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# Synthesis and biological evaluation of 7-azaindolocarbazoles

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**Abstract**—In the course of a program aimed at designing antitumor agents containing an indolocarbazole framework, an efficient synthetic scheme based on the use of 3,4-dibromo-*N*-methylmaleimide and 7-azaindole has been developed to elaborate a series of mono- and di-aza derivatives of arcyriaflavin. The procedure was further exploited to introduce a hydroxyl group at different positions on the indole moiety of the non-symmetrical compounds. The DNA binding capacity and cytotoxic potential of these 7-azaindolocarbazole derivatives was evaluated. © 2002 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Indolocarbazoles represent an important family of anti-cancer agents targeting certain kinases (e.g. staurosporine) or topoisomerase **I** (e.g. rebeccamycin).[1]

Numerous efforts have been undertaken to modify the heterocyclic indolocarbazole structure to obtain analogues with improved pharmacological profiles (Fig. 1).[1]

For instance, the homologation of the central benzene ring of the indolocarbazole chromophore gave the 7-membered ring characteristic of the homoarcyriaflavin derivatives.[2] Similarly, the introduction of another (hetero)aromatic moiety leads to the synthesis of gratulatimide **II** or isogranulatimide **III** and related derivatives (Fig. 2).[3,4]

In a recent work, the bioisostery indole/indene was exploited to generate new carbazoles by a solid phase synthesis.[5] In the same vein, we decided to use the indole/naphthalene bioisostery and the synthesis of naphtho[3,4-*c*]carbazole **IV** was recently described.[6] The heterocyclic skeleton could be modified by deleting one of the two indolic moiety.[7]

The huge synthetic efforts developed in this field have lead to the design of a large variety of structural analogues but there are still many under-exploited routes. The most convenient syntheses of symmetrical or non-symmetrical indolocarbazoles generally rely on the use of indolyl

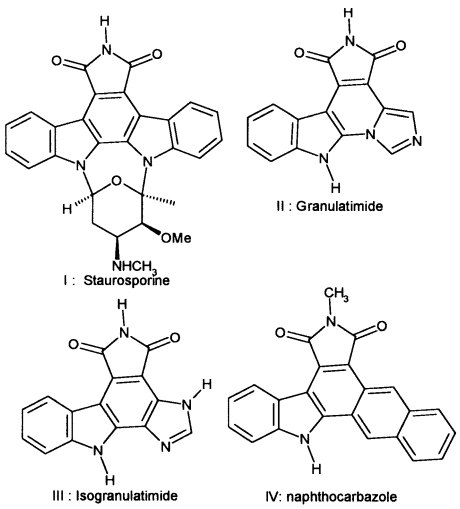


**Figure 1.** Selected examples of carbazoles.

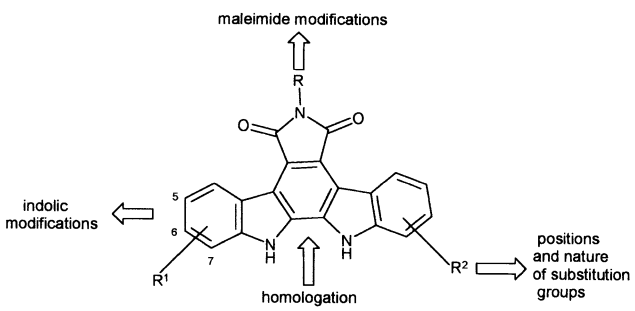


**Figure 2.** Structural modifications on carbazoles.

*Keywords*: indolocarbazole; 7-azaindole; synthesis.

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Grignard reagents with maleimide derivatives. Then a cyclization between the two indolic carbon atoms provides the required derivatives.[8–10] Direct formation of the maleimide framework through reaction of indole-3-acetamidate[11] or by oxidative coupling of indolyl acetate dianion have also been used.[12–13] Generation of the second indole moiety via nitrene insertion has been reported and the use of 2,2-bisindole and diazolactam[14] or dimethylacetylene carboxylate[15] provided other alternative approaches. Palladium cross-coupling was scarcely described but Suzuki, Stille and intramolecular Heck reactions proved quite efficient.[16,17] Various other synthetic accesses to modify the indolocarbazole skeleton have been described.[18]

In the course of a program aimed at elaborating new indolocarbazole-based antitumor drugs targeting DNA–topoisomerase **I** complexes, we present here an original route for the synthesis of novel 7-azaindolocarbazoles. The important role of hydroxyl groups on the indolocarbazole chromophore for efficient inhibition of topoisomerase **I**[19,20] prompted us to synthesize different hydroxylated aza-indolocarbazoles and to examine their DNA binding and topoisomerase **I** inhibitory activities.

## 2. Results and discussion

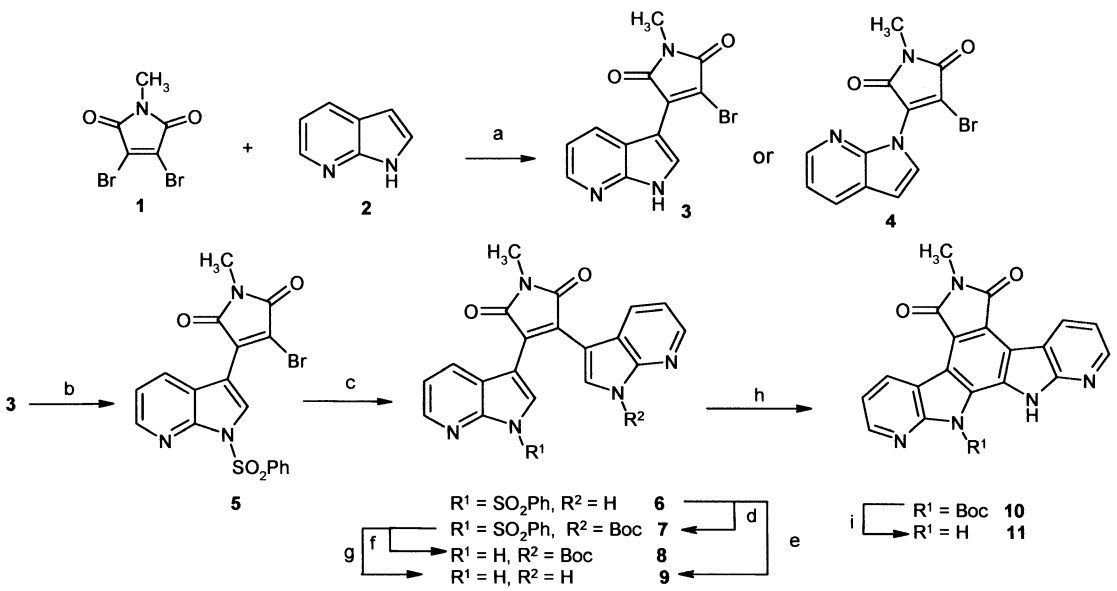
In this report, we present the synthesis of symmetrical compounds obtained in seven steps from the 3,4-dibromo-*N*-methylmaleimide,[21] **1** whereas non-symmetrical compounds were prepared in five steps from the same easily prepared starting compound **1**.

### 2.1. Chemistry

In a previous brief communication, we described an access to two 7-azaindolic aglycones.[22] Symmetrical compounds was also obtained from the 3,4-dibromo-*N*-methylmaleimide **1** (Scheme 1). Thus the condensation of the Grignard reagent of the 7-azaindole **2** (2 equiv.) in a mixture of toluene and $CH_2Cl_2$ 2/1 at 50°C for 24 h with 2,3-dibromo-*N*-methylmaleimide **1** afforded only the mono C3-alkylated compound **3** in 64% yield. The use of THF or toluene as a solvent and LiHMDS as a base afforded the *N*-alkylated compound **4**. The regioselectivity was both base- and solvent-dependent.

**2.1.1. Synthesis of symmetrical compounds.** The protection of the indolic nitrogen atom of **3** by a benzenesulfonyl group was carried out with benzenesulfonyl chloride in the presence of NaH in a mixture of THF and DMF 2/1 for 2 h to give **5** in 74% yield. Introduction of a second 7-azaindole moiety was realized by condensing the lithium salt of **2** (obtained by treating a toluene solution of **2** (2 equiv.) with LiHMDS (3 equiv.)) and compound **5** in toluene at room temperature. The desired compound **6** was thus obtained in 64% yield. The steric hindrance around the bromo atom favored the C3-alkylation of the incoming 7-azaindole lithium salt and the *N*-alkylation was sterically disfavored. Increasing the amount of 7-azaindole **2** to 4 equiv. shortened the reaction time to 6 h to provide a similar yield without formation of the *N*-alkylated compound.

Numerous attempts to perform the final cyclization step were unsuccessful using compound **6** as a starting material. Alternatively, *t*-Boc protection of **6** was carried out in THF at 30°C for 1 h using a catalytic amount of 4-DMAP to afford the fully protected compound **7** in 92% yield. Recently, we described a selective method to remove *t*-Boc groups using fluoride anion.[23] The same reagent was also reported to remove *N*-indolic benzenesulfonic group[24] and a similar behavior of $F^-$ has been reported in the course of the synthesis of 2-substituted indole. An incomplete lacking was briefly reported.[25] We have shown later that this




**Scheme 1.** *Conditions*: (a) (i) compound **2** (2 equiv.), EtMgBr (2.05 equiv.), toluene/$CH_2Cl_2$ 2/1, 50°C, 24 h, 64% (**3**); (ii) compound **2** (1 equiv.), LiHMDS (2.2 equiv.), THF, rt, 3 h 25% (**4**); (b) NaH (1.6 equiv.), $PhSO_2Cl$ (1.4 equiv.), THF/DMF 9/1, rt, 4 h, 74%; (c) compound **2** (2 equiv.), LiHMDS (3 equiv.), toluene, rt, 12 h, 64%; (d) $Boc_2O$ (2 equiv.), 4-DMAP (1 equiv.), THF, 30°C, 92%; (e) $Bu_4NF$ (2 equiv.), THF, rt, 5 h, 83%; (f) $Bu_4NF$ (1.2 equiv.), THF, rt, 2 h, 80%; (g) $Bu_4NF$ (10 equiv.), THF, rflx., 2 h, quant.; (h) compound **8**, $h\nu$, 500 W UV Lamp TQ-718 DEMA, $I_2$, benzene, 3.5 h, 74%; (i) formic acid, rt, 2 h, quant.

**Table 1**. Attempts of cyclization of compounds **6**, **8** and **9**

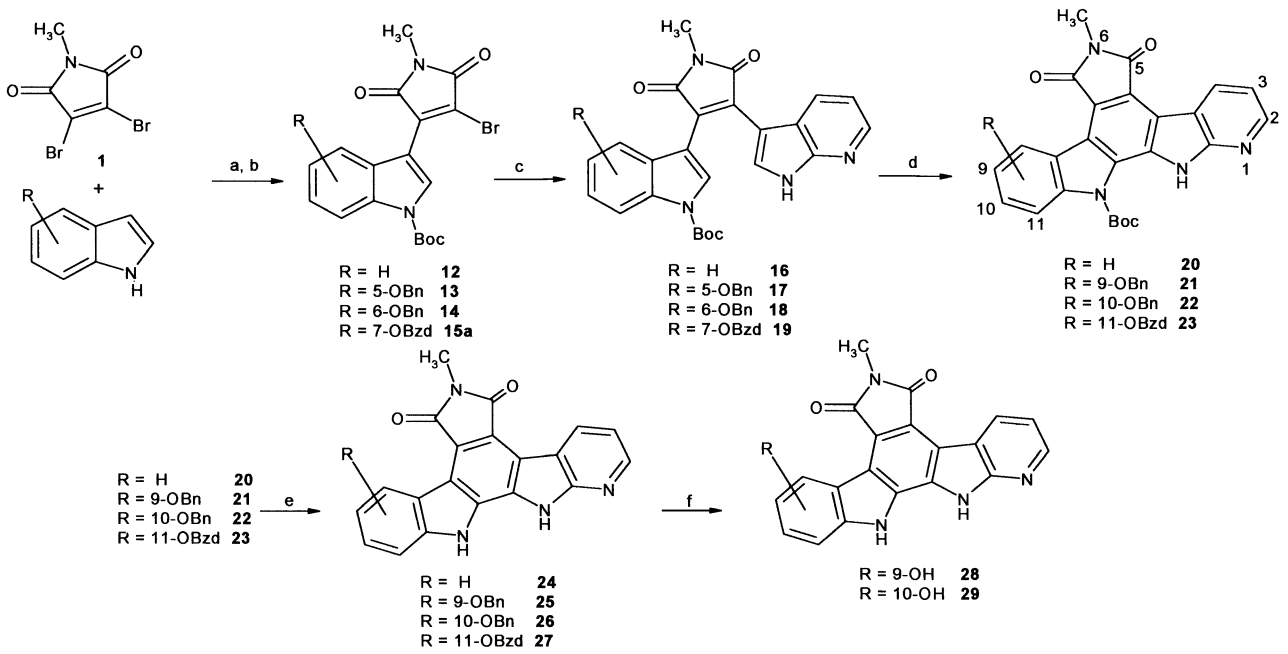
| Entry | Reagent | Conditions | Time (h) | Yield |
|---|---|---|---|---|
| 1 | **6** | DDQ (10 equiv.), toluene, rflx. | 12 | SM |
| 2 | **6** | DDQ (10 equiv.), APTS cat., benzene, rflx. | 24 | SM |
| 3 | **6** | $Pd(CF_3CO_2)_2$, 10% DMF, 100°C | 12 | D |
| 4 | **6** | *hν*, 500 W, $I_2$, benzene | 1.5 | D |
| 5 | **8** | *hν*, 500 W, $I_2$, benzene | 3.5 | **10** (74%) |
| 6 | **8** | *hν*, 500 W, $I_2$, benzene | 1.5 | **10** (60%) |
| 7 | **8** | *hν*, 500 W, $I_2$, $CH_3CN$ | 1.5 | D |
| 8 | **9** | *hν*, 500 W, $I_2$, $CH_3CN$ | 1.5 | D |
| 9 | **9** | $Pd(CF_3CO_2)_2$ 10% DMF, 100°C | 12 | D |
| 10 | **9** | DDQ (10 equiv.), APTS cat., toluene, rflx. | 12 | SM |

D: decomposition; SM: starting material recovered.

protective group could be removed in the presence of an *N*-indolic *t*-Boc protection. This method applied to compound **7** ($Bu_4NF$, 1 M in THF, 1.2 equiv., rt) afforded compound **8** in 80% yield. If the reaction was performed on **7** with $Bu_4NF$ (10 equiv.) in refluxing THF, the bis-deprotected compound **9** was obtained quantitatively (also prepared from **6** using $Bu_4NF$ (2 equiv.) at rt in 83% yield). These examples illustrate the high lability of *N*-indolic or *N*-aza indolic *t*-Boc protective groups under basic conditions.

The next step of the synthesis concern the intramolecular C–C cross-coupling reaction. Palladium coupling pathways failed using **6**–**8** as starting materials.[26–29] Compounds **6** and **7** which both bear a benzenesulfonyl group and the fully deprotected bis-7-azaindolic compound **9** did not afford any cyclized products. According to the described procedures,[26–29] introduction of palladium derivatives in the reaction mixture induces the complete precipitation of organic compounds with the palladium (immediately with compound **9**, after some hours with *t*-Boc derivative **8** which generated **9** in situ by cleavage of the *t*-Boc group). We postulate that the organic moiety was complexed by the palladium via the nitrogen atoms. Interestingly, the photocyclization of **8** using a 500 W UV-lamp DEMA in benzene at rt for 3.5 h afforded compound **10** in 74% yield. Increasing the reaction time does not increase the yield of this reaction. The replacement of benzene with less toxic solvents such as $CH_3CN$ and toluene lead to a decomposition of the starting material. The choice of the protective group and the solvent seems to be crucial factors in this photo-irradiation step. In our hands, palladium cyclization using compound **8** failed. All these experimental conditions and their respective efficiency are summarized in Table 1.

The final *N*-*t*-Boc deprotection of **10** could be realized either in the presence of an excess of $Bu_4NF$ in refluxing THF for 2 h, in formic acid at rt (2 h) or by using a solution of $MeNH_2$ (2 M in MeOH) for 2 h at rt. Compound **11** was obtained in 84% from the first deprotection method or in a quantitative yield for the two last reactions. The lower yield observed with basic fluorinated anion was notably due to the presence of the *N*-methyl maleimide group, which exhibited a sensibility to basic conditions. A quantitative reaction without degradation was initially observed using $Bu_4NF$ and by-products appeared only after aqueous treatment. With methylamine, no hydrolysis being necessary, the purifi-




**Scheme 2.** Synthesis of the non-symmetrical aglycones **24**, **28** and **29**: (a) and (b) see Ref. 28; (c) compound **3** (3 equiv.), LiHMDS (4 equiv.), toluene, rt, 30 min, 48–74%; (d) *hν*, 500 W UV Lamp TQ-718 DEMA, $I_2$, benzene, 50 min to 1 h 45 min, 75–88%; (e) and (f) see Table 1.

cation was carried out after elimination of the reagent and solvents under reduced pressure.

**2.1.2. Synthesis of non-symmetrical compounds.** Surprisingly, the synthesis of non-symmetrical compounds which possess only one 7-azaindolic unit was straightforward and was realized in five steps from 3,4-dibromo-*N*-methylmaleimide **1** and substituted indolic derivatives. 7-Benzhydryloxyindole and 6-benzyloxyindole were prepared according to the described procedures[30,31] with minor modifications. 7-Benzhydryloxyindole was condensed with lithio derivatives of **2** using the same procedure as described for compounds **12**–**14**[32] to afford compound **15** in 75% yield. *N*-Boc protection ($Boc_2O$/DMAP/$CH_3CN$) gave compound **15a** in 83% yield. The lithio 7-azaindole **2** lithium salt (3 equiv.) in toluene was reacted with compounds **12**–**14**, **15a** to afford solely the C-3 alkylated derivatives **16**–**19** in 53, 60, 48 and 74% yields, respectively (Scheme 2). This interesting feature confirms the hypothesis of a regioselective approach of the reactant as described for **6**.

Photocyclization of compounds **16**–**19** gave the desired products **20**–**23** in 75, 88, 75 and 77% yields, respectively. Results and yields for the following deprotection reactions leading to compounds **24**–**29** are summarized in Table 2.

The *t*-Boc removing was carried out using $Bu_4NF$ and the desired products **24**–**27** were isolated in good yields. Trifluoroacetic acid was also used to remove the *t*-Boc groups but all the attempts carried out on compounds **20**–**23** were unsuccessful. In addition, benzhydryl deprotection using catalytic hydrogenation of compound **27** failed.[31] This result suggests that the expected deprotected compound **30** is not stable. Degradation via the *ortho* quinone–imine system formed can be hypothesized. Final deprotection of *O*-benzyl groups on compounds **25**–**26** was carried out using $BBr_3$ to give compounds **28** and **29** in high yields.

**Table 2**. Cleavage of the protective groups

| Entry | Reagent | Conditions | Time (h) | Products |
|---|---|---|---|---|
| 1 | **20** | $Bu_4NF$ (10 equiv.), THF, rflx. | 1.5 | 24 (88%) |
| 2 | **21** | TFA (2 equiv.), $CH_2Cl_2$, rt | 1 | D |
| 3 | **21** | $Bu_4NF$ (10 equiv.), THF, rflx. | 2 | 25 (quant.) |
| 4 | **22** | TFA (2 equiv.), $CH_2Cl_2$, rt | 0.75 | D |
| 5 | **22** | $Bu_4NF$ (10 equiv.), THF, rflx. | 2 | 26 (82%) |
| 6 | **23** | TFA (2 equiv.), $CH_2Cl_2$, rt | 1.25 | D |
| 7 | **23** | $Bu_4NF$ (8 equiv.), THF, rflx. | 7.5 | 27 (quant.) |
| 8 | **25** | $BBr_3$ (6 equiv.), $CH_2Cl_2$, rt | 1.5 | 28 (quant.) |
| 9 | **26** | $BBr_3$ (6 equiv.), $CH_2Cl_2$, rt | 1.5 | 29 (85%) |
| 10 | **27** | $H_2$, Pd(C) 10%, acetone/MeOH 1/1 | 12 | SM |
| 11 | **27** | $H_2$, $Pd(OH)_2$, acetone/MeOH 1/1 | 12 | D |
| 12 | **27** | $BBr_3$ (6 equiv.), $CH_2Cl_2$, rt | 12 | D |

D: decomposition; SM: starting material recovered.

## 2.2. Biological study

**2.2.1. DNA interaction.** As shown in Fig. 3, addition of DNA to a solution of compound **11** induces a slight hypochromism in the 320 nm absorption band but no red shift. Similar effects were observed with **24** and **29**. In contrast, a 7 nm bathochromic effect is observed with compound **28**, owing to the perturbation of the azaindolocarbazole chromophore upon binding to DNA.

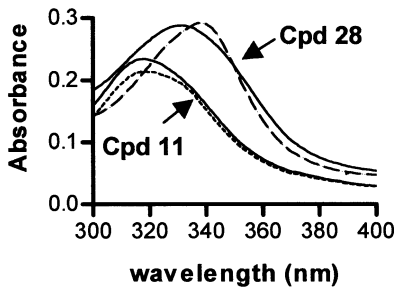



**Figure 3.** Absorption spectra of **11** and **28** (20 μM each) in the absence (solid line) and presence (dashed line) of 200 μM calf thymus DNA.

Melting temperature experiments provided further evidences that the 9-OH-substituted compound binds to more strongly to DNA than the other analogues. Compound **28** significantly stabilizes poly(dAT)$_2$ against thermal denaturation. A $\Delta T_m$ value ($T_m^{complex} - T_m^{DNA}$) of 6°C was observed at a drug/DNA ratio of 0.5, whereas the $\Delta T_m$ was limited to 1–2°C with **24**, **11** and **29**. Altogether, the absorption measurements indicate that compound **28** has significant interaction with DNA, suggesting that position 9 is the most favorable to introduce the OH group.

A topoisomerase **I**-mediated DNA unwinding assay[33] was used to evaluate the interaction of the drug with DNA (Fig. 4). Here again, **28** altered the reactivity of the enzyme more potently than the other analogues. The distribution of the topoisomers is modified in the presence of the 9-OH derivative **28**, whereas the 10-OH analogue **29** showed little effect, even at a much higher concentration. The hydroxy group introduced at position 9 is a positive element for DNA recognition.

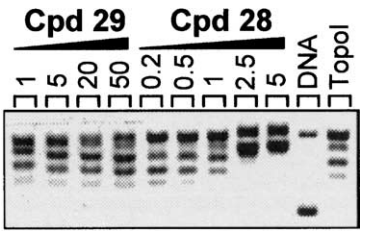



**Figure 4.** Effects of compounds **28** and **29** on the relaxation of supercoiled plasmid DNA by topoisomerase **I**.

**2.2.2. Cytotoxicity.** The murine L1210 leukemia cell line was used for a preliminary evaluation of the cytotoxic potential of the compounds using a conventional microculture tetrazolium assay.[35] The concentrations required to reduce cell growth by 50% ($IC_{50}$) were 14.5, 2.3, 4.5 and 9.6 μM for **24**, **11**, **29** and **28**, respectively. No correlation between DNA binding and cytotoxicity can be established at present but a more detailed biological evaluation is in progress.

## 3. Conclusion

An original procedure has been developed to synthesize

functionalized azaindolocarbazoles. The efficient synthetic routes reported here will be useful for the ongoing preparation of glycosylated compounds susceptible to target topoisomerase **I** and/or certain protein kinases, as in the rebeccamycin and staurosporine series.

## 4. Experimental

### 4.1. Chemistry

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker 250 instrument using $CDCl_3$ or DMSO-$d_6$. The chemical shifts are reported in ppm ($\delta$ scale) and all $J$ values are in Hz. Melting point are uncorrected. IR absorption were recorded on a Perkin Elmer PARAGON 1000 PC and values were reported in $cm^{-1}$. MS spectra (Ion Spray) were performed on a Perkin Elmer Sciex PI 300. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 $F_{254}$). Spots were visualized by UV light at 254 and 356 nm. Column chromatography were performed using silica gel 60 (0.063–0.200 mm, Merck).

**4.1.1. 3-Bromo-1-methyl-4-(1*H*-pyrrolo[2,3-*b* ]pyridin-3-yl)pyrrole-2,5-dione (3).** A solution EtMgBr (4.44 mL, 3 M in $Et_2O$) was added dropwise under argon to a well-stirred solution of 7-azaindole **2** (1.5 g, 12.71 mmol) in dry toluene (45 mL) at room temperature. After 1 h, a solution of compound **1** (1.70 g, 6.35 mmol) in toluene (40 mL) was slowly added to the mixture. After 15 min, freshly distilled $CH_2Cl_2$ (50 mL) was added and the reaction mixture was heated to 50°C for 24 h. Hydrolysis was performed by a saturated solution of $NH_4Cl$ till pH 7. After extraction with AcOEt (2×100 mL), the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Compound **3** was precipitated from methanol (20 mL), filtered, washed with methanol (10 mL) and dried under vacuum. Compound **3** was obtained as an orange solid (1.24 g, 64%). Mp 158°C dec. $R_f$ (petroleum ether/EtOAc 4/6): 0.13; IR (KBr, $cm^{-1}$); $\nu$ 3460, 2846, 1708, 1584, 1440, 1419, 1384; $^1$H NMR (DMSO-$d_6$) $\delta$: 3.04 (s, 3H, $NCH_3$), 7.23 (m, 1H), 8.21 (s, 1H), 8.33 (m, 2H), 12.72 (s, 1H); $^{13}$C NMR (DMSO-$d6$) $\delta$: 25.2 ($CH_3$), 103.4 (Cq), 115.4 (Cq), 117.5 (CH), 117.6 (Cq), 131.4 (CH), 131.8 (CH), 137.4 (Cq), 144.6 (CH), 149.3 (Cq), 167.0 (CO), 169.6 (CO); MS (IS) 306–308 $(M+H)^+$.

**4.1.2. 3-Bromo-1-methyl-4-(pyrrolo[2,3-*b* ]pyridin-1-yl)pyrrole-2,5-dione (4).** A solution of LiHMDS (14.5 mL, 1 M in THF) was added dropwise, under argon, to a stirred solution of 7-azaindole **2** (725 mg, 6.14 mmol) in dry THF (15 mL) at −20°C. After stirring for 1 h at −20°C, a solution of compound **1** (1.64 g, 6.14 mmol) in THF (15 mL) was added. Stirring was continued for 1 h at −20°C, then 2 h at room temperature. Hydrolysis was performed by a saturated solution of $NH_4Cl$ till pH 7. After extraction by AcOEt (2×100 mL), the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Compound **4** was precipitated as a yellow solid from methanol (20 mL), filtered, washed with MeOH (10 mL) and dried under vacuum (471 mg, 25%). Mp 178°C; IR (KBr, $cm^{-1}$) $\nu$ 3242, 1736, 1645, 1426, 1210, 992; $^1$H NMR ($CDCl_3$) $\delta$: 3.28 (s, 3H, $NCH_3$), 6.69 (d, 1H, $J$=3.75 Hz), 7.16 (m, 1H), 7.47 (d, 1H, $J$=3.75 Hz), 7.94 (dd, 1H, $J$=8.0, 1.5 Hz), 8.34 (dd, 1H, $J$=4.7, 1.2 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$: 26.2 ($CH_3$), 105.2 (CH), 118.3 (CH), 122.0 (2Cq), 127.8 (CH), 129.8 (CH), 135.2 (Cq), 144.1 (CH), 147.6 (Cq), 162.1 (CO), 165.6 (CO); MS (IS) 306–308 $(M+H)^+$.

**4.1.3. 3-(1-Benzenesulfonyl-1*H*-pyrrolo[2,3-*b* ]pyridin-3-yl)-4-bromo-1-methylpyrrole-2,5-dione (5).** A solution of compound **3** (1.0 g, 3.26 mmol) in a mixture of THF (15 mL) and DMF (5 mL) was added under argon to a suspension of NaH (210 mg, 60% in oil, 5.25 mmol) in THF (15 mL) at 0°C. After 1 h at this temperature, a solution of benzenesulfonyl chloride (0.83 ml, 4.52 mmol) in THF (10 mL) was added and the mixture was stirred for 4 h at rt. Ice (150 g) was slowly added and the organic layers were extracted with EtOAc (3×100 mL). The organic solvents were washed with brine (50 mL) and dried over $Na_2SO_4$. After filtration, the solvents were removed under reduced pressure. Compound **5** was obtained as a yellow solid (1.07 g, 74%). Mp 198°C; IR (KBr, $cm^{-1}$) $\nu$ 3144, 2928, 1777, 1272, 1203, 1180; $^1$H NMR ($CDCl_3$) $\delta$: 3.19 (s, 3H), 7.27–7.31 (m, 1H), 7.51–7.64 (m, 3H), 8.26–8.30 (m, 4H), 8.51 (s, 1H); $^{13}$C NMR ($CDCl_3$) $\delta$: 25.4 ($CH_3$), 107.6 (Cq), 119.9 (CH), 120.2 (Cq), 121.4 (Cq), 128.9 (2CH), 129.6 (2CH), 129.9 (Cq), 132.3 (CH), 135.0 (CH), 135.6 (Cq), 137.8 (CH), 146.3 (CH), 147.3 (Cq), 166.0 (CO), 168.8 (CO); MS (IS) 446–448 $(M+H)^+$.

**4.1.4. 3-(1-Benzenesulfonyl-1*H*-pyrrolo[2,3-*b* ]pyridin-3-yl)-1-methyl-4-(1*H*-pyrrolo[2,3-*b* ]pyridin-3-yl)pyrrole-2,5-dione (6).** A solution of LiHMDS (2.01 mL, 1 M in hexane) was added dropwise under argon to a well-stirred solution of 7-azaindole **2** (158 mg, 1.34 mmol) in dry toluene (10 mL) at −15°C. After stirring for 1 h, a solution of compound **5** (300 mg, 0.672 mmol) in toluene (15 mL) was slowly added at rt to the mixture. After 12 h, hydrolysis was performed by adding a saturated solution of $NH_4Cl$ till pH 7. After extraction with EtOAc (3×20 mL), the combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Compound **6** was purified by flash chromatography (petroleum ether/EtOAc 6/4) as a pale orange solid (207 mg, 64%). Mp 180°C dec.; IR (KBr, $cm^{-1}$) $\nu$ 3438, 3136, 1693, 1383, 1184; $^1$H NMR ($CDCl_3$) $\delta$: 3.21 (s, 3H, $NCH_3$), 6.63 (m, 1H), 6.87 (m, 1H), 7.08 (d, 1H, $J$=5 Hz), 7.31 (d, 1H, $J$=7.5 Hz), 7.50–7.62 (m, 3H), 8.16–8.24 (m, 5H), 8.35 (dd, 1H, $J$=4.75, 1.2 Hz), 11.52 (s, 1H, NH); $^{13}$C NMR ($CDCl_3$) $\delta$: 23.9 ($CH_3$), 104.1 (Cq), 108.6 (Cq), 116.3 (Cq), 117.5 (CH), 118.5 (CH), 120.3 (Cq), 123.4 (Cq), 127.7 (2CH), 128.7 (CH), 129.7 (2CH), 130.0 (CH), 130.1 (CH), 130.8 (CH), 133.9 (CH), 137.3 (Cq), 142.9 (CH), 145.1 (Cq), 146.3 (CH), 148.3 (Cq), 170.5 (CO), 170.7 (CO); MS (IS) 484 $(M+H)^+$.

**4.1.5. 3-[4-(1-Benzenesulfonyl-1*H*-pyrrolo[2,3-*b* ]pyridin-3-yl)-1-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl]-pyrrolo[2,3-*b* ]pyridine-1-carboxylic acid *tert*-butyl ester (7).** A solution containing compound **6** (0.26 g, 0.538 mmol), 4-dimethylaminopyridine (70 mg, 0.573 mmol) and $Boc_2O$ (0.30 g, 1.37 mmol) in THF (30 mL) was stirred under argon at 30°C for 4 h. The solvent was removed under reduced pressure and the crude

product was purified by flash chromatography (petroleum ether/EtOAc 4/6, 1% $NEt_3$). Compound **7** was obtained as a yellow solid (207 mg, 92%). Mp 132°C; IR (KBr, $cm^{-1}$) $\nu$ 2978, 2931, 1762, 1736, 1705, 1151; $^1H$ NMR (acetone-$d_6$) $\delta$: 1.71 (s, 9H, Boc), 3.20 (s, 3H, $NCH_3$), 6.69 (m, 1H), 7.04 (m, 1H), 7.14 (dd, 1H, $J$=8.1, 1.7 Hz), 7.31 (dd, 1H, $J$=8.0, 1.5 Hz), 7.72–7.83 (m, 3H), 8.24–8.35 (m, 6H); $^{13}C$ NMR (acetone-$d_6$) $\delta$: 24.1 ($CH_3$), 27.6 ($CH_3$), 84.8 (Cq), 104.0 (Cq), 107.5 (Cq), 109.3 (Cq), 118.7 (CH), 119.5 (CH), 120.4 (Cq), 121.0 (Cq), 127.4 (Cq), 128.1 (2CH), 128.5 (CH), 129.6 (CH), 129.8 (2CH), 130.7 (CH), 130.9 (CH), 135.2 (CH), 138.2 (Cq), 145.6 (CH), 147.0 (Cq), 147.9 (Cq), 169.4 (CO), 170.56 (CO); MS (IS) 584.5 $(M+H)^+$.

**4.1.6. 3-[1-Methyl-2,5-dioxo-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,5-dihydro-1*H*-pyrrol-3-yl]-pyrrolo[2,3-*b*]pyridine-1-carboxylic acid *tert*-butyl ester (8).** A solution of $Bu_4NF$ (0.493 mL, 1 M in THF, 0.493 mmol) was added to a solution of compound **7** (0.24 g, 0.411 mmol) in dry THF (5 mL) under argon at rt. After 2 h, water (20 mL) was added and extraction was performed with EtOAc (3×20 mL). The organic layer was dried over $Na_2SO_4$, filtered and the solvents were evaporated under reduced pressure. Flash chromatography (petroleum ether/EtOAc 4/6, 1% $NEt_3$ then petroleum ether/EtOAc 2/8, 1% $NEt_3$) afforded compound **8** as an orange solid (146 mg, 80%). Mp 164°C dec.; $R_f$ (petroleum ether/EtOAc 4/6): 0.34; IR (KBr, $cm^{-1}$) $\nu$ 3452, 1702, 1640, 1477, 1382; $^1H$ NMR (acetone-$d_6$) $\delta$: 1.68 (s, 9H, Boc), 3.14 (s, 3H, $NCH_3$), 6.80 (m, 1H), 6.86 (m, 1H), 7.26 (dd, 1H, $J$=8.1, 1.6 Hz), 7.35 (dd, 1H, $J$=8.0, 0.9 Hz), 8.14–8.22 (m, 3H), 8.39 (dd, 1H, $J$=5.0, 1.6 Hz); $^{13}C$ NMR (acetone-$d_6$) $\delta$: 12.75 ($CH_3$), 27.4 ($CH_3$), 84.5 (Cq), 104.1 (Cq), 107.45 (Cq), 116.1 (CH), 117.9 (CH), 120.2 (Cq), 123.5 (Cq), 128.2 (CH), 129.3 (CH), 129.7 (CH), 130.0 (CH), 130.1 (Cq), 142.5 (CH), 145.1 (CH), 146.7 (Cq), 147.2 (Cq), 148.1 (Cq), 147.0 (Cq), 170.6 (CO), 170.7 (CO); MS (IS) 444.5 $(M+H)^+$.

**4.1.7. 1-Methyl-3,4-bis-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-pyrrole-2,5-dione (9).** Using the same procedure as for **8**: compound **6** and 2 equiv. of a $Bu_4NF$ solution (1 M in THF) were heated in refluxing THF for 5 h. After addition of water, the organic products were extracted with $CH_2Cl_2$. The solvents were removed under reduced pressure, flash chromatographied (EtOAc) to afford compound **9** as an orange solid in 83% yield. Similarly, compound **7** gave **9** in quantitative yield after heating a 1 M THF solution of $Bu_4NF$ (10 equiv.) for 2 h. Mp 250°C dec.; IR (KBr, $cm^{-1}$) $\nu$ 3132, 3090, 3032, 2890, 1697; $^1H$ NMR (DMSO-$d_6$) $\delta$: 3.04 (s, 3H, $NCH_3$), 6.74 (m, 2H), 7.12 (d, 2H, $J$=8.2 Hz), 7.94 (s, 2H), 8.15 (d, 2H, $J$=5.0 Hz), 12.34 (s, 2H, 2NH); $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 24.30 ($CH_3$), 104.3 (2Cq), 116.2 (2CH), 177.8 (2Cq), 129.1 (2CH), 130.0 (2CH+2Cq), 143.6 (2CH), 148.7 (2Cq), 171.7 (2CO); MS (IS) 344 $(M+H)^+$.

**4.1.8. 6-Methyl-13*H*-pyrido[2,3-*b*]pyrrolo[3,4-*e*]pyrido[3′,2′:4,5]pyrrolo[3,2-*g*]indole-5,7-dione-12-carboxylic acid *tert*-butylester (10).** Compound **8** (150 mg, 0.225 mmol) and iodine (1.5 g, 5.9 mmol) were dissolved in benzene (500 mL). Irradiation was performed with a DEMA UV-lamp TQ-718 (500 W) for 3.5 h. The reaction mixture was washed with $Na_2S_2O_3$ (1 N) until complete reduction of iodine. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (petroleum ether/EtOAc 4/6, then pure EtOAc). The resulting compound **10** was washed with MeOH (10 mL) and was dried under vacuum to give a yellow solid (49 mg, 74%). Mp 212°C dec.; $R_f$ (petroleum ether/EtOAc 5/5): 0.53; IR (KBr, $cm^{-1}$) $\nu$ 3381, 2984, 2942, 1755, 1709, 1374, 772; $^1H$ NMR ($CDCl_3$) $\delta$: 1.85 (s, 9H, Boc), 3.31 (s, 3H, $NCH_3$), 7.37 (m, 1H), 7.45 (m, 1H), 8.64 (m, 2H), 9.37 (d, 1H, $J$=7.8), 9.49 (dd, 1H, $J$=8.1, 1.8 Hz), 11.38 (s, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 24.1 ($CH_3$), 28.6 ($CH_3$), 86.9 (Cq), 114.1 (Cq), 116.9 (2Cq), 117.4 (CH), 117.6 (Cq), 118.7 (Cq), 120.1 (CH), 123.5 (Cq), 125.6 (Cq), 129.2 (Cq), 133.7 (CH), 133.9 (CH), 148.5 (CH), 149.0 (CH), 151.1 (Cq), 151.6 (Cq), 151.7 (Cq), 168.9 (CO), 169.1 (CO); MS (IS) 442 $(M+H)^+$.

**4.1.9. 6-Methyl-12,13-dihydro-pyrido[2,3-*b*]pyrrolo[3,4-*e*]pyrido[3′,2′:4,5]pyrrolo[3,2-*g*]indole-5,7-dione (11).** A solution of compound **10** (25 mg, 0.192 mmol) in formic acid was stirred at rt for 2 h. The solution was diluted with THF (5 mL) and $Et_3N$ was slowly added till pH 8. The solvents were evaporated under reduced pressure and the crude solid washed by a solution of MeOH/water 1/1 (3×10 mL). After filtration, the solid was dried under vacuum to afford compound **11** as a pale yellow solid (19 mg, quant.). Mp 154°C dec.; $R_f$ (EtOAc): 0.24; IR (KBr, $cm^{-1}$) $\nu$ 3352, 2902, 2698, 1385; $^1H$ NMR (DMSO-$d_6$) $\delta$: 3.07 (s, 3H, $NCH_3$), 7.26–7.33 (m, 2H), 8.57 (d, 2H, $J$=5 Hz), 8.94 (d, 2H, $J$=7 Hz), 12.5 (s, 2H); $^{13}C$ NMR (DMSO-$d_6$, 80°C) 26.2 ($CH_3$), 91.3 (2Cq), 116.1 (2Cq), 116.6 (2CH), 123.5 (2Cq), 124.1 (2CH), 132.9 (2CH), 153.8 (2Cq), 162.2 (2Cq), 165.9 (2CO); MS (Maldi-Tof) 342 $(M+H)^+$. Anal. calcd for $C_{19}H_{11}N_5O_2$: C, 66.86; H, 3.25; N, 20.52. Found: C, 66.49; H, 3.39; N, 20.70.

**4.1.10. 3-(7-Benzhydryloxy-1*H*-indol-3-yl)-4-bromo-1-methylpyrrole-2,5-dione (15).** A solution of LiHMDS (5.58 mL, 1 M in hexane, 5.58 mmol) was added under argon to a solution of 7-benzhydryloxyindole (0.668 g, 2.23 mmol) in dry THF (25 mL) at rt. The mixture was stirred for 1 h and a solution of compound **1** (0.50 g, 1.86 mmol) in dry THF (15 mL) was added. After 2 h, hydrolysis was performed using $NH_4Cl$ till pH 7. The organic layers were extracted with EtOAc (3×75 mL), combined and evaporated under reduced pressure. Precipitation by addition of MeOH afforded compound **15** as a red solid (720 mg, 75%). Mp 205°C dec.; IR (KBr, $cm^{-1}$) $\nu$ 3344, 3038, 2930, 1698, 1587, 1433, 1247; $^1H$ NMR ($CDCl_3$) $\delta$: 3.14 (s, 3H, $NCH_3$), 6.38 (s, 1H), 6.65 (d, 1H, $J$=7.5 Hz), 7.01 (t, 1H, $J$=7.8 Hz), 7.30–7.44 (m, 10H), 7.61 (d, 1H, $J$=8.1 Hz), 9.49 (d, 1H, $J$=3.15 Hz), 9.09 (s, 1H, NH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 24.9 ($CH_3$), 82.5 (CH), 106.1 (Cq), 106.73 (CH), 115.2 (Cq), 115.9 (CH), 121.9 (CH), 126.0 (Cq), 127.2 (4CH), 127.6 (Cq), 128.2 (2CH), 128.8 (4CH), 129.2 (CH), 137.2 (Cq), 140.8 (2Cq), 144.9 (Cq), 166.9 (CO), 169.6 (CO); MS (IS) 486–488 $(M+H)^+$.

**4.1.11. 7-Benzhydryloxy-3-(4-bromo-1-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)indole-1-carboxylic acid *tert*-butyl ester (15a).** A solution of compound **15** (0.70 g, 1.43 mmol), 4-DMAP (13 mg, 0.107 mmol) and $Boc_2O$ (470 mg, 2.14 mmol) in dry THF (10 mL) was stirred at rt under argon for 18 h; the solvent was evaporated

under reduced pressure and methanol (3 mL) was added. The precipitate was filtered, washed with MeOH (3×2 mL) and dried under vacuum to give compound **15a** as an orange solid (702 mg, 83%). Mp 148°C; IR (KBr, $cm^{-1}$) $\nu$ 2927, 1761, 1715, 1228, 1148; $^1H$ NMR ($CDCl_3$) $\delta$: 1.60 (s, 9H, Boc), 3.16 (s, 3H, $NCH_3$), 6.31 (s, 1H), 6.74 (d, 1H, $J$=7.8 Hz), 7.07 (t, 1H, $J$=8.1 Hz), 7.20–7.40 (m, 6H), 7.61–7.63 (m, 4H,), 8.00 (s, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$: 25.0 ($CH_3$), 28.01 ($CH_3$), 82.6 (CH), 84.6 (Cq), 108.3 (Cq), 109.7 (CH), 113.8 (Cq), 114.9 (CH), 119.8 (Cq), 124.3 (4CH), 126.9 (2CH), 127.8 (4CH), 128.7 (CH), 129.7 (Cq), 132.2 (CH), 136.7 (2Cq), 141.5 (Cq), 146.6 (Cq), 147.9 (Cq), 166.3 (CO), 168.9 (CO); MS (IS) 586–588 $(M+H)^+$.

### 4.2. General procedure for synthesis of compounds (16–19)

LiHMDS (4 equiv., 1 M in hexane) was added dropwise to a solution of 7-azaindole **2** (3 equiv.) in dry toluene at rt. After 1 h, the reaction was cooled to −20°C and a solution of compounds **12**–**15a** (0.02 M) in toluene was added. The mixture was stirred for 15 min prior to cooling down to 0°C for 15 min. Hydrolysis was performed using $NH_4Cl$ till pH 7 (for compound **19**, the reaction was performed at −20°C for 2 h then at rt for 4 h). After extraction of the organic material with EtOAc, the organic layers were dried over $Na_2SO_4$, filtered and the solvents were evaporated under reduced pressure.

**4.2.1. 3-[1-Methyl-2,5-dioxo-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,5-dihydro-1*H*-pyrrol-3-yl]indole-1-carboxylic acid *tert*-butyl ester (16).** Precipitation from MeOH. 53%. Mp 180°C dec.; IR (KBr, $cm^{-1}$) 3127, 3085, 3005, 2925, 1739, 1703, 1153, 1068; $^1H$ NMR (DMSO-$d_6$) $\delta$: 1.71 (s, 9H, Boc), 3.22 (s, 3H, $NCH_3$), 6.76–6.82 (m, 3H), 7.19 (t, 1H, $J$=6.6 Hz), 7.31 (d, 1H, $J$=7.8 Hz), 7.94 (s, 1H), 8.01 (s, 1H), 8.07 (d, 1H, $J$=8.1 Hz) 8.15 (d, 1H, $J$=4.7 Hz), 11.46 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 24.9 ($CH_3$), 28.4 ($CH_3$), 85.5 (Cq), 104.8 (Cq), 111.0 (Cq), 115.6 (CH), 117.0 (CH), 118.4 (Cq), 122.0 (CH), 123.3 (CH), 124.8 (Cq), 125.5 (CH), 128.3 (Cq), 128.8 (CH), 129.8 (CH), 131.5 (CH), 131.9 (Cq), 135.1 (Cq), 144.3 (CH), 149.3 (Cq), 149.5 (Cq), 171.7 (CO), 171.7 (CO); MS (IS) 443.5 $(M+H)^+$.

**4.2.2. 5-Benzyloxy-3-[1-methyl-2,5-dioxo-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,5-dihydro-1*H*-pyrrol-3-yl]indole-1-carboxylic acid *tert*-butyl ester (17).** Flash chromatography (petroleum ether/EtOAc 6/4). 60%. Mp 164°C; IR (KBr, $cm^{-1}$) 3445, 3170, 1735, 1700, 1583, 1423, 1273; $^1H$ NMR ($CDCl_3$) $\delta$: 1.70 (s, 9H, Boc), 3.22 (s, 3H, $NCH_3$), 4.21 (s, 2H), 6.30 (d, 1H, $J$=2.3 Hz), 6.80–6.87 (m, 2H), 7.04–7.08 (m, 2H), 7.16–7.19 (m, 3H), 7.46 (dd, 1H, $J$=7.9, 1.1 Hz), 7.97–8.03 (m, 2H), 8.17 (s, 1H), 8.24 (d, 1H, $J$=3.8 Hz), 11.83 (s, 1H, NH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 24.5 ($CH_3$), 28.3 ($CH_3$), 70.0 ($CH_2$), 84.7 (Cq), 105.0 (CH), 105.5 (Cq), 110.5 (Cq), 115.2 (CH), 116.0 (CH), 116.7 (CH), 119.4 (Cq), 125.7 (Cq), 127.2 (2CH), 127.7 (CH), 128.3 (2CH), 128.6 (Cq), 128.7 (CH), 130.0 (Cq), 130.2 (CH), 130.5 (CH), 136.7 (Cq), 143.3 (CH), 149.1 (Cq), 149.3 (Cq), 154.9 (Cq), 171.7 (CO), 171.9 (CO); MS (IS) 549 $(M+H)^+$.

**4.2.3. 6-Benzyloxy-3-[1-methyl-2,5-dioxo-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,5-dihydro-1*H*-pyrrol-3-yl]-indole-1-carboxylic acid *tert*-butyl ester (18).** Flash chromatography (petroleum ether/EtOAc 6/4). 48%. Mp 163°C dec.; IR (KBr, $cm^{-1}$) $\nu$, 3154, 2930, 1736, 1702, 1137, 1072, 1442, 1153; $^1H$ NMR (DMSO-$d_6$) $\delta$: 1.64 (s, 9H, Boc), 3.07 (s, 3H, $NCH_3$), 5.07 (s, 2H), 6.58 (dd, 1H, $J$=8.7, 2.5 Hz), 6.78 (d, 1H, $J$=8.7 Hz), 6.85 (m, 1H), 7.31–7.41 (m, 6H), 7.71 (d, 1H, $J$=2.1 Hz), 7.90 (s, 1H), 7.92 (d, 1H, $J$=2.5 Hz), 8.17 (d, 1H, $J$=4.7 Hz), 12.38 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 22.6 ($CH_3$), 26.0 ($CH_3$), 67.8 (Cq) 70.2 ($CH_2$), 85.5 (Cq), 100.8 (CH), 104.8 (Cq), 111.1 (Cq), 112.9 (CH), 117.1 (CH), 118.8 (Cq), 122.1 (Cq), 122.7 (CH), 126.2 (2CH), 127.7 (2CH), 128.7 (CH), 129.2 (CH), 129.9 (CH), 131.4 (CH), 131.7 (Cq), 136.2 (Cq), 137.7 (Cq), 144.4 (CH), 149.3 (Cq), 149.6 (Cq), 157.2 (Cq), 171.7 (CO), 171.8 (CO); MS (IS) 549 $(M+H)^+$.

**4.2.4. 7-Benzhydryloxy-3-[1-methyl-2,5-dioxo-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-2,5-dihydro-1*H*-pyrrol-3-yl]-indole-1-carboxylic acid *tert*-butyl ester (19).** Flash chromatography (petroleum ether/EtOAc 6/4). 74%. Mp 114°C dec.; IR (KBr, $cm^{-1}$) $\nu$ 3422, 3027, 2978, 2926, 1758, 1701, 1231, 1149; $^1H$ NMR (DMSO-$d_6$) $\delta$: 1.63 (s, 9H, Boc), 3.19 (s, 3H, $NCH_3$), 6.25 (s, 1H), 6.36 (dd, 1H, $J$=6.6, 2.2 Hz), 6.80–6.83 (m, 2H), 6.82 (m, 1H), 7.25–7.28 (m, 6H), 7.42 (d, 1H, $J$=8.1 Hz), 7.61 (d, 4H, $J$=7.2 Hz), 7.96 (m, 2H), 8.20 (d, 1H, $J$=4.3 Hz), 11.86 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 24.4 ($CH_3$), 28.1 ($CH_3$), 82.5 (CH), 84.2 (Cq), 105.5 (Cq), 109.4 (CH), 110.1 (Cq), 114.1 (CH), 116.9 (CH), 118.8 (Cq), 123.8 (CH), 125.2 (Cq), 125.4 (Cq), 126.7 (4CH), 127.7 (2CH), 128.7 (4CH), 129.2 (Cq), 130.2 (CH), 130.4 (CH), 130.5 (Cq), 131.2 (CH), 141.8 (Cq), 143.3 (CH), 146.3 (Cq), 148.3 (Cq), 148.7 (Cq), 171.7 (CO), 171.9 (CO); MS (IS) 625 $(M+H)^+$.

### 4.3. Compounds (20–23) were obtained as described for compound (10)

**4.3.1. 6-Methyl-13*H*-pyrrolo[2,3-*a*]pyrrole[3,4-*c*]pyrido[3′,2′:4,5]carbazole-5,7-dione-12-carboxylic acid *tert*-butyl ester (20).** Irradiation for 1.5 h Flash chromatography (petroleum ether/EtOAc 5/5, then EtOAc). The residual solid obtained after evaporation was triturated in MeOH. After filtration, compound **20** was obtained as a yellow solid in 75% yield. Mp 192°C dec.; IR (KBr, $cm^{-1}$) $\nu$ 3364, 2928, 1704, 1371, 1163, 1091, 747; $^1H$ NMR ($CDCl_3$) $\delta$: 1.86 (s, 9H, Boc), 3.20 (s, 3H, $NCH_3$), 7.29–7.32 (m, 2H), 7.44–7.49 (m, 2H), 8.02 (d, 1H, $J$=7.5 Hz), 8.57 (s, 1H, $J$=5 Hz), 8.25 (d, 1H, $J$=7.5 Hz), 11.46 (s, 1H, NH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 23.9 ($CH_3$), 28.2 ($CH_3$), 86.6 (Cq), 113.6 (Cq), 115.3 (CH), 116.3 (Cq), 116.7 (CH), 118.2 (Cq), 121.3 (Cq), 122.9 (Cq), 123.6 (Cq), 123.8 (CH), 125.1 (Cq), 125.7 (CH), 128.1 (CH), 128.9 (Cq), 133.4 (CH), 137.8 (Cq), 148.0 (CH), 150.8 (Cq), 151.3 (Cq), 168.2 (CO), 168.4 (CO); MS (IS) 441 $(M+H)^+$.

**4.3.2. 6-Methyl-9-benzyloxy-13*H*-pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]pyrido[3′,2′:4,5]carbazole-5,7-dione-12-carboxylic acid *tert*-butyl ester (21).** Irradiation for 50 min. After hydrolysis, extractions were performed using $CH_2Cl_2$. After removing the solvents under reduced pressure, the crude solid was washed successively by EtOAc and MeOH.

The residual solid was dissolved in DMSO and the solution was filtered. DMSO was distillated under reduced pressure to afford compound **21** as a yellow solid in 88% yield. Mp 250°C dec.; IR (KBr, $cm^{-1}$) $\nu$ 3440, 2927, 1703, 1487, 1356, 1091, 747; $^1H$ NMR ($CDCl_3$) $\delta$: 1.83 (s, 9H, Boc), 3.23 (s, 3H, $NCH_3$), 5.25 (s, 2H), 7.08 (dd, 1H, $J$=2.8, 9.4 Hz), 7.24–7.29 (m, 1H), 7.33–7.47 (m, 3H), 7.59–7.62 (m, 2H), 7.86 (d, 1H, $J$=9.4 Hz), 8.56 (dd, 1H, $J$=4.8, 1.5 Hz), 8.91 (d, 1H, $J$=2.5 Hz), 9.23 (dd, 1H, $J$=7.8, 0.9 Hz), 11.5 (s, 1H, NH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 24.0 ($CH_3$), 28.5 ($CH_3$), 70.4 ($CH_2$), 86.9 (Cq), 108.2 (CH), 114.2 (Cq), 116.8 (CH), 117.0 (Cq), 117.1 (CH), 118.1 (Cq), 118.3 (CH), 121.6 (Cq), 123.9 (Cq), 125.2 (Cq), 127.0 (Cq), 128.2 (2CH), 128.3 (CH), 128.7 (2CH), 129.7 (Cq), 132.8 (Cq), 133.9 (CH), 137.2 (Cq), 148.5 (CH), 151.5 (Cq), 151.8 (Cq), 155.7 (Cq), 169.0 (CO), 169.4 (CO); MS (IS) 547 $(M+H)^+$.

**4.3.3. 6-Methyl-10-benzyloxy-13*H*-pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]pyrido[3′,2′:4,5]carbazole-5,7-dione-12-carboxylic acid *tert*-butyl ester (22).** Irradiation for 1.75 h. The residual solid obtained after evaporation was triturated in MeOH. After filtration, compound **22** was obtained as a yellow solid in 75% yield. Mp 250°C dec.; IR (KBr, $cm^{-1}$) $\nu$ 3431, 2926, 1705, 1613, 1092; $^1H$ NMR ($CDCl_3$) $\delta$: 1.83 (s, 9H, Boc), 3.20 (s, 3H, $NCH_3$), 5.10 (s, 2H), 7.07 (dd, 1H, $J$=7.8, 1.9 Hz), 7.24–7.5 (m, 6H), 7.57 (d, 1H, $J$=1.7 Hz), 8.53–8.55 (m, 1H), 9.07 (d, 1H, $J$=8.9 Hz), 9.23 (d, 1H, $J$=7.8 Hz), 11.42 (s, 1H, NH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 24.0 ($CH_3$), 28.4 ($CH_3$), 70.2 ($CH_2$), 87.0 (Cq), 101.9 (CH), 113.2 (CH), 112.5 (Cq), 114.4 (Cq), 115.9 (Cq), 116.8 (CH), 117.1 (CH), 118.3 (Cq), 122.0 (Cq), 124.1 (Cq), 126.0 (Cq), 126.6 (CH), 127.6 (2CH), 128.3 (2CH), 128.8 (Cq), 139.9 (CH), 136.7 (Cq), 137.0 (Cq), 148.4 (CH), 151.7 (Cq), 151.8 (Cq), 153.4 (Cq), 169.3 (CO), 169.5 (CO); MS (IS) 547 $(M+H)^+$.

**4.3.4. 6-Methyl-11-benzhydryloxy-13*H*-pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]pyrido[3′,2′:4,5]carbazole-5,7-dione-12 carboxylic acid *tert*-butyl ester (23).** Irradiation for 1.75 h. Flash chromatography (EtOAc/MeOH 8/2) then trituration with MeOH, 77% yield. Mp 220°C dec.; IR (KBr, $cm^{-1}$) $\nu$ 3431, 2954, 2923, 1724, 1693, 1145; $^1H$ NMR ($CDCl_3$) $\delta$: 1.33 (s, 9H, Boc), 3.49 (s, 3H, $NCH_3$), 6.38 (s, 1H), 7.07 (d, 1H, $J$=7.8 Hz), 7.25–7.44 (m, 12H), 8.58 (dd, 1H, $J$=4.7, 1.6 Hz), 8.87 (d, 1H, $J$=7.2 Hz), 9.35 (dd, 1H, $J$=7.8, 1.5 Hz), 11.21 (s, 1H, NH); $^{13}C$ NMR ($CDCl_3$) $\delta$: 27.7 ($CH_3$), 35.2 ($CH_3$), 87.5 (CH), 88.7 (Cq), 114.4 (Cq), 115.4 (CH), 117.1 (Cq), 117.3 (CH), 118.9 (CH), 119.1 (Cq), 121.9 (Cq), 123.6 (Cq), 125.4 (CH), 127.2 (Cq), 127.7 (4CH), 128.3 (2CH), 128.8 (4CH), 129.0 (Cq), 130.0 (Cq), 130.9 (Cq), 134.0 (CH), 140.5 (2Cq), 147.8 (Cq), 158.6 (CH), 152.1 (Cq), 152.6 (CO), 169.3 (CO), 169.5 (CO); MS (IS) 623 $(M+H)^+$.

### 4.4. General procedure for synthesis of compounds (24–27)

A solution of $Bu_4NF$ (1 M in THF) was added at rt to the desired compounds **20**–**23** dissolved in dry THF. The mixture was refluxed. After cooling, the solvents were removed under reduced pressure and the crude mixture was purified according the above-described procedure to afford the desired products **24**–**27**.

**4.4.1. 6-Methyl-12,13-dihydropyrrolo[2,3-*a*]pyrrolo[3,4-*c*]pyrido[3′,2′:4,5]carbazole-5,7-dione (24).** $Bu_4NF$ (5 equiv.), reaction time 1.5 h, flash chromatography (petroleum ether/EtOAc 1/9), pale yellow solid, 88%. Mp 235°C dec.; IR (KBr, $cm^{-1}$) $\nu$ 3932, 3357, 1749, 1694, 1383; $^1H$ NMR (DMSO-$d_6$) $\delta$: 2.98 (s, 3H, $NCH_3$), 7.26–7.33 (m, 2H), 7.50 (t, 1H, $J$=7.5 Hz), 7.70 (t, 1H, $J$=7.5 Hz), 8.49 (d, 1H, $J$=5 Hz), 8.81 (d, 1H, $J$=5 Hz), 8.94 (d, 1H, $J$=7 Hz), 11.30 (s, 1H, NH), 11.92 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 23.7 ($CH_3$), 111.9 (Cq), 112.3 (CH), 113.2 (Cq), 115.9 (Cq), 116.3 (CH), 119.2 (Cq), 119.5 (Cq), 120.5 (CH), 121.5 (Cq), 124.4 (CH), 127.2 (CH), 127.8 (Cq), 128.8 (Cq), 132.3 (CH), 140.5 (Cq), 146.3 (CH), 152.4 (Cq), 169.6 (CO), 169.7 (CO); MS (IS) 341 $(M+H)^+$. Anal. calcd for $C_{20}H_{12}N_4O_2$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.34; H, 3.68; N, 16.62.

**4.4.2. 6-Methyl-9-benzyloxy-12,13-dihydropyrrolo[2,3-*a*]pyrrolo[3,4-*c*]pyrido[3′,2′:4,5]carbazole-5,7-dione (25).** $Bu_4NF$ (10 equiv.), reaction time 2 h, precipitation by addition of MeOH, filtration, yellow solid, quant. Mp 290°C dec.; IR (KBr, $cm^{-1}$) $\nu$ 3374, 2924, 1382, 1693, 1222; $^1H$ NMR (DMSO-$d_6$) $\delta$: 3.11 (s, 3H, $NCH_3$), 5.20 (s, 2H), 7.25 (dd, 1H, $J$=9.1, 2.1 Hz), 7.33–7.47 (m, 4H), 7.57–7.60 (m, 2H), 7.70 (d, 1H, $J$=8.8 Hz), 8.83–8.54 (m, 2H), 9.06 (dd, 1H, $J$=7.8, 1.2 Hz), 11.25 (s, 1H, NH), 12.07 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 23.5 ($CH_3$), 69.8 ($CH_2$), 107.4 (CH), 112.7 (Cq), 112.9 (CH), 114.3 (Cq), 116.1 (Cq), 116.6 (CH), 117.1 (CH), 118.7 (Cq), 119.4 (Cq), 121.7 (Cq), 127.6 (Cq), 127.9 (CH), 128.0 (2CH), 128.5 (2CH), 129.1 (Cq), 132.1 (CH), 135.3 (Cq), 137.3 (Cq), 147.2 (CH), 152.9 (Cq), 157.9 (Cq), 169.5 (CO), 169.7 (CO); MS (IS) 447 $(M+H)^+$.

**4.4.3. 6-Methyl-10-benzyloxy-12,13-dihydropyrrolo[2,3-*a*]pyrrolo[3,4-*c*]pyrido[3′,2′:4,5]carbazole-5,7-dione (26).** $Bu_4NF$ (10 equiv.), reaction time 2 h, precipitation by addition of MeOH, filtration, yellow solid, 82%. Mp 290°C dec.; IR (KBr, $cm^{-1}$) $\nu$ 3421, 2924, 2054, 1690, 1370, 1132; $^1H$ NMR (DMSO-$d_6$) $\delta$: 3.02 (s, 3H, $NCH_3$), 5.24 (s, 2H), 6.99 (d, 1H, $J$=8.5 Hz), 7.33–7.57 (m, 7H), 8.45–8.55 (m, 1H), 8.68 (d, 1H, $J$=7.7 Hz), 8.99 (d, 1H, $J$=8.5 Hz), 11.28 (s, 2H, 2NH); $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 23.4 ($CH_3$), 69.6 ($CH_2$), 96.3 (CH), 111.3 (CH), 112.5 (Cq), 114.2 (Cq), 115.2 (Cq), 116.4 (CH), 118.2 (CH), 118.8 (Cq), 119.2 (Cq), 120.8 (Cq), 124.9 (CH), 127.3 (Cq), 127.9 (CH), 128.3 (Cq), 128.5 (2CH), 131.9 (2CH), 137.1 (Cq), 141.8 (Cq), 147.0 (CH), 152.0 (Cq), 158.6 (Cq), 169.5 (CO), 169.7 (CO); MS (IS) 447 $(M+H)^+$.

**4.4.4. 6-Methyl-11-benzhydriloxy-12,13-dihydropyrrolo[2,3-*a*]pyrrolo[3,4-*c*]pyrido[3′,2′:4,5]carbazole-5,7-dione (27).** $Bu_4NF$ (8 equiv.), reaction time 7.5 h, precipitation by addition of MeOH, filtration, yellow solid, quant. Mp 254°C dec.; IR (KBr, $cm^{-1}$) $\nu$ 3361, 3915, 2030, 1685, 1298; $^1H$ NMR (DMSO-$d_6$) $\delta$: 3.08 (s, 3H, $NCH_3$), 6.91 (s, 1H), 7.14 (d, 1H, $J$=8.5 Hz), 7.27–7.46 (m, 9H), 7.64 (d, 3H, $J$=7.2 Hz), 8.43 (m, 1H), 8.56 (d, 1H, $J$=3.8 Hz), 9.07 (d, 1H, $J$=7.5 Hz), 11.55 (s, 1H, NH), 12.06 (s, 1H, NH); $^{13}C$-Dept135 NMR (DMSO-$d_6$) $\delta$: 24.5 ($CH_3$), 81.36 (CH), 98.3 (CH), 111.6 (CH), 118.0 (CH), 122.03 (CH), 127.9 (4CH), 129.1 (2CH), 130.0 (4CH), 133.4 (CH), 148.6 (CH); MS (IS) 523 $(M+H)^+$.

### 4.5. General procedure for the synthesis of compounds (28–29)

A solution of $BBr_3$ (6 equiv., 1 M in $CH_2Cl_2$) was added dropwise to a solution of compounds **25–26** in $CH_2Cl_2$ at 0°C under vigorous stirring. After 1 h 30 min at rt, the reaction mixture was poured in ice and the layers were extracted with $CH_2Cl_2$. The solvents were removed under reduced pressure and the products were purified by flash chromatography to afford compounds **28–29**.

**4.5.1. 6-Methyl-9-hydroxy-12,13-dihydropyrrolo[2,3-*a*]pyrrolo[3,4-*c*]pyrido[3′,2′:4,5]carbazole-5,7-dione (28).** Flash chromatography (EtOAc/MeOH/$Et_3N$ 8/1.7/0.3), yellow solid, quant. Mp 170°C dec.; $R_f$ (EtOAc/MeOH/$Et_3N$ 8/1.7/0.3) 0.75; IR (KBr, $cm^{-1}$) $\nu$ 3441, 2933, 1695, 1475, 1385; $^1H$ NMR (DMSO-$d_6$) $\delta$: 3.17 (s, 3H, $NCH_3$), 7.07 (dd, 1H, $J$=8.6, 2.5 Hz), 7.41 (dd, 1H, $J$=7.8, 5.0 Hz), 7.64 (d, 1H, $J$=8.4 Hz), 7.64 (d, 1H, $J$=8.4 Hz), 8.41 (d, 1H, $J$=2.5 Hz), 9.15 (dd, 1H, $J$=7.8, 1.5 Hz), 9.28, (s, 1H, OH, exchangeable with $D_2O$), 9.28 (s, 1H, NH), 12.27 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 23.6 ($CH_3$), 99.1 (Cq), 108.7 (CH), 112.5 (CH), 112.6 (Cq), 114.3 (Cq), 116.6 (CH), 117.0 (CH), 118.5 (Cq), 119.7 (Cq), 122.1 (Cq), 127.8 (Cq), 129.4 (Cq), 132.0 (CH), 134.4 (Cq), 147.2 (CH), 151.7 (Cq), 151.9 (Cq), 169.8 (2CO); MS (Maldi-Tof) 357 $(M+H)^+$. Anal. calcd for $C_{20}H_{12}N_4O_3$: C, 67.41; H, 3.39; N, 15.72. Found: C, 67.03; H, 3.54; N, 15.88.

**4.5.2. 6-Methyl-10-hydroxy-12,13-dihydropyrrolo [2,3-*a*]pyrrolo[3,4-*c*]pyrido[3′,2′:4,5]carbazole-5,7-dione (29).** Flash chromatography (EtOAc/MeOH/$Et_3N$ 5/4.9/0.1), yellow solid, 85%. Mp 195°C dec.; $R_f$ (EtOAc/MeOH/$Et_3N$ 5/4.9/0.1) 0.75; IR (KBr, $cm^{-1}$) $\nu$ 3423, 3262, 2937, 1696, 1384, 1124; $^1H$ NMR (DMSO-$d_6$) $\delta$: 3.03 (s, 3H, $NCH_3$), 6.81 (dd, 1H, $J$=8.4, 2.2 Hz), 7.04 (d, 1H, $J$=2.2 Hz), 7.28–7.34 (m, 1H) 8.48 (d, 1H, $J$=4.1 Hz), 8.63 (d, 1H, $J$=8.4 Hz), 8.98 (dd, 1H, $J$=7.8, 1.3 Hz), 9.82, (s, 1H, OH, exchangeable with $D_2O$), 11.41 (s, 1H, NH), 12.03 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$) $\delta$: 28.2 ($CH_3$), 86.6 (Cq), 106.9 (CH), 113.6 (CH), 115.3 (CH), 116.3 (Cq), 116.7 (CH), 123.6 (Cq), 123.8 (Cq), 125.1 (Cq), 125.7 (Cq), 128.1 (Cq), 128.9 (Cq), 133.4 (CH), 137.8 (Cq), 148.0 (CH), 150.8 (Cq), 151.3 (Cq), 168.2 (CO), 168.4 (CO); MS (Maldi-Tof) 357 $(M+H)^+$. Anal. calcd for $C_{20}H_{12}N_4O_3$: C, 67.41; H, 3.39; N, 15.72. Found: C, 67.12; H, 3.50; N, 15.86.

### 4.6. Biology

The procedures used for the DNA binding studies and inhibition of topoisomerases have been previously described.[34] Similarly, a conventional protocol was used to performed the cytotoxicity.[35]

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