



HAL
open science

Synthesis of analogues of the marine pyrroloiminoquinone alkaloid wakayin as potential IDO1 inhibitors

Evelyne Delfourne, Thomas Levy

► **To cite this version:**

Evelyne Delfourne, Thomas Levy. Synthesis of analogues of the marine pyrroloiminoquinone alkaloid wakayin as potential IDO1 inhibitors. 2020. hal-03064848

HAL Id: hal-03064848

<https://hal.science/hal-03064848>

Preprint submitted on 14 Dec 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Synthesis of analogues of the marine pyrroloiminoquinone alkaloid wakayin as potential IDO1 inhibitors

Thomas Levy and Evelyne Delfourne*

Université Paul Sabatier, UMR CNRS 5068, Laboratoire de Synthèse et Physicochimie de Molécules d'Intérêt Biologique, 118 Route de Narbonne, 31062 Toulouse Cédex 9, France.

Abstract: Two strategies have been investigated for the synthesis of the marine alkaloid wakayin resulting in the generation of different intermediates of potential value as inhibitors of indoleamine-2,3-dioxygenase (IDO1), a target enzyme involved in the capacity of tumors to escape the immune process. The first one, based on the condensation of a β -hydroxyamine on an indole-dione for the formation of the bispyrroloiminoquinone framework, has led to wakayin analogues in which one of the pyrrole ring was not completely aromatic. The second, involving the condensation of methyltryptamine on an indole-dione and subsequent oxidative cyclisation of the resulting adduct, allowed to define an original method for constructing the bispyrroloquinoline motif. Different analogues comprising a methyl group on the nitrogen of the pyrrole cycle not constituting the pyrroloiminoquinone unit have been obtained.

Keywords: marine alkaloid, bispyrroloquinone, pyrroloiminoquinone, wakayin, tsitsikammamine.

* Corresponding author, Tel 33 561 55 62 93 ; Fax 33 561 55 60 11
E-mail : delfourn@chimie.ups-tlse.fr

Many alkaloids based on the pyrrolo[4,3,2-*de*]quinolone scaffold have been isolated from sponges, ascidians and more recently from a hydroid.^{1,2} Due to their potential for drug discovery,³ a number of synthetic methodologies have been developed to prepare natural products and analogues.^{4,5}

In our group, we are more particularly interested in a subfamily of this class of compounds including wakayin⁶ and tsitsikammamines A-C^{7,8} which possess a unique tetracyclic bispyrroloiminoquinone ring system (Figure 1).

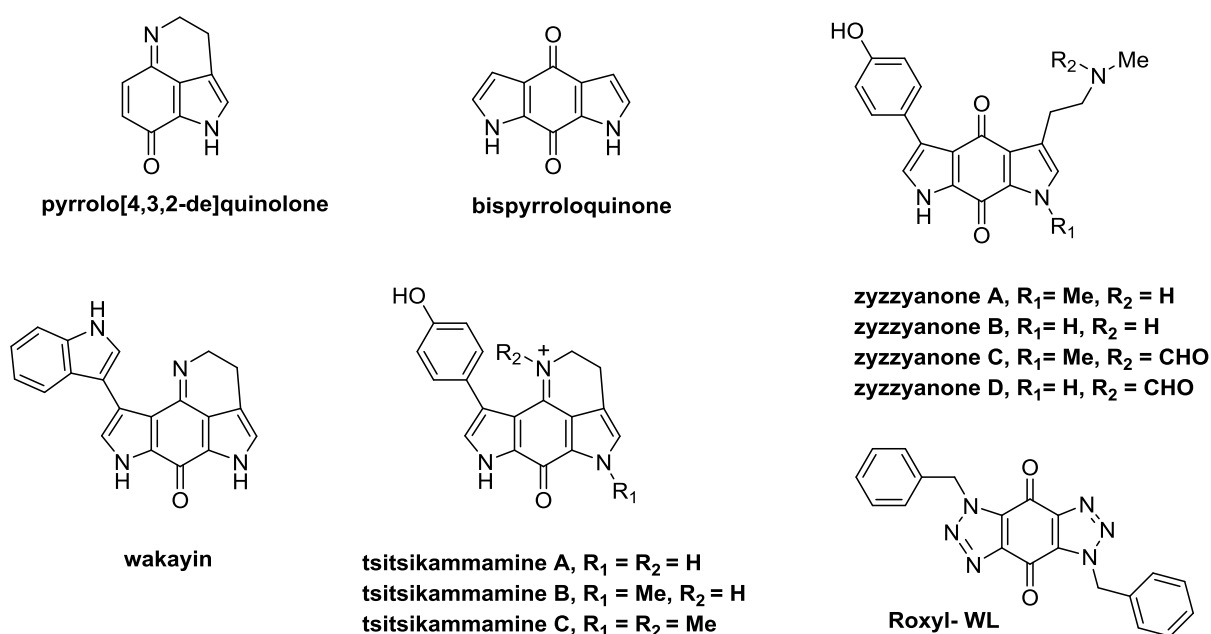


Figure 1: Natural marine alkaloids possessing a bispyrroloquinonic frame and RoxyI-WL.

As part of our research program to define new anticancer therapeutic agents, we have described series of analogues of these metabolites with valuable biological potential including topoisomerase inhibition.⁹⁻¹¹ Recently, interest in this family of compounds has been revived due to the description of some of related compounds as potential inhibitors of indoleamine-2,3-dioxygenase (IDO1), an enzyme involved in the ability of some tumors to suppress most of immune response.¹² In addition, the structurally related derivative RoxyI-WL which constitutes one of the most highly potent and selective inhibitor targeting IDO1, discovered so far, has been reported.¹³ This context makes necessary to find new methods to prepare them.

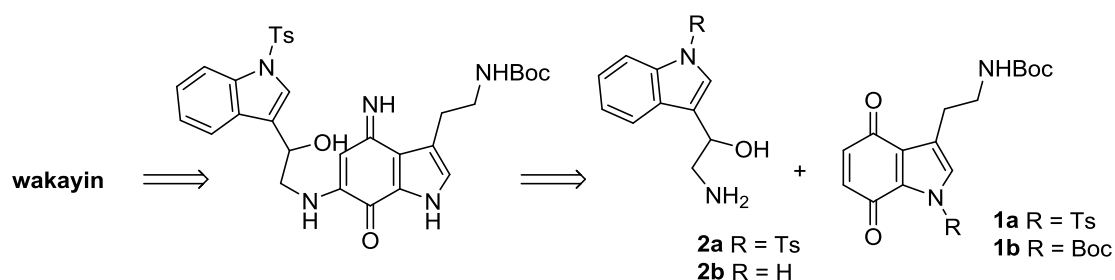
In 2009, we have proposed a total synthesis of tsitsikammamine A based on a Michael reaction between a tosyl-indole-dione and 2'-amino-1-(4-methoxyphenyl)ethanol.¹⁴ Despite

the synthetic efforts of different teams, including Velu's route to the marine alkaloids zyzzyanone A-D¹⁵, to form the bispyrroloquinone unit, no synthesis of wakayin has been carried out to date.

In continuation of our interest for this research, we report herein a study on the total synthesis of wakayin which allowed to define new analogues of potential value as IDO1 inhibitors.

RESULTS AND DISCUSSION

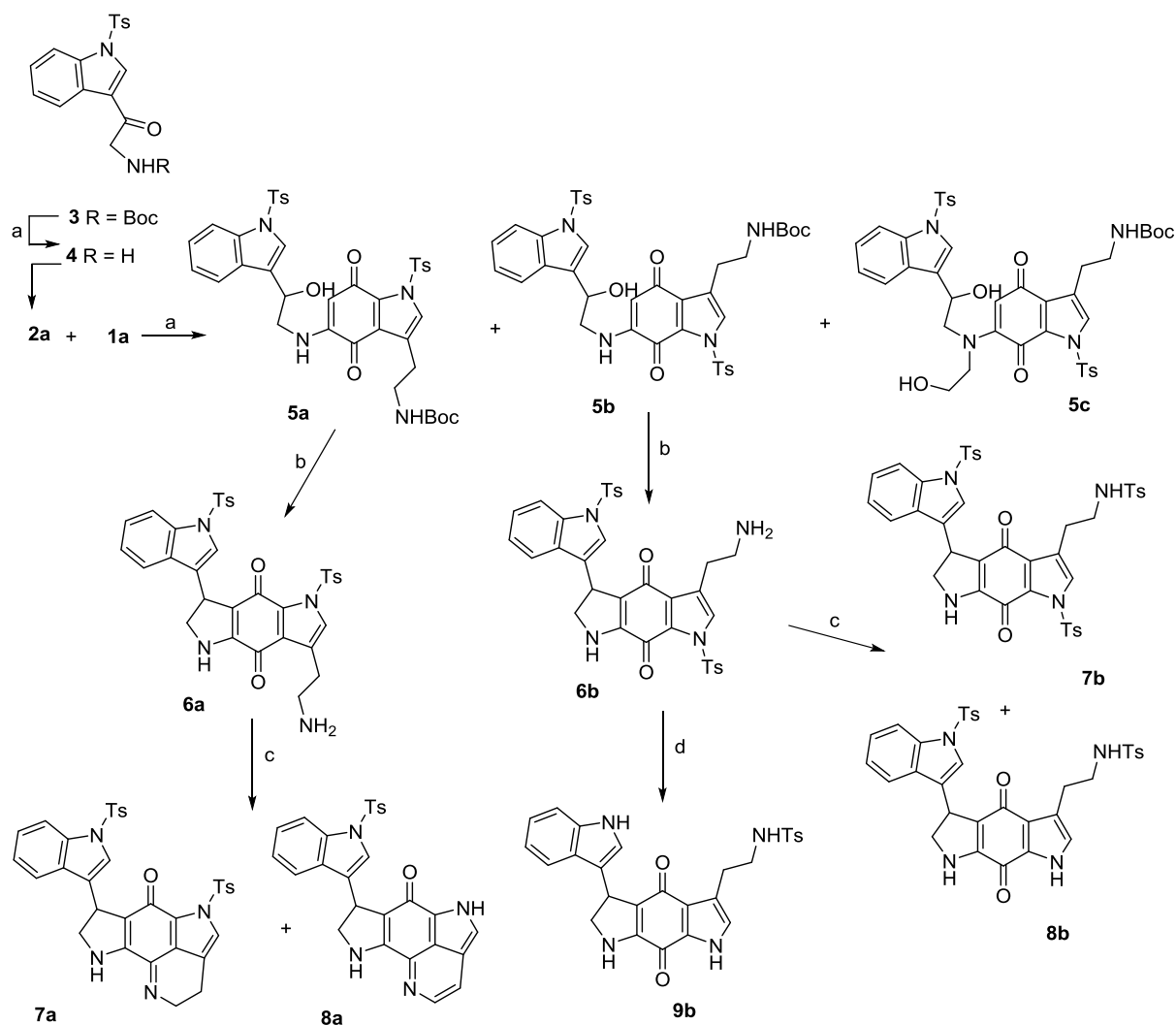
In a first approach to prepare wakayin, we adapted the retrosynthetic scheme based on the Michael reaction between the indoledione **1a** and 2'-amino-(4-methoxyphenyl)ethanol that led to tsitsikammamine A (Scheme 1).



Scheme 1: First retrosynthetic scheme of wakayin.

For this purpose, the β -hydroxyamine **2a**, was synthesized in two steps from the known corresponding β -Boc-ketoamine **3**,¹⁶ namely, cleavage of the Boc protective group by TFA in CH_2Cl_2 to give compound **4** and subsequent NaBH_4 reduction of the alcohol function (Scheme 2). As expected, the Michael condensation of **1a** with indoledione **2** in ethanol led in 70 % yield to a mixture of the two regioisomers **5a** and **5b** and an additional by-product **5c** (10 %). Compounds **5a** and **5b** were reacted with TFA in CH_2Cl_2 to give the formation of the second five-membered nitrogen ring, concomitantly with the cleavage of the Boc-protective group, leading to the cyclized derivatives **6a** and **6b** respectively. The structural assignment of these compounds was achieved from a previously described empirical method.¹⁷ Different conditions including i) MnO_2 , HCCl_3 , Δ , ii) 10% Pd/C, toluene, Δ , iii) DDQ, THF/ H_2O , rt, have been tried in vain to complete the aromatization of the last cycle. However, the sequence was continued on each derivative in order to perform the formation of the pyrroloquinoline

skeleton. Thus **6a** was refluxed in absolute ethanol with 4A molecular sieves yielding to a mixture of the expected compound **7a** and to an additional compound **8a** corresponding to the aromatization of the newly formed six-membered ring. The same reaction applied to **6b** did not lead to the expected compound (**7a** regioisomer) but to a mixture of tritosylated compound **7b** and ditosylated compound **8b** resulting both of an unexpected migration of the indole-dione tosyl group.



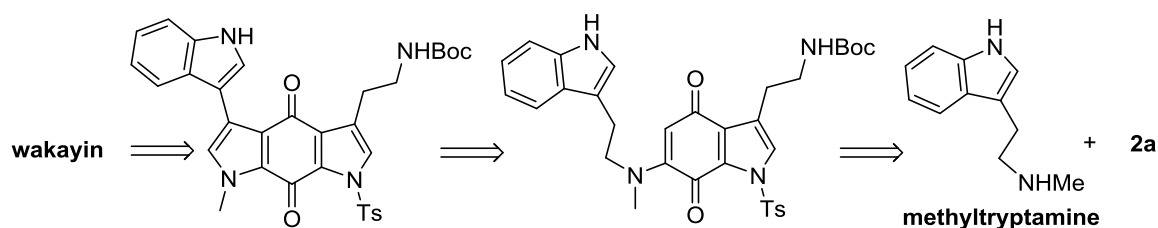
a- abs EtOH, rt, 3h. b- TFA, CH₂Cl₂, rt, 4h. c- abs EtOH, 4A mol sieves, reflux, 3h. d- 1M NaOH, dioxane, rt, 12h.

Scheme 2: Adaptation of the tsitsikammamine scheme to wakayin

It should be noted that no reaction was observed if the reaction was carried out at room temperature. In order to avoid migration of the indole-dione tosyl group, cleavage of this protective group was considered prior to the reaction of formation of the 6-membered ring.

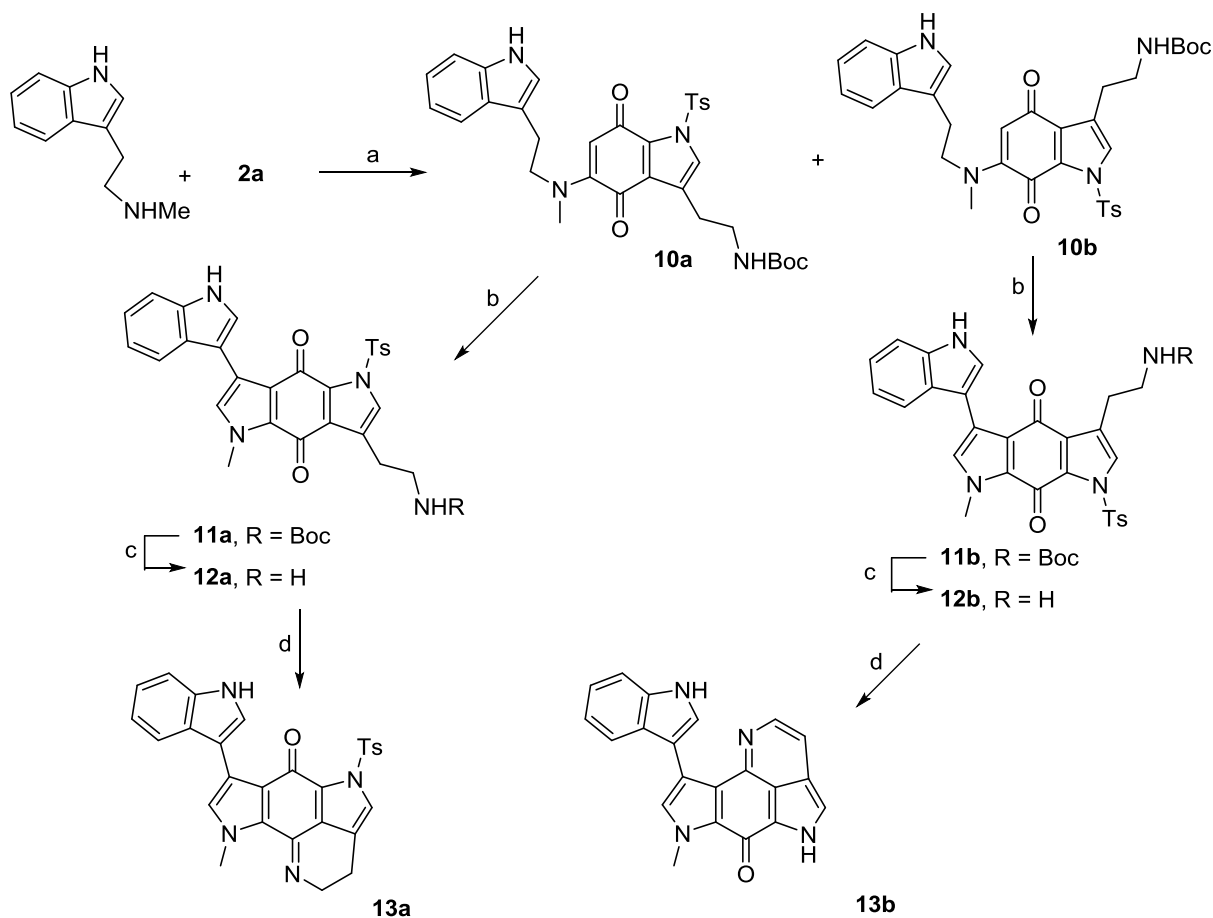
Thus, compound **6b** was reacted with 1N NaOH in dioxane to give the unexpected compound **9b** in which the same tosyl migration was also observed. The formation of the last cycle was also undertaken directly on the TFA salt of compound **6b** obtained before work-up in the reaction with TFA. In this case, the reaction which was accomplished in the presence of NaHCO₃ led also to compounds **7b** and **8b**. Finally, attempts to remove the remaining tosyl group of **9b** failed which prompted us to choose Boc as a protective group for the indole-dione. The condensation reactions of the previously reported indole-dione **1b**¹⁸ with both β -hydroxyamines **2a** and **2b** performed according to conditions described above gave complex mixtures.

A second reaction scheme inspired by the method of Zhang and co-workers, involving in a first step the condensation of methyltryptamine and 2-methoxynaphthalene-1,4-dione, for the formation of the second pyrrole ring was investigated (Scheme 3).¹⁹



Scheme 3: Second retrosynthetic scheme of wakayin.

In our strategy, this last compound was replaced by indole-dione **2a**. Reaction of **2a** with methyltryptamine in ethanol at room temperature gave the regioisomers **10a** and **10b** in 33 and 39% yield respectively (Scheme 4). The oxidative cyclisation of these compounds by DDQ in CH₂Cl₂ led to the bispyrroloquinonic derivatives **11a** and **11b** (47 and 60% yield). It can be noticed that these two steps constitute an original method to build the bispyrroloquinone skeleton. The cleavage of the Boc protective group leading to compounds **12a** and **12b** was carried out by action of TFA. The closing reaction of the last cycle to form the six membered ring was performed on the TFA salts of compounds **12a** and **12b** to give the expected pyrroloiminoquinone derivatives **13a** and the completely aromatic and detosyld tetracyclic compound **13b** respectively. The demethylation reaction using a metalloporphyrin-catalyzed oxidation²⁰ which has been studied for both compounds **11b** and **13b**, did not lead to the expected compounds.



a- abs EtOH, rt, 3h. b- DDQ, AcOH, 3h. c- TFA, CH₂Cl₂, rt, 4h. d- i) TFA, CH₂Cl₂, ii) NaHCO₃, abs EtOH, 4A mol sieves, reflux, 12h.

Scheme 4: Synthesis of methyl wakayin analogues.

In conclusion, two different strategies have been studied for the synthesis of wakayin. The first one, based on the condensation of a β -hydroxyamine on an indole-dione led to the formation of analogues in which one of the pyrrole ring of the bispyrroloiminoquinone framework was not completely aromatic. The second, involved the condensation of methyltryptamine on an indole-dione and subsequent oxidative cyclisation of the resulting adduct. It allowed to define an original method for constructing the bispyrroloquinoline moiety and to obtain different analogues comprising a methyl group on the nitrogen of the pyrrole cycle not constituting the pyrroloiminoquinone unit. Further IDO1 inhibitory evaluation of all derivatives generated in this study are currently in progress

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were performed on Bruker Avance 300 or Avance 500 (cryoprobe TCI $^1\text{H}\{^{13}\text{C}, ^{31}\text{P}\}$) spectrometers with the chemical shifts of the remaining protons of the deuterated solvents serving as internal standards. IR spectra were obtained on a Perkin-Elmer 883 spectrophotometer. Mass spectra were recorded on a GCT premier waters mass spectrometer for CI and High resolution mass spectra (HRMS) were recorded on a UPLC Xevo G2 Q TOF Waters spectrometer for ESI. Reagents were purchased from commercial sources and used as received. Flash-chromatography was performed on silica gel (15-40 μM) by means of the solvent systems indicated below.

2-amino-1-(1-tosyl-1H-indol-3-yl)ethan-1-one (4)

To a suspension of compound **3** (1g, 2.33 mmol) in CH_2Cl_2 (50 mL) was added dropwise TFA (5 mL). The mixture was stirred for 3h. After concentration under reduced pressure, the residue was triturated in Et_2O . Filtration gave the expected compound as a white solid (1 g, 97 %). ^1H NMR (DMSO-d_6): 2.34 (s, 3H), 4.60 (br. s, 2H), 4.62 (d, 2H, $J = 4.7$ Hz), 7.28 (d, 2H, $J = 8.2$ Hz), 7.43-7.51 (m, 2H), 8.01 (d, 1H, $J = 7.5$ Hz), 8.05 (d, 2H, $J = 8.2$ Hz), 8.18-8.23 (m, 1H), 9.02 (s, 1H).. ^{13}C NMR (DMSO-d_6) 21.57, 40.34, 113.67, 117.61, 122.40, 125.74, 126.62, 127.05, 127.84 (2C), 131.04 (2C), 133.73, 134.30, 135.67, 147.06, 189.19. HRMS (DCI- CH_4) calcd for $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}_3\text{S}$ 329.0960, found 329.0966.

2-amino-1-(1-tosyl-1H-indol-3-yl)ethan-1-ol (2a)

To a suspension of compound **4** (450 mg, 1.37 mmol) in MeOH (15 mL) was added portionwise, NaBH_4 (260 mg, 6.8mmol). The reaction media was stirred for 3 h. After concentration under reduce pressure, water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over MgSO_4 and concentrated to give the product as a yellow powder (370 mg, 82 %). ^1H NMR (DMSO-d_6): 1.16 (t, 2H, $J = 7.1$ Hz), 2.28 (s, 1H), 2.76 (m, 2H), 4.75 (t, 1H), 7.21 (t, 1H, $J = 7.2$ Hz), 7.31 (t, 1H, $J = 7.2$ Hz), 7.35 (d, 2H, $J = 8.2$ Hz), 7.59 (s, 1H), 7.66 (d, 1H, $J = 7.2$ Hz), 7.82 (d, 2H, $J = 8.2$ Hz), 7.89 (d, 1H, $J = 7.2$ Hz). ^{13}C NMR (DMSO-d_6): 21.48, 42.24, 67.90, 113.68, 119.60, 121.28, 123.61, 125.16, 125.97, 127.16 (2C), 130.27, 130.68 (2C), 130.88, 134.27, 134.64. MS (EI): m/z 330.10 (100.0%), 331.11 (18.4%), 332.10 (4.5%).

tert-butyl (2-(5-((2-hydroxy-2-(1-tosyl-1H-indol-3-yl)ethyl)amino)-4,7-dioxo-1-tosyl-4,7-dihydro-1H-indol-3-yl)ethyl)carbamate (5a) and tert-butyl (2-(6-((2-hydroxy-2-(1-tosyl-

1H-indol-3-yl)ethyl)amino)-4,7-dioxo-1-tosyl-4,7-dihydro-1H-indol-3-yl)ethyl)carbamate (5b) and tert-butyl (2-((2-hydroxy-2-(1-tosyl-1H-indol-3-yl)ethyl)(2-hydroxyethyl)amino)-4,7-dioxo-1-tosyl-4,7-dihydro-1H-indol-3-yl)ethyl)carbamate (5c)

To a solution of hydroxylamine **37** (1.6 g, 4.85 mmol) in EtOH (15 mL) was added dropwise a solution of quinone **1** (1.1 g, 2.43 mmol) in EtOH (35 mL). After 4 h stirring at room temperature, the mixture was concentrated under vacuum and the crude product was purified by flash-chromatography (CH₂Cl₂/MeOH 99:1) to give the products

5a: dark fuschia solid (630 mg, 34 %). ¹H NMR (CDCl₃): 1.45 (s, 9H), 2.37 (s, 3H), 2.44 (s, 3H), 2.97 (t, 2H, J = 6 Hz and 6 Hz), 3.45 (t, 2H, J = 6 Hz), 4.72 (br s, 1H), 5.19 (m, 2H, J = 6 Hz), 5.22 (s, 1H), 6.13 (t, 1H, J = 6 Hz), 7.26 (m, 3H), 7.36 (m, 3H), 7.55 (s, 1H), 7.60 (d, 1H, J = 6 Hz), 7.61 (s, 1H), 7.80 (d, 2H, J = 6 Hz), 8.00 (d, 1H, J = 9 Hz), 8.02 (d, J = 6 Hz). ¹³C NMR (CDCl₃): 21.62, 21.79, 26.24, 28.39 (3C), 40.03, 48.10, 65.64, 79.41, 97.77, 113.88, 119.90, 122.08, 122.34, 123.41, 123.50, 124.52, 125.25, 126.92 (2C), 129.06 (2C), 129.47 (2C), 129.94, 130.05 (2C), 132.80, 134.23, 134.96, 135.35, 145.25, 145.30, 145.83, 147.16, 155.99, 175.01, 179.59. HRMS (ESI) calcd for C₃₉H₄₀N₄O₉NaS₂ 795.2134 (MNa⁺), found 795.2146.

5b: dark fuschia solid (680 mg, 36 %). ¹H NMR (CDCl₃): 1.45 (s, 9H), 2.37 (s, 3H); 2.46 (s, 3H), 3.01 (t, 2H, J = 6 Hz), 3.43 (m, 2H), 4.87 (br. s, 1H), 5.22 (m, 2H, J = 6 Hz), 5.31 (s, 1H), 6.13 (t, 1H, J = 6 Hz), 7.26 (m, 3H), 7.36 (m, 3H), 7.59-7.70 (m, 3H), 7.80 (d, 2H, J = 6 Hz), 8.00 (d, 1H, J = 9 Hz), 8.02 (d, 2H, J = 6 Hz). ¹³C NMR (CDCl₃): 21.61, 21.80, 25.75, 28.40 (3C), 40.50, 48.13, 65.67, 79.22, 97.68, 113.88, 119.91, 122.30, 123.47, 123.51, 123.57, 125.26, 126.91 (2C), 127.31, 128.15, 128.92 (2C), 129.82 (2C), 129.99, 130.09 (2C), 130.61, 133.85, 134.87, 135.35, 145.31, 146.22, 147.71, 156.11, 169.89, 183.30. HRMS (ESI) calcd for C₃₉H₄₀N₄O₉NaS₂ 795.2134 (MNa⁺), found 795.2123.

5c dark fuschia solid (220 mg, 10 %). ¹H NMR (CDCl₃): 1.43 (s, 9H), 2.35 (s, 3H), 2.45 (s, 3H), 2.99 (t, 2H, J = 6 Hz), 3.40 (q, 2H, J = 6Hz), 3.52 (d, 2H, J = 6 Hz), 3.93 (dd, 2H, J = 6 Hz and 9 Hz), 4.11 (dd, 2H, J = 6 Hz and 9 Hz), 4.88 (br s, 1H), 5.30 (s, 1H), 6.01 (t, 1H, J = 6 Hz), 7.24-7.26 (m, 3H), 7.32-7.37 (m, 3H), 7.66 (s, 1H), 7.67 (s, 1H), 7.69 (d, 1H, J = 6 Hz), 7.79 (d, 2H, J = 6 Hz), 7.96 (d, 1H, J = 6 Hz), 8.00 (d, 2H, J = 6 Hz). ¹³C NMR (CDCl₃): 21.59, 21.78, 25.69, 28.39 (3C), 40.56, 49.03 (2C), 79.15, 97.94, 106.44, 113.71, 120.78, 121.21, 123.53, 123.65, 124.84, 125.09, 126.90 (2C), 127.18, 127.35, 128.85 (2C), 129.13, 129.69, 129.81 (2C), 130.08 (2C), 130.60, 133.98, 134.88, 135.51, 145.34, 146.17, 147.80, 156.07, 170.05, 183.36. HRMS (DCI-CH₄) calcd for C₄₁H₄₁N₄O₁₀S₂ 813.2264, found 813.2264.

7-(2-aminoethyl)-5-tosyl-3-(1-tosyl-1H-indol-3-yl)-2,3-dihydropyrrolo[2,3-f]indole-4,8(1H,5H)-dione (6a)

To a solution of compound **5a** (50 mg, 0.065 mmol) in CH₂Cl₂ (1.6 mL) was added dropwise TFA (0.8 mL). The mixture was stirred for 4 h. After concentration over vacuum, NaOH 1N (5 mL) was added and this aqueous layer was extracted by CH₂Cl₂ (3 x 5 mL). The organic layer was dried over MgSO₄ and concentrated. The crude product was purified by flash-chromatography (CH₂Cl₂/MeOH, 95:5) to give the expected product as a blue solid (15 mg, 36 %). ¹H NMR (DMSO-d₆): 2.29 (s, 3H), 2.41 (s, 3H), 2.69-3.20 (m, 6H), 4.36 (d, 1H, J = 6 Hz), 4.70 (t, 1H, J = 6 Hz), 7.01 (d, 1H, J = 3 Hz), 7.12 (t, 1H, J = 6 Hz), 7.28-7.34 (m, 3H), 7.49 (d, 2H, J = 9 Hz), 7.55 (d, 1H, J = 6 Hz), 7.61 (d, 1H, J = 9 Hz), 7.65 (d, 2H, J = 9 Hz), 7.81 (s, 1H), 8.01 (d, 2H, J = 9 Hz). ¹³C NMR (CDCl₃): 21.49, 21.71, 29.71, 39.63, 51.66, 66.36, 107.82, 108.59, 115.60, 120.23, 121.37, 124.79, 127.58 (2C), 127.81, 129.01, 129.08 (2C), 129.60, 129.82 (2C), 129.88 (2C), 129.93, 131.4, 132.95, 133.37, 135.23, 141.89, 142.27, 144.81, 146.60, 170.23, 182.40. HRMS (DCI-CH₄) calcd for C₃₄H₂₉N₄O₆S₂ 655.1685, found 655.1653.

3-(2-aminoethyl)-1-tosyl-5-(1-tosyl-1H-indol-3-yl)-6,7-dihydropyrrolo[3,2-f]indole-4,8(1H,5H)-dione (6b)

Same procedure as for compound **6a**, involving compound **5b** (50 mg, 0.065 mmol), CH₂Cl₂ (1.6 mL) and TFA (0.8 mL). Purification by flash-chromatography (CH₂Cl₂/MeOH, 95:5) gave the expected compound as a blue solid (27 mg, 64 %). ¹H NMR (DMSO-d₆): 2.29 (s, 3H), 2.41 (s, 3H), 2.90-3.01 (m, 6H), 4.08 (br. s, 2H), 4.32 (m, 1H), 4.69 (m, 1H), 7.01 (d, 1H, J = 3 Hz), 7.12 (t, 1H, J = 6 Hz), 7.28-7.32 (m, 3H), 7.48 (d, 2H, J = 9 Hz), 7.55 (d, 1H, J = 6 Hz), 7.61 (d, 1H, J = 9 Hz), 7.65 (d, 2H, J = 9 Hz), 7.78 (s, 1H), 8.01 (d, 2H, J = 9 Hz). ¹³C NMR (CDCl₃): 21.49, 21.72, 29.72, 39.86, 51.53, 66.39, 107.82, 109.22, 115.58, 120.25, 121.37, 124.64, 127.67 (2C), 127.82, 128.78, 129.16, 129.19 (2C), 129.60, 129.62 (2C), 129.77 (2C), 129.93, 132.95, 133.33, 135.23, 141.89, 142.27, 144.81, 146.60, 174.26, 179.27. IR (ATR): 3380, 1821, 1621, 1580, 1542, 1354, 1167 cm⁻¹ HRMS (DCI-CH₄, MH⁺) calcd for C₃₄H₃₁N₄O₆S₂ 655.1685, found 655.1664.

5-tosyl-7-(1-tosyl-1H-indol-3-yl)-2,3,5,7,8,9-hexahydro-6H-dipyrrolo[4,3,2-de:3',2'-h]quinolin-6-one (7a) and 7-(1-tosyl-1H-indol-3-yl)-5,7,8,9-tetrahydro-6H-dipyrrolo[4,3,2-de:3',2'-h]quinolin-6-one (8a)

A mixture of compound **6a** (200 mg, 0.306 mmol) and 4Å molecular sieve (2 g) in absolute EtOH (17 mL) was refluxed overnight. After filtration, the filtrate was concentrated and purified by flash-chromatography (CH₂Cl₂/ MeOH 99: 1) to give:

7a: violin solid (45 mg, 23%). ¹H NMR (CDCl₃): 2.34 (s, 3H), 2.43 (s, 3H), 2.83 (td, 2H, J = 1.1 Hz and J = 7.5Hz), 3.11 (m, 1H), 4.20 (m, 3H), 4.68 (m, 1H), 7.05 (br. m, 1H), 7.11 (td, 1H, J = 0.9 and 7.7 Hz), 7.16 (d, 2H, J = 8 Hz), 7.26 (td, 1H, J = 0.9 and 7.7 Hz), 7.34 (s, 1H), 7.35 (d, 2H, J = 7.1 Hz), 7.40 (t, 1H, J = 1.1 Hz), 7.50 (d, 1H, J = 7.6 Hz), 7.58 (d, 2H, J = 8.4 Hz), 7.80 (d, 1H, J = 7.9 Hz), 8.09 (d, 2H, J = 8.4 Hz). ¹³C NMR (CDCl₃): 18.16, 21.51, 21.74, 29.71, 49.71, 51.72, 109.07, 111.42, 115.89, 116.23, 120.43, 122.63, 123.61, 124.26, 124.87, 127.32 (2C), 128.60, 128.73 (2C), 129.64 (2C), 129.79 (2C), 130.64, 133.03, 133.44, 134.95, 141.90, 143.17, 144.57, 145.47, 152.85, 174.00. HRMS (DCI-CH₄) calcd for C₃₄H₂₈N₄O₅S₂ 636.1501, found 636.1525.

8a: yellow solid (90 mg, 62%). ¹H NMR (CDCl₃): 2.33 (s, 3H), 3.34 (m, 1H), 4.43 (m, 1H), 4.89 (m, 1H), 7.16 (m, 2H), 7.17 (d, 2H, J = 8 Hz), 7.62 (t, 1H, J = 8 Hz), 7.63 (d, 2H, J = 8.3 Hz), 7.70 (d, 1H, J = 2.7 Hz), 7.74 (d, 1H, J = 5.9 Hz), 7.75 (s, 1H), 7.86 (d, 1H, J = 8 Hz), 8.43 (d, 1H, J = 5.9 Hz). ¹³C NMR (CDCl₃): 21.50, 19.71, 66.75, 110.62, 111.82, 115.87, 117.67, 119.39, 120.30, 120.36, 124.39, 124.77, 127.42 (2C), 128.45, 129.78 (2C), 129.84, 130.83, 132.80, 133.18, 140.77, 141.99, 143.81, 144.52, 146.57, 174.02. HRMS (DCI-CH₄) calcd for C₂₇H₂₁N₄O₃S 481.1334, found 481.1330.

N-(2-(4,8-dioxo-5-(1-tosyl-1H-indol-3-yl)-1,4,5,6,7,8-hexahydropyrrolo[3,2-f]indol-3-yl)ethyl)-4-methylbenzenesulfonamide (7b) and N-(2-(4,8-dioxo-1-tosyl-5-(1-tosyl-1H-indol-3-yl)-1,4,5,6,7,8-hexahydropyrrolo[3,2-f]indol-3-yl)ethyl)-4-methylbenzenesulfonamide (8b)

Same procedure as for **7a/8a** involving, compound **6b** (60 mg, 0.092 mmol) in absolute EtOH (5 mL) and 4Å molecular sieve (720 mg). Purification by flash-chromatography (CH₂Cl₂/MeOH 99: 1) gave:

7b: blue solid (17 mg, 28%). ¹H NMR (CDCl₃): 2.33 (s, 3H); 2.39 (s, 3H); 2.93 (t, 2H, J = 6.2 Hz); 3.10 (m, 1H); 3.31 (m, 2H); 4.24 (m, 1H); 4.82 (m, 1H); 5.22 (m, 1H); 6.90 (s, 1H); 6.92 (m, 1H); 7.09 (t, 1H, J = 7.35 Hz); 7.19 (d, 2H, J = 8.2 Hz); 7.23 (s, 1H); 7.24 (d, 2H, J = 7.8 Hz); 7.29 (t, 1H, J = 7.7 Hz); 7.43 (d, 1H, J = 7.4 Hz); 7.63 (d, 2H, J = 8.3 Hz); 7.69 (d, 2H, J = 8.2Hz); 7.81 (d, 1H, J = 8.1 Hz); 9.45 (br. s, 1H). ¹³C NMR (CDCl₃) 21.49, 21.54, 25.55, 43.63, 51.87, 66.74, 108.79, 109.73, 115.88, 120.51, 123.76, 124.62, 125.00, 126.50, 126.93 (2C), 127.39 (2C), 128.99, 129.08, 129.56 (2C), 129.90 (2C), 130.34, 132.95, 134.73, 137.25,

141.99, 142.23, 143.09, 144.82, 172.01, 183.44. HRMS (DCI-CH₄) calcd for C₃₄H₃₁N₄O₆S₂ 655.1685, found 655.1703.

8b: blue solid (48 mg, 65%). ¹H NMR (CDCl₃): 2.34 (s, 3H), 2.37 (s, 3H), 2.51 (s, 3H), 2.95 (t, 2H, J = 6.2 Hz), 3.06 (m, 1H), 3.34 (q, 2H, J = 6.2 Hz), 4.13 (m, 1H), 4.75 (m, 1H), 5.00 (t, 1H), 6.83 (m, 1H), 7.14 (t, 1H), 7.15 (s, 1H), 7.18 (d, 2H), 7.19 (d, 2H), 7.31 (t, 1H), 7.44 (d, 2H, J = 8.2 Hz), 7.50 (d, 1H, J = 7.5 Hz), 7.59 (d, 2H, J = 8.3 Hz), 7.60 (s, 1H), 7.66 (d, 2H, J = 8.2 Hz), 7.82 (d, 1H, J = 8.0 Hz), 8.08 (d, 2H, J = 8.5 Hz). ¹³C NMR (CDCl₃) 21.47, 21.54, 21.86, 25.50, 43.63, 51.89, 66.48, 108.09, 108.79, 115.98, 120.62, 122.85, 125.02, 126.85 (2C), 127.35 (2C), 129.22 (2C), 129.39, 129.51, 129.65 (2C), 129.69 (2C), 129.88 (2C), 130.01, 130.37, 132.81, 133.67, 135.45, 137.28, 142.12, 142.21, 143.21, 144.82, 146.48, 169.92, 182.890. HRMS (DCI-CH₄) calcd for C₄₁H₃₆N₄O₈S₃ 808.1695, found 808.1727.

N-(2-(5-(1H-indol-3-yl)-4,8-dioxo-1,4,5,6,7,8-hexahydropyrrolo[3,2-f]indol-3-yl)ethyl)-4-methylbenzenesulfonamide (9b)

A solution of **6b** (26 mg, 0.04 mmol) in dioxane/NaOH 1M (1: 1, 4ml), was stirred overnight. CH₂Cl₂ (5ml) and some drops MeOH were added. The resulting organic layer was dried over MgSO₄ and evaporated under reduce pressure. The crude product was purified by flash chromatography (CH₂Cl₂/MeOH) 90: 10) to give the expected compound as a grey/blue solid (18 g, 90%). ¹H NMR (DMSO-d₆): 2.30 (s, 3H), 2.93 (t, 2H, J = 6.2 Hz), 3.17 (m, 1H), 3.30 (m, 2H), 4.08 (m, 1H), 4.34 (m, 1H), 4.75 (m, 1H), 7.12 (t, 1H, J = 7.35 Hz), 7.16 (s, 1H), 7.25 (d, 1H, J = 8.2 Hz), 7.29 (t, 1H, J = 7.7 Hz), 7.31 (d, 2H, J = 8.2Hz), 7.49 (s, 1H), 7.62 (d, 1H, J = 8.1 Hz), 7.69 (d, 2H, J = 8.2Hz), 8.16 (br. s, 2H). ¹³C (DMSO-d₆): 21.44, 24.19, 39.15, 52.02, 65.39, 106.99, 110.64, 115.76, 120.33, 121.27, 124.25, 125.46, 127.83 (2C), 128.38, 129.14, 129.36, 130.47 (2C), 130.66, 132.82, 133.02, 141.59, 144.21, 145.30, 172.10, 182.90. HRMS (EI, M+H) calcd for C₂₇H₂₅N₄O₄S 501.1518, found 501.1586.

tert-butyl (2-(5-((2-(1H-indol-3-yl)ethyl)(methyl)amino)-4,7-dioxo-1-tosyl-4,7-dihydro-1H-indol-3-yl)ethyl)carbamate (10a) and tert-butyl (2-(6-((2-(1H-indol-3-yl)ethyl)(methyl)amino)-4,7-dioxo-1-tosyl-4,7-dihydro-1H-indol3-yl)ethyl)carbamate (10b)

A solution of methyl tryptamine (1.55 g, 9.0 mol) in EtOH (10 mL) was added dropwise to a solution of indoledione **1** (2 g, 4.5 mol) in EtOH (10 mL). After 2h stirring at room

temperature, the mixture was concentrated under vacuum and the crude product was purified by flash-chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99 :1) to give the expected compounds:

10a : fushia solid (0.91 g, 33%), (%). ^1H NMR (CDCl_3): 1.47 (s, 9H), 2.44 (s, 3H), 2.78 (t, 2H, $J = 8.5$ Hz), 2.93 (s, 3H), 3.06 (t, 2H, $J = 8.5$ Hz), 3.36 (q, 2H, $J = 8.5$ Hz), 4.00 (t, 2H, $J = 8.5$ Hz), 5.20 (s, 1H), 6.94 (d, 1H, $J = 2.9$ Hz), 7.10 (m, 2H), 7.34 (d, 2H, $J = 10$ Hz), 7.55 (m, 1H), 7.69 (m, 1H), 8.01 (d, 2H, $J = 10.5$ Hz), 8.28 (br. s, 1H). ^{13}C NMR (CDCl_3): 21.77, 24.21, 25.96, 28.42 (3C), 40.08, 40.89, 55.13, 79.33, 104.52, 111.15, 112.30, 118.65, 119.56, 123.17, 122.21, 123.06, 125.34, 125.95, 126.99, 129.05 (2C), 129.39 (2C), 134.55, 136.24, 145.60, 148.29, 152.05, 156.05, 174.05, 181.60. HRMS (DCI CH_4 , MH^+) calcd for $\text{C}_{33}\text{H}_{37}\text{N}_4\text{O}_6\text{S}$ 617.2434, found 617.2433.

10b : fushia solid (1.06 g, 39%), (%). ^1H NMR (CDCl_3): 1.46 (s, 9H), 2.41 (s, 3H), 2.78 (m, 4H), 3.08 (t, 2H, $J = 8.5$ Hz), 3.40 (q, 2H, $J = 8.5$ Hz), 3.93 (t, 2H, $J = 8.5$ Hz), 5.14 (s, 1H), 7.02 (d, 1H, $J = 2.9$ Hz), 7.18 (m, 2H), 7.32 (d, 3H, $J = 10$ Hz), 7.54 (m, 1H), 7.65 (m, 1H), 7.70 (m, 1H), 8.05 (d, 2H, $J = 10.5$ Hz), 8.32 (br. s, 1H). ^{13}C NMR (CDCl_3): 21.73, 24.03, 25.76, 28.44 (3C), 40.46, 40.65, 55.47, 79.26, 104.87, 111.17, 112.56, 118.84, 119.67, 122.16, 122.35, 122.77, 127.34, 128.52, 128.65, 128.89 (2C), 129.60 (2C), 129.92, 134.64, 136.32, 145.70, 152.95, 156.10, 172.84, 182.26. HRMS (DCI CH_4 , MH^+) calcd for $\text{C}_{33}\text{H}_{37}\text{N}_4\text{O}_6\text{S}$ 617.2434, found 617.2426.

tert-butyl (2-(5-(1H-indol-3-yl)-7-methyl-4,8-dioxo-1-tosyl-1,4,7,8-tetrahydropyrrolo[3,2-f]indol-3-yl)ethyl)carbamate (11a)

To a solution of compound **10a** (600 mg, 0.97 mmol) in CH_2Cl_2 (32 mL) was added DDQ (438 mg, 1.95 mmol). The mixture was stirred at room temperature for 2h. After concentration under vacuum, the crude product was purified by flash-chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99 :1) to give the expected compound as a violine solid (280 mg, 47%), (%). ^1H -NMR (CDCl_3): 1.44 (s, 9H), 2.46 (s, 3H), 3.04 (t, 2H, $J = 6.6$ Hz), 3.45 (q, 2H, $J = 6.6$ Hz), 4.00 (s, 3H), 7.17 (s, 1H), 7.18 (t, 1H, $J = 8.1$ Hz), 7.23 (t, 1H, $J = 8.1$ Hz), 7.28 (s, 1H), 7.36 (d, 2H, $J = 8.3$ Hz), 7.43 (d, 1H, $J = 8$ Hz), 7.59 (s, 1H), 7.72 (d, 1H, $J = 8$ Hz), 8.05 (d, 2H, $J = 8.3$ Hz), 8.26 (d, 1H, $J = 2.5$ Hz), 8.44 (br. s, 1H). ^{13}C -NMR (CDCl_3): 21.82, 26.05, 28.42 (3C), 37.14, 40.45, 79.17, 107.73, 111.61, 119.57, 119.61, 120.23, 122.19, 122.49, 123.20, 126.16, 126.47, 127.83, 128.90 (2C), 129.03, 129.55 (2C), 130.28, 130.31, 131.20, 134.60, 136.09, 145.67, 156.03, 170.92, 178.43. HRMS (DCI CH_4 , MH^+) calcd for $\text{C}_{33}\text{H}_{33}\text{N}_4\text{O}_6\text{S}$ 613.2121, found 613.2119.

tert-butyl (2-(7-(1H-indol-3-yl)-5-methyl-4,8-dioxo-1-tosyl-1,4,5,8-tetrahydropyrrolo[2,3-f]indol-3-yl)ethyl)carbamate (11b)

Same procedure as for compound **11a** involving compound **10b** (570 mg, 0.93 mmol), DDQ (417 mg, 1.85 mmol), CH₂Cl₂ (31 mL). Purification by flash-chromatography (CH₂Cl₂/MeOH 99 :1) gave the expected compound as a violine solid (340 mg, 60%), (%). ¹H NMR (CDCl₃): 1.44 (s, 9H), 2.46 (s, 3H), 3.04 (t, 2H, J = 6.6 Hz), 3.45 (q, 2H, J = 6.6 Hz), 4.00 (s, 3H), 7.17 (s, 1H), 7.18 (t, 1H, J = 8.1Hz), 7.23 (t, 1H, J = 8.1 Hz), 7.28 (s, 1H), 7.36 (d, 2H, J = 8.3 Hz), 7.43 (d, 1H, J = 8 Hz), 7.59 (s, 1H), 7.72 (d, 1H, J = 8 Hz), 8.05 (d, 2H, J = 8.3 Hz), 8.26 (d, 1H, J = 2.5 Hz), 8.44 (br. s, 1H). ¹³C NMR (CDCl₃): 21.78, 26.07, 28.41 (3C), 37.13, 40.48, 79.18, 107.72, 111.60, 119.56, 119.60, 120.22, 122.17, 122.48, 123.21, 126.17, 126.48, 127.82, 128.89 (2C), 129.02, 129.55 (2C), 130.27, 130.30, 131.21, 134.61, 136.08, 145.66, 156.04, 166.98, 180.42. HRMS (DCI CH₄, MH⁺) calcd for C₃₃H₃₃N₄O₆S 613.2121, found 613.2111.

3-(2-aminoethyl)-7-(1H-indol-3-yl)-5-methyl-1-tosylpyrrolo[2,3-f]indole-4,8(1H,5H)-dione (12a)

Same procedure as for compound **6a**, involving compound **11a** (100 mg, 0.16 mmol), CH₂Cl₂ (4 mL), TFA (2 mL). Purification by flash-chromatography (CH₂Cl₂/MeOH 90: 10) gave the expected compound as a violine solid (40 mg, 49%). ¹H NMR (CDCl₃): 1.77 (m, 2H), 2.40 (s, 3H), 3.07 (t, 2H, J = 7.2 Hz), 3.16 (t, 2H, J = 7.2 Hz), 4.03 (s, 3H), 7.08 (t, 1H, J = 7.8 Hz), 7.17 (t, 1H, J = 7.8 Hz), 7.45 (d, 1H, J = 7.9 Hz), 7.47 (d, 2H, J = 8.2Hz), 7.72 (d, 1H, J = 8 Hz), 7.74 (s, 1H), 7.83 (s, 1H), 7.99 (d, 2H, J = 8.5Hz), 8.1 (d, 1H, J = 2.6 Hz), 11.38 (br. s, 1H). ¹³C NMR (CDCl₃): 21.65, 24.44, 37.09, 39.05, 106.87, 112.33, 119.92, 120.10, 120.24, 121.45, 121.90, 126.01, 127.26, 128.38, 128.64 (2C), 128.94, 129.68, 130.19 (2C), 130.66, 132.80, 134.73, 136.58, 146.25, 171.56, 174.76. HRMS (DCI CH₄, MH⁺) calcd for C₂₈H₂₄N₄O₄S 513.1597, found 513.1608.

3-(2-aminoethyl)-5-(1H-indol-3-yl)-7-methyl-1-tosylpyrrolo[3,2-f]indole-4,8(1H,7H)-dione (12b)

Same procedure as for compound **12a** involving compound **11b** (120 mg, 0.196 mmol), CH₂Cl₂ (8 mL), TFA (4 mL). Purification by flash-chromatography (CH₂Cl₂/MeOH 90 :10) gave the expected compound as a violine solid (58 mg, 50%). ¹H NMR (CDCl₃): 1.77 (m, 2H); 2.43 (s, 3H); 3.08 (t, 2H, J = 7.2 Hz); 3.12 (t, 2H, J = 7.2 Hz); 3.96 (s, 3H); 7.09 (t, 1H, J = 7.8 Hz); 7.16 (t, 1H, J = 7.8 Hz); 7.46 (d, 1H, J = 7.9 Hz); 7.51 (d, 2H, J = 8.2Hz); 7.74 (s,

1H); 7.80 (d, 1H, J = 8 Hz); 7.84 (s, 1H); 8.03 (d, 2H, J = 8.5Hz); 8.32 (d, 1H, J = 2.6 Hz) 10.76 (s, 1H). ¹³C-NMR (CDCl₃): 21.68, 24.36, 37.23, 38.97, 106.95, 112.33, 119.89, 119.95, 120.23, 121.14, 121.86, 125.97, 126.09, 127.56, 128.49, 128.78 (2C), 129.75, 130.19, 130.31 (2C), 131.09, 134.52, 136.63, 146.40, 166.39, 179.89. HRMS (DCI CH₄, MH⁺) calcd for C₂₈H₂₄N₄O₄S 513.1597, found 513.1580.

7-(1H-indol-3-yl)-9-methyl-5-tosyl-2,3,5,9-tetrahydro-6H-dipyrrolo[4,3,2-de:3',2'-h]quinolin-6-one (13a)

A mixture of compound **12a** (mg, mmol), and TFA (1.9 mL) in CH₂Cl₂ (3.8 mL) was stirred at RT for 15 min and concentrated under vacuum. NaHCO₃ (13 mg) and 4Å molecular sieve (770 mg) in absolute EtOH (2.5 mL) were added and the mixture was refluxed overnight. After filtration, the filtrate was concentrated and purified by flash-chromatography (CH₂Cl₂/ MeOH 98: 2) to give the expected compound as a dark fushia solid (18.4 mg, 38%). ¹H NMR (DMSO-d₆): 2.29 (s, 3H) 2.79 (t, 2H, J = 7 Hz), 3.06 (q, 2H, J = 7 Hz), 4.02 (s, 3H), 6.84 (d, 1H, J = 2.7 Hz), 7.06-7.17 (m, 2H), 7.28 (d, 2H, J = 8.3 Hz), 7.45 (d, 1H, J = 8 Hz), 7.60 (d, 2H, J = 8.2 Hz), 7.61 (s, 1H), 7.84 (d, 1H, J = 7.9), 8.37 (d, 1H, J = 2.8 Hz), 11.29 (s, 1H). ¹³C NMR (DMSO-d₆): 21.38, 22.56, 37.04, 55.38, 107.36, 112.21, 119.21, 119.76, 120.30, 121.67, 121.92, 122.33, 124.29, 126.17, 126.92 (2C), 127.35, 128.75, 129.84 (2C), 131.35, 134.25, 136.55, 136.62, 138.04, 142.84, 174.19. HRMS (DCI CH₄, MH⁺) calcd for C₂₈H₂₂N₄O₃S 494.1413, found 494.1429.

9-(1H-indol-3-yl)-7-methyl-5-tosyl-2,3,5,7-tetrahydro-6H-dipyrrolo[4,3,2-de:2',3'-h]quinolin-6-one (13b)

Same procedure as for compound 13a involving compound **12b** (80 mg, 0.13 mmol), TFA (2.5 mL) in CH₂Cl₂ (5 mL) and NaHCO₃ (20 mg) and 4Å molecular sieve (1 g) in absolute EtOH (3 mL). Purification by flash-chromatography (CH₂Cl₂/ MeOH 98: 2) gave the expected compound as a yellow solid (21 mg, 47%). ¹H NMR (DMSO-d₆): 4.28 (s, 3H), 7.06-7.20 (m, 2H), 7.48 (d, 1H, J = 8 Hz), 7.65 (d, 1H, J = 5.9 Hz), 7.75 (s, 1H), 7.96 – 7.86 (m, 1H), 8.01 (s, 1H), 8.38 (d, 1H, J = 5.9 Hz), 8.96 (d, 1H, J = 2.5 Hz), 10.76 (s, 1H), 11.22 (s, 1H). ¹³C (DMSO-d₆): 37.26, 108.42, 112.08, 114.14, 116.34, 120.30, 120.88, 121.41, 121.83, 122.89, 123.52, 124.35, 124.35, 126.50, 127.86, 128.74, 132.05, 136.67, 140.88, 147.00, 166.25. HRMS (DCI-CH₄): calcd for C₂₁H₁₄N₄O 338.1156 found 338.1168.

REFERENCES

- 1- Antunes, E. M.; Copp, B. R.; Davies-Coleman, M. T.; Samaai, T. *Nat. Prod. Rep.* **2005**, *22*, 62-72.
- 2- Yan, P.; Ritt, D. A.; Zlotkowski, K.; Bokesch, H. R.; Reinhold, W. C.; Schneekloth, Jr, J. S.; Morrison, D. K.; Gustafson, K. R. *J. Nat. Prod.* **2018**, *81*, 1666-1672.
- 3- Hu, J.-F.; Fan, H.; Xiong, J.; Wu, S. –B. *Chem. Rev.* **2011**, *111*, 5465.
- 4- Delfourne, E. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 910.
- 5- Kita, Y.; Fujioka, H. *Top. Curr. Chem.* **2012**, *309*, 131-162.
- 6- Copp, B. R.; Ireland, C. M.; Barrows, L. R. *J. Org. Chem.* **1991**, *56*, 4596-4597
- 7- Hooper, G. J.; Davies-Coleman, M. T. ; Borges, K. ; Coetze, P. S. *Tetrahedron Lett.* **1996**, *37*, 7135-7138
- 8- Davis, R. A.; Buchanan, M. S.; Duffy, S.; Avery, V. M.; Charman, S. A.; Charman, W. N.; White, K. L.; Shackelford, D. M.; Edstein, M. D.; Andrews, K. T.; Camp, D.; Quinn, R. J. *J. Med. Chem.* **2012**, *55*, 5851-5858.
- 9- Legentil, L.; Lesur, B.; Delfourne, E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 427.
- 10- Legentil, L.; Benel, L.; Bertrand, V.; Lesur, B.; Delfourne, E. *J. Med. Chem.* **2006**, *49*, 2979
- 11- Rives, A.; Le Calvé, B.; Delaine, T. ; Legentil, L. Kiss, R. ; Delfourne, E. *Eur. J. Med. Chem.* **2010**, *45*, 343.
- 12- Dolusic, E. ; Larrieu, P. ; Colette, D. ; Rives, A.; Blanc, S. ; Fraser, G. ; Wouters, J. ; Van den Eynde, B. ; Maseree, B. ; Delfourne, E. ; Frédérick, R. *Bioorg. Med. Chem. Lett.* **2013**, *11*, 4351.
- 13- Xu, G.; Wang, T.; Li, Y.; Huang, Z.; Wang, X.; Zheng, J.; Yang, S.; Fan, Y.; Xiang, R. *J. Enz. Inhib. Med. Chem.* **2018**, *33*, 1089-1094.
- 14- Rives, A.; Delaine, T.; Legentil, L.; Delfourne, E. *Tetrahedron Lett.* **2009**, *50*, 1128.
- 15- Nadkarni, D. H.; Murugesan, S.; Velu, S. E. *Tetrahedron* **2013**, *69*, 4105.
- 16- De la Fuente, C.; Dominguez, D. *Tetrahedron* **2011**, *67*, 3997.
- 17- Chassaing, S.; Delfourne, E. *Magn. Res. Chem.* **2010**, *47*, 9.
- 18- Bénéteau, V.; Besson, T. *Tetrahedron Lett.* **2001**, *42*, 2673.
- 19- Zhang, L.; Cava, M. P.; Rogers, R. D.; Rogers, L. M. *Tetrahedron Lett.* **1998**, *39*, 7677-7678.
- 20- Nicolas, I. ; Bijani, C. ; Brasseur, D. ; Pratviel, G. ; Bernadou, J. ; Robert, A. *Comptes Rendus Chimie*, **2013**, *16*, 1002.

