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Total synthesis of zyzzyanones A-D

Dwayaja H. Nadkarni, Srinivasan Murugesan, and Sadanandan E. Velu

Department of Chemistry, University of Alabama at Birmingham, 901 14th Street South, Birmingham, Alabama 35294, USA

Abstract

Zyzzyanones A-D is a group of biologically active marine alkaloids isolated from Australian marine sponge *Zyzzya fuliginosa*. They contain a unique bispyrroloquinone ring system as the core structure. The first total synthesis of all four zyzzyanones is described here. The synthesis of these alkaloids started from a previously known 6-benzylamino indole-4,7-quinone derivative and involves 6–7 steps. The key step in the synthesis involves the construction of a pyrrole ring in one step using a Mn(OAc)₃ mediated oxidative free radical cyclization reaction of a 6-benzylamino indole-4,7-quinone derivative with 4-benzyloxyphenyl acetaldehyde diethyl acetal in CH₃CN.

Keywords

Zyzzyanone; Marine; Alkaloid; Quinone; Mn(OAc)₃

Introduction

Marine natural products are chemical substances that exist as secondary metabolites in marine invertebrates such as sponges, bryozoans, tunicates and ascidians. Marine bacteria have also been found to be a source of marine natural products. Among these, marine sponges have been identified as the largest source of marine natural products.^{1,2} Over the course of past four decades, marine natural products have provided a number of challenging synthetic targets for organic chemists. In addition to this, several lead drug molecules have been identified from bioactive marine natural products, some of which have been approved for clinical use for the treatment of various diseases. Examples of recently approved marine derived drugs for clinical use are Ziconitide (Prialt™)³ used in the treatment of chronic pain, Ecteinascidin 743 (Yondelis™)⁴ used in the treatment of ovarian cancer and Eribulin mesylate (Halaven™) used in the treatment of breast cancer.⁵ Additionally, several other compounds derived from marine natural products are currently undergoing Phase II and Phase III cancer clinical trials.^{6–10} Marine natural products are often isolated only in minute quantities that are insufficient for extensive biological evaluations. They often have unique structures which provide challenging synthetic targets for organic chemists. For these reasons development of new synthetic methods for marine natural products remains an important research area.

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Correspondence to: Sadanandan E. Velu.

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Supplementary Material Copies of ¹H NMR, ¹³C NMR spectra of all compounds and a comparison of spectral data of synthetic and natural zyzzyanones are available as Supplementary Material. This can be found at ---

As a part of our interest in deriving marine natural product analogs as lead molecules for drug discovery,^{11–16} we are particularly interested in a class of marine alkaloids bearing a pyrrolo[4,3,2-*de*]quinoline skeleton. The main source of pyrrolo[4,3,2-*de*]quinoline alkaloids are marine sponges of the genera *Latrunculia*, *Batzella*, *Prianos* and *Zyzzya*.^{17,18} This series of alkaloids comprise of about 60 metabolites including makaluvamines,^{19–24} discorhabdins,²⁵ batzellines,²⁶ epinardins,²⁷ isobatzellines,²⁶ veitamine,²⁸ tsitsikammamines (**2a,b**)^{29,30} and wakayin (**3**).³¹ Bioactivity of this class of alkaloids include topoisomerase I¹⁹ and II²² inhibition, antiproliferative activity against different cancer cell lines,^{32,22} and antimicrobial activities.³³ There has been a rapid growth of interest in the synthesis and biological evaluation of this class of compounds as evidenced by the number of recent reviews published.^{17,34–36}

A related class of tetracyclic bispyrroloquinone alkaloids called Zyzzyanones A-D (**1a-d**, Fig. 1) has been isolated from the Australian marine sponge *Zyzzya fuliginosa*.^{37,38}

A facile synthesis of bispyrroloquinone ring system present in zyzzyanones has been recently reported from our laboratory.³⁹ However, the total synthesis of any of the zyzzyanones has not been reported in the literature till date. As a part of our work on the synthesis of marine natural products and their analogs^{12,13}, we have been interested in the synthesis of zyzzyanones A-D. As a continuation of this research interest, we report herein the first total synthesis of four zyzzyanones A-D featuring a novel Mn(OAc)₃ mediated oxidative free radical cyclization of a 6-benzylamino indole-4,7-quinone derivative with 4-benzyloxyphenyl acetaldehyde diethyl acetal.

Results and discussion

Our previously reported synthesis³⁹ of bispyrroloquinone ‘ring system’ present in zyzzyanones utilized a ceric ammonium nitrate (CAN) mediated oxidative free radical cyclization of 6-benzylamino-N-tosylindole quinone with 1,3-dicarbonyl compounds. However, the bispyrroloquinone derivative (compound **4**, Figure 2) obtained from this reaction did not contain the phenolic ring and the aminoethyl side chain that are present in zyzzyanones. In addition to this problem, compound **4** contained additional substituents on one of the pyrrole rings such as a methyl group and ethoxycarbonyl groups that are not present in zyzzyanones. The presence of such undesirable substituents and the absence of certain desirable substituents in compound **4** presented a challenge when we set out for the synthesis of zyzzyanones using this methodology. Our attempts to modify CAN mediated cyclization to produce appropriately substituted bispyrroloquinone ring for zyzzyanone synthesis proved difficult. Structural modification of compound **4** to make zyzzyanones did not work, either. So, it was clear that a modification of this reaction is needed to accomplish the total synthesis of zyzzyanones.

During the literature search for alternative methods for similar cyclization reactions, we came across a reaction where Mn(OAc)₃ has been used as a reagent in the oxidative free radical cyclization of aminoquinones with acetals described by Shanab et al.⁴⁰ The Mn(OAc)₃ mediated cyclization strategy was more attractive as it formed the pyrrole ring to the quinone without substituents. Besides, it also provided us opportunities for adding additional desired substituents to the pyrrole ring.

Based on this literature report, it is envisaged that the core tetracyclic system present in zyzzyanones (**5**) could be prepared in one step by coupling the synthon, 6-aminoindole-4,7-quinone (**7**) with 4-hydroxyphenyl acetaldehyde diethyl acetal (**6**) as outlined in the retro synthetic Scheme 1.

A benzyl protected derivative of 4-hydroxyphenyl acetaldehyde diethyl acetal (**11**) was required for this reaction. This protected acetal was synthesized as shown in Scheme 2.

Commercially available 4-hydroxyphenethyl alcohol (**8**) was benzylated using benzyl bromide in the presence of K_2CO_3 in anhydrous DMF to give compound **9** in 97 % yield. Compound **9** was then oxidized to aldehyde **10** using IBX in DMSO in 95 % yield and the aldehyde **10** was converted to the diethyl acetal **11** in 90 % yield by treatment with anhydrous EtOH in the presence of con. H_2SO_4 using a Dean-Stark trap and condenser.

To test the synthetic strategy, we carried out a model synthesis of the bispyrroloquinone ring system (**13**) starting from appropriately protected 6-aminoindole-4,7-quinone (**12**) and acetal (**11**) as outlined in Scheme 3. The synthesis started with the previously reported *N*-tosyl-6-(benzylamino)-*1H*-indole-4,7-dione (**12**)⁴¹. Treatment of compound **12** with 4-benzyloxyphenyl acetaldehyde diethyl acetal (**11**) in the presence of $Mn(OAc)_3$ in anhydrous CH_3CN under refluxing conditions resulted in the formation of bispyrroloquinone derivative **13** in 80 % yield.

This cyclization reaction proceeded via an oxidative free radical mechanism as reported previously in the cases of 2-amino-1,4-naphthoquinones^{42–44} and 2-amino-1,4-benzoquinones⁴⁵. We have also demonstrated that the protecting groups present in compound **13** can be removed without affecting the bispyrroloquinone ring system. The tosyl group present in compound **13** was removed by the treatment with NaOMe in anhydrous MeOH to afford the product **14** in 76 % yield. Alternatively, tosyl group was removed by treatment of compound **13** with NaN_3 in DMF to obtain **14** in 74 % yield. Both O- and N-benzyl groups present in compound **14** were removed in one step by treatment with Pd black in the presence of $HCOONH_4$ in anhydrous EtOH to afford compound **5** in 50 % yield. A stronger debenzylating agent such as Pd black was required in this reaction as we had to remove both N- and O- benzyl groups in one step. Attempts to debenzylate compound **14** using 10 % Pd/C and H_2 resulted only in the selective removal of O- benzyl group. N-benzyl group was harder to remove under these conditions. Attempts to debenzylate **14** using alternate reagents like $AlCl_3$ did not result in the expected products, either.

After working out the model chemistry, we decided to extend this synthetic strategy for the synthesis of zyzzyanones. The structure of zyzzyanones contained an additional amino ethyl side chain at the 3-position of bispyrrole quinone ring as compared to compound **5**. So, we decided to start the synthesis of zyzzyanones with previously known⁴¹ *N*-tosyl-6-(methoxy)-*1H*-indole-4,7-dione derivative containing a (N-Boc)ethyl amine side chain (compound **15**, Scheme 4). Treatment of compound **15** with benzyl amine in a mixture of MeOH and THF (1:1) at room temperature gave the aminated compound **16** in 78 % yield. Treatment of compound **16** with 4-benzyloxyphenyl acetaldehyde diethyl acetal (**11**) in the presence of $Mn(OAc)_3$ in acetonitrile at 80 °C resulted in the formation of bispyrroloquinone derivative **17** in 72 % yield. Since zyzzyanone A contained two N-methyl groups, the next attempt was to introduce a methyl group on the side chain N atom compound **17**. Methylation was carried out by the treating of compound **17** with MeI in the presence of NaH in anhydrous DMF at room temperature. To our surprise, this reaction gave the expected monomethylated compound **18** along with the unexpected dimethylated compound **19** in 46 % and 34 % yields, respectively. Compound **19** is presumably formed by the removal of N-tosyl group from **18** followed by N-methylation, both steps occurring in the same reaction. The dimethylated product (**19**) obtained in this reaction was also a useful compound because our next logical step in the synthesis was to prepare the very same compound by detosylating compound **18** and N-methylating the product obtained. Since we have already obtained compound **19** in one step, we proceeded to debenzylate compound **19**

by treatment with Pd black in the presence of HCOONH_4 in anhydrous EtOH to afford compound **20** in 55 % yield. Finally, N-Boc group present in compound **20** was removed by treatment with TFA in CH_2Cl_2 to afford zyzzyanone A as TFA salt (**1a**) in 81 % yield. The spectral data of synthetic zyzzyanone A was found to be exactly identical to the values reported for the natural product.³⁸

Conversion of compound 18 to zyzzyanone B

The next attempt was to synthesize zyzzyanone B from compound **18**. The synthesis of zyzzyanone B is outlined in Scheme 5. In order to convert compound **18** to zyzzyanone B, we had to remove N-benzyl, O-benzyl, N-tosyl and N-Boc protecting groups from the compound **18**. Compound **18** was first detosylated by treatment with NaN_3 in anhydrous DMF for 4 hours to obtain detosylated product **21** in 75 % yield. Compound **21** was then debenzylated using Pd black in the presence of HCOONH_4 in anhydrous EtOH which resulted in the removal of both O- and N- benzyl groups to afford debenzylated compound **22** in 53 % yield. Removal of the Boc group from compound **22** using 1:1 mixture of TFA and CH_2Cl_2 at room temperature resulted in the formation of zyzzyanone B as TFA salt in 85 % yield. The spectral data of synthetic zyzzyanone B was found to be in good agreement with the values reported for this natural product.³⁷

Conversion of compound 18 to zyzzyanone C

Next objective was to synthesize zyzzyanones C and D. Zyzzyanone C contained an N-formyl group in the side chain. So, it was important to standardize conditions for the N-formylation of the side chain N-atom of compound **19**. Compound **19** contained an N-Boc group in the side chain. So, Boc group was removed from compound **19** before the formylation reaction was carried out. Compound **19** was first treated with TFA/ CH_2Cl_2 to remove the Boc group and the crude product thus obtained was subjected to N-formylation reactions without further purification. N-formylation has been reported in literature using $\text{HCOOH}/\text{Ac}_2\text{O}$.⁴⁶ Following this procedure, we first attempted N-formylation using HCOOH and Ac_2O at room temperature and under reflux conditions. At room temperature reaction for 36 hours mostly resulted in the recovery of starting material. However, the same reaction at reflux condition for 15 hours resulted in a number of side reactions along with the formation of about 5% expected product in isolated yield. Further literature search revealed an alternate reaction condition using trifluoroethyl formate, Et_3N and ether resulting in N-formylation.⁴⁷ The formylation of our compound using trifluoroethyl formate, Et_3N resulted in an improved yield of 40 % of the product. Reactions where the use of HCOOEt as a formylation agent has also been reported in the literature.⁴⁸ This is what has worked best in our hands. Formylation of compound **19** using HCOOEt and Et_3N at reflux conditions after the removal of Boc group resulted in the formation of N-formylated product **23** in 72 % yield (Scheme 6). Transformation of compound **23** to zyzzyanone C is given in Scheme 6. Removal of both O- and N- benzyl groups present in compound **23** using Pd black in the presence of HCOONH_4 in refluxing EtOH afforded zyzzyanone C in 55 % yield. The spectral data of synthetic zyzzyanone C was found to be exactly identical to the values reported for the natural product.³⁷

Conversion of compound 18 to zyzzyanone D

Conversion of compound **18** to zyzzyanone D is shown in Scheme 7. Compound **18** was treated with a 1:1 mixture of TFA and CH_2Cl_2 to remove the Boc group to obtain the amino compound. The crude amino compound, thus obtained was subjected to formylation using HCOOEt in the presence of Et_3N under reflux conditions. This reaction resulted in the expected formylation along with detosylation to afford the compound **24** in 64 % yield.

Since HCOOEt was used as a formylation agent the ethoxide ion is the leaving group in the formylation reaction. Ethoxide ion is also an excellent reagent for N-detosylation. This could possibly be the reason for the observed detosylation in this reaction. Both N-benzyl and O-benzyl groups present in compound **24** were removed by treatment with Pd-black in the presence of HCOONH₄ in EtOH under reflux conditions to afford zyzzyanone D in 58 % yield. The spectral data of synthetic zyzzyanone D was found to be exactly identical to the values reported for the natural product.³⁷

Conclusions

In conclusion, first total synthesis of zyzzyanones A-D starting from a 6-benzylamino indole-4,7-quinone derivative is accomplished. The key step of the synthesis is the construction of a pyrrole ring by a Mn(OAc)₃ mediated oxidative free radical cyclization of 6-benzylamino indole-4,7-quinone derivative with 4-benzyloxyphenyl acetaldehyde diethyl acetal in CH₃CN. This methodology has the potential to provide rapid access to other bispyrroloquinone natural products such as tsitsikammamines and wakayin. In addition, this synthetic methodology will be useful in the synthesis of various analogs of these alkaloids with specific substitution patterns. This will eventually assist in the structure activity relationship studies and optimization of the lead drug molecules derived from these marine natural products. Further studies along these lines are currently in progress.

Experimental

General Methods for Synthesis

Solvent evaporations were carried out *in vacuo* with rotary evaporator. Thin layer chromatography (TLC) was performed on silica gel plates with fluorescent indicator (Whatmann, silica gel, UV254, 25 µm plates). Spots were visualized by UV light (254 and 365 nm). Purification by column and flash chromatography was carried out using 'BAKER' silica gel (40 µm) in the solvent systems indicated. The amount (weight) of silica gel for column chromatography was in the range of 50–100 times the amount (weight) of the crude compounds being separated. Melting points were determined on a Mel-Temp II melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (¹H NMR) and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Bruker DPX 300 spectrometer using TMS or appropriate solvent signals as internal standard. The values of chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane and coupling constants (*J*) in Hz. Mass spectra were recorded on a MicroMass Platform LCC instrument. HRMS were obtained on a Waters AutoSpec-Ultima™ NT mass spectrometer with an EI source. Anhydrous solvents used for reactions were purchased in Sure-Seal™ bottles from Aldrich Chemical Company. Other reagents were purchased from Aldrich, Lancaster or Acros chemical companies and used as received.

2-[4-(Benzyloxy)phenyl]ethanol (**9**)

To a solution of 2-(4-hydroxyphenyl) ethanol, **8** (5.0 g, 36.23 mmol) in anhydrous DMF (20 mL), K₂CO₃ (15.0 g, 108.7 mmol) was added and the reaction mixture was stirred at room temperature for 30 minutes. Benzyl bromide (6.24 g, 36.5 mmol) was added to the reaction mixture and stirred for 4 hours at room temperature. The TLC examination (EtOAc / Hexane, 1:3) showed the completion of the reaction. The reaction mixture was quenched with water (200 mL) and EtOAc (200 mL) was added. The organic layer was separated and the aqueous layer was once again extracted with EtOAc (100 mL). The combined EtOAc layer was washed with water (3 × 100 mL), brine (1 × 100 mL) and dried over anhydrous Na₂SO₄. The drying agent was filtered off and the solvent was evaporated under low pressure to obtain the compound **9** as a white solid (8.0 g, 97 %). The proton and ¹³C NMR

data matched well with those reported in literature.⁴⁹ ¹H NMR (CDCl₃) δ 2.78 (t, 2H, *J* = 6.4 Hz), 3.78 (t, 2H, *J* = 6.4 Hz), 5.03 (s, 2H), 6.92 (d, 2H, *J* = 8.4 Hz), 7.12 (d, 2H, *J* = 8.4 Hz), 7.35–7.45 (m, 5H); ¹³C NMR δ 38.7, 64.2, 70.5, 115.4(2C), 127.9(2C), 128.4, 129.0(2C), 130.5(2C), 131.2, 137.5, 157.9 and MS (ES⁺) *m/z* 227 (M-H).

2-[4-(Benzyloxy)phenyl]ethanal (10)

To a solution of compound **9** (7.0 g, 30.7 mmol) in DMSO (15 mL), IBX (12.9 g, 46 mmol) was added and suspension was stirred for 3 hours at room temperature. TLC examination (EtOAc/Hexane, 1:3) indicated the completion of the reaction. EtOAc (350 mL) was added to the reaction mixture. The insoluble solids were filtered off under suction. The EtOAc layer was washed with water (3 × 150 mL), brine (1 × 150 mL) and dried over anhydrous Na₂SO₄. The drying agent was filtered off and the solvent was evaporated under reduced pressure to afford the product, **10** (6.6 g, 95 %) was characterized by proton and ¹³C NMR. The proton NMR matched well with the one reported in literature.⁵⁰ ¹H NMR (CDCl₃) δ 3.63 (d, 2H, *J* = 2.1 Hz), 5.06 (s, 2H), 6.98 (d, 2H, *J* = 8.4 Hz), 7.13 (d, 2H, *J* = 8.4 Hz), 7.30–7.60 (m, 5H), 9.72(t, 1H, *J* = 2.1 Hz); ¹³C NMR δ 49.7, 70.0, 115.3(2C), 124.0, 127.5(2C), 128.0, 128.6(2C), 130.7(2C), 136.8, 158.1, 199.8 and MS (ES⁺) *m/z* 227 (M+H).

1-(Benzyloxy)-4-(2,2-diethoxyethyl)benzene (11)

To a solution of compound **10** (6.0 g, 26.43 mmol) in EtOH (100 mL), conc. H₂SO₄ (0.1 g, 1.02 mmol) was added and the reaction mixture was stirred for 3 hours. The TLC examination (EtOAc /Hexane, 1:1) showed the completion of the reaction. The reaction mixture was neutralized with saturated NaHCO₃. The solvent was evaporated under reduced pressure and the residual slurry was partitioned between EtOAc (250 mL) and water (250 mL). The aqueous layer was drained off and the organic layer was washed with water (3 × 100 mL), brine (1 × 100 mL) and dried over anhydrous Na₂SO₄. After the removal of drying agent, solvent was evaporated off and the crude product obtained was purified by column chromatography over Si gel using EtOAc / hexanes (1:10) to obtain pure acetal, **11** (7.14 g, 90 %); ¹H NMR (CDCl₃) δ 1.16 (t, 6H, *J* = 7.2 Hz), 2.86 (d, 2H, *J* = 5.7 Hz), 3.38–3.48 (m, 2H), 3.62–3.72 (m, 2H), 4.57 (t, 1H, *J* = 5.7 Hz), 5.02 (s, 2H), 6.89 (d, 2H, *J* = 8.4 Hz), 7.16 (d, 2H, *J* = 8.4 Hz), 7.27–7.51 (m, 5H); ¹³C NMR δ 15.3, 40.0, 61.9, 70.0, 104.0, 114.6, 127.5, 127.9, 128.6, 129.7, 130.6, 137.2, 157.4; and MS (ES⁺) *m/z* 323 (M + Na).

1-Benzyl-3-(4-benzyloxyphenyl)-7-(tosyl)-1H,7H-pyrrolo[3,2-f]indole-4,8-dione (13)

To a solution of *N*-tosyl-6-(benzylamino)-*1H*-indole-4,7-dione, **12** (0.1 g, 0.25 mmol) in CH₃CN (50 mL), 4-benzyloxyphenyl acetaldehyde diethyl acetal, **11** (0.525 g, 1.8 mmol) and Mn(OAc)₃ (0.462 g, 1.8 mmol) were added and the reaction mixture was refluxed for 40 h. TLC examination (EtOAc / hexanes, 1:1) revealed that the reaction was complete. The reaction mixture was then allowed to attain room temperature and the solvent was evaporated off in vacuo. The residue obtained was dissolved in EtOAc (50 mL), washed with a saturated solution of NaHSO₃ (1 × 20 mL), water (2 × 20 mL), brine (1 × 20 mL) and dried over anhydrous Na₂SO₄. Removal of solvent from the dried extract afforded the crude product which was purified by column chromatography over Si gel using EtOAc / hexanes (1:3) as eluent to afford the pure product **13** as a red solid (0.123 g, 80 %); Mp 164–165 °C; ¹H NMR (CDCl₃) δ 2.42 (s, 3H), 5.07 (s, 2H), 5.57 (s, 2H), 6.72 (d, 1H, *J* = 3.3 Hz), 6.80 (s, 1H), 6.96 (d, 2H, *J* = 7.8 Hz), 7.15–7.26 (m, 2H), 7.27–7.48 (m, 10H), 7.54 (d, 2H, *J* = 7.8 Hz), 7.71 (d, 1H, *J* = 3.3 Hz), 7.98 (d, 2H, *J* = 8.4 Hz); ¹³C NMR (CDCl₃) δ 21.8, 52.4, 70.1, 108.4, 114.5, 122.7, 125.1, 126.6, 127.5 (2C), 128.0, 128.2, 128.3, 128.7, 128.9, 129.1, 129.5, 130.1, 130.5, 130.6, 132.4, 133.6, 134.4, 136.2, 137.1, 145.8, 158.7, 167.3, 178.7; and HRMS calcd for C₃₇H₂₈N₂O₅S, [M]⁺: 612.1719, found 612.1702.

1-Benzyl-3-(4-benzyloxyphenyl)-1H,7H-pyrrolo[3,2-f]indole-4,8-dione (14). Method A

To a solution of compound **13** (0.05 g, 0.082 mmol) in anhydrous MeOH (5 mL), NaOMe (0.044 g, 0.81 mmol) was added and the reaction mixture was stirred at room temperature for 45 min. TLC examination (CHCl₃ / EtOAc, 9:1) revealed that the reaction was complete. The reaction mixture was then quenched with water (5 mL), and the solvent was evaporated off in vacuo. The resulting aqueous layer was extracted with EtOAc (2 × 10 mL). The EtOAc extract was washed with water (3 × 5 mL), brine (1 × 5 mL) and dried over anhydrous Na₂SO₄. Removal of the solvent from the dried extract afforded the crude product which was purified by column chromatography over Si gel using EtOAc/hexanes (1:4) as eluent to yield the pure product, **14** (0.028 g, 76 %).

Method B

Alternatively, NaN₃ (0.004 g, 0.06 mmol) was added to a solution of compound **13** (0.025 g, 0.041 mmol) in anhydrous DMF (1 mL), and the reaction mixture was stirred for 4 hours at room temperature. The reaction was quenched with water and extracted with EtOAc (2 × 10 mL). The EtOAc extract was washed with water (3 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na₂SO₄. The drying agent was filtered and the solvent was evaporated off. The residue obtained was purified by column chromatography over Si gel using EtOAc / Hexane (1:4) to yield the pure product, **14**. (0.014 g, 74%); Mp 236–237°C; ¹H NMR (CDCl₃) δ 5.10 (s, 2H), 5.64 (s, 2H), 6.62 (t, 1H, *J* = 2.7 Hz), 6.87 (s, 1H), 6.97 (d, 2H, *J* = 9.0 Hz), 7.30–7.50 (m, 11H), 7.60 (d, 2H, *J* = 9.0 Hz), 9.53 (bs, 1H); ¹³C NMR (CDCl₃) δ 52.3, 70.1, 108.8, 114.4, 124.3, 124.4, 125.4, 127.3, 127.4, 127.5, 128.0, 128.1 (2C), 128.4, 128.6, 128.9, 130.2, 130.3, 132.1, 136.4, 137.1, 158.5, 169.6, 179.6; MS (ES⁺) *m/z* 459 (M + H); HRMS calcd for C₃₀H₂₂N₂O₃ [M]⁺: 458.1630, found 458.1646.

3-(4-Hydroxyphenyl)-1H,7H-pyrrolo[3,2-f]indole-4,8-dione (5)

To a solution of compound **14** (0.015 g, 0.033 mmol) in EtOH (15 mL), HCOONH₄ (0.050 g, 0.8 mmol) and Pd black (0.03 g, 0.28 mmol) were added and the reaction mixture was refluxed for 15 hours. TLC examination (CHCl₃ / MeOH, 20:1) revealed that the reaction is complete. The reaction mixture was then allowed to attain room temperature and filtered through a pad of celite 585 and washed with EtOAc / CHCl₃ (1:1). The combined filtrate and washings were evaporated in vacuo. The residue obtained was dissolved in EtOAc (10 mL) and washed with water (2 × 5 mL), brine (1 × 5 mL) and dried over anhydrous Na₂SO₄. The drying agent was removed by filtration and the solvent was evaporated off in vacuo to obtain the crude product which was purified by column chromatography over Si gel using MeOH / CHCl₃ (1:25) as eluent to furnish the pure product **5** (0.0046 g, 50 %); ¹H NMR (CD₃OD) δ 6.54 (d, 1H, *J* = 2.7 Hz), 6.79 (d, 2H, *J* = 8.7 Hz), 7.01 (d, 1H, *J* = 2.7 Hz), 7.04 (s, 1H), 7.55 (d, 2H, *J* = 8.7 Hz); ¹³C NMR (CD₃OD) δ 109.3, 115.6, 123.3, 124.6, 126.1, 126.2, 129.2, 130.0, 131.1, 132.9, 134.9, 157.9, 169.8, 182.5; MS (ES⁺) *m/z* 279 (M + H), 277 (M-H); HRMS calcd for C₁₆H₁₀N₂O₃ [M]⁺ 278.0691, found 278.0700.

tert-Butyl-2-(6-(benzylamino)-4,7-dihydro-4,7-dioxo-1-tosyl-1H-indol-3-yl)ethylcarbamate (16)

To a solution of quinone, **15** (0.77g, 1.62 mmol) in MeOH / THF (1:1, 150 mL), benzyl amine (0.261 g, 2.43 mmol) was added and the reaction mixture was stirred at room temperature for 20 hours. TLC examination (EtOAc / hexanes, 1:1) revealed that the reaction was complete. The solvent was evaporated off in vacuo and the residue obtained was purified by column chromatography over Si gel using EtOAc / hexanes (1:4) as eluent to afford the pure aminated product **16** (0.69g, 78%); Mp. 154–155 °C; ¹H NMR (CDCl₃) δ 1.41 (s, 9H), 2.43 (s, 3H), 2.98 (t, 2H, *J* = 6.4 Hz), 3.39 (q, 2H, *J* = 6.4 Hz), 4.23 (d, 2H, *J* = 5.6 Hz), 4.87 (bs, 1H), 5.29 (s, 1H), 6.02 (bt, 1H, *J* = 5.6 Hz), 7.24 (d, 2H, *J* = 8.4 Hz), 7.30–

7.40 (m, 5H), 7.67 (s, 1H), 7.97 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR (CDCl_3) δ 21.8, 25.7, 28.4, 40.5, 47.2, 79.1, 98.0, 123.6, 127.3, 127.7, 128.1, 128.9(2C), 129.7, 130.1, 130.6, 133.9, 135.8, 146.1, 147.4, 156.0, 170.2, 183.2; MS (ES^+) m/z 550 (M+H) and HRMS calcd for $\text{C}_{25}\text{H}_{22}\text{N}_3\text{O}_6\text{S}$ $[\text{M}-\text{C}_4\text{H}_9]^+$ 492.1229, found 492.1227.

2-[7-Benzyl-5-(4-benzyloxyphenyl)-4,8-dioxo-1-(tosyl)-1,4,7,8-tetrahydro-pyrrolo[3,2-f]indol-3-yl]-ethyl-carbamic acid tert-butyl ester (17)

To a solution of quinone **16** (0.7 g, 1.27 mmol) and acetal, **9** (2.66 g, 8.9 mmol) in CH_3CN (100 mL), $\text{Mn}(\text{OAc})_3$ (2.4 g, 8.9 mmol) was added and the reaction mixture was refluxed for 40 hours. TLC examination (EtOAc / hexanes, 1:1) revealed that the reaction was complete. The reaction mixture was then allowed to attain room temperature and the solvent was evaporated off in vacuo. The residue obtained was dissolved in EtOAc (100 mL), washed with saturated NaHSO_3 (2×50 mL), water (2×50 mL), brine (1×50 mL) and dried over anhydrous Na_2SO_4 . The drying agent was removed by filtration and the solvent was removed to obtain the crude product which was purified by column chromatography over Si gel using EtOAc / hexanes (1:3) as eluent to furnish the product **17** as an orange solid (0.693 g, 72 %); mp 193–194 °C; ^1H NMR (CDCl_3) δ 1.38 (s, 9H), 2.42 (s, 3H), 2.98 (t, 2H, $J = 6.4$ Hz), 3.38 (q, 2H, $J = 6.4$ Hz), 4.76 (bs, 1H), 5.08 (s, 2H), 5.55 (s, 2H), 6.78 (s, 1H), 6.97 (d, 2H, $J = 8.8$ Hz), 7.15–7.45 (m, 12H), 7.50 (d, 2H, $J = 8.4$ Hz), 7.57 (s, 1H), 7.97 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR (CDCl_3) δ 21.8, 25.8, 28.4, 40.6, 52.2, 70.0, 79.1, 114.4, 122.8, 123.3, 125.1, 126.4, 127.5(2C), 127.9, 128.0, 128.4, 128.6(3C), 128.7, 129.0, 129.4, 129.9(2C), 130.0, 131.1, 134.2, 136.2, 137.0, 145.5, 156.0, 158.5, 167.0, 180.4; MS (ES^+) m/z 756 (M+H) and HRMS calcd for $\text{C}_{39}\text{H}_{32}\text{N}_3\text{O}_5\text{S}$ $[\text{M}-\text{C}_4\text{H}_9\text{CO}_2]^+$ 654.2063, found 654.2061.

N-(2-[7-Benzyl-5-(4-benzyloxyphenyl)-4,8-dioxo-1-(tosyl)-1,4,7,8-tetrahydro-pyrrolo[3,2-f]indol-3-yl]-ethyl)-N-methyl-carbamic acid tert-butylester (18) and N-(2-(7-benzyl-5-(4-benzyloxy-phenyl)-1-methyl-4,8-dioxo-1,4,7,8-tetrahydro-pyrrolo[3,2-f]indol-3-yl)-ethyl)-N-methyl-carbamic acid tert-butyl ester (19)

To a solution of compound **17** (0.3 g, 0.4 mmol) in anhydrous DMF (3 mL), NaH (0.032 g, 0.8 mmol, 60 % dispersion in mineral oil) was added at 0 °C. The reaction mixture was stirred for 30 minutes followed by addition of CH_3I (0.25 g, 1.75 mmol). The temperature was gradually increased to room temperature and stirred for 30 hours. TLC examination (EtOAc / hexanes, 1:1) revealed that the reaction was complete. The reaction mixture was quenched with saturated solution of NH_4Cl and extracted with EtOAc (100 mL). The EtOAc extract was further washed with water (3×40 mL), brine (1×40 mL) and dried over Na_2SO_4 . The drying agent was filtered off and the solvent was evaporated off to obtain the crude product which was purified by column chromatography over Si gel using EtOAc / hexanes (1:1) as eluent to afford pure compounds **18** (0.141 g, 46 %) and **19** (0.085 g, 34 %) as orange and yellow solids. Compound **18**: Mp 165–166 °C; ^1H NMR (CDCl_3) δ 1.30–1.50 (m, 9H), 2.41 (s, 3H), 2.83 (s, 3H), 2.89–3.11 (m, 2H), 3.5 (t, 2H, $J = 7.2$ Hz), 5.08 (s, 2H), 5.56 (s, 2H), 6.78 (s, 1H), 6.97 (d, 2H, $J = 8.7$ Hz), 7.10–7.55 (m, 13H), 7.52 (d, 2H, $J = 8.7$ Hz), 7.96 (d, 2H, $J = 8.4$ Hz); ^{13}C NMR (CDCl_3) δ 21.7, 24.2, 28.4, 34.7, 48.4, 52.3, 70.0, 79.3, 114.5, 122.9, 123.4, 125.2, 126.4, 127.4(2C), 127.9, 128.0, 128.4, 128.6(2C), 128.8 (2C), 129.0, 129.4, 130.0(2C), 131.1, 134.4, 136.3, 137.0, 145.5, 155.7, 158.5, 167.1, 180.1; MS (ES^+) m/z 770 (M+H) and HRMS calcd for $\text{C}_{40}\text{H}_{34}\text{N}_3\text{O}_5\text{S}$ $[\text{M}-\text{C}_4\text{H}_9\text{CO}_2]^+$ 668.2219, found 668.2215. Compound **19**: Mp 120–122 °C (dec); ^1H NMR (CDCl_3) δ 1.30–1.55 (m, 9H), 2.79 (s, 3H), 2.88–3.07 (m, 2H), 3.46 (t, 2H, $J = 6.9$ Hz), 3.89 (s, 3H), 5.09 (s, 2H), 5.65 (s, 2H), 6.77 (s, 1H), 6.98 (d, 2H, $J = 8.7$ Hz), 7.21–7.45 (m, 11H), 7.60 (d, 2H, $J = 8.7$ Hz); ^{13}C NMR (CDCl_3) δ 24.2, 28.4, 34.3, 36.4, 48.9, 52.1, 70.1, 79.0, 114.4, 123.1, 124.0, 125.7, 125.8, 126.3, 127.3, 127.5, 127.9, 128.0, 128.1, 128.6, 128.8, 129.4, 130.1, 130.3,

130.7, 136.7, 137.1, 155.8, 158.3, 170.6, 180.5; MS (ES⁺) m/z 630 (M+H) and HRMS calcd for C₃₉H₃₉N₃O₅ 629.2890, found 629.2884.

N-{2-[5-(4-Hydroxy-phenyl)-1-methyl-4,8-dioxo-1,4,7,8-tetrahydro-pyrrolo[3,2-f]-indol-3-yl]-ethyl}-N-methyl-carbamic acid tert-butyl ester (20)

To a solution of compound **19** (0.014 g, 0.022 mmol) in anhydrous EtOH (10 mL), HCOONH₄ (0.05 g, 0.8 mmol) and Pd black (0.022 g, 0.20 mmol) were added and refluxed for 15 hours. TLC examination (CHCl₃ / MeOH, 20:1) revealed that the reaction was complete. The reaction mixture was allowed to attain room temperature and filtered through a pad of celite 585 and washed with EtOAc / CHCl₃ (1:1). The filtrate and washings were combined and the solvent was evaporated off in vacuo. The residue obtained was dissolved in EtOAc (20 mL) and washed with water (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na₂SO₄. The drying agent was filtered off and the solvent was evaporated off to obtain the crude product which was purified by column chromatography over Si gel using MeOH / CHCl₃ (1:25) as eluent to furnish the pure product **20** (0.0055 g, 55 %); ¹H NMR (CD₃OD) δ 1.21–1.55 (m, 9H), 2.88 (s, 3H), 2.94 (t, 2H, *J* = 6.0 Hz), 3.39–3.61 (m, 2H), 3.95 (s, 3H), 6.76 (s, 1H), 6.81 (d, 2H, *J*_I = 6.6 Hz), 7.04 (s, 1H), 7.58 (d, 2H, *J*_I = 6.6 Hz); ¹³C NMR (CD₃OD) δ 25.0, 28.5(3C), 30.7, 34.2, 36.3, 80.6, 115.5, 115.6, 123.3, 124.4, 124.5, 126.3, 127.7, 128.8, 131.1, 131.3, 131.4, 131.5, 157.9, 170.6, 182.7; MS (ES⁺) m/z 448 (M-H); and HRMS calcd for C₂₀H₁₈N₃O₃ [M-C₄H₉CO₂]⁺ 348.1348, found 348.1341.

5-(4-Hydroxy-phenyl)-1-methyl-3-(2-methylaminoethyl)-1H,7H-pyrrolo[3,2-f]indole-4,8-dione (Zyzzyanone A)

To a suspension of compound **20** (0.005 g, 0.011 mmol) in CH₂Cl₂ (1 mL) was added a 1:1 mixture of TFA and CH₂Cl₂ (0.2 mL) drop wise at room temperature. The reaction mixture was stirred at room temperature for 2 hours following which the TLC (MeOH / CHCl₃, 1:25) indicated the completion of the reaction. The solvent was evaporated off and co-evaporated with CHCl₃ (3 × 3 mL) to yield pure zyzzyanone A as TFA salt (0.0041 g, 81 %); ¹H NMR (CD₃OD) δ 2.69 (s, 3H), 3.07 (t, 2H, *J* = 7.2 Hz), 3.23 (t, 2H, *J* = 7.2 Hz), 3.97 (s, 3H), 6.78 (d, 2H, *J* = 8.7 Hz), 6.89 (s, 1H), 7.04 (s, 1H), 7.55 (d, 2H, *J* = 8.7 Hz); ¹³C NMR (CD₃OD) δ 23.7, 33.7, 36.5, 50.7, 115.7, 120.9, 123.0, 124.7, 126.1, 127.4, 128.9, 131.1, 131.3, 131.8, 135.0, 158.0, 170.5, 182.9; MS (ES⁺) m/z 350 (M+H); and HRMS calcd for C₂₀H₁₉N₃O₃ 349.1426, found 349.1429.

N-{2-[7-Benzyl-5-(4-benzyloxyphenyl)-4,8-dioxo-1,4,7,8-tetrahydro-pyrrolo[3,2-f]indol-3-yl]-ethyl}-N-methyl-carbamic acid tert-butyl ester (21)

To a solution of compound **18** (0.067 g, 0.087 mmol) in DMF (1 mL), NaN₃ (0.012 g, 0.174 mmol) was added and stirred for 4 hours at room temperature following which the TLC (EtOAc / Hexane, 1:1) indicated the completion of the reaction. The reaction mixture was quenched with water and extracted with EtOAc (2 × 20 mL). The EtOAc extract was further washed with water (3 × 20 mL), brine (1 × 20 mL) and dried over anhydrous Na₂SO₄. The drying agent was filtered off and the solvent was evaporated off to obtain the crude product which was purified by column chromatography over Si gel using EtOAc / Hexane (1:10) as eluent to furnish the pure product **21**. (0.040 g, 75 %); ¹H NMR (CDCl₃) δ 1.29–1.48 (m, 9H), 2.82 (s, 3H), 2.89–3.08 (m, 2H), 3.48 (t, 2H, *J* = 6.9 Hz), 5.10 (s, 2H), 5.64 (s, 2H), 6.83 (s, 1H), 7.00 (d, 2H, *J* = 7.2 Hz), 7.20–7.50 (m, 11H), 7.59 (d, 2H, *J* = 7.2 Hz), 9.48 (bs, 1H); ¹³C NMR δ 24.3, 28.4, 34.3, 48.9, 52.2, 70.1, 79.1, 114.4, 123.3, 124.5, 124.7, 125.6, 127.1, 127.4, 127.5(2C), 127.9, 128.1, 128.6, 128.9, 129.7, 130.2(2C), 132.5, 136.5, 137.1, 155.9, 158.5, 169.3, 180.7; MS (ES⁺) m/z 614 (M-H), 516 (M+H-C₄H₉CO₂) and HRMS: calcd for C₃₈H₃₇N₃O₅ 615.2733, found 615.2742.

N-{2-[5-(4-Hydroxyphenyl)-4,8-dioxo-1,4,7,8-tetrahydro-pyrrolo[3,2-f]indol-3-yl]-ethyl}-N-methyl-carbamic acid tert-butyl ester (22)

To a solution of **21** (0.038 g, 0.062 mmol) in anhydrous EtOH (10 mL), HCOONH₄ (0.15 g, 2.38 mmol) and Pd black (0.07 g, 0.66 mmol) were added and refluxed for 15 hours. TLC examination (CHCl₃ / MeOH, 20:1) revealed that the reaction was complete. The reaction mixture was allowed to attain room temperature and filtered through a pad of celite 585 and washed with EtOAc / CHCl₃ (1:1). The combined filtrate and washings were concentrated in vacuo. The residue obtained was dissolved in EtOAc (25 mL) and washed with water (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na₂SO₄. The drying agent was removed by filtration and the solvent was evaporated off in vacuo to obtain the crude product which was purified by column chromatography over Si gel using MeOH / CHCl₃ (1:25) as eluent to furnish the pure product **22** (0.014 g, 53 %); ¹H NMR (CD₃OD) δ 1.31–1.45 (m, 9H), 2.84(s, 3H), 2.94(t, 2H, *J* = 6.3 Hz), 3.35–3.65(m, 2H), 6.70–6.85 (m, 3H), 7.01(s, 1H), 7.55(d, 2H, *J* = 6.9 Hz); ¹³C NMR δ 25.1, 28.6, 30.7, 34.2, 80.6, 115.7, 123.9, 124.7, 125.3, 125.4, 125.6, 126.3, 126.7, 129.1, 131.1, 133.3, 134.5, 157.9, 169.8, 183.2; MS (ES⁺)*m/z* 434 (M-H), 336 (M+H-C₄H₉CO₂) and HRMS: calcd for C₂₄H₂₅N₃O₅ 435.1794, found 435.1796.

3-(4-Hydroxy-phenyl)-5-(2-methylamino-ethyl)-1H,7H-pyrrolo[3,2-f]indole-4,8-dione (Zyzzyanone B)

To a suspension of compound **22** (0.007 g, 0.016 mmol) in CH₂Cl₂ (1 mL) a 1:1 mixture of TFA and CH₂Cl₂ (0.2 mL) was added drop wise at room temperature. The reaction mixture was stirred at room temperature for 2 hours following which the TLC (MeOH / CHCl₃, 1:25) indicated the completion of reaction. The solvent was evaporated off and co-evaporated with CHCl₃ (3 × 3 mL) to yield pure zyzzyanone B as TFA salt. (0.0061 g, 85 %); ¹H NMR (CD₃OD) δ 2.69 (s, 3H), 3.09 (t, 2H, *J* = 7.2 Hz), 3.26 (t, 2H, *J* = 7.2 Hz), 6.77 (d, 2H, *J* = 8.7 Hz), 6.95(s, 1H), 7.03 (s, 1H), 7.54(d, 2H, *J* = 8.7 Hz); ¹³C NMR δ 23.9, 33.7, 50.8, 115.6, 121.6, 123.6, 124.9, 125.7, 126.1, 126.4, 129.2, 131.2, 133.9, 134.5, 158.0, 169.7, 183.3; MS (ES⁺) *m/z* 336 (M+H) and HRMS: calcd for C₁₉H₁₇N₃O₃ 335.1270, found 335.1262.

N-{2-[7-Benzyl-5-(4-benzyloxyphenyl)-1-methyl-4,8-dioxo-1,4,7,8-tetrahydro-pyrrolo[3,2-f]indol-3-yl]-ethyl}-N-methyl-formamide (23)

To a solution of **19** (0.040 g, 0.064 mmol) in CH₂Cl₂ (4 mL), a 1:1 mixture of TFA and CH₂Cl₂ (1 mL) was added drop wise at room temperature. The reaction mixture was stirred for 2 hours following which TLC (MeOH / CHCl₃, 1:25) indicated the completion of the reaction. The solvent was evaporated off and the residue co-evaporated with CHCl₃ (3 × 10 mL). To this residue in HCOOEt (15 mL), Et₃N (1 mL) was added and refluxed for 24 hours. TLC analysis (CHCl₃ / MeOH, 20:1) indicated completion of the reaction. The HCOOEt was evaporated off and the residue was purified by column chromatography over Si gel using CHCl₃ as eluent to obtain (**23**). (0.026 g, 72 %); ¹H NMR (CDCl₃) δ 2.89 (2.92) (s, 3H), 2.85–3.05 (m, 2H), 3.46–3.65 (m, 2H), 3.92 (s, 3H), 5.1 (s, 2H), 5.66 (s, 2H), 6.48 (6.65) (s, 1H), 6.80 (6.81) (s, 1H), 7.00 (d, 2H, *J* = 9.0 Hz), 7.25–7.50 (m, 10H), 7.56–7.64 (m, 2H), 7.82 (8.01) (s, 1H); ¹³C NMR (CDCl₃) δ 23.1(24.8), 29.8, 34.9(36.6), 43.8, 49.6(52.2), 70.1, 114.49, 121.4(122.4), 123.95(124.01), 125.5(125.7), 125.76(125.79), 126.4(126.5), 127.5(127.6), 128.02(128.08), 128.12(128.19), 128.4, 128.7, 128.96(128.98), 129.50(129.56), 130.2, 130.5(130.7), 130.8(130.9), 136.6(136.7), 137.1, 158.46, 162.7, 163.1, 170.57(170.62), 180.6(180.7); MS (ES⁺) *m/z* 558 (M+H); and HRMS: calcd for C₃₅H₃₁N₃O₄ 557.2315, found 557.2328.

N-{2-[5-(4-Benzyloxyphenyl)-1-methyl-4,8-dioxo-1,4,7,8 tetrahydropyrrolo[3,2-f]indol-3-yl]-ethyl}-N-methyl-formamide (Zyzzyanone C)

To a solution of compound **23** (0.035 g, 0.063 mmol) in anhydrous EtOH (10 mL), HCOONH₄ (0.15 g, 2.5 mmol) and Pd black (0.07 g, 0.65 mmol) were added and refluxed for 15 hours. TLC examination (CHCl₃ / MeOH, 20:1) revealed that the reaction is complete. The reaction mixture was allowed to attain room temperature and filtered through a pad of celite 585 and washed with EtOAc / CHCl₃ (1:1). The filtrate and washings were combined and the solvent was evaporated off in vacuo. The residue obtained was dissolved in EtOAc (25 mL) and washed with water (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na₂SO₄. The drying agent was filtered and the solvent was evaporated off to obtain the crude product which was purified by column chromatography over Si gel using MeOH / CHCl₃ (1:25) as eluent to furnish zyzzyanone C. (0.013 g, 55 %); ¹H NMR (DMSO-d₆) δ 2.76(2.88) (s, 3H), 2.83–2.93 (m, 2H), 3.40–3.53 (m, 2H), 3.89 (s, 3H), 6.75(d, 2H, *J* = 8.7 Hz), 6.99(7.01) (s, 1H), 7.17(s, 1H), 7.56(d, 2H, *J* = 8.7 Hz), 7.77(7.95) (s, 1H), 9.44(bs, 1H), 12.62(bs, 1H); ¹³C NMR (DMSO-d₆) δ 22.7(24.2), 29.0(34.1), 35.9, 43.2 (48.6), 114.6, 121.4, 121.5(122.2), 123.8(123.9), 124.1, 125.4(125.5), 126.5(126.6), 129.3(129.4), 129.8, 130.0(130.5), 133.4, 156.7, 162.3, 168.7, 180.5; MS (ES⁺) *m/z* 378 (M + H); and HRMS: calcd for C₂₁H₁₉N₃O₄ 377.1376, found 377.1383.

N-{2-[7-Benzyl-5-(4-benzyloxyphenyl)-4,8-dioxo-1,4,7,8-tetrahydropyrrolo[3,2-f]indol-3-yl]-ethyl}-N-methyl-formamide (24)

To a solution of compound **18** (0.055 g, 0.072 mmol) in CH₂Cl₂ (4 mL), a 1:1 mixture of TFA and CH₂Cl₂ (1 mL) was added drop wise at room temperature. The reaction mixture was stirred for 2 hours. TLC (MeOH / CHCl₃, 1:25) indicated the completion of the reaction. The solvent was evaporated off and the residue co-evaporated with CHCl₃ (3 × 10 mL). To this residue in HCOOEt (15 mL) Et₃N (1 mL) was added and refluxed for 24 hours following which TLC (CHCl₃ / MeOH, 20:1) indicated completion of the reaction. The HCOOEt was evaporated off and the residue was purified by column chromatography over Si gel using MeOH / CHCl₃ (1:50) as eluent to obtain **24** (0.025 g, 64 %); ¹H NMR (CDCl₃) δ 2.89(2.91) (s, 3H), 2.85–3.15 (m, 2H), 3.55–3.65 (m, 2H), 5.1 (s, 2H), 5.58(5.61) (s, 2H), 6.53(6.70) (s, 1H), 6.82 (s, 1H), 7.01 (d, 2H, *J* = 9.0 Hz), 7.19–7.48 (m, 10H), 7.58 (d, 2H, *J* = 9.0 Hz), 7.83(8.02) (s, 1H), 9.95(10.2) (bs, 1H); ¹³C NMR (CDCl₃) δ 23.0(24.7), 29.8(34.9), 43.9, 49.5(52.2), 70.0, 114.3, 122.4, 123.6(123.8), 124.3(124.4), 124.5(124.6), 125.4(125.5), 127.1(127.2), 127.3, 127.4, 127.5, 127.9, 128.1, 128.5, 128.6, 128.9, 130.1(130.2), 132.5(133.1), 136.4(136.5), 137.1, 158.4, 162.8(163.4), 169.3, 180.6(180.7); MS (ES⁺) *m/z* 544 (M + H); and HRMS: calcd for C₃₄H₂₉N₃O₄ 543.2158, found 543.2180.

N-{2-[5-(4-Hydroxyphenyl)-4,8-dioxo-1,4,7,8-tetrahydropyrrolo[3,2-f]indol-3-yl]-ethyl}-N-methyl-formamide (Zyzzyanone D)

To a solution of compound **24** (0.023 g, 0.042 mmol) in anhydrous EtOH (10 mL), HCOONH₄ (0.1 g, 1.6 mmol) and Pd black (0.05 g, 0.47 mmol) were added and refluxed for 15 hours. TLC examination (CHCl₃/MeOH, 20:1) revealed that the reaction was complete. The reaction mixture was allowed to attain room temperature and filtered through a pad of celite 545 and washed with EtOAc / CHCl₃ (1:1). The filtrate and washings were combined and the solvent was evaporated off in vacuo. The residue obtained was dissolved in EtOAc (25 mL), washed with water (2 × 10 mL), brine (1 × 10 mL) and dried over anhydrous Na₂SO₄. The drying agent was filtered and the solvent was evaporated off to obtain the crude product which was purified by column chromatography over Si gel using MeOH / CHCl₃ (1:25) as eluent to furnish zyzzyanone D. (0.009 g, 58 %); ¹H NMR (DMSO-d₆) δ 2.75 (2.85)(s, 3H), 2.87–2.95(m, 2H), 3.42–3.52 (m,2H), 6.75 (d, 2H, *J* = 8.7 Hz), 6.95 (s, 1H), 7.17 (s, 1H), 7.55(d, 2H, *J* = 8.7 Hz), 7.72(7.94) (s, 1H), 9.45 (bs, 1H), 12.43 (bs, 1H),

12.60 (bs, 1H); ^{13}C NMR (DMSO- d_6) δ 22.7(24.2), 29.0(34.0), 43.2(48.7), 114.6, 121.8, 122.4(123.1), 123.9, 124.0(124.1), 124.4(124.5), 124.6(125.1), 126.7(126.8), 129.9, 131.5(131.7), 133.0, 156.6, 162.2(162.3), 167.9, 180.9; MS (ES^+) m/z 364(M+H), 362(M-H) and HRMS: calcd for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_4$ 363.1219, found 363.1225.

Supplementary Material

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1a , Zyzzyanone A,	$R_1 = \text{CH}_3$,	$R_2 = \text{H}$
1b , Zyzzyanone B,	$R_1 = \text{H}$,	$R_2 = \text{H}$
1c , Zyzzyanone C,	$R_1 = \text{CH}_3$,	$R_2 = \text{CHO}$
1d , Zyzzyanone D,	$R_1 = \text{H}$,	$R_2 = \text{CHO}$

- 2a**, tsitsikammamine A, $R_3 = \text{H}$
2b, tsitsikammamine B, $R_3 = \text{CH}_3$

- 3**. Wakayin

Figure 1.
 Zyzzyanones, tsitsikammamines and wakayin.

4, Substituted
bispyrroloquinone

1a, Zyzzyanone A

Figure 2.
Comparison of structures of CAN mediated cyclization product (**4**) with zyzzyanone A (**1a**).

Scheme 1.
Proposed synthesis of bispyrroloquinone ring system

Scheme 2.
Synthesis of 4-benzyloxyphenyl acetaldehyde diethyl acetal (**11**).

Scheme 3.
Synthesis of bispyrroloquinone ring system.

Scheme 4.
Synthesis of zyzzyanone A (**1a**).

Scheme 5.
Synthesis of zyzzyanone B (**1b**).

Scheme 6.
Synthesis of zyzzyanone C (**1c**).

Scheme 7.
Synthesis of zyzzyanone D (**1d**).