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Novel 5-azaindolocarbazoles as cytotoxic agents and Chk1 inhibitors

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Abstract—We describe here an efficient synthesis of new 5-azaindolocarbazoles designed for cytotoxic and Chk1 inhibiting properties. The synthesis of 'symmetrical' and 'dissymmetrical' structures is discussed. Concerning the dissymmetrical 5-azaindolocarbazoles derivatives, with both an indole moiety and a 5-azaindole moiety, the synthesis was achieved using two very efficient key steps. The first one is a Stille reaction with a 3-trimethylstannyl-5-azaindole derivative and the second one a photochemical step leading to the proposed polycyclic structure. Various pharmacomodulations were performed to investigate the structure–activity relationships (SAR). Several substituents such as OBn, OH, and methylenedioxy groups were successfully introduced on the indole moiety of the 5-azaindolocarbazole. Compounds with or without substituents on the nitrogen atom of the maleimide were prepared, as well as derivatives with glucopyranosyl substituent on the nitrogen atom of the indole moiety. The cytotoxicity of these new compounds was evaluated on two cell lines (L1210, HT29). Several compounds showed cytotoxicity in the sub-micromolar range. Among the most cytototoxic was the 1,3-dioxolo[4,5-*b*]-6-(2-dimethylaminoethyl)-1*H*-pyrido[3′,4′:4,5]pyrrolo[3,2-*i*]pyrrolo[3,4-*g*]carbazole-5,7(6*H*,12*H*)-dione (**35**, IC_{50} = 195 nM on L1210). The compounds were also investigated for their Chk1 inhibiting activity. Compounds without any substitution on the maleimide moiety were the most potent. This is the case of compounds **45**–**47** with IC_{50} of, respectively, 72, 27, and 14 nM toward Chk1. Compound **46**, which exhibits moderate cytotoxicity, appears to be a good candidate for development in a multi-drug anticancer therapy.

1. Introduction

The cell division cycle is controlled by various protein kinases such as CDKs, Aurora or checkpoint kinases. The importance of kinase pathways is highlighted by observations that genes encoding kinases are sometimes mutated or overexpressed in human tumors.[1] In the search for new anticancer agents, intensive efforts have been developed to find novel inhibitors of CDKs and more generally of protein kinases that regulate cell cycle and apoptosis. In this field, indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids (indolocarbazoles) form a class of compounds with potent antitumor properties due to inhibition of topoisomerase and/or strong cytotoxicity.[2,3]

These compounds have also attracted considerable attention because of their ability to inhibit protein kinases.[4–6] The structure–activity relationships (SARs) of indolocarbazole series have been extensively studied as topoisomerase I inhibitors.[2,7] For example, compounds such as NB-506 and J-107088 (also known as Edotecarin, Fig. 1) have entered into clinical trials for cancer treatment.[8] More recently, it was published that the members of the CDKs[9] family can be inhibited by indolocarbazoles (see Fig. 2).

We have recently described the bioisosteric replacement of an indole moiety of arcyriaflavin[10,11] skeleton by a 7-azaindole unit affording the first symmetrical and

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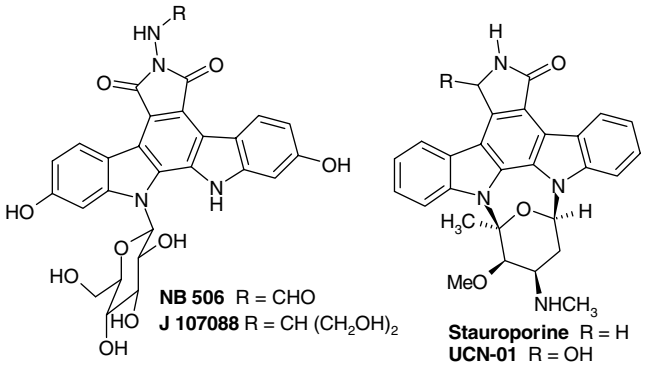


Figure 1. Glycosylated indolocarbazoles.

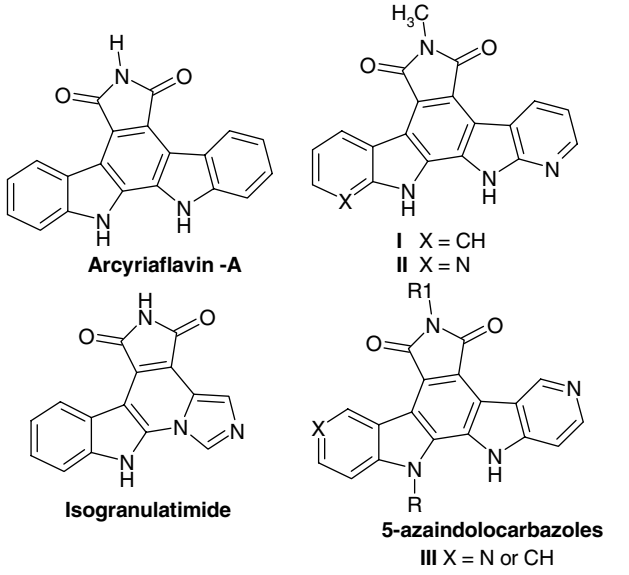


Figure 2. Aglycones indolocarbazoles derivatives and analogues.

dissymmetrical 7-azaindolocarbazoles **I** and **II**.[12–14] Replacement of one of the two indoles moieties by other aromatic units such as phenyl,[15,16] pyridine,[15,17] quinoline or isoquinoline,[15] indene,[18] naphthalene[19,20] led to the identification of new and potent cyclin kinase inhibitors.[21–23]

Previously, we have published a synthesis of some naphtho[19,20] and benzocarbazole[16] derivatives with strong cytotoxicity and interesting CDK1 inhibiting activity. Modification of the attachment of one indole unit such as in indolo[6,7-*a*]pyrrolo[3,4-*c*]carbazoles[22] or in arcyriacyanin A[24] led to potent CDK4/Cyclin D1 inhibitors. Chk1 plays a very important role in the cell cycle regulation via the DNA damage checkpoint.[27,28] Several glycosylated compounds, such as UCN-01, are potent Chk1 inhibitors.[25] Crystallographic data on complexes between Chk1 and indolocarbazole derivatives such as staurosporine or UCN-01 have been published and the interactions in the ATP pocket described.[26]

Recently, it has been reported that small natural molecules such as granulatimide and isogranulatimide are potent Chk1 inhibitors[29] with nanomolar activities for isogranulatimide. This compound can be, to some extent, considered as a bioisostere of indolocarbazole, by the replacement of one of the two indole moities by an imidazole ring. In the continuation of our previous work on 7-azaindolocarbazoles, we postulated that the replacement of the 7-azaindole moiety by the more basic 5-azaindole moiety could be of interest. In this paper, we described the synthesis of new 5-azaindolocarbazole derivatives **III**. These compounds were investigated in vitro for both their cytotoxicity on L1210 and HT29 cancer cell lines, and their inhibiting activity on Chk1 kinases. The SAR were investigated by adding various substituents on the indole ring, and/or the maleimide moiety.

2. Chemistry

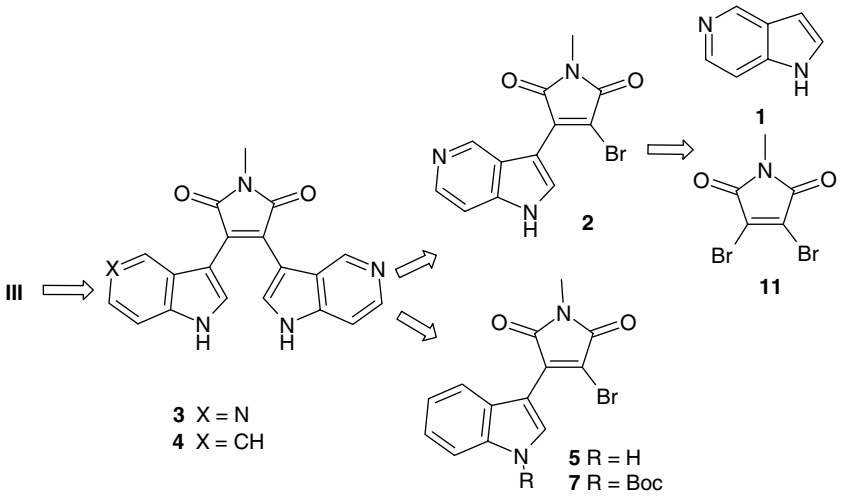
The first synthetic pathway envisaged to prepare the 5-azaindolocarbazoles of type **III** (Scheme 1) was derived from the one we had previously used for the synthesis of the 7-azaindolocarbazoles approach, and implies the preparation of bis-arylmaleimides followed by a central ring closure in 5-azaindolocarbazoles. The first step consists in a regioselective Michael addition of 5-azaindole **1** in position *C*-3 under basic media.[12,13]

2.1. Synthesis of bis-substituted maleimide compounds

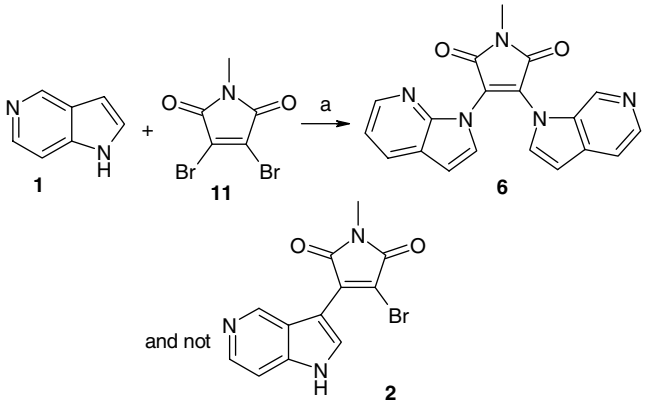
Our first attempt was to prepare compound **2** by reacting the 5-azaindole **1** with the *N*-methyl dibromomaleimide **11** in the presence of EtMgBr in a mixture of toluene and dichloromethane[30–34] but only the degradation of the reaction mixture was observed. No trace of compound **2** was obtained even by changing the base for LiHMDS or the solvent for THF as for indole itself.[19] Interestingly, the bis-5-azaindole derivative **6**, resulting from a bis-*N*-alkylation,[35] was obtained in a low yield (29%) in refluxing toluene instead of expected compounds **2** or even **3** (Scheme 2). This result stopped our attempts to obtain the symmetrical 5-azaderivative **3** (X = N) through this pathway.

We then focused our efforts on the synthesis of the dissymmetrical compound **4** (X = CH) by direct and regioselective reaction of the lithium salt of 5-azaindole **1** and the easily prepared compound **7** (Scheme 3, Table 1).[31] Compound **7** was prepared according to the literature by protecting the indole nitrogen atom of compound **5** with a Boc group. All the anionic reactions were performed at −30 °C during 1 h and the temperature was allowed to reach −20 °C during 45 min after the addition of electrophile **7**.

Whatever the conditions used, the overall yield of the reaction remained low (38% in the best case, entry 1) and the reaction appeared to be not regioselective in toluene, a mixture of *N*-alkylated compound **8** and *C*-alkylated derivative **9** being obtained (entries 1–2). The best yield of **9** was obtained by using 2 equiv of 5-azaindole **1** with 4.2 equiv of LiHMDS (entry 3). Replacement of toluene by THF led, in a low yield (11%, entry 5) to a regioselective *N*-alkylation leading to compound **8**.



Scheme 1. Retrosynthetic scheme of 5-azaindolocarbazoles (**V**).

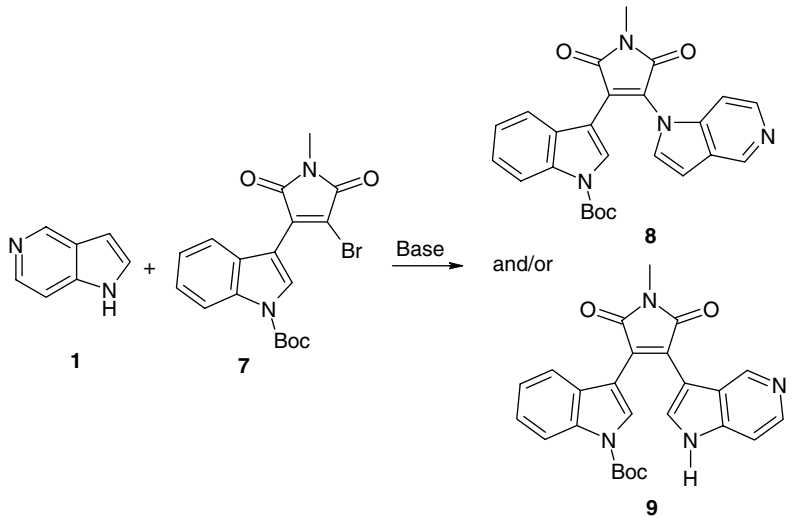


Scheme 2. Reagents and conditions: (a) Compound **1** (3.0 equiv), LiHMDS (6.6 equiv), toluene, rt, 1 h then **11** (1 equiv), reflux, 5 h, 29%.

Although it seems possible to obtain compound **9** by a regioselective addition of the 5-azaindole on **7**, we were unable to increase the yield despite numerous efforts (data not shown). Since this strategy was very efficient in the 7-azaindole series,[12,13] these results show dramatic differences in the chemical behavior of the 5-azaindole compounds compared to their counterpart in indole and 7-azaindole series.

We then switched toward palladium catalyzed cross-coupling reactions, using the Stille methodology in order to obtain compound **3**. First we prepared the 1-Boc-3-trimethylstannyl-5-azaindole **10** from 1-Boc-7-azaindole following our just recently described route.[36] This stannyl derivative **10** was then engaged in a Stille coupling reaction with the dibromomaleimide **11** using various experimental conditions (Scheme 4, Table 2).

All the reactions were performed with 5–10% mol of catalyst, several additives (10–20% mol) and various solvents. Most of the assays led to a rapid degradation of the reaction mixture in the presence of copper (I) derivatives. The results with LiCl addition were also disap-

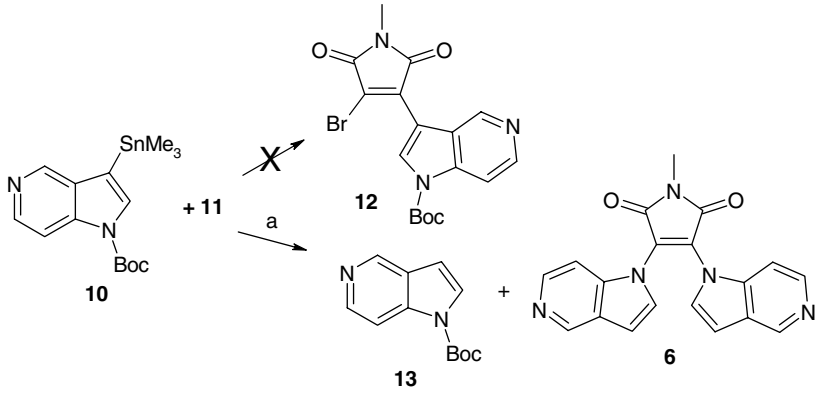


Scheme 3. Synthesis of **8** and/or **9** by lithiation of 5-azaindole **1**. For conditions see Table 1.

Table 1. Anionic reaction of compound **1** with compound **7** (1 equiv)[a]

Entry	Equivalent of **1**	Solvent	Base (equiv)	Yield of **8**	Yield of **9**
1	1.0	Toluene	LiHMDS (1.0)	13%	25%
2	1.2	Toluene	LiHMDS (2.5)	10%	19%
3	2	Toluene	LiHMDS (4.2)	ND	25%
4	4	Toluene	LiHMDS (4.2)	ND	24%
5	1.2	THF	LiHMDS (2.5)	11%	ND

[a] The reaction was conducted in anoxic conditions.



Scheme 4. Stille reaction of compound **10** with dibromomaleimide **11**.

Table 2. Conditions of Stille reaction of **10**

Entry	Catalyst	Solvent	Temperature	Additives	Time (h)	Yields			
						12	**10**	**13**	**6**
1	$Pd(PPh_3)_4$	THF	Reflux	$CuBr{\cdot}Me_2S$	4	Degradation			
2	Idem	DMF	50 °C	CuI, CsF	1	Degradation			
3	$PdCl_2(PPh_3)_2$	THF	Reflux	CuI	1	Degradation			
4	Idem	Toluene	95 °C	LiCl	15	—	20%	57%	—
5	Idem	Toluene	Reflux	LiCl	15	—	11%	68%	17%

pointing. We did not obtain the desired derivative **12** and instead we detected the hydrodestannylated compound **13**, with some starting material **10** and bis-5-azaindole maleimide **6**. A possible explanation could be that compound **10** is subjected to a hydrodestannylation followed by the removal of the Boc protective group under thermal conditions leading to 5-azaindole **1** that reacts via a Michael addition with the dibromomaleimide **11**. Replacement of the Boc by other protective groups such as benzenesulfonyl or MOM did not allow us to obtain the expected compound **12**.

Another possibility, allowing only the preparation of the dissymmetrical bis-5-azaindolemaleimide **14**, was to start from the monobromoindoylmaleimide **5**[31] and the stannyl derivative **10** (Scheme 5, Table 3). All reactions were performed using 10% mol of catalyst and several additives and the solvents were retested. The expected compound **14** was obtained in 92% yield by using $Pd(PPh_3)_4$ in the presence of $CuBr{\cdot}Me_2S$ (entry 5). Under the same conditions, the use of the safer 3-tributylstannyl-1-Boc-5-azaindole instead of **10**, gave also **14** but in much more lower yield (36%).

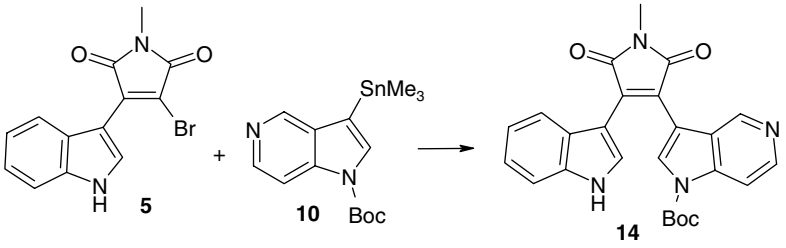
This very efficient approach was then extended to the 5-benzyloxyindole **15**, 6-benzyloxyindole **16** and 5,6-methylenedioxyindole **17** (Scheme 6).

First the monobromoindolylmaleimides **18**,[32] **19**,[32] and **20** were obtained in good yields (79–88%) by reacting the dibromomaleimide **11** with the lithium anion of indoles **15**–**17**. The unsymmetrical maleimides derivatives **21**–**23** were then obtained in good yields (72–87%, Scheme 6) via the Stille reaction.

2.2. Central ring closure and reaction on the maleimide

We tried first unsuccessfully (Scheme 7) to obtain the 5-azaindolocarbazole **3** by the treatment of compound **25** in the presence of trifluoroacetic acid according to what was observed in the indole series.[11,35,37] Compound **25** was obtained in very good yield (98%) by the removal of the Boc group of **14** in the presence of formic acid at room temperature, followed by hydrogenation over palladium on carbon.

This failure, probably due to the protonation of the pyridine nitrogen atom, led us to try a photochemical oxidative cyclization,[12,19,23] (Scheme 8) despite the following drawbacks: (i) it was difficult to perform on large scale; (ii) it required high dilution minimizing throughput; (iii) removal of the I_2 by-products by extractive workup was problematic due to the low insolubility of the 5-azaindolocarbazole product. Compounds **14**, **21**–**23** were irradiated 30 min with a 500 W

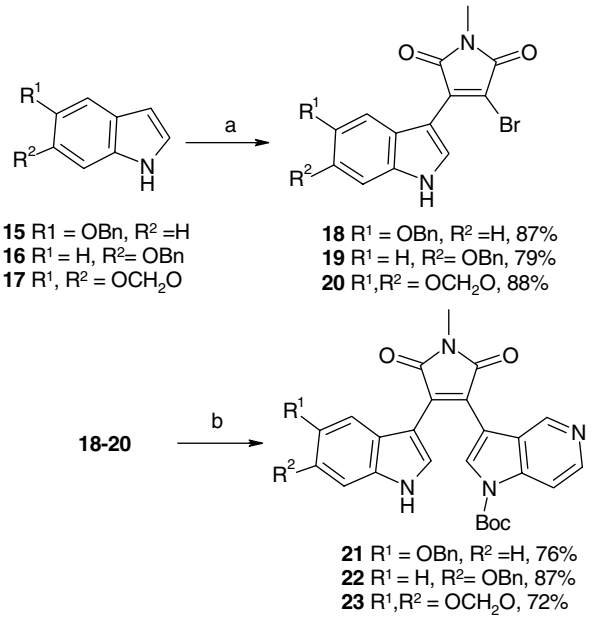


Scheme 5. Stille reaction of **5**.

Table 3. Conditions of Stille reaction of **5**[a]

Entry	Catalyst	Additives (equiv)	Solvent	Time	Yield of **14**
1	$PdCl_2(PPh_3)_2$	CuI (0.2)	THF	5 h	31%
2	$PdCl_2(PPh_3)_2$	CuI (0.1)	THF	22 h	36%
3	$PdCl_2(PPh_3)_2$	CuI (1.0) LiCl (1.0)	THF	6 h	Deg.
4	$Pd_2(dba)_3$	$AsPh_3$ (0.4)	Dioxane	6 h	Deg.
5	$Pd(PPh_3)_4$	$CuBr.Me_2S$ (1.5)	THF	30 min	92%

[a] The reaction was conducted in anoxic conditions. Deg., Degradation. All reactions were performed at reflux.



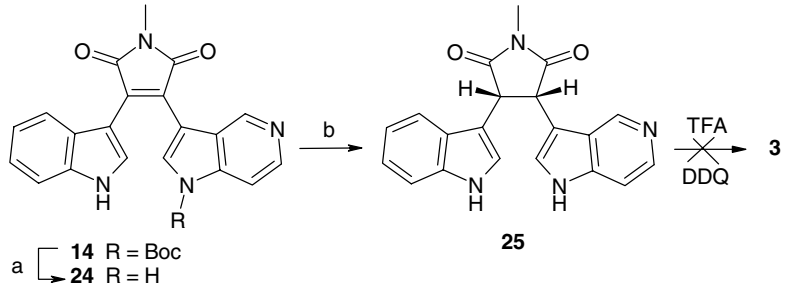
Scheme 6. Reagents and conditions: (a) for **20**: i—LiHMDS (2.9 equiv), THF, −15 °C, 1 h 30 min; ii—**11** (1.0 equiv), THF, −15 °C, 15 min then 0 °C, 15 min, 88%; (b) **10** (1.5 equiv), $Pd(PPh_3)_4$ (10%), $CuBr{\cdot}Me_2S$ (1.5 equiv), THF, reflux, 30 min.

Hg lamp on a 100 mg scale in toluene (500 mL) in the presence of diiodine and the expected indolocarbazoles **26**–**29** were obtained in very good yields (89–96%). The cleavage of the Boc group, occurred during the purification process (Scheme 8).

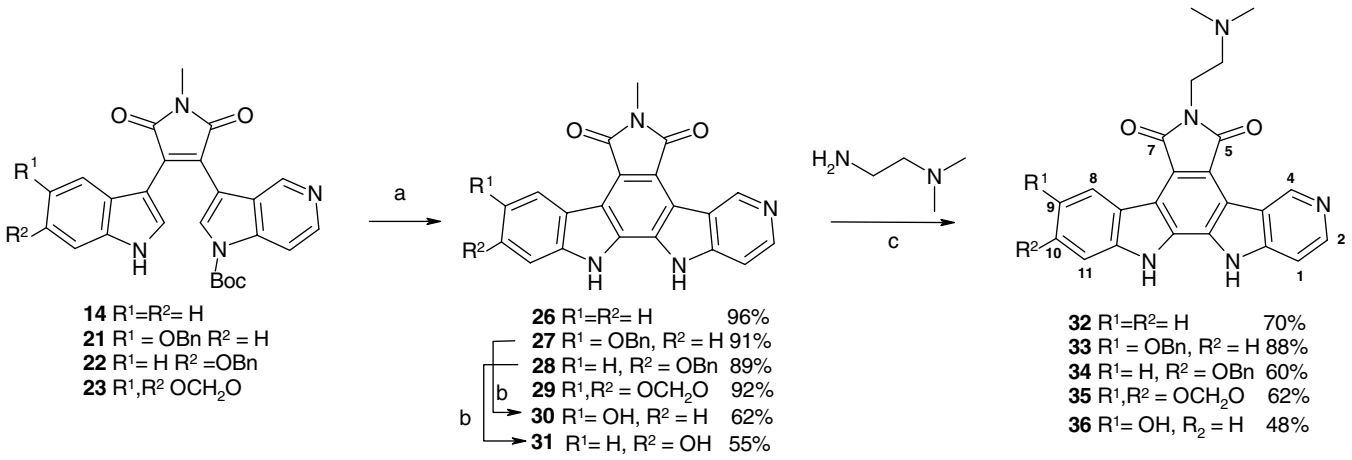
The benzoxy groups of compounds **27** and **28** were deprotected with BBr_3 in dichloromethane (30 min at room temperature) and compounds **30** and **31** were obtained in 62% and 55% yields, respectively. The reaction appeared to be complete on TLC, but the purification by trituration in methanol decreased the yields. The methylenedioxy substituent of compound **29** was stable under these conditions. Reactions of **26**–**31** in boiling dimethylaminoethylamine led after 24 h to compounds **32**–**36** in satisfying yields (48–88%). It should be noted that **31** did not afford the corresponding dimethylaminoethyl derivative but led only to a degradation of the mixture. The presence of the basic sensitive hydroquinone-imine system could explain this result. In addition, we noted that the hydroxyl protected 5-azaindolocarbazoles **33** and **34** did not react with BBr_3.

2.3. Preparation of analogues bearing unsubstituted maleimide moieties

Since some kinase inhibitors within the indolocarbazole series are unsubstituted on the maleimide nitrogen, we have synthesized the *N*-unsubstituted derivatives **40**–**47**. Compounds **40**–**42** were similarly obtained in satisfying yields (except for **42**) from a Stille reaction



Scheme 7. Reagents and conditions: (a) formic acid, rt 12 h, 99%; (b) H_2, Pd(C) 10%, DMF, 5 days, 98%.



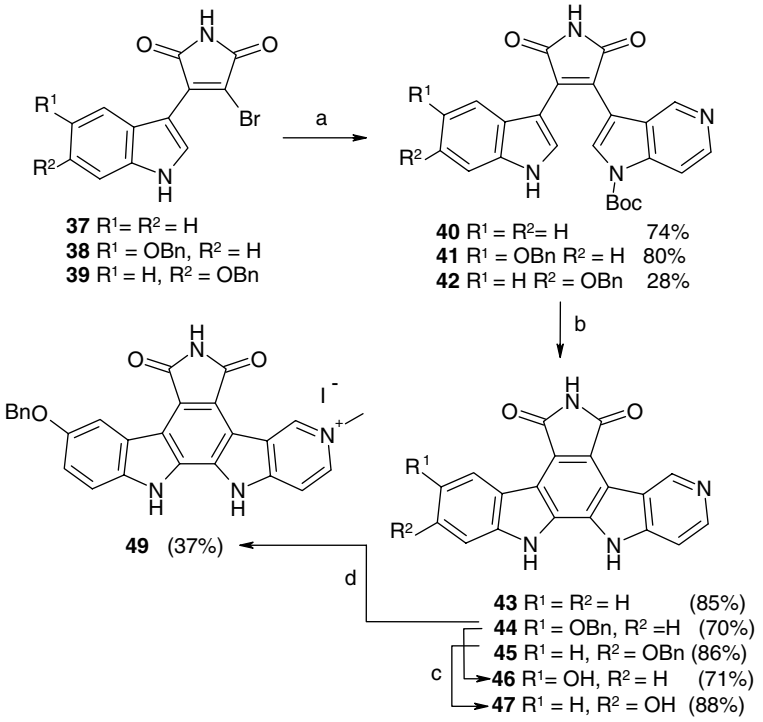
Scheme 8. Oxidative photocyclization and maleimide substitution. Reagents and conditions: (a) hν, 500 W DEMA-lamp, I_2 (10 equiv), toluene, 30 min; (b) BBr_3 (10 equiv), CH_2Cl_2, 0 °C to rt, 30 min; (c) refluxing amine, 24 h.

of **10** with the NH maleimide derivatives **37–39** (Scheme 9).[38] In a second step, the photocyclization afforded compounds **43–45** in good yields. Compounds **46** and **47** were also obtained in good yields via deprotection of the hydroxyl group of **44** and **45** with BBr_3 in dichloromethane.

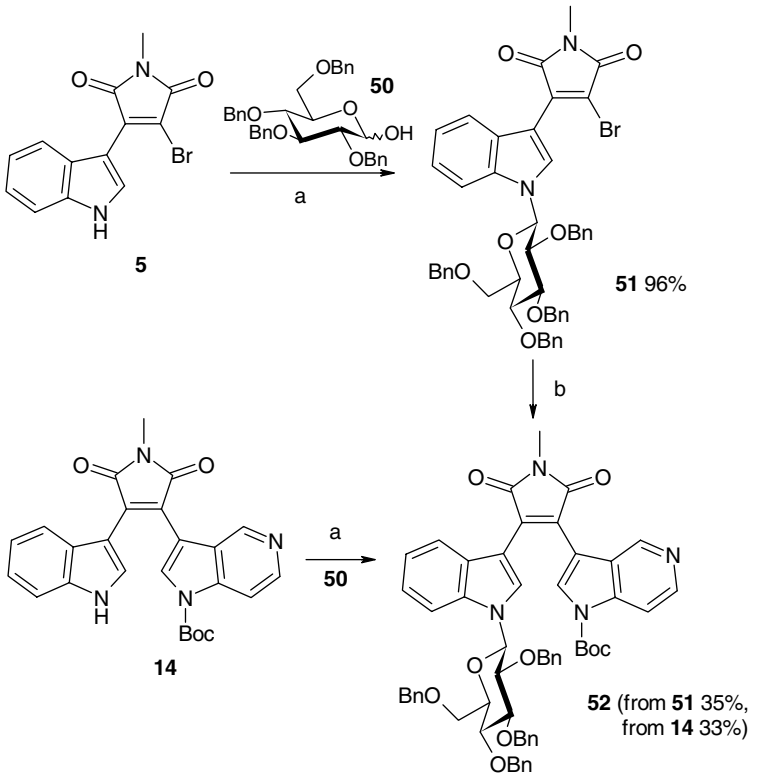
It should be noted that compound **44** reacted with an excess of iodomethane **48** in a sealed tube to give compound **49** (37%) that is *N*-alkylated on the pyridine moiety. The maleimide function was not alkylated in the absence of base, and the starting material was recovered.

2.4. Glycosylation reactions

Introduction of a sugar moiety could improve both the solubility and biodisponibility of indolocarbazoles derivatives. Whatever the methods be, all our attempts starting from indolocarbazole **26** remained unsuccessful. Glycosylation of compound **5** by a Mitsunobu reaction involving tetraacetyl-D-glucopyranoside, was also unproductive. By replacing the tetraacetyl-D-glucopyranoside with the corresponding tetrabenzyl-D-glucopyranoside **50** (Scheme 10), compound **51**[39] was obtained as a single β anomer in very good yield (96%). Compound **52** was isolated in a moderate yield



Scheme 9. Reagents and conditions: (a) **10** (1.5 equiv) $Pd(PPh_3)_4$ (10%), $CuBr{\cdot}Me_2S$ (1.5 equiv), THF, reflux, 30 min; (b) hν, 500 W DEMA-lamp, I_2 (10 equiv), toluene, 30 min; (c) BBr_3 (10 equiv), CH_2Cl_2, 0 °C to rt, 30 min; (d) **48** (3.5 equiv), DMF, 60 °C, 24 h, sealed tube.



Scheme 10. Reagents and conditions: (a) **50** (1.5 equiv), PPh_3 (3.0 equiv), DIAD (3.0 equiv), THF, 0 °C then rt, 1 h. (b) 10 (1.5 equiv), $Pd(PPh_3)_4$ (10%), $CuBr{\cdot}Me_2S$ (1.5 equiv), THF, reflux, 30 min.

(35%) by performing on **51** the Stille reaction previously described. This compound can also be obtained in approximately the same overall yield (33%) via a Mitsunobu reaction involving **14** and tetrabenzyl-D-glucopyranoside **50**.

Deprotection of the azaindole moiety of **52** was achieved using formic acid and led to compound **53** in excellent yield (99%, the deprotection was necessary in order to carry out the oxidative photocyclization with good yield).[19] Compound **54** was then obtained in a 69% yield (Scheme 11).

Our attempts to debenzylate the sugar moiety by hydrogenolysis were unsuccessful. Independent of the hydrogen pressure, the temperature and the amount of Pd/C, a mixture of partially debenzylated derivatives was always obtained. The use of BBr_3 at −78 °C (reaction completed in 10 min) led, in 57% yield, to the compound **55** bearing an unexpected quaternary pyridine nitrogen atom.

The peracetylation of **55** using acetic anhydride in pyridine at room temperature, afforded the expected compound **56** in a 24% yield, but also the triacetylated compound **57**, which was isolated by flash chromatography in a 19% yield (Scheme 11). The obtention of **57** confirmed the lack of reactivity of the 2′-hydroxy group on the sugar, which was, as described for the rebeccamycin derivatives, engaged in a intramolecular hydrogen bond with the NH of the 'indole' moiety.[40,41]

3. Results and discussion

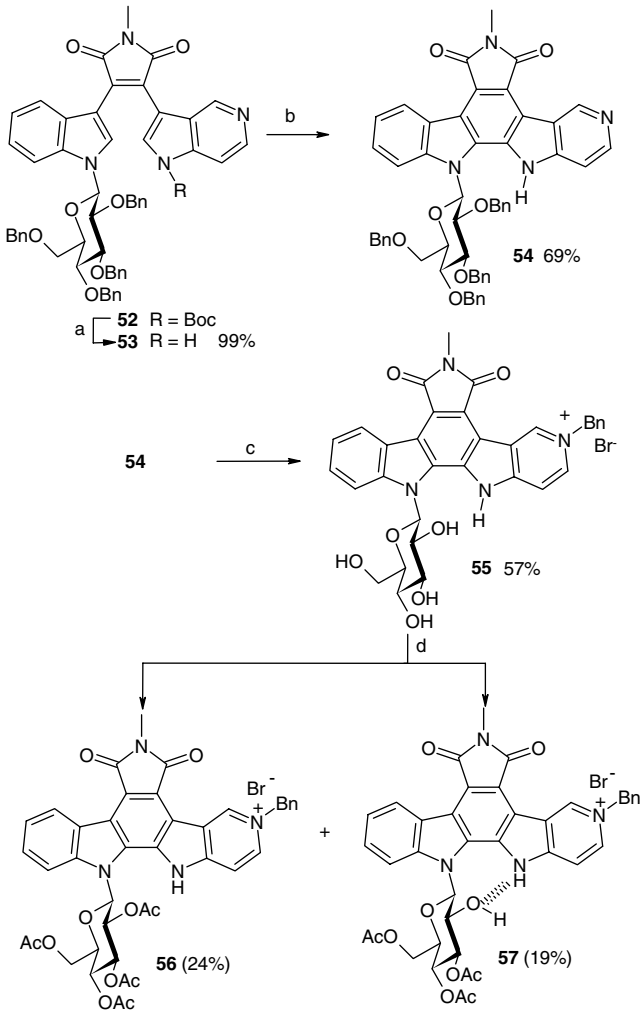
All the new 5-azaindolocarbazole derivatives were first evaluated in vitro for their cytotoxicity against two tumor cell lines, a murine leukemia cell line (L1210) and a human colon carcinoma cell line (HT29). The results (IC_{50}) are reported in Table 4. These compounds were then evaluated in vitro for their Chk1 inhibiting properties.

3.1. Cytotoxicity

As expected, significant variations of the cytotoxicity were observed according to the nature and the position of the substituents. The structure–activity relationships discussed hereafter are those obtained from the cytotoxicity data on L1210 cell line (Table 4).

The unsubstituted compound **43** was relatively cytotoxic with an IC_{50} of 0.6 μM against L1210 cells. Its direct analogues substituted in position 10 (on the indole part of the structures) with an hydroxy or a benzyloxy (compounds **47** and **45**) retained some cytotoxicity with IC_{50} (L1210) of, respectively, 3.3 and 1.1 μM, whilst patterns for cytotoxicity for the compounds substituted in position 9 were less obvious. The 9-benzyloxy substituted compounds **44** remained rather active (IC_{50} (L1210) = 1.5 μM) whilst the 9-hydroxy substituted compound **46** was inactive (IC_{50} (L1210) = 80.7 μM).

Contrary to **30**, which was clearly 7-fold more cytotoxic than its nonmethylated direct analogue **46**, compounds



Scheme 11. Reagents and conditions: (a) HCOOH, rt, 12 h; (b) hν, 500 W DEMA-lamp, I_2 (10 equiv), toluene, 30 min; (c) BBr_3 (5.0 equiv), CH_2Cl_2, −78 °C, 10 min; (d) Ac_2O, pyridine, rt, 24 h.

28 and **31** bearing a methyl on the nitrogen of the maleimide were in the same range of potency as their direct unsubstituted counterparts **45** and **47**. Compound **29** bearing a 9,10-methylenedioxy group was the most potent of this subset of derivatives with an IC_{50} (L1210) of 0.495 μM. On this particular point (*N*-methylation of the maleimide), the structure–activity relationships in the 5-azaindolocarbazole series were different from those obtained with the previous studies on naphtho-[20,21] and phenyl- carbazoles[16] where *N*-methylation of the maleimide moiety led to micromolar cytotoxic derivatives. From these results, it can be noticed that the increase of the basicity due to the 5-azaindole ring improved the cytotoxicity of aglycones.

Substitution of the maleimide with a *N*,*N*-dimethylaminoethyl chain resulted in more soluble derivatives that, with the exception of compound **33** (IC_{50} (L1210) = 16.3 μM; 9-benzyloxy substituent), retained good cytotoxicity. For compounds **35** (IC_{50} (L1210) = 0.195 μM) and **36** (IC_{50} (L1210) = 2.6 μM) bearing, respectively, a 9,10-methylenedioxy and a 9-hydroxy group, the *N*,*N*-dimethylaminoethyl substitution induced a clear improvement of the cytotoxicity compared to their *N*-methyl substituted counterparts **29** and **30** (IC_{50} (L1210) of, respectively, 0.495 and 11.9 μM).

This was less obvious for compound **34** (IC_{50} (L1210) = 1.4 μM, 10-benzyloxy substituent), which was slightly less active than its direct counterpart (compound **28**, IC_{50} (L1210) = 0.6 μM) in the '*N*-methyl maleimide' series. Surprisingly, compound **34** (10-benzyloxy; IC_{50} (L1210) = 1.4 μM) was clearly more cytotoxic than compound **33** (9-benzyloxy; IC_{50} (L1210) = 16.3 μM), whereas their analogues **44** and **45**, devoid of a substitution on the maleimide moiety were equiactive (1.5 and 1.1 μM).

Whatever the substituent (methyl or *N*,*N*-dimethylaminoethyl) on the maleimide be, the introduction of the 9,10-methylenedioxy group clearly improved the cytotoxicity. Compounds **35** and **29** were the most active of their subset with IC_{50} (L1210) of 0.195 and 0.495 μM, respectively.

The glycosylated compounds **54**, **55**, and **56** were less active than anticipated based upon previous results. A possible explanation could be the protective groups (*O*-benzyl or *O*-acetyl) on the sugar moiety and/or the ammonium benzyl salt.

Without exception, all the compounds described were significantly less cytotoxic on the HT29 than on the L1210 cell lines with in some case (compounds **45** or **47**) a good selectivity. As seen with tests on L1210 compound **35** was the most potent with an IC_{50} (HT29) of 1.76 μM.

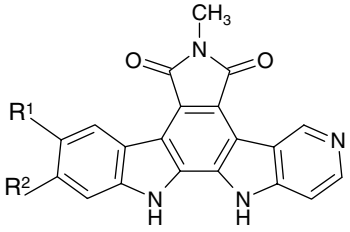
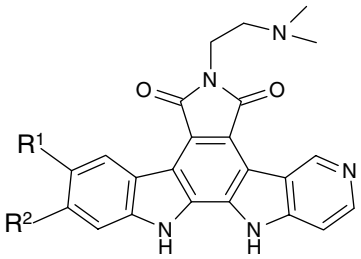
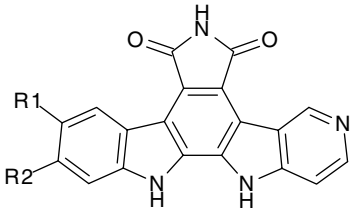
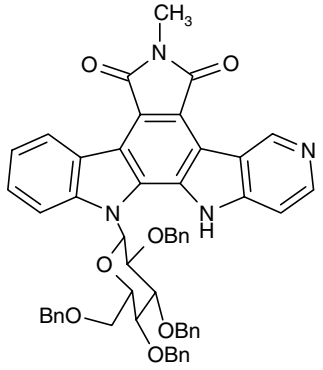
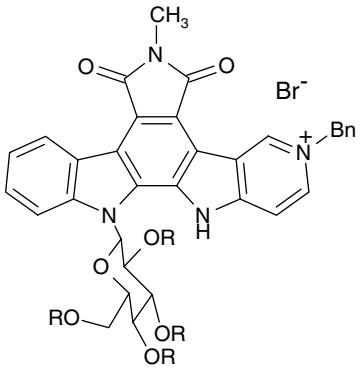
DNA flow cytometric analyses were next performed on compounds **31**, **35**, **43**, **45** using propidium iodide staining. Compound **31** was toxic at 20 μM whereas **43** was the sole derivative inducing an accumulation of cells in G1 phase (60% at 1 μM). Compounds **35** and **45** showed a G2 + M phase accumulation of cells (**35**, 62% at 1 μM; **45**, 43% at 5 μM). The most cytotoxic compound **35** was also the most active on the cell cycle. Nevertheless, there was not direct relationship between the high value of Chk1 inhibition for **45** and the antiproliferative activity.

3.2. Chk1 inhibition

The role of Chk1 in regulating the S phase: G2 phase has been demonstrated, and validates this kinase as a target for anticancer drug candidates.[25,27] Some compounds such as staurosporine and UCN-01 are described as potent but nonselective Chk1 inhibitors (Fig. 1). Another compound, isogranulatimide, is a potent Chk1 inhibitor (IC_{50} 0.438 μM) with moderate cytotoxicity (10 μM on L1210).[29]

Our compounds bearing a substitution on the maleimide moiety were without significant Chk1 inhibition. The unsubstituted compound **43** was found slightly active. Whilst substitution with a 9-benzyloxy group resulted in a moderate improvement of the activity (compound

Table 4. In vitro antiproliferative activities toward murine leukemia L1210 and human colon HT29[a]

Entry	Structures	Substitutions	Compound	L1210 (IC_{50} μM)	HT29 (IC_{50} μM)	% of Chk1 inhibition at 10 μM	Chk1 inhibition (IC_{50} μM)
1		R^1 = H, R^2 = OBn	**28**	0.6	2.0	27.0	ND
2		R^1, R^2 = —OCH_2O—	**29**	0.495	3.345	26.7	ND
3		R^1 = OH, R^2 = H	**30**	11.9	>100	38.5	ND
4		R^1 = H, R^2 = OH	**31**	2.7	16.2	66.6	5
5		R^1 = R^2 = H	**32**	0.47	3.8	49.4	ND
6		R^1 = OBn, R^2 = H	**33**	16.3	19.5	17.6	ND
7		R^1 = H, R^2 = OBn	**34**	1.4	2.9	32.7	ND
8		R^1, R^2 = —OCH_2O—	**35**	0.195	1.76	6.7	ND
9		R^1 = OH, R^2 = H	**36**	2.6	50.9	48.9	ND
10		R^1 = H, R^2 = H	**43**	0.6	1.5	98.6	5
11		R^1 = OBn, R^2 = H	**44**	1.5	7.6	90.6	1.32
12		R^1 = H, R^2 = OBn	**45**	1.1	32.4	95.9	0.025
13		R^1 = OH, R^2 = H	**46**	80.7	>100	99.1	0.027
14		R^1 = H, R^2 = OH	**47**	3.3	>100	98.7	0.014
15		—	**54**	>100	ND	49	ND
16		R = OH	**55**	12.8	63.7	51.4	ND
17		R = OAc	**56**	14.3	>100	46.5	ND

[a] IC_{50} values are presented as means of duplicate experiments.

44, IC_{50} (Chk1) = 1.02 μM), substitution with 10-benzyloxy, 9-or 10-hydroxy led to the very potent compounds **45**, **46**, and **47** with IC_{50} (Chk1) of, respectively, 72, 27, and 14 nM. The 15-fold lower activity of the 9-benzyloxy substituted compound **44** by comparison with the 10-benzyloxy compound **45** could be explained by steric hindrance in the ATP pocket of the kinase. Like reference compounds such as staurosporine, UCN-01, and isogratulatimide, our most potent original Chk1 inhibitors (compounds **45**, **46**, and **47**), which inhibited the enzyme in a nanomolar range are not substituted on the nitrogen atom of the maleimide moiety.

4. Conclusions

A new class of 1*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*a*] pyrrolo[3,4-*c*]carbazole currently named 5-azaindolocarbazole have been prepared using a Stille approach for assembling the 5-azaindole unit with the indolic counterpart. Our results highlighted the different chemical behaviors of the 5-azaindole unit compared to indole and 7-azaindole. A photocyclization strategy led to the corresponding carbazoles, which were easily glycosylated. Some of these compounds bearing a 9,10-methylenedioxy group and a substituent on the maleimide part (compounds **29** and **35**) are potent cytotoxic with IC_{50} of, respectively, 0.495 and 0.195 μM against the murine L1210 cell line. Three other compounds **45**, **46**, and **47**, which are unsubstituted on the maleimide moiety, are promising novel Chk1 inibitors with IC_{50} of 72, 27, and 14 nM, respectively.

We designed a new family of active products, which offers numerous possibilities to design either cytotoxic or Chk1 inhibitors. The 5-azaindolocarbazoles derivatives appear very promising, and are currently under further investigations to improve their Chk1 inhibiting properties. Their selectivity over other kinases including CDKs would be evaluated in a near future.

5. Experimental

5.1. General methods

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 250 or 500 instruments using $CDCl_3$ or DMSO-d_6. ^{13}C NMR was performed at 62.9 or 125.75 Hz. The chemical shifts are reported in ppm (δ scale) and all *J* values are in Hz. The following abbreviations are used: singlet (s), doublet (d), doubled doublet (dd), triplet (t), multiplet (m), quaternary carbon (Cq). Melting points are uncorrected. IR absorptions 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 API 300 or a Bruker MALDI-TOF Omniflex. 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 was performed using silica gel 60 (0.063–0.200 mm, Merck). In the attribution of chemical shift i refers to the indole part and a to the 5-azaindole moiety. Abbreviation HSQC, Heteronuclear Single Quantum Coherence.

5.1.1. 1-Methyl-3,4-bis(1*H*-pyrrolo[3,2-*c*]pyridin-1-yl)-pyrrole-2,5-dione (6). To a solution of 5-azaindole **1** (50 mg, 0.42 mmol) in toluene (2 mL), a solution of LiHMDS (1 M in hexanes, 0.92 mL, 0.92 mmol) was dropwise added. After 15 min, 3,4-dibromo-*N*-methylmaleimide **11** (40 mg, 0.14 mmol) was added and the mixture heated at reflux for 5 h. Hydrolysis was performed with water (10 mL) and the mixture extracted three times with EtOAc (3× 20 mL). After drying over $MgSO_4$ and evaporation in vacuo the residue was purified by silica gel column (AcOEt/MeOH 9:1) to afford compound **6** as a yellow solid (15 mg, 29%). Mp: 152–155 °C (degradation); IR (KBr, cm^{-1}) *ν* 723, 1465, 1713 (C═O), 2927 (CH arom); ^1H NMR ($CDCl_3$) *δ* 3.28 (s, 3H, NCH_3), 6.27 (d, 2H, H-6,$J_{H6–H7}$ = 5.7 Hz), 6.89 (d, 2H, H-3, $J_{H3–H2}$ = 3.4 Hz), 7.56 (d, 2H, H-2, $J_{H3–H2}$ = 3.4 Hz), 7.94 (d, 2H, H-7, $J_{H6–H7}$ = 5.7 Hz), 8.83 (s, 2H, H-4); ^{13}C NMR ($CDCl_3$) *δ* 24.8 (NCH_3), 105.7 (2 CH), 107.5 (2 CH), 126.2 (2 Cq), 127.7 (2 CH), 139.8 (2 Cq), 143.2 (2 CH), 144.4 (2 CH), 150.6 (2 Cq) 165.7 (2 C═O); MS (IS) *m*/*z* 344 $[M+H]^+$. Anal. Calcd for $C_{19}H_{13}N_5O_2$: C, 66.47; H, 3.82; N, 20.40. Found: C, 66.89; H, 3.74; N, 20.56.

5.1.2. 3-[1-(*tert*-Butyloxycarbonyl)-1*H*-indol-3-yl]-1-methyl-4-(1H-pyrrolo[3,2-*c*]pyridin-1-yl)pyrrole-2,5-dione (8). A 1 M solution of LiHMDS in hexanes (1.5 mL, 1.5 mmol) was added to a cooled solution (−30 °C) of compound **1** (83 mg, 0.70 mmol) in THF (3 mL). After 1 h at −30 °C a solution of compound **7** (237 mg, 0.59 mmol) in THF (5 mL) was added dropwise. The mixture was stirred for 15 min at −20 °C then 45 min at −10 °C. After the addition of an aqueous solution of 0.3 M HCl, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and evaporated under reduced pressure. The residue was purified by silica gel column (EtOAc) to yield **8** as an orange oil (29 mg, 11%). ^1H NMR ($CDCl_3$) *δ* 1.72 (s, 9H, $C(CH_3)_3$), 3.24 (s, 3H, NCH_3), 6.05 (d, 1H, $J_{H4i–H5i}$ = 8.0 Hz, H-4i,), 6.68 (dd, 1H, $J_{H5i–H6i}$ = 7.3 Hz, $J_{H4i–H5i}$ = 8.0 Hz, H-5i), 6.85 (d, 1H, $J_{H3a–H2a}$ = 3.4 Hz, H-3a), 6.90 (d, 1H, $J_{H6a–H7a}$ = 6.0 Hz, H-6a), 7.13 (dd, 1H, $J_{H6i–H7i}$ = 8.1 Hz, $J_{H5i–H6i}$ = 7.3 Hz, H-6i), 7.48 (d, 1H, $J_{H3a–H2a}$ = 3.4 Hz, H-2a), 8.07 (m, 2H, H-7i, H-7a), 8.36 (s, 1H, H-2i), 8.87 (s, 1H, H-4a); ^{13}C NMR ($CDCl_3$)*δ* 24.6 (NCH_3), 28.2 ($C(CH_3)_3$), 85.4 (CMe_3), 106.1 (CH-3a), 107.3 (CH-6a), 108.3 (Cq), 115.4 (CH-7i), 119.6 (CH-4i), 123.0 (Cq), 123.6 (CH-5i), 125.4 (CH-6i), 127.3 (Cq), 128.8 (CH-2a), 129.4 (Cq), 130.4 (CH-2i), 135.0 (Cq), 140.1 (Cq), 142.1 (CH-7a), 143.8 (CH-4a), 149.0 (COO^tBu), 167.4 (C═O), 169.2 (C═O); MS (IS) *m*/*z*: 443.5 $[M+H]^+$, 387.0 $[M+H^tBu]^+$, 343.0 $[M+H\text{-Boc}]^+$. Anal. Calcd for $C_{25}H_{22}N_4O_4$: C, 67.86; H, 5.01; N, 12.66. Found: C, 68.24; H, 5.15; N, 12.41.

5.1.3. 3-[1-(*tert*-Butyloxycarbonyl)-1*H*-indol-3-yl]-1-methyl-4-(1H-pyrrolo[3,2-*c*]pyridin-3-yl)pyrrole-2,5-dione (9). A 1 M solution of LiHMDS in hexanes (1.8 mL,

1.77 mmol) was added to a cooled solution (−30 °C) of compound **1** (200 mg, 1.69 mmol) in toluene (5 mL). After 1 h at −30 °C a solution of compound 7 (170 mg, 0.42 mmol) in toluene (5 mL) was added dropwise. The mixture was stirred for 15 min at −20 °C then 45 min at −10 °C. After addition of an aqueous solution of 0.3 M HCl (pH 7), the aqueous layer was extracted with EtOAc (3× 25 mL). The combined organic layers were washed with water and evaporated under reduced pressure. The residue was purified on a silica gel column (petroleum ether/EtOAc 6:4) to yield a solid (44 mg, 24%). Mp: 175–177 °C; IR (KBr, cm^{-1}) ν 1703 (C=O), 1740 (C=O), 3388 (NH); ^{1}H NMR ($CDCl_3$) δ 1.68 (s, 9H, $C(CH_3)_3$), 3.22 (s, 3H, NCH_3), 6.03 (d, 1H, $J_{H4i–H5i}$ = 8.1 Hz, H-4i), 6.60 (dd, 1H, $J_{H5i–H6i}$ = 7.2 Hz, $J_{H4i–H5i}$ = 8.1 Hz, H-5i), 7.01 (dd, 1H, $J_{H6i–H7i}$ = 7.8 Hz, $J_{H5i–H6i}$ = 7.2 Hz, H-6i), 7.10–7.17 (m, 1H, H-6a), 7.27 (d, 1H, $J_{H6i–H7i}$ = 7.8 Hz, H-7i), 7.50 (d, 1H, $J_{H2a–NH}$ = 3.4 Hz, H-2a), 7.89 (s, 1H, H-2i), 8.11–8.16 (m, 2H, H-4a, H-7a), 9.82 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 24.5 (NCH_3), 28.3 ($C(CH_3)_3$), 84.8 (CMe_3), 104.9 (Cq), 110.3 (Cq), 111.9 (CH), 115.6 (Cq), 120.0 (CH), 121.2 (CH), 121.7 (CH), 122.7 (CH), 123.5 (CH), 124.9 (CH), 125.2 (CH), 126.4 (CH), 126.7 (Cq), 127.6 (Cq), 128.9 (Cq), 130.9 (Cq), 136.2 (Cq), 149.4 (COO^tBu), 171.5 (C=O), 171.7 (C=O); MS (IS) *m/z*: 443.5 $[M+H]^+$, 387.0 $[M+H^tBu]^+$, 343.0 $[M+H\text{-Boc}]^+$. Anal. Calcd for $C_{25}H_{22}N_4O_4$: C, 67.86; H, 5.01; N, 12.66. Found: C, 67.51; H, 4.88; N, 12.83.

5.1.4. 4-[1-(*tert*-Butyloxycarbonyl)-1*H*-pyrrolo[3,2-*c*]-pyridin-3-yl]-1-methyl-3-(1*H*-indol-3-yl)pyrrole-2,5-dione (14). To a solution of compound **10**[36] (3.63 g, 9.53 mmol) in THF (30 mL), compound **5** (2.20 g, 6.35 mmol), $CuBr.Me_2S$ (1.96 g, 9.53 mmol) and $Pd[P(C_6H_5)_3]_4$ (0.370 g, 0.32 mmol) were added. The mixture was heated to reflux for 30 min, then a 33% aqueous NH_4OH was added (2 mL/mmol). The catalyst was filtered over Celite and washed with EtOAc (2× 30 mL). The organic layer was then washed with a 20% aqueous solution of sodium carbonate until the disappearance of the blue color then with brine, and finally evaporated in vacuo. The crude residue was purified by chromatography over silica gel (petroleum ether/EtOAc 7:3) to afford **14** as an orange solid (2.6 g, 92%). Mp: 174–176 °C (degradation); IR (KBr, cm^{-1})ν 1703 (C=O), 3380 (NH); ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 9H, $C(CH_3)_3$), 3.22 (s, 3H, NCH_3), 6.64 (ddd, 1H, $J_{H5i–H4i}$ = 7.8 Hz, $J_{H5i–H6i}$ = 7.8 Hz, $J_{H5i–H7i}$ = 1.6 Hz, H-5i), 6.74 (d, 1H, $J_{H5i–H4i}$ = 7.8 Hz), H-4i, 6.90-7.00 (m, 2H, H-7i and H-6i), 7.88 (d, 1H, $J_{H2i–NH}$ = 2.8 Hz, H-2i), 8.00 (s, 1H, H-2a), 8.03 (d, 1H, $J_{H6a–H7a}$ = 5.7 Hz, H-6a), 8.28 (d, 1H,$J_{H6a–H7a}$ = 5.7 Hz, H-7a), 8.30 (s, 1H, H-4a), 11.40 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$)δ 24.5 (NCH_3), 28.2 ($C(CH_3)_3$), 85.9 (CMe_3), 106.1 (Cq), 110.2 (Cq), 110.4 (CH-6a); 112.3 (CH-6i), 120.5 (CH-5i), 120.6 (Cq), 122.4 (Cq), 122.7 (CH-7i), 125.3 (Cq), 125.7 (CH-4i), 128.8 (CH-4a), 130.0 (CH-2i), 132.5 (Cq); 136.5 (Cq), 139.5 (Cq), 143.3 (CH-7a), 143.9 (CH-2a), 148.8 (COO^tBu), 171.8 (C=O), 171.9 (COO^tBu); MS (IS) *m/z*: 443.0 $[M+H]^+$, 387.0 $[M+H\text{-}tert\text{-butyl}]^+$, 343.0 $[M+H\text{-Boc}]^+$. Anal. Calcd for $C_{25}H_{22}N_4O_4$: C, 67.86; H, 5.01; N, 12.66. Found: C, 68.07; H, 5.17; N, 12.50.

5.1.5. 3-Bromo-4-(5*H*-[1,3]dioxolo[4,5-*f*]indol-7-yl)-1-methylpyrrole-2,5-dione (20). A solution of **17** (1.92 g, 11.90 mmol) in THF (50 mL) was cooled to −15 °C and a solution of LiHMDS (1 M in hexanes, 35.7 mL, 35.7 mmol) was dropwise added in 30 min. The mixture was stirred at −15 °C for 1 h before adding in 30 min the 3,4-dibromo-*N*-methylmaleimide **11** (3.20 g, 11.91 mol) dissolved in THF (20 mL). After stirring at −15 °C for 15 min then at 0 °C for 15 min, an aqueous 0.3 M HCl is added till pH 3. Extraction with EtOAc (2× 50 mL) and washing with brine (2× 20 mL) leaved to a solid residue after evaporation. The residue was triturated in the minimum of methanol to yield after filtration **20** as a pale brown solid (3.6 g, 88%). Mp: 150–152 °C; IR (KBr, cm^{-1})ν 1452, 1708 (C=O), 3376 (NH); ^{1}H NMR ($CDCl_3$)δ 3.16 (s, 3H, NCH_3), 5.99 (s, 2H, OCH_2O), 6.87 (s, 1H, H-7), 7.43 (s, 1H, H-4), 7.85 (d, 1H, $J_{H2–NH}$ = 3.0, H-2), 8.63 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6)δ 4.5 (NCH_3), 92.8 (CH-7), 100.7 (OCH_2O), 100.9 (CH-4), 104.3 (Cq), 113.0 (Cq), 120.7 (Cq), 129.4 (CH-2), 131.5 (Cq), 137.6 (Cq), 143.1 (Cq), 144.7 (Cq), 166.5 (C=O), 169.1 (C=O). Anal. Calcd for $C_{14}H_9BrN_2O_4$: C, 48.16; H, 2.60; N, 8.02. Found: C, 48.55; H, 2.43; N, 7.86.

5.1.6. 3-(5-Benzyloxy-1*H*-indol-3-yl)-4-[1-(*tert*-butyl oxycarbonyl)-1 *H*-pyrrolo[3,2-*c*]pyridin-3-yl]-1-methyl pyrrole-2,5-dione (21). Similar preparation as for **14** starting from **18**.[32] After a flash chromatography (EtOAc/MeOH 95:5), compound **21** was obtained as an orange solid (504 mg, 76%). Mp: 145–146 °C; IR (KBr, cm^{-1}) ν 1152 (C–O–C), 1712 (C=O), 1756 (C=O), 3430 (NH); ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 9H, $C(CH_3)_3$), 3.22 (s, 3H, NCH_3), 4.26 (s, 2H, CH_2Ph), 6.25 (d, 1H, $J_{H4i–H6i}$ = 2.2 Hz, H-4i), 6.64 (dd, 1H, $J_{H6i–H7i}$ = 8.7, $J_{H4i–H6i}$ = 2.2 Hz, H-6i), 6.91 (d, 1H, $J_{H6i–H7i}$ = 8.7 Hz, H-7i), 7.19-7.34 (m, 5H, CH_2Ph), 7.94 (d, 1H, $J_{H2i–NH}$ = 2.6 Hz, H-2i), 8.06 (d, 1H, $J_{H6a–H7a}$ = 5.2 Hz, H-6a), 8.12 (s, 1H, H-2a), 8.23 (s, 1H, H-4a), 8.34 (d, 1H, $J_{H6a–H7a}$ = 5.2 Hz, H-7a), 10.87 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$)δ 24.5 (NCH_3), 28.1 ($C(CH_3)_3$), 70.3 (CH_2Ph), 86.0 (CMe_3), 103.9 (CH-4i), 106.0 (Cq), 110.3 (CH-6a), 110.9 (Cq), 113.2 (CH-7i), 113.9 (CH-6i), 121.2 (Cq), 126.0 (Cq), 126.1 (Cq), 127.5 (2 CH), 128.0 (CH), 128.5 (CH-4a), 128.6 (2 CH), 130.8 (CH-2i), 131.7 (Cq), 133.1 (Cq), 137.1 (Cq), 139.5 (Cq), 143.4 (CH-7a), 143.8 (CH-2a), 148.7 (Cq), 153.7 (COO^tBu), 171.8 (C=O), 171.9 (C=O); MS (IS) *m/z*: 549.5 $[M+H]^+$, 493.5 $[M+H\text{-}tert\text{-butyl}]^+$, 449.0 $[M+H\text{-Boc}]^+$. Anal. Calcd for $C_{32}H_{28}N_4O_5$: C, 70.06; H, 5.14; N, 10.21. Found: C, 69.70; H, 5.01; N, 10.37.

5.1.7. 3-(6-Benzyloxy-1*H*-indol-3-yl)-4-[1-(*tert*-butyloxy carbonyl)-1*H*-pyrrolo[3,2-*c*]pyridin-3-yl]-1-methyl pyrrole-2,5-dione (22). Similar preparation as for **21** starting from **19**.[32] After a flash chromatography (EtOAc), compound **22** was obtained as an orange solid (1.1 g, 87%). Mp: 153–155 °C (degradation); IR (KBr, cm^{-1}) ν 1153 (C–O–C), 1692 (C=O), 1754 (C=O), 3444 (NH); ^{1}H

NMR ($CDCl_3$)δ 1.75 (s, 9H, $C(CH_3)_3$), 3.18 (s, 3H, NCH_3), 4.79 (s, 2H, CH_2Ph), 6.36 (d, 1H, $J_{H4i–H5i}$ = 8.8 Hz, H-4i), 6.58 (d, 2H, H-5i, H-7i), 7.26 (m, 5H, H arom), 7.73 (s, 1H, H-2i), 8.02–8.04 (m, 2H, H-2a, H-6a), 8.28 (s, 2H, H-4a, H-7a), 11.57 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 24.5 (NCH_3), 28.3 ($C(CH_3)_3$), 70.3 (CH_2Ph), 85.9 (CMe_3), 96.6 (CH-7i), 106.1 (Cq), 110.3 (CH-6a), 111.2 (CH-4i), 120.1 (CH-5i), 121.3 (Cq), 122.1 (Cq), 124.3 (Cq), 125.3 (Cq), 127.6 (2 CH), 127.9 (CH), 128.5 (2 CH), 128.8 (CH-4a), 129.3 (CH-2i), 132.5 (Cq), 137.2 (Cq), 137.4 (Cq), 139.5 (Cq), 143.4 (CH-7a), 144.0 (CH-2a), 148.8 (Cq), 155.7 (COO^tBu), 171.7 (C=O), 171.9 (C=O); MS (IS) *m/z*: 549.5 [M+H]+. Anal. Calcd for $C_{32}H_{28}N_4O_5$: C, 70.06; H, 5.14; N, 10.21. Found: C, 70.37; H, 5.33; N, 10.08.

5.1.8. 3-(5*H*-[1,3]Dioxolo[4,5-*f*]indol-7-yl)-4-[1-(*tert*-butyloxycarbonyl)-1*H*-pyrrolo[3,2-*c*]pyridin-3-yl]-1-methylpyrrole-2,5-dione (23). Similar preparation as for **21** starting from **20**. After a flash chromatography (petroleum ether/EtOAc 2/8), compound **23** was obtained as a red solid (841 mg, 72%). Mp: 179–181 °C; IR (KBr, cm^{-1}) ν 1151, 1701 (C=O), 1754 (C=O), 3200-3600 (NH); ^1H NMR ($CDCl_3$) δ 1.75 (s, 9H, $C(CH_3)_3$), 3.19 (s, 3H, NCH_3), 5.71 (s, 2H, OCH_2O), 6.15 (s, 1H, H-4i), 6.36 (s, 1H, H-7i), 7.70 (s, 1H, H-2i), 8.01 (s, 1H, H-2a), 8.06 (d, 1H, H-6a, $J_{H6a–H7a}$ = 5.6 Hz), 8.30–8.32 (m, 2H, H-7a and H-4a), 11.93 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 24.4 (NCH_3), 28.2 ($C(CH_3)_3$), 85.9 (CMe_3), 92.9 (CH-7i), 99.0 (CH-4i), 100.5 (OCH_2O), 106.2 (Cq), 110.1 (Cq), 110.3 (CH-6a), 119.9 (Cq), 121.9 (Cq), 125.3 (Cq), 128.7 (CH-7a), 132.2 (CH-2i), 139.7 (Cq), 143.1 (CH-4a), 143.2 (Cq), 143.8 (CH-2a), 144.9 (Cq), 148.7 (COO^tBu), 171.7 (C=O), 171.8 (C=O); MS (IS) *m/z*: 487 $[M+H]^+$. Anal. Calcd for $C_{26}H_{22}N_4O_6$: C, 64.19; H, 4.56; N, 11.52. Found: C, 64.56; H, 4.74; N, 11.36.

5.1.9. 3-(1*H*-Indol-3-yl)-1-methyl-4-(1*H*-pyrrolo[3,2-*c*]-pyridin-3-yl) pyrrole-2,5-dione (24). A solution of compound **14** (100 mg, 0.23 mmol) in formic acid was stirred overnight at room temperature. Evaporation of the mixture under vacuum left a residue, which is dissolved in EtOAc (10 mL) and washed with a saturated solution of $NaHCO_3$ till pH 7 then with brine (10 mL). After evaporation compound **24** was obtained as a red solid (76 mg, 99%). Mp: 190–192 °C; IR (KBr, cm^{-1}) ν 1695 (C=O), 3380 (NH); ^1H NMR (DMSO-d_6) δ 3.06 (s, 3H, NCH_3), 6.60 (d, 1H, $J_{H4i–H5i}$ = 7.8 Hz, H-4i), 6.68 (dd, 1H, $J_{H5i–H6i}$ = 7.6 Hz, $J_{H4i–H5i}$ = 7.8 Hz, H-5i), 6.98 (dd, 1H, $J_{H6i–H7i}$ = 8.1 Hz, $J_{H5i–H6i}$ = 7.6 Hz, H-6i), 7.35 (d, 1H, $J_{H6a–H7a}$ = 5.4 Hz, H-6a), 7.39 (d, 1H, $J_{H6a–H7a}$ = 5.4 Hz, H-7i), 7.83-7.85 (m, 2H, H-2i, H-7a), 8.00 (br s, 2H, H-2a, H-4a), 11.79 (s, 1H, NH), 12.00 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 24.0 (NCH_3), 105.1 (CH), 105.2 (CH), 107.1 (CH), 112.0 (Cq), 119.5 (CH), 120.7 (CH), 121.8 (CH), 122.3 (Cq), 125.0 (Cq), 125.6 (Cq), 128.5 (CH), 129.9 (Cq), 136.1 (Cq), 139.4 (CH), 140.4 (Cq), 143.5 (CH), 171.5 (C=O), 171.6 (C=O); MS (MALDI) *m/z* : 343 $[M+H]^+$. Anal. Calcd for $C_{20}H_{14}N_4O_2$: C, 70.17; H, 4.12; N, 16.36. Found: C, 70.41; H, 4.23; N, 16.19.

5.1.10. 3-(1*H*-Indol-3-yl)-1-methyl-4-(1*H*-pyrrolo[3,2-*c*]pyridin-3-yl)pyrrolidine-2,5-dione (25). A suspension of compound **24** (95 mg, 0.028 mmol) and palladium over carbon 10% (10 mg, 0.009 mmol) in DMF (10 mL) was stirred under hydrogen pressure (50 psi) for 5 days at 30 °C, in a Parr apparatus. The catalyst was filtered and washed with methanol, the filtrate was evaporated in vacuum and the residue was purified by silica gel column (petroleum ether/EtOAc 9:1) to yield compound **25** as a red solid (94 mg, 98%). Mp: 182–184 °C; IR (KBr, cm^{-1}) ν 1699 (C=O), 3397 (NH); ^1H NMR (MeOD) δ 3.14 (s, 3H, NCH_3), 4.45 (d, 1H, $J_{CH–CH}$ = 6.7 Hz), 4.60 (d, 1H, $J_{CH–CH}$ = 6.7 Hz), 6.92 (ddd, 1H, $J_{H5i–H6i}$ = 7.1 Hz, $J_{H5i–H4i}$ = 7.9 Hz, $J_{H5i–H7i}$ = 1.0 Hz, H-5i), 7.05 (ddd, 1H, $J_{H6i–H7i}$ = 8.1 Hz, $J_{H6i–H4i}$ = 1.0 Hz, $J_{H5i–H6i}$ = 7.1 Hz, H-6i), 7.15 (s, 1H, H-2i), 7.23–7.35 (m, 4H, H-7i, H-4i, H-2a, H-6a), 8.05 (br s, 1H, H-7a), 8.39 (s, 1H, H-4a); ^{13}C NMR (MeOD) δ 25.6 (NCH_3), 47.7 (CH), 48.4 (CH), 110.8 (CH-6a), 112.8 (CH-7i), 119.3 (CH-5i), 120.3 (CH-6i), 120.8 (Cq), 122.1 (Cq), 122.9 (CH-2i), 123.2 (Cq), 125.1 (CH-4i), 126.5 (CH-2a), 130.6 (Cq), 131.4 (Cq), 138.4 (Cq), 140.2 (CH-7a), 142.2 (CH-4a), 178.7 (C=O), 179.3 (C=O); MS (IS) *m/z*: 345.0 $[M+H]^+$. Anal. Calcd for $C_{20}H_{16}N_4O_2$: C, 69.76; H, 4.68; N, 16.27. Found: C, 70.13; H, 4.52; N, 16.12.

5.1.11. 6-Methyl-1*H*-pyrido[3′4′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*] carbazole-5,7(6*H*,12*H*)-dione (26). A solution of **14** (100 mg, 0.226 mmol) and diiodine (575 mg, 2.26 mmol) in toluene (450 mL) was irradiated for 30 min in a quartz vessel with a 'DEMA UV-lamp TQ-718 500 W'. The mixture was then treated with a solution of 10% aqueous sodium metabisulfite (100 mL). The aqueous layer was extracted with EtOAc (2× 25 mL) and the combined organic layers were washed twice with water (25 mL). After evaporation, the residue was washed first with methanol (20 mL) then with hot DMF (2× 20 mL). The DMF extract was concentrated till 2 mL. After cooling and addition of EtOAc (2 mL) the obtained precipitate was filtered and washed successively with 10 mL of water, methanol, and diethyl ether to give **26** as a yellow solid (74 mg, 96%). Mp: >250 °C; IR (KBr, cm^{-1}) ν 973, 1146, 1264, 1705 (C=O), 3158–3585 (NH); ^1H NMR (DMSO-d_6, 500 MHz) δ 3.15 (s, 3H, NCH_3), 7.34 (dd, 1H,$_{JH8–H9}$ = 7.8 Hz, $J_{H9–H10}$ = 7.7 Hz, H-9), 7.53 (dd, 1H, $J_{H10–H11}$ = 7.5 Hz, $J_{H9–H10}$ = 7.7 Hz, H-10), 7.72 (d, 1H, $J_{H8–H9}$ = 7.8 Hz, H-8), 7.95 (br s, 1H, H-2), 8.62 (br s, 1H, H-1), 8.88 (d, 1H, $J_{H10–H11}$ = 7.5 Hz, H-11), 9.89 (br s, 1H, H-4), 9.95 (br s, 1H, NH), 11.83 (s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6) δ 23.5 (NCH_3), 108.2 (C-10), 111.6 (C-2), 111.9 (C-4), 120.4 (C-3), 122.9 (C-11), 123.8 (C-1), 140.4 (C-8) ; MS (MALDI) *m/z*: 341 $[M+H]^+$. Anal. Calcd for $C_{20}H_{12}N_4O_2$: C, 70.58; H, 3.55; N, 16.46. Found: C, 70.94; H, 3.37; N, 16.28.

5.1.12. 9-Benzyloxy-6-methyl-1*H*-pyrido[3′4′:4,5]pyrrolo-[2,3-*a*]pyrrolo[3,4-c]carbazole-5,7(6*H*,12*H*)-dione (27). Similar preparation as for **26** starting from **21**. Compound **27** was obtained as a yellow solid (74 mg, 91%). Mp: >250 °C; IR (KBr, cm^{-1}) ν 1124, 1706 (C=O), 3466 (NH); ^1H NMR (DMSO-d_6, 500 MHz) δ 3.20 (s, 3H, NCH_3), 5.25 (s, 2H, CH_2Ph), 7.29–7.31 (dd, 1H,

$J_{H11–H10}$ = 8.8 Hz, $J_{H10–H8}$ = 2.4 Hz, H-10), 7.35–7.37 (m, 1H, H arom), 7.42–7.45 (m, 2H, H arom), 7.57–7.59 (m, 3H, 2H arom, H-8), 7.75 (d, 1H, $J_{H10–H11}$ = 8.8 Hz, H-11), 7.79 (d, 1H, $J_{H1–H2}$ = 5.5 Hz, H-2), 8.56 (d, 1H, $J_{H1–H2}$ = 5.5 Hz, H-1), 8.66 (d, 1H, $J_{H4–H2}$ = 2.2 Hz, H-4), 10.03 (s, 1H, NH), 11.71 (s, 1H, NH). ^{13}C NMR HSQC (DMSO-d_6, 500 MHz) δ 23.2 (NCH_3), 69.4 (CH_2Ph), 107.1 (CH-11), 107.3 (CH-8), 107.3 (CH-10), 112.3 (CH-4), 112.6 (CH-1), 117.0 (CH-2), 127.5 (2 CH), 127.5 (CH), 128.0 (2 CH); MS (MALDI) *m*/*z*: 447 $[M+H]^+$. Anal. Calcd for $C_{27}H_{18}N_4O_3$: C, 72.64; H, 4.06; N, 12.55. Found: C, 72.97; H, 3.87; N, 12.41.

5.1.13. 10-Benzyloxy-6-methyl-1*H*-pyrido[3′4′:4,5]pyrrolo-[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*,12*H*)-dione (28). Similar preparation as for **26** starting from **22**. Compound **28** was obtained as a yellow solid (72 mg, 89%). Mp: >250 °C; IR (KBr, cm^{-1}) *v* 746, 1120, 1379, 1701 (C═O), 3000–3450 (NH); ^{1}H NMR (DMSO-d_6, 500 MHz, 40 °C) δ 3.17 (s, 3H, NCH_3), 5.27 (s, 2H, CH_2Ph), 7.06 (dd, 1H, $J_{H8–H9}$ = 8.7 Hz, $J_{H9–H11}$ = 2.2 Hz, H-9), 7.36–7.38 (m, 2H, CH, H-11), 7.42–7.45 (m, 2H), 7.54–7.55 (m, 2H), 7.77 (d, 1H, $J_{H1–H2}$ = 5.6 Hz, H-2), 8.55 (d, 1H, $J_{H1–H2}$ = 5.6 Hz, H-1), 8.81 (d, 1H, $J_{H8–H9}$ = 8.7 Hz, H-8), 9.98 (s, 1H, H-4), 11.67 (s, 1H, NH), 12.22 (s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6, 40 °C) δ 23.3 (NCH_3), 69.4 (CH_2Ph), 93.3 (CH-1), 107.1 (CH-10), 110.2 (CH-3), 124.8 (CH-4), 127.2 (2 CH), 127.7 (CH), 128.2 (2 CH), 144.0 (CH-11), 144.8 (CH-8); MS (MALDI) *m*/*z*: 447 $[M+H]^+$. Anal. Calcd for $C_{27}H_{18}N_4O_3$: C, 72.64; H, 4.06; N, 12.55. Found: C, 72.33; H, 4.15; N, 12.37.

5.1.14. 1,3-Dioxolo[4,5-*b*]-6-methyl-1*H*-pyrido[3′,4′:4,5]pyrrolo[3,2-*i*]pyrrolo[3,4-*g*]carbazole-5,7-dione (29). Similar preparation as for **26** starting from **23**. Compound **29** was obtained as a pale brown solid (73 mg, 92%); Mp: >250 °C. IR (KBr, cm^{-1})*v* 1470, 1699 (C═O), 3430 (NH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.05 (s, 3H, NCH_3), 6.09 (s, 2H, OCH_2O), 7.13 (s, 1H, H-8), 7.58 (br s, 1H, H-2), 8.10 (s, 1H, H-11), 8.44 (br s, 1H, H-1), 9.80 (s, 1H, H-4), 11.51 (br s, 1H, NH), 11.86 (br s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6)δ 23.7 (NCH_3), 92.6 (CH-4), 101.0 (OCH_2O), 102.0 (CH-1), 107.0 (CH-10), 144.5 (CH-11), 145.5 (CH-8). MS (MALDI) *m*/*z*: 385 $[M+H]^+$. Anal. Calcd for $C_{21}H_{12}N_4O_4$: C, 65.63; H, 3.15; N, 14.58. Found: C, 65.90; H, 3.22; N, 14.43.

5.1.15. 9-Hydroxy-6-methyl-1*H*-pyrido[3′4′:4,5] pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*,12*H*)-dione (30). A 1 M solution of BBr_3 in dichloromethane (3.4 mL, 3.4 mmol) was added to an ice-cooled solution of compound **27** (150 mg, 0.34 mmol) in dichloromethane (2 mL), under nitrogen. After 30 min at room temperature, methanol was added. The precipitate was filtered and washed with methanol (2× 10 mL) to give compound **30** as a yellow solid (74 mg, 62%). Mp: >250 °C; IR (KBr, cm^{-1}) *v* 1700 (C═O), 3224–3430 (NH, OH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.12 (s, 3H, NCH3), 7.07 (dd, 1H, $J_{H10–H11}$ = 8.7 Hz, $J_{H8–H10}$ = 2.3 Hz, H-10), 7.57 (d, 1H, $J_{H10–H11}$ = 8.7 Hz, H-11), 8.19 (d, 1H, $J_{H8–H10}$ = 2.3 Hz, H-8), 8.24 (d, 1H, $J_{H1–H2}$ = 6.6 Hz, H-2), 8.77 (d, 1H, $J_{H1–H2}$ = 6.6 Hz, H-1), 9.34 (br s, 1H, OH), 9.81 (s, 1H, H-4), 11.67 (s, 1H, NH), 13.06 (s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6)δ 23.3 (NCH_3), 108.1 (CH-4), 109.2 (CH-10), 112.6 (CH-1), 117.5 (CH-2), 135.6 (CH-11), 137.1 (CH-8); MS (MALDI) *m*/*z*: 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, 3.54; N, 15.55.

5.1.16. 10-Hydroxy-6-methyl-1*H*-pyrido[3′4′:4,5]pyrrolo-[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*,12*H*)-dione (31). Similar preparation as for **30** starting from **28**. Compound **31** was obtained as a red solid (21 mg, 55%). Mp: >250 °C; IR (KBr, cm^{-1})*v* 1378, 1699 (C═O), 3210–3444 (NH, OH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.07 (s, 3H, NCH_3), 6.79 (d, 1H, $J_{H8–H9}$ = 8.5 Hz, H-9), 7.03 (s, 1H, H-11), 8.19 (d, 1H, $J_{H2–H1}$ = 6.6 Hz, H-2), 8.49 (d, 1H, $J_{H8–H9}$ = 8.5 Hz, H-8), 8.74 (d, 1H, $J_{H1–H2}$ = 6.6 Hz, H-1), 9.74 (s, 1H, H-4), 9.96 (s, 1H, OH), 11.61 (s, 1H, NH), 12.90 (br s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6) δ 23.4 (NCH_3), 96.8 (CH-1), 109.4 (CH-10), 110.8 (CH-3), 125.0 (CH-4), 135.8 (CH-11), 137.2 (CH-8); MS (MALDI) *m*/*z*: 357 $[M+H]^+$. Anal. Calcd for $C_{20}H_{12}N_4O_3$: C, 67.41; H, 3.39; N, 15.72. Found: C, 67.76; H, 3.50; N, 15.63.

5.1.17. 6-(2-Dimethylaminoethyl)-1*H*-pyrido[3′4′:4,5]-pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*,12*H*)-dione (32). A solution of compound **26** (50 mg, 0.15 mmol) in *N*,*N*-dimethylethylenediamine (1 mL) was heated to reflux for 24 h. After evaporation, the residue was triturated in methanol and filtered to afford a brown-orange solid (41 mg, 70%). Mp: >200 °C; IR (KBr, cm^{-1}) *v* 800, 1019, 1260, 1697 (C═O), 2956 (CH arom), 3250 (NH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.26 (s, 6H, $N(CH_3)_2$), 2.64–2.65 (m, 2H, CH_2NMe_2), 3.84 (t, 2H, *J* = 6.5 Hz, CH_2N), 7.36 (dd, 1H, $J_{H8–H9}$ = 7.6 Hz, $J_{H9–H10}$ = 7.4 Hz, H-9), 7.57 (dd, 1H, $J_{H10–H11}$ = 7.9 Hz, $J_{H9–H10}$ = 7.4 Hz, H-10), 7.71–7.74 (m, 2H, H-8 and H-2), 8.56 (d, 1H, $J_{H1–H2}$ = 5.5 Hz, H-1), 8.98 (d, 1H, $J_{H10–H11}$ = 7.9 Hz, H-11), 10.03 (s, 1H, H-4), 12.89 (s, 1H, NH), 13.25 (br s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6) δ 35.2 (CH_2N), 45.2 ($N(CH_3)_2$), 56.7 (CH_2NMe_2), 107.0 (CH-10), 111.5 (CH-4), 120.3 (CH-3), 124.1 (CH-1), 127.1 (CH-2), 145.0 (CH-11), 146.1 (CH-8); MS (I) *m*/*z*: 398 $[M+H]^+$. Anal. Calcd for $C_{23}H_{19}N_5O_2$: C, 69.51; H, 4.82; N, 17.62. Found: C, 69.27; H, 4.89; N, 17.78.

5.1.18. 9-Benzyloxy-6-(2-dimethylaminoethyl)-1*H*-pyrido[3′4′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*,12*H*)-dione (33). Similar preparation as for **32** starting from**27**. Compound **33** was obtained as a red solid (62 mg, 88%). Mp: >200 °C; IR (KBr, cm^{-1}) *v* 1385 (C–O–C), 1705 (C═O), 3432 (NH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.24 (s, 6H, $N(CH_3)_2$), 2.61 (t, 2H, *J* = 6.5 Hz, CH_2NMe_2), 3.81 (t, 2H, *J* = 6.5 Hz, $C(O)NCH_2$), 5,23 (s, 2H, CH_2Ph), 7.28 (dd, 1H, $J_{H10–H11}$ = 8.8 Hz, $J_{H11–NH}$ = 2.4 Hz, H-11), 7.35 (t, 1H, *J* = 7.5 Hz, H arom), 7.42 (dd, 2H,[3] *J* = 7.5 Hz, *J* = 7.2 Hz, H arom), 7.58 (d, 2H, *J* = 7.2 Hz, H arom),

7.65 (dd, 1H,$J_{H8–H10}$ = 1.7 Hz, $J_{H10–H11}$ = 8.8 Hz, H-10), 7.69 (d, 1H, $J_{H1–H2}$ = 5.0 Hz, H-2), 8.54 (d, 1H, $J_{H2–H1}$ = 5.0 Hz, H-1), 8.61 (d, 1H, $J_{H10–H8}$ = 1.7 Hz, H-8), 10.00 (s, 1H, H-4), 12.63 (s, 1H, NH), 13.11 (s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6) δ 35.8 (NCH_2), 40.6 ($N(CH_3)_2$), 57.6 (CH_2NMe_2), 70.7 (CH_2Ph), 107.6 (CH-10), 108.6 (CH-4), 113.3 (CH-2) 117.8 (CH-1), 128.2 (CH), 128.5 (2 CH) 129.1 (2 CH), 145.1 (CH-8), 145.9 (CH-11); MS (MALDI) *m/z*: 504 $[M+H]^+$. Anal. Calcd for $C_{30}H_{25}N_5O_3$: C, 71.56; H, 5.00; N, 13.91. Found: C, 71.30; H, 4.82; N, 14.05.

5.1.19. 10-Benzyloxy-6-(2-dimethylaminoethyl)-1*H*-pyrido[3′4′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*, 12*H*)-dione (34). Similar preparation as for **32** starting from **28**. Compound **34** was obtained as a red solid (42 mg, 60%). Mp: >200 °C; IR (film, cm^{-1}) *v* 1387 (C–O–C), 1691 (C═O), 3097–3355 (NH) ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.22 (s, 6H, $N(CH_3)_2$), 2.58 (t, 2H, *J* = 6.5 Hz, CH_2NMe_2), 3.78 (t, 2H, *J* = 6.5 Hz, $C(O)NCH_2$), 5.27 (s, 2H, CH_2Ph), 7.06 (dd, 1H, $J_{H9–H11}$ = 1.9 Hz, $J_{H9–H8}$ = 8.7 Hz, H-9), 7.37 (t, 1H, *J* = 7.3 Hz, H arom), 7.41 (s, 1H, H-11), 7.44 (dd, 2H, *J* = 7.3 Hz, *J* = 7.5 Hz, H arom), 7.55 (d, 2H, *J* = 7.5 Hz, H arom), 7.76 (d, 1H, $J_{H1–H2}$ = 5.6 Hz, H-2), 8.55 (d, 1H, $J_{H1–H2}$ = 5.6 Hz, H-1), 8.81 (d, 1H, $J_{H9–H8}$ = 8.7 Hz, H-8), 9.99 (s, 1H, H-4), 11.77 (br s, 1H, NH), 12.07 (br s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6)δ 35.1 (CH_2NMe_2), 45.0 ($N(CH_3)_2$), 56.9 (NCH_2), 69.2 (CH_2Ph), 96.4 (CH-1), 107.1 (CH-10), 110.3 (CH-3), 125.0 (CH-4), 127.3 (CH), 127.3 (2 CH), 128.1 (2 CH), 144.7 (CH-8), 145.1 (CH-11); MS (MALDI) *m/z*: 504 $[M+H]^+$. Anal. Calcd for $C_{30}H_{25}N_5O_3$: C, 71.56; H, 5.00; N, 13.91. Found: C, 71.24; H, 5.17; N, 13.82.

5.1.20. 1,3-Dioxolo[4,5-*b*]-6-(2-dimethylaminoethyl)-1*H*-pyrido[3′,4′:4,5]pyrrolo[3,2-*i*]pyrrolo[3,4-*g*]carbazole-5,7(6*H*,12*H*)-dione (35). Similar preparation as for **32** starting from **29**. Compound **35** was obtained as a brown-red solid (71 mg, 62%). Mp: >200 °C; IR (KBr, cm^{-1}) *v* 1036, 1134, 1468, 1691 (C═O), 3200–3450 (NH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.28 (s, 6H, $N(CH_3)_2$), 2.65 (t, 2H, *J* = 6.0 Hz, CH_2NMe_2), 3.78 (t, 2H, *J* = 6.0 Hz, NCH_2), 6.13 (s, 2H, OCH_2O), 7.30 (s, 1H, H-8), 7.70 (d, 1H, $J_{H1–H2}$ = 6.1 Hz, H-2), 8.28 (s, 1H, H-11), 8.51 (d, 1H, $J_{H1–H2}$ = 6.1 Hz, H-1), 9.93 (s, 1H, H-4), 11.87 (s, 1H, NH), 12.19 (br s, 1H, NH); ^{13}C HSQC (DMSO-d_6) δ 35.1 (NCH_2), 44.8 ($N(CH_3)_2$), 56.8 (CH_2NMe_2), 92.9 (CH-4), 101.4 (OCH_2O), 102.1 (CH-1), 107.3 (CH-10), 144.5 (CH-11), 145.8 (CH-8); MS (MALDI) *m/z*: 442 $[M+H]^+$. Anal. Calcd for $C_{24}H_{19}N_5O_4$: C, 65.30; H, 4.34; N, 15.86. Found: C, 65.65; H, 4.50; N, 15.79.

5.1.21. 6-(2-Dimethylaminoethyl)-9-hydroxy-1*H*-pyrido[3′4′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*, 12*H*)-dione (36). Similar preparation as for **32** starting from **30**. Compound **36** was obtained as a brown-red solid (28 mg, 48%). Mp: >250 °C; IR (KBr, cm^{-1})*v* 1386, 1691 (C═O); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.40 (s, 6H, $N(CH_3)_2$), 2.82 (m, 2H, CH_2NMe_2), 3.87 (t, 2H, *J* = 6.0 Hz, NCH_2), 7.07 (dd, 1H, $J_{H10–H11}$ = 8.7 Hz, $J_{H8–H10}$ = 2.3 Hz, H-10), 7.61 (d, 1H,$J_{H10–H11}$ = 8.7 Hz, H-11), 7.75 (d, 1H, $J_{H1–H2}$ = 5.5 Hz, H-2), 8.42 (d, 1H, $J_{H10–H8}$ = 2.3 Hz, H-8), 8.54 (d, 1H,$J_{H1–H2}$ = 5.5 Hz, H-1), 9.27 (br s, 1H, OH), 10.00 (s, 1H, H-4), 11.69 (s, 1H, NH), 12.01 (br s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6) δ 34.6 (NCH_2), 44.3 ($N(CH_3)_2$), 56.3 (CH_2NMe_2), 107.3 (CH-10), 108.4 (CH-4), 112.1 (CH-1), 116.5 (CH-2), 144.6 (CH-11), 145.2 (CH-8); MS (MALDI) *m/z*: 414 $[M+H]^+$. Anal. Calcd for $C_{23}H_{19}N_5O_3$: C, 66.82; H, 4.63; N, 16.94. Found: C, 66.57.; H, 4.52; N, 17.11.

5.1.22. 3-(5-Benzyloxy-1*H*-indol-3-yl)-4-bromo-1*H*-pyrrole-2,5-dione (38). Similarly prepared as for **37**[38] from 5-benzyloxyindole. Compound **38** was obtained as an orange solid (1.4 g, 80%). Mp: 277–278 °C; IR (KBr, cm^{-1}) *v* 1704 (C═O), 3296 (NH); ^{1}H NMR (DMSO-d_6) δ 5.12 (s, 2H, CH_2Ph), 6.95 (dd, 1H, $J_{H6–H7}$ = 8.8 Hz,$J_{H6–H4}$ = 2.4 Hz, H-6), 7.31–7.49 (m, 7H, H arom, H-7, H-4), 7.97 (s, 1H, H-2), 11.29 (br s, 1H, NH), 11.98 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6)δ 69.7 (CH_2Ph), 103.6 (Cq), 106.1 (Cq), 106.1 (CH-7 or CH-4), 113.0 (CH-7 or CH-4), 113.0 (CH-6), 113.6 (Cq), 127.5 (CH), 127.6 (2 CH), 128.4 (2 CH), 131.6 (CH-2 and Cq), 137.5 (Cq), 137.9 (Cq), 153.1 (Cq), 167.5 (C═O), 170.4 (C═O); MS (IS) *m/z*: 397 $[M+H]^+$ ^{79}Br, 399 $[M+H]^+$ ^{81}Br. Anal. Calcd for $C_{19}H_{13}BrN_2O_3$: C, 57.45; H, 3.30; N, 7.05. Found: C, 57.08.; H, 3.45; N, 7.17.

5.1.23. 3-(6-Benzyloxy-1*H*-indol-3-yl)-4-bromo-1*H*-pyrrole-2,5-dione (39). Similarly prepared as for **37**[38] from 6-benzyloxyindole. Compound **39**was obtained as a red solid (1.1 g, 76%). Mp: 151–152 °C; IR (KBr, cm^{-1})*v* 1714 (C═O), 3346 (NH); ^{1}H NMR (DMSO-d_6)δ.15 (s, 2H, CH_2Ph), 6.88 (dd, 1H, $J_{H5–H4}$ = 8.8 Hz, $J_{H5–H7}$ = 2.5 Hz, H-5), 7.06 (d, 1H, $J_{H5–H7}$ = 2.5 Hz, H-7), 7.32–7.50 (m, 5H, CH), 7.82 (d, 1H, $J_{H5–H4}$ = 8.8 Hz, H-4), 7.94 (s, 1H, H-2), 11.31 (br s, 1H, NH), 11.90 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 69.5 (CH_2Ph), 96.5 (CH-7), 103.9 (Cq), 111.1 (CH-5), 113.9 (Cq), 118.8 (Cq), 123.1 (CH-4), 125.4 (Cq), 127.6 (2 CH), 127.7 (CH), 128.4 (2 CH), 130.3 (CH-2), 137.3 (Cq), 137.9 (Cq), 155.1 (Cq), 167.5 (C═O), 170.2 (C═O); MS (IS+) *m/z*: 397 $[M+H]^+$ ^{79}Br, 399 $[M+H]^+$ ^{81}Br. Anal. Calcd for $C_{19}H_{13}BrN_2O_3$: C, 57.45; H, 3.30; N, 7.05. Found: C, 57.84; H, 3.13; N, 7.20.

5.1.24. 4-[1-(*tert*-Butyloxycarbonyl)-1*H*-pyrrolo[3,2-*c*]pyridin-3-yl]-3-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (40). Similar preparation as for **14** starting from **37**.[38] Compound **40** was isolated as an orange solid (1.1 g, 74%). Mp: 198–199 °C (dec); IR (Br, cm^{-1}) *v* 1152 (C–O–C), 1709 (C═O), 1739 (C═O), 2977 (CH), 3274 (NH); ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 9H, $C(CH_3)_3$), 6.64-6.74 (m, 2H, CHi), 6.92–6.94 (m, 2H, CHi), 7.89 (s, 1H, H-2i), 8.01-8,03 (m, 2H, H-2a, H-6a), 8.17 (br s, 1H, NH), 8.29–8.31 (m, 2H, H-4a, H-7a), 11.70 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 28.3 ($C(CH_3)_3$); 86.0 (CMe_3), 105.8 (Cq), 110.2 (CH-6a), 112.5 (CH), 120.6 (2 CH), 122.7 (CH), 122.9 (Cq), 125.7 (2 Cq), 129.0 (CH-4a), 130.4 (CH-2i), 133.2 (Cq), 136.6 (2 Cq), 139.5 (Cq), 143.1 (CH-7a), 143.8 (CH-2a), 148.8 (COO′Bu), 171.4

(C=O), 171.7 (C=O); MS *m/z*: 429 $[M+H]^+$, 373 [M+H-*tert*-butyl]$^+$, 329 [M+H-Boc]$^+$. Anal. Calcd for $C_{24}H_{20}N_4O_4$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.53; H, 4.51; N, 13.22.

5.1.25. 3-(5-Benzyloxy-1*H*-indol-3-yl)-4-[1-(*tert*-butyl oxycarbonyl)-1*H*-pyrrolo[3,2-*c*]pyridin-3-yl]-1*H*-pyrrole-2,5-dione (41). Similar preparation as for **14** starting from **38**. Compound **41** was isolated as an orange solid (1.6 g, 80%). Mp: 169–170 °C; IR (KBr, cm^{-1}) *v* 1151 (C–O), 1710 (C=O), 1747 (C=O), 2914 (CH arom), 3238 (NH), 3436 (NH); ^{1}H NMR ($CDCl_3$) δ 1.60 (s, 9H, $C(CH_3)_3$), 4.22 (s, 2H, CH_2Ph), 6.18 (d, 1H, $J_{H4i–H6i}$ = 1.7 Hz, H-4i), 6.56 (dd, 1H, $J_{H6i–H7i}$ = 8.8 Hz, $J_{H4i–H6i}$ = 1.7 Hz, H-6i), 6.78 (d, 1H, $J_{H6i–H7i}$ = 8.8 Hz, H-7i), 7.16–7.31 (m, 5H, H arom), 7.91 (d, 1H, $J_{H2i–NH}$ = 2.6 Hz, H-2i), 8.04 (d, 1H, $J_{H6a–H7a}$ = 5.7 Hz, H-6a), 8.12 (s, 1H, H-2a), 8.21 (s, 1H, H-4a), 8.31 (d, 1H, $J_{H6a–H7a}$ = 5.7 Hz, H-7a), 8.88 (br s, 1H, NH), 11.77 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 28.0 ($C(CH_3)_3$), 70.3 (CH_2Ph), 86.0 (CMe_3), 103.9 (CH-4i), 105.7 (Cq), 110.2 (CH-6a), 110.7 (Cq), 113.2 (CH-7i), 113.7 (CH-6i), 121.5 (Cq), 125.7 (Cq), 126.0 (Cq), 127.4 (2 CH), 127.9 (CH), 128.5 (2 CH), 128.6 (CH-4a), 131.2 (CH-2i), 131.7 (Cq), 133.8 (Cq), 137.0 (Cq), 139.4 (Cq), 143.3 (CH-7a), 143.8 (CH-2a), 148.6 (Cq), 153.6 (COO^tBu), 171.7 (C=O), 172.0 (C=O); MS *m/z*: 535 $[M+H]^+$, 479 [M+H-*tert*-butyl]$^+$, 435 [M+H-Boc]$^+$. Anal. Calcd for $C_{31}H_{26}N_4O_5$: C, 69.65; H, 4.90; N, 10.48. Found: C, 69.30; H, 5.04; N, 10.37.

5.1.26. 3-(6-Benzyloxy-1*H*-indol-3-yl)-4-[1-(*tert*-butyloxy carbonyl)-1*H*-pyrrolo[3,2-*c*]pyridin-3-yl]-1*H*-pyrrole-2,5-dione (42). Similar preparation as for **14** starting from **39**. Compound **42** was isolated as a red solid (0.3 g, 28%). Mp: 149–150 °C; IR (KBr, cm^{-1}) *v* 1148 (C–O–C), 1358, 1714 (C=O), 1747 (C=O), 3150 (NH); ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 9H, $C(CH_3)_3$), 4.74 (s, 2H, CH_2Ph), 6.36 (dd, 1H, $J_{H5i–H4i}$ = 8.7 Hz, $J_{H5i–H7i}$ = 2.0 Hz, H-5i), 6.59–6.62 (m, 2H, H-4i, H-7i), 7.23–7.27 (m, 5H, CH), 7.76 (d, 1H,$J_{H2i–NH}$ = 2,6 Hz, H-2i), 8.00 (d, 1H, $J_{H6a–H7a}$ = 5.8 Hz, H-6a), 8.13 (s, 1H, H-2a), 8.20 (s, 1H, H-4a), 8.29 (d, 1H, $J_{H6a–H7a}$ = 5.8 Hz, H-7a), 8.99 (br s, 1H, NH), 11.28 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 28.3 ($C(CH_3)_3$), 70.3 (CH_2Ph), 86.0 (CMe_3), 96.6 (CH-7i), 106.0 (Cq), 110.1 (CH-6a), 111.3 (CH-5i), 120.0 (Cq), 121.4 (CH-4i), 122.8 (Cq), 127.6 (2 CH), 127.9 (CH), 128.6 (2 CH), 128.8 (CH-4a), 129.0 (Cq), 129.6 (CH-2i), 132.3 (Cq), 133.2 (Cq), 137.2 (Cq), 137.4 (Cq), 139.5 (Cq), 143.4 (CH-7a), 144.0 (CH-2a), 148.8 (Cq), 155.8 (COO^tBu), 171.3 (C=O), 171.6 (C=O); MS (IS) *m/z*: 535 $[M+H]^+$, 479 [M+H-*tert*-butyl]$^+$, 435 [M+H-Boc]$^+$. Anal. Calcd for $C_{31}H_{26}N_4O_5$: C, 69.65; H, 4.90; N, 10.48. Found: C, 70.02.; H, 5.04; N, 10.31.

5.1.27. 1*H*-pyrido[3′4′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]-carbazole-5,7-(6*H*,12*H*)-dione (43). Similar preparation as for **26** starting from **40**. Compound **43** was obtained as a yellow solid (319 mg, 85%). Mp: >250 °C; IR (KBr, cm^{-1}) *v* 1242, 1718 (C=O), 3100–3330 (NH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.37 (dd, 1H, $J_{H9–H8}$ = 7.8 Hz, $J_{H9–H10}$ = 7.5 Hz, H-9), 7.56 (dd, 1H, $J_{H10–H11}$ = 7.8 Hz, $J_{H9–H10}$ = 7.5 Hz, H-10), 7.73 (d, 1H, $J_{H9–H8}$ = 7.8 Hz, H-8), 8.11 (d, 1H,$J_{H1–H2}$ = 5.4 Hz, H-2), 8.69 (br s, 1H, H-1), 8.90 (d, 1H,$J_{H10–H11}$ = 7.8 Hz, H-11), 9.90 (s, 1H, H-4), 11.26 (s, 1H, NH), 11.98 (s, 1H, NH) 12.49 (br s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6) δ 109.0 (CH-10), 112.2 (CH-4), 120.9 (CH-3), 124.3 (CH-1), 127.7 (CH-2), 138.2 (CH-11), 140.0 (CH-8); MS (MALDI) *m/z*: 327 $[M+H]^+$. Anal. Calcd for $C_{19}H_{10}N_4O_2$: C, 69.94; H, 3.09; N, 17.17. Found: C, 69.65; H, 3.23; N, 17. 29.

5.1.28. 9-Benzyloxy-1*H*-pyrido[3′4′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*,12*H*)-dione (44). Similar preparation as for **26** starting from **41**. Compound **44** was obtained as an orange solid (228 mg, 70%). Mp: >250 °C; IR (KBr, cm^{-1}) *v* 1326, 1712 (C=O), 1746 (C=O), 3212 (NH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 5.20 (CH_2Ph), 7.18 (d, 1H, $J_{H10–H11}$ = 8.0 Hz, H10), 7.34–7.43 (m, 3H, CH), 7.56 (d, 3H, $J_{H10–H11}$ = 8.0 Hz, H-11, H arom), 7.83 (br s, 1H, H-2), 8.50–8.54 (m, 2H, H-8, H-1), 9.87 (s, 1H, H-4), 11.08 (s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6) δ 69.8 (CH_2Ph), 107.5 (CH-4), 107.7 (CH-10), 112.9 (CH-1), 116.8 (CH-2), 128.0 (2 CH), 128.0 (CH), 128.4 (2 CH), 142.2 (CH-11), 143.6 (CH-8); MS (MALDI) *m/z*: 433 $[M+H]^+$. Anal. Calcd for $C_{26}H_{16}N_4O_3$: C, 72.21; H, 3.73; N, 12.96. Found: C, 71.96; H, 3.60; N, 13.12.

5.1.29. 10-Benzyloxy-1*H*-pyrido[3′4′:4,5]pyrrolo[2,3-*a*]-pyrrolo[3,4-*c*]carbazole-5,7-(6*H*,12*H*)-dione (45). Similar preparation as for **26** starting from **42**. Compound **45** was obtained as a yellow solid (141 mg, 86%). Mp: >250 °C; IR (KBr, cm^{-1}) *v* 1131, 1332, 1712 (C=O), 1748 (C=O), 3226 (NH), 3382 (NH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 5.24 (s, 2H, CH_2Ph) 7.05 (d, 1H, $J_{H8–H9}$ = 8.0 Hz, H-9), 7.34–7.44 (m, 4H, H arom, H-11), 7.53 (d, 2H, *J* = 7.3 Hz, H arom), 7.90 (s, 1H, H-2), 8.59 (s, 1H, H-1), 8.77 (d, 1H, $J_{H8–H9}$ = 8.0 Hz, H-8), 9.94 (br s, 1H, H-4), 11.10 (s, 1H, NH), 11.79 (s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6) δ 69.6 (CH_2Ph), 96.3 (CH-1), 107.8 (CH-10), 110.7 (CH-3), 125.1 (CH-4), 127.7 (2 CH), 127.7 (CH), 128.5 (2 CH), 142.1 (CH-11), 143.3 (CH-8); MS (MALDI) *m/z*: 433 $[M+H]^+$. Anal. Calcd for $C_{26}H_{16}N_4O_3$: C, 72.22; H, 3.73; N, 12.96. Found: C, 72.58; H, 3.59; N, 12.78.

5.1.30. 9-Hydroxy-1*H*-pyrido[3′4′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*,12*H*)-dione (46). Similar preparation as for **30** starting from **44**. Compound **46** was obtained as a red solid (22 mg, 71%). Mp: >250 °C; IR (KBr, cm^{-1}) *v* 1328 (C–O–C), 1714 (C=O), 1757 (C=O), 3198 (NH, OH), 3424 (NH, OH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.08 (dd, 1H, $J_{H10–H11}$ = 8.7 Hz, $J_{H8–H10}$ = 2.3 Hz, H-10), 7.61 (d, 1H,$J_{H10–H11}$ = 8.7 Hz, H-11), 8.25 (d, 1H, $J_{H1–H2}$ = 6.6 Hz, H-2), 8.27 (d, 1H, $J_{H8–H10}$ = 2.3 Hz, H-8), 8.75 (d, 1H,$J_{H1–H2}$ = 6.6 Hz, H-1), 9.34 (s, 1H, H-4), 9.87 (s, 1H, OH), 11.24 (s, 1H, NH), 11.73 (s, 1H, NH), 13.11 (br s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6)δ 108.5 (CH-4), 109.8 (CH-10), 112.8 (CH-1), 118.0 (CH-2), 135.8 (CH-11), 137.8 (CH-8); MS (MALDI) *m/z*: 343 $[M+H]^+$. Anal. Calcd for $C_{19}H_{10}N_4O_3$: C, 66.67; H, 2.94; N, 16.37. Found: C, 66.33; H, 3.07; N, 16.53.

5.1.31. 10-Hydroxy-1*H*-pyrido[3′4′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*,12*H*)-dione (47). Similar preparation as for **30** starting from **45**. Compound **47** was obtained as a yellow solid (33 mg, 88%). Mp: >250 °C; IR (KBr, cm^{-1}) *v* 1329 (C–O–C), 1712 (C═O), 1756 (C═O), 3212 (NH, OH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 6.89 (dd, 1H, $J_{H8–H9}$ = 8.6 Hz, $J_{H9–H11}$ = 1.7 Hz, H-9), 7.15 (s, 1H, H-11), 8.26 (d, 1H,$J_{H1–H2}$ = 6.5 Hz, H-2), 8.72 (d, 1H, $J_{H8–H9}$ = 8.6 Hz, H-8), 8.77 (d, 1H, $J_{H1–H2}$ = 6.5 Hz, H-1), 9.96 (s, 1H, H-4), 9.98 (s, 1H, OH), 11.27 (s, 1H, NH), 11.80 (s, 1H, NH), 13.05 (br s, 1H, NH); ^{13}C NMR (HSQC DMSO-d_6)δ 97.3 (CH-1), 109.4 (CH-10), 111.2 (CH-3), 125.2 (CH-4), 136.6 (CH-11), 138.2 (CH-8); MS (MALDI) *m*/*z*: 343 $[M+H]^+$. Anal. Calcd for $C_{19}H_{10}N_4O_3$: C, 66.67; H, 2.94; N, 16.37. Found: C, 66.92.; H, 2.80; N, 16.21.

5.1.32. 9-Benzyloxy-3-methyl-1*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*,12*H*)-dione-3-ium iodide (49). A solution of **44** (48 mg, 0.11 mmol) and iodomethane (0.50 mL) in DMF (1 mL) was heated at 60 °C for 24 h in a sealed tube. After cooling and evaporation, the residue was taken in methanol (1 mL) and filtered to afford compound **49** as a yellow solid (23 mg, 37%). Mp: >250 °C; IR (KBr, cm^{-1})*v* 1329 (C–O–C), 1712 (C═O), 1756 (C═O), 3210 (NH, OH), 3418 (NH, OH); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 4.48 (s, 3H, N^+CH_3), 5.25 (s, 2H, CH_2Ph), 7.33–7.37 (m, 2H, H arom, H-10), 7.43 (dd, 2H, *J* = 7.4 Hz, *J* = 7.6 Hz, H arom), 7.58 (d, 2H, *J* = 7.4 Hz, H arom), 7.76 (d, 1H,$J_{H10–H11}$ = 8.8 Hz, H-11), 8.29 (d, 1H, $J_{H1–H2}$ = 6.7 Hz, H-2), 8.58 (s, 1H, H-8), 8.74 (d, 1H, $J_{H1–H2}$ = 6.7 Hz, H-1), 9.85 (s, 1H, H-4), 11.34 (s, 1H, NH) 13.23 (br s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6)δ 47.0 (N^+CH_3), 69.4 (CH_2Ph), 107.5 (CH-4), 110.1 (CH-10), 113.2 (CH-1), 117.7 (CH-2), 127.8 (2 CH), 127.9 (CH), 128.4 (2 CH), 138.9 (CH-11), 140.9 (CH-8); MS (MALDI)*m*/*z*: 447 [M−I]. Anal. Calcd for $C_{27}H_{19}IN_4O_3$: C, 56.46; H, 3.33; N, 9.75. Found: C, 56.78; H, 3.17; N, 9.64.

5.1.33. 1-Methyl-3-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-4-[1-(*tert*-butyloxycarbonyl)-1*H*-pyrrolo[3,2-*c*]pyridin-3-yl]pyrrole-2,5-dione (52). *Method A*: Similar preparation as for **14**, starting from **51**.[39] After a flash chromatography (petroleum ether/EtOAc 7:3), compound **52** was obtained as a red solid (524 mg, 35%). *Method B*: To a solution of compound **14** (0.100 g, 0.23 mmol) in THF (3 mL), 2,3,4,6-tetra-*O*-benzyl-sc d-glucopyranoside **50** (0.184 g, 0.34 mmol) and PPh_3 (0.181 g, 0.69 mmol) were added. After cooling to 0 °C, DIAD (0.136 mL, 0.69 mmol) was added. The mixture was stirred for 1 h at room temperature, hydrolyzed with water (10 mL) and extracted with EtOAc (3× 20 mL). The combined organic layers were washed with brine and evaporated. The residue was purified by flash chromatography on a silica gel column (petroleum ether/EtOAc 7:3) to yield **52** a red solid (73 mg, 33%). Mp: 75–76 °C; IR (KBr, cm^{-1}) *v* 1703 (C═O), 1736 (C═O), 2924 (CH arom); ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 9H, $C(CH_3)_3$), 3.22 (s, 3H, NCH_3), 3.66 (d, 1H, *J* = 10.2 Hz, CH_2Ph), 3.71–3.77 (m, 1H, CH sugar), 3.81–4.03 (m, 5H, H-2′, H-6′, 2CH sugar), 4.20 (d, 1H, *J* = 10.2 Hz, CH_2Ph), 4.53 (d, 1H, *J* = 12.0 Hz, CH_2Ph), 4.65 (d, 1H, *J* = 12.0 Hz, CH_2Ph), 4.67 (d, 1H, *J* = 10.7 Hz, CH_2Ph), 4.88 (d, 1H, *J* = 11.0 Hz, CH_2Ph), 4.89 (d, 1H, *J* = 10.7 Hz, CH_2Ph), 4,93 (d, 1H, *J* = 11.0 Hz, CH_2Ph), 5.45 (d, 1H,$J_{H1′–H2′}$ = 8.8 Hz, H-1′), 6.65 (d, 1H, *J* = 3.8 Hz, CH), 6.68 (d, 2H, CH), 6.74-6.76 (m, 2H, CH), 6.99–7.10 (m, 4H, CH), 7.19–7.34 (m, 16H, CH), 7.52 (d, 1H, *J* = 8.5 Hz, CH), 7.61 (d, 1H, *J* = 4.1 Hz, CH), 8.05 (s, 1H, H-2a), 8.18 (s, 1H, H-4a); ^{13}C NMR ($CDCl_3$) δ 24.5 (NCH_3), 28.2 ($C(CH_3)_3$), 68.5 (C-6′), 73.7 (CH_2Ph), 75.1 (CH_2Ph), 75.4 (CH_2Ph), 75.8 (CH_2Ph), 77.5 (CH sugar), 78.2 (CH sugar), 81.6 (CH sugar), 85.4 (C-2′), 85.6 (CMe_3), 86.5 (C-1′), 106.7 (Cq), 110.2 (Cq), 112.2 (CH), 121.4 (CH), 121.7 (CH), 123.3 (CH), 123.5 (Cq), 126.0 (CH), 126.3 (Cq), 127.7 (CH), 127.8 (CH), 127.8 (Cq), 127.9 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 128.8 (CH), 131.1 (CH-4a), 131.8 (Cq), 132.1 (Cq), 136.1 (Cq), 137.0 (Cq), 138.1 (Cq), 138.2 (Cq), 138.5 (Cq), 148.8 (COO^tBu), 171.4 (C═O), 171.6 (C═O); MS (IS) *m*/*z*: 966 $[M+H]^+$. Anal. Calcd for $C_{59}H_{56}N_4O_9$: C, 73.43; H, 5.85; N, 5.81. Found: C, 73.81; H, 5.66; N, 5.63.

5.1.34. 1-Methyl-3-[1-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1*H*-indol-3-yl]-4-[1*H*-pyrrolo[3,2-*c*]pyridin-3-yl]pyrrole-2,5-dione (53). A solution of compound **52** (495 mg, 0.51 mmol) in formic acid (10 mL) was stirred overnight at room temperature. After evaporation, the residue was dissolved in EtOAc (25 mL) and washed with a 20% aqueous solution of Na_2CO_3 till pH 7 to afford after evaporation compound **53** as a red-orange solid (437 mg, 99%). Mp: 115–116 °C; IR (KBr, cm^{-1}) *v* 1084, 1694 (C═O), 3441 (NH); ^{1}H NMR ($CDCl_3$) δ 3.14 (s, 3H, NCH_3), 3.67 (d, 1H, *J* = 10.0 Hz, CH_2Ph), 3.73-3.81 (m, 2H, 2 CH sugar), 3.87 (d, 1H, *J* = 8.8 Hz, CH_2Ph), 3.92 (d, 1H, *J* = 8.8 Hz, CH_2Ph), 4.00–4.08 (m, 2H, H-2′, CH sugar), 4.20 (d, 1H, *J* = 10.0 Hz, CH_2Ph), 4.46 (d, 1H, *J* = 12.2 Hz, CH_2Ph), 4.56 (d, 1H, *J* = 12.2 Hz, CH_2Ph), 4.65 (d, 1H, *J* = 10.7 Hz, CH_2Ph), 4.85–4.95 (m, 3H, CH_2Ph), 5.48 (d, 1H,$J_{H1′–H2′}$ = 8.5 Hz, H-1′), 6.50 (d, 1H, $J_{H4i–H5i}$ = 8.2 Hz, H-4i), 6.62–6.70 (m, 3H, H-5i, 2H arom), 6.96–7.05 (m, 5H, H-6i, 4H arom), 7.18–7.30 (m, 14 H, H arom), 7.38 (d, 1H, $J_{H6a–H7a}$ = 6.0 Hz, H-6a), 7.51 (d, 1H, $J_{H7i–H6i}$ = 8.5 Hz, H-7i), 7.57 (s, 1H, H-2i), 7.91 (d, 1H,$J_{H6a–H7a}$ = 6.0 Hz, H-7a), 8.11 (s, 1H, H-2a), 8.55 (s, 1H, H-4a), 10.10 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$)δ 24.4 (NCH_3), 68.6 (CH_2), 73.5 (CH_2), 75.0 (CH_2), 75.3 (CH_2), 75.7 (CH_2), 77.4 (CH sugar), 77.9 (CH sugar), 81.4 (CH sugar), 85.4 (CH sugar), 86.1 (CH-1′ sugar), 106.4 (Cq), 107.2 (Cq), 108.6 (CH-6a), 111.9 (CH-7i), 121.2 (CH-5i), 122.0 (CH-4i), 122.8 (Cq), 123.2 (CH-6i), 125.3 (Cq), 127.7 (CH), 127.8 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.0 (CH), 130.8 (CH-2a), 132.1 (CH-2i), 135.9 (CH-7a), 136.2 (Cq), 136.9 (Cq), 138.0 (Cq), 138.4 (Cq), 141.0 (CH-4a), 141.4 (Cq), 171.5 (C═O), 171.9 (C═O); MS (IS +) *m*/*z*: 866 $[M+H]^+$. Anal. Calcd for $C_{54}H_{48}N_4O_7$: C, 74.98; H, 5.59; N, 6.48. Found: C, 74.67; H, 5.75; N, 6.66.

5.1.35. 6-Methyl-12-(2,3,4,6-tetra-*O*-benzyl-β-D-gluco pyranosyl)-1*H*-pyrido[3′4′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*] carbazole-5,7-(6*H*,12*H*)-dione (54). Similar preparation as for **26** starting from **53**. Compound **54** was obtained as an orange solid (214 mg, 69%). Mp: 108–109 °C; IR (KBr, cm^{-1}) *v* 1076 (C–O–C), 1698 (C=O), 3444 (NH); ^1H NMR ($CDCl_3$) δ 3.30 (s, 3H, NCH_3), 3.33 (d, 1H, J = 11.3 Hz, CH_2Ph), 3.80 (d, 1H, J = 11.3 Hz, CH_2Ph), 3.97–3.99 (m, 2H, H-6′), 4.06–4.11 (m, 2H, H-3′ and H-4′), 4.26–4.29 (m, 1H, H-5′), 4.38 (dd, 1H, $J_{H2'-H3'} = 7.8$ Hz, $J_{H1'-H2'} = 9.0$ Hz, H-2′), 4.56 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.68 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.76 (d, 1H, J = 11.0 Hz, CH_2Ph), 4.82 (s, 2H, CH_2Ph), 4.98 (d, 1H, J = 11.0 Hz, CH_2Ph), 6.12 (d, 2H, J_{H4-H3} = 7.2 Hz, H-8 and H arom), 6.61 (m, 2H, H-9 and H-11), 6.81 (dd, 1H, J = 7.5 Hz, J = 7.2 Hz, H-10), 6.96–7.00 (m, 2H, CH), 7.19–7.57 (m, 17 H, H-2 and 16 H arom), 8.02 (d, 1H,J = 6.9 Hz, H arom), 8.08–8.11 (m, 2H, H-1′), 9.24 (s, 1H, H-4), 9.28 (d, 1H, J_{H1-H2} = 7.2 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 23.8 (NCH_3), 69.3 (CH-6′), 73.5 (CH_2Ph), 73.8 (CH_2Ph), 75.3 (CH_2Ph), 75.8 (CH_2Ph), 77.4 (CH-5′), 78.3 (CH-4′), 79.0 (CH-2′), 85.6 (CH-1′), 85.9 (CH-3′), 114.0 (CH), 114.2 (CH), 117.2 (Cq), 117.8 (Cq), 118.2 (Cq), 120.4 (Cq), 121.4 (CH), 121.5 (Cq), 123.7 (Cq), 125.7 (CH-11), 126.7 (CH-10), 127.1 (CH), 127.3 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.9 (CH), 129.3 (CH), 132.0 (CH), 132.1 (Cq), 132.3 (Cq), 133.8 (Cq), 135.3 (Cq), 136. 8 (CH-8), 137.1 (Cq), 138.5 (Cq), 138.7 (Cq), 139.7 (Cq), 170.8 (C=O), 171.3 (C=O). Anal. Calcd for $C_{54}H_{46}N_4O_7$: C, 75.16; H, 5.37; N, 6.49. Found: C, 75.48; H, 5.19; N, 6.68.

5.1.36. 3-Benzyl-12-(β-D-glucopyranosyl)-6-methyl-1*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7 (6*H*,12*H*)-dione-3-ium bromide (55). To a cooled solution of compound **54** (0.292 g, 0.34 mmol) in CH_2Cl_2 (2 mL), at −78 °C under nitrogen was added a 1 M solution of BBr_3 in dichloromethane (1.68 mL, 1.68 mmol). After 1 h at −78 °C, addition of water (5 mL) at −70 °C led to a precipitate, which was filtered off. The solid was washed several times with methanol (3× 10 mL) and the filtrate was concentrated to 0.5 mL to afford a suspension. After filtration, the powder was dissolved with a small amount of methanol and the addition of EtOAc gave a precipitate. The obtained solid was washed with diethyl ether to yield 55 as a yellow solid (131 mg, 57%). Mp: >250 °C; IR (film, cm^{-1}) *v* 1225, 1376, 1696 (C=O), 1749 (C=O), 3156–3689 (NH); ^1H NMR (DMSO-d_6) δ 3.21 (s, 3H, NCH_3), 3.35–3.39 (m, 1H, H-2′), 3.64 (dd, 1H, $J_{H2'-H3'} = 8.8$ Hz, $J_{H3'-H4'} = 9.1$ Hz, H-3′), 3.87–3.96 (dd, 1H, $J_{H6'a-H5'} = 2.8$ Hz, $J_{H6'a-H6'b} = 9.6$ Hz, H-6′a), 3.93 (dd, 1H, $J_{H5'-H4'} = 9.6$ Hz, H-4′), 4.04 (dd, 1H, $J_{H6'a-H5'} = 2.8$ Hz, $J_{H5'-H4'} = 9.6$ Hz, H-5′), 4.13 (dd, 1H, $J_{H6'b-H5'} = 2.8$ Hz, $J_{H6'a-H6'b} = 9.6$ Hz, H-6′b), 4,98 (br s, 1H, OH), 5.19 (br s, 1H, OH), 5.44 (br s, 1H, OH), 6.09 (s, 2H, CH_2Ph), 6.42 (d, 2H, $J_{H1'-H2'} = 9.0$ Hz, H-1′ and OH), 7.43–7.54 (m, 6H, H arom, H-10), 7.68 (dd, 1H, J_{H8-H9} = 8.2 Hz, J_{H9-H10} = 7.2 Hz, H-9), 8,06 (d, 1H, J_{H8-H9} = 8.2 Hz, H-8), 8.11 (d, 1H,J_{H1-H2} = 7.2 Hz, H-2), 9.13-9.16 (m, 2H, H-11, H-1), 10.25 (s, 1H, H-4), 12.86 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.7 (NCH_3), 58.2 (CH-6′), 62.3 (CH_2Ph), 67.2 (CH-4′), 73.5 (CH-2′), 76.6 (CH-3′), 78.8 (CH-5′), 84.3 (CH-1′), 109.6 (CH-10), 112.8 (CH-4), 121.4 (CH-2), 124.5 (CH-1), 128.0 (CH-3), 128.2 (2 CH), 129.6 (2 CH), 129.6 (CH), 140.0 (CH-11), 140.8 (CH-8); MS (MALDI) *m/z*: 594 $[M-Br]^+$.

5.1.37. 3-Benzyl-6-methyl-12-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*a*]pyrrolo [3,4-*c*]carbazole-5,7-(6*H*,12*H*)dione-3-ium bromide (56). A solution of compound **55** (173 mg, 0.26 mmol) in pyridine/acetic anhydride (4/2 mL) was stirred at room temperature for 24 h. After the addition of toluene (5 mL), the mixture was evaporated in vacuo and the residue was purified by flash chromatography on a silica gel column (EtOAc) to yield **56** as a yellow solid (52 mg, 24%). Mp: 148–150 °C; ^1H NMR (DMSO-d_6, 500 MHz) δ 1.01 (s, 3H, $COCH_3$-2′), 1.98 (s, 3H, $COCH_3$-3′), 2.14 (s, 3H, $COCH_3$-4′), 2.15 (s, 3H, $COCH_3$-6′), 3.32 (s, 3H, NCH_3), 4.47-4.45 (m, 3H, H-6′, H-5′), 5.13 (d, 1H, J = 15.0 Hz, CH_2Ph), 5.30 (d, 1H, J = 15.0 Hz, CH_2Ph), 5.49 (dd, 1H, $J_{H4'-H5'} = 9.8$ Hz, $J_{H4'-H3'} = 9.6$ Hz, H-4′), 5.75 (dd, 1H, $J_{H3'-H2'} = 9.4$ Hz, $J_{H4'-H3'} = 9.6$ Hz, H-3′), 5.93 (dd, 1H, $J_{H2'-H1'} = 9.2$ Hz, $J_{H3'-H2'} = 9.4$ Hz, H-2′), 7.19 (d, 2H, J = 7.8 Hz, CH) Hz, 7.20–7.38 (m, 3H, H arom), 7.42 (d, 1H, J_{H1-H2} = 7.5 Hz, H-2), 7.46 (dd, 1H, J_{H9-H10} = 7.3 Hz, $J_{H10-H11}$ = 8.0 Hz, H-10), 7.60 (dd, 1H, J_{H8-H9} = 7.1 Hz, J_{H9-H10} = 7.3 Hz, H-9), 7.67 (d, 1H, J_{H8-H9} = 7.1 Hz, H-8), 7.98 (d, 1H, $J_{H10-H11}$ = 8.0 Hz, H-11), 8.31 (d, 1H, $J_{H2'-H1'} = 9.2$ Hz, H-1′), 9.22 (d, 1H, J_{H1-H2} = 7.5 Hz, H-1), 9.54 (s, 1H, H-4), 12.48 (s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6) δ 19.5 ($COCH_{3\,2'}$), 20.7 ($COCH_{3\,3'}$), 20.8 ($COCH_{3\,4'}$), 20.8 ($COCH_{3\,6'}$), 23.9 (NCH_3), 62.3 (CH-6′), 62.4 (CH_2Ph), 68.9 (CH-4′), 69.2 (CH-2′), 73.7 (CH-3′), 74.4 (CH-5′), 84.3 (CH-1′), 113.5 (CH-1), 113.7 (CH-4), 121.6 (CH-2), 125.5 (CH-11), 127.1 (CH-3), 127.6 (2 CH), 129.2 (3 CH), 132.0 (CH-10), 137.1 (CH-8), 168.5 ($COCH_3$2′), 169.3 ($COCH_3$4′), 170.3 ($COCH_3$-3′), 170.9 (2 C=O), 171.1 ($COCH_3$-6′). MS (MALDI) *m/z*:761.8 $[M-Br]^+$. Anal. Calcd for $C_{41}H_{37}BrN_4O_{11}$: C, 58.51; H, 4.43; N, 6.66. Found: C, 58.15; H, 4.60; N, 6.84.

5.1.38. 3-Benzyl-6-methyl-12-(3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl)-1*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*a*]pyrrolo-[3,4-*c*]carbazole-5,7(6*H*,12*H*)-dione-3-ium bromide (57). Compound **57** was isolated during the synthesis of **56** and was purified by flash chromatography (EtOAc) as a yellow solid. (40 mg, 19%). Mp: >250 °C; IR (film; cm^{-1})*v*1043, 1227, 1688 (C=O), 1745 (C=O), 2919 (CH arom); ^1H NMR (DMSO-d_6, 500 MHz) δ 1.98 (s, 3H, $COCH_3$), 2.01 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 3.18 (s, 3H, NCH_3), 4.23–4.29 (m, 3H, H-6′ and H-5′), 4.52–4.57 (m, 1H, H-2′), 5.26 (dd, 1H, $J_{H3'-H4'} = 9.3$ Hz, $J_{H3'-H2'} = 9.5$ Hz, H-3′), 5.34 (dd, 1H, $J_{H4'-H5'} = 9.4$ Hz, $J_{H3'-H4'} = 9.3$ Hz, H-4′), 5.60 (d, 1H, $J_{OH-H2'} = 5.2$ Hz, OH), 5.84 (s, 2H, CH_2Ph), 7.38–7.48 (m, 6H, 5H arom, H-10), 7.56 (dd, 1H, J_{H8-H9} = 7.2 Hz, J_{H9-H10} = 7.2 Hz, H-9), 7.96 (d, 1H, J_{H1-H2} = 7.1 Hz, H-1), 8.08 (d, 1H, J_{H8-H9} = 7.2 Hz, H-8), 8.17 (d, 1H, $J_{H1'-H2'} = 9.2$ Hz, H-1′), 8.44 (dd, 1H,

$J_{H2–H4}$ = 1.4 Hz, H-2), 9.12 (d, 1H, $J_{H10–H11}$ = 7.9 Hz, H-11), 9.84 (s, 1H, H-4), 12.57 (s, 1H, NH); ^{13}C NMR HSQC (DMSO-d_6) δ 20.1 ($COCH_3$), 20.1 ($COCH_3$), 20.2 ($COCH_3$), 23.3 (NCH_3), 60.5 (CH_2Ph), 62.0 (CH-6′), 67.5 (CH-2′), 68.1 (CH-4′), 73.5 (CH-5′), 75.5 (CH-3′), 85.6 (CH-1′), 113.1 (CH-11), 113.9 (CH-4), 120.5 (CH-2), 124.1 (CH-1), 126.0 (CH-3), 127.3 (CH), 128.3 (2 CH), 128.9 (2 CH), 134.1 (CH-10), 137.6 (CH-8), 169.5 ($COCH_3$), 169.5 ($COCH_3$), 170.0 (2 C=O), 170.1 ($COCH_3$); MS (IS) *m/z*: 719.5 $[M\text{-}Br]^+$. Anal. Calcd for $C_{39}H_{35}BrN_4O_{10}$: C, 58.58; H, 4.41; N, 7.01. Found: C, 58.93; H, 4.24; N, 7.12.

5.2. Pharmacology

5.2.1. Chk1 inhibition. Human Chk1 full-length enzyme with an N-terminal GST sequence was either purchased from Upstate Biochemicals (No. 14-346) or purified from extracts of Sf9 cells infected with a baculovirus encoding GST-Chk1. Assays for compound testing were based upon the method described by Davies.[42]

5.2.2. Cell culture and cytotoxicity. L1210 and HT29 cells were cultivated in RPMI 1640 (Gibco) supplemented with 10% fetal calf serum, 2 mM L-glutamine, 100 U/mL penicillin, 100 mg/mL streptomycin, and 10 mM Hepes buffer (pH 7.4). Cytotoxicity was measured by the microculture tetrazolium assay (MTA) as described.[43] Cells were exposed to graded concentrations of compound (nine serial dilutions in triplicate) for four doubling times (48 h for L1210 cells and 96 h for HT29 cells). Results are expressed as IC_{50}, the concentration which reduced by 50% the optical density of treated cells with respect to the optical density of untreated controls.

5.2.3. Cell cycle analysis[44,45]. L1210 cells (2.5×105 cells/mL) were incubated for 21 h with various concentrations of the compounds. Cells were then fixed in 70% ethanol (v/v), washed, and incubated in Dulbecco's phosphate buffered saline (D-PBS) containing 100 mg/mL RNAse and 25 mg/mL propidium iodide for 30 min. at 20 °C. For each sample, 126 cells were analyzed on a Epics XL/MCL flow cytometer (Beckman Coulter, France)

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