m/z calculated for $C_{21}H_{26}N_2O_5$ 386.2, found 386.2 (M+). Anal. calculated for $C_{21}H_{26}N_2O_5$ C, 65.3; H, 6.78; N, 7.25, found: C, 65.0; H, 6.81; N, 7.21.

4.8. Indole-3-acetamide synthesis

4.8.1. 2-(2,3-Dihydro-1*H*-indol-3-yl)-acetamide (12). Indole-3-acetamide **2** (45.0 g, 0.258 mol) was dissolved in MeOH (225 mL) and cooled to 0–5°C. 12N HCl (123 mL, 1.48 mol, 5.7 equiv.) was added dropwise, keeping the reaction temperature below 25°C. The reaction was cooled

to 0–10°C. Borane–pyridine complex (88.6 mL, 0.877 mol, 3.4 equiv.) was added dropwise, keeping the reaction temperature below 25°C. The reaction was stirred for 1 h at rt, then cooled to 0°C. Water (450 mL) was slowly added keeping the temperature <25°C. 50% NaOH (97 mL, 1.85 mol, 7.2 equiv.) was added dropwise to adjust the pH to 8. The product was extracted into EtOAc (3×225 mL) and washed with aqueous saturated $NaHCO_3$ (225 mL) and aqueous saturated NaCl (225 mL). The organic layer was dried ($MgSO_4$) filtered and concentrated in vacuo. Purification by silica gel chromatography (95:5 to 90:10 EtOAc/MeOH) afforded 26.5 g (58%) racemic **12**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.34 (bs, 1H), 7.01 (d, 1H, J=6.95 Hz), 6.90 (app. t, 1H, J=7.5 Hz), 6.83 (bs, 1H), 6.54–6.47 (m, 2H), 5.39 (s, 1H), 3.57–3.45 (m, 2H), 3.12–3.03 (m, 1H), 2.52–2.45 (m, 1H), 2.28–2.20 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 152.0, 131.7, 127.2, 123.6, 116.7, 108.4, 52.4, 40.0, 38.1; IR ($CHCl_3$) ν 3529, 3410, 3010, 2857, 1681, 1609, 1592, 1488, 1465 cm^{-1}. HRMS (ES) m/z calculated for $C_{10}H_{12}N_2O$ 176.0950, found 176.0950.

4.8.2. 2-(1-Piperidin-4-yl-1*H*-indol-3-yl)-acetamide (8a). Compound **8g** (1.38 g, 3.86 mmol) was stirred at rt as a slurry in EtOAc (28 mL). 4 M HCl in dioxane (19 mL, 76 mmol, 20 equiv.) was added dropwise over 5 min. The resulting dark purple slurry was stirred at rt overnight. The mixture was cooled to 10–15°C and deionized water (15 mL) added. The pH of the biphasic solution was adjusted to 10–11 with aqueous 50% NaOH. The product was extracted with EtOAc (3×), adding solid NaCl to the aqueous layer to help the extraction process. The combined organic layers were dried ($MgSO_4$), filtered and rinsed with EtOAc. The filtrate was concentrated in vacuo to obtain 410 mg (41%) **8a** as a solid (note: suspect yield loss to aqueous layer). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (d, 1H, J=7.91 Hz), 7.47 (d, 1H, J=8.35 Hz), 7.31 (bs, 1H), 7.27 (s, 1H), 7.09 (app. t, 1H, J=7.91 Hz), 6.98 (app. t, 1H, J=7.03 Hz), 6.82 (bs, 1H), 4.34 (m, 1H), 3.46 (s, 2H), 3.05 (m, 3H), 2.67 (m, 2H), 1.86 (m, 2H), 1.82–1.69 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.4, 135.0, 127.3, 123.2, 120.6, 118.9, 118.2, 109.5, 108.6, 53.0, 45.6, 33.6, 32.5; IR (KBr) ν 3304, 3104, 2944, 2914, 2824, 2737, 1687, 1464 cm^{-1}. HRMS (ES) m/z calculated for $C_{15}H_{19}N_3O$ 258.1606 (M+1), found 258.1602.

4.9. General methods for the synthesis of *N*-(azacycloalkyl) indole-3-acetamides (8). Route 1 via reductive amination/oxidation of 2-(2,3-dihydro-1*H*-indol-3-yl)-acetamide (12) and 1-alkyl-4-piperidones

2-(2,3-Dihydro-1*H*-indol-3-yl)-acetamide **12** (1.0 equiv.) in HOAc was stirred at rt for 20–30 min to obtain a solution, then 1-alkyl-4-piperidone (1.1 equiv.) was added in one portion. After cooling to rt, powdered $NaBH(OAc)_3$ (1.5 equiv.) was added in portions over 10–15 min, keeping the reaction temperature below 30°C. After stirring for 1–2 h at rt, the reaction was diluted with deionized water and an organic solvent. Aqueous concentrated NaOH was added dropwise to adjust the pH to 10–11 keeping the reaction temperature below 35°C. The precipitated product was isolated by filtration and rinsed with water and an organic solvent. The solid was dried in a vacuum oven at 50°C to afford the intermediate indoline.

A solution of the crude indoline intermediate in THF was stirred at 0–5°C under N_2. A solution of DDQ (1.0 equiv.) in THF was prepared and added dropwise to the reaction keeping the reaction temperature below 10°C. The dark, thick reaction was allowed to warm to rt and stirred overnight (21 h). Upon completion aqueous 5N NaOH was added dropwise to adjust the pH to 10–11 keeping the reaction temperature below 25°C. The layers were separated and the aqueous layer extracted. The combined organic layers were washed with aqueous saturated NaCl and dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate concentrated in vacuo to afford crude product that was purified using the conditions specified for each indole.

4.9.1. 2-[1-(1-Methyl-piperidin-4-yl)-1*H*-indol-3-yl]-acetamide (8b). Synthesis via route 1. Indoline formation employed indoline **12** (2.00 g, 11.3 mmol) in HOAc (10 mL) 1-methyl-4-piperidone (1.55 mL, 12.6 mmol) and powered $NaBH(OAc)_3$ (3.59 g, 16.9 mmol). Work-up employed deionized water (50 mL) and EtOAc (20 mL). Yield of crude indoline was 2.29 g (74%).

Indole-3-acetamide formation employed indoline intermediate (2.0 g, 7.32 mmol) in THF (20 mL) and DDQ (1.68 g, 7.4 mmol) in THF (20 mL). Work-up employed aqueous 5N NaOH until pH 10–1 and EtOAc. Overall yield (obtained in two crops) 0.46 g (24%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, 1H, J=7.91 Hz), 7.45 (d, 1H, J=8.35 Hz), 7.29 (app bs, 2H), 7.09 (t, 1H, J=7.03 Hz), 6.98 (t, 1H, J=7.03 Hz), 6.81 (bs, 1H), 4.26 (m, 1H), 3.45 (s, 2H), 2.89 (app bd, 2H), 2.23 (s, 3H), 2.13 (m, 2H), 1.99–1.83 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 135.2, 127.4, 123.2, 120.7, 118.9, 118.3, 109.5, 108.7, 54.6, 52.1, 45.8, 39.6, 39.5, 32.5, 32.0. HRMS (ES) m/z calculated for $C_{16}H_{21}N_3O$ 272.1763 (M+1), found 272.1753.

4.9.2. 2-[1-(1-Pyridin-2-ylmethyl-piperidin-4-yl)-1*H*-indol-3-yl]-acetamide (8e). Synthesis via route 1. Indoline formation employed **12** (2.00 g, 11.3 mmol), 1-pyridin-2-yl methyl-piperidin-4-one **9e** (2.38 g, 12.5 mmol) in HOAc (10 mL), and powdered $NaBH(OAc)_3$ (3.59 g, 16.9 mmol). After stirring for 3–4 h at rt, the reaction was diluted with deionized water (50 mL), EtOAc (50 mL) and MeOH (5 mL). Purification by silica gel chromatography (90:10:1 EtOAc/MeOH/c.NH_4OH), followed by reslurry of the product in 9:1 EtOAc/MeOH (10 vol.) afford 3.00 g (75%) of the indoline intermediate.

Indole-3-acetamide formation employed indoline intermediate (3.00 g, 8.56 mmol) in THF (45 mL) and DDQ (2.04 g, 8.98 mmol) in THF (15 mL). Work-up employed deionized water (75 mL), followed by aqueous 5% $NaHCO_3$ solution (75 mL) but the product did not precipitate. The mixture was partially concentrated in vacuo to remove the organic solvent. MTBE (50 mL) was added and the biphasic mixture stirred at 50°C for 10–15 min to precipitate the product. The slurry was cooled to rt, filtered, rinsed with water and MTBE to isolate the solid. The solid was reslurried in 5:1 EtOAc/MeOH at 50°C for 10–15 min, cooled to rt, filtered, rinsed with 5:1 EtOAc/MeOH and dried to afford 1.96 g (66%) **8e**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (app. d, 1H), 7.79 (app. t, 1H, J=7.69 Hz), 7.59–7.41 (m, 3H), 7.38–7.20 (m, 3H), 7.13

(t, 1H, J=7.32 Hz), 7.01 (t, 1H, J=7.32 Hz), 6.84 (bs, 1H), 4.32 (m, 1H), 3.70 (s, 2H), 3.48 (s, 2H), 2.98 (app. d, 2H), 2.33 (m, 2H), 2.07–1.88 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.7, 158.6, 148.7, 136.4, 135.5, 127.6, 123.4, 122.7, 122.1, 120.9, 119.0, 118.5, 109.6, 108.9, 63.5, 52.5, 52.3, 32.4; IR (KBr) ν 3377, 3159, 3111, 2945, 2794, 2758, 1676, 1585, 1463, 1385, 1362, 1342 cm^{-1}. HRMS (ES) m/z calculated for $C_{21}H_{24}N_4O$ 349.2028 (M+1), found 349.2022.

4.9.3. 2-[1-(1-Cyclopropylmethyl-piperidin-4-yl)-1*H*-indol-3-yl]-acetamide (8f). Synthesis via route 1. Indoline formation employed **12** (1.18 g, 6.70 mmol), 1-cyclopropylmethyl-piperidin-4-one **9f** (1.13 g, 7.38 mmol) in HOAc (5 mL) and powdered $NaBH(OAc)_3$ (2.13 g, 10.1 mmol). Reaction was stirred at rt for 1 h. Work-up involved deionized water (20 mL) and EtOAc (10 mL). The filtrate was concentrated in vacuo to afford the crude indoline intermediate as a solid that was triturated with MTBE (53 mL) and dried to afford 1.68 g (81%) of purified indoline intermediate.

Indole-3-acetamide formation employed indoline intermediate (1.00 g, 3.19 mmol) in THF (10 mL) and a solution of DDQ (797 mg, 3.51 mmol) in THF (5 mL). Purification using 100 g silica gel 60 (80:20:1 EtOAc/MeOH/c.NH_4OH) afforded 620 mg (62%) of **8f**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.47 (d, 1H, J=7.47 Hz), 7.40 (d, 1H, J=8.35 Hz), 7.20 (app. bs, 2H), 7.04 (d, 1H, J=7.47 Hz), 6.93 (d, 1H, J=7.47 Hz), 6.76 (bs, 1H), 4.22 (m, 1H), 3.40 (s, 2H), 3.05 (m, 2H), 2.22–2.07 (m, 4H), 1.95–1.83 (m, 4H), 0.81 (m, 1H), 0.42 (m, 2H), 0.05 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.3, 135.2, 127.4, 123.2, 120.7, 118.9, 118.3, 109.5, 108.6, 62.7, 52.6, 52.4, 39.6, 39.6, 39.4, 32.5, 32.1, 8.6, 3.9; IR (KBr) ν 3301, 3129, 2925, 2782, 1670, 1611, 1464, 1408, 1286, 1227 cm^{-1}. HRMS (ES) m/z calculated for $C_{19}H_{25}N_3O$ 312.2076 (M+1), found 312.2066.

4.9.4. 4-(3-Carbamoylmethyl-indol-1-yl)-piperidine-1-carboxylic acid *tert*-butyl ester (8g). Synthesis via route 1. Indoline formation employed 2-(2,3-dihydro-1*H*-indol-3-yl)-acetamide **12** (45.0 g, 0.255 mol), 1-(*tert*-butoxycarbonyl)-4-piperidone (55.9 g, 0.281 mol) in HOAc (360 mL) and powdered $NaBH(OAc)_3$ (81.1 g, 0.383 mol) in HOAc (45 mL, 0.79 mol). Work-up employed deionized water (1 L), followed by aqueous concentrated NaOH (371 mL, 7.09 mol). The product oiled out of solution and was dissolved with EtOAc (500 mL) and MeOH (100 mL). Additional concentrated NaOH (35 mL, 0.67 mol) was added to adjust the pH to 10. The product precipitated from solution. The thick slurry was stirred for 1 h at rt, then filtered and rinsed with water and EtOAc (minimal). The white solid was dried overnight to afford 67.3 g (73%) of the indoline intermediate. The filtrate was re-extracted with EtOAc and water and concentrated in vacuo to a solid (34 g), that was triturated with MTBE (150 mL), filtered and dried to afford an additional 15.4 g (17%) indoline intermediate. A third crop of 5.9 g (6%) was isolated from the MTBE filtrate by concentrating to dryness, adding cold MTBE (minimal), filtering and rinsing with cold MTBE. The total yield was 88.6 g (96%) of indoline intermediate.

Indole formation employed indoline intermediate (82.3 g, 0.229 mol) in THF (590 mL) and DDQ (52.0 g, 0.229 mol) in THF (145 mL). Work-up employed EtOAc and saturated aqueous $NaHCO_3$ solution. The product precipitated in the separatory funnel, causing bad emulsions and the solids were then filtered. The first crop of product was rinsed with EtOAc and water and dried to afford 36.3 g (44%) **8g** The filtrate was re-extracted to afford a second crop of product. Overall yield 69.6 g (85%) **8g**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55 (d, 1H, J=7.69 Hz), 7.50 (d, 1H, J=8.42 Hz), 7.31 (s, 1H), 7.27 (bs, 1H), 7.12 (app. t, 1H, J=7.0 Hz), 7.01 (app. t, 1H, J=8.1 Hz), 6.82 (bs, 1H), 4.53–4.51 (m, 1H), 4.13–4.09 (bm, 2H), 3.46 (app. s, 2H), 2.99–2.92 (bm, 2H), 1.94–1.91 (bm, 2H), 1.84–1.74 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6, 153.8, 135.4, 127.6, 123.4, 120.9, 119.1, 118.5, 109.6, 109.0, 78.7, 59.7, 52.0, 42.8, 32.4, 32.0, 28.3, 28.1, 20.7, 14.0; IR ($CHCl_3$) ν 3515, 3400, 1681, 1575, 1463, 1427 cm^{-1}. HRMS (ES) m/z calculated for $C_{20}H_{27}N_3O_3$ 357.2054, found 357.2052.

4.10. Route 2 via alkylation of 2-(1-piperidin-4-yl-1*H*-indol-3-yl)-acetamide (8a)

(1-Piperidin-4-yl-1*H*-indol-3-yl)-acetamide **8a** (1 equiv.) and powdered K_2CO_3 (1.2 equiv.), were stirred as a slurry in DMF at 0–5°C under N_2-blanket. The alkylating agent (1.2 equiv.) was added in one portion. The cooling bath was removed and the reaction was allowed to stir at rt until complete. The reaction was quenched with deionized water and after stirring for 2 h, the product was isolated using the conditions specified.

4.10.1. 2-[1-(1-Methyl-piperidin-4-yl)-1*H*-indol-3-yl]-acetamide (8b). Synthesis via route 2. Quantities employed (1-piperidin-4-yl-1*H*-indol-3-yl)-acetamide **8a** (257 mg, 1.0 mmol), powdered K_2CO_3 (166 mg, 1.20 mmol) in DMF (4 mL) and iodomethane (0.075 mL, 1.20 mmol) was added in one portion and the reaction stirred for 3 h. Additional iodomethane (0.02 mL, 0.32 mmol) was added and the reaction stirred at rt for 2 h until complete. Work-up employed deionized water (4 mL). The product was isolated by filtration, rinsed with minimal 2:1 water/DMF and dried to afford 150 mg (55%) **8b**.

4.10.2. 2-[1-(1-Pyridin-2-ylmethyl-piperidin-4-yl)-1*H*-indol-3-yl]-acetamide (8e). Synthesis via route 2. Quantities employed piperidin-4-yl-1*H*-indol-3-yl-acetamide **8a** (225 mg, 0.874 mmol), powdered K_2CO_3 (266 mg, 1.92 mmol, 2.2 equiv.) in DMF (3.4 mL) and 2-picolyl chloride monohydrochloride **20** (160 mg, 0.975 mmol). The reaction was stirred at rt overnight, then at 50°C for 1 h. Work-up employed deionized water (5 mL). After stirring 1–2 h the product was isolated by filtration, rinsed with water and dried to afford 250 mg (82%) **8e**.

4.10.3. 2-[1-(1-Cyclopropylmethyl-piperidin-4-yl)-1*H*-indol-3-yl]-acetamide (8f). Synthesis via route 2. Quantities employed piperidin-4-yl-1*H*-indol-3-yl-acetamide **8a** (210 mg, 0.816 mmol), powdered K_2CO_3 (135 mg, 0.977 mmol) in DMF (3.2 mL) and (bromomethyl)cyclopropane (0.090 mL, 0.928 mmol). Upon heating to 50°C for 3 h the reaction was incomplete and additional (bromomethyl)cyclopropane (0.115 mL, 1.19 mmol) was added.

The reaction slurry was stirred at rt overnight. And quenched with deionized water (3.5 mL). After stirring 1 h the product was isolated by filtration, rinsed with minimal 2:1 water/DMF and dried to afford 174 mg (69%) **8f**.

4.10.4. 2-[1-(1-Benzyl-pyrrolidin-3-yl)-1*H*-indol-3-yl]acetamide (8d). NaH (7.80 g, 196 mmol) was slurried in DMF (100 mL) and cooled to 0°C. Indole-3-acetamide **2** (22.7 g, 131 mmol) was added as a solution in DMF (100 mL) and the reaction was allowed to stir at rt for 1 h. The reaction was cooled back to 0°C. 1-Benzyl-3-mesyloxy pyrrolidine **26** (50.0 g, 196 mmol) in DMF (100 mL) was added and the reaction was heated to 50°C for 20 h. After cooling to rt, the reaction was diluted with EtOAc and washed with water (3×). The organic layer was washed with aqueous saturated NaCl, dried ($MgSO_4$) and the solvent was removed in vacuo to give an oil. Purification by silica gel chromatography (1:1 hexanes/acetone) afforded 37.6 g (86%) **8d** as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56 (d, 2H, J=7.9 Hz), 7.42–7.22 (m, 7H), 7.10 (t, 1H, J=7.1 Hz), 7.00 (t, 1H, J=7.9 Hz), 6.86 (bs, 1H), 5.08–5.05 (m, 1H), 3.66 (q, 2H, J=13.2 Hz), 3.49 (s, 2H), 2.99–2.94 (m, 1H), 2.79–2.76 (m, 2H), 2.51–2.40 (m, 1H), 1.97–1.90 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.6, 138.8, 135.5, 128.4, 128.2, 127.7, 126.8, 124.9, 124.4, 120.9, 118.9, 118.4, 109.8, 109.0, 59.4, 59.1, 53.6, 52.8, 32.4, 31.7; IR ($CHCl_3$) ν 3516, 3401, 2799, 1675, 1575, 1463, 1454, 1366, 1350 cm^{-1}. MS (FD) calculated for $C_{21}H_{23}N_3O$ 333, found m/z (M+1) 334 (100%). Anal. calculated for $C_{21}H_{23}N_3O$ C, 75.65, H, 6.95, N, 12.60, found C, 75.64, H, 6.92, N, 12.84.

4.11. General method for the synthesis of bisindolylmaleimides

A slurry of the indolyl-3-glyoxylate (1.1 equiv.) and indole-3-acetamide (1.0 equiv.) in THF were stirred under a N_2-blanket and cooled to −15°C. *tert*-KOBu (1.0 M solution in THF, 2.2 equiv.) was added dropwise, keeping the reaction temperature below −5°C. The cooling bath was removed and the reaction allowed to warm to rt, then heated to 45°C for 1–2 h until complete. The reaction solution was cooled to rt overnight, then partitioned between EtOAc and aqueous 5% $NaHCO_3$ solution. The product crystallized from the biphasic mixture. It was filtered and rinsed and dried to yield the desired product.

4.11.1. 3-(1-Methyl-1*H*-indol-3-yl)-4-[1-(1-methyl-piperidin-4-yl)-1*H*-indol-3-yl]-pyrrole-2,5-dione (1b). Synthesis via strategy A. Quantities employed **4b** (1.00 g, 3.33 mmol), **3** (628 mg, 3.34 mmol) in THF (10 mL) and *tert*-KOBu (7.4 mL, 7.4 mmol). Yield after filtration 1.21 g (83%) **1b** as an orange solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.89 (bs, 1H), 7.85 (s, 1H), 7.59 (s, 1H), 7.53 (d, 1H, J=8.35 Hz), 7.41 (d, 1H, J=7.91 Hz), 7.06 (m, 3H), 6.77 (t, 1H, J=7.47 Hz), 6.60 (t, 1H, J=7.91 Hz), 6.52 (d, 1H, J=7.91 Hz), 4.34 (m, 1H), 3.85 (s, 3H), 2.82 (m, 2H), 2.19 (s, 3H), 2.10 (m, 2H), 1.79 (m, 4H); IR ($CHCl_3$) ν 3007, 2945, 2851, 2793, 1606, 1489, 1473, 1379, 1275, 1249, 1125, 1068, 1024 cm^{-1}. HRMS (ES) m/z (M+1) calculated for $C_{27}H_{26}N_4O_2$ 439.2134, found 439.2100.

4.11.2. 3-[1-(1-Benzyl-piperidin-4-yl)-1*H*-indol-3-yl]-4-(1-methyl-1*H*-indol-3-yl)-pyrrole-2,5-dione (1c). Synthesis via strategy A. Quantities employed **4c** (4.00 g, 10.6 mmol), **7** (2.00 g, 10.6 mmol) in dry THF (15 mL) and *tert*-KOBu (23.4 mL, 23.4 mmol). Yield after filtration 4.00 g (73%) **1c** as a red/orange solid. ^{1}H NMR (DMSO-d_6) δ 1.84 (m, 3H), 2.17 (m, 2H), 2.48 (m, 1H), 2.87 (d, 2H, J=11.4 Hz), 3.32 (s, 2H), 3.84 (s, 3H), 4.40 (m, 1H), 6.57 (m, 2H), 6.76 (t, 1H, J=7.2 Hz), 7.03 (m, 3H), 7.30 (m, 5H), 7.41 (d, 1H, J=8.4 Hz), 7.54 (d, 1H, J=8.7 Hz), 7.64 (s, 1H), 7.86 (s, 1H), 10.93 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 172.9, 172.8, 138.3, 136.6, 135.4, 133.4, 128.7, 128.1, 128.0, 126.8, 126.6, 126.1, 125.1, 121.6, 121.4, 121.3, 119.6, 119.5, 110.1, 110.0, 105.4, 104.5, 61.8, 52.9, 52.0, 32.8, 31.7. IR (KBr) ν 3133, 3108, 3051, 3024, 2940, 2661, 1726, 1702, 1625, 1606, 1531, 1452, 1373, 1327, 1241, 1212 cm^{-1}. HRMS (ES) m/z (M+1) calculated for $C_{33}H_{30}N_4O_2$ 515.2447, found 515.2455.

4.11.3. 3-(1-Methyl-1*H*-indol-3-yl)-4-[1-[1-benzyl-4-pyrrolidinyl]-1*H*-indol-3-yl]-1*H*-pyrrole-2,5-dione (1d). Synthesis via strategy A. Quantities employed **4d** (4.20 g, 11.6 mmol), **3** (2.18 g, 11.6 mmol) in THF (50 mL) and *tert*-KOBu (57.9 mL, 57.9 mmol). Purification after work-up by silica gel chromatography (4:1 CH_2Cl_2/EtOAc) afforded 4.09 g **1d** (71%) as a bright red solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.94 (s, 1H), 7.91 (d, 1H, J=5.3 Hz), 7.81 (d, 1H, J=4.9 Hz), 7.60 (dt, 1H, J=7.9, 4.9 Hz), 7.32–7.23 (m, 4H), 7.14–7.02 (m, 4H), 6.86–6.81 (m, 1H), 6.66–6.56 (m, 2H), 5.09 (bs, 1H), 3.80 (s, 3H), 3.43–3.33 (m, 2H), 2.75–2.38 (m, 4H), 2.19–2.14 (m, 1H), 1.79–1.72 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 138.8, 136.7, 135.5, 133.3, 129.4, 128.1, 128.1, 127.5, 126.9, 126.7, 125.9, 124.9, 124.8, 121.6, 121.3, 119.6, 119.4, 110.2, 110.0, 105.5, 104.4, 59.4, 58.7, 53.7, 52.2, 32.8, 32.1, 14.0; IR ($CHCl_3$) ν 1762, 1715, 1532, 1463, 1374, 1359, 1336, 1310, 1245, 1230 cm^{-1}. MS (FD) calculated for $C_{32}H_{28}N_4O_2$ 500, found m/z (M+1) 501 (100%). Anal. calculated for $C_{32}H_{28}N_4O_2$ C, 76.78, H, 5.64, N, 11.19, found C, 76.58, H, 5.82, N, 10.96.

4.11.4. 3-(1-Methyl-1*H*-indol-3-yl)-4-[1-[1-(2-pyridinylmethyl)-4-piperidinyl]-1*H*-indol-3-yl]-1*H*-Pyrrole-2,5-dione (1e). Synthesis via strategy A. Quantities employed **4e** (779 mg, 2.06 mmol), **3** (377 mg, 2.00 mmol) in THF (5.7 mL) and *tert*-KOBu (14.4 mL, 4.4 mmol). After work-up the product precipitated and was filtered and rinsed with cold 3:1 water/THF to afford 772 mg (75%) **1e** as an orange solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.94 (s, 1H), 8.49 (d, 1H, J=4.0 Hz), 7.87 (s, 1H), 7.77 (dt, 1H, J=7.6, 1.8 Hz), 7.66 (s, 1H), 7.56 (d, 1H, J=8.5 Hz), 7.44 (t, 2H, J=7.6 Hz), 7.26 (t, 1H, J=7.3 Hz), 7.15–7.00 (m, 3H), 6.77 (t, 1H, J=7.5 Hz), 6.64–6.54 (m, 2H), 4.48–4.35 (m, 1H), 3.86 (s, 3H), 3.65 (s, 2H), 2.89 (bd, 2H, J=12.0 Hz), 2.29 (bt, 2H, J=8.2 Hz), 1.98–1.76 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 172.8, 158.5, 148.7, 136.6, 136.4, 135.4, 133.4, 128.1, 127.9, 126.6, 126.1, 125.1, 124.9, 122.6, 122.0, 121.6, 121.3, 121.2, 119.6, 119.5, 110.2, 110.0, 105.5, 104.4, 63.5, 52.7, 52.2, 32.8, 31.8; IR ($CHCl_3$) ν 2951, 1760, 1717, 1532, 1463, 1354, 1336, 1244, 1133 cm^{-1}. MS (FD) calculated for $C_{32}H_{29}N_5O_2$ 515, found m/z (M+1) 516 (100%). Anal. calculated for $C_{32}H_{29}N_5O_2$ C, 74.54, H, 5.67, N, 13.58, found C, 74.68, H, 5.96, N, 13.38.

4.11.5. 3-[1-[1-(Cyclopropylmethyl)-4-piperidinyl]-1*H*-indol-3-yl]-4-(1-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (1f). Synthesis via strategy A. Quantities employed **4f** (3.94 g, 11.6 mmol), **3** (2.18 g, 11.6 mmol) in THF (16 mL) and *tert*-KOBu (25.5 mL). After work-up the product precipitated was filtered and rinsed with water to afford after drying 3.1 g (56%) **1f** as an orange solid. ^{1}H NMR (DMSO-d_6) δ 0.06 (m, 2H), 0.44 (m, 2H), 0.82 (m, 1H), 1.80 (m, 4H), 2.18 (m, 4H), 3.03 (d, 2H, J=11.1 Hz), 3.84 (s, 3H), 4.35 (m, 1H), 6.52 (m, 1H), 6.60 (t, 1H, J=7.5 Hz), 6.77 (t, 1H, J=7.5 Hz), 7.05 (m, 3H), 7.41 (d, 1H, J=8.1 Hz), 7.53 (d, 1H, J=8.4 Hz), 7.62 (s, 1H), 7.86 (s, 1H), 10.92 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 135.4, 133.4, 128.1, 121.6, 121.4, 121.2, 119.6, 119.5, 110.1, 110.0, 52.1, 32.8, 31.6, 8.3, 3.7; IR (KBr) ν 1748, 1703, 1531, 1464, 1330, 1215 cm^{-1}. MS (ES) *m/z* calculated for $C_{30}H_{30}N_4O_2$ 478, found M+1= 479. Anal. calculated for $C_{30}H_{30}N_4O_2$: C, 75.29; H, 6.32; N, 11.70, found: C, 75.03; H, 6.25; N, 11.42.

4.11.6. 1,1-Dimethylethyl ester 4-[3-[2,5-dihydro-4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-1*H*-pyrrol-3-yl]-1*H*-indol-1-yl]-1-piperidinecarboxylic acid (1g). Synthesis via strategy A. Quantities employed **4g** (2.66 g, 6.88 mmol), **3** (1.29 g, 6.88 mmol) in Et_2O (25 mL) and *tert*-KOBu (20.7 mL, 20.7 mmol). Purification, after work-up, by silica gel chromatography (2:1 hexanes/EtOAc) afforded 2.23 g (62%) **1g** as a red foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.92 (s, 1H), 7.88 (s, 1H), 7.64 (s, 1H), 7.59 (d, 1H, J=8.4 Hz), 7.42 (d, 1H, J=8.4 Hz), 7.12–6.99 (m, 3H), 6.79 (app. t, 1H, J~8 Hz), 6.62 (app. t, 1H, J~7 Hz), 6.53, (d, 1H, J=7.7 Hz), 4.67–4.54 (m, 1H), 4.12–4.05 (m, 2H), 3.86 (s, 3H), 3.02–2.82 (m, 2H), 1.88 (bd, 2H, J=12.1 Hz), 1.72–1.55 (m, 2H), 1.41, (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 172.7, 153.7, 136.6, 135.3, 133.4, 128.2, 128.1, 126.6, 126.1, 125.1, 121.6, 121.5, 121.4, 121.2, 119.7, 119.5, 110.1, 110.0, 105.6, 104.4, 78.8, 59.7, 52.4, 32.8, 31.6, 28.0. IR ($CDCl_3$) ν 3543, 3491, 3197, 3047, 3007, 2976, 1755, 1702, 1630, 1609 cm^{-1}. HRMS (ES) exact mass calculated for $C_{31}H_{32}N_4O_4$ M^+ 524.2424, found 524.2442. Anal. calculated for $C_{31}H_{32}N_4O_4$, C, 70.9; H, 6.15; N, 10.7, found; C, 70.5; H, 6.43. N, 10.1.

4.11.7. 3-(1-Methyl-1*H*-indol-3-yl)-4-(1-piperidin-4-yl-1*H*-indol-3-yl)-pyrrole-2,5-dione (1a). Concentrated HCl (2.74 mL, 33.2 mmol, 15 equiv.) was added to a solution of **1g** (1.16 g, 2.21 mmol) in EtOAc (11 mL) at reflux. The reaction mixture was stirred at reflux for 2 h then cooled to 0°C, filtered and rinsed with EtOAc. The red product was dried at 50°C in vacuo to give 710 mg (70%) **1a**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.46 (bs, 1H), 9.23 (bs, 1H), 7.88 (s, 1H), 7.68 (d, 1H, J=8.4 Hz), 7.62 (s, 1H), 7.42 (d, 1H, J=8.1 Hz), 7.10–6.94 (m, 4H), 6.75 (app. t, 1H, J~7 Hz), 6.65–6.54 (m, 2H), 4.90–4.75 (m, 1H), 3.88 (s, 3H), 3.40 (d, 2H, J=11.7 Hz), 3.10 (app. t, 2H, J~11 Hz), 2.31–2.12 (m, 1H), 2.11–2.00 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.8, 136.5, 135.1, 133.4, 128.3, 127.6, 126.2, 126.1, 125.3, 121.8, 121.7, 121.3, 121.1, 119.8, 119.5, 110.4, 110.1, 105.9, 104.4, 50.3, 42.7, 32.9, 28.3, 28.2; IR (KBr) ν 3110, 2887, 2762, 2677, 2487, 1750, 1697 cm^{-1}. MS (ES) calculated for $C_{26}H_{24}N_4O_2Cl$ 459.96 (–HCl=423.51), found *m/z* (M−HCl) 423.24. Anal. calculated for $C_{26}H_{24}N_4O_2Cl$ C, 67.90, H, 5.26, N, 12.18, found C, 67.96, H, 5.46, N, 12.01.

4.11.8. 3-(1*H*-Indol-3-yl)-4-[1-(1-pyridin-2-ylmethyl-piperidin-4-yl)-1*H*-indol-3-yl]-pyrrole-2,5-dione (1h). Synthesis via strategy A. Quantities employed **4e** (3.00 g, 7.95 mmol), **2** (1.26 g, 7.23 mmol) in THF (60 mL) and *tert*-KOBu (36.1 mL, 36.1 mmol). After work-up the product was recrystallized from hot MeOH (30 mL, 0.8 vol.) to give 2.43 mg (61%) **1h**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.67 (d, 1H, J=2.22 Hz), 10.91 (s, 1H), 8.51 (d, 1H, J=4.03 Hz), 7.80 (d, 1H, J=2.93 Hz), 7.77 (td, 1H, J=7.69 Hz, 1.46 Hz), 7.69 (s, 1H), 7.55 (d, 1H, J=8.05 Hz), 7.47 (d, 1H, J=7.69 Hz), 7.39 (d, 1H, J=8.05 Hz), 7.26 (app. d, 1H, J=6.95, 5.49 Hz), 7.10–6.90 (m, 3H), 6.80–6.55 (m, 3H), 4.50–4.30 (m, 1H), 3.66 (s, 2H), 3.37 (s,.2H), 2.93 (d, 2H, J=11.34 Hz), 2.31 (dd, 2H, J=10.98, 8.42 Hz), 1.85 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.9, 172.8, 158.5, 148.7, 136.4, 136.0, 135.4, 129.4, 128.3, 128.2, 127.0, 126.0, 124.8, 122.6, 122.1, 121.6, 121.5, 121.3, 121.0, 119.7, 119.3, 111.7, 110.2, 105.4, 105.4, 63.5, 53.8, 52.5, 52.3, 31.8; IR (KBr) ν 3323, 1751, 1698, 1614, 1530 cm^{-1}. HRMS (ES) exact mass calculated for $C_{31}H_{27}N_5O_2$ M^+ 501.2165, found 501.2165.

4.11.9. 3-(1*H*-Indol-3-yl)-4-[1-(1-methyl-piperidin-4-yl)-1*H*-indol-3-yl]-pyrrole-2,5-dione (1i). Synthesis via strategy A. Quantities employed **4b** (1.00 g, 3.33 mmol), **2** (580 mg, 3.33 mmol) in THF (10 mL) and *tert*-KOBu (17.4 mL, 7.4 mmol). After work-up 1.02 g (72%) **1i** was isolated as an orange solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.7 (bs, 1H), 10.9 (bs, 1H), 7.77 (s, 1H), 7.62 (s, 1H), 7.52 (d, 1H, J=8.35 Hz), 7.38 (app d, 1H), 7.05 (m, 2H), 6.95 (m, 1H), 6.75 (t, 1H, J=7.47 Hz), 6.6 (m, 2H), 4.34 (m, 1H), 2.83 (app d, 2H), 2.19 (s, 3H), 2.10 (m, 2H), 1.85 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 135.8, 135.2, 128.2, 127.9, 126.8, 125.8, 124.6, 121.4, 121.3, 121.2, 120.8, 119.5, 119.1, 110.0, 105.3, 105.2, 54.3, 52.5, 45.7, 40.0, 39.9, 39.8, 39.6, 39.2, 39.2, 31.7; IR (KBr) ν 3339, 3125, 3040, 2942, 2800, 2671, 1702, 1616, 1531, 1462, 1340, 1304, 1231, 1199, 1128 cm^{-1}. HRMS (ES) *m/z* (M+1) calculated for $C_{26}H_{24}N_4O_2$ 425.1978, found 425.1995.

4.11.10. 3-(1-Methyl-1*H*-indol-3-yl)-4-[1-(1-methyl-piperidin-4-yl)-1*H*-indol-3-yl]-pyrrole-2,5-dione (1b). Synthesis via strategy B. Quantities employed **8b** (106 mg, 0.391 mmol), **7** (85 mg, 0.391 mmol) in THF (2 mL) and *tert*-KOBu, (0.862 mL, 0.862 mmol). After work-up the product was filtered, rinsed with water and EtOAc, then dried to afford 92 mg (54%) **1b** as an orange solid.

4.11.11. 3-[1-(1-Benzyl-piperidin-4-yl)-1*H*-indol-3-yl]-4-(1-methyl-1*H*-indol-3-yl)-pyrrole-2,5-dione (1c). Synthesis via strategy B. Quantities employed **8c** (160 mg, 0.460 mmol), **7** (100 mg, 0.460 mmol) in THF (3 mL) and *tert*-KOBu (1.00 mL, 1.00 mmol). The reaction was heated to 45°C for 2 h but was incomplete (stalled at the intermediate hydroxyimide stage). Additional *tert*-KOBu (1.74 mL, 1.74 mmol) was added but further heating for 2 h was still incomplete. However, the reaction was quenched and worked up via the standard procedure. Purification using 50 g silica gel 60 (1:1 CH_2Cl_2/EtOAc) to afford 121 mg (51%) **1c**.

4.11.12. 3-(1-Methyl-1*H*-indol-3-yl)-4-[1-[1-benzyl-4-pyrrolidinyl]-1*H*-indol-3-yl]-1*H*-pyrrole-2,5-dione (1d). Synthesis via strategy B. Quantities employed **8d** (25.0 g, 75.0 mmol), **7** (17.0 g, 78.7 mmol) in THF (250 mL) and *tert*-KOBu (375 mL, 375 mmol). Purification, after work-up, by silica gel chromatography (4:1 CH_2Cl_2/EtOAc) afforded 22.4 g **1d** (60%) as a bright red solid.

4.11.13. 3-(1-Methyl-1*H*-indol-3-yl)-4-[1-[1-(2-pyridinyl-methyl)-4-piperidinyl]-1*H*-indol-3-yl]-1*H*-pyrrole-2,5-dione (1e). Synthesis via strategy B. Quantities employed **8e** (697 mg, 2.00 mmol), **7** (447 mg, 2.06 mmol) in THF (5.7 mL) and *tert*-KOBu (4.4 mL, 4.4 mmol). After work-up the product precipitated was filtered and rinsed with cold 3:1 water/THF to afford 550 mg (53%) **1e** as an orange solid.

4.11.14. 1,1-Dimethylethyl ester 4-[3-[2,5-dihydro-4-(1-methyl-1*H*-indol-3-yl)-2,5-dioxo-1*H*-pyrrol-3-yl]-1*H*-indol-1-yl]-1-piperidinecarboxylic acid (1g). Synthesis via strategy B. Quantities employed **8g** (450 mg, 1.26 mmol), **7** (274 mg, 1.26 mmol) in THF (5 mL) and *tert*-KOBu, (2.80 mL, 2.80 mmol). Purification, after work-up, using 50 g silica gel 60 (1:1 EtOAc/heptane) afforded 528 mg (80%) **1g**.

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