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Synthesis and anticancer activity of new pyrrolocarbazoles and pyrrolo-β-carbolines

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Abstract—'Bended' **1**, **3** or 'linear' **2** pyrrolidino-fused (aza)carbazoles were prepared and screened towards a few cancer-related targets. Whereas 'bended' derivatives **1** and **3** proved to be weakly toxic, several members of the 'linear' family strongly interact with DNA, especially derivative **28a**.
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1. Introduction

2,5-Pyrrolidinedione (succinimide) or 2-pyrrolidone appended polycyclic (hetero)aromatics are of interest in at least two families of anticancer drugs: (i) inhibitors of kinases implicated in cell signaling like the PKC inhibitor staurosporine[1a,b] or/and in cell-cycle control like the CDK or CHK inhibitors granulatimide[2a,b] or UCN-01[3] (connections between checkpoint kinases, cyclin-dependent kinases, p53 and chemosensitization have been recently reviewed[4]); (ii) inhibitors of topoisomerase I like rebeccamycin.[5] Synthetic analogues of these products have been developed in the field of topoisomerase I[6] inhibitors, CDK[7a,b] or CHK[8] inhibitors. Recent reviews cover the staurosporine-like kinase or phosphatase inhibitors,[9] the structure of kinase/inhibitor complexes[10a,b] and the potential use of pharmacological inhibitors of CDKs[11] and GSK-3.[12a,b] Such pyrrolidine(di)ones could be useful in pathologies other than cancer such as diabetes and neurodegenerative diseases (for example, GSK-3β inhibitors[13a–c]), viral[14] or fungal[15] pathologies.

The succinimide part interacts with the ATP binding pocket via an hydrogen-bonds network. The nature and the substitution pattern of the fused heterocycle provide some selectivity towards specific enzymes. For anti-topoisomerase agents, the requirement for a five membered lactam or imide is less obvious[16] but it contributes both to the conformational rigidity and to the DNA binding ability of the inhibitor.

The substitution of the heterocycle alkylamino chain(s) increases the affinity for DNA, generally by filling up the DNA minor groove.[17]

The location of the merging bond between the heterocycle and the pyrrole ring, as well as the bioisosteric replacement of a carbon atom by nitrogen, allow other structural variations, which could improve biological activity.

2. Chemistry

In this work, we describe our chemical approach towards 'bended' (**1**) or 'linear' (**2**) 2-pyrrolidone or 2,5-pyrrolidinedione derivatives fused to carbazole as well

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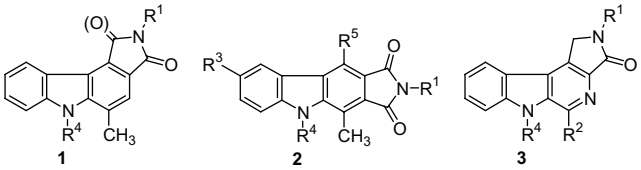


Scheme 1. 'Bended' and 'linear' pyrrolo-(aza)carbazoles.

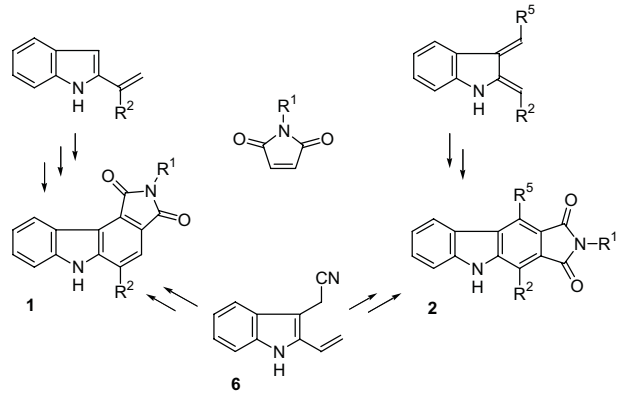
as 'bended' 2-azacarbazoles (β-carbolines) **3**: indeed oxygenated derivatives of **3** have been shown to present interesting anti-topoisomerase I activities[18a,b] (Scheme 1). Their in vitro pharmacological activities are reported.

2.1. Carbazole annulated derivatives

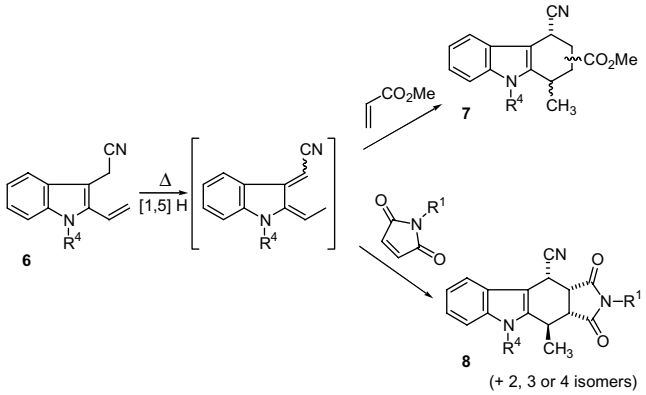
Diels–Alder reaction combined with simple functional group transformations is a frequently selected method for the preparation of various biologically active carbazole alkaloids.[19] Thus, pyrrolo[3,4-*b*]carbazole ('linear') derivatives (type **2**) are accessible by Diels–Alder reaction involving indolo-2,3-quinodimethane intermediates.[20a–j] Similarly, towards pyrrolo[3,4-*c*] counterparts (type **1**)('bended' pyrrolocarbazoles) Diels–Alder approach using 2-vinylindoles has been developed[21a–h] (Scheme 2). However, Caballero et al. have proposed a combined Diels–Alder reaction–Fischer indolization pathway affording both 'linear' and 'bended' pyrrolocarbazole derivatives in varying proportion.[22] As the moderate yield[23] and the difficulties of separation excluded this method to be taken into consideration, we chose our recently disclosed sigmatropic [1,5]-H shift/Diels–Alder tandem reaction[24] to synthesize both 'bended' carbazoles **1** and 'linear' ones **2**, from a common starting material **6**.[25]

Depending on the dienophile, vinylindole **6** led to tetrahydrocarbazoles **7** and **8**, precursors of **1** and **2** series, respectively (Scheme 3).

As the best yields were observed for R^4 = SEM (SEM: trimethylsilylethoxymethyl) cycloadducts **7** (R^4 = SEM) and **8** (R^4 = SEM) were chosen as intermediates for further transformations. Theoretical calculations have been



Scheme 2. Diels–Alder strategies towards 2,5-pyrrolidinedione-appended carbazoles **1** and **2**.



Scheme 3. *Tandem* [1,5]H sigmatropic shift/Diels–Alder reaction of 2-vinylindole **6**.

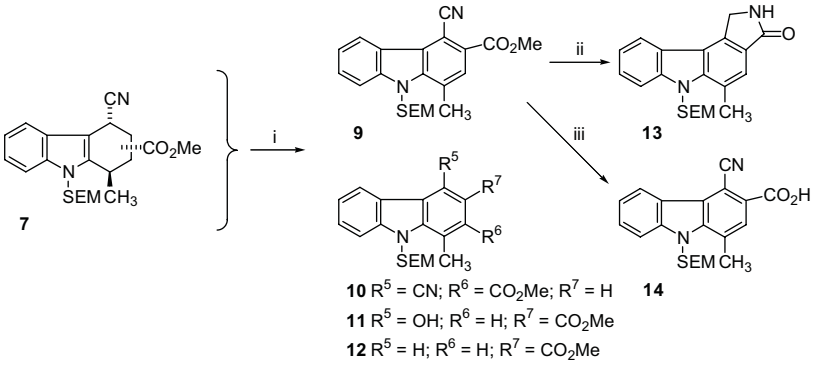
performed in order to understand the dramatic role of the indole nitrogen substituent on the course and the yield of the reaction.[26] Nevertheless it appears that the SEM chain could mostly account for a better solubility in the nonpolar solvent used in the reaction.

Pyrrolo[3,4-*c*]carbazoles were all synthesized from tetrahydrocarbazoles **7** (Scheme 4). Aromatization to **9** was cleanly performed by activated MnO_2.[27] After purification by chromatography on silica gel, regioisomer **10** and further transformed **11** and **12** carbazoles were also isolated in slight quantities. The cyano group was reduced into amine, allowing spontaneous cyclization to **13**. The SEM-group was cleaved by aqueous HCl to give **15** but N(lactam) appendage functionalization by dimethylaminoethyl chain failed: under forced conditions a mixture of masked imminium species [alkylated **16** or nonalkylated **17**] were obtained in low yields (Scheme 5). This serendipitous oxidation of the methylene group of the pyrrolidone moiety adjacent to the nitrogen atom has already been encountered by us[28] and by others.[29]

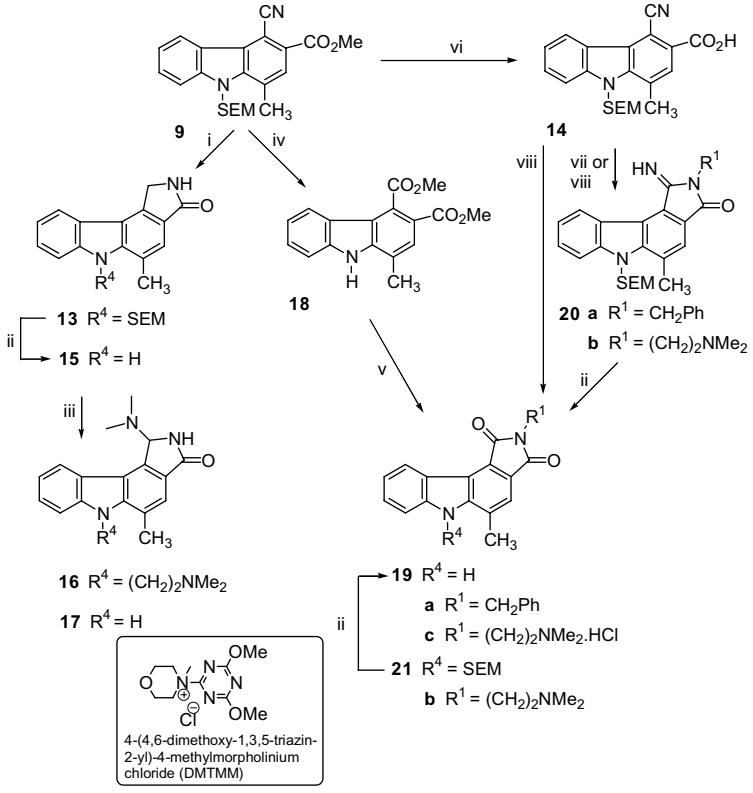
Imide **19c** was synthesized in three steps from cyanoester **9**: solvolysis to **18** by concentrated methanolic HCl caused also the cleavage of the SEM group. Double lactamization of **18** with 2-dimethylaminoethylamine afforded **19c** in good yield.

The same type pyrrolo[3,4-*c*]carbazole derivatives **20** could be obtained in a one step condensation of aromatic cyano acid **14** with various primary amines in the presence of DMTMM[30] or isobutylchloroformate. Acidic cleavage of the imino group afforded the expected tetracyclic imides **19** (only two examples given in this work). Imide **21b** could be obtained directly from **14** without isolation of **20b**.

Linear pyrrolo[3,4-*b*]carbazoles **22**–**28** were synthesized from the common intermediates **8**, which were submitted to various aromatization conditions, most of them giving complex mixtures due to the undesirable indole protecting group cleavage (Scheme 6). Using TCCA (trichloroisocyanuric acid) resulted in the chlorination of the activated position of the carbazole and led to aromatic derivative **22**. Fortunately, activated MnO_2



Scheme 4. Reagents and conditions: (i) activated MnO_2, dry toluene, reflux, **9**+**10**+**11**+**12** (59%); (ii) H_2, Raney-Ni, 6 bars, abs EtOH, dry toluene, rt, 94%; (iii) KOH (powdered), *t*-BuOH, toluene, CH_2Cl_2, H_2O, 80 °C, 86%.



Scheme 5. Reagents and conditions: (i) H_2, Raney-Ni, 6 bars, abs EtOH, dry toluene, rt, 94%; (ii) 3 M aq HCl solution, rt, 84–95%; (iii) NaH 50%, dry DMF, $Cl(CH_2)_2NMe_2$·HCl, rt, 23% (**16**–**17**); (iv) 9 M HCl/MeOH, reflux, 71%; (v) $H_2N(CH_2)_2NMe_2$, 100 °C, 59%; (vi) KOH (powdered), *t*-BuOH, toluene, CH_2Cl_2, H_2O, 80 °C, 86%; (vii) $H_2N(CH_2)_2NMe_2$, $ClCO_2$-*i*-Bu, Et_3N, CH_2Cl_2, BuOH, rt, 28% (**20b**); (viii) R^1NH_2, DMTMM, MeOH, rt, 52% (**21b**)-83% (**20a**).

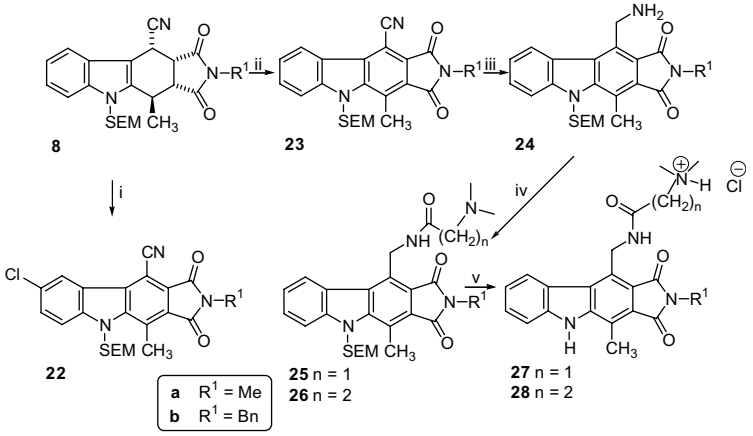
worked well giving **23** in good yield without side reaction. The reduction of the cyano group gave the primary amine **24**, whose acylation with *N*,*N*-dimethylglycine or 3-dimethylaminopropanoic acid, in the presence of DMTMM nicely afforded the corresponding amides. It is important to note that classical peptide synthesis coupling reagents other than DMTMM proved to be completely inoperative, with exception of isobutylchloroformiate for $n = 1$.

2.2. β-Carboline annulated derivatives (Scheme 7)

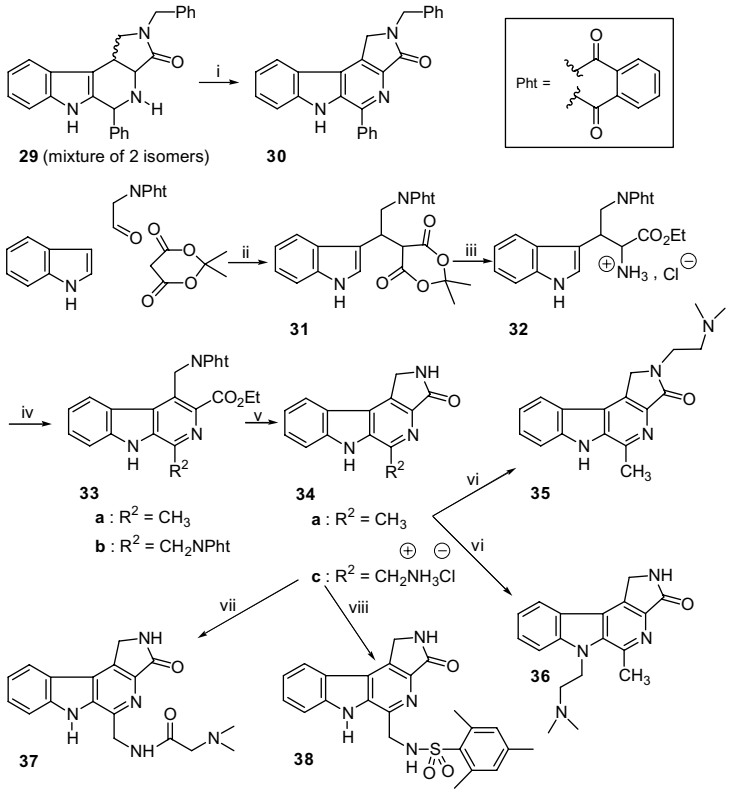
The tetrahydropyridine ring of **29**[31] was aromatized by TCCA to the target derivative **30**.

Pyrrolo-β-carbolines **34**–**38** were obtained from a common intermediate **31**[32] resulting from our trimolecular condensation reaction between indole, Meldrum's acid and *N*-phthalimidoaminoacetaldehyde (for a recent review, see[33]).

Meldrum's acid moiety was transformed into α-amino-ester **32**[34] following our procedure[35] (i.e., ring opening of the Meldrum's ring by ethanol, Curtius rearrangement and urethane reductive cleavage). Free base **32** spontaneously reacted with the imide carbonyl group, resulting in considerable loss of material upon storage. But fortunately, the hydrochloric acid salt was stable enough. The well-known Pictet–Spengler cyclization of **32**



Scheme 6. Reagents and conditions: (i) TCCA, Et_3N, dry DMF, rt, 26–36%; (ii) activated MnO_2, dry toluene, reflux, 57–69%; (iii) H_2, Raney-Ni, 6 bars, abs EtOH, dry toluene, rt, 52–70%; (iv) $Me_2NCH_2CO_2H$, $ClCO_2$-*i*-Bu, Et_3N, CH_2Cl_2, BuOH, rt, 57% (**25a**) and 37% (**25b**) or $Me_2N(CH_2)_nCO_2H$, DMTMM, MeOH, rt, 59–75% (**25a**, **26a** and **26b**); (v) 3 M aq HCl solution, rt, 68–97%.



Scheme 7. Reagents and conditions: (i) TCCA, Et_3N, rt, 83%; (ii) see Ref. 32, 73%; (iii) see Ref. 34, three steps, overall yield 39%; (iv) R^2CHO, CH_2Cl_2, Et_3N, TFA, molecular sieves 4 Å, then TCCA, Et_3N, rt, 45–57%; (v) **34a**: $BuNH_2$, reflux, 90%; **34c**: 6 M HCl solution, reflux, 78%; (vi) NaH, DMF, $Cl(CH_2)_2NMe_2{\cdot}HCl$, 17% (**35**) and 26% (**36**); (vii) $Me_2NCH_2CO_2H$, Et_3N, $ClCO_2$-*i*-Bu, CH_2Cl_2, BuOH, 78%; (viii) mesitylenesulfonylchloride, Et_3N, DMF, rt, 71%.

with various aldehydes R^2CHO (only two examples are described in this work: $R^2 = CH_3$ and CH_2NPht) cleanly afforded the tetrahydro-β-carboline system, which was not isolated but directly aromatized into **33** by TCCA.

Pyrrolidone ring formation has not been performed by the same manner for **33a** as for **33b**. In the first case, phthalimido group was classically removed by displacement with butylamine. For **33b** harsh conditions (concentrated HCl) proved to be useful to prevent either side reactions resulting from the created amino group, or incomplete cleavage of one of the phthalimido groups.

Tetracyclic compound **34** was selectively appended on either pyrrolidinone nitrogen or indole one, by alkylation of the dianion (NaH, DMF). Depending on the conditions of the reaction, lactams **35** or **36** were selectively obtained albeit in low yields.

The introduction of a dimethylaminoalkyl chain or of a large hydrophobic group on the amino group of **34** was classically performed by nitrogen acylation giving the amide **37** and the sulfonamide **38**, respectively.

3. Biology (Tables 1 and 2)

3.1. Cytotoxicity and cell-cycle effects

L1210 murine leukemia cells were used to estimate the cytotoxic potential of the compounds. IC_{50} values are collated in Tables 1 and 2.[36] Some of the molecules showed submicromolar activities, such as **20b** and **28a** for example. This latter compound, which is the most cytotoxic molecule in the series, proved to be a potent DNA binder (see below). In parallel, the effect of the most cytotoxic compounds on the cycle of L1210 cells was investigated (Tables 1 and 2). In general, these compounds (e.g., **28a** and **20b**) induced a strong accumulation of the cells in the G2 + M phases at 2 μM.

3.2. Effect on topoisomerase I

A DNA relaxation assay was used to evaluate the inhibition of topoisomerase I.[37] A minor inhibitory effect was observed in some cases, in particular with **26a** but this inhibition occurred at a concentration largely exceeding the IC_{50} values determined in the above cytotoxicity assay. Nevertheless, for this reason we compared the cytotoxicity of those molecules towards P388 and P388CPT5 murine leukemia cells, sensitive and resistant to camptothecin, respectively. In the case of camptothecin, which is a reference topoisomerase I inhibitor,[38] the mutation of the *top* 1 gene in the P388CPT5 cells[39] considerably decreases (by a factor of 166) the cytotoxic potential of the drug, indicating thus that topoisomerase I plays a dominant role in the antiproliferative activity. This is not the case for the compounds tested here. The resistance index ($IC_{50}^{P388CPT5}$)/IC_{50}^{P388}) does not exceed 3.2 with compound **28a**. We therefore conclude that topoisomerase I is not a target for these molecules.

3.3. DNA binding

Several biochemical and biophysical methods were deployed to investigate the interactions of the compounds with DNA. DNA sequence recognition was studied by DNase I footprinting[40] and a representative polyacrylamide gel is shown in Figure 1. Some of the compounds modify the pattern of DNA cleavage by the enzyme

Table 1. Cytotoxicities (IC_{50} in μM) of 'bended' pyrrolocarbazoles **13**, **15**–**17**, **20b**–**21b** and pyrrolo-β-carbolines **30**, **34**–**38**

Compound	L1210	Cell cycle[a]	P338	P338 CPT5[b]	GSK3
Camptothecin	NT	NT	0.024	3.98	NT
13	12.1	NT	NT	NT	>10
15	11.2	NT	NT	NT	>10
16	>10	NT	NT	NT	NT
17	>10	NT	NT	NT	NT
20b	0.77	G2M 56% + toxic at 2.5 μM	3.20	2.70	>10
21b	11.2	NT	NT	NT	>10
30	6.4	G1 at 50 μM	5.35	5.28	>10
34a	28	NT	NT	NT	>10
34c	>10	NT	NT	NT	5.5
35	>10	NT	NT	NT	>10
36	2.7	G2M + 8N 87% at 5 μM	2.58	3.59	7
37	>10	NT	NT	NT	8
38	>10	NT	NT	NT	1.5

[a] 24% of untreated control cells were recovered in the G2+M phases of the cell cycle, 44% in the G1 phase.
[b] Drug concentration (μM) that inhibits leukemia cell growth by 50% after incubation in liquid medium for 72 h.

Table 2. Cytotoxicities (IC_{50} in μM) of 'linear' pyrrolocarbazoles **22a**, **23a** and **24**–**28**

Compound	L1210	Cell cycle[a]	P338	P338 CPT5[b]	GSK3
Camptothecin	NT	NT	0.024	3.98	NT
22a	4.3	NS toxic at 20 μM	NT	NT	>10
23a	>10	NT	NT	NT	>10
24a	3.2	G2M 48% at 10 μM	5.06	5.60	>10
24b	3.8	G2M 56% at 10 μM	NT	NT	>10
25a	0.8	G2M 38% at 2.5 μM	1.41	2.82	>10
25b	8.5	NS toxic at 50 μM	NT	NT	>10
26a	0.5	NS toxic at 2 μM	2.06	3.36	>10
26b	0.64	NS toxic at 5 μM	NT	NT	>10
27a	1	G2M 76% at 10 μM	3.24	3.23	>10
27b	4.2	NS toxic at 25 μM	NT	NT	>10
28a	0.34	G2M 80% at 2 μM	0.52	1.69	>10
28b	0.53	Inactive at 2 μM	NT	NT	>10

[a] 24% of untreated control cells were recovered in the G2+M phases of the cell cycle, 44% in the G1 phase.
[b] Drug concentration (μM) that inhibits leukemia cell growth by 50% after incubation in liquid medium for 72 h.

indicating that they exhibit preferential interactions with defined sequences. The most pronounced effects were observed with **28a**, which recognizes a subset of sequences. The differential cleavage plot shown in Figure 2 indicates that **28a** protects some sequences against DNase I cutting and promotes the activity of the enzyme at adjacent sites. Both AT- and GC-rich sequences can provide binding sites for **28a** and no clear sequences preference can be deduced. A more detailed biochemical study will be needed to better understand the sequence recognition property of this molecule.

Compound **28a** binds strongly to DNA. This is also evident from melting temperature experiments where it was observed that the molecule protects DNA from heat denaturation. The drug-induced increase of the melting temperature (T_m) of calf thymus DNA (58%AT, $T_m = 63$ °C) and poly(dAT)$_2$ (100%AT, $T_m = 41$ °C) is proportional to the drug concentration (Fig. 3).

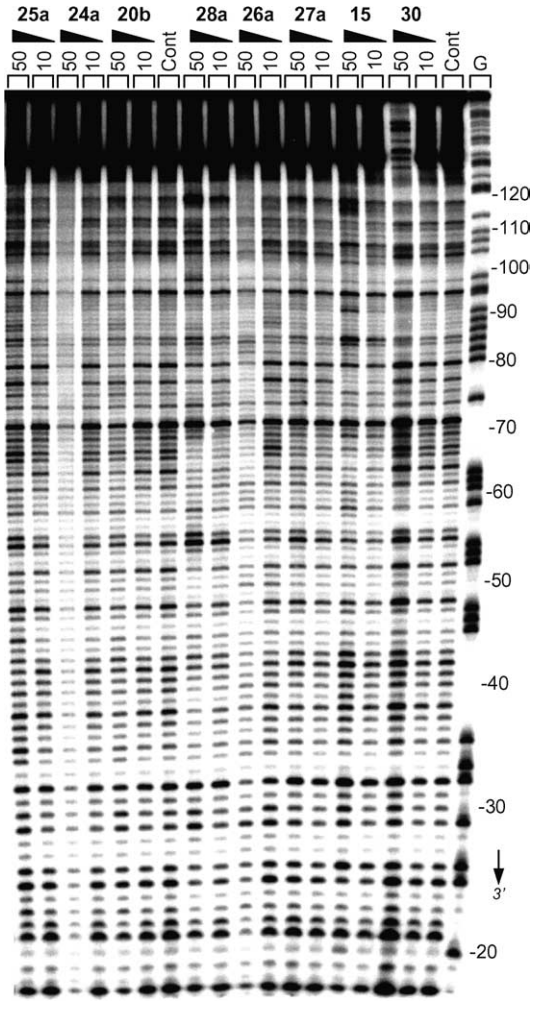


Figure 1. DNase I footprinting of **28a** on a 3′-end radiolabelled 176-bp DNA fragment from pTUC. The products of nuclease digestion were resolved on an 8% polyacrylamide gel containing 8 M urea. The concentration in μM of the drug is shown at the top of the appropriate gel lanes. Control tracks (Cont.) contained no drug. The track labelled 'G' represents dimethylsulfate–piperidine markers specific for guanines.

DNA induces significant shifts in the UV–vis spectrum of the pyrrolo[3,4-*b*]carbazole **28a** (Fig. 4A). Addition of calf thymus DNA to the compound results in a significant decrease in extinction coefficient at the peak wavelength centred at 290 nm and 380 nm and these two peaks are shifted to longer wavelengths. The marked hypochromic and bathochromic effects together with the occurrence of well defined isosbestic points at 300 and 340 nm reflect the strong interaction with DNA and a homogeneous type of binding. The exact mode of interaction with DNA is not precisely known at present, but circular dichroism measurements (Fig. 4B) suggest a minor groove binding process. Addition of calf thymus DNA to a solution of **28a** at a fixed concentration leads to the appearance of a positive CD band in the drug absorption band around 310 nm. Such a positive CD is commonly observed with minor groove binders whereas intercalating drugs generally produce negative CD (or no CD at all). At this stage, we consider **28a** as a DNA minor groove binder. This hypothesis is consistent with the footprinting measurements but here again it will be necessary to investigate further the DNA binding properties of this molecule using high resolution methods to fully validate this hypothesis.

3.4. CDK-1 inhibition

All the derivatives of Tables 1 and 2 were screened against affinity chromatography purified CDK1/cyclin B. None of these compounds showed any significant inhibitory activity at a 10 μM final concentration.

3.5. GSK-3α/β inhibition

Compounds were also tested on affinity chromatography purified GSK-3α/β. A few derivatives showed a near micromolar inhibitory activity in the β-carbolines series. The most active one was compound **38**, which is not surprising, considering the large lipophilic group appended on the β-carboline moiety, which exists in most potent GSK-3 inhibitors derived from pyrrolidine(di)ones. The presence of nitrogen(s) in the aromatic ring(s) (for example, β-carboline vs carbazole) appears to be a stringent requirement[13b,c] to develop a GSK-3 inhibitory activity.

4. Conclusion

Nearly all the derivatives we synthesized showed a micromolar range activity on L1210 cells. It could be noticed that the *N*-substitution of the pyrrolocarbazoles by the SEM group (vs NH compounds) did not modify the activity. In the camptothecin family, it has already been observed that appendage with a lipophilic trialkylsilyl chain are not detrimental to the anticancer activity.[41] Some of the molecules tested induce a strong accumulation of L1210 cells in the G1 or G2+M phases of the cell cycle probably via a CDK-independent pathway (no CDK1 inhibition by our compounds was observed). The exact targets of these cytotoxic compounds remain unknown at present but it is plausible that DNA interaction plays a role in the cytotoxic

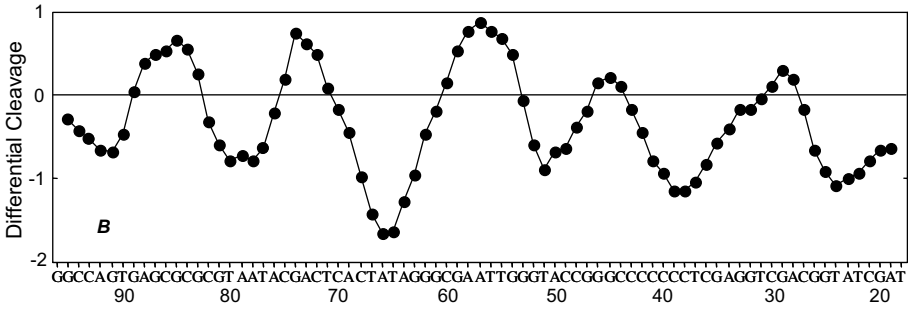


Figure 2. Differential cleavage plots comparing the susceptibility of the 176-bp DNA fragment to DNase I cutting in the presence of 50 μM **28a**. Negative values correspond to a ligand-protected site and positive values represent enhanced cleavage. Vertical scales are in units of ln(fa)−ln(fc), where fa is the fractional cleavage at any bond in the presence of the drug and fc is the fractional cleavage of the same bond in the control, given closely similar extents of overall digestion. Each line drawn represents a 3-bond running average of individual data points, calculated by averaging the value of ln(fa)−ln(fc) at any bond with those of its two nearest neighbors. Only the region of the restriction fragment analyzed by densitometry is shown.

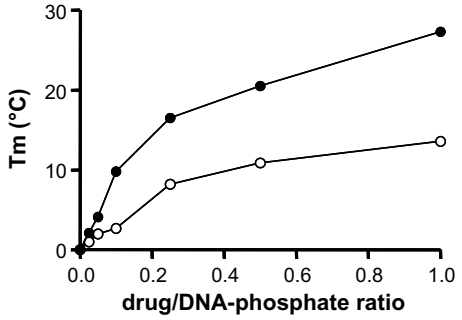


Figure 3. Melting temperature variation ΔT_m ($T^{\text{drug–DNA complex}} - T^{\text{DNA alone}}$ in °C) of poly(dAT)$_2$ (●) calf thymus DNA (○) after incubation with **28a**. The T_m measurements were performed at increasing drug/DNA-phosphate ratio with a fixed DNA concentration (20 μM). T_m measurements were performed in BPE buffer pH 7.1 (6 mM Na_2HPO_4, 2 mM NaH_2PO_4, 1 mM EDTA), in 1 cm quartz cuvettes at 260 nm with a heating rate of 1 °C/min. The T_m values were obtained from first-derivative plots.

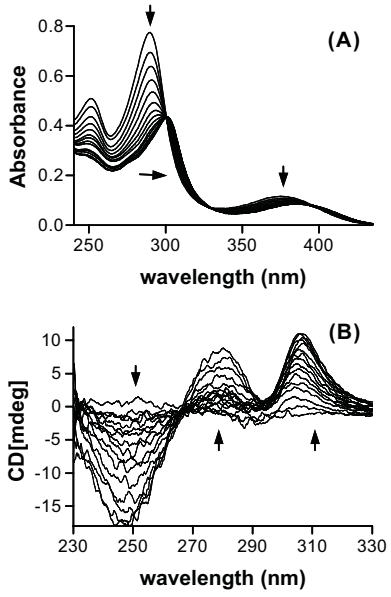


Figure 4. DNA titration of **28a** followed by (A) absorption and (B) circular dichroism spectroscopies. To 1 mL of drug solution at 20 μM were added aliquots of a concentrated calf thymus DNA solution. The phosphate-DNA/drug ratio increased from 0 to 20. Measurements were performed in BPE buffer pH 7.1 (6 mM Na_2HPO_4, 2 mM NaH_2PO_4, 1 mM Na_2EDTA). Spectra are referenced against DNA solutions of exactly the same DNA concentration and were adjusted to a common baseline.

action because the most cytotoxic molecule **28a** was found to be a potent DNA binder. This compound stands as an usual sequence selective minor groove binder and it provides novel opportunities to design drugs acting on DNA and DNA-manipulating enzymes. However, we cannot exclude the involvement of enzymes implicated in the cell-cycle control. Whatever the exact mechanism of action, we have discovered a new class of antiproliferative agents. Work are in progress in our laboratories to evaluate their anticancer activities and develop additional pyrrolocarbazoles.

5. Experimental

5.1. Materials and methods

Melting points were determined with a Reichert Thermovar hot-stage apparatus and are uncorrected. IR spectra (film or KBr) were measured with a Bomem FTIR instrument. UV spectra were measured in MeOH, using a UNICAM 8700 UV–vis spectrophotometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were acquired on a Bruker AC 300 spectrometer in $CDCl_3$ with TMS as internal standard, or in DMSO-d_6 and chemical shifts were expressed in ppm (δ). Mass spectra were recorded with a VG Autospec apparatus. All solvents were purified by following standard literature methods. Trimethylsilylethoxymethyl chloride (SEMCl) was purchased from Aldrich and activated MnO_2 from Merck. *N*,*N*-Dimethyl-β-alanine hydrochloride[42] and 4-(4,6-dimethoxy[1,3,5]-triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM)[30] were prepared as described in literature. (1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetaldehyde was synthesized as described in our previous work.[32] Chromatography was performed on silica gel

60 (Merck). Reactions were monitored using Merck TLC aluminium sheets (Kieselgel $60F_{254}$). Elemental analyses were carried out by the Microanalysis Service of the University of Reims and their results were found to be in satisfactory agreement (±0.5%) with the calculated values.

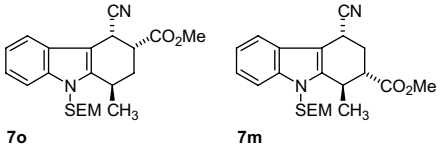
5.2. Synthesis

5.2.1. [1-(2-Trimethylsilanyl-ethoxymethyl)-2-vinyl-1*H*-indol-3-yl]-acetonitrile (6, R^4 = SEM). A solution of **6** (R^4 = H) (6.0 g; 33.0 mmol) in dry THF (60 mL) was added at 0 °C under N_2 atmosphere to a suspension of NaH 50% (2.84 g; 59.4 mmol) in dry THF (60 mL). After 30 min stirring at 0 °C, was added dropwise trimethylsilylethoxymethyl chloride (SEMCl) (9.92 mL; 56.0 mmol) under N_2 atmosphere. The orange suspension was stirred for 45 min at 0 °C then for 3 h at room temperature. The mixture was then quenched at 0 °C by a brine solution (50 mL) and extracted three times with diethyl ether (3 × 20 mL). The combined organic layers were first neutralized (pH 6–7) with a 5% aqueous solution of $NaHCO_3$ (60 mL) then washed with a brine solution (60 mL). The organic layer was finally dried over anhydrous $MgSO_4$ and filtered. After concentration under reduced pressure, the crude brown oil (1.61 g) was purified by column chromatography (eluent: cyclohexane/ethyl acetate, 95:5) to afford 9.30 g of **6** (R^4 = SEM) as a yellow oil (90%). IR (film) = 3055, 2953 (br), 2922 (s), 2895 (s), 2247 (CN), 1626, 1464 (s), 1327, 1248 (s), 1095, 1046 (s) (–CH_2–O–CH_2–), 860, 837 (s) (TMS), 748 cm^{-1}; UV: λ_{max} = 224, 236, 297 nm; ^1H NMR ($CDCl_3$): δ = 0.02 (s, 9H), 0.90 (t, J = 8.6 Hz, 2H), 3.59 (t, J = 8.6 Hz, 2H), 3.90 (s, 2H), 5.50 (s, 2H), 5.77 (d, J = 18.0 Hz, 1H), 5.79 (d, J = 12.6 Hz, 1H), 6.90 (dd, J = 12.6; 18.0 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.50, 13.7, 17.7, 65.8, 72.5, 102.7, 109.7, 117.9, 118.3, 120.8, 122.1, 123.3, 124.8, 126.7, 136.0, 136.9; EI-MS (*m*/*z*, %): 312 (M^+, 72), 254 (43), 195 (75), 155 (100), 154 (64). HREIMS ($C_{18}H_{24}N_2OSi$): calcd 312.1658; found 312.1665.

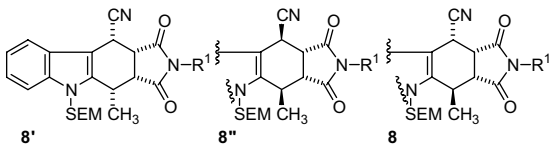
5.2.2. 4-Cyano-1-methyl-9-(2-trimethylsilanyl-ethoxymethyl)-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylic acid methyl ester (7, '*ortho* (*o*)' isomer, R^4 = SEM) and 4-cyano-1-methyl-9-(2-trimethylsilanyl-ethoxy-methyl)-2,3,4,-9-tetrahydro-1*H*-carbazole-2-carboxylic acid methyl ester (7, '*meta* (*m*)' isomer, R^4 = SEM) (Scheme 8). Cycloadduct **7** (mixture of two inseparable regioisomers) was obtained as described in our previous work.[24] After purification by column chromatography (eluent: cyclohexane/ethyl acetate, 92:8), pure **7** (mixture of two inseparable regioisomers '*o*' and '*m*', ratio 3:1) was isolated as an unstable vivid yellow oil (56%). IR (film): ν = 3053, 2953 (br), 2236 (CN), 1738 (s) (C═O), 1464, 1246, 1071 (br) (–CH_2–O–CH_2–), 837 (TMS) cm^{-1}; UV: λ_{max} = 222, 270, 280, 290 nm. The relative proportions of the two regioisomers ('*o*'/'*m*', ratio 3:1) were determined by ^1H NMR spectroscopy; ^1H NMR ($CDCl_3$): $\delta = -0.05^{7o,7m}$ (s, 18H), $0.93^{7o,7m}$ (m, 4H), 1.37^{7m} (d, J = 6.9 Hz, 3H), 1.40^{7o} (d, J = 7.0 Hz, 3H), 2.14^{7m} (ddd, J = 7.2; 9.4; 13.9 Hz, 1H), 2.35^{7o} (ddd, J = 1.5; 2.6; 13.3 Hz, 1H), 2.44^{7o} (ddd, J = 5.3; 12.9; 13.3 Hz, 1H), 2.56^{7m} (ddd, J = 3.6; 6.0; 13.9 Hz, 1H), 3.18^{7m} (ddd, J = 3.6; 7.2; 9.4 Hz, 1H), 3.24^{7o} (ddd, J = 2.6; 5.3; 12.9 Hz, 1H), 3.28^{7m} (dq, J = 6.9; 7.2 Hz, 1H), 3.36^{7o} (ddq, J = 1.5; 5.3; 7.0 Hz, 1H), $3.57^{7o,7m}$ (m, 4H), 3.83^{7m} (s, 3H), 3.91^{7o} (s, 3H), 4.51^{7o} (d, J = 5.3 Hz, 1H), 4.52^{7m} (dd, J = 6.0; 9.4 Hz, 1H), 5.42^{7o} (d, J = 11.2 Hz, 1H), 5.44^{7m} (d, J = 10.4 Hz, 1H), 5.47^{7o} (d, J = 11.2 Hz, 1H), 5.48^{7m} (d, J = 10.4 Hz, 1H), $7.23^{7o,7m}$ (t, J = 8.0 Hz, 2H), $7.29^{7o,7m}$ (t, J = 8.0 Hz, 2H), 7.44^{7m} (d, J = 8.0 Hz, 1H), 7.46^{7o} (d, J = 8.0 Hz, 1H), 7.59^{7o} (d, J = 8.0 Hz, 1H), 7.81^{7m} (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = -1.5^{7o,7m}$, 17.8^{7m}, 18.0^{7o}, 20.4^{7o}, 20.6^{7m}, 25.9^{7o}, 26.9^{7m}, $27.0^{7o,7m}$, 29.8^{7o}, 34.0^{7m}, 38.4^{7o}, 43.3^{7m}, 52.5^{7m}, 52.6^{7o}, 66.0^{7m}, 66.1^{7o}, 72.2^{7o}, 72.8^{7m}, 102.9^{7m}, 103.6^{7o}, 109.6^{7m}, 109.8^{7o}, 117.6^{7o}, 118.5^{7m}, 118.6^{7o}, 119.8^{7m}, 120.7^{7m}, 120.8^{7o}, 122.6^{7m}, 122.7^{7o}, $125.4^{7o,7m}$, 137.6^{7o}, 137.9^{7m}, 139.3^{7m}, 140.6^{7o}, 171.9^{7o}, 172.8^{7m}; EI-MS (*m*/*z*, %): 398 (M^+, 49), 340 (14), 281 (88), 280 (76), 241 (44), 182 (100), 181 (60). HREIMS ($C_{22}H_{30}N_2O_3Si$): calcd 398.2026; found 398.2029.

5.2.3. General procedure for the synthesis of the three isomers (8: major isomer) and (8′,8″: mixture of two inseparable isomers) (Scheme 9) (GP). Cycloadduct **8** and **8′**,**8″** (mixture of two inseparable isomers) were obtained as described in our previous work[24] and purified by column chromatography.

5.2.3.1. 2,4-Dimethyl-1,3-dioxo-5-(2-trimethylsilanyl-ethoxymethyl)-1,2,3,3a,4,5,10,10a-octahydro-pyrrolo-[3,4-*b*]carbazole-10-carbonitrile ((8a) and (8′a,8″a), R^4 = SEM, R^1 = Me). The purification by column chromatography afforded: **8′a**,**8″a** (mixture of two inseparable isomers, ratio 2:9) as an unstable vivid yellow oil (11%) (eluent: cyclohexane/ethyl acetate, 90:10) and **8a** as an unstable pale yellow foam (68%) (eluent: ethyl acetate). For **8′a**,**8″a**: IR (film): ν = 3057, 2953 (br), 2238 (CN), 1780 (C═O), 1703 (s) (C═O), 1460, 1439, 1080 (br) (–CH_2–O–CH_2), 837 (TMS) cm^{-1}; UV: λ_{max} = 221, 270, 280, 290 nm. The relative proportions of the two isomers



Scheme 8.



Scheme 9.

(**8′a/8″a**, ratio 2:9) were determined by ^{1}H NMR spectroscopy; ^{1}H NMR ($CDCl_3$): $\delta = -0.05^{\mathbf{8''a}}$ (s, 9H), $-0.01^{\mathbf{8'a}}$ (s, 9H), $0.90^{\mathbf{8'a,8''a}}$ (m, 4H), $1.05^{\mathbf{8'a}}$ (d, J = 7.0 Hz, 3H), $1.66^{\mathbf{8''a}}$ (d, J = 7.3 Hz, 3H), $2.88^{\mathbf{8''a}}$ (s, 3H), $3.12^{\mathbf{8'a}}$ (s, 3H), $3.42^{\mathbf{8''a}}$ (dd, J = 1.0; 9.1 Hz, 1H), 3.45–3.60$^{\mathbf{8'a,8''a}}$ (m, 4H), $3.53^{\mathbf{8'a}}$ (dd, J = 3.8; 9.5 Hz, 1H), $3.70^{\mathbf{8'a}}$ (dd, J = 6.8; 9.5 Hz, 1H), $3.82^{\mathbf{8''a}}$ (dd, J = 0.9; 9.1 Hz, 1H), $3.84^{\mathbf{8'a}}$ (dq, J = 3.8; 7.0 Hz, 1H), $3.98^{\mathbf{8''a}}$ (dq, J = 1.0; 7.3 Hz, 1H), $4.47^{\mathbf{8'a}}$ (d, J = 6.8 Hz, 1H), $4.88^{\mathbf{8''a}}$ (d, J = 0.9 Hz, 1H), $5.38^{\mathbf{8''a}}$ (d, J = 11.4 Hz, 1H), $5.43^{\mathbf{8'a}}$ (d, J = 11.4 Hz, 1H), $5.52^{\mathbf{8'a}}$ (d, J = 11.4 Hz, 1H), $5.53^{\mathbf{8''a}}$ (d, J = 11.4 Hz, 1H), 7.19–7.38$^{\mathbf{8'a,8''a}}$ (m, 6H), $7.60^{\mathbf{8''a}}$ (d, J = 8.0 Hz, 1H), $8.05^{\mathbf{8'a}}$ (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = -1.5^{\mathbf{8'a,8''a}}$, $15.8^{\mathbf{8'a}}$, $17.2^{\mathbf{8''a}}$, $17.8^{\mathbf{8'a}}$, $22.0^{\mathbf{8''a}}$, $23.1^{\mathbf{8'a}}$, $23.9^{\mathbf{8''a}}$, $24.9^{\mathbf{8'a}}$, $25.7^{\mathbf{8''a}}$, $27.0^{\mathbf{8'a}}$, $28.2^{\mathbf{8''a}}$, $43.3^{\mathbf{8''a}}$, $43.8^{\mathbf{8'a}}$, $44.4^{\mathbf{8'a}}$, $46.3^{\mathbf{8''a}}$, $66.2^{\mathbf{8'a,8''a}}$, $72.0^{\mathbf{8'a}}$, $72.1^{\mathbf{8''a}}$, $101.6^{\mathbf{8'a,8''a}}$, $109.6^{\mathbf{8'a}}$, $110.0^{\mathbf{8''a}}$, $117.7^{\mathbf{8''a}}$, $118.7^{\mathbf{8'a}}$, $119.4^{\mathbf{8'a}}$, $120.3^{\mathbf{8''a}}$, $121.1^{\mathbf{8'a,8''a}}$, $123.0^{\mathbf{8'a,8''a}}$, $125.1^{\mathbf{8'a}}$, $125.2^{\mathbf{8''a}}$, $137.0^{\mathbf{8'a,8''a}}$, $138.5^{\mathbf{8'a}}$, $139.3^{\mathbf{8''a}}$ $176.3^{\mathbf{8'a,8''a}}$, $177.8^{\mathbf{8'a,8''a}}$; EI-MS (*m*/*z*, %): 423 (M^+, 23), 365 (22), 306 (52), 266 (71), 181 (100). HREIMS ($C_{23}H_{29}N_3O_3Si$): calcd 423.1978; found 423.1991. For **8a**: IR (film): ν = 3053, 2953 (br), 2247 (CN), 1780 (C═O), 1709 (s) (C═O), 1460, 1439, 1078 (br) (–CH_2–O–CH_2–), 837 (TMS) cm^{-1}; UV: λ_{max} = 221, 272, 281, 290 nm. ^{1}H NMR ($CDCl_3$): $\delta = -0.02$ (s, 9H), 0.91 (m, 2H), 1.40 (d, J = 7.3 Hz, 3 H), 2.88 (s, 3H), 3.31 (dd, J = 0.5; 8.7 Hz, 1H), 3.48 (m, 2H), 3.75 (dd, J = 6.8; 8.7 Hz, 1H), 3.98 (dq, J = 0.5; 7.3 Hz, 1H), 4.56 (d, J = 6.8 Hz, 1H), 5.40 (d, J = 11.4 Hz, 1H), 5.57 (d, J = 11.4 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = -1.5$, 17.9, 25.1, 25.5, 27.8, 41.4, 46.7, 66.0, 72.0, 100.4, 109.7, 117.0, 118.5, 121.0, 122.6, 124.9, 136.9, 137.7, 174.9, 177.4; EI-MS (*m*/*z*, %): 423 (M^+, 48), 365 (37), 306 (68), 266 (100), 181 (80). HREIMS ($C_{23}H_{29}N_3O_3Si$): calcd 423.1978; found 423.1991.

5.2.3.2. 2-Benzyl-4-methyl-1,3-dioxo-5-(2-trimethylsilanyl-ethoxymethyl)-1,2,3,3a,4,5,10,10a-octahydro-pyrrolo[3,4-*b*]carbazole-10-carbonitrile ((8b) and (8′b,8″b), R^4 = SEM, R^1 = Bn). The purification by column chromatography afforded: **8′b**,**8″b** (mixture of two inseparable isomers, ratio 1:8) as an unstable vivid yellow oil (9%) (eluent: cyclohexane/ethyl acetate, 85:15) and **8b** as an unstable pale orange foam (59%) (eluent: cyclohexane/ethyl acetate, 70:30). For **8b**,**8″b**: IR (film): ν = 3063, 3034, 2951 (br), 2241 (CN), 1460, 1780 (C═O), 1076 (br) (–CH_2–O–CH_2–), 837 (TMS) cm^{-1}; UV: λ_{max} = 221, 270, 280, 290 nm. The relative proportions of the two isomers (**8′b/8″b**, ratio 1:8) were determined by ^{1}H NMR spectroscopy; ^{1}H NMR ($CDCl_3$): $\delta = -0.01^{\mathbf{8'b,8''b}}$ (s, 18H), $0.86^{\mathbf{8'b}}$ (d, J = 7.1 Hz, 3H), 0.88–0.93$^{\mathbf{8'b,8''b}}$ (m, 4H), $1.69^{\mathbf{8''b}}$ (d, J = 7.4 Hz, 3H), $3.34^{\mathbf{8'b}}$ (dd, J = 3.9; 10.3 Hz, 1H), $3.39^{\mathbf{8''b}}$ (dd, J = 1.0; 8.9 Hz, 1H), 3.42–3.52$^{\mathbf{8'b,8''}}$ (m, 4H), $3.52^{\mathbf{8'b}}$ (dd, J = 7.0; 10.3 Hz, 1H), $3.77^{\mathbf{8''b}}$ (dd, J = 1.0; 8.9 Hz, 1H), $3.79^{\mathbf{8'b}}$ (dq, J = 3.9; 7.1 Hz, 1H), $3.98^{\mathbf{8''b}}$ (dq, J = 1.0; 7.4 Hz, 1H), $4.38^{\mathbf{8'b}}$ (d, J = 7.0 Hz, 1H), $4.49^{\mathbf{8''b}}$ (s, 2H), $4.77^{\mathbf{8'b}}$ (s, 2H), $4.89^{\mathbf{8''b}}$ (d, J = 1.0 Hz, 1H), $5.34^{\mathbf{8''b}}$ (d, J = 11.4 Hz, 1H), $5.39^{\mathbf{8'b}}$ (d, J = 11.6 Hz, 1H), $5.47^{\mathbf{8''b}}$ (d, J = 11.4 Hz, 1H), $5.48^{\mathbf{8'b}}$ (d, J = 11.6 Hz, 1H), $6.80^{\mathbf{8'b}}$ (d, J = 7.0 Hz, 4H), $6.94^{\mathbf{8'b}}$ (t, J = 7.0 Hz, 4H), $7.09^{\mathbf{8'b}}$ (t, J = 7.0 Hz, 2H), 7.17–7.44$^{\mathbf{8'b,8''b}}$ (m, 4H), $7.46^{\mathbf{8'b}}$ (d, J = 8.0 Hz, 1H), $7.51^{\mathbf{8''b}}$ (d, J = 8.0 Hz, 1H), $7.58^{\mathbf{8''b}}$ (d, J = 8.0 Hz, 1H), $8.02^{\mathbf{8'b}}$ (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = -1.6^{\mathbf{8'b,8''b}}$, $15.3^{\mathbf{8'b}}$, $17.7^{\mathbf{8''b}}$, $17.9^{\mathbf{8'b}}$, $21.4^{\mathbf{8''b}}$, $23.0^{\mathbf{8'b}}$, $24.0^{\mathbf{8''b}}$, $27.1^{\mathbf{8'b}}$, $28.6^{\mathbf{8''b}}$, $42.6^{\mathbf{8'b}}$, $42.7^{\mathbf{8''b}}$, $43.5^{\mathbf{8''b}}$, $46.3^{\mathbf{8''b}}$, $43.6^{\mathbf{8'b}}$, $44.1^{\mathbf{8'b}}$, $66.0^{\mathbf{8''b}}$, $66.2^{\mathbf{8'b}}$, $71.7^{\mathbf{8'b}}$, $71.9^{\mathbf{8''b}}$, $101.3^{\mathbf{8'b}}$, $101.7^{\mathbf{8''b}}$, $109.5^{\mathbf{8'b}}$, $109.9^{\mathbf{8''b}}$, $117.5^{\mathbf{8''b}}$, $118.3^{\mathbf{8'b}}$, $119.3^{\mathbf{8'b}}$, $120.2^{\mathbf{8''b}}$, $120.9^{\mathbf{8'b}}$, $121.0^{\mathbf{8''b}}$, $122.6^{\mathbf{8'b}}$, $122.9^{\mathbf{8''b}}$, $124.7^{\mathbf{8'b}}$, $125.0^{\mathbf{8''b}}$, $126.9^{\mathbf{8'b}}$, $127.1^{\mathbf{8''b}}$, $127.6^{\mathbf{8'b}}$, $127.7^{\mathbf{8''b}}$, $128.3^{\mathbf{8'b}}$, $128.4^{\mathbf{8''b}}$, $134.4^{\mathbf{8''b}}$, $135.0^{\mathbf{8'b}}$, $136.8^{\mathbf{8''b}}$, $137.1^{\mathbf{8'b}}$, $138.6^{\mathbf{8'b}}$, $139.3^{\mathbf{8''b}}$, $176.0^{\mathbf{8''b}}$, $176.3^{\mathbf{8'b}}$, $177.4^{\mathbf{8''b}}$, $177.6^{\mathbf{8'b}}$; EI-MS (*m*/*z*, %): 499 (M^+, 47), 441 (24), 382 (43), 342 (36), 181 (100). HREIMS ($C_{29}H_{33}N_3O_3Si$): calcd 499.2291; found 499.2267. For **8b**: IR (film): ν = 3063, 3034, 2953 (br), 2247 (CN), 1779 (C═O), 1707 (s) (C═O), 1400, 1078 (br) (–CH_2–O–CH_2–), 837 (TMS) cm^{-1}; UV: λ_{max} = 222, 272, 280, 289 nm; ^{1}H NMR ($CDCl_3$): $\delta = -0.20$ (s, 9H), 0.87 (m, 2H), 1.39 (d, J = 7.3 Hz, 3H), 3.28 (dd, J = 1.0; 8.5 Hz, 1H), 3.44 (m, 2H), 3.72 (dd, J = 6.2; 8.5 Hz, 1H), 3.93 (dq, J = 1.0; 7.3 Hz, 1H), 4.46 (d, J = 14.5 Hz, 1H), 4.55 (d, J = 6.2 Hz, 1H), 4.56 (d, J = 14.5 Hz, 1H), 5.30 (d, J = 11.4 Hz, 1H), 5.47 (d, J = 11.4 Hz, 1H), 6.79 (d, J = 7.0 Hz, 2H), 6.89 (t, J = 7.0 Hz, 2H), 7.08 (t, J = 7.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): $\delta = -1.5$, 17.8, 19.6, 25.4, 28.6, 42.0, 42.6, 46.8, 66.0, 71.9, 100.7, 109.7, 117.2, 118.5, 121.1, 122.6, 124.8, 127.4, 127.5, 128.3, 134.6, 136.8, 137.6, 174.6, 177.0; EI-MS (*m*/*z*, %): 499 (M^+, 73), 441 (39), 382 (59), 342 (100), 181 (74). HREIMS ($C_{29}H_{33}N_3O_3Si$): calcd 499.2291; found 499.2286.

5.2.4. General procedure for the aromatization of carbazoles 7 and 8 (GP). Cycloadducts **7** (mixture of 2 inseparable regioisomers) or **8** (major isomer) and activated MnO_2 were refluxed for 8 h in dry toluene under N_2 atmosphere. After filtration on Celite, followed by concentration under reduced pressure, the crude solid was purified either by column chromatography or by crystallization from MeOH/diethyl ether (90:10).

5.2.4.1. 4-Cyano-1-methyl-9-(2-trimethylsilanyl-ethoxymethyl)-9*H*-carbazole-3-carboxylic acid methyl ester (9), 4-cyano-1-methyl-9-(2-trimethylsilanyl-ethoxymethyl)-9*H*-carbazole-2-carboxylic acid methyl ester (10), 4-hydroxy-1-methyl-9-(2-trimethylsilanyl-ethoxymethyl)-9*H*-carbazole-3-carboxylic acid methyl ester (11), 1-methyl-9-(2-trimethylsilanyl-ethoxy-methyl)-9*H*-carbazole-3-carboxylic acid methyl ester (12). These compounds were synthesized from **7** according to GP: cycloadducts **7** (1.13 g, 2.85 mmol) and activated MnO_2 (3.72 g, 48.2 mmol) were refluxed in dry toluene (20 mL). After filtration, concentration the purification by column chromatography afforded: 59.0 mg of **11** as a white powder (5%) (eluent: cyclohexane/ethyl acetate, 85:15), 7.6 mg of **12** as an orange oil (1%) (eluent: cyclohexane/ethyl acetate, 80:20), 34.0 mg of **10** as a dark yellow amorphous solid (3%) (eluent: cyclohexane/ethyl acetate, 60:40) and 561.5 mg of **9** as a white powder (50%) (eluent: cyclohexane/ethyl acetate, 50:50). For **9**: mp 144–146 °C; IR

(KBr): ν = 3090, 2949 (br), 2218 (CN), 1721 (s) (CO), 1584, 1572 (s), 1464, 1456, 1439, 1250 (br), 1072,5 (br) (–CH_2–O–CH_2–), 833 (TMS) cm^{-1}; UV: λ_{max} = 228, 253, 262, 289, 342 nm; ^{1}H NMR ($CDCl_3$): δ = −0.10 (s, 9H), 0.89 (m, 2H), 2.90 (s, 3H), 3.54 (m, 2H), 4.03 (s, 3H), 5.79 (s, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.88 (s, 1H), 8.79 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 17.8, 19.9, 52.4, 66.2, 72.9, 102.4, 109.1, 117.4, 121.0, 121.4, 122.4, 124.3, 125.6, 125.7, 128.1, 130.9, 140.9, 142.5, 165.3; EI-MS (*m*/*z*, %): 394 (M^+, 45), 363 (14), 336 (92), 277 (82), 232 (100). HREIMS ($C_{22}H_{26}N_2O_3Si$): calcd 394.1713; found 394.1721. Anal. Calcd for $C_{22}H_{26}N_2O_3Si$: C, 66.97; H, 6.64; N, 7.10. Found: C, 66.95; H, 6.21; N, 6.83. For **10**: IR (film): ν = 3065, 2951 (br), 2224 (CN), 1616 (s), 1458, 1248 (br), 1072 (br), 837 (TMS) cm^{-1}; UV: λ_{max} = 223, 255, 269, 320, 355 nm; ^{1}H NMR ($CDCl_3$): δ = −1.5 (s, 9H), 0.95 (m, 2H), 3.11 (s, 3H), 3.62 (m, 2H), 3.99 (s, 3H), 5.87 (s, 2H), 7.41 (t, J = 8.0 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 8.07 (s, 1H), 8.69 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 16.4, 17.9, 52.5, 66.2, 73.9, 101.3, 109.6, 118.2, 120.5, 121.4, 122.4, 126.3, 127.5, 128.8, 129.3, 129.5, 139.8, 143.6, 167.6; EI-MS (*m*/*z*, %): 394 (M^+, 32), 363 (9), 336 (81), 277 (90), 232 (100), 205 (84). HREIMS ($C_{22}H_{26}N_2O_3Si$): calcd 394.1713; found 394.1722. For **11**: mp 106–107 °C; IR (KBr): ν = 2955 (br), 2851, 1674 (s) (C=O), 1628, 1447, 1350, 1213 (br), 1055 (br) (–CH_2–O–CH_2–), 835 (TMS) cm^{-1}; UV: λ_{max} = 232, 253, 263, 292, 302, 328, 341 nm; ^{1}H NMR ($CDCl_3$): δ = −0.05 (s, 9H), 0.89 (m, 2H), 2.76 (s, 3H), 3.58 (m, 2H), 4.00 (s, 3H), 5.75 (s, 2H), 7.35 (t, J = 8.0 Hz, 1H), 7.41–7.51 (m, 2H), 7.62 (s, 1H), 8.45 (d, J = 8.0 Hz, 1H), 11.53 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 17.9, 19.1, 51.8, 65.9, 72.9, 103.4, 108.7, 112.3, 112.7, 121.1, 122.8, 123.2, 125.2, 129.2, 140.8, 143.7, 157.8, 171.2; EI-MS (*m*/*z*, %): 385 (M^+, 70), 296 (36), 295 (100), 268 (53), 236 (38), 180 (29). HREIMS ($C_{21}H_{27}NO_4Si$): calcd 385.1709; found 385.1705. Anal. Calcd for $C_{21}H_{27}NO_4Si$: C, 65.42; H, 7.06; N, 3.63. Found: C, 65.39; H, 7.00; N, 3.41. For **12**: IR (film): ν = 3053, 2949 (br), 1717 (s) (C=O), 1601, 1485, 1456, 1435, 1252 (br), 837 (TMS) cm^{-1}; UV: λ_{max} = 215, 235, 244, 264, 277, 306, 319, 333 nm; ^{1}H NMR ($CDCl_3$): δ = −0.08 (s, 9H), 0.89 (m, 2H), 2.88 (s, 3H), 3.58 (m, 2H), 3.99 (s, 3H), 5.83 (s, 2H), 7.31 (t, J = 8.0 Hz, 1H), 7.48–7.59 (m, 2H), 7.96 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 17.9, 19.6, 51.9, 65.9, 73.2, 109.3, 120.3, 120.4, 120.7, 121.1, 121.8, 123.4, 124.2, 126.4, 130.2, 141.8, 142.1, 167.8; EI-MS (*m*/*z*, %): 369 (M^+, 48), 338 (9), 311 (27), 252 (97), 208 (50), 207 (100), 192 (55), 180 (54), 179 (60). HREIMS ($C_{21}H_{27}NO_3Si$): calcd 369.1760; found 369.1772.

5.2.4.2. 2,4-Dimethyl-1,3-dioxo-5-(2-trimethylsilanyl-ethoxymethyl)-1,2,3,5-tetrahydro-pyrrolo[3,4-*b*]-carbazole-10-carbonitrile (23a, R^1 = Me). Tetracyclic compound **23a** was synthesized from **8a** (R^1 = Me) according to GP: **8a** (103.0 mg, 0.24 mmol) and activated MnO_2 (169.0 mg, 1.95 mmol) were refluxed in dry toluene (10 mL). After filtration, concentration the purification by crystallization afforded:70.0 mg of **23a** as a grey powder (69%). Mp 215 °C; IR (KBr): ν = 3026, 2951, 2228 (CN), 1767 (s) (CO), 1705 (s) (CO), 1614, 1599, 1462, 1439 (s), 1381, 1352, 1055 (br) (–CH_2–O–CH_2–), 841 (TMS) cm^{-1}; UV: λ_{max} = 232, 253, 267, 304, 359, 378 nm; ^{1}H NMR ($CDCl_3$): δ = −0.05 (s, 9H), 0.92 (m, 2H), 3.13 (s, 3H), 3.20 (s, 3H), 3.59 (m, 2H), 5.83 (s, 2H), 7.17 (t, J = 8.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.8, 12.8, 17.7, 23.6, 66.3, 73.2, 95.5, 109.8, 114.2, 119.8, 121.5, 121.8, 125.1, 126.0, 126.1, 127.9, 129.0, 141.3, 142.7, 165.0, 167.4; EI-MS (*m*/*z*, %): 419 (M^+, 20), 361 (100), 302 (61). HREIMS ($C_{23}H_{25}N_3O_3Si$): calcd 419.1665; found 419.1673. Anal. Calcd for $C_{23}H_{25}N_3O_3Si$: C, 65.84; H, 6.00; N, 10.02. Found: C, 65.30; H, 5.68; N, 9.62.

5.2.4.3. 2-Benzyl-4-methyl-1,3-dioxo-5-(2-trimethylsilanyl-ethoxymethyl)-1,2,3,5-tetrahydro-pyrrolo[3,4-*b*]-carbazole-10-carbonitrile (23b, R^1 = Bn). Tetracyclic compound **23b** was synthesized from **8b** (R^1 = Bn) according to GP: **8b** (1.14 g, 4.29 mmol) and activated MnO_2 (2.98 g, 34.0 mmol) were refluxed in dry toluene (60 mL). After filtration, concentration the purification by crystallization afforded: 1.21 g of **23b** as a yellow powder (57%). Mp 211–213 °C; IR (KBr): ν = 3034, 2951 (br), 2226 (CN), 1761 (s) (CO), 1709 (s) (CO), 1614, 1431, 1400, 1342, 1074 (br) (–CH_2–O–CH_2–), 835 (TMS) cm^{-1}; UV: λ_{max} = 232, 253, 266, 306, 362, 380 nm; ^{1}H NMR ($CDCl_3$): δ = −0.07 (s, 9H), 0.92 (m, 2H), 3.29 (s, 3H), 3.58 (m, 2H), 4.83 (s, 2H), 5.92 (s, 2H), 7.23 (t, J = 8.0 Hz, 1H), 7.28–7.52 (m, 5 H), 7.57 (d, J = 7.0 Hz, 2H), 8.48 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 13.1, 17.8, 41.8, 66.5, 73.3, 95.5, 109.7, 114.7, 120.2, 122.0, 122.1, 125.6, 126.4, 126.7, 128.0, 128.1, 128.7, 129.2, 129.4, 136.2, 141.7, 143.0, 165.0, 167.4; EI-MS (*m*/*z*, %): 495 (M^+, 21), 437 (100), 378 (36). HREIMS ($C_{29}H_{29}N_3O_3Si$): calcd 495.1978; found 495.1977. Anal. Calcd for $C_{29}H_{29}N_3O_3Si$: C, 70.27; H, 5.90; N, 8.48. Found: C, 69.83; H, 5.72; N, 8.11.

5.2.5. 5-Methyl-6-(2-trimethylsilanyl-ethoxymethyl)-1,2-dihydro-6*H*-pyrrolo[3,4-c]carbazol-3-one (13). Nitrile-ester **9** (128.0 mg, 0.325 mmol) and Raney-Nickel (1.30 g) were stirred for 51 h in dry toluene/absolute ethanol (4 mL:10 mL) under pressure atmosphere of hydrogen (6 bars, autoclave). After filtration on Celite and concentration under reduced pressure, 112.0 mg of **13** were obtained as a white powder (94%). Mp 234–235 °C; IR (KBr): ν = 3206 (br), 3078, 3063, 2953 (br), 1697 (s) (CO), 1628, 1608, 1452 (s), 1358, 1074 (br) (–CH_2–O–CH_2–), 835 (TMS) cm^{-1}; UV: λ_{max} = 238, 244, 261, 270, 284, 321, 334, 306 nm; ^{1}H NMR (DMSO-d_6): δ = −0.12 (s, 9H), 0.85 (m, 2H), 2.91 (s, 3H), 3.56 (m, 2H), 4.81 (s, 2H), 5.97 (s, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 8.50 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = −1.2, 17.5, 19.4, 44.5, 65.3, 72.9, 110.3, 118.4, 120.8, 121.4, 121.7, 121.9, 122.8, 125.0, 126.4, 136.8, 140.4, 141.9, 170.9; EI-MS (*m*/*z*,

%): 366 (M^+, 38), 308 (100), 249 (62). HREIMS ($C_{21}H_{26}N_2O_2Si$): calcd 366.1763; found 366.1752. Anal. Calcd for $C_{21}H_{26}N_2O_2Si$: C, 68.81; H, 7.15; N, 7.64. Found: C, 68.35; H, 7.10; N, 7.45.

5.2.6. 4-Cyano-1-methyl-9-(2-trimethylsilanyl-ethoxymethyl)-9*H*-carbazole-3-carboxylic acid (14). Distilled water (2 mL) and powdered potassium hydroxide (175.0 mg, 3.12 mmol) were successively added to a solution of **9** (410.0 mg, 1.04 mmol) in *t*-BuOH/toluene/CH_2Cl_2 (30 mL:7 mL:3 mL) and were heated for 4 h at 80 °C under N_2 atmosphere. After concentration under reduced pressure, the residue was diluted with a 5% aqueous solution of hydrochloric acid (6.24 mL) at 0 °C (ice bath) and extracted with ethyl acetate (10 mL × 2). The combined organic layers were washed with water (8 mL × 2), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. After crystallization in diethyl ether (4 mL), 339.0 mg of **14** as a white powder were isolated (86%). Mp 179 °C; IR (KBr): ν = 3187–3005 (br), 2953 (s), 2899, 2861, 2808, 2220 (CN), 1690 (s) (CO), 1614, 1566 (s), 1454, 1406, 1395, 1369, 1331 (s), 1281, 1248 (s), 1238 (s), 1096, 1080 (s) (–CH_2–O–CH_2–), 858 (br), 842 (br) (TMS), 746, 727 cm^{-1}; UV: λ_{max} = 227, 252, 261, 284, 323, 339 nm; ^{1}H NMR (DMSO-d_6): δ = −0.10 (s, 9H), 0.87 (t, J = 7.8 Hz, 2H), 3.58 (t, J = 7.8 Hz, 2H), 3.92 (s, 3H), 5.98 (s, 2H), 7.43 (t, J = 8.0 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.00 (s, 1H), 8.69 (d, J = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ = −1.3, 17.4, 19.4, 65.5, 72.8, 101.7, 110.8, 117.5, 120.2, 121.2, 121.4, 124.8, 125.6, 126.7, 128.5, 131.0, 140.5, 142.8, 165.9; EI-MS (*m*/*z*, %): 380 (M^+, 42), 322 (93), 263 (100), 232 (92). HREIMS ($C_{21}H_{24}N_2O_3Si$): calcd 380.1556; found 380.1568.

5.2.7. 5-Methyl-1,2-dihydro-6*H*-pyrrolo[3,4-c]carbazol-3-one (15). *N*-Protected compound **13** (252.0 mg, 0.69 mmol) was stirred for 7 h under N_2 atmosphere at room temperature in a 3 M solution of hydrochloric acid (concentrated aqueous solution of HCl/ethanol/toluene, 40:34:26) (13.5 mL). After concentration under reduced pressure, the beige solid was diluted in water (10 mL), decanted, washed with water (10 mL), filtered under reduced pressure and finally washed with CH_2Cl_2 (5 mL × 3). After filtration, 154.0 mg of **15** were isolated as a white powder (95%). Mp 272 °C; IR (KBr): ν = 3352–3119 (br), 2930, 2911, 2852, 1667 (s) (CO), 1626 (s), 1610 (s), 1501, 1451, 1424, 1337, 1298, 1232 (s), 1209, 1059, 873, 781, 737 (s) cm^{-1}; UV: λ_{max} = 220, 238, 245, 263, 271, 285, 305.5, 321, 335 nm; ^{1}H NMR (DMSO-d_6): δ = 2.68 (s, 3H), 4.81 (s, 2H), 7.29 (t, J = 8.0 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 17.3, 44.5, 111.7, 119.7, 116.6, 120.1, 120.4, 121.8, 121.9, 123.8, 126.0, 136.8, 140.3, 141.3, 171.5; EI-MS (*m*/*z*, %): 236 (M^+, 100), 221 (58), 206 (33), 207 (52), 180 (27). HREIMS ($C_{15}H_{12}N_2O$): calcd 236.0950; found 236.0949.

5.2.8. 1-Dimethylamino-6-(2-dimethylaminoethyl)-5-methyl-1,2-dihydro-6*H*-pyrrolo[3,4-c]carbazol-3-one (16) and 1-dimethylamino-5-methyl-1,2-dihydro-6*H*-pyrrolo[3,4-c]carbazol-3-one (17). To a solution of **15** (220.0 mg, 0.93 mmol) in dry DMF (10 mL) was added at 0 °C (ice bath), NaH 50% (134. 0 mg, 2.80 mmol). After 45 min stirring at 0 °C, the chlorhydrate of the 2-dimethylaminoethylchloride (148.0 mg, 1.025 mmol) was added. The suspension was stirred for 72 h at room temperature under N_2 atmosphere. Then the mixture was diluted with water (4 mL) and distilled under reduced pressure. The residue was purified by column chromatography to afford 27.0 mg of **16** as a yellow powder (eluent: CH_2Cl_2/acetone, 60:40) (10%) and 43.0 mg of **17** as a yellow powder (eluent: acetone) (13%). For **16**: mp 189–191 °C; IR (KBr): ν = 3408, 3225 (br), 3073, 2962, 2931, 2861, 2820, 2780, 1683 (s) (CO), 1648, 1642, 1602, 1451, 1381, 1361, 1326, 1044, 1014 cm^{-1}; UV: λ_{max} = 222, 239, 246, 269, 277, 310, 328, 344 nm; ^{1}H NMR (DMSO-d_6): δ = 2.20 (s, 6H), 2.29 (s, 6H), 2.63 (t, J = 7.5 Hz, 2H), 2.94 (s, 3H), 4.74 (t, J = 7.5 Hz, 2H), 5.81 (s, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.67 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 20.1, 39.0, 43.0, 45.7, 58.6, 75.2, 109.4, 118.6, 119.7, 121.1, 121.3, 122.3, 124.3, 124.6, 126.2, 137.9, 140.7, 141.3, 170.4; EI-MS (*m*/*z*, %): 350 (M^+, 94), 306 (89), 292 (22), 261 (33), 248 (100), 247 (75), 235 (51), 219 (95), 205 (58), 193 (76), 192 (80), 178 (49), 165 (39), 151 (30). HREIMS ($C_{21}H_{26}N_4O$): calcd 350.2107; found 350.2131. For **17**: mp > 350 °C; IR (KBr) = 3397, 3215 (br), 3053, 2932, 2861, 2820, 2780, 1673 (s) (CO), 1623, 1602, 1451, 1421, 1376, 1351, 1331, 1024, 732 cm^{-1}; UV: λ_{max} = 219, 237, 246, 265, 275, 310, 325, 338 nm; ^{1}H NMR (DMSO-d_6): δ = 2.20 (s, 6H), 2.67 (s, 3H), 5.80 (s, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.50 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 8.39 (d, J = 8.0 Hz, 1H), 8.60 (s, 1H), 11.67 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 17.4, 39.0, 75.4, 111.3, 117.5, 119.5, 119.7, 121.4, 121.9, 124.1, 124.6, 126.1, 137.9, 140.6, 141.8, 171.0; EI-MS (*m*/*z*, %): 279 (M^+, 8), 236 (56), 235 (99), 207 (100), 192 (49), 179 (18). HREIMS ($C_{17}H_{17}N_3O$): calcd 279.1372; found 279.1382.

5.2.9. 1-Methyl-9*H*-carbazole-3,4-dicarboxylic acid dimethyl ester (18). A suspension of **9** (158.0 mg, 0.40 mmol) in a 9 M methanolic solution of hydrochloric acid (85 mL) was refluxed for 120 h under N_2 atmosphere. After concentration under reduced pressure, the pale yellow residue was crystallized and recrystallized in diethyl ether/methanol (80:20) (5 mL × 2) to afford 84.0 mg of **18** as a white crystalline powder (71%). Mp 199 °C; IR (KBr): ν = 3395 (br), 3005, 2951, 1726 (s) (CO), 1684 (s) (CO), 1587, 1456, 1429, 1339, 1271 (s), 1244 (s), 1215, 1192, 1165, 1132, 1103, 1049, 997, 797, 772, 746, 737 cm^{-1}; UV: λ_{max} = 229, 245, 264, 279, 312, 326, 336 nm; ^{1}H NMR (DMSO-d_6): δ = 2.68 (s, 3H), 3.91 (s, 3H), 4.05 (s, 3H), 7.27 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 11.3 (s, 1H); ^{13}C

NMR (DMSO-d_6): δ = 17.0, 52.4, 52.9, 112.1, 117.1, 118.3, 120.2, 120.9, 121.1, 121.7, 126.9, 127.1, 127.5, 140.9, 141.9, 166.4, 169.5; EI-MS (*m*/*z*, %): 297 (M^+, 78), 266 (100), 179 (30). HREIMS ($C_{17}H_{15}NO_4$): calcd 297.1001; found 297.1010.

5.2.10. Dimethyl-[2-(5-methyl-1,3-dioxo-3,6-dihydro-1*H*-pyrrolo[3,4-*c*]carbazol-2-yl)-ethyl]-ammonium chloride (19c)[‡]. Salt **19c** was obtained by following the procedure described in the literature[21g] with pyrido[2,3-*b*]indoles:115.0 mg of **18** (0.39 mmol) were heated at 100 °C for 5 days in *unsym*-dimethylethylenediamine (1 mL). The purification was led as followed: the crude mixture was diluted in CH_2Cl_2 (3 mL) and extracted with a 10% aqueous solution of hydrochloric acid (2 mL). The orange aqueous layer was washed with ethyl acetate (3 mL) to get rid of the unreacted **18**. The resultant aqueous layer was diluted in CH_2Cl_2 (7 mL) and alkalized with a saturated aqueous solution of potassium carbonate (3 mL). The aqueous layer was washed with ethyl acetate (6 mL) and the organic layers (CH_2Cl_2 and ethyl acetate) were washed with water (4 mL × 2), combined, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was diluted in a 9 M methanolic solution of hydrochloric acid (3 mL) and stirred for 1 h at room temperature. After concentration under reduced pressure, the crude solid was purified by crystallization in diethyl ether/methanol (5:1) to afford 81.6 mg of **19c** as a vivid yellow solid (59%). Mp 286 °C; IR (KBr): ν = 3296 (s), 3053, 3033, 2962, 2942, 1748 (CO), 1683 (s) (CO), 1612, 1597, 1492, 1446, 1426 (s), 1406, 1386, 1346, 1331, 1245, 1290, 742 (s), 732, 646, 626, 616 cm^{-1}; UV: λ_{max} = 228, 230, 252, 273, 286, 309, 362 nm; ^{1}H NMR (DMSO-d_6): δ = 2.73 (s, 3H), 2.86 (s, 6H), 3.45 (t, *J* = 5.6 Hz, 2H), 4.01 (t, *J* = 5.6 Hz, 2H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 8.81 (d, *J* = 8.0 Hz, 1H), 12.19 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 17.8, 33.1, 42.6, 55.0, 112.1, 118.1, 120.1, 120.4, 120.5, 123.6, 124.0, 124.7, 126.6, 128.4, 141.9, 143.4, 169.3, 169.4; EI-MS (*m*/*z*, %): 321 (M^+ − HCl, 100), 276 (13), 263 (39), 250 (28), 205 (17), 192 (11), 180 (45), 179 (57), 178 (34), 152 (21). HREIMS ($C_{19}H_{19}N_3O_2$): calcd 321.1477; found 321.1485.

5.2.11. 2-Benzyl-1-imino-5-methyl-6-(2-trimethylsilanyl-ethoxy-methyl)-1,2-dihydro-6*H*-pyrrolo[3,4-*c*]carbazol-3-one (20a). Benzylamine (0.498 mL, 4.57 mmol) was added at 0 °C (ice bath) to a white suspension of **14** (204.0 mg, 0.54 mmol) in methanol (20 mL). After 15 min stirring at room temperature under N_2 atmosphere, DMTMM (772.0 mg, 2.81 mmol) was added at 0 °C to the solution and the mixture was stirred for 45 h at room temperature under N_2 atmosphere until the disappearance of **14** (TLC monitoring). The suspension was filtered under reduced pressure to afford 156.0 mg of **20a**. The mother liquors was concentrated under reduced pressure, diluted in CH_2Cl_2 (19 mL) and extracted with a saturated solution of potassium carbonate (5 mL). The organic layer was acidified with a 5% aqueous citric acid solution (5 mL), washed with water (5 mL × 2), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue (566.0 mg) was purified by column chromatography (eluent: cyclohexane/CH_2Cl_2, 40:60) to afford 54.0 mg of **20a** (overall yield:83%). Mp 92 °C; IR (KBr): ν = 3288, 3061, 3036, 2951, 2922, 2905, 2876, 1728 (s) (CO), 1647 (s) (CO), 1604, 1460, 1454, 1410 (s), 1352, 1331, 1223, 1067 (s) (–CH_2–O–CH_2–), 1040, 858, 835 (s) (TMS), 752, 729, 698 cm^{-1}; UV: λ_{max} = 229, 262, 272, 299, 305, 352 nm; ^{1}H NMR (DMSO-d_6): δ = −0.15 (s, 9H), 0.82 (t, *J* = 7.8 Hz, 2H), 2.98 (s, 3H), 3.56 (t, *J* = 7.8 Hz, 2H), 5.07 (s, 2H), 5.99 (s, 2H), 7.25 (t, *J* = 7.0 Hz, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.31–7.40 (m, 4H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.72 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 9.59 (d, *J* = 8.0 Hz, 1H), 9.76 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = −1.2, 17.5, 19.8, 40.3, 65.4, 72.9, 110.0, 119.8, 120.7, 120.9, 122.7, 124.2, 126.1, 126.7, 127.3, 127.5, 127.9, 128.2, 128.8, 137.5, 142.3, 142.9, 156.5, 167.8; EI-MS (*m*/*z*, %): 469 (M^+, 73), 411 (100), 352 (56). HREIMS ($C_{28}H_{31}N_3O_2$Si): calcd 469.2186; found 469.2160.

5.2.12. 2-(2-Dimethylaminoethyl)-1-imino-5-methyl-6-(2-trimethylsilanyl-ethoxymethyl)-1,2-dihydro-6*H*-pyrrolo[3,4-*c*]carbazol-3-one (20b). To a solution of **14** (74.0 mg, 0.195 mmol) in CH_2Cl_2 (4 mL) were successively added under N_2 atmosphere, triethylamine (0.124 mL, 0.88 mmol) at room temperature and isobutylchloroformiate at −26 °C. After 2 h stirring at −26 °C, *unsym*-dimethylethylenediamine (0.066 mL, 0.60 mmol) was added at −26 °C to the mixture. The yellow solution was stirred 70 h at room temperature and concentrated under reduced pressure. The yellow residue (343.0 mg) was diluted in CH_2Cl_2 (6 mL) and washed successively with brine (4 mL) and water (4 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to afford a dark yellow oil (152.0 mg), which was purified by preparative TLC (eluent: CH_2Cl_2/methanol, 95:5) to give 23.0 mg of **20b** as a yellow amorphous solid (26%). Unreacted starting material **14** (13.0 mg; 17.5%). Mp 80–82 °C; IR (KBr): ν = 3262, 2951, 2895, 2859, 2822, 2772, 1721 (s) (CO), 1647 (s) (CO), 1458, 1454, 1414, 1331, 1223, 1072 (s) (–CH_2–O–CH_2–), 858, 835 (s) (TMS), 752, 733 cm^{-1}; UV: λ_{max} = 229, 262, 270, 299, 304, 352 nm; ^{1}H NMR ($CDCl_3$): δ = −0.1 (s, 9H), 0.88 (m, 2H), 2.60 (t, *J* = 6.3 Hz, 2H), 2.92 (s, 3H), 3.56 (m, 2H), 3.88 (t, *J* = 6.3 Hz, 2H), 5.80 (s, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 9.10 (s, 1H), 9.58 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 17.9, 20.3, 36.4, 45.6, 58.0, 66.0, 73.1, 108.7, 120.4, 121.0, 121.7, 122.9, 124.5, 125.2, 126.9, 127.4, 142.6, 142.8, 158.8, 168.5; EI-MS (*m*/*z*, %): 450 (M^+, 8), 380 (100), 333 (39), 218 (40). HREIMS ($C_{25}H_{34}N_4O_2$Si): calcd 450.2451; found 450.2413.

5.2.13. 2-(2-Dimethylaminoethyl)-5-methyl-6-(2-tri-methylsilanyl-ethoxymethyl)-6*H*-pyrrolo[3,4-*c*]-carba-zole-3-dione (21b). *Unsym*-dimethylethylenediamine (0.093 mL,

[‡]Derivative **19c** prepared by an independent way is claimed in a patent.[43]

0.845 mmol) was added at 0 °C (ice bath) to a white suspension of **14** (214.0 mg, 0.56 mmol) in methanol (20 mL). After 15 min stirring at room temperature under N_2 atmosphere, DMTMM (459.0 mg, 1.66 mmol) was added at 0 °C to the solution and the mixture was stirred for 7h at room temperature under N_2 atmosphere until the disappearance of **14** (TLC monitoring). After concentration under reduced pressure, the crude residue (1.01 g) was diluted in CH_2Cl_2 (9 mL) and extracted with a saturated potassium carbonate solution (5 mL). The organic layer was acidified with a 5% aqueous citric acid solution (5 mL), washed with water (5 mL × 3), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The yellow residue (1.53 g) was purified by column chromatography (eluent: CH_2Cl_2/methanol, 90:10) to afford 132.0 mg of **21b** as a vivid yellow foam (52%). IR (film): ν = 3491–3368 (br), 3239, 3053, 2951 (s), 2895, 2868, 2824, 2793, 1759 (s) (CO), 1705 (s) (CO), 1603, 1456, 1410, 1383, 1356, 1331, 1248, 1229, 1092, 1072 (s) (–CH_2–O–CH_2–), 858, 837 (s) (TMS), 750 cm^{-1}; UV: λ_{max} = 230, 247, 266, 273, 307, 337, 358 nm; ^{1}H NMR ($CDCl_3$): δ = −0.05 (s, 9H), 0.89 (m, 2H), 2.41 (s, 6H), 2.72 (t, J = 6.5 Hz, 2H), 2.92 (s, 3H), 3.54 (m, 2H), 3.89 (t, J = 6.5 Hz, 2H), 5.81 (s, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 9.11 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 17.9, 20.3, 35.2, 45.0, 56.9, 66.1, 73.1, 109.0, 121.1, 121.3, 121.4, 123.1, 124.2, 124.9, 126.0, 127.0, 128.3, 142.9, 143.2, 169.2, 169.4; EI-MS (*m*/*z*, %): 451 (M^+, 73), 334 (100), 193 (58). HREIMS ($C_{25}H_{33}N_3O_3Si$): calcd 451.2291; found 451.2308.

5.2.14. General procedure for the *N*-SEM cleavage of (20a) and (21b) (GP). Compound **20a** or **21b** were stirred at room temperature in a 3 M solution of hydrochloric acid (concentrated aqueous HCl/ethanol/CH_2Cl_2, 26:74). The suspension was filtered under reduced pressure to afford **19** as a solid. The filtrate was concentrated under reduced pressure and recrystallized in diethyl ether/methanol several times to isolate the further **19**.

5.2.14.1. 2-Benzyl-5-methyl-6*H*-pyrrolo[3,4-*c*]-carbazole-1,3-dione (19a)[§]. Imide **19a** was synthesized from **20a** according to GP: **20a** (74.0 mg, 0.16 mmol) was stirred for 7 h in 10 mL of a 3 M HCl solution (concd aq HCl/ethanol/CH_2Cl_2, 2.6 mL:6.4 mL:1.0 mL). After filtration, 45.0 mg of **19a** were obtained as a vivid yellow powder. By recrystallization of the filtrate in diethyl ether/methanol (3:1) further 10.0 mg of **19a** were obtained. (overall yield: 84%). Mp 245–246 °C; IR (KBr): ν = 3428 (br), 3205 (s), 3175 (s), 3104, 3063, 2952, 2911, 1748 (s) (CO), 1693 (s) (CO), 1612, 1597, 1497, 1461, 1441 (s), 1411, 1391, 1381 (s), 1356, 1336, 1195, 1009, 747 (s), 727, 646, 621 cm^{-1}; UV: λ_{max} = 229, 255, 273, 287, 308, 361 nm; ^{1}H NMR (DMSO-d_6): δ = 2.69 (s, 3H), 4.81 (s, 2H), 7.29 (t, J = 7.0 Hz, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.35–7.39 (m, 4H), 7.58 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.71 (s, 1H), 8.80 (d, J = 8.0 Hz, 1H), 12.01 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 17.6, 40.9, 112.0, 118.1, 120.2, 120.4, 120.5, 123.2, 123.6, 124.7, 126.6, 127.5, 127.6, 128.3, 128.8, 137.4, 141.8, 143.4, 169.0, 169.1; EI-MS (*m*/*z*, %): 340 (M^+, 100), 208 (36), 207 (35), 180 (28). HREIMS ($C_{22}H_{16}N_2O_2$): calcd 340.1212; found 340.1248.

5.2.14.2. Dimethyl-[2-(5-methyl-1,3-dioxo-3,6-dihydro-1*H*-pyrrolo[3,4-*c*]carbazol-2-yl)-ethyl]-ammonium chloride (19c). Imide **19c** was synthesized from **21b** according to GP: **21b** (90.0 mg, 0.20 mmol) was stirred for 3.5 h in 12 mL of a 3 M HCl solution (concd aq HCl/ethanol/CH_2Cl_2, 3.1 mL:6.9 mL:2.0 mL). After filtration, 50.0 mg of **19c** were obtained as a vivid yellow powder. By recrystallization of the filtrate in diethyl ether/methanol (5:1) further 17.0 mg of **19c** were obtained. (overall yield: 94%).

5.2.15. General procedure for the preparation of compounds (22) (GP). To a stirred solution of **8** in dry DMF was added at −25 °C under N_2 atmosphere, a solution of trichloroisocyanuric acid (TCCA) in dry DMF. After 10 min of stirring at −25°C, triethylamine was added and the solution was stirred at room temperature until disappearance of **8** (TLC monitoring). After concentration under reduced pressure, the residue was purified by column chromatography (eluent: CH_2Cl_2) to afford **22**.

5.2.15.1. 8-Chloro-2,4-dimethyl-1,3-dioxo-5-(2-trimethylsilanyl-ethoxymethyl)-1,2,3,5-tetrahydro-pyrrolo-[3,4-*b*]carbazole-10-carbonitrile (22a, R^1 = Me). Nitrile **22a** was synthesized from **8a** according to GP: to 125.0 mg (0.30 mmol) of **8a** in 4.5 mL of dry DMF were added at −25 °C 206.0 mg (0.89 mmol) of TCCA in 4.5 mL of dry DMF and 0.399 mL (2.86 mmol) of triethylamine. The solution was stirred for 3.5 h at room temperature, concentrated and purified to afford 49.0 mg of **22a**, as a yellow powder (36%). Mp 191–193 °C; IR (KBr): ν = 3073, 2953 (br), 2230 (CN), 1769 (s) (CO), 1713 (s) (CO), 1600, 1460, 1439, 1379, 1292, 1078, 1069 (br) (–CH_2–O–CH_2–), 837 (TMS), 750 cm^{-1}; UV: λ_{max} = 212, 238, 256, 270, 304, 325, 366, 380 nm; ^{1}H NMR (DMSO-d_6): δ = −0.09 (s, 9H), 0.83 (m, 2H), 3.05 (s, 3H), 3.22 (s, 3H), 3.57 (m, 2H), 5.95 (s, 2H), 7.65 (dd, J = 1.0; 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 1.0 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ = −1.4, 12.6, 17.5, 24.0, 65.8, 73.2, 95.9, 112.9, 114.4, 120.1, 120.7, 124.5, 126.1, 126.6, 126.8, 128.5, 129.3, 141.6, 141.7, 164.9, 167.4; EI-MS (*m*/*z*, %): 455 (M^+, 7), 453 (M^+, 18), 431 (33), 429 (47), 397 (39), 395 (100), 370 (24), 338 (18), 336 (55). HREIMS ($C_{23}H_{24}N_3O_3SiCl^{35}$): calcd 453.1275; found 453.1301. HREIMS ($C_{23}H_{24}N_3O_3SiCl^{37}$): calcd 455.1246; found 455.1363.

5.2.15.2. 2-Benzyl-8-chloro-4-methyl-1,3-dioxo-5-(2-trimethylsilanyl-ethoxymethyl)-1,2,3,5-tetrahydro-pyrrolo[3,4-*b*]carbazole-10-carbonitrile (22b, R^1 = Bn). Nitrile **22b** was synthesized from **8b** according to GP: to 138.0 mg (0.30 mmol) of **8b** in 6 mL of dry DMF were added at −25 °C 193.0 mg (0.83 mmol) of TCCA in 6 mL of dry DMF and 0.432 mL (3.10 mmol) of triethylamine. The solution was stirred for 4.5 h at room temperature, concentrated and purified to afford 39.0 mg of **22b**, as

[§] Derivative **19a** prepared by an independent way is claimed in a patent.[43]

a pale yellow powder (26%). Mp 219 °C; IR (KBr): ν = 3069, 3032, 2949 (br), 2228 (CN), 1765 (s) (CO), 1713 (s) (CO), 1601, 1458, 1435, 1400 (s), 1339, 1072 (–CH_2–O–CH_2–), 837 (TMS), 748 cm^{-1}; UV: λ_{max} = 211, 238, 257, 270, 305, 364, 383 nm; ^{1}H NMR ($CDCl_3$): δ = −0.01 (s, 9H), 0.98 (m, 2H), 3.29 (s, 3H), 3.63 (m, 2H), 4.96 (s, 2H), 5.98 (s, 2H), 7.35–7.52 (m, 5 H), 7.62 (d, J = 7.0 Hz, 2H), 8.41 (d, J = 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.7, 13.0, 17.7, 41.7, 66.5, 73.4, 96.6, 110.8, 114.0, 121.0, 121.1, 125.3, 125.7, 126.8, 127.7, 127.9, 128.5, 128.9, 129.0, 129.4, 135.9, 141.1, 141.9, 164.6, 167.0; EI-MS (*m*/*z*, %): 531 (M^+, 9), 529 (M^+, 20), 473 (41), 471 (100), 414 (12), 412 (34). HREIMS ($C_{29}H_{28}N_3O_3SiCl$[35]): calcd 529.1588; found 529.1531. HREIMS ($C_{29}H_{28}N_3O_3SiCl$[37]): calcd 531.1559; found 531.1521.

5.2.16. General procedure for the synthesis of the amines (24). Nitrile **23** and Raney-Nickel were stirred in dry toluene/absolute ethanol under pressure of hydrogen (6 bars) in an autoclave. After filtration on Celite and concentration under reduced pressure, the crude product was crystallized in methanol/diethyl ether (90:10) to obtain **24**, as a solid.

5.2.16.1. 10-Aminoethyl-2,4-dimethyl-5-(2-trimethylsilanyl-ethoxymethyl)-5*H*-pyrrolo[3,4-*b*]carbazole-1,3-dione (24a, R^1 = Me). Amine **24a** was synthesized from **23a** according to GP: **23a** (500.0 mg, 1.19 mmol) and Raney-Nickel (5.20 g) were stirred for 26 h in dry toluene/absolute ethanol (39 mL:15 mL) under H_2 atmosphere. After filtration, the concentrated residue was crystallized in 8 mL of methanol/diethyl ether to obtain 353.0 mg of **24a**, as a pale yellow powder (70%). Mp 151°C; IR (KBr): ν = 3370 (br), 3059, 2951 (br), 1744 (s) (CO), 1694 (s) (CO), 1613, 1587, 1437, 1379, 1354, 1074 (br) (–CH_2–O–CH_2–), 835 (TMS) cm^{-1}; UV: λ_{max} = 227, 251, 288, 372 nm; ^{1}H NMR ($CDCl_3$): δ = −0.05 (s, 9H), 0.92 (m, 2H), 2.04 (s, 2H), 3.13 (s, 3H), 3.20 (s, 3H), 3.59 (m, 2H), 4.81 (s, 2H), 5.83 (s, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.52–7.66 (m, 2H), 8.29 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 12.8, 17.9, 26.6, 38.0, 66.2, 73.2, 109.7, 120.4, 121.8, 122.1, 122.5, 123.1, 125.6, 126.9, 127.3, 136.0, 142.4, 142.8, 169.0, 169.5; EI-MS (*m*/*z*, %): 423 (M^+, 64), 365 (33), 306 (53), 276 (100). HREIMS ($C_{23}H_{29}N_3O_3Si$): calcd 423.1978; found 423.1972.

5.2.16.2. 10-Aminoethyl-2-benzyl-4-methyl-5-(2-trimethylsilanyl-ethoxymethyl)-5*H*-pyrrolo[3,4-*b*]-carbazole-1,3-dione (24b, R^1 = Bn). Amine **24b** was synthesized from **23b** according to GP: **23b** (300.0 mg, 0.61 mmol) and Raney-Nickel (2.60 g) were stirred for 91 h in dry toluene/absolute ethanol (7 mL:17 mL) under H_2 atmosphere. After filtration, the concentrated residue was crystallized in 6 mL of methanol/diethyl ether to obtain 156.0 mg of **24b**, as a vivid yellow powder (52%). Mp 135°C; IR (KBr): ν = 3482 (br), 3069, 2951, 1749 (s) (CO), 1694 (s) (CO), 1611, 1429, 1400, 1350, 1072, 835 (TMS) cm^{-1}; UV: λ_{max} = 226, 253, 290, 322, 374 nm; ^{1}H NMR ($CDCl_3$): δ = −0.05 (s, 9H), 0.92 (m, 2H), 1.90 (s, 2H), 3.20 (s, 3H), 3.58 (m, 2H), 4.79 (s, 2H), 4.81 (s, 2H), 5.81 (s, 2H), 7.18–7.40 (m, 4H), 7.49 (d, J = 7.0 Hz, 2H), 7.51–7.61 (m, 2H), 8.24 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 12.7, 17.8, 38.0, 41.2, 66.1, 73.1, 109.7, 120.1, 121.7, 122.0, 122.7, 123.0, 125.7, 126.2, 127.3, 127.5, 128.4, 128.5, 136.1, 137.1, 142.7, 142.9, 168.4, 169.0; EI-MS (*m*/*z*, %): 499 (M^+, 100), 441 (32), 382 (45), 352 (55). HREIMS ($C_{29}H_{33}N_3O_3Si$): calcd 499.2291; found 499.2262.

5.2.17. General procedures for the acylation of the amines (24). General procedure A (GPA): To a solution of **24** in methanol was added at 0 °C (ice bath) the dimethylamino acid. After 1 h stirring at 0 °C under N_2 atmosphere, DMTMM was added to the solution. The mixture was stirred at room temperature until the disappearance of **24** (TLC monitoring) and then concentrated under reduced pressure. The crude product was diluted with CH_2Cl_2 and extracted with a saturated aqueous solution of potassium carbonate. The organic layer was extracted with a 5% aqueous citric acid solution, the resultant organic layer was extracted with water three times, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude solid was purified by column chromatography (eluent: CH_2Cl_2/methanol) to afford **25** or **26**. General procedure B (GPB): triethylamine was added at room temperature to a solution of *N*,*N*-dimethylglycine in CH_2Cl_2/*n*-butanol. After 30 min stirring at room temperature under N_2 atmosphere, isobutylchloroformiate was added at −15 °C to the solution and stirred for 2 h at −15 °C. Then a solution of **24** in CH_2Cl_2 was added at −15 °C to the mixture. The solution was stirred at room temperature under N_2 atmosphere and concentrated under reduced pressure. The crude product was diluted with CH_2Cl_2 and extracted twice with brine. The combined organic layers were washed with water, dried over anhydrous magnesium sulfate and filtered. After concentration under reduced pressure, the residue was crystallized in diethyl ether to afford **25**.

5.2.17.1. 2-Dimethylamino-*N*-[2,4-dimethyl-1,3-dioxo-5-(2-trimethylsilanyl-ethoxymethyl)-1,2,3,5-tetra-hydropyrrolo[3,4-*b*]carbazol-10-ylmethyl]-acetamide (25a, R^1 = Me). From **24a** according to GPA: to **24a** (58.0 mg, 0.14 mmol) in methanol (10 mL) was added *N*,*N*-dimethyl glycine (35.0 mg, 0.34 mmol) and after 1 h stirring, DMTMM (113.0 mg, 0.41 mmol). The mixture was stirred for 22 h and the concentrated product was diluted with CH_2Cl_2 (10 mL), extracted with saturated aqueous K_2CO_3 (7 mL). The organic layer was extracted successively with 5% aqueous citric acid (7 mL), with saturated aqueous K_2CO_3 (7 mL), with water (9 mL × 3), dried, filtered and concentrated. After purification by column chromatography (eluent: CH_2Cl_2/methanol, 99:1), 41.0 mg of **25a** were obtained as a beige powder (59%). From **24a** according to GPB: triethylamine (0.581 mL, 4.14 mmol) was added to *N*,*N*-dimethylglycine (256.0 mg, 2.48 mmol) in CH_2Cl_2/*n*-butanol (15 mL:5 mL). After 30 min stirring, isobutylchloroformiate (0.429 mL, 3.31 mmol) was added to the solution and stirred for 2 h. After addition of **24a** (560.0 mg, 1.65 mmol) in CH_2Cl_2 (19 mL), the mixture was stirred for 13 h at room temperature and concen-

trated. The crude residue was diluted with CH_2Cl_2 (30 mL) and extracted with brine (26 mL). The organic layer was washed with water (30 mL × 2), dried, filtered and concentrated. After crystallization in diethyl ether (6 mL), 380.0 mg of **25a** were isolated as a beige powder (57%). Mp 156–158 °C; IR (KBr): ν = 3437–3285 (br), 3074, 2949 (br), 2897, 2778, 1751 (s) (CO), 1697 (s) (CO), 1668 (s) (CO), 1613, 1508, 1468, 1439, 1381, 1354, 1250, 1078 (s) (–CH_2–O–CH_2–), 1011, 860 (s), 837 (s) (TMS), 756 cm^{-1}; UV: λ_{max} = 226, 251, 288, 371 nm; ^{1}H NMR ($CDCl_3$): δ = −0.05 (s, 9H), 0.93 (m, 2H), 2.27 (s, 6H), 3.11 (s, 2H), 3.18 (s, 3H), 3.22 (s, 3H), 3.61 (m, 2H), 5.43 (d, J = 5.0 Hz, 2H), 5.84 (s, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.81 (s, 1H), 8.50 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 12.9, 17.9, 23.8, 36.0, 45.5, 62.4, 66.3, 73.3, 109.5, 122.0, 122.2 (×2), 123.4, 124.0, 126.4, 126.8, 127.6, 129.6, 142.5, 143.0, 169.0 (×2), 169.4; EI-MS (*m*/*z*, %): 508 (M^+, 100), 465 (30), 391 (63), 291 (78), 290 (57), 289 (50), 276 (41). HREIMS ($C_{27}H_{36}N_4O_4Si$): calcd 508.2506; found 508.2521.

5.2.17.2. *N*-[2-Benzyl-4-methyl-1,3-dioxo-5-(2-trimethylsilanyl-ethoxymethyl)-1,2,3,5-tetrahydro-pyrrolo[3,4-*b*]carbazol-10-ylmethyl]-2-dimethylamino-acetamide (25b, R^1 = Bn). From **24b** according to **GPB**:triethylamine (0.106 mL, 0.75 mmol) was added to *N*,*N*-dimethylglycine (46.0 mg, 0.45 mmol) in CH_2Cl_2/*n*-butanol (4.5 mL:1.5 mL). After 30 min stirring, isobutylchloroformiate (0.078 mL, 0.60 mmol) was added to the solution and stirred for 2 h. After addition of **24b** (150.0 mg, 0.30 mmol) in CH_2Cl_2 (10 mL), the mixture was stirred for 17 h at room temperature and concentrated. The crude residue was diluted with CH_2Cl_2 (10 mL) and extracted with brine (5 mL). The organic layer was washed with water (10 mL × 2), dried, filtered and concentrated. After crystallization in diethyl ether (2.5 mL), 64.0 mg of **25b** were isolated as a pale yellow powder (37%). Mp 95–97 °C; IR (KBr): ν = 3526–3217 (br), 3073, 2951 (br), 2895, 2826, 2778, 1749 (s) (CO), 1697 (s) (CO), 1660 (s) (CO), 1613, 1504, 1438, 1387, 1348, 1250, 1072 (s) (–CH_2–O–CH_2–), 860 (s), 837 (s) (TMS), 748 cm^{-1}; UV: λ_{max} = 226, 253, 289, 375 nm; ^{1}H NMR ($CDCl_3$): δ = −0.03 (s, 9H), 0.93 (m, 2H), 2.19 (s, 6H), 3.05 (s, 2H), 3.29 (s, 3H), 3.61 (m, 2H), 4.89 (s, 2H), 5.48 (d, J = 5.3 Hz, 2H), 5.89 (s, 2H), 7.30 (t, J = 7.0 Hz, 1H), 7.35 (t, J = 7.0 Hz, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.50 (d, J = 7.0 Hz, 2H), 7.55 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H), 8.57 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 12.9, 18.0, 36.0, 41.4, 45.6, 62.7, 66.3, 73.3, 109.5, 121.9, 122.0, 122.2, 123.5, 124.2, 126.5, 126.8, 127.6, 127.7, 128.6, 128.7, 130.1, 136.8, 142.7, 143.0, 168.6, 169.1 (×2); EI-MS (*m*/*z*, %): 584 (M^+, 48), 540 (44), 367 (48), 365 (50), 206 (53), 192 (86), 191 (100). HREIMS ($C_{33}H_{40}N_4O_4Si$): calcd 584.2819; found 584.2780.

5.2.17.3. 3-Dimethylamino-*N*-[2,4-dimethyl-1,3-dioxo-5-(2-trimethylsilanyl-ethoxymethyl)-1,2,3,5-tetra-hydro-pyrrolo[3,4-*b*]carbazol-10-ylmethyl]-propionamide (26a, R^1 = Me). From **24a** according to **GPA**: to **24a** (65.0 mg, 0.15 mmol) in methanol (10 mL) was added the chlorhydrate of *N*,*N*-dimethylaminopropanoic acid (50.0 mg, 0.33 mmol) and after 1 h stirring, DMTMM (123.0 mg, 0.445 mmol). The mixture was stirred 9 h and the concentrated product was diluted with CH_2Cl_2 (10 mL), extracted with saturated aqueous K_2CO_3 (7 mL). The organic layer was extracted with 5% aqueous citric acid (7 mL) and the resultant organic layer was extracted successively with saturated aqueous K_2CO_3 (7 mL), with water (9 mL × 3), dried, filtered and concentrated. After purification by column chromatography (eluent: CH_2Cl_2/methanol, 90:10), 60.0 mg of 26a were obtained as a pale yellow powder (75%). Mp 163–165 °C; IR (KBr) = 3306 (s), 3053, 2942 (s), 2891, 2820, 2769, 1748 (s) (CO), 1693 (s) (CO), 1633 (s) (CO), 1532 (s), 1466, 1431 (s), 1376 (s), 1351 (s), 1295, 1250 (s), 1240 (s), 1079 (s) (–CH_2–O–CH_2–), 1009 (s), 858 (s), 842 (s) (TMS), 747 cm^{-1}; UV: λ_{max} = 226, 251, 288, 369 nm; ^{1}H NMR ($CDCl_3$): δ = −0.05 (s, 9H), 0.92 (m, 2H), 2.00 (s, 6H), 2.29–2.40 (m, 2H), 2.40–2.55 (m, 2H), 3.17 (s, 3H), 3.26 (s, 3H), 3.60 (m, 2H), 5.43 (d, J = 5.1 Hz, 2H), 5.88 (s, 2H), 7.40 (t, J = 8.0 Hz, 1H), 7.48–7.68 (m, 2H), 8.57 (d, J = 8.0 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 12.9, 18.0, 23.7, 33.3, 36.1, 44.4, 55.0, 66.2, 73.3, 109.4, 121.9, 122.3, 123.0, 124.3, 126.3, 126.9, 127.5, 130.8, 142.6, 143.0, 168.9, 169.6, 172.4; EI-MS (*m*/*z*, %): 522 (M^+, 86), 422 (47), 405 (33), 306 (38), 292 (63), 291 (89), 277 (52), 276 (100). HREIMS ($C_{28}H_{38}N_4O_4Si$): calcd 522.2662; found 522.2648.

5.2.17.4. *N*-[2-Benzyl-4-methyl-1,3-dioxo-5-(2-trimethyl-silanyl-ethoxymethyl)-1,2,3,5-tetrahydro-pyrrolo[3,4-*b*]carbazol-10-ylmethyl]-3-dimethylamino-propionamide (26b, R^1 = Bn). From **24b** according to **GPA**: to **24b** (75.0 mg, 0.15 mmol) in methanol (10 mL) was added the chlorhydrate of *N*,*N*-dimethylaminopropanoic acid (52.0 mg, 0.34 mmol) and after 1 h stirring, DMTMM (148.0 mg, 0.54 mmol). The mixture was stirred 30 h and the concentrated product was diluted with CH_2Cl_2 (10 mL), extracted with saturated aqueous K_2CO_3 (7 mL). The organic layer was extracted successively with 5% aqueous citric acid (7 mL), with saturated aqueous K_2CO_3 (7 mL), with water (9 mL × 3), dried, filtered and concentrated. After purification by column chromatography (eluent: CH_2Cl_2/methanol, 95:5), 59.0 mg of **26b** were obtained as a pale yellow powder (66%). Mp 149–150 °C; IR (KBr): ν = 3367, 3266 (br), 3053, 3023, 2942 (s), 2891, 2810, 2759, 1748 (s) (CO), 1693 (s) (CO), 1668 (s) (CO), 1612, 1527 (br), 1462, 1426, 1386 (s), 1346 (s), 1295, 1250 (br), 1069 (s) (–CH_2–O–CH_2–), 858, 832 (s) (TMS), 747, 697 cm^{-1}; UV: λ_{max} = 225, 252, 289, 369 nm; ^{1}H NMR ($CDCl_3$): δ = −1.01 (s, 9H), 0.89 (m, 2H), 1.93 (s, 6H), 2.28–2.38 (m, 2H), 2.38–2.49 (m, 2H), 3.21 (s, 3H), 3.57 (m, 2H), 4.84 (s, 2H), 5.39 (d, J = 5.3 Hz, 2H), 5.84 (s, 2H), 7.26 (t, J = 7.0 Hz, 1H), 7.29 (t, J = 7.0 Hz, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.46 (d, J = 7.0 Hz, 2H), 7.48–7.58 (m, 2H), 8.59 (d, J = 8.0 Hz, 1H), 8.68 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = −1.5, 12.9, 18.0, 33.1, 36.2, 41.4, 44.3, 55.0, 66.2, 73.3, 109.4, 121.6, 121.9, 122.3, 123.2, 124.4, 126.4, 126.8, 127.5, 127.6, 128.6, 131.0, 136.9, 142.6, 143.0, 168.5, 169.2, 172.3; EI-MS (*m*/*z*, %): 598 (M^+, 100), 498 (35), 481 (39), 367 (65), 352 (34), 115

(88). HREIMS ($C_{34}H_{42}N_4O_4Si$): calcd 598.2975; found 598.2979.

5.2.18. General procedure for the *N*-SEM cleavage of compounds (25) and (26). Protected compounds **25** or **26** was stirred at room temperature under N_2 atmosphere in a 3 M solution of hydrochloric acid (concentrated aqueous HCl/ethanol/toluene, 40:34:26). After concentration under reduced pressure, the residue was either crystallized in methanol/water (97:3) or in methanol/diethyl ether/water to afford **27** or **28**.

5.2.18.1. {[(2,4-Dimethyl-1,3-dioxo-1,2,3,5-tetrahydro-pyrrolo[3,4-*b*]carbazol-10-ylmethyl)-carbamoyl]-methyl}-dimethyl-ammonium chloride (27a, R^1 = Me). Deprotected salt **27a** was synthesized from **25a** according to GP: **25a** (389.0 mg, 0.77 mmol) was stirred for 5 h in an aqueous 3 M solution of HCl (33.6 mL). After concentration, followed by crystallization in methanol/water (4 mL), 308.0 mg of **27a** were obtained as a pale yellow crystalline powder (97%). Mp 285 °C; IR (KBr): ν = 3572–3340 (br), 3198 (br), 3051, 2803, 1748 (s) (CO), 1697 (s) (CO), 1674 (s) (CO), 1620, 1551, 1460, 1439, 1383 (s), 1362, 1233, 1011, 758 cm^{-1} ; UV: λ_{max} = 226, 252, 290, 372 nm; ^{1}H NMR (DMSO-d_6): δ = 2.70 (s, 6H), 2.90 (s, 3H), 3.01 (s, 3H), 3.70 (s, 2H), 5.25 (s, 2H), 7.25 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 8.69 (s, 1H), 12.45 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 12.3, 35.8, 43.6, 58.3, 109.5, 119.9, 120.5, 121.3, 122.0, 122.8, 123.7, 124.9, 127.1, 128.6, 141.3, 142.5, 165.5, 168.6; EI-MS (*m*/*z*, %): 378 (M^+ – HCl, 100), 335 (45), 278 (41), 277 (85). HREIMS ($C_{21}H_{22}N_4O_3$): calcd 378.1692; found 378.1705.

5.2.18.2. {[(2-Benzyl-4-methyl-1,3-dioxo-1,2,3,5-tetrahydro-pyrrolo[3,4-*b*]carbazol-10-ylmethyl)-carbamoyl]-methyl}-dimethyl-ammonium chloride (27b, R^1 = Bn). Deprotected salt **27b** was synthesized from **25b** according to GP: **25b** (650.0 mg, 1.11 mmol) was stirred for 19 h in an aqueous 3 M solution of HCl (56.2 mL). After concentration, followed by crystallization in methanol/water (5 mL), 370.0 mg of **27b** were obtained as a beige crystalline powder (68%). Mp 237 °C; IR (KBr): ν = 3578–3354 (br), 3237–3198 (s), 3057, 2936 (s), 1749 (s) (CO), 1697 (s) (CO), 1674 (s) (CO), 1622, 1541, 1458, 1433, 1393 (s), 1346, 1234, 1068, 750 cm^{-1}; UV: λ_{max} = 225, 253, 292, 374 nm; ^{1}H NMR (DMSO-d_6): δ = 2.79 (s, 6H), 2.93 (s, 3H), 3.89 (s, 2H), 4.77 (s, 2H), 5.31 (d, J = 3.8 Hz, 2H), 7.27 (t, J = 8.0 Hz, 1H), 7.29 (t, J = 7.0 Hz, 1H), 7.32–7.42 (m, 4H), 7.52 (t, J = 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.89 (s, 1H), 12.48 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 12.4, 36.0, 40.7, 43.3, 57.4, 112.4, 119.7, 120.7, 121.8, 122.0, 122.8, 124.0, 124.6, 127.3, 127.6, 127.9, 128.7, 128.8, 137.3, 141.4, 142.7, 164.5, 168.3, 168.4; EI-MS (*m*/*z*, %): 454 (M^+ – HCl, 13), 411(34), 239 (62), 149 (54), 133 (100). HREIMS ($C_{27}H_{26}N_4O_3$): calcd 454.2005; found 454.1985.

5.2.18.3. {2-[(2-Dimethyl-1,3-dioxo-1,2,3,5-tetra-hydro-pyrrolo[3,4-*b*]carbazol-10-ylmethyl)-carbamoyl]-ethyl}-dimethyl-ammonium chloride (28a, R^1 = Me). Deprotected salt **28a** was synthesized from **26a** according to GP: **26a** (700.0 mg, 1.34 mmol) was stirred for 4 h30 in an aqueous 3 M solution of HCl (50.0 mL). After concentration, followed by crystallization in methanol/diethyl ether/water (10:10:1) (6 mL), 344.0 mg of **28a** were obtained as a pale yellow crystalline powder (60%). Mp 332 °C; IR (KBr): ν = 3572–3397 (br), 3185 (br), 2942, 1743 (s) (CO), 1688 (s) (CO), 1663 (s) (CO), 1542, 1532, 1451, 1431, 1381, 1361, 1245, 1230, 998, 757 cm^{-1}; UV: λ_{max} = 227, 251, 290, 372 nm; ^{1}H NMR (DMSO-d_6): δ = 2.63 (t, J = 7.5 Hz, 2H), 2.68 (s, 6H), 2.86 (s, 3H), 2.95 (s, 3H), 3.10 (t, J = 7.5 Hz, 2H), 5.18 (d, J = 4.0 Hz, 2H), 7.21 (t, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 8.38 (m, 1H), 10.60 (s, 1H), 12.30 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 12.2, 23.4, 29.7, 35.9, 42.1, 52.8, 112.2, 119.8, 120.5, 121.0, 122.0, 122.8, 123.7, 124.7, 127.0, 129.0, 141.2, 142.4, 168.5, 169.1; EI-MS (*m*/*z*, %): 392 (M^+ – HCl, 12), 347 (16), 293 (27), 292 (100), 277 (13). HREIMS ($C_{22}H_{24}N_4O_3$): calcd 392.1848; found 392.1879.

5.2.18.4. {2-[(2-Benzyl-4-methyl-1,3-dioxo-1,2,3,5-tetrahydro-pyrrolo[3,4-*b*]carbazol-10-ylmethyl)-carbamoyl]-ethyl}-dimethyl-ammonium chloride (28b, R^1 = Bn). Deprotected salt **28b** was synthesized from **26b** according to GP: **26b** (81.0 mg, 0.135 mmol) was stirred for 7 h in an aqueous 3 M solution of HCl (10 mL). After concentration, followed by crystallization in methanol/diethyl ether/water (3:2:0.1) (2 mL), 39.0 mg of **28b** were obtained as a yellow crystalline powder (57%). Mp 300 °C; IR (KBr): ν = 3418 (br), 3205 (br), 3043, 2931, 1748 (CO), 1693 (s) (CO), 1663 (s) (CO), 1617, 1537, 1456, 1431, 1391 (s), 1351, 1235, 1124, 752, 732 cm^{-1}; UV: λ_{max} = 227, 253, 292, 372 nm; ^{1}H NMR (DMSO-d_6): δ = 2.60 (t, J = 7.3 Hz, 2H), 2.71 (s, 6H), 2.89 (s, 3H), 3.30 (t, J = 7.3 Hz, 2H), 4.75 (s, 2H), 5.27 (d, J = 4.1 Hz, 2H), 7.27 (t, J = 8.0 Hz, 1H), 7.28–7.37 (m, 3H), 7.38 (d, J = 7.0 Hz, 2H), 7.52 (t, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.45 (t, J = 4.1 Hz, 1H), 10.23 (s, 1H), 12.35 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 12.3, 29.8, 36.0, 40.7, 42.3, 52.9, 112.3, 119.7, 120.7, 121.6, 122.1, 122.9, 124.2, 124.6, 127.2, 127.6, 127.8, 128.7, 129.5, 137.3, 141.3, 142.6, 168.3, 168.4, 169.2; EI-MS (*m*/*z*, %): 468 (M^+ – HCl, 13), 423 (18), 369 (28), 368 (100). HREIMS ($C_{28}H_{28}N_4O_3$): calcd 468.2161; found 468.2263.

5.2.19. 2-Benzyl-5-phenyl-1,2-dihydro-6*H*-2,4,6-triaza-cyclopenta[*c*]fluoren-3-one (30). Triethylamine (0.320 mL, 2.3 mL) was added at room temperature to a solution of **29** (mixture of two isomers) (74.0 mg, 0.19 mmol) in DMF (20 mL). To the cooled mixture (−20 °C) was added dropwise a solution of trichloroisocyanuric acid (114.0 mg, 0.49 mmol) in DMF (20 mL). After 24 h stirring at room temperature under N_2 atmosphere, the solution was concentrated under reduced pressure. The residue was diluted in CH_2Cl_2 (50 mL) and washed with water (40 mL × 2). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: CH_2Cl_2/

ethyl acetate, 80:20) to afford 61.0 mg of **30** as a white crystalline powder (83%). Mp 251 °C; IR (KBr) = 3455, 3218, 1686, 1603, 1497, 1462, 1417, 1406, 1242, 1026, 737, 698 cm^{-1}; UV: λ_{max} = 206, 235, 260, 280, 361 nm; ^1H NMR (DMSO-d_6): δ = 4.90 (s, 2H, CH_2), 4.95 (s, 2H, CH_2), 7.30–8.20 (m, 14H, H_{arom}), 11.95 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 46.1 (CH_2), 46.8 (CH_2), 113.0, 119.8, 120.6, 123.0, 123.9, 127.5, 127.8, 128.7, 128.9, 129.0, 129.1, 129.3, 133.9, 137.9, 138.0, 139.5, 141.5, 143.7, 167.0; EI-MS (*m/z*, %): 389 (M^+, 80), 284 (30), 256 (100), 195 (10), 143 (40). HREIMS ($C_{26}H_{19}N_3O$): calcd 389.1528; found 389.1595.

5.2.20. 3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-1-ethoxycarbonyl-2-(1*H*-indol-3-yl)-propyl-ammonium chloride (32). This compound was prepared from **31** in three steps as described in our previous unpublished work.[34]

5.2.21. 4-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-1-methyl-9*H*-β-carboline-3-carboxylic acid ethyl ester (33a). To a suspension of **32** (2.62 g, 6.13 mmol) in CH_2Cl_2 (200 mL) were added at room temperature triethylamine (1.70 mL, 12.26 mmol), acetaldehyde (0.685 mL, 12.26 mmol) and molecular sieves (4 Å). After 1h refluxing under N_2 atmosphere, the solution was cooled to room temperature then trifluoroacetic acid (1.42 mL, 18.40 mmol) was added and then refluxed for 12 h. The mixture was extracted with a 5% aqueous solution of sodium bicarbonate (100 mL × 3) and washed with brine (100 mL × 2). The organic layer (CH_2Cl_2) was dried over sodium sulfate, filtered and concentrated under reduced pressure. To the solution of the residue in DMF (50 mL) was added triethylamine (5.97 mL, 42.90 mmol). To the cooled (−20 °C) mixture was added dropwise a solution of trichloroisocyanuric acid (2.14 g, 9.20 mmol) in DMF (50 mL) under N_2 atmosphere. The solution was stirred for 12 h at room temperature. After concentration under reduced pressure, the residue was diluted in CH_2Cl_2 (120 mL) and washed with water (50 mL × 3). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: cyclohexane/ethyl acetate, 50:50) to afford a brown solid. After crystallization in ethyl acetate/methanol (30:70), 1.44 g of **33a** were obtained as a transparent crystalline powder (57%). Mp 196 °C; IR (KBr): ν = 3200, 1773, 1717, 1618, 1393, 1339, 1264, 1207, 1071, 739, 716 cm^{-1}; UV: λ_{max} = 205, 219, 232, 239, 269, 289, 337 nm; ^1H NMR ($CDCl_3$): δ = 1.20 (t, *J* = 7.3 Hz, 3H), 2.45 (s, 3H), 4.30 (q, *J* = 7.3 Hz, 2H), 5.74 (s, 2H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.30 (m, 2H), 7.55 (m, 2H), 7.68 (m, 2H), 8.25 (d, *J* = 8.0 Hz, 1H), 9,90 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 14.1, 19.6, 37.5, 61.8, 112.1, 120.6, 121.6, 123.2, 123.7, 123.8, 127.7, 128.1, 131.8, 133.9, 135.3, 138.8, 140.7, 141.3, 167.5, 168.1; EI-MS (*m/z*, %): 413 (M^+, 50), 384 (18), 367 (20), 339 (18), 311 (20), 284 (20), 274 (20), 211 (15), 182 (18), 159 (100), 144 (28), 130 (65). HREIMS ($C_{24}H_{19}N_3O_4$): calcd 413.1376; found 413.1393.

5.2.22. 1,4-Bis-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-9*H*-β-carboline-3-carboxylic acid ethyl ester (33b). To a suspension of 1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetaldehyde[32] (2.65 g, 14.04 mmol) in CH_2Cl_2 (140 mL) were added at room temperature triethylamine (1.95 mL, 14.04 mmol), 32 (3.00 g, 7.02 mmol) and molecular sieves (4 Å). After 2 h refluxing under N_2 atmosphere, the solution was cooled to room temperature then trifluoroacetic acid (1.62 mL, 21.06 mmol) was added and then refluxed for 12 h. The mixture was extracted with a 5% aqueous solution of sodium bicarbonate (100 mL × 3) and washed with brine (100 mL × 2). The organic layer (CH_2Cl_2) was dried over sodium sulfate, filtered and concentrated under reduced pressure. To the solution of the pale orange foam (3.67 g) in DMF (50 mL) was added triethylamine (3.18 mL, 22.86 mmol). To the cooled (−20 °C) mixture was added dropwise a solution of trichloroisocyanuric acid (1.79 g, 7.72 mmol) in DMF (50 mL) under N_2 atmosphere. The solution was stirred for 12 h at room temperature. After concentration under reduced pressure, the residue was diluted in CH_2Cl_2 (150 mL) and washed with water (100 mL × 3). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by a column chromatography on silica gel (eluent: CH_2Cl_2/ethyl acetate, 95:5) to afford 1.75 g of **33b**, as a transparent crystalline powder (45%). Mp 218 °C; IR (KBr): ν = 3322, 2926, 1773, 1715, 1393, 1339, 1279, 1209, 1071, 949, 714 cm^{-1}; UV: λ_{max} = 204, 220, 238, 268, 289, 349 nm; ^1H NMR ($CDCl_3$): δ = 1.35 (t, *J* = 7.1 Hz, 3H), 4.41 (q, *J* = 7.1 Hz, 2H), 5.39 (s, 2H), 5.79 (s, 2H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.65 (m, 3H), 7.71 (m, 4H), 7.86 (m, 2H), 8.38 (d, *J* = 8.0 Hz, 1H), 10.12 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 14.2, 37.2, 41.1, 61.8, 112.4, 120.9, 121.6, 123.2, 123.7, 125.7, 128.7, 129.7, 131.9, 133.9, 134.3, 135.1, 137.1, 139.7, 140.9, 167.9, 168.7; EI-MS (*m/z*, %): 558 (M^+, 90), 529 (40), 512 (75), 487 (55), 457 (30), 413 (95), 402 (100), 356 (40), 339 (38), 327 (60), 267 (34), 209 (40). HREIMS ($C_{32}H_{22}N_4O_6$): calcd 558.1539; found 558.1550.

5.2.23. 5-Methyl-1,2-dihydro-6*H*-2,4,6-triaza-cyclopenta[*c*]fluoren-3-one (34a). A solution of **33a** (900.0 mg, 2.18 mmol) in butylamine (25 mL) was refluxed for 12 h under N_2 atmosphere. The mixture was concentrated under reduced pressure and the residue was suspended in ethyl acetate (20 mL). After filtration under reduced pressure, the precipitate was washed with diethyl ether (5 mL × 3) to afford 468.0 mg of **34a**, as a white powder (90%). Mp 325 °C; IR (KBr): ν = 3453, 1667, 1593, 1497, 1433, 1364, 1258, 1233, 1111, 739 cm^{-1}; UV: λ_{max} = 198, 215, 239, 261, 268, 285, 336, 349 nm; ^1H NMR (DMSO-d_6): δ = 2.86 (s, 3H), 4.81 (s, 2H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 8.68 (s, 1H), 12.00 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 20.7, 42.2, 112.5, 120.2, 120.3, 122.0, 123.1, 128.3, 130.8, 135.2, 139.2, 140.7, 143.4, 169.7; FAB-MS (*m/z*): 244 (M^++Li, 100).

5.2.24. 5-Aminomethyl-1,2-dihydro-6*H*-2,4,6-triaza-cyclopenta[*c*]fluoren-3-one (34c). Concentrated aqueous solution of hydrochloric acid (15 mL) was added to a suspension of **33b** (100.0 mg, 0.18 mmol) in ethanol

(10 mL). The mixture was refluxed for 12 h. After concentration under reduced pressure, the residue was suspended in ethanol (10 mL). After filtration under reduced pressure, the precipitate was washed successively with CH_2Cl_2 (3 mL × 2) and diethyl ether (3 mL × 2) to afford 41.0 mg of **34c**, as a yellow powder (78%). Mp > 300 °C; IR (KBr): ν = 3459, 3190, 3034, 2764, 1692, 1632, 1512, 1474, 1447, 1337, 1282, 1234, 1043, 907, 761, 741, 691 cm^{-1}; UV: λ_{max} = 216, 239, 262, 268, 287, 347 nm; ^1H NMR (DMSO-d_6): δ = 4.72 (d, J = 4.6 Hz, 2H), 4.92 (s, 2H), 7.41 (t, J = 8.0 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.80 (bs, 3H), 8.88 (s, 1H), 12.86 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 40.2, 42.4, 112.7, 119.7, 120.8, 123.3, 123.4, 129.0, 132.5, 133.9, 138.6, 138.8, 141.1, 168.9; EI-MS (*m*/*z*, %): 252 (M^+, 100), 237 (50), 223 (43), 207 (35), 194 (22), 179 (25), 166 (15), 152 (12), 140 (20).

5.2.25. 2-(2-Dimethylaminoethyl)-5-methyl-1,2-di-hydro-6*H*-2,4,6-triaza-cyclopenta[*c*]fluoren-3-one (35). NaH 50% (61.0 mg, 1.26 mmol) was added at 0 °C (ice bath) to a solution of **34a** (100.0 mg, 0.42 mmol) in DMF (8 mL). After 45 min stirring at 0 °C, the chlorhydrate of 2-dimethylaminoethylchloride (61.0 mg, 0.42 mmol) was added to the suspension and the mixture was stirred for 12 h at room temperature. The suspension was diluted in water (1 mL) and the solvent was concentrated under reduced pressure. The residue was purified by a column chromatography on silica gel (eluent: CH_2Cl_2/methanol, 99:1 then gradient to methanol 100%) to afford 22.0 mg of **35** as a white foam (17%). IR (KBr): ν = 3416, 3217, 2959, 2932, 1667, 1595, 1454, 1346, 1246, 1117, 737 cm^{-1}; UV: λ_{max} = 200, 217, 238, 263, 270, 337, 351 nm; ^1H NMR (DMSO-d_6): δ = 2.35 (s, 6H), 2.78 (t, J = 6.3 Hz, 2H), 2.88 (s, 3H), 3.78 (t, J = 6.3 Hz, 2H), 4.95 (s, 2H), 7.35 (t, J = 8,0 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 12.40 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 20.8, 39.5, 44.7, 47.0, 56.6, 112.7, 120.0, 120.3, 121.6, 122.9, 128.3, 128.8, 135.3, 138.8, 140.9, 143.5, 167.2; EI-MS (*m*/*z*, %): 293 (8), 199 (75), 150 (100), 143 (98), 128 (45), 115 (44).

5.2.26. 6-(2-Dimethylaminoethyl)-5-methyl-1,2-di-hydro-6*H*-2,4,6-triaza-cyclopenta[*c*]fluoren-3-one (36). The chlorhydrate of 2-dimethylaminoethylchloride (61.0 mg, 0.42 mmol) and NaH 50% (61.0 mg, 1.26 mmol) were successively added to a solution of **34a** (100.0 mg, 0.42 mmol) in DMF (8 mL). After 24 h stirring at room temperature under N_2 atmosphere, water (1 mL) was added to the suspension and the solvent was concentrated under reduced pressure. The residue was purified by column chromatography (eluent: CH_2Cl_2/methanol, 99:1 then gradient to methanol 100%) to afford 33.0 mg of **36**, as a white powder (26%). Mp 225 °C; IR (KBr): ν = 3416, 3225, 2926, 2629, 1697, 1607, 1435, 1358, 1238, 1117, 1063, 750, 729 cm^{-1}; UV: λ_{max} = 198, 239, 261, 267, 283, 339, 351 nm; ^1H NMR (DMSO-d_6): δ = 2.95 (s, 6H), 3.18 (s, 3H), 3.50 (t, J = 8.0 Hz, 2H), 4.85 (s, 2H), 5.20 (t, J = 8.0 Hz, 2H), 7.47 (t, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H); 8.80 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 23.7, 39.7, 42.3, 42.4, 54.1, 111.3, 119.9, 121.5, 123.3, 123.9, 129.1, 130.9, 134.9, 139.6, 141.3, 142.7, 169.0; EI-MS (*m*/*z*, %): 308 (M^+, 27), 250 (27), 161 (64), 144 (100), 130 (20), 116 (35). HREIMS ($C_{18}H_{20}N_4O$): calcd 308.1637; found 308.1681.

5.2.27. 2-Dimethylamino-*N*-(3-oxo-1,2,3,6-tetrahydro-2,4,6-triaza-cyclopenta[*c*]fluoren-5-ylmethyl)-acetamide (37). Triethylamine (0.328 mL, 2.36 mmol) was added to a solution of *N*,*N*-dimethylglycine (81.0 mg, 0.79 mmol) in CH_2Cl_2/*n*-butanol (15 mL:5 mL). Then isobutyl-chloroformiate (0.153 mL, 1.18 mmol) was added at −15 °C to the solution. The mixture was stirred for 1 h at −15°C under N_2 atmosphere and a solution of **34c** (227.0 mg, 0.79 mmol) in methanol (2 mL) was added. After 12 h stirring at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (eluent: CH_2Cl_2/methanol, 100:1 then gradient to methanol 100%) to afford a white amorphous solid, which was suspended in water (10 mL). After filtration under reduced pressure and washing with water (3 mL × 3), the solid was dried to afford 210.0 mg of **37**, as a white powder (78%). Mp > 340 °C; IR (KBr): ν = 3430, 3231, 1692, 1678, 1532, 1449, 1358, 1234, 784 cm^{-1}; UV: λ_{max} = 200, 215, 239, 261, 268, 284, 334, 347 nm; ^1H NMR (DMSO-d_6): δ = 2.38 (s, 6H), 3.20 (s, 2H), 4.85 (s, 2H), 4.92 (d, J = 5.6 Hz, 2H), 7.35 (t, J = 8.0 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 8.80 (s, 2H), 12.40 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 42.5, 45.5, 45.6, 62.1, 112.8, 120.1, 120.7, 123.1, 123.3, 128.8, 131.9, 134.3, 139.1, 141.1, 142.9, 169.5, 169.7; EI-MS (*m*/*z*, %): 337 (M^+, 92), 294 (10), 379 (100), 251 (25), 237 (45), 210 (30), 181 (35), 153 (45), 143 (30), 131 (46), 105 (54). HREIMS ($C_{18}H_{19}N_5O_2$): calcd 337.1539; found 337.1537.

5.2.28. 2,4,6-Trimethyl-*N*-(3-oxo-1,2,3,6-tetrahydro-2,4,6-triaza-cyclopenta[*c*]fluoren-5-ylmethyl)-benzene-sulfonamide (38). Triethylamine (0.740 mL, 5.30 mmol) and methylenesulfonylchloride (464.0 mg, 2.12 mmol) were added to a suspension of **34c** (612.0 mg, 2.12 mmol). After 12 h stirring at room temperature under N_2 atmosphere, the mixture was concentrated under reduced pressure and the residue was diluted in CH_2Cl_2 (30 mL). The organic layer was successively extracted with a 5% aqueous sodium bicarbonate solution (20 mL × 3), a 5% aqueous citric acid solution (30 mL × 3) and brine (30 mL × 3). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by crystallization (CH_2Cl_2/methanol, 1:1) to afford 653.0 mg of **38**, as a pale yellow crystalline powder (71%). Mp > 300 °C; IR (KBr): ν = 3455, 3322, 3148, 1686, 1603, 1458, 1337, 1317, 1246, 1157, 1094, 752, 654 cm^{-1}; UV: λ_{max} = 206, 237, 270, 350 nm; ^1H NMR (DMSO-d_6): δ = 1.99 (s, 3H), 2.45 (s, 6H), 4.67 (d, J = 6.0 Hz, 2H), 4.74 (s, 2H), 6.43 (s, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.90 (t, J = 6.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 8.53 (s, 1H), 11.89 (s, 1H); ^{13}C NMR (DMSO-d_6): δ = 20.4, 22.6, 42.3, 44.9, 112.3, 119.9,

120.3, 122.7, 122.8, 128.5, 130.8, 131.7, 133.8, 134.3, 137.8, 138.7, 140.6, 140.7, 141.2, 169.2; EI-MS (*m/z*, %): 341 (20), 251 (75), 223 (75), 194 (30), 184 (40), 168 (20), 140 (20).

5.3. Growth inhibition assays

Tumour cells were obtained from the American Type Culture Collection (Frederick, MD, USA). They were cultivated in RPMI 1640 medium (Life Science Technologies, Cergy-Pontoise, France) supplemented with 10% foetal calf serum, 2 mM L-glutamine, 100 units/mL penicillin, 100 μg/mL streptomycin and 10 mM HEPES buffer (pH 7.4). Cytotoxicity was measured by the microculture tetrazolium assay as described.[36] Cells were continuously exposed to graded concentrations of the compounds for four doubling times, then 15 μL of 5 mg/mL 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetra-zolium bromide were added to each well and the plates were incubated for 4 h at 37 °C. The medium was then aspirated and the formazan solubilized by 100 μL of DMSO. The results are expressed as IC_{50}, that is, the concentration, which reduced by 50% the optical density of treated cells with respect to untreated controls.

5.4. Cell-cycle analysis

For cell-cycle analysis, L1210 cells (2.5×10^5 cells/mL) were incubated for 21 h with various concentrations of the compounds, then fixed by 70% ethanol (v/v), washed and incubated in PBS containing 100 μg/mL RNAse and 25 μg/mL propidium iodide for 30 min at 20 °C. For each sample, 10^4 cells were analyzed on a XL/MCL flow cytometer (Beckman Coulter). The fluorescence of propidium iodide was recorded through a 615 nm long-pass filter.

5.5. Topoisomerase I inhibition

The complete protocol to measure topoisomerase I inhibition by a relaxation assay has been previously detailed.[37]

5.6. DNA interaction

Sequence recognition was determined by DNase I footprinting using a protocol recently described in details.[44] Similarly, the biophysical methods to examine the binding to DNA have been described earlier.[45a,b]

5.7. Kinase inhibition assays

Kinase activities were assayed in Buffer A or C, at 30 °C, at a final ATP concentration of 15 μM. Blank values were subtracted and activities calculated as pmoles of phosphate incorporated for a 10 min. incubation. The activities are usually expressed in % of the maximal activity, that is in the absence of inhibitors. Controls were performed with appropriate dilutions of dimethylsulfoxide.

GSK-3α/β was purified from porcine brain by affinity chromatography on immobilized axin.[46] It was assayed, following a 1/100 dilution in 1 mg BSA/mL 10 mM DTT, with 5 μL 40 μM GS-1 peptide as a substrate, in buffer A (10 mM $MgCl_2$, 1 mM EGTA, 1 mM DTT, 25 mM Tris–HCl pH 7.5, 50 μg heparin/mL), in the presence of 15 μM [γ-[33] P] ATP (3000 Ci/mmol; 1 mCi/mL) in a final volume of 30 μL. After 30 min incubation at 30 °C, 25 μL aliquots of supernatant were spotted onto 2.5×3 cm pieces of Whatman P81 phosphocellulose paper, and, 20 s later, the filters were washed five times (for at least 5 min each time) in a solution of 10 mL phosphoric acid/liter of water. The wet filters were counted in the presence of 1 mL ACS (Amersham) scintillation fluid.

CDK1/cyclin B was extracted from M phase starfish oocytes and purified by affinity chromatography on $p9^{CKShs1}$-sepharose beads as previously described.[47] The kinase activity was assayed in buffer C (60 mM β-glycerophosphate, 15 mM *p*-nitrophenylphosphate, 25 mM Mops (pH 7.2), 5 mM EGTA, 15 mM $MgCl_2$, 1 mM DTT, 1 mM sodium vanadate, 1 mM phenylphosphate), with 1 mg histone H1/mL, in the presence of 15 μM [γ-[33] P] ATP (3000 Ci/mmol; 1 mCi/mL) in a final volume of 30 μL. After 10 min incubation at 30 °C, 25 μL aliquots of supernatant were spotted onto P81 phosphocellulose papers and treated as described above.

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