Synthesis of granulatimide bis-imide analogues

Hélène Henon, S. Messaoudi, B. Hugon, Fabrice Anizon, B. Pfeiffer, M. Prudhomme

Synthesis of granulatimide bis-imide analogues

Hélène Hénon,[a] Samir Messaoudi,[a] Bernadette Hugon,[a] Fabrice Anizon,[a] Bruno Pfeiffer[b] and Michelle Prudhomme[a,*]

[a]*Laboratoire SEESIB, Université Blaise Pascal, UMR 6504 du CNRS, 63177 Aubière, France*
[b]*Institut de Recherches SERVIER, Division Recherche Cancérologie, 125 Chemin de ronde, 78290 Croissy sur Seine, France*

Abstract—The synthesis of dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraones, structurally related to granulatimide is reported. These compounds can be considered as granulatimide analogues in which a maleimide heterocycle replaces the imidazole moiety. The synthesis of pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraones is also reported. In these compounds, a 7-azaindole unit replaces the indole moiety present in the granulatimide and isogranulatimide structures.

1. Introduction

Many antitumor compounds from natural sources contain a carbazole maleimide or maleamide framework. Rebeccamycin is a topoisomerase I inhibitor[1] whereas staurosporine is a non specific kinase inhibitor interacting with the ATP binding site of the enzymes.[2] UCN-01, structurally related to staurosporine, also inhibits various kinases. Moreover, like granulatimide and isogranulatimide, natural compounds isolated from an ascidian, UCN-01 inhibits the cell cycle checkpoint in the G2 phase which is activated in response to DNA damage (Fig. 1).[3–6] This cell cycle checkpoint is mainly regulated by the two kinases Chk1 and Chk2.

Compounds structurally related to granulatimide, isogranulatimide isomers and analogues bearing modified heterocycles, have been recently synthesized.[7–11]

To get an insight into the possible interactions of granulatimide and isogranulatimide with the ATP binding site of the target kinases, a detailed computational study was performed.[12] The electronic density in specific regions of the molecules appears to play a pivotal role toward activity. Both granulatimide and isogranulatimide are almost planar. The molecular planarity creates a broad negative electrostatic potential on the two sides which are lypophilic sites whereas the positive potential resulting from a low electron density in the central core increases their hydrophilicity.

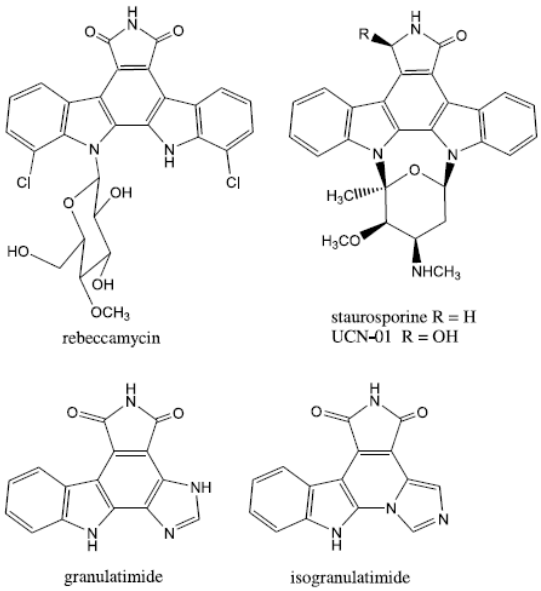
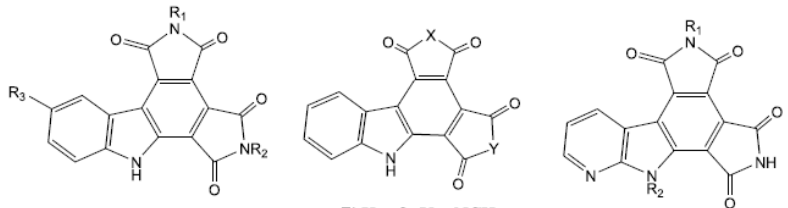


Figure 1. Chemical structures of rebeccamycin, staurosporine, UCN-01, granulatimide and isogranulatimide.

In a previous brief communication, we reported the synthesis of the first granulatimide analogues bearing a maleimide instead of an imidazole heterocycle.[13] In this paper, the synthesis of new analogues in this series **7a–7l** is described (Fig. 2).

Keywords: Granulatimide; Pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone; Dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone; 7-Azaindole.
* Corresponding author. Tel.: +33 4 73 40 71 24; fax: +33 4 73 40 77 17; e-mail: Michelle.PRUDHOMME@univ-bpclermont.fr



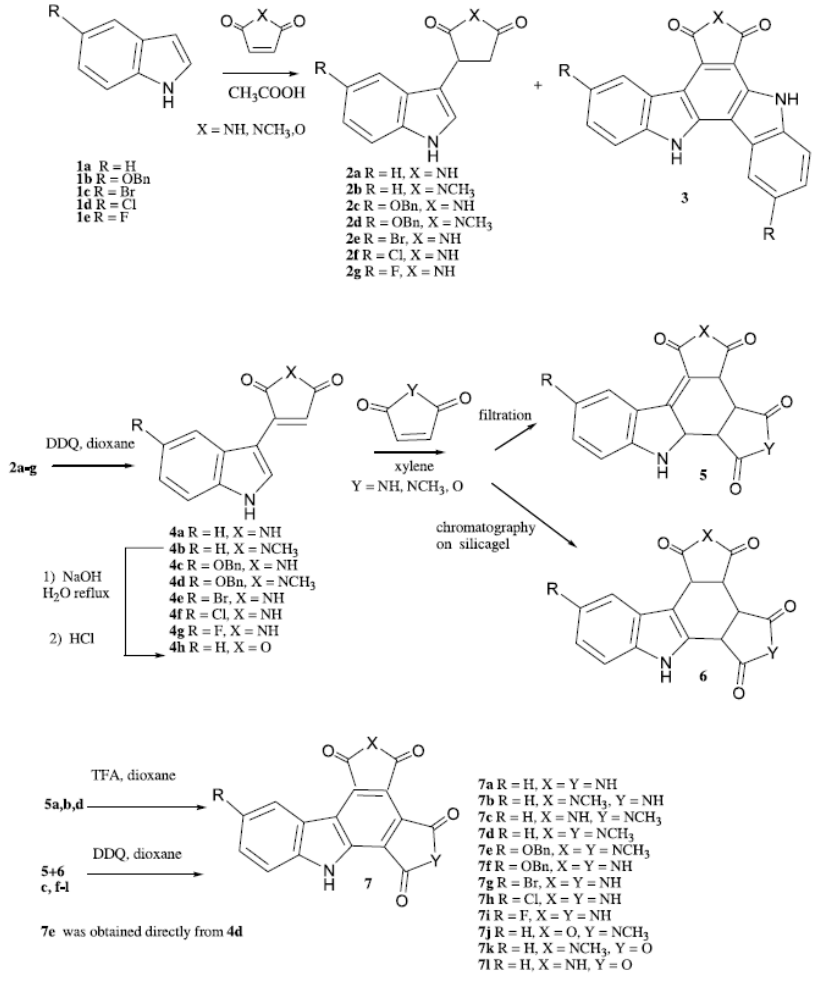
7a $R_1 = R_2 = R_3 = H$
7b $R_1 = CH_3$, $R_2 = R_3 = H$
7c $R_1 = R_3 = H$, $R_2 = CH_3$
7d $R_1 = R_2 = CH_3$, $R_3 = H$
7e $R_1 = R_2 = CH_3$, $R_3 = OBn$
7f $R_1 = R_2 = H$, $R_3 = OBn$
7m $R_1 = R_2 = H$, $R_3 = OH$
7g $R_1 = R_2 = H$, $R_3 = Br$
7h $R_1 = R_2 = H$, $R_3 = Cl$
7i $R_1 = R_2 = H$, $R_3 = F$
7n $R_1 = CH_3$, $R_2 = -(CH_2)_2-NEt_2,HCl$, $R_3 = H$
7o $R_1 = -(CH_2)_2-NEt_2,HCl$, $R_2 = CH_3$, $R_3 = H$

7j X = O, Y = NCH_3
7k X = NCH_3, Y = O
7l X = NH, Y = O

13a $R_1 = CH_3$, $R_2 = H$
13b $R_1 = CH_2OH$, $R_2 = H$
13c $R_1 = R_2 = H$
20 R_1 =H, R_2 = β-glucosyl

Figure 2. Granulatimide bis-imide analogues and related compounds.

Azaindoles, biosters of indole, are found in many natural and synthetic compounds of biological interest.[14–16] The replacement of a carbon atom by a nitrogen atom could increase the affinity for the binding site on the target enzyme(s) and also modify the electronic distribution of the aromatic framework and the lipophilicity of the molecule. In this paper, the synthesis of new bis-imide analogues in which a 7-azaindole replaces the indole unit is also reported **13a–c** (Fig. 2). To mimic the sugar part present in UCN-01 and ATP, compound **20** in which a β-glucopyranosyl moiety is attached to the azaindole was also synthesized.



1a R = H
1b R = OBn
1c R = Br
1d R = Cl
1e R = F

CH_3COOH
X = NH, NCH_3, O

2a R = H, X = NH
2b R = H, X = NCH_3
2c R = OBn, X = NH
2d R = OBn, X = NCH_3
2e R = Br, X = NH
2f R = Cl, X = NH
2g R = F, X = NH

3

DDQ, dioxane
2a-g

4a R = H, X = NH
4b R = H, X = NCH_3
4c R = OBn, X = NH
4d R = OBn, X = NCH_3
4e R = Br, X = NH
4f R = Cl, X = NH
4g R = F, X = NH
4h R = H, X = O

1) NaOH
H_2O reflux
2) HCl

xylene
Y = NH, NCH_3, O

filtration

5

chromatography
on silicagel

6

TFA, dioxane
5a,b,d

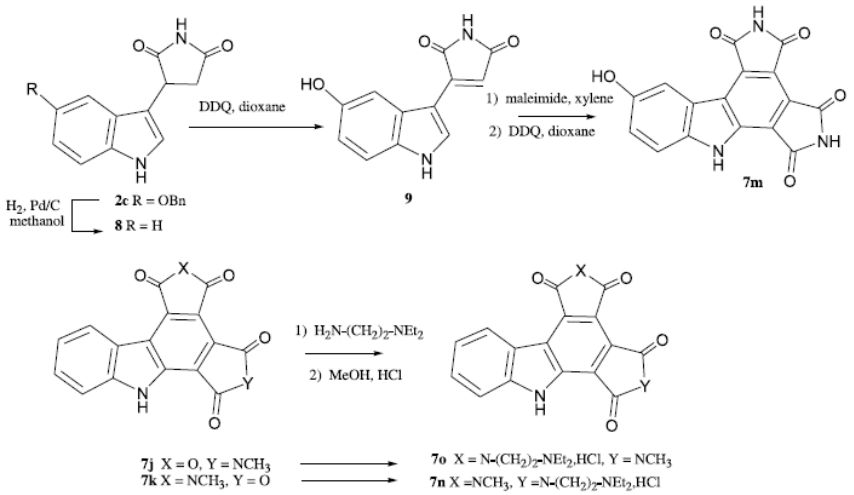
DDQ, dioxane
5+6
c, f-l

7

7e was obtained directly from **4d**

7a R = H, X = Y = NH
7b R = H, X = NCH_3, Y = NH
7c R = H, X = NH, Y = NCH_3
7d R = H, X = Y = NCH_3
7e R = OBn, X = Y = NCH_3
7f R = OBn, X = Y = NH
7g R = Br, X = Y = NH
7h R = Cl, X = Y = NH
7i R = F, X = Y = NH
7j R = H, X = O, Y = NCH_3
7k R = H, X = NCH_3, Y = O
7l R = H, X = NH, Y = O

Scheme 1. Synthesis of compounds **7a–7l**.

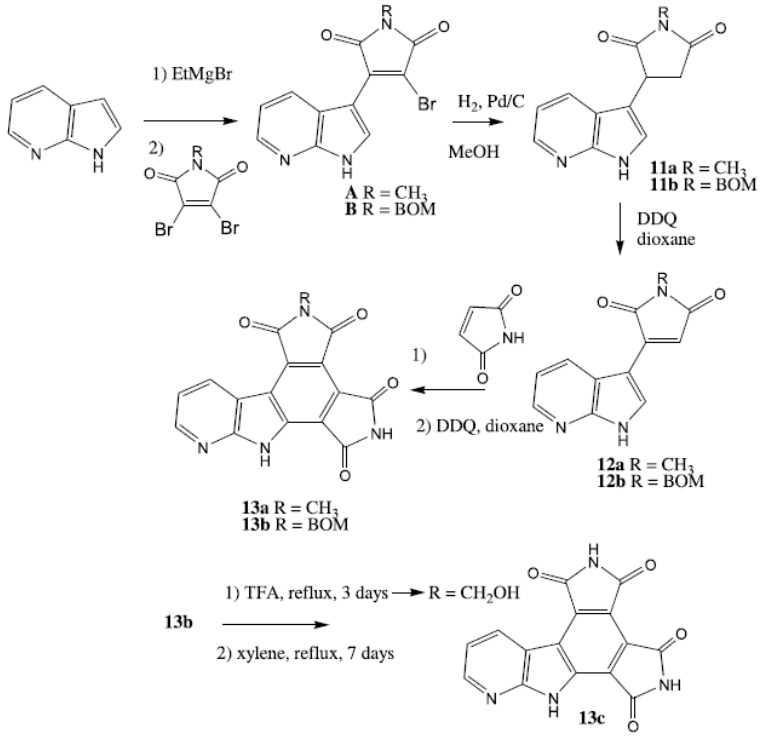


Scheme 2. Synthesis of **7m–7o**.

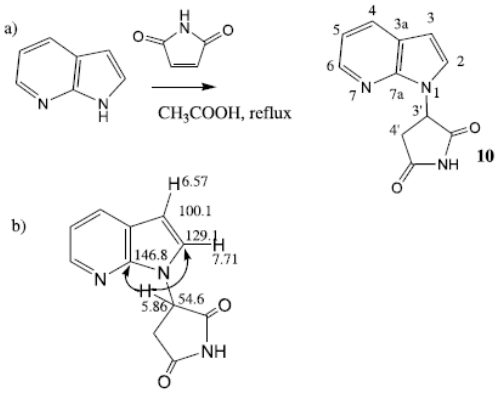
2. Results and discussion

In our previous communication, we described the synthetic pathways to access to compound **7a** and its analogues **7b**, **7d**, **7e**, **7j** and **7o**.[13] The key step consists in a Diels–Alder reaction between 3-indolylmaleimides and maleimides or maleic anhydride.[17] The 3-indolylmaleimides or maleic anhydrides **4a–g** were obtained either by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) of the corresponding 3-(indol-3-yl)-succinimides or succinic anhydrides **2a–g** resulting from acid induced addition of indoles to maleimides[18] (Scheme 1). In some cases, together with compound **2a–g**, small amounts of compounds **3** have been isolated. According to the work-up (filtration or chromatography on silicagel), the Diels–Alder cycloadduct **5a** or its isomer **6a** were isolated. The non-aromatic intermediates were further oxidized in the presence of either TFA or DDQ to yield **7a–7l**. Compound **4h** was obtained from **4b** by opening of the imide heterocycle in a basic medium followed by acidic treatment.

To synthesize the analogue **7m** bearing a hydroxy substituent (Scheme 2), hydrogenolysis of **2c** led to succinimide **8**. The same sequence of reactions as described in Scheme 1 from compounds **2a–g** yielded **7m**. To obtain more soluble compounds, a *N*,*N*-diethylaminoethyl



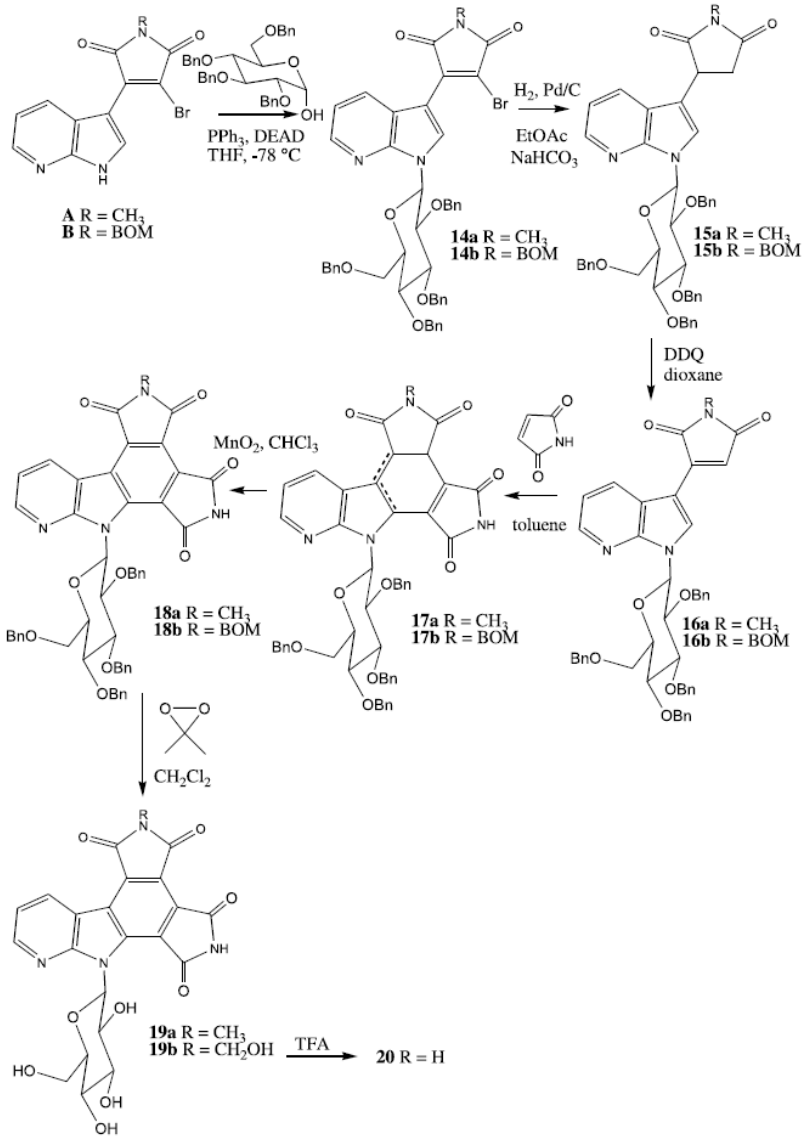
Scheme 3. Synthesis of **13c**.



Scheme 4. (a) Reaction of 7-azaindole with maleimide. (b) Long range $^{1}H–^{13}C$ coupling (chemical shifts in ppm).

substituent was introduced on one of the imide nitrogens via the corresponding anhydrides according to a method previously developed in indolocarbazole series (Scheme 2).[1]

In the aza series, the method used for the synthesis of compounds **12a** and **12b** (Scheme 3) was a little bit different from that previously described for the synthesis of the non aza analogues. The advantage of the Michael addition used for the non aza compounds was to avoid the steps of hydrogenolysis/hydrogenation then oxidation (compare Schemes 1 and 3). Unfortunately, in aza series, the reaction between 7-azaindole and maleimide in refluxing acetic acid afforded compound **10** (Scheme 4). The structure of compound **10** was assigned from NMR $^{1}H–^{1}H$ COSY correlations, HMBC and HSQC experiments (Scheme 4). Consequently, the strategy described on Scheme 3 was chosen. Moreover, the presence of an electron-withdrawing



Scheme 5. Synthesis of compound **20**.

group such as Br is necessary to increase the reactivity of the Mitsunobu reaction used for the coupling of the sugar part (Scheme 5).[19,20]

Compounds **A** and **B** were prepared as previously described.[16] Hydrogenolysis with Pd/C in methanol led to **11a** and **11b** in 90 and 68% yields, respectively, from **A** and **B**. Oxidation of **11a** and **11b** with DDQ gave **12a** and **12b** in 94 and 100% yields, respectively. Diels–Alder reactions were carried out in refluxing *p*-xylene leading to a mixture of isomers which were further oxidized with DDQ to give **13a** and **13b** in 83 and 77% yields, respectively. For the removal of the benzyloxymethyl protective group of compound **13b**, the classical method by hydrogenolysis then aminolysis could not be performed due to, firstly the insolubility of **13b** which could not be separated from the catalyst and secondly to the sensitivity of the maleimide units to basic media which often led to the opening of the maleimide heterocycles. The BOM group was eliminated in two steps: reaction with trifluoroacetic acid[21,22] which led to the *N*-hydroxymethyl-tetraone followed by refluxing in xylene[23] to give the required compound **13c**. A glucose moiety was attached to the azaindolic nitrogen. The carbohydrate could reinforce the hydrogen bond net in the target enzyme(s) (Scheme 5). A Mitsunobu reaction was carried out with compounds **A** and **B** and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose leading to **14a** and **14b** as the major products of the reactions in 46 and 64% yields, respectively. Hydrogenolysis/hydrogenation was performed using 10% Pd/C in EtOAc and $NaHCO_3$[24] affording **15a** and **15b** in 48 and 46% yields, respectively, as a mixture of two diastereoisomers. Oxidation with DDQ gave **16a** and **16b** in 61 and 64% yields, respectively. Diels–Alder reaction with maleimide in refluxing toluene afforded **17a** and **17b** in 41 and 85% yields, respectively, as a mixture of isomers. Oxidation with DDQ only gave degradation products whereas using MnO_2 in chloroform[25] **18a** and **18b** were isolated in 61 and 86% yields, respectively. For debenzylation, several methods were tried. Reaction with boron tribromide[26] or trimethylsilyliodide[27] led to a mixture of partially debenzylated compounds which could not be easily recovered from an aqueous phase during the work-up. Classical hydrogenolysis using Pd/C or $Pd(OH)_2$/C as catalysts reduced the pyridine moiety. A method for the removal of the protective groups carried out from **18b** using trifluoroacetic acid led to **19b** in 73% yield. Surprisingly, in these conditions, **20** was not directly obtained from **18b**. After isolation **19b** could be converted to **20** with TFA in 43% yield. A second method for debenzylation using dimethyldioxirane[28,29] led to **19a** and **19b** in 59 and 76% yields from **18a** and **18b**, respectively.

3. Conclusion

In conclusion, this work reports the synthesis of dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraones and pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraones, bearing or not a methyl group on the nitrogen of the upper maleimide heterocycle. These compounds are structurally related to granulatimide.

In the first series, various substituents were introduced on the indole moiety and a diethylaminoethyl chain was attached to the imide nitrogen of the upper heterocycle. In the aza series, in contrast to what observed in non aza series, the Michael addition between 7-azaindole and maleimide did not work. A different sequence of reactions has to be performed from dibromomaleimide. An analogue in which a glucose moiety is attached to the 7-azaindole unit was prepared. According to the presence or the absence of a sugar part, the methods carried out for the oxidation of the Diels–Alder adducts were different. The classical methods usually used for the deprotection of the benzyl groups did not afford the required compounds and the debenzylation procedures were modified. The biological evaluation of these new compounds is now under investigation

4. Experimental

4.1. General

IR spectra were recorded on a Perkin–Elmer 881 spectrometer (ν in cm^{-1}). NMR spectra were performed on a Bruker AVANCE 400 and AVANCE 500 (chemical shifts δ in ppm, the following abbreviations are used: singlet (s), broad singlet (br s), doublet (d), doubled doublet (dd), triplet (t), pseudo triplet (pt), multiplet (m), tertiary carbons (C tert), quaternary carbons (C quat). The signals were assigned from ^1H–^1H COSY and ^{13}C–^1H correlation. Low resolution mass spectra (ESI+, CI) were determined on a Hewlett Packard MS engine. HRMS (FAB+) were determined at CESAMO (Talence, France) on a high resolution Fisons Autospec-Q spectrometer. Chromatographic purifications were performed by flash silicagel Geduran SI 60 (Merck) 0.040–0.063 mm column chromatography.

4.1.1. 3-(Indol-3-yl)-succinimide (2a). A mixture of indole (2.34 g, 20 mmol) and maleimide (1.96 g, 20 mmol) in acetic acid (18 mL) was refluxed for 36 h. After evaporation, the residue was purified by flash chromatography (eluent: EtOAc/cyclohexane from 1:1 to 4:1) to give **2a** (3.33 g, 15.6 mmol, 74% yield) as a pale yellow solid.

Mp 196–197 °C. IR (KBr): $\nu_{C=O}$ 1696 cm^{-1}, ν_{NH} 3292–3370 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): 2.78 (1H, dd, J_1=18.0 Hz, J_2=5.5 Hz), 3.18 (1H, dd, J_1=18.0 Hz, J_2=9.5 Hz), 4.33 (1H, dd, J_1=9.5 Hz, J_2=5.5 Hz), 7.00 (1H, t, J=7.0 Hz), 7.10 (1H, t, J=7.0 Hz), 7.33 (1H, d, J=2.5 Hz), 7.38 (1H, d, J=8.0 Hz), 7.42 (1H, d, J=8.0 Hz), 11.07 (1H, s, NH), 11.34 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 37.5 (CH_2), 39.1 (CH), 111.8, 118.5, 118.9, 121.5, 123.5 (C tert arom), 110.0, 126.0, 136.6 (C quat arom), 178.2, 180.1 (C=O).

4.1.2. 1-Methyl-3-(indol-3-yl)-pyrrolidine-2,5-dione (2b) and 2-methyl-1,3-dihydro-2*H*,4*H*,9*H*-indolo[3,2-*a*]pyrrolo[3,4-*c*]carbazole-1,3-dione (3b). A mixture of indole (2.34 g, 20 mmol) and *N*-methylmaleimide (2.22 g, 20 mmol) in acetic acid (18 mL) was refluxed for 48 h. After evaporation, the residue was purified by flash

chromatography (eluent: EtOAc/cyclohexane from 3:7 to 7:3) to give **3b** (66 mg, 0.195 mmol, 1% yield) as an orange solid and **2b** (2.50 g, 11 mmol, 55% yield) as a pale yellow solid.

Compound **2b**: Mp 172–174 °C. IR (KBr): $\nu_{C=O}$ 1670, 1680 cm^{-1}, ν_{NH} 3340 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): 2.83 (1H, dd, $J_1=18.0$ Hz, $J_2=5.0$ Hz), 2.96 (3H, s, CH_3), 3.27 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.40 (1H, dd, $J_1=9.5$ Hz, $J_2=5.0$ Hz), 7.03 (1H, dt, $J_1=7.5$ Hz, $J_2=1.0$ Hz), 7.13 (1H, dt, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 7.37 (1H, d, $J=2.5$ Hz), 7.41 (1H, d, $J=8.0$ Hz), 7.43 (1H, d, $J=7.5$ Hz), 11.12 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 24.5 (CH_3), 36.1 (CH_2), 37.6 (CH), 110.7, 125.9, 136.4 (C quat arom), 111.7, 118.4, 118.8, 121.3, 123.4 (C tert arom), 176.6, 178.4 (C=O).

Compound **3b**: ^1H NMR (400 MHz, DMSO-d_6): 3.21 (3H, s, CH_3), 7.40 (1H, t, $J=7.0$ Hz), 7.45 (1H, t, $J=8.0$ Hz), 7.55 (1H, d, $J=5.5$ Hz), 7.59 (1H, d, $J=6.5$ Hz), 7.77 (1H, d, $J=8.0$ Hz), 7.80 (1H, d, $J=8.0$ Hz), 8.80 (1H, d, $J=8.0$ Hz), 8.98 (1H, d, $J=8.0$ Hz), 12.22 (1H, s, NH), 12.35 (1H, s, NH).

4.1.3. 3-(5-Benzyloxy-indol-3-yl)-pyrrolidine-2,5-dione (2c). Identical method as described for the preparation of **2b** gave from 5-benzyloxyindole (1.79 g, 8.0 mmol) and maleimide (776 mg, 8.0 mmol) compound **2c** (1.01 g, 3.16 mmol, 39% yield) as a pale yellow solid.

Mp 175 °C. IR (KBr) $\nu_{C=O}$ 1690, 1780 cm^{-1}, ν_{NH} 3210, 3420 cm^{-1}.

HRMS (FAB+) $[M]^+$ calcd. for $C_{19}H_{16}N_2O_3$ 320.1161, found 320.1168.

^1H NMR (400 MHz, DMSO-d_6): 2.76 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.21 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.33 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 5.10 (2H, s), 6.88 (1H, dd, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.06 (1H, d, $J=2.5$ Hz), 7.31 (1H, d, $J=9.0$ Hz), 7.31 (1H, d, $J=2.5$ Hz), 7.36 (1H, m), 7.43 (2H, m), 7.51 (2H, m), 10.92 (1H, d, $J=2.0$ Hz, NH), 11.32 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 37.3, 69.9 (CH_2), 38.9 (CH), 102.2, 111.8, 112.3, 123.9, 127.6, 127.7 (2C), 128.3 (2C) (C tert arom), 110.6, 126.4, 131.7, 137.6, 152.1 (C quat arom), 178.0, 179.8 (C=O).

4.1.4. 1-Methyl-3-(5-benzyloxy-indol-3-yl)-pyrrolidine-2,5-dione (2d) and 2-methyl-7,12-dibenzyloxy-4*H*,9*H*-indolo[3,2-*a*]pyrrolo[3,4-*c*]-carbazole-1,3-dione (3d). Identical procedure as described for the synthesis of **2b** and **3b** gave from 5-benzyloxy-indole (1.79 g, 8 mmol) and *N*-methylmaleimide (0.89 g, 8 mmol) compound **3d** (68 mg, 0.123 mmol, 2% yield), and **2d** (1.10 g, 3.29 mmol, 41% yield) as a light brown solid.

Compound **2d**: Mp 49–53 °C. IR (KBr): $\nu_{C=O}$ 1690, 1700 cm^{-1}, ν_{NH} 3300–3500 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{20}H_{19}N_2O_3$ 335.1396, found 335.1397.

^1H NMR (400 MHz, DMSO-d_6): 2.79 (1H, dd, $J_1=18.0$ Hz, $J_2=5.0$ Hz), 2.96 (3H, s, CH_3), 3.26 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.35 (1H, dd, $J_1=9.5$ Hz, $J_2=5.0$ Hz), 5.11 (2H, s, CH_2), 6.88 (1H, dd, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.00 (1H, d, $J=2.0$ Hz), 7.30–7.38 (3H, m), 7.43 (2H, t, $J=7.5$ Hz), 7.49 (2H, d, $J=7.0$ Hz), 10.95 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 24.5 (CH_3), 36.0 (CH_2), 37.5 (CH), 69.8 (CH_2), 102.0, 111.9, 112.3, 124.0, 127.6 (3C), 128.3 (2C) (C tert arom), 110.4, 126.3, 131.7, 137.7, 152.2 (C quat arom), 176.6, 178.4 (C=O).

Compound **3d**: Mp 286 °C. IR (KBr): $\nu_{C=O}$ 1680, 1790 cm^{-1}, ν_{NH} 3300–3400 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): 3.18 (3H, s, CH_3), 5.26 (2H, s, CH_2), 5.32 (2H, s, CH_2), 7.28 (1H, dd, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.30 (1H, dd, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.39–7.51 (6H, m), 7.62 (4H, t, $J=7.0$ Hz), 7.68 (1H, d, $J=9.0$ Hz), 7.70 (1H, d, $J=9.0$ Hz), 8.42 (1H, d, $J=2.0$ Hz), 8.65 (1H, d, $J=2.5$ Hz), 12.01 (1H, s, NH), 12.14 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 23.6 (CH_3), 69.9, 70.5 (CH_2), 106.3, 110.5, 111.7, 120.6, 121.8, 123.8, 132.9, 135.8, 136.0, 137.3, 137.4, 138.7, 153.0, 153.3 (C quat arom), 106.0, 107.8, 112.0, 112.7, 115.6, 115.8, 127.6 (2C), 127.8 (2C), 128.1 (2C), 128.4 (4C) (C tert arom), 168.9, 169.7 (C=O).

4.1.5. 3-(5-Bromo-indol-3-yl)-pyrrolidine-2,5-dione (2e). Identical method as described for the preparation of **2b** gave from 5-bromo-indole (1.0 g, 5.10 mmol) and maleimide (495 mg, 5.10 mmol) compound **2c** (647 mg, 2.21 mmol, 43% yield) as a pale yellow solid.

Mp 208–215 °C. IR (KBr) $\nu_{C=O}$ 1700, 1775 cm^{-1}, ν_{NH} 3420 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{12}H_{10}N_2O_2Br$ 292.9926 found 292.9915.

^1H NMR (400 MHz, DMSO-d_6): 2.84 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.20 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.40 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 7.25 (1H, dd, $J_1=8.5$ Hz, $J_2=2.0$ Hz), 7.38 (1H, d, $J=8.5$ Hz), 7.45 (1H, d, $J=2.5$ Hz), 7.68 (1H, d, $J=2.0$ Hz), 11.30 (1H, s, NH), 11.35 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 34.0 (CH_2), 35.6 (CH), 113.7, 120.9, 123.8, 124.8 (C tert arom), 110.8, 111.3, 128.1, 135.1 (C quat arom), 177.9, 179.7 (C=O).

4.1.6. 3-(5-Chloro-indol-3-yl)-pyrrolidine-2,5-dione (2f). Identical method as described for the preparation of **2b** gave from 5-chloro-indole (1,0 g, 6.6 mmol) and maleimide (640 mg, 6.6 mmol) compound **2f** (412 mg, 1.66 mmol, 25% yield) as an amorphous orange solid.

IR (KBr) $\nu_{C=O}$ 1700, 1780 cm^{-1}, ν_{NH} 3200–3500 cm^{-1}.

HRMS (FAB+) $[M]^+$ calcd. for $C_{12}H_9N_2O_2Cl$ 248.0353, found 248.0354.

^1H NMR (400 MHz, DMSO-d_6): 2.84 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.21 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.40 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 7.14 (1H, dd, $J_1=8.5$ Hz, $J_2=2.0$ Hz), 7.43 (1H, d, $J=8.5$ Hz), 7.46 (1H, d, $J=2.5$ Hz), 7.53 (1H, d, $J=2.0$ Hz), 11.29 (1H, s, NH), 11.34 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 37.0 (CH_2), 38.6 (CH), 113.2, 117.9, 121.3, 125.0 (C tert arom), 110.8, 123.4, 127.3, 134.9 (C quat arom), 177.9, 179.7 (C=O).

4.1.7. 3-(5-Fluoro-indol-3-yl)-pyrrolidine-2,5-dione (2g). Identical method as described for the preparation of **2b** gave from 5-fluoro-indole (1.0 g, 7.40 mmol) and maleimide (718 mg, 7.40 mmol) compound **2g** (679 mg, 2.92 mmol, 40% yield) as an orange solid.

Mp 190–195 °C. IR (KBr) $\nu_{C=O}$ 1690, 1775 cm^{-1}, ν_{NH} 3360 cm^{-1}.

HRMS (FAB+) $[M]^+$ calcd. for $C_{12}H_9N_2O_2F$ 232.0648, found 232.0644.

^1H NMR (400 MHz, DMSO-d_6): 2.83 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.21 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.37 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 6.99 (1H, dt, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.24 (1H, dd, $J_1=10$ Hz, $J_2=2.5$ Hz), 7.40 (1H, dd, $J_1=9.0$ Hz, $J_2=4.5$ Hz), 7.45 (1H, d, $J=2.5$ Hz), 11.18 (1H, s, NH), 11.33 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 37.1 (CH_2), 38.7 (CH), 103.3 (d, $J_{C,F}=23$ Hz), 109.5 (d, $J_{C,F}=26$ Hz), 112.6 (d, $J_{C,F}=9.5$ Hz), 125.2 (C tert arom), 111.2 (d, $J_{C,F}=4.5$ Hz), 126.4 (d, $J_{C,F}=10$ Hz), 133.1, 156.7 (d, $J_{C,F}=232$ Hz) (C quat arom), 177.9, 179.7 (C=O).

4.1.8. 2,5-Dihydro-1-methyl-3-(indol-3-yl)-pyrrole-2,5-dione (4b). A solution of DDQ (456 mg, 2 mmol) in dioxane (20 mL) was slowly added to a solution of **2b** (454 mg, 2 mmol) in dioxane (20 mL). The mixture was stirred at room temperature for 12 h. After filtration and removal of the solvent, the residue was dissolved in isopropanol (23 mL). After cooling for 12 h at 0 °C, the precipitate was filtered off, and the solid was washed with isopropanol before purification by flash chromatography (eluent: EtOAc/cyclohexane 3:7) to give **4b** (112 mg, 0.496 mmol, 25% yield). The filtrate was concentrated and purified by flash chromatography (eluent: EtOAc/cyclohexane 3:7) to give **4b** (197 mg, 0.872 mmol, 44% yield), total yield: 69%.

Mp 188 °C. IR (KBr) $\nu_{C=C}$ 1610 cm^{-1}, $\nu_{C=O}$ 1680, 1690 cm^{-1}, ν_{NH} 3220 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): 2.95 (3H, s, CH_3), 6.92 (1H, s), 7.24 (1H, t, $J=7.5$ Hz), 7.30 (1H, dt, $J_1=7.5$ Hz, $J_2=1.0$ Hz), 7.56 (1H, d, $J=8.0$ Hz), 8.01 (1H, d, $J=8.0$ Hz), 8.44 (1H, d, $J=3.0$ Hz), 12.10 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 23.4 (CH_3), 105.5, 125.4, 136.7, 139.0 (C quat), 112.6, 114.0, 120.4, 121.4, 123.0, 131.0 (C tert), 171.6, 171.9 (C=O).

4.1.9. 3-(5-Benzyloxy-indol-3-yl)-2,5-dihydro-1*H*-pyrrole-2,5-dione (4c). A solution of DDQ (339 mg, 1.49 mmol) in dioxane (15 mL) was slowly added to a solution of **2c** (456 mg, 1.42 mmol) in dioxane (15 mL). The mixture was stirred at room temperature for 12 h. After filtration, the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (eluent cyclohexane/EtOAc 7:3) to give **4c** (409 mg, 1.28 mmol, 90% yield) as an orange solid.

Mp 211 °C. IR (KBr) $\nu_{C=C}$ 1600 cm^{-1}, $\nu_{C=O}$ 1705, 1755 cm^{-1}, ν_{NH} 3150–3450 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{19}H_{15}N_2O_3$ 319.1083, found 319.1089.

^1H NMR (400 MHz, DMSO-d_6): 5.25 (2H, s), 6.86 (1H, s), 6.99 (1H, dd, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.36 (1H, m), 7.44 (2H, m), 7.46 (1H, d, $J=9.0$ Hz), 7.50 (1H, d, $J=2.5$ Hz), 7.54 (2H, m), 8.35 (1H, s), 10.77 (1H, br s, NH), 11.93 (1H, br s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 69.9 (CH_2), 103.9, 113.3, 113.5, 114.7, 127.6, 127.7 (2C), 128.4 (2C), 131.2 (C tert), 105.3, 126.2, 131.6, 137.6, 139.4, 154.2 (C quat), 173.3, 173.5 (C=O).

4.1.10. 2,5-Dihydro-1-methyl-3-(5-benzyloxy-indol-3-yl)-pyrrole-2,5-dione (4d). Identical method as described for the preparation of **4b** gave from **2d** (668 mg, 2 mmol) compound **4d** (442 mg, 1.33 mmol, 67% yield).

Mp 176–182 °C. IR (KBr): $\nu_{C=O}$ 1690, 1700 cm^{-1}, ν_{NH} 3300–3440 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{20}H_{17}N_2O_3$ 333.1239, found 333.1238.

^1H NMR (400 MHz, DMSO-d_6): 2.98 (3H, s, CH_3), 5.28 (2H, s, CH_2), 6.98 (1H, s), 7.00 (1H, dd, $J_1=9.0$ Hz, $J_2=2.0$ Hz), 7.36 (1H, t, $J=7.5$ Hz), 7.41 (1H, d, $J=7.5$ Hz), 7.45 (2H, t, $J=8.5$ Hz), 7.53 (1H, d, $J=2.0$ Hz), 7.56 (2H, d, $J=7.5$ Hz), 8.39 (1H, d, $J=3.0$ Hz), 11.96 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 23.4 (CH_3), 69.9 (CH_2), 103.9, 113.4, 113.6 (2C), 127.6 (2C), 127.7, 128.3 (2C), 131.3 (C tert), 105.4, 126.1, 131.6, 137.6, 138.9, 154.3 (C quat), 171.7, 172.1 (C=O).

4.1.11. 3-(5-Bromo-indol-3-yl)-2,5-dihydro-1*H*-pyrrole-2,5-dione (4e). Identical method as described for the preparation of **4c** gave from **2e** (499 mg, 1.70 mmol) compound **4e** (476 mg, 1.64 mmol, 96% yield) as an orange solid.

Mp 268 °C. IR (KBr) $\nu_{C=C}$ 1595 cm^{-1}, $\nu_{C=O}$ 1705, 1750 cm^{-1}, ν_{NH} 3200, 3340 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{12}H_8N_2O_2Br$ 290.9769, found 290.9766.

^{1}H NMR (400 MHz, DMSO-d_6): 6.95 (1H, d, J=1.0 Hz), 7.41 (1H, dd, J_1=8.5 Hz, J_2=2.0 Hz), 7.52 (1H, d, J=8.5 Hz), 8.19 (1H, d, J=2.0 Hz), 8.41 (1H, d, J=2.5 Hz), 10.82 (1H, s, NH), 12.19 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 114.4, 116.5, 122.5, 125.6, 131.9 (C tert), 104.9, 114.2, 127.2, 135.4, 138.7 (C quat), 173.0, 173.2 (C=O).

4.1.12. 3-(5-Chloro-indol-3-yl)-2,5-dihydro-1*H*-pyrrole-2,5-dione (4f). Identical method as described for the preparation of **4c** gave from **2f** (394 mg, 1.58 mmol) compound **4f** (219 mg, 0.89 mmol, 56% yield) as an orange solid.

Mp 254–264 °C. IR (KBr) $\nu_{C=C}$ 1605 cm^{-1}, $\nu_{C=O}$ 1710, 1750 cm^{-1}, ν_{NH} 3100–3350 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{12}H_8N_2O_2Cl$ 247.0274, found 247.0278.

^{1}H NMR (400 MHz, DMSO-d_6): 6.95 (1H, d, J=1.0 Hz), 7.29 (1H, dd, J_1=8.5 Hz, J_2=2.0 Hz), 7.57 (1H, d, J=8.5 Hz), 8.06 (1H, d, J=2.0 Hz), 8.43 (1H, d, J=3.0 Hz), 10.82 (1H, s, NH), 12.18 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 114.0, 116.4, 119.6, 123.0, 132.1 (C tert), 105.1, 126.2, 126.6, 135.1, 138.7 (C quat), 173.0, 173.3 (C=O).

4.1.13. 3-(5-Fluoro-indol-3-yl)-2,5-dihydro-1*H*-pyrrole-2,5-dione (4g). Identical method as described for the preparation of **4c** gave from **2g** (569 mg, 2.45 mmol) compound **4g** (464.5 mg, 2.02 mmol, 82% yield) as an orange solid.

Mp 255–265 °C. IR (KBr) $\nu_{C=C}$ 1605 cm^{-1}, $\nu_{C=O}$ 1720, 1750 cm^{-1}, ν_{NH} 3150–3350 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{12}H_8N_2O_2F$ 231.0570, found 231.0567.

^{1}H NMR (400 MHz, DMSO-d_6): 6.91 (1H, d, J=0.5 Hz), 7.14 (1H, dt, J_1=9.0 Hz, J_2=2.5 Hz), 7.56 (1H, dd, J_1=9.0 Hz, J_2=4.5 Hz), 7.83 (1H, dd, J_1=10 Hz, J_2=2.5 Hz), 8.44 (1H, d, J=2.5 Hz), 10.81 (1H, s, NH), 12.13 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 105.7 (d, $J_{C,F}$=25 Hz), 111.0 (d, $J_{C,F}$=26 Hz), 113.6 (d, $J_{C,F}$=10 Hz), 115.8, 132.4 (C tert), 105.5, 125.9 (d, $J_{C,F}$=11 Hz), 133.2, 139.0, 158.3 (d, $J_{C,F}$=234 Hz) (C quat), 173.1, 173.3 (C=O).

4.1.14. 2,5-Dihydro-3-(indol-3-yl)-furane-2,5-dione (4h). A mixture of **4b** (200 mg, 0.884 mmol) and NaOH (500 mg) in water (100 mL) was refluxed for 2 h. After cooling, concentrated HCl was added dropwise until formation of a yellow precipitate. The precipitate was filtered off, washed with water to give **4h** (125 mg, 0.59 mmol, 66% yield) as a yellow solid.

Mp 210–214 °C. IR (KBr) $\nu_{C=O}$ 1740, 1800 cm^{-1}, ν_{NH} 3320 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): 7.30 (1H, t, J=7.3 Hz), 7.32 (1H, s), 7.35 (1H, t, J=7.2 Hz), 7.60 (1H, d, J=7.7 Hz), 8.08 (1H, d, J=7.7 Hz), 8.46 (1H, d, J=2.9 Hz), 12.38 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 105.0, 125.2, 136.9, 141.3 (C quat), 112.9, 113.9, 120.5, 122.1, 123.6, 133.0 (C tert), 166.1, 166.6 (C=O).

4.1.15. 1,3,4,6-Tetrahydro-2-methyl-5*H*,7*H*-dipyrrolo-[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7b). A mixture of **4b** (226 mg, 1 mmol) and maleimide (106 mg, 1.10 mmol) in *p*-xylene (17 mL) was refluxed for 48 h. After cooling, the yellow precipitate was filtered off, washed with xylene and dried. The residue was purified by flash chromatography (eluent: EtOAc/cyclohexane from 1:1 to 100% EtOAc, then EtOAc/methanol 98:2) to give an orange solid. A mixture of this solid in dioxane (40 mL) and trifluoroacetic acid (636 μL) was refluxed for 48 h. After evaporation, EtOAc was added to the residue, and the mixture was successively washed with saturated aqueous $NaHCO_3$ and brine. The solid at the interface was filtered off to give **7b** (48 mg, 0.150 mmol, 15% yield) as an orange solid.

Mp>300 °C. IR (KBr): $\nu_{C=O}$ 1710, 1720, 1760, 1780 cm^{-1}, ν_{NH} 3260, 3395 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{17}H_{10}N_3O_4$ 320.0671, found 320.0666.

^{1}H NMR (400 MHz, DMSO-d_6): 3.16 (3H, s, CH_3), 7.45 (1H, t, J=6.5 Hz), 7.70 (1H, t, J=6.0 Hz), 7.78 (1H, d, J=7.5 Hz), 9.00 (1H, br s), 11.59 (1H, s, NH), 12.76 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 24.0 (CH_3), 117.5, 118.5, 119.3, 124.3, 125.5, 130.6, 136.8, 144.1 (C quat arom), 112.9, 121.6, 125.4, 130.1 (C tert arom), 165.1, 166.3, 167.9, 168.5 (C=O).

4.1.16. 1,3,4,6-Tetrahydro-5-methyl-2*H*,7*H*-dipyrrolo-[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7c). A mixture of **4a** (193 mg, 0.91 mmol) and *N*-methylmaleimide (121 mg, 1.09 mmol) in *p*-xylene (19 mL) was refluxed for 12 h. After cooling, the mixture was filtered off and the orange solid was washed with xylene and dried. This solid (223 mg) was dissolved in dioxane (12 mL). DDQ (344 mg, 1.52 mmol) was added and the mixture was refluxed for 3 days. After cooling, water and EtOAc were added. The solid at the interface was filtered off and washed with water then EtOAc to give compound **7c** (187 mg, 0.586 mmol, 64% yield) as an orange solid.

Mp>300 °C. IR (KBr) $\nu_{C=O}$ 1695, 1725, 1765, 1775 cm^{-1}, ν_{NH}=3220, 3330 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{17}H_{10}N_3O_4$ 320.0671, found 320.0677.

^{1}H NMR (400 MHz, DMSO-d_6): 3.16 (3H, s, NCH_3), 7.48 (1H, t, J=7.5 Hz), 7.73 (1H, dt, J_1=7.5 Hz, J_2=1.0 Hz),

7.82 (1H, d, J=8.0 Hz), 9.04 (1H, d, J=8.0 Hz), 11.65 (1H, s, NH), 12.83 (1H, s, NH).

4.1.17. 1,3,4,6-Tetrahydro-2,5-dimethyl-7*H*-dipyrrolo-[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7d). A mixture of **4b** (226 mg, 1 mmol) and *N*-methylmaleimide (122 mg, 1.10 mmol) in xylene (17 mL) was refluxed for 24 h. After cooling, the precipitate was filtered off, washed with xylene and dried. The solid residue was purified by flash chromatography (eluent: EtOAc/cyclohexane from 1:1 to 100% EtOAc then EtOAc/methanol 98:2) to give an orange solid (156 mg). A mixture of this solid (156 mg, 0.465 mmol) in dioxane (25 mL) and trifluoroacetic acid (480 μL) was refluxed for 84 h. After evaporation, EtOAc was added to the residue. Identical work-up as for **7b** gave **7d** (91 mg, 0,271 mmol, 27% yield) as an orange solid.

Mp 300 °C. IR (KBr): $\nu_{C=O}$ 1695–1720 cm^{-1}, ν_{NH} 3410 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{18}H_{12}N_3O_4$ 334.0828, found 334.0825.

^1H NMR (400 MHz, DMSO-d_6): 3.12 (3H, s, CH_3), 3.13 (3H, s, CH_3), 7.41 (1H, t, J=7.5 Hz), 7.68 (1H, t, J=7.0 Hz), 7.73 (1H, d, J=8.0 Hz), 8.88 (1H, d, J=8.0 Hz), 12.67 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 24.0 ($2CH_3$), 116.5, 118.4, 119.3, 124.4, 124.6, 131.2, 136.6, 144.2 (C quat arom), 112.9, 121.7, 125.4, 130.2 (C tert arom), 165.0, 166.8, 167.2, 167.8 (C=O).

4.1.18. 2,5-Dimethyl-10-benzyloxy-1,3,3a,3b,4,6,6a,6b-octahydro-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (5 R=OBn, X=Y=NCH_3) and 1,3,4,6-tetrahydro-2,5-dimethyl-10-benzyloxy-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7e). A mixture of **4d** (216 mg, 0.650 mmol) and *N*-methylmaleimide (80 mg, 0.715 mmol) in *p*-xylene (17 mL) was refluxed for 48 h. After cooling, the yellow precipitate was filtered off, washed with *p*-xylene and dried. The solid was washed with CH_2Cl_2 to give **7e** (20 mg, 0.046 mmol, 7% yield) as a yellow solid. The filtrate was evaporated and the residue purified by flash chromatography (eluent: EtOAc/cyclohexane from 3:2 to 100% EtOAc then EtOAc/methanol 95:5) to give **5** (R=OBn, X=Y=NCH_3) (59 mg, 0.133 mmol, 21% yield) as an orange solid.

Compound **5** (R=OBn, X=Y=NCH_3): Mp 173–174 °C. IR (KBr): $\nu_{C=O}$ 1700, 1710, 1760, 1770 cm^{-1}, ν_{NH} 3400 cm^{-1}. Mass (EI) $[M+H]^+$: 444.

^1H NMR (400 MHz, DMSO-d_6): 2.56 (3H, s, CH_3), 3.00 (3H, s, CH_3), 3.64 (4H, s, CH), 5.00 (2H, s, CH_2), 6.92 (1H, d, J=9.0 Hz), 7.13 (1H, dd, J_1=9.0 Hz, J_2=2.5 Hz), 7.36 (1H, t, J=7.0 Hz), 7.42 (2H, t, J=7.0 Hz), 7.48 (2H, d, J=7.0 Hz), 7.53 (1H, d, J=2.5 Hz), 8.01 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 24.5 (2C) (NCH_3), 41.2 (2C), 45.7 (2C), 69.8 (CH_2), 108.8, 117.7, 137.0, 146.8, 150.4, 153.4 (C quat), 109.0, 111.6, 125.2, 127.9 (3C), 128.3 (2C) (C tert arom), 164.0, 172.1, 172.6, 173.9 (C=O).

Compound **7e**: Mp>300 °C. IR (KBr) $\nu_{C=O}$ 1700, 1720, 1775 cm^{-1}, ν_{NH} 3480 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{25}H_{18}N_3O_5$ 440.1246, found 440.1246.

^1H NMR (400 MHz, DMSO-d_6): 3.08 (3H, s, CH_3), 3.10 (3H, s, CH_3), 5.16 (2H, s, CH_2), 7.33 (1H, d, J=8.5 Hz), 7.43 (1H, d, J=7.0 Hz), 7.47 (2H, t, J=7.0 Hz), 7.55 (1H, d, J=9.0 Hz), 7.63 (2H, d, J=7.5 Hz), 8.35 (1H, s), 12.40 (1H, br s, NH).

4.1.19. 10-Benzyloxy-1,3,4,6-tetrahydro-7*H*-dipyrrolo-[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7f). Identical method as described for the preparation of **7c** gave from **4c** (190 mg, 0.597 mmol) and maleimide (64 mg, 0.66 mmol) compound **7f** (172.5 mg, 0.419 mmol, 70% yield) as a red solid.

Mp>300 °C. IR (KBr) $\nu_{C=O}$ 1725, 1755, 1780 cm^{-1}, ν_{NH} 3150–3500 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{23}H_{14}N_3O_5$ 412.0933, found 412.0933.

^1H NMR (400 MHz, DMSO-d_6): 5.24 (2H, s), 7.38 (1H, m), 7.42 (1H, dd, J_1=9.0 Hz, J_2=2.5 Hz), 7.46 (2H, m), 7.60 (2H, m), 7.67 (1H, d, J=9.0 Hz), 8.60 (1H, d, J=2.5 Hz), 11.54 (1H, br s, NH), 11.56 (1H, br s, NH), 12.58 (1H, br s, NH).

^{13}C NMR (125 MHz, DMSO-d_6): 69.9 (CH_2), 108.6, 113.6, 120.0, 127.8, 127.9 (2C), 128.4 (2C) (C tert arom), 117.9, 119.0, 119.8, 124.1, 125.5, 131.5, 136.9, 137.0, 139.0, 153.5 (C quat arom), 166.4, 166.5, 168.6, 169.3 (C=O).

4.1.20. 10-Bromo-1,3,4,6-tetrahydro-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7g). Identical method as described for the preparation of **7c** gave from **4e** (150 mg, 0.515 mmol) and maleimide (55 mg, 0.567 mmol) compound **7g** (125 mg, 0.325 mmol, 63% yield) as an orange solid.

Mp>300 °C. IR (KBr) $\nu_{C=C}$ 1600 cm^{-1}, $\nu_{C=O}$ 1710, 1720, 1760 cm^{-1}, ν_{NH} 3150–3350 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{16}H_7N_3O_4Br$ 383.9620, found 383.9619.

^1H NMR (400 MHz, DMSO-d_6): 7.75 (1H, d, J=8.5 Hz), 7.86 (1H, d, J=8.5 Hz), 9.15 (1H, s), 11.64 (1H, s, NH), 11.69 (1H, s, NH), 12.93 (1H, s, NH).

4.1.21. 10-Chloro-1,3,4,6-tetrahydro-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7h). Identical method as described for the preparation of **7c** gave from **4f** (158 mg, 0.64 mmol) and maleimide (62 mg, 0.64 mmol) compound **7h** (104 mg, 0.306 mmol, 48% yield) as an orange solid.

Mp>300 °C. IR (KBr) $\nu_{C=C}$ 1600 cm^{-1}, $\nu_{C=O}$ 1710, 1720, 1760 cm^{-1}, ν_{NH} 3120–3380 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{16}H_7N_3O_4Cl$ 340.0125, found 340.0121.

^1H NMR (400 MHz, DMSO-d_6): 7.75 (1H, dd, $J_1=9.0$ Hz, $J_2=2.0$ Hz), 7.81 (1H, d, $J=9.0$ Hz), 9.01 (1H, d, $J=2.0$ Hz), 11.64 (1H, s, NH), 11.69 (1H, s, NH), 12.94 (1H, s, NH).

4.1.22. 10-Fluoro-1,3,4,6-tetrahydro-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7i). Identical method as described for the preparation of **7c** gave from **4g** (347 mg, 1.51 mmol) and maleimide (146 mg, 1.51 mmol) compound **7i** (464 mg containing 11.4% dioxane (w/w) measured from ^1H NMR spectrum, 1.27 mmol, 84% yield) as an orange solid.

Mp > 300 °C. IR (KBr) $\nu_{C=O}$ 1710, 1780 cm^{-1}, ν_{NH} 3100–3350 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{16}H_7N_3O_4F$ 324.0421, found 324.0424.

^1H NMR (400 MHz, DMSO-d_6): 7.57 (1H, dt, $J_1=9.0$ Hz, $J_2=2.5$ Hz), 7.75 (1H, dd, $J_1=9.0$ Hz, $J_2=4.5$ Hz), 8.63 (1H, dd, $J_1=9.5$ Hz, $J_2=2.5$ Hz), 10.61 (2H, br s, 2 NH), 12.77 (1H, br s, NH).

^{13}C NMR (125 MHz, DMSO-d_6): 110.2 (d, $J_{C,F}=25$ Hz), 114.2 (d, $J_{C,F}=9$ Hz), 118.0 (d, $J_{C,F}=26$ Hz) (C tert arom), 118.4, 119.4, 119.6 (d, $J_{C,F}=11$ Hz), 123.5 (d, $J_{C,F}=4.5$ Hz), 126.2, 131.9 137.3, 140.5, 157.2 (d, $J_{C,F}=236$ Hz) (C quat arom), 166.2, 166.3, 168.4, 169.2 (C=O).

4.1.23. 2-Methyl-1,3,4,6-tetrahydro-7*H*-furo[3,4-*c*]pyrrolo[3,4-*a*]carbazole-1,3,4,6-tetraone (7j). Identical method as described for the preparation of **7c** gave from **4h** (213 mg, 0.997 mmol) and *N*-methylmaleimide (122 mg, 1.26 mmol) compound **7j** (40 mg, 0.125 mmol, 13% yield) as an orange solid.

Mp 294 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1775, 1840 cm^{-1}, ν_{NH} 3370 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{17}H_9N_2O_5$ 321.0511, found 321.0494.

^1H NMR (400 MHz, DMSO-d_6): 3.20 (3H, s, NCH_3), 7.58 (1H, t, $J=8.0$ Hz), 7.82 (1H, t, $J=8.0$ Hz), 7.90 (1H, d, $J=8.0$ Hz), 8.91 (1H, d, $J=8.0$ Hz), 13.20 (1H, s, NH).

4.1.24. 1,3,4,6-Tetrahydro-2-methyl-7*H*-furo[3,4-*a*]pyrrolo[3,4-*c*]carbazole-1,3,4,6-tetraone (7k). Identical procedure as described for the preparation of **7c** gave from **4b** (315 mg, 1.39 mmol) and maleic anhydride (164 mg, 1.67 mmol) compound **7k** (235 mg, 0.734 mmol, 53% yield) as a yellow solid.

Mp > 300 °C. IR (KBr) $\nu_{C=O}$ 1705, 1760, 1835 cm^{-1}, ν_{NH} 3370 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{17}H_9N_2O_5$ 321.0511, found 321.0513.

^1H NMR (400 MHz, DMSO-d_6): 3.20 (3H, s, NCH_3), 7.51 (1H, ddd, $J_1=8.0$ Hz, $J_2=6.0$ Hz, $J_3=2.0$ Hz), 7.78 (2H, m), 8.99 (1H, d, $J=8.0$ Hz), 13.22 (1H, s, NH).

^{13}C NMR (125 MHz, DMSO-d_6): 23.9 (CH_3), 113.0, 121.2, 124.8, 129.1 (C tert arom), 112.6, 117.8, 119.3, 120.2, 128.5, 130.4, 142.6, 143.0 (C quat arom), 166.0, 167.0, 167.1, 167.6 (C=O).

4.1.25. 1,3,4,6-Tetrahydro-2*H*,7*H*-furo[3,4-*a*]pyrrolo-[3,4-*c*]carbazole-1,3,4,6-tetraone (7l). Identical method as described for the preparation of **7c** gave from **4a** (200 mg, 0.942 mmol) and maleic anhydride (111 mg, 1.13 mmol) compound **7l** (235 mg, 0.767 mmol, 81% yield) as an orange solid.

Mp > 300 °C. IR (KBr) $\nu_{C=C}$ 1610 cm^{-1}, $\nu_{C=O}$ 1700–1850 cm^{-1}, ν_{NH} 3240, 3380 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{16}H_7N_2O_5$ 307.0355, found 307.0357.

^1H NMR (400 MHz, DMSO-d_6): 7.55 (1H, t, $J=7.5$ Hz), 7.79 (1H, t, $J=7.5$ Hz), 7.85 (1H, d, $J=8.0$ Hz), 9.06 (1H, d, $J=8.0$ Hz), 11.86 (1H, br s, NH), 13.28 (1H, br s, NH).

4.1.26. 2,5-Dihydro-3-(5-hydroxy-indol-3-yl)-1*H*-pyrrole-2,5-dione (9). A mixture of compound **2c** (450 mg, 1.40 mmol), methanol (90 mL) and Pd/C 10% (135 mg) was hydrogenated (1 bar) for 3 h. After filtration over celite, the filtrate was evaporated to give compound **8** as a grey oil. A solution of DDQ (318 mg, 1.40 mmol) in dioxane (15 mL) was slowly added to a solution of **8** (323 mg, 1.40 mmol) in dioxane (15 mL). The mixture was stirred at room temperature overnight then filtered off. After removal of the solvent, the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 1:1) to give **9** (166 mg, 0.73 mmol, 52% yield) as an orange solid.

Compound **8**: IR (film) $\nu_{C=O}$ 1700 cm^{-1}, $\nu_{NH,OH}$ 3000–3700 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): 2.75 (1H, dd, $J_1=18$ Hz, $J_2=5.0$ Hz), 3.18 (1H, dd, $J_1=18$ Hz, $J_2=9.5$ Hz), 4.26 (1H, dd, $J_1=9.5$ Hz, $J_2=5.0$ Hz), 6.65 (1H, dd, $J_1=8.5$ Hz, $J_2=2.0$ Hz), 6.75 (1H, d, $J=2.0$ Hz), 7.20 (1H, d, $J=8.5$ Hz), 7.24 (1H, d, $J=2.5$ Hz), 8.74 (1H, s, OH), 10.74 (1H, s, NH), 11.34 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 37.2 (CH_2), 39.1 (CH), 102.3, 111.7, 112.1, 123.9 (C tert arom), 109.9, 126.4, 131.0, 150.4 (C quat arom), 178.1, 180.0 (C=O).

Compound **9**: Mp 292–298 °C. IR (KBr) $\nu_{C=C}$ 1610 cm^{-1}, $\nu_{C=O}$ 1690, 1760 cm^{-1}, $\nu_{NH,OH}$ 3260, 3370, 3430 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{12}H_9N_2O_3$ 229.0613, found 229.0609.

^1H NMR (400 MHz, DMSO-d_6): 6.47 (1H, s), 6.80 (1H, dd, $J_1=8.5$ Hz, $J_2=2.0$ Hz), 7.20 (1H, d, $J=2.0$ Hz), 7.36 (1H, d, $J=8.5$ Hz), 8.29 (1H, d, $J=3.0$ Hz), 9.09 (1H, s, OH), 10.74 (1H, s, NH), 11.85 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 104.7, 112.7, 113.1, 113.5, 131.1 (C tert), 104.6, 126.7, 130.7, 139.9, 152.8 (C quat), 173.1, 173.3 (C=O).

4.1.27. 1,3,4,6-Tetrahydro-10-hydroxy-7*H*-dipyrrolo-[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7m). Identical method as described for the preparation of **7c** gave from **9** (79.5 mg, 0.348 mmol) and maleimide (33.8 mg, 0.348 mmol) compound **7m** (38.5 mg, 0.120 mmol, 34% yield) as a brown solid.

Mp > 300 °C. IR (KBr) $\nu_{C=O}$ 1715, 1770 cm^{-1}, $\nu_{NH,OH}$ 3100–3650 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{16}H_8N_3O_5$ 322.0464, found 322.0460.

^{1}H NMR (400 MHz, DMSO-d_6): 7.21 (1H, dd, J_1=2.5 Hz, J_2=9.0 Hz), 7.63 (1H, d, J=9.0 Hz), 8.45 (1H, d, J=2.5 Hz), 9.52 (1H, br s, OH), 11.49 (1H, s, NH), 11.52 (1H, s, NH), 12.51 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 109.7, 113.4, 120.0 (C tert arom), 117.7, 118.7, 120.2, 124.2, 125.4, 131.6, 137.1, 138.1, 152.5 (C quat arom), 166.5, 166.6, 168.8, 169.4 (C=O).

4.1.28. 2-(2-*N*,*N*-Diethylaminoethyl)-1,3,5,6-tetrahydro-5-methyl-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone hydrochloride (7o). To a solution of **7j** (28.3 mg, 0.088 mmol) in THF (5.2 mL) was added dropwise *N*-*N*-diethylethylenediamine (19 μL, 0.132 mmol). The light-protected mixture was stirred at 65 °C for 4 days. After cooling, 1 N HCl (40 mL) was added. The mixture was washed with EtOAc and the aqueous phase was adjusted to pH 8 by addition of saturated aqueous $NaHCO_3$ then extracted with EtOAc. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduce pressure at 20 °C to give the free amine (29 mg) as a yellow solid. To a solution of the amine at 0 °C in methanol (400 μL) was added dropwise 1 N HCl (190 μL). The mixture was stirred for 30 min. The solvent was removed to give hydrochloride **7o** (32.3 mg, 0.071 mmol, 81% yield) as a yellow solid.

Mp 184 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1710, 1720, 1765, 1775 cm^{-1}, ν_{NH} 3300–3600 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{23}H_{23}N_4O_4$ 419.1719, found 419.1713.

^{1}H NMR (400 MHz, DMSO-d_6): 1.27 (6H, t, J=7.0 Hz), 3.18 (3H, s, NCH_3), 3.35 (4H, m), 3.50 (2H, m), 4.09 (2H, t, J=6.5 Hz), 7.51 (1H, t, J=8.0 Hz), 7.75 (1H, t, J=8.0 Hz), 7.84 (1H, d, J=8.5 Hz), 9.04 (1H, d, J=8.5 Hz), 9.43 (1H, br s), 12.95 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 8.2 (2C) (CH_3), 24.0 (NCH_3), 32.6, 46.1 (2C), 47.9 (CH_2), 113.0, 121.8, 125.4, 130.4 (C tert arom), 116.7, 118.2, 119.2, 124.5, 124.7, 130.1, 136.6, 144.3 (C quat arom), 164.8, 165.0, 167.1, 167.6 (C=O).

4.1.29. 5-(2-*N*,*N*-Diethylaminoethyl)-1,3,4,6-tetrahydro-2-methyl-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone hydrochloride (7n). To a solution of **7k** (30 mg, 0.094 mmol) in THF (5.5 mL) was added dropwise *N*,*N*-diethylethylenediamine (20 μL, 0.142 mmol). The light-protected mixture was stirred at 65 °C for 4 days. After cooling, the solvent was removed. Acetic anhydride (1 mL) and NaOAc (75 mg, 0.91 mmol) were added to the residue. The mixture was stirred at 90 °C for 4 h. After cooling, 1 N HCl (40 mL) then EtOAc were added. After extraction, EtOAc and saturated aqueous $NaHCO_3$ were added to the aqueous phase. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure without heating. The free amine (33 mg) was obtained as a yellow solid. To a solution of the free amine in methanol (1 mL) at 0 °C was added dropwise 1 N HCl (172 μL). The mixture was stirred for 30 min. The solvent was removed to give **7n** (31 mg, 0.068 mmol, 72% yield) as a yellow-orange solid.

Mp 278–280 °C. IR (KBr) $\nu_{C=O}$ 1710, 1770 cm^{-1}, ν_{NH} 3200, 3600 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd. for $C_{23}H_{23}N_4O_4$ calcd. for 419.1719, found 419.1720.

^{1}H NMR (400 MHz, DMSO-d_6): 1.29 (6H, t, J=7.0 Hz), 3.19 (3H, s, NCH_3), 3.31 (4H, m), 3.46 (2H, m), 4.08 (2H, t, J=6.5 Hz), 7.48 (1H, t, J=7.5 Hz), 7.74 (1H, t, J=7.5 Hz), 7.81 (1H, d, J=8.0 Hz), 9.00 (1H, d, J=8,0 Hz), 10.04 (1H, br s), 12.87 (1H, s).

^{13}C NMR (100 MHz, DMSO-d_6): 8.2 (2C), 24.0 (CH_3), 32.5, 46.1 (2C), 47.9 (CH_2), 112.9, 121.8, 125.4, 130.3 (CH arom), 116.3, 118.3, 119.1, 124.3 (2C), 130.0, 136.5, 144.2 (C quat arom), 164.7, 164.9, 166.8, 167.5 (C=O).

4.1.30. 1-(2,5-Dioxopyrrolidin-3-yl)-pyrrolo[2,3-*b*]pyridine 10. A solution of 7-azaindole (1 g, 8.47 mmol) and maleimide (904 mg, 9.32 mmol) in acetic acid (10 mL) was refluxed for 60 h. Acetic acid was evaporated and EtOAc was added. The solution was washed with saturated aqueous $NaHCO_3$ then dried over Na_2SO_4. The solvent was removed and the residue was purified by flash chromatography (eluent EtOAc/cyclohexane from 1:2 to 7:3) to give a solid which was washed with EtOAc then with Et_2O to give **10** (184 mg, 0.86 mmol, 10% yield) as a white solid.

Mp > 200 °C (sublimation). IR (KBr) $\nu_{C=O}$ 1720, 1780 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{11}H_{10}N_3O_2$ 216.0773, found 216.0770.

^{1}H NMR (400 MHz, DMSO-d_6): 3.14 (1H, dd, J_1=17.5 Hz, J_2=6.0 Hz), 3.26 (1H, dd, J_1=17.5 Hz, J_2=9.5 Hz), 5.86 (1H, dd, J_1=9.5 Hz, J_2=6.0 Hz), 6.57 (1H, d, J=3.5 Hz), 7.16 (1H, dd, J_1=8.0 Hz, J_2=4.5 Hz), 7.71 (1H, d, J=3.5 Hz), 8.04 (1H, d, J=8.0 Hz), 8.26 (1H, d, J=4.5 Hz), 11.69 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 36.4 (CH_2), 54.6, 100.1, 116.2, 129.0, 129.1, 142.5 (CH), 120.5, 146.8 (C quat arom), 175.8, 176.3 (C=O).

4.1.31. 1-Methyl-3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-pyrrolidine-2,5-dione 11a. A mixture of **A** (199 mg, 0.65 mmol) and 10% Pd/C (20 mg) in methanol (40 mL) was hydrogenated (1 bar) for 3.5 h. The mixture was filtered over Celite, the filtrate was evaporated and the residue was purified by flash chromatography (eluent from EtOAc 100% to EtOAc/MeOH 9:1) to give **11a** (135 mg, 0.59 mmol, 90% yield) as a white solid.

Mp 199–202 °C. IR (KBr) $\nu_{C=O}$ 1690, 1770 cm^{-1}, ν_{NH} 3250–3500 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{12}H_{12}N_3O_2$ 230.0930, found 230.0925.

^1H NMR (400 MHz, DMSO-d_6): 2.92 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 2.95 (3H, s, NCH_3), 3.25 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.42 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 7.10 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 7.53 (1H, d, $J=2.5$ Hz), 7.92 (1H, dd, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 8.26 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 11.64 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 24.6 (CH_3), 37.5 (CH_2), 35.6 (CH), 115.2, 123.8, 127.0, 142.9 (C tert arom), 109.5, 118.4, 148.6 (C quat arom), 176.5, 178.1 (C=O).

4.1.32. 1-Benzyloxymethyl-3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-pyrrolidin-2,5-dione 11b. A mixture of **B** (607 mg, 1.47 mmol), $NaHCO_3$ (618 mg, 7.36 mmol) and 10% Pd/C (607 mg) in EtOAc (57 mL) was hydrogenated (1 bar) for 24 h. The mixture was filtered over Celite, the filtrate was evaporated and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 3:7) to give **11b** (334 mg, 1.00 mmol, 68% yield) as a white solid.

Mp 136–138 °C. IR (KBr) $\nu_{C=O}$ 1707, 1776 cm^{-1}, ν_{NH} 3143 cm^{-1}.

Mass (ESI+) $[M+H]^+$ 336. ^1H NMR (400 MHz, DMSO-d_6): 3.00 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.30 (1H, dd, $J_1=18.0$ Hz, $J_2=9.5$ Hz), 4.47 (1H, dd, $J_1=9.5$ Hz, $J_2=5.5$ Hz), 4.60 (2H, s, CH_2), 4.99 (2H, s, CH_2), 7.07 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 7.30–7.42 (5H, m), 7.54 (1H, d, $J=2.5$ Hz), 7.93 (1H, dd, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 8.26 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 11.66 (1H, br s, NH).

^{13}C NMR (100 MHz, $CDCl_3$): 35.9, 68.0, 72.4 (CH_2), 38.2 (CH), 116.0, 123.1, 127.6 (2C), 127.8, 127.9, 128.5 (2C), 143.1 (C tert arom), 109.4, 118.8, 137.5, 149.0 (C quat arom), 175.8, 177.4 (C=O).

4.1.33. 2,5-Dihydro-1-methyl-3-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-pyrrole-2,5-dione 12a. A solution of DDQ (138 mg, 0.61 mmol) in dioxane (10 mL) was added dropwise to a solution of **11a** (133 mg, 0.581 mmol) in dioxane (5 mL). After stirring for 15 h at room temperature, the solvent was removed and CH_2Cl_2 was added to the residue. After filtration, the solid was washed with CH_2Cl_2 then with methanol to give **12a** (124 mg, 0.546 mmol, 94% yield) as a white solid.

Mp > 250 °C. IR (KBr) $\nu_{C=O}$ 1700, 1760 cm^{-1}, ν_{NH} 3300–3600 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{12}H_{10}N_3O_2$ 228.0773, found 228.0774.

^1H NMR (400 MHz, DMSO-d_6): 2.98 (3H, s, NCH_3), 7.08 (1H, s), 7.29 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 8.40 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 8.47 (1H, d, $J=2.5$ Hz), 8.52 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 12.59 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 23.4 (CH_3), 115.9, 117.4, 128.9, 130.9, 144.3 (C tert), 104.3, 117.7, 138.3, 149.1 (C quat), 171.3, 171.8 (C=O).

4.1.34. 1-Benzyloxymethyl-2,5-dihydro-3-(1*H*-pyrrolo-[2,3-*b*]pyridin-3-yl)-pyrrole-2,5-dione 12b. DDQ (234 mg, 1.03 mmol) was added slowly to a solution of **11b** (329 mg, 0.98 mmol) in dioxane (20 mL). The mixture was stirred at room temperature overnight. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 1:1 then THF/cyclohexane 1:1) to give **12b** (327 mg, 0.98 mmol, 100% yield) as a yellow solid.

Mp 186 °C. IR (KBr): $\nu_{C=C}$ 1585, 1600 cm^{-1}, $\nu_{C=O}$ 1705, 1760 cm^{-1}. Mass (ESI+) $[M+H]^+$ 334, $[M+Na]^+$ 356.

^1H NMR (400 MHz, DMSO-d_6): 4.60 (2H, s, CH_2), 5.02 (2H, s, CH_2), 7.16 (1H, s), 7.31 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 7.31 (1H, m), 7.37 (4H, m), 8.41 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 8.51 (1H, d, $J=3.0$ Hz), 8.54 (1H, dd, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 12.66 (1H, br s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 66.4, 70.3 (CH_2), 116.0, 117.5, 127.4 (2C), 127.5, 128.2 (2C), 129.0, 131.4, 144.4 (C tert), 104.1, 117.7, 137.7, 138.5, 149.1 (C quat), 171.0, 171.2 (C=O).

4.1.35. 2-Methyl-1,3,4,6-tetrahydro-5*H*,7*H*-pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 13a. A mixture of **12a** (55 mg, 0.242 mmol) and maleimide (26 mg, 0.267 mmol) in *p*-xylene (5 mL) was refluxed for 20 h. After cooling, then filtration, the solid was washed with *p*-xylene. A mixture of the solid (70.8 mg) and DDQ (116 mg, 0.509 mmol) in dioxane (5 mL) was refluxed for 3 days. After removal of the solvent, water was added. After filtration, the residue was washed with water then with EtOAc affording **13a** (64.7 mg, 0.202 mmol, 83% yield) as a yellow-orange solid.

Mp > 300 °C. IR (KBr) $\nu_{C=C}$ 1600 cm^{-1}, $\nu_{C=O}$ 1710, 1730, 1770, 1780 cm^{-1}, ν_{NH} 3200 cm^{-1}.

Mass (FAB+) $[M+H]^+$ 321.

^1H NMR (400 MHz, DMSO-d_6): 3.19 (3H, s, NCH_3), 7.56 (1H, dd, $J_1=8.0$ Hz, $J_2=4.5$ Hz), 8.77 (1H, dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz), 9.29 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 11.67 (1H, s, NH), 13.39 (1H, s, NH).

Due to its insolubility, the ^{13}C NMR spectrum could not be recorded.

4.1.36. 2-Benzyloxymethyl-5*H*,7*H*-pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 13b. A mixture of

12b (329 mg, 0.99 mmol) and maleimide (101 mg, 1.04 mmol) in *p*-xylene (17 mL) was refluxed for 24 h. After cooling, then filtration, the solid was washed with *p*-xylene. A mixture of the solid (361 mg) and DDQ (417 mg, 1.84 mmol) in dioxane (15 mL) was refluxed for 40 h. After filtration, the residue was washed with water then with EtOAc affording **13b** (325 mg, 0.76 mmol, 77% yield) as a pale-yellow solid.

Mp > 300 °C. IR (KBr) $\nu_{C=O}$ 1715, 1780 cm^{-1}, ν_{NH} 3200 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{23}H_{14}N_4O_5$ 427.1042, found 427.1042.

^1H NMR (400 MHz, DMSO-d_6): 4.69 (2H, s, CH_2), 5.22 (2H, s, CH_2), 7.28 (1H, m), 7.32–7.42 (4H, m), 7.54 (1H, dd, J_1 = 8.0 Hz, J_2 = 4.5 Hz), 8.74 (1H, dd, J_1 = 4.5 Hz, J_2 = 1.5 Hz), 9.21 (1H, dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz), 11.70 (1H, s, NH), 13.39 (1H, s, NH).

Due to its insolubility, the ^{13}C NMR spectrum could not be recorded.

4.1.37. 1,3,4,6-Tetrahydro-2*H*,5*H*,7*H*-pyridino[2,3-*b*]-dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 13c. A solution of compound **13b** (100 mg, 0.234 mmol) in TFA (14 mL) was refluxed for 3 days. After removal of the solvent, water was added. After fitration the solid residue was washed with EtOAc then dried under vacuum. A mixture of the solid residue in *p*-xylene (3 mL) was refluxed for 7 days. After cooling then filtration, the solid was washed with *p*-xylene, water, EtOAc, and finally with THF to give **13c** (45 mg, 0.147 mmol, 63% yield) as a green-yellow solid.

Mp > 300 °C. IR (KBr) $\nu_{C=C}$ 1590 cm^{-1}, $\nu_{C=O}$ 1718, 1780 cm^{-1}, ν_{NH} 3000–3300 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{15}H_6N_4O_4$ 307.0467, found 307.0477.

^1H NMR (400 MHz, DMSO-d_6): 7.53 (1H, dd, J_1 = 8.0 Hz, J_2 = 4.5 Hz), 8.74 (1H, dd, J_1 = 4.5 Hz, J_2 = 1.5 Hz), 9.24 (1H, dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz), 11.63 (1H, br s, NH), 11.68 (1H, br s, NH), 13.32 (1H, br s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 117.9, 134.0, 150.5 (C tert arom), 112.4, 118.8, 120.3, 122.1, 126.8, 132.4, 136.2, 155.4 (C quat arom), 166.2, 166.3, 167.9, 169.1 (C=O).

4.1.38. 3-Bromo-2,5-dihydro-1-methyl-4-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo[2,3-*b*]-pyridin-3-yl]-pyrrole-2,5-dione 14a. To a solution of **A** (50 mg, 0.172 mmol) in THF (4 mL) were added 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (264 mg, 0.488 mmol) and triphenylphosphine (128 mg, 0.488 mmol). The mixture was cooled to −78 °C then diisopropyl azodicarboxylate (DIAD, 97 μL, 0.488 mmol) was added dropwise. The mixture was allowed to reach room temperature then was stirred at room temperature for 15 h. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 8:2 to 7:3) to give **14a** (65 mg, 0.078 mmol, 46% yield) as the major product of the reaction and as a yellow oil.

IR (NaCl film) $\nu_{C=O}$ 1710, 1760 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{46}H_{43}N_3O_7Br$ 828.2284, found 828,2283.

^1H NMR (400 MHz, $CDCl_3$): 3.21 (3H, s, NCH_3), 3.74–3.87 (3H, m), 3.74 (1H, t, J = 9.5 Hz), 3.97–4.05 (2H, m), 4.51 (1H, d, J = 11.0 Hz), 4.53 (1H, d, J = 12.0 Hz), 4.63 (1H, d, J = 12.0 Hz), 4.70 (1H, d, J = 10.5 Hz), 4.92 (1H, d, J = 10.5 Hz), 4.98 (3H, s), 6.17 (1H, d, J = 7.5 Hz, $H_{1'}$), 6.60 (2H, d, J = 7.0 Hz), 6.99 (2H, t, J = 7.5 Hz), 7.06 (1H, t, J = 7.5 Hz), 7.22–7.40 (15H, m), 8.27 (1H, s), 8.47 (1H, d, J = 5.0 Hz), 8.49 (1H, d, J = 8.0 Hz).

RMN ^{13}C (100 MHz, $CDCl_3$): 24.9 (N–CH_3), 68.5 ($C_{6'}$), 73.5, 74.9, 75.2, 75.8 (CH_2), 77.5, 78.0, 81.7, 82.2, 85.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 118.0, 127.6–128.5, 130.0, 132.0, 144.4, 152.6 (C tert arom), 104.7, 116.2, 118.2, 136.4, 136.9, 137.9, 138.0, 138.3, 148.0 (C quat arom), 166.4, 169.0 (C=O).

4.1.39. 3-Bromo-1-benzyloxymethyl-2,5-dihydro-4-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo-[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione 14b. To a solution of **B** (774 mg, 1.88 mmol) in THF (5 mL) were added 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (3.04 g, 5.62 mmol) and triphenylphosphine (1.74 g, 5.62 mmol). The mixture was cooled to −78 °C then DIAD (1.12 mL, 5.62 mmol) was added dropwise. The mixture was allowed to reach room temperature then was stirred at room temperature for 15 h. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 8:2 then CH_2Cl_2/EtOAc 95:5) to give **14b** (1.12 mg, 1.20 mmol, 64% yield) as the major product of the reaction and as a yellow oil.

IR (NaCl film) $\nu_{C=O}$ 1720–1780 cm^{-1}.

Mass (ESI+) $[M+Na]^+$ 956, 958, $[M+K]^+$ 972, 974.

^1H NMR (400 MHz, $CDCl_3$): 3.66 (1H, m), 3.72 (2H, d, J = 9.0 Hz), 3.83 (1H, m), 3.89–3.93 (3H, m), 4.42 (1H, d, J = 11.0 Hz), 4.43 (1H, d, J = 12.0 Hz), 4.52 (1H, d, J = 12.0 Hz), 4.59 (1H, d, J = 11.0 Hz), 4.60 (2H, s), 4.82 (1H, d, J = 11.0 Hz), 4.87 (2H, s), 5.09 (2H, s), 6.09 (1H, br s, $H_{1'}$), 6.49 (2H, d, J = 7.0 Hz), 6.86–6.97 (3H, m), 7.10–7.25 (21H, m), 8.14 (1H, s), 8.36–8.42 (2H, m).

^{13}C NMR (100 MHz, $CDCl_3$): 67.6, 68.6, 72.0, 73.6, 74.9, 75.3, 75.8 (CH_2), 77.6, 78.1, 81.5, 82.2, 85.8 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 118.1, 127.7–128.5, 130.5, 132.4, 132.5, 144.1 (C tert arom), 118.6, 125.3, 136.9, 137.4, 138.0 (2C), 138.4 (C quat arom), 165.5, 168.0 (C=O).

4.1.40. 1-Methyl-3-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-gluco-pyranos-1-yl)-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrolidine-2,5-dione 15a. To a suspension of **14a** (65 mg, 0.078 mmol)

in EtOAc (10 mL) were added $NaHCO_3$ (66 mg, 0.93 mmol) and 10% Pd/C (65 mg). The mixture was hydrogenated (1 bar) at room temperature for 24 h. After filtration over Celite, the filtrate was evaporated and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 8:2 to 7:3) to give **15a** (28 mg, 0.037 mmol, 48% yield) as a colourless oil and as a mixture of two diastereoisomers (diastereoisomeric ratio: 1:1 calculated from ^{1}H NMR spectrum on signals at 3.04 and 3.05 ppm).

IR (NaCl film) $\nu_{C=O}$ 1700–1750 cm^{-1}.

HRMS (FAB+) $[M+H]^+$ calcd for $C_{46}H_{46}N_3O_7$ 752.3335, found 752.3333.

^{1}H NMR (400 MHz, $CDCl_3$): 2.80 (1H, dd, $J_1=18.0$ Hz, $J_2=5.0$ Hz), 2.83 (1H, dd, $J_1=18.0$ Hz, $J_2=5.0$ Hz), 3.04 (3H, s, NCH_3), 3.05 (3H, s, NCH_3), 3.18 (1H, dd, $J_1=18.0$ Hz, $J_2=9.0$ Hz), 3.21 (1H, dd, $J_1=18.0$ Hz, $J_2=9.0$ Hz), 3.65–3.94 (14H, m), 4.21 (2H, m), 4.34 (2H, d, $J=11.0$ Hz), 4.45 (2H, d, $J=12.0$ Hz), 4.54 (2H, d, $J=12.0$ Hz), 4.60 (2H, d, $J=11.0$ Hz), 4.84 (2H, d, $J=11.0$ Hz), 4.87–4.91 (4H, m), 6.03 (1H, br s, $H_{1'}$), 6.55 (4H, d, $J=7.0$ Hz), 6.98 (4H, t, $J=7.5$ Hz), 7.00–7.18 (8H, m), 7.20–7.33 (28H, m), 7.82 (1H, d, $J=8.0$ Hz), 7.85 (1H, d, $J=8.0$ Hz), 8.35 (2H, d, $J=5.0$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 25.0 (NCH_3), 35.4, 35.9 (CH_2), 38.0, 38.1 (CH), 68.6 ($C_{6'}$), 73.5, 74.4, 74.5, 75.1, 75.6, 75.7 (CH_2), 77.7, 81.5, 81.7, 82.0, 85.7, 85.8 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 116.8, 122.2, 127.4–128.4, 144.0 (C tert arom), 110.7, 110.8, 119.2, 119.3, 137.2, 138.0, 138.5, 148.3 (C quat arom), 175.3, 175.8, 175.9, 176.5 (C=O).

4.1.41. 1-Benzyloxymethyl-3-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrolidine-2,5-dione 15b. To a suspension of **14b** (117 mg, 0.125 mmol) in EtOAc (10 mL) were added $NaHCO_3$ (53 mg, 0.625 mmol) and 10% Pd/C (117 mg). The mixture was hydrogenated (1 bar) at room temperature for 24 h. After filtration over Celite, the filtrate was evaporated and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 8:2) to give **15b** (50 mg, 0.058 mmol, 46% yield) as a colourless oil and as a mixture of two diastereoisomers (diastereoisomeric ratio: 1:1 calculated from ^{1}H NMR spectrum on signals at 7.77 and 7.81 ppm).

IR (NaCl film) $\nu_{C=O}$ 1715–1780 cm^{-1}. Mass (ESI+) $[M+Na]^+$ 880, $[M+K]^+$ 896.

^{1}H NMR (400 MHz, $CDCl_3$): 2.71 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 2.73 (1H, dd, $J_1=18.0$ Hz, $J_2=5.5$ Hz), 3.04 (1H, dd, $J_1=18.0$ Hz, $J_2=9.0$ Hz), 3.07 (1H, dd, $J_1=18.0$ Hz, $J_2=9.0$ Hz), 3.64–3.89 (12H, m), 4.00–4.10 (2H, m), 4.31 (2H, d, $J=11.0$ Hz), 4.42 (2H, d, $J=12.0$ Hz), 4.51 (2H, d, $J=12.0$ Hz), 4.57 (2H, d, $J=11.0$ Hz), 4.60 (2H, s), 4.83 (2H, d, $J=11.0$ Hz), 4.86 (2H, dd, $J_1=5.0$ Hz, $J_2=3.5$ Hz), 5.03 (2H, d, $J=3.5$ Hz), 6.00 (2H, br s), 6.50 (4H, d, $J=7.5$ Hz), 6.90–6.95 (4H, m), 6.98–7.10 (4H, m), 7.12–7.15 (4H, m), 7.18–7.31 (36H, m), 7.76 (1H, d, $J=8.0$ Hz), 7.81 (1H, d, $J=8.0$ Hz), 8.32 (2H, d, $J=4.5$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 35.2, 35.8 (CH_2), 37.9, 38.1 (CH), 68.0, 68.1, 68.6, 72.4, 73.5, 74.4, 74.6, 75.2, 75.6, 75.7 (CH_2), 77.6, 81.5, 81.7, 85.6, 85.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 110.3, 110.4, 119.2, 137.2, 137.5, 137.9, 138.0, 138.5 (C quat arom), 116.8, 122.4, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5, 129.7, 144.0 (C tert arom), 175.4, 175.5, 176.6, 176.7 (C=O).

4.1.42. 2,5-Dihydro-1-methyl-3-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo[2,3-*b*]pyridin-3-yl]-pyrrole-2,5-dione 16a. To a solution of **15a** (420 mg, 0.56 mmol) in dioxane (20 mL) was slowly added a solution of DDQ (227 mg, 0.98 mmol) in dioxane (20 mL). The mixture was stirred for 48 h at room temperature. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 8:2) to give **16a** (270 mg, 0.360 mmol, 61% yield) as a yellow oil.

IR (NaCl film) $\nu_{C=O}$ 1710, 1770 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 3.04 (3H, s, NCH_3), 3.63–3.75 (3H, m), 3.79 (1H, t, $J=9.5$ Hz), 3.87–3.98 (2H, m), 3.91 (1H, d, $J=11.0$ Hz), 4.41 (1H, d, $J=10.5$ Hz), 4.44 (1H, d, $J=12.0$ Hz), 4.52 (1H, d, $J=12.0$ Hz), 4.59 (1H, d, $J=10.5$ Hz), 4.83 (1H, d, $J=11.0$ Hz), 4.87 (2H, s), 6.02 (1H, d, $J=8.0$ Hz, $H_{1'}$), 6.49 (2H, d, $J=7.5$ Hz), 6.55 (1H, s), 6.87 (2H, t, $J=7.5$ Hz), 6.96 (1H, t, $J=7.5$ Hz), 7.12–7.30 (16H, m), 7.99 (1H, dd, $J_1=8.0$ Hz, $J_2=1.0$ Hz), 8.38 (1H, dd, $J_1=5.0$ Hz, $J_2=1.0$ Hz), 8.44 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$): 23.8 (NCH_3), 68.6, 73.5, 74.9, 75.3, 75.7 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 77.7, 78.0, 81.6, 82.1, 85.8 (CH_2 of OBn, $C_{6'}$), 105.7, 119.0, 136.9, 137.9, 138.0, 138.4, 138.6, 148.5 (C quat arom), 116.8, 118.3, 127.5–128.6, 144.7 (C tert arom), 171.2, 171.8 (C=O).

4.1.43. 1-Benzyloxymethyl-2,5-dihydro-3-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-pyrrolo[2,3-*b*]-pyridin-3-yl]-pyrrole-2,5-dione 16b. To a solution of **15b** (420 mg, 0.490 mmol) in dioxane (20 mL) was slowly added a solution of DDQ (227 mg, 0.98 mmol) in dioxane (20 mL). The mixture was stirred for 48 h at room temperature. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 8:2) to give **16b** (270 mg, 0.315 mmol, 64% yield) as a yellow oil.

IR (NaCl film) $\nu_{C=O}$ 1710, 1770 cm^{-1}.

Mass (ESI+) $[M+Na]^+$ 878, $[M+K]^+$ 894.

^{1}H NMR (400 MHz, $CDCl_3$): 3.76–3.95 (4H, m), 3.98–4.08 (2H, m), 4.04 (1H, d, $J=11.0$ Hz), 4.53 (1H, d, $J=11.0$ Hz), 4.56 (1H, d, $J=11.0$ Hz), 4.64 (1H, d, $J=12.0$ Hz), 4.71 (1H, d, $J=10.0$ Hz), 4.72 (2H, s), 4.95 (1H, d, $J=11.0$ Hz), 5.00 (2H, s), 5.17 (2H, s), 6.15 (1H, d, $J=7.0$ Hz, $H_{1'}$), 6.60 (2H, d, $J=7.5$ Hz), 6.69 (1H, s), 6.97 (2H, t, $J=7.5$ Hz), 7.06 (1H, t, $J=7.5$ Hz), 7.23–7.46 (21H, m), 8.08 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 8.49 (1H, dd, $J_1=5.0$ Hz, $J_2=1.0$ Hz), 8.55 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$): 66.7, 68.6, 71.5, 73.5, 74.8, 75.3, 75.7 (CH_2), 77.7, 78.0, 81.5, 82.0, 85.8 ($C_{1'}$, $C_{2'}$, $C_{3'}$,

$C_{4'}$, $C_{5'}$), 116.9, 118.4, 126.5–128.6, 130.5, 144.8 (C tert arom), 105.4, 118.9, 136.9, 137.5, 137.9 (2C), 128.4, 138.6, 148.5 (C quat arom), 170.8, 171.2 (C=O).

4.1.44. 2-Methyl-7-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-1,3,4,6-tetrahydro-5*H*-pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 18a. A mixture of **16a** (605 mg, 0.790 mmol) and maleimide (384 mg, 3.95 mmol) in toluene (12 mL) was refluxed for 14 h. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 8:2 to 7:3) to give the mixture of isomers **17a** (277 mg, 0.327 mmol, 41% yield) as a pale yellow solid. To a solution of **17a** (277 mg, 0.327 mmol) in $CHCl_3$ (13 mL) was added MnO_2 (491 mg, 5.65 mmol). The mixture was refluxed for 24 h. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc 7:3) to give **18a** (168 mg, 0.199 mmol, 61% yield) as a pale yellow solid.

Mp 68–70 °C.

IR (KBr) $\nu_{C=O}$ 1710, 1720, 1735, 1780 cm^{-1}, ν_{NH} 3280 cm^{-1}.

Mass (ESI+) $[M+Na]^+$ 865.

^1H NMR (400 MHz, $CDCl_3$): 3.17 (3H, s), 3.72–3.80 (2H, m), 3.81 (1H, d, $J=9.5$ Hz), 3.85 (1H, d, $J=8.0$ Hz), 3.93 (1H, t, $J=9.0$ Hz), 4.12 (1H, m), 4.43 (1H, d, $J=12.0$ Hz), 4.47 (1H, d, $J=12.0$ Hz), 4.60 (2H, d, $J=12.0$ Hz), 4.85–4.95 (3H, m), 5.43 (1H, t, $J=9.0$ Hz), 6.26 (2H, d, $J=7.5$ Hz), 6.60 (2H, t, $J=7.5$ Hz), 6.71 (1H, t, $J=7.5$ Hz), 7.00–7.30 (16H, m), 7.34 (1H, d, $J=9.0$ Hz), 8.54 (1H, dd, $J_1=5.0$ Hz, $J_2=1.5$ Hz), 9.20 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz), 9.34 (1H, s,NH).

^{13}C NMR (100 MHz, $CDCl_3$): 24.5 (CH_3), 69.1, 73.1, 74.4, 75.0, 75.2, 75.9 (CH_2), 59.1, 69.3, 76.8, 78.1, 78.5 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 86.3, 87.0, 119.0, 126.9–129.5, 135.2, 150.4 (C tert arom), 114.5, 118.3, 119.8, 123.7, 131.0, 137.0, 137.6, 137.8, 138.0, 138.4, 140.2, 154.1 (C quat arom), 163.4, 164.1, 166.4, 167.1 (C=O).

4.1.45. 2-Benzyloxymethyl-7-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-yl)-1,3,4,6-tetrahydro-5*H*-pyridino-[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 18b. A mixture of **16b** (100 mg, 0.117 mmol) and maleimide (56.6 mg, 0.584 mmol) in toluene (2 mL) was refluxed for 14 h. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane/EtOAc from 8:2 to 7:3) to give the mixture of isomers **17b** (95 mg, 0.100 mmol, 85% yield) as a pale yellow solid. To a solution of **17b** (192 mg, 0.202 mmol) in $CHCl_3$ (9 mL) was added MnO_2 (352 mg, 4.06 mmol). The mixture was refluxed for 24 h. The solvent was removed and the residue was purified by flash chromatography (eluent cyclohexane:EtOAc 7:3) to give **18b** (166 mg, 0.174 mmol, 86% yield) as a pale yellow solid.

Mp 59–61 °C. IR (KBr) $\nu_{C=O}$ 1725, 1770, 1790 cm^{-1}, ν_{NH} 3200–3300 cm^{-1}.

Masse (ESI+) $[M+H]^+$ 949.

^1H NMR (400 MHz, $CDCl_3$): 3.84 (1H, d, $J=11.0$ Hz, $H_{6'}$), 3.92 (1H, dd, $J_1=12.0$ Hz, $J_2=5.0$ Hz, $H_{6'}$), 3.95 (1H, d, $J=12.0$ Hz), 4.01–4.05 (2H, m, $H_{3'}+H_{4'}$), 4.17 (1H, m, $H_{5'}$), 4.51 (1H, d, $J=12.0$ Hz), 4.59 (1H, d, $J=12.0$ Hz), 4.71 (2H, d, $J=12.0$ Hz), 4.75 (2H, s), 4.97 (1H, d, $J=11.0$ Hz), 4.99 (1H, d, $J=11.0$ Hz), 5.02 (1H, d, $J=11.0$ Hz), 5.34 (2H, s), 5.50 (1H, m, $H_{2'}$), 6.38 (2H, d, $J=7.5$ Hz), 6.60–6.75 (2H, m), 6.83 (1H, t, $J=7.5$ Hz), 7.15–7.50 (22H, m), 8.65 (1H, dd, $J_1=5.0$ Hz, $J_2=1.5$ Hz), 8.82 (1H, s, NH), 9.37 (1H, dd, $J_1=8.0$ Hz, $J_2=1.5$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 67.4, 68.9, 72.1, 73.2, 74.4, 75.2, 75.9 (CH_2), 77.2, 78.1, 78.2, 86.4, 87.0 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 119.2, 126.9, 127.1, 127.4–128.5, 135.3, 150.5 (C tert arom), 114.5, 119.0, 119.8, 124.2, 130.9, 137.3, 137.8, 138.0, 138.1, 138.5, 140.5, 154.1 (C quat arom), 163.5, 164.0, 166.2, 166.9 (C=O).

4.1.46. 2-Methyl-7-(β-D-glucopyranos-1-yl)-1,3,4,6-tetrahydro-5*H*-pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 19a. To a solution of **18a** (168 mg, 0.199 mmol) in CH_2Cl_2 (6 mL) was added during 48 h a solution of dimethyldioxirane (0.8 1.0 M, 56 mL). After evaporation, EtOAc was added. After filtration, the solid residue was washed with EtOAc, then with CH_2Cl_2 and finally with acetone to give **19a** (57 mg, 0.118 mmol, 59% yield) as a yellow solid.

Mp > 300 °C. IR (KBr) $\nu_{C=O}$ 1700, 1710, 1720, 1770 cm^{-1}, $\nu_{NH,\ OH}$ 3000–3660 cm^{-1}.

HRMS (FAB+) $[M+Na]^+$ calcd for $C_{22}H_{18}N_4O_9Na$ 505.0971, found 505.0981.

^1H NMR (400 MHz, DMSO-d_6): 3.19 (3H, s, NCH_3), 3.30–3.39 (2H, m), 3.51 (1H, m), 3.66–3.82 (2H, m), 4.56 (1H, pt, $J=5.5$ Hz), 5.01 (1H, d, $J=5.5$ Hz, OH), 5.08–5.17 (2H, m, 2OH), 5.19 (1H, d, $J=4.0$ Hz, OH), 7.27 (1H, d, $J=9.0$ Hz, $H_{1'}$), 7.64 (1H, m), 8.82 (1H, d, $J=3.5$ Hz), 9.48 (1H, d, $J=7.5$ Hz), 11.93 (1H, s).

^{13}C NMR (100 MHz, DMSO-d_6): 24.2 (CH_3), 61.2 ($C_{6'}$), 68.8, 70.3, 78.1, 79.4, 87.2 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 118.8, 134.1, 150.1 (C tert arom), 113.9, 120.3, 122.3 (2C), 128.5, 131.8, 140.1, 153.7 (C quat arom), 164.4, 165.2, 167.4, 167.8 (C=O).

4.1.47. 2-Hydroxymethyl-7-(β-D-glucopyranos-1-yl)-1,3,4,6-tetrahydro-5*H*-pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 19b. To a solution of **18b** (20 mg, 0.021 mmol) in CH_2Cl_2 (1.5 mL) was added during 72 h a solution of dimethyldioxirane (0.8–1.0 M, 13 mL). After evaporation, EtOAc was added. After filtration, the solid residue was washed with EtOAc, then with CH_2Cl_2 and finally with acetone to give **19b** (8 mg, 0.016 mmol, 76% yield) as a yellow solid.

Mp > 250 °C (decomposition).

HRMS (FAB+) $[M+Na]^+$ calcd for $C_{22}H_{18}N_4O_{10}Na$ 521.0921, found 521.0938.

IR (KBr) $\nu_{C=O}$ 1710, 1720, 1760, 1780 cm^{-1}, $\nu_{NH,\ OH}$ 2900–3600 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): 3.34–3.45 (2H, m), 3.52 (1H, m), 3.71 (1H, m), 3.77 (1H, m), 4.55 (1H, t, J=5.5 Hz, OH), 5.01 (1H, d, J=5.5 Hz, $H_{2'}$), 5.10–5.16 (4H, m, CH_2OH +2OH), 5.18 (1H, d, J=4.0 Hz, OH), 6.55 (1H, t, J=7.5 Hz), 7.29 (1H, d, J=8.5 Hz, $H_{1'}$), 7.65 (1H, dd, J_1= 7.0 Hz, J_2=5.0 Hz), 8.83 (1H, d, J=3.0 Hz), 9.50 (1H, d, J=8.0 Hz), 11.94 (1H, s).

^{13}C NMR (100 MHz, DMSO-d_6): 60.6, 61.2 ($C_{6'}$, CH_2OH), 68.8, 70.3, 78.1, 79.5, 87.2 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 118.8, 134.1, 150.2 (C tert arom), 113.9, 119.5, 120.0, 122.6, 129.0, 131.3, 140.2, 153.7 (C quat arom), 163.7, 165.1, 166.9, 167.7 (C=O).

4.1.48. 7-(β-D-Glucopyranos-1-yl)-1,3,4,6-tetrahydro-5*H*-pyridino[2,3-*b*]dipyrrolo[3,4-*e*:3,4-*g*]indole-1,3,4,6-tetraone 20. A solution of **19b** (32 mg, 0.064 mmol) in TFA (2.5 mL) was refluxed for 3 days. After evaporation, the residue was purified by flash chromatography (eluent EtOAc 100%) to give a solid to which was added EtOAc. The precipitate was filtered off washed with EtOAc, then with CH_2Cl_2 and finally with Et_2O to give **20** (13 mg, 0.028 mmol, 43% yield) as a yellow solid.

Mp>260 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1720, 1740, 1755, 1780 cm^{-1}, $\nu_{NH,\ OH}$ 3100–3600 cm^{-1}.

HRMS (FAB+) $[M+Na]^+$ calcd for $C_{21}H_{16}N_4O_9Na$ 491.0815, found 491.0818.

^1H NMR (400 MHz, DMSO-d_6): 3.32–3.48 (2H, m), 3.51 (1H, m), 3.67–3.80 (2H, m), 4.55 (1H, t, J=6.0 Hz, $OH_{6'}$), 4.99 (1H, d, J=5.5 Hz), 5.13 (1H, m, $H_{2'}$), 5.12 (1H, d, J= 4.5 Hz, OH), 5.18 (1H, d, J=4.5 Hz, OH), 7.28 (1H, d, J= 9.0 Hz, $H_{1'}$), 7.62 (1H, dd, J_1=8.0 Hz, J_2=5.0 Hz), 8.81 (1H, dd, J_1=4.5 Hz, J_2=1.5 Hz), 9.47 (1H, dd, J_1=8.0 Hz, J_2=1.5 Hz), 11.79 (1H, s, NH), 11.80 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 61.2 ($C_{6'}$), 68.8, 70.3, 78.1, 79.4, 87.2 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$), 118.7, 134.3, 150.0 (C tert arom), 113.9, 119.2, 121.3, 122.4, 128.7, 132.7, 140.1, 153.7 (C quat arom), 165.3, 165.7, 167.9, 168.7 (C=O).

References and notes

1. Rodrigues Pereira, E.; Belin, L.; Sancelme, M.; Prudhomme, M.; Ollier, M.; Rapp, M.; Sevère, D.; Riou, J.-F.; Fabbro, D.; Meyer, T. *J. Med. Chem.* **1996**, *39*, 4471–4477.
2. Prudhomme, M. *Curr. Pharm. Des.* **1997**, *3*, 265–290.
3. Zhao, B.; Bower, M. J.; McDevitt, P. J.; Zhao, H.; Davis, S. T.; Johanson, K. O.; Green, S. M.; Concha, N. O.; Zhou, B.-B.S. *J. Biol. Chem.* **2002**, *277*, 46609–46615.
4. Berlinck, R. G. S.; Britton, R.; Piers, E.; Lim, L.; Roberge, M.; Moreira da Rocha, R.; Andersen, R. J. *J. Org. Chem.* **1998**, *63*, 9850–9856.
5. Roberge, M.; Berlinck, R. G. S.; Xu, L.; Anderson, H. J.; Lim, L. Y.; Curman, D.; Stringer, C. M.; Friend, S. H.; Davies, P.; Vincent, I.; Haggarty, S. J.; Kelly, M. T.; Britton, R.; Piers, E.; Andersen, R. J. *Cancer Res.* **1998**, *58*, 5701–5706.
6. Jiang, X.; Zhao, B.; Britton, R.; Lim, L. Y.; Leong, D.; Sanghera, J. S.; Zhou, B.-B.S.; Piers, E.; Andersen, R. J.; Roberge, M. *Mol. Cancer Ther.* **2004**, *3*, 1221–1227.
7. Piers, E.; Britton, R.; Andersen *J. Org. Chem.* **2000**, *65*, 530–535.
8. Yoshida, T.; Nishiyachi, M.; Nakashima, N.; Murase, M.; Kotani, E. *Chem. Pharm. Bull.* **2002**, *50*, 872–876.
9. Yoshida, T.; Nishiyachi, M.; Nakashima, N.; Murase, M.; Kotani, E. *Chem. Pharm. Bull.* **2003**, *51*, 209–214.
10. Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, *44*, 3927–3930.
11. Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, *44*, 4607–4611.
12. Camargo, A. J.; Oliveira, J. H. H. L.; Trsic, M.; Berlinck, R. S. G. *J. Mol. Struct.* **2001**, *559*, 67–77.
13. Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, *44*, 3935–3937.
14. Desarbre, E.; Coudret, S.; Meheust, C.; Mérour, J. Y. *Tetrahedron* **1997**, *53*, 3637–3648.
15. Marminon, C.; Pierré, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Joubert, A.; Bailly, C.; Renard, P.; Hickman, J.; Prudhomme, M. *J. Med. Chem.* **2003**, *46*, 609–622.
16. Marminon, C.; Pierré, A.; Pfeiffer, B.; Pérez, V.; Léonce, S.; Renard, P.; Prudhomme, M. *Bioorg. Med. Chem.* **2003**, *11*, 679–687.
17. Bergman, J.; Janosik, T.; Koch, E.; Pelcman, B. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2615–2621.
18. Bergman, J.; Desarbre, E.; Koch, E. *Tetrahedron* **1999**, *55*, 2363–2370.
19. Zembower, D. E.; Zhang, H.; Lineswala, J. P.; Kuffel, M. J.; Aytes, S. A.; Ames, M. M. *Bioorg. Med. Chem.* **1999**, *9*, 145–150.
20. Ohkubo, M.; Nishimura, T.; Jona, H.; Honma, T.; Ito, S.; Morishima, H. *Tetrahedron* **1997**, *53*, 5937–5950.
21. DeFrees, S. A.; Reddy, K. S.; Cassady, J. M. *Syn. Commun.* **1988**, *18*, 213–220.
22. Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249–282.
23. Battersby, A. R.; Westwood, S. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1679–1687.
24. Gottstein, W. J.; Haynes, U. J.; McGregor, D. N. *J. Med. Chem.* **1985**, *28*, 518–522.
25. Terpin, A.; Winklhofer, C.; Schumann, S.; Steiglich, W. *Tetrahedron* **1998**, *54*, 1745–1752.
26. Messaoudi, S.; Anizon, F.; Pfeiffer, B.; Golsteyn, R.; Prudhomme, M. *Tetrahedron Lett.* **2004**, *45*, 4643–4647.
27. Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761–3765.
28. Marples, B. A.; Muxworthy, J. P.; Baggaley, K. H. *Synlett* **1992**, 646.
29. Csuk, R.; Dörr, P. *Tetrahedron* **1994**, *50*, 9983–9988.