Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 13 (2005) 819–837
Bioorganic & Medicinal Chemistry

Synthesis, antitumour activity and structure–activity relationships of 5*H*-benzo[*b*]carbazoles

Christian Asche,[a,*] Walter Frank,[b] Antje Albert[b] and Uwe Kucklaender[c]

[a]*LEDSS, UMR CNRS 5616, Université Joseph Fourier, BP 53, 38041 Grenoble Cédex 9, France*
[b]*Institute for Inorganic Chemistry and Structural Chemistry, Heinrich-Heine-Universitaet Duesseldorf, 40225 Duesseldorf, Germany*
[c]*Institute for Pharmaceutical Chemistry, Heinrich-Heine-Universitaet Duesseldorf, 40225 Duesseldorf, Germany*

Received 1 July 2004; accepted 18 October 2004
Available online 11 November 2004

Abstract—A series of novel 5*H*-benzo[*b*]carbazoles related to the ellipticines was obtained from the reactions of *p*-benzoquinones with 2-aminomethylene-1-indanones. Most of the compounds were evaluated for their antitumour activity in the National Cancer Institute's in vitro human tumour cell line screening panel. Among them, particularly derivative **15c** bearing a *p*-quinone methide moiety in ring C of the heterocycle was found to show in vitro activity comparable to clinically well established anticancer agents such as amsacrine or mitomycin C. Compounds **9d**, **9e** and **12k** showed increased potency to distinct cell lines like the leukemia or melanoma subpanel of cell lines. Based on the test results, structure–activity relationships for this series of compounds were developed. For instance, it was found that a quinonoid substructure in ring C leads to a noticeable increase in activity. The same observation was made for a 2-hydroxyl substituent at the ring system. 2-Acetoxy and 2-methoxy derivatives as well as 2-unsubstituted 5*H*-benzo[*b*]carbazoles either had a decreased potency or were found to be inactive. A COMPARE analysis with some of these compounds showed poor or no correlation with anticancer drugs of the NCI's standard agents database indicating a novel mechanism of action. Additionally, UV–vis titrations in the series of 5*H*-benzo[*b*]carbazoles indicated interactions with calf thymus DNA only for the highly active quinone methide **15c**.

1. Introduction

DNA intercalating agents still comprise a large and important class of antitumour drugs. Among them, the ellipticines exhibit pronounced cytotoxic activity. Their coplanar aromatic heterocycle allows these molecules to slip between adjacent base pairs of a DNA double helix and, therefore, to interfere with fundamental nuclear processes like replication and transcription. Many derivatives of the naturally occurring alkaloids ellipticine **I** and 9-methoxyellipticine **II**[1] have been developed and tested for their anticancer activity. The most prominent one, 9-hydroxy-2-methylellipticinium acetate **III** ('elliptinium'), has even been used clinically in the treatment of osteolytic metastases of breast cancers (Fig. 1).[2,3] Due to its similarity to the ellipticines, the 5*H*-benzo[*b*]carbazole heterocycle **IV** appears to be an interesting lead structure for the development of novel

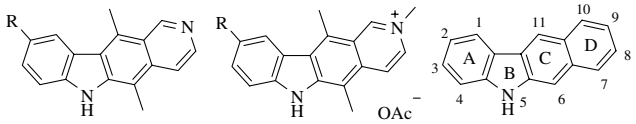


Figure 1.

antineoplastic agents. Additionally, many well established and clinically used anticancer drugs such as the anthracycline antibiotics, mitoxantrone or mitomycin C contain a quinone moiety, which is absolutely necessary for their activity, even if the precise contribution of the quinone substructure to the cytotoxic effect remains frequently uncertain.[4,5] By fitting a quinone moiety into the 5*H*-benzo[*b*]carbazole ring skeleton, the quinone should not only be cytotoxic by itself (quinone redox-cycling, generation of reactive oxygen species), but also facilitate and strengthen the intercalative binding to DNA by the formation of charge-transfer interactions with the electron rich DNA bases.[6] As an extension of our synthesis of promising highly cytotoxic

Keywords: 5*H*-Benzo[*b*]carbazoles; Quinone methide; Antitumour activity.
* Corresponding author. Tel.: +33 476 514434; fax: +33 476 514946; e-mail: christian.asche@ujf-grenoble.fr

0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.10.038

5*H*-benzo[*b*]carbazoles related to ellipticine[7] and in order to gain insight into the structure–activity relationships of this chemical series, we synthesized novel derivatives with different substitution patterns at the 5*H*-benzo[*b*]carbazole skeleton and examined their antitumour effects in the National Cancer Institute's (NCI) in vitro anticancer cell line panel.[8,9] Based on our former experiences with this class of compounds, we were only interested in variations of the substitution pattern at rings A, B and C of the heterocycle, since modifications at ring D led to derivatives with decreased activity.[10]

2. Results and discussion

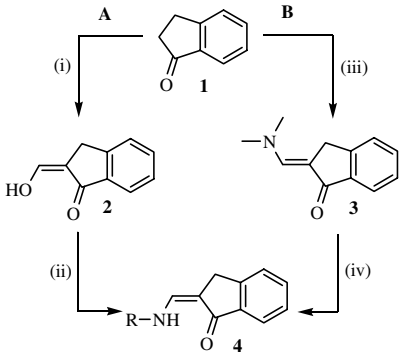
2.1. Chemistry

The access to the 5*H*-benzo[*b*]carbazoles was achieved via a modified Nenitzescu reaction[11] by reaction of *p*-benzoquinones **5** with 2-aminomethylene-1-indanones. Compounds **4** were conveniently prepared starting from commercially available 1-indanone **1** in two different routes (Scheme 1). In route A, reaction of 1-indanone **1** with methyl formiate and sodium methylate in diethyl ether and subsequent hydrolysis with cold water afforded 2-hydroxymethlene-1-indanone **2** in 58% yield.[12] Amination of **2** with the respective primary amine in the presence of catalytic amounts of *p*-toluenesulfonic acid in chloroform yielded the 2-aminomethylene-1-indanones **4** (68–98% yield). Alternatively, compounds **3** were also obtained by reaction of 1-indanone **1** with dimethylformamiddimethylacetal (route B) (75% yield).[13] Afterwards, the resulting 2-dimethylaminomethylene-1-indanone **3** was heated with the appropriate primary amine and *p*-toluenesulfonic acid as catalyst in ethanol to give the secondary enaminones **4** corresponding to the procedure for amine exchanges by Martin et al. (49–81% yield).[14] The two routes led to similar yields of secondary enaminones, but one major advantage of route A was the independence of the electronic properties of the substituent R at the nitrogen of the enaminone, whereas the synthesis of compounds **4** via the tertiary enaminone **3** only succeeded in the case of electron pushing substituents R.

All reactions of *p*-benzoquinones **5** with enaminones **4** were carried out in glacial acetic acid. The quinonoid 2-hydroxy-5*H*-benzo[*b*]carbazole-6,11-diones **6** were obtained in yields between 20% and 35% employing a 4-fold excess of quinone component and stirring for 16 h at room temperature, whereas the isolation of the corresponding nonquinonoid 2,6-diols **7** only succeeded after stirring the reaction mixture for 30 min under argon atmosphere and using stoichiometric amounts of enaminones **4** (50% yield) (Scheme 2). Inert gas atmosphere was not necessary for the synthesis of the methyl 2,6-dihydroxy-5*H*-benzo[*b*]carbazole-1-carbaoxylates **8** resulting from the reactions of the monosubstituted *p*-quinone **5b** (60–70% yield). These heterocycles appeared to be more stable and less sensitive to oxidation than their at position 1 unsubstituted counterparts **7**. Nevertheless, these compounds could be oxidized in basic conditions yielding their corresponding quinones **9** (~70–90% yield). Despite the moderate yields particularly in the cases of at position 1 unsubstituted heterocycles, these novel pathways seem to be attractive, since they afford quinonoid 5*H*-benzo[*b*]carbazoles in only three or four steps from commercially available and cheap compounds. Unfortunately, this synthesis is restricted to enaminones **4** bearing electron pushing substituents R. 2-Aminomethylen-1-indanones **4** containing withdrawing residues either did not react with the utilized quinones or led to the formation of spirocyclic benzofuran derivatives **10** after heating. In the case of the reaction of the 4-methoxyphenyl-substituted enaminone **4p** we were able to isolate both the 5*H*-benzo[*b*]carbazole **7p** as well as the spirocycle **10p**.

^{1}H NMR studies on the primary 5*H*-benzo[*b*]carbazoles **7** and **8** in DMSO-d_6 indicated the presence of an equilibrium mixture of the tautomeric 6-keto and 6-enol forms. Directly after dissolving in most cases the 6-keto tautomer was present, whereas after 24 h in solution the 6-enol tautomer predominated.

The reaction of quinones with enaminones has been documented for many years and remains very versatile.[15] Several pathways are competitive and depending on the nature of the quinones and enaminones as well as the utilized solvents. A probable mechanism of the



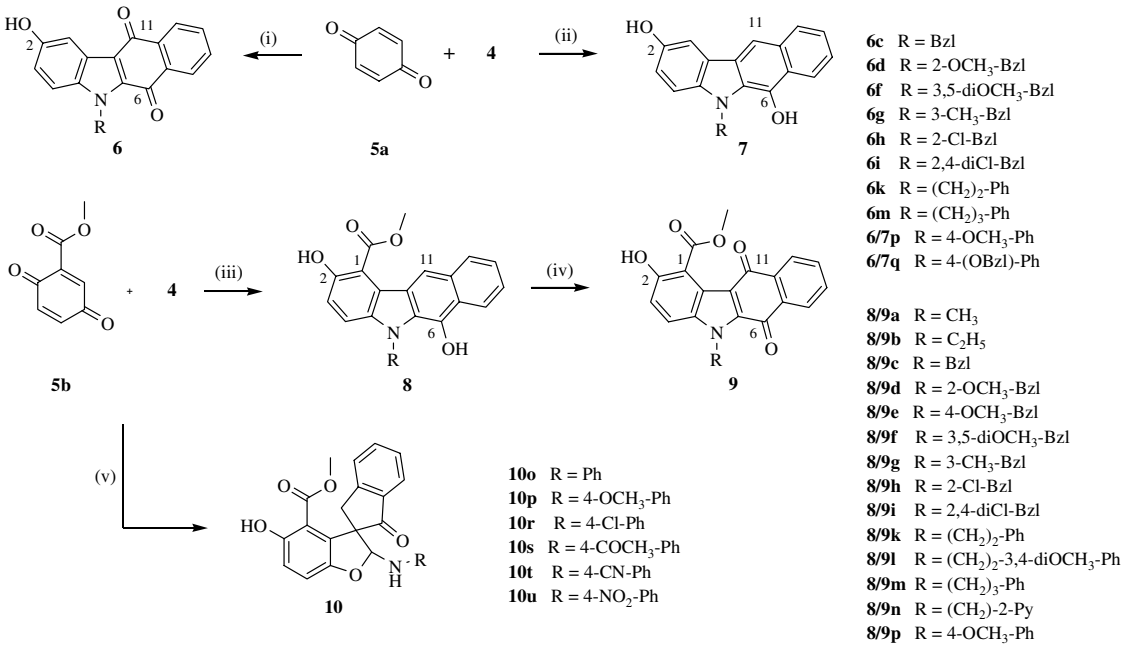
Route A and B:

4a R = CH_3
4b R = C_2H_5
4c R = Bzl
4d R = 2-OCH_3-Bzl
4e R = 4-OCH_3-Bzl
4f R = 3,5-diOCH_3-Bzl
4g R = 3-CH_3-Bzl
4h R = 2-Cl-Bzl
4i R = 2,4-diCl-Bzl
4k R = $(CH_2)_2$-Ph
4l R = $(CH_2)_2$-3,4-diOCH_3-Ph
4m R = $(CH_2)_3$-Ph
4n R = CH_2-2-Py

Only route A:

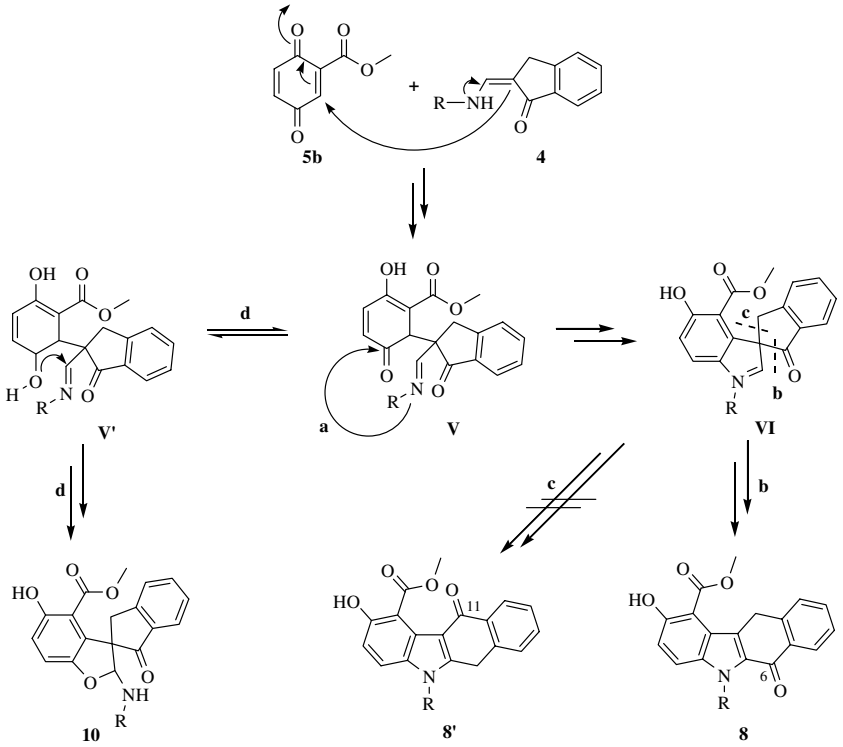
4o R = Ph
4p R = 4-OCH_3-Ph
4q R = 4-(OBzl)-Ph
4r R = 4-Cl-Ph
4s R = 4-$COCH_3$-Ph
4t R = 4-CN-Ph
4u R = 4-NO_2-Ph

Scheme 1. Reagents and conditions: (i) $NaOCH_3/NaCH_3/Et_2O/0\,°C$, then H_2O; (ii) R–NH_2/*p*-TSA/CH_2Cl_2/reflux/1 h; (iii) DMFA/100 °C/1 h; (iv) R–NH_2/*p*-TSA/EtOH/reflux/4 h.



Scheme 2. Reagents and conditions: (i) 4 equiv **4**/HOAc/rt/16 h; (ii) 1 equiv **4**/HOAc/argon/rt/30 min; (iii) 1 equiv **4**/HOAc/rt/15 min; (iv) acetone/NaOH/rt/24 h; (v) 1 equiv **4**/HOAc/Δ*T*.

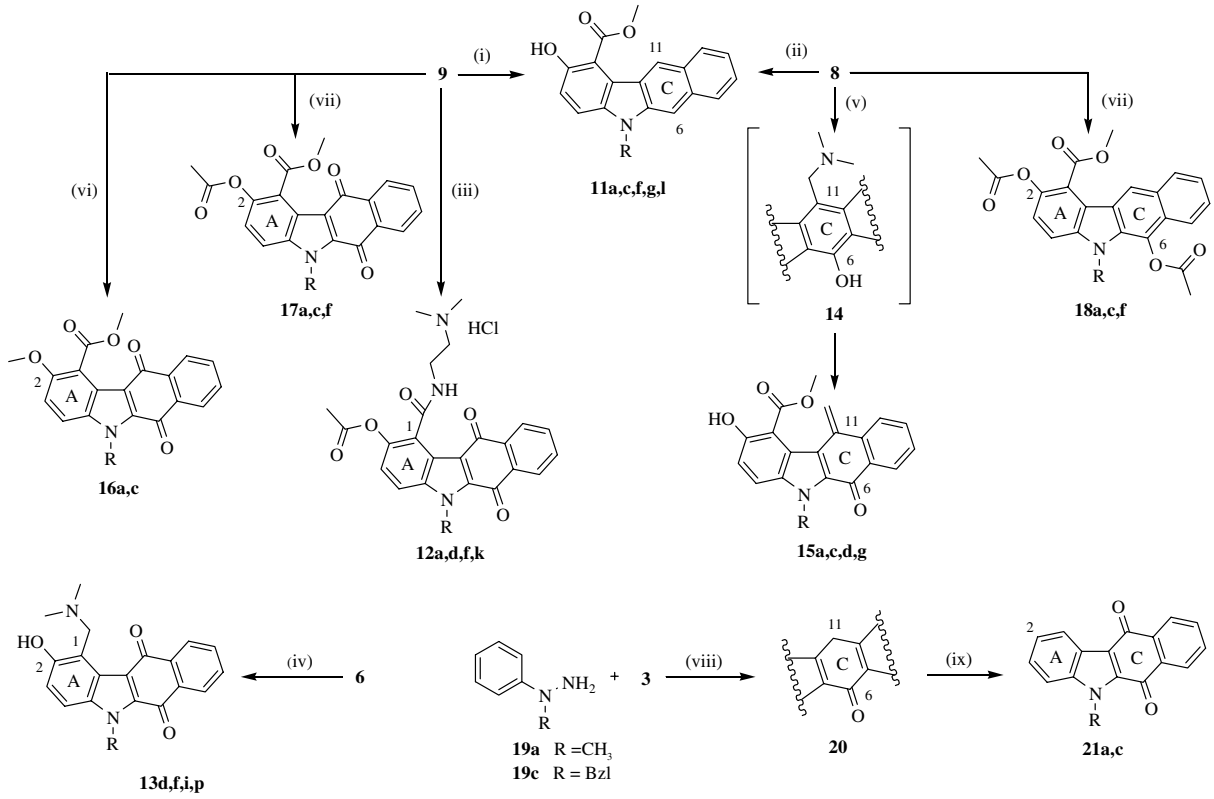
reaction course for the reactions with the monosubstituted quinone **5b** is shown in Scheme 3. Due to the planarity of the enaminones **4** allowing maximal conjugation within the vinylogous amide, the nucleophilic strength of the nitrogen is weakened, which leads to an increase in nucleophilicity at the β-carbon and at the oxygen, respectively. By using acetic acid as solvent, the nucleophilicity of the solvated oxygen is decreased. Therefore, the first step should be a regioselective Michael-type addition of the enaminone β-carbon to the activated position 3 of the quinone forming the Michael-adduct **V**. Next, upon intramolecular attack of the imine nitrogen on the carbonyl C-atom of the quinone moiety, the spirocyclic cation results **VI** (route a). The primary



Scheme 3. Proposed mechanism for the formation of the 5H-benzo[*b*]carbazoles **8** and the spirocyclic benzofuran derivatives **10**.

5*H*-benzo[*b*]carbazoles **8** are now formed via an ionotropic rearrangement by migration of the carbonyl group to the carbon atom of the carbenium–iminium moiety of **VI** (route b). The conceivable formation of the isomers **8′** resulting from migration of the methylene group at the spirocyclic carbon was not observed (route c). Assignment of the constitution of **8** was made on the basis of NOE experiments. Irradiation of H-11 in **8k** led to NOE's for the 1-methyl protons (5%) and H-10 (5%). Additionally, saturation of the *N*-methylene protons led to NOE's for the neighbouring methylene protons (7%) and the aromatic protons H-2′ and H-6′ (4%) as well as H-4 (6%). The fact that only electron pushing residues R such as alkyl or benzyl allow the formation of 5*H*-benzo[*b*]carbazoles may be attributed to the decreased nucleophilic properties of the imine nitrogen within the adduct **V** in the case of electron withdrawing residues. The spirocyclic benzofurans **10** are formed by tautomerization of adduct **V** to the hydroquinone form **V′** and subsequent nucleophilic attack of the former carbonyl oxygen on the carbon atom of the imine substructure (route d).

Different derivatives of the 5*H*-benzo[*b*]carbazoles have been synthesized. Our first interest was focused on ring C. Apart from *p*-quinonoid (**6** and **9**) and hydroxylated compounds (**7** and **8**), we were interested in 5*H*-benzo[*b*]carbazoles lacking substituents at the positions 6 and 11, in order to reveal the contribution of the quinone moiety to the cytotoxicity of these heterocycles. As outlined in Scheme 4, the methyl 2-hydroxy-5*H*-benzo[*b*]carbazol-1-carboxylates **11** were prepared in good yields (60–75%) by reductive dehydration with zinc in acetic acid from both the corresponding quinones **9** and the corresponding 6-hydroxyl compounds **8**. For a large variety of polycyclic compounds it was found that basic side chains attached to the ring system not only improve the solubility under physiological conditions, but also lead to an increase in anticancer activity. For instance, the *N*-(2-dimethylaminoethyl)-carboxamide side chain is a common functional group of some antitumour acridines and phenazines.[16,17] Among our compounds, the 1-methoxycarbonyl substituent in **9** displays a suitable target for the attachment of a basic side chain. Thus, aminolysis of **9** with *N*,*N*-diethylamine afforded the desired carboxamides **12**, which were isolated as the hydrochloride salts (39–46% yield). As it is already known for 5-hydroxyindoles,[18] compounds **6** lacking a substituent at position 1 were found to act regioselectively in the Mannich reaction. Heating of **6** for 2 h with bisdimethyldiaminomethane and catalytic amounts of acetic acid in dioxane yielded the *ortho*-phenolic Mannich bases **13** (45–58% yield). An attempt was then made to attach the dimethylaminomethyl residue to the nonquinonoid carboxylates **8**. However, instead of isolating phenolic Mannich bases, we obtained interesting *p*-quinone methides **15** after heating for 6 h under argon atmosphere. They result from thermal desamination of **14** (29–38% yield). In comparison to conventional quinones, quinone methides constitute highly reactive



Scheme 4. Reagents and conditions: (i) 4 equiv Zn/HOAc/reflux/6 h; (ii) 4 equiv Zn/HOAc/reflux/12 h; (iii) (1) *N*,*N*-diethylamine/2 h, (2) HCl; (iv) bisdimethylaminomethane/cat. HOAc/dioxane/reflux/2 H; (v) bisdimethylaminomethane/cat. HOAc/dioxane/argon/reflux/6 h; (vi) dimethylsulfate/10% NaOH; (vii) acetic anhydride/cat. pyridine/2 h; (viii) 2 N HCl/isopropanol/reflux/3 h; (ix) $KMnO_4/CH_2Cl_2$: acetone 3:1/rt/12 h.

electrophilic and alkylating compounds. Some of the well established anticancer drugs such as mitomycin C are known to exhibit their activity mainly via an intermediate quinone methide species.[19] But surprisingly compounds **15** displayed decreased reactivity towards nucleophiles and could even be recrystallized from ethanol. The structure of **15c** was confirmed by X-ray crystallography (Fig. 2). Interestingly, due to the repulsion between the H-bonded 1-carboxylate group and the 11-methylene group, the latter is pushed out of the coplanar arrangement of the heterocycle which might contribute to its low reactivity.

Ellipticine analogues possessing a 9-oxygen function exhibit greater activity than their counterparts lacking this function. It is suggested that an electrophilic and strongly alkylating quinone imine intermediate resulting from metabolic oxidation of the *p*-aminophenol moiety is responsible for this finding.[20,21] 5*H*-Benzo[*b*]carbazoles derived from the reaction of quinones with aminomethylenindanones constantly contain a 2-hydroxyl substituent in ring A. Therefore, to examine whether it increases cytotoxicity or even is absolutely necessary to obtain a biological effect, we prepared different derivatives of the 2-hydroxy-5*H*-benzo[*b*]carbazoles. First, methylation of the *N*-methyl- and *N*-benzyl-substituted quinones **9a** and **9c** with dimethylsulfate in NaOH (10%) afforded the corresponding 2-methoxy derivatives **16a** and **16c** (63% and 78% yield). Furthermore, upon heating with acetic anhydride and catalytic amounts of pyridine, we were also able to obtain various mono- and bisacetylated 5*H*-benzo[*b*]carbazoles in yields between 55% and 73% (Scheme 4, compounds **17a**,**c**,**f** and **18a**,**c**,**f**). For the preparation of 2-unsubstitued 5*H*-benzo[*b*]carbazoles we had to design a new route differing from the modified Nenitzescu reaction. We chose a variation of the well known Fischer indole synthesis.[22] By heating the respective phenylhydrazine **19** with an equimolar amount of the tertiary enaminone **3** in a mixture of isopropanol and 2 M hydrochloric acid, we obtained compounds **20**. Spectral data revealed that oxidation to the corresponding quinones **21** had partially taken place. Instead of a further workup, we directly completed the oxidation of crude **20a**,**c** with $KMnO_4$ in a methylene chloride–acetone mixture (~50% yield).

2.2. In vitro anticancer activity

Most of the synthesized 5*H*-benzo[*b*]carbazoles were evaluated in the in vitro human disease-oriented tumour cell line screening panel developed at the NCI.[8,9] The antitumour activity of a test compound is given by three different dose response parameters for each of the approximately 60 cell lines derived from nine different types of cancer: GI_{50} (molar concentration required for half growth inhibition), TGI (molar concentration leading to total growth inhibition) and LC_{50} (molar concentration required for 50% cell death). Moreover, a mean graph midpoint (MGM) is calculated for each of the above mentioned parameters, which displays an averaged activity parameter over all cell lines.

In Table 1 MGM $\log GI_{50}$, $\log TGI$ and $\log LC_{50}$ values over all cell lines for each tested compound are given. The results indicate that the extent of cytotoxicity is largely linked to the presence of a quinone moiety in ring C of the benzo[*b*]carbazole heterocycle. For instance, the quinonoid methyl 5*H*-benzo[*b*]carbazole-1-carboxylates **9** showed MGM $\log GI_{50}$ values in the range of −5.21 to −4.36, whereas the corresponding nonquinonoid 6-hydroxyl compounds **8** only showed values in the range of −4.82 to −4.16. In the particular case of the *N*-4-methoxybenzyl substituted heterocycle the oxidation of the 6-hydroxylated ring C in **8e** to the *p*-quinone **9e** even led to an increase in activity of almost one log unit (MGM $\log GI_{50}$ (**8e**) = −4.32 and MGM $\log GI_{50}$ (**9e**) = −5.21) (Fig. 3). Furthermore,

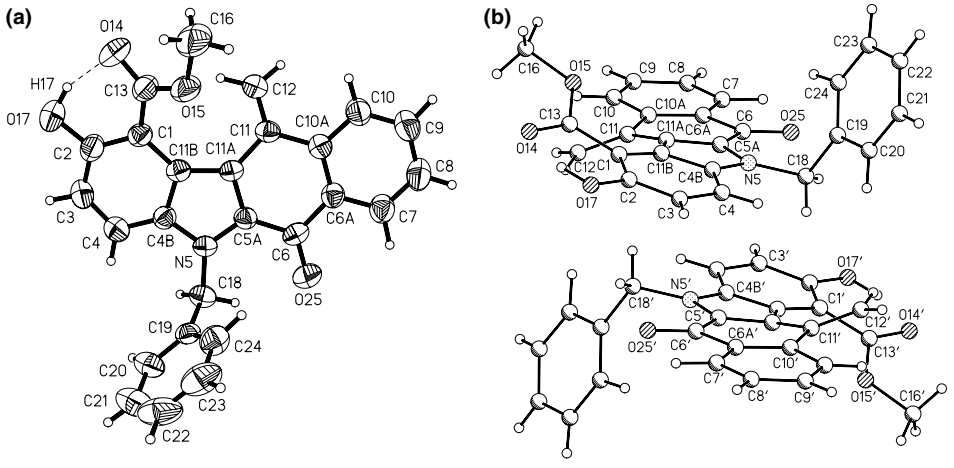


Figure 2. (a) Diagram of **15c**. Displacement ellipsoids are drawn at the 50% probability level, radii of hydrogen atoms are chosen arbitrarily, and the hydrogen atom labels are omitted for clarity. Selected geometric features: C11–C12 1.322(3), C11–C11A 1.448(3), C11–C10A 1.475(3), C11A–C5A 1.379(2), C10A–C6A 1.386(3), C5A–C6 1.450(3), C6A–C6 1.470(3), C6–O25 1.223(2), C5A–N5 1.369(3), C4B–N5 1.368(2), C18–N5 1.472(3), C4B–C11B 1.395(2), C11B–C11A 1.433(3), O17–H17 0.94(2), H17···O14 1.69(3), O17···O14 2.578(3) Å; O15–C13–C1–C11B −19.7(3), C13–C1–C11B–C11A −22.6(4), C1–C11B–C11A–C11 −17.1(5), C11B–C11A–C11–C12 −15.0(4), C12–C11–C10A–C10 23.3(4), C4B–N5–C18–C19 −77.9(3)°. (b) View of the dimer of **15c** formed in crystals, which is stabilized by π–π-interactions (N5···C4B′ 3.455 Å); atomic radii are chosen arbitrarily.

Table 1. In vitro anticancer activity of 5*H*-benzo[*b*]carbazoles[a]

Compound	MGM $-\log GI_{50}$[b]	MGM $-\log TGI$[c]	MGM $-\log LC_{50}$[d]	Compound	MGM $-\log GI_{50}$[b]	MGM $-\log TGI$[c]	MGM $-\log LC_{50}$[d]
6d	−4.54	−4.12	−4.01	**9h**	−4.92	−4.51	−4.17
6f	−5.28	−4.51	−4.10	**9i**	−5.07	−4.64	−4.23
6g	−4.78	−4.17	−4.01	**9k**	−4.96	−4.58	−4.23
6i	−5.13	−4.57	−4.20	**9m**		Inactive	
6p	−5.15	−4.30	−4.04	**9n**	−4.36	−4.06	−4.01
6q		Inactive		**9p**	−4.73	−4.27	−4.07
7p	−4.54	−4.08	>−4.00[e]	**11a**		Inactive	
7q		Inactive		**11c**		Inactive	
8b	−4.79	−4.27	−4.02	**11g**		Inactive	
8c	−4.54	−4.08	−4.01	**11l**		Inactive	
8d	−4.25	−4.02	>−4.00[e]	**12d**	−5.78	−5.41	−4.92
8e	−4.32	−4.05	>−4.00[e]	**12f**	−5.77	−5.35	−4.84
8f	−4.47	−4.08	−4.01	**12k**	−5.41	−5.00	−4.49
8g	−4.82	−4.29	−4.15	**13f**	−4.77	−4.38	−4.12
8h	−4.64	−4.17	−4.02	**13i**		Inactive	
8i	−4.30	−4.04	>−4.00[e]	**13p**	−5.32	−4.77	−4.21
8k	−4.68	−4.23	−4.01	**15c**	−6.42	−5.88	−5.25
8l	−4.25	−4.02	−4.01	**16a**		Inactive	
8m		Inactive		**16c**		Inactive	
8n	−4.16	−4.02	>−4.00[e]	**17a**	−4.68	−4.14	−4.04
9a	−4.73	−4.17	−4.02	**17c**	−4.67	−4.29	−4.06
9c	−4.86	−4.50	−4.18	**18a**	−4.75	−4.11	>−4.00[e]
9d	−5.09	−4.57	−4.17	**18c**		Inactive	
9e	−5.21	−4.63	−4.20	**21a**		Inactive	
9f	−5.15	−4.47	−4.08	**21c**		Inactive	
9g	−5.02	−4.61	−4.22				

Inactive: compound was already found to be inactive in the NCI's 3 cell line pretest and did not reach the 60 cell line main test.
[a] Data were obtained from the NCI's in vitro anticancer cell line screen (for details see Refs. 8,9).
[b] Averaged log molar concentration for all tested cancer cell lines which led to 50% growth inhibition.
[c] Averaged log molar concentration for all tested cancer cell lines which led to total growth inhibition.
[d] Averaged log molar concentration for all tested cancer cell lines which led to 50% cell death.
[e] The highest tested concentration (10^{-4} M) of the drug did not lead to 50% cell death.

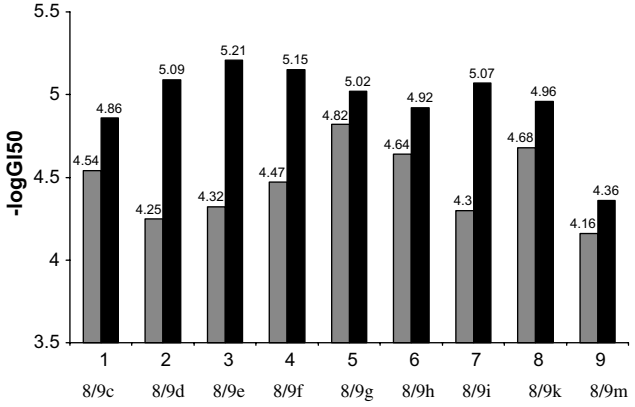


Figure 3. Comparison of the growth inhibitory effects of the quinonoid compounds **9** and their corresponding 6-hydroxyl derivatives **8**. MGM $-\log GI_{50}$ values of the quinonoid compounds **9** [black] and the corresponding 6-hydroxylated compounds **8** [grey].

the 5*H*-benzo[*b*]carbazoles **11** lacking substituents at the positions 6 and 11 of the heterocycle showed no activity and were already found to be inactive in the three cell line one-dose primary anticancer assay. On the basis of these results one can make the following gradation: among our compounds those without substituents at ring C are inactive, 6-hydroxylated compounds show activity, which is highly increased by oxidation to the corresponding quinone.

Relating to the substitution at position 2 of the heterocycle, it was found that 2-hydroxy derivatives exhibited the largest activity (e.g., MGM $\log GI_{50}$ (**9c**) = −4.86), whereas acetylation decreased the activity (e.g., MGM $\log GI_{50}$ (**17c**) = −4.67) and methylation even led to inactive compounds (e.g., **16c**). Additionally, compounds **21** derived from the modified Fischer indole synthesis were also shown to be inactive. These findings suggest that 2-hydroxylation is not only an essential structural feature in the case of the ellipticine series, but also among our synthesized compounds.

Among the compounds differing in the substitution at position 1, the carboxamides **12** were found to be more effective (MGM $\log GI_{50}$ (**12d**) = −5.78, MGM $\log GI_{50}$ (**12f**) = −5.77, MGM $\log GI_{50}$ (**12k**) = −5.41) than their 1-methoxycarbonyl substituted counterparts **9** (MGM $\log GI_{50}$ (**9d**) = −5.09, MGM $\log GI_{50}$ (**9f**) = −5.15, MGM $\log GI_{50}$ (**9k**) = −4.96). But the test results did not indicate any superiority of the 1-methoxycarbonyl substituted 5*H*-benzo[*b*]carbazoles **9** to their corresponding 1-unsubstitued analogues **6**. While in the cases of a *N*-2-methoxybenzyl and *N*-3-methylbenzyl substitution the compounds **9d** and **9g** displayed higher growth inhibitory effects (MGM $\log GI_{50}$ (**12d**) = −5.09 vs

MGM $\log GI_{50}$ (**6d**) = −4.54, MGM $\log GI_{50}$ (**9g**) = −5.02 vs MGM $\log GI_{50}$ (**6g**) = −4.78), the results were reversed in the cases of a *N*-3,5-dimethoxybenzyl, *N*-2,4-dichlorobenzyl and *N*-4-methoxyphenyl substitution (MGM $\log GI_{50}$ (**9f**) = −5.15 vs MGM $\log GI_{50}$ (**6f**) = −5.28, MGM $\log GI_{50}$ (**9i**) = −5.07 vs MGM $\log GI_{50}$ (**6i**) = −5.13, MGM $\log GI_{50}$ (**9p**) = −4.73 vs MGM $\log GI_{50}$ (**6p**) = −5.15). For the *ortho*-phenolic Mannich bases **13f**,**i**,**p** the results obtained were disappointing. Only **13p** showed higher activity than the corresponding 1-unsubstituted quinone **6p** (MGM $\log GI_{50}$ (**13p**) = −5.32 vs MGM $\log GI_{50}$ (**6p**) = −5.15). The *N*-2,4-dichlorobenzyl substituted derivative **13i** was even shown to be inactive in the three cell line pretest.

Moreover, with regard to the substitution of the ring nitrogen, the investigated compounds were shown to have conspicuous differences in activity. For instance, the replacement of the benzyl substituent in compound **9c** by a 2-pyridylmethyl group caused a decrease in potency of 0.5 log units (MGM $\log GI_{50}$ (**9c**) = −4.86 vs MGM $\log GI_{50}$ (**9n**) = −4.36). The same observation was made for the nonquinonoid heterocycles **8c** and **8n**. Large substituents at the N-5 such as the *N*-phenylpropyl residue of compounds **8m** and **9m** led to inactivity in the pretest. Among our compounds, particularly in the 1-methoxycarbonyl series, a benzyl residue—preferably mono- or bismethoxylated—supplied the best activity.

Apart from the highly active carboxamides **12**, the largest activity of all compounds over all cell lines was obtained for the *N*-benzyl substituted *p*-quinone methide **15c** with a MGM $\log GI_{50}$ of −6.42. This value is even comparable to those ones obtained for clinically well established anticancer drugs such as amsacrine (MGM $\log GI_{50}$ = −6.36) or mitomycin C (MGM $\log GI_{50}$ = −6.13). Compared with its *p*-quinonoid analogue **9c**, merely the formal exchange of one oxygen for a methylene group led to an increase in growth inhibitory potential of more than 1.5 log units.

In addition to its high overall activity, the *N*-2-phenethyl substituted carboxamide **12k** showed selective effects on the melanoma subpanel of cell lines at all levels, but especially at the LC_{50} level (e.g., MGM (all cell lines) $\log LC_{50}$ = −4.49 vs MGM (melanoma cell lines) $\log LC_{50}$ = −5.21) (Fig. 4). Although **12k** showed the lowest potency over all cell lines among the carboxamide series of compounds, the sensitivity of the melanoma cell lines to **12k** is the reason why this derivative is now being reviewed by the NCI for further testing. We also observed selective activity for the quinonoid methyl 5*H*-benzo[*b*]carbazole-1-carboxylates **9d** and **9e** to the leukemia subpanel of cell lines, which was particularly pronounced at the GI_{50} level (e.g., **9e**: MGM (all cell lines) $\log GI_{50}$ = −5.21 vs MGM (leukemia cell lines) $\log GI_{50}$ = −6.52) (Fig. 5). This selectivity seemed to be linked to the monomethoxybenzyl substituent at the ring nitrogen, since it is less marked in the case of the only benzyl substituted quinone **9c** as well as in the case of the bismethoxylated derivative **9f**.

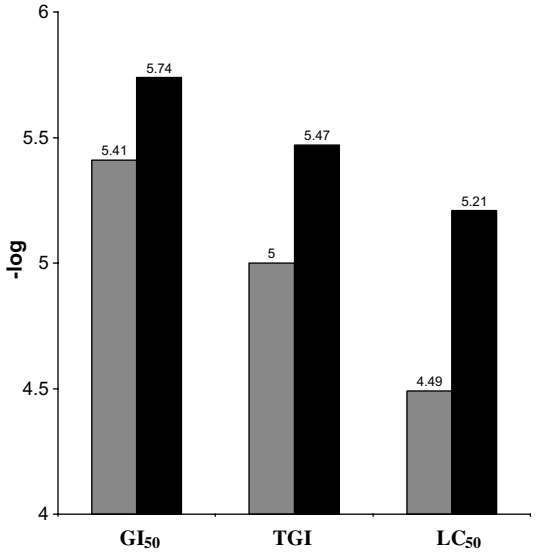


Figure 4. Selective activity of **12k** on the melanoma subpanel of cell lines. $-\log GI_{50}$, $-\log TGI$, $-\log LC_{50}$ values of the carboxamide **12k** for the melanoma subpanel of cell lines [black] and MGM $-\log GI_{50}$, $-\log TGI$ and $-\log LC_{50}$ values for all cell lines [grey].

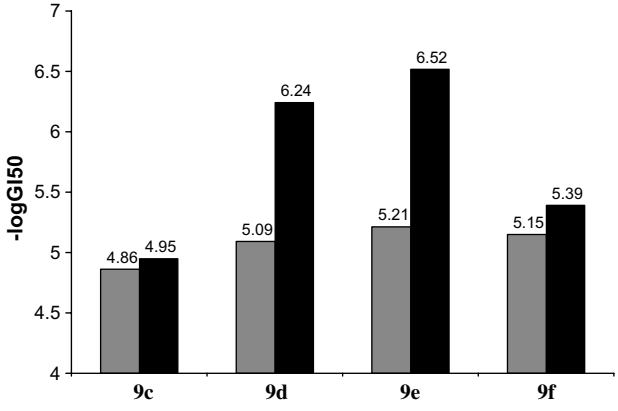


Figure 5. Selective activity of **9d** and **9e** on the leukemia subpanel of cell lines. MGM $-\log GI_{50}$ [grey] and $-\log GI_{50}$ values for the leukemia subpanel of cell lines [black] of the compounds **9c**, **9d**, **9e** and **9f**.

2.3. COMPARE analysis

A COMPARE analysis[23] was performed with some of our compounds at the GI_{50} level to investigate whether they resemble anticancer drugs of the NCI's standard agent database and to probably predict their mechanism of action. The COMPARE algorithm was developed to determine the degree of similarity of mean graph fingerprints obtained from the in vitro anticancer screen with patterns of activity of standard agents. The hypothesis is that, if the data pattern of a compound correlates well with the data pattern of compounds belonging to the standard agent database (Pearson correlation coefficients (PCCs) > 0.6), the compound of interest may have the same mechanism of action as those agents with known mechanism. On the other hand, if the tested compound does not show any correspondence in its

activity pattern with those of the standard agents, it is believed that it has a novel mechanism of action.

For the leukemia selective *N*-2-methoxybenzyl substituted quinone **9d** we obtained high correlations with the topoisomerase II inhibitors etoposide (PCC = 0.752) and menogaril (PCC = 0.640), but other topoisomerase II inhibitors such as amsacrine or doxorubicin did not correlate well with **9d**. Therefore, these results provide only a limited clue concerning the mechanism of action. Interestingly, for the carboxamides **12d** and **12f** the highest correlations were obtained with alkylating agents. For instance, the *N*-3,5-dimethoxybenzyl substituted compound **12f** shows relative high similarity with the (2-chloroethyl)nitrosourea lomustine (PCC = 0.643). Although other standard agents led to PCCs smaller than 0.6, among the most similar compounds we could only find alkylating agents like cyclodisone (PCC = 0.530) or carmustine (0.478). With the carboxamide **12d** as seed compound, the highest PCCs were also obtained with alkylating agents (carmustine (PCC = 0.575), semustine (PCC = 0.537), lomustine (PCC = 0.516)). The melanoma selective carboxamide **12k** showed no similarity with the standard agents. The same observation was made for the highly active quinone methide **15c**, the 1-unsubstituted quinones **6f** and **6p**, the Mannich base **13p** and the bishydroxy derivative **8g**. All in all the COMPARE analysis for the 5*H*-benzo[*b*]carbazoles against the standard agent database showed poor or no correlation indicating a novel mechanism of action for this class of compounds.

2.4. Interaction with DNA

Interaction with DNA and in particular intercalation causes changes in the UV spectra of drugs. Therefore, the reactivity of compounds **6p**, **9c**, **9d**, **9k**, **11c**, **12d** and **15c** with calf thymus DNA was studied in Tris buffer at 25 °C (pH 7.2). We employed the classical intercalator ethidium bromide as comparison. DNA solutions were added in three different concentrations to solutions of the respective 5*H*-benzo[*b*]carbazole, and the concentration of the drug was adjusted to reach 5×10^{-4} M each time. With ethidium bromide we obtained both strong bathochromic and hypochromic effects, as it is found for almost all classical intercalators.[24,25] But disappointingly, the UV–vis titration spectra of our compounds with DNA did not show any changes when compared to the spectra of the 5*H*-benzo[*b*]carbazoles alone, which indicates that DNA is not a target for our compounds and that the underlying mechanism of cytotoxicity is independent of interaction with DNA. However, only in the case of the quinone methide **15c** we observed time dependent spectral changes (Fig. 6). After an incubation time of 5 min we obtained a bathochromic shift of the maximum at 379–385 nm accompanied with a light hyperchromic effect ($A = 0.79$ vs $A = 0.81$). Afterwards, up to an incubation time of 30 min the binding to DNA was homogeneous with clear isosbestic behaviours. This interaction of **15c** with DNA was different from other intercalators and DNA interacting agents, but it may provide an explanation for the strong anticancer activity of this compound observed in the in vitro test. The high cytotoxic activity of this compound apparently correlates with the extraordinary quinone methide structure.

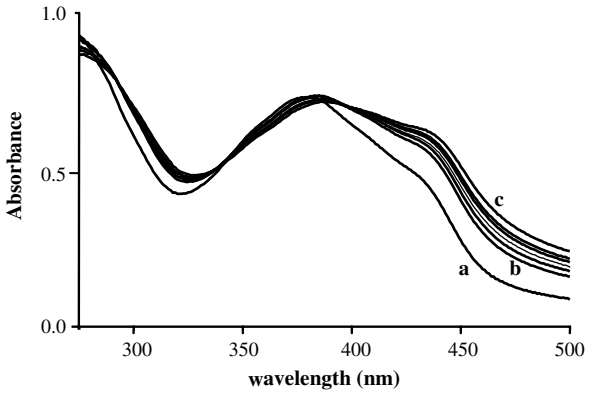


Figure 6. Time dependent UV spectra of **15c** with calf thymus DNA. (a) **15c** (5×10^{-4} M) without DNA in Tris buffer (50 mM NaCl, 5 mM tromethamol), pH 7.2. (b) and (c) To 300 μL **15c** were added 2200 μL Tris buffer and 500 μL of a concentrated DNA solution in Tris buffer: (b) incubation time: 5 min, (c) incubation time: 30 min.

3. Conclusion

The reaction of *p*-benzoquinones with aminomethyleneindanones afforded new 5*H*-benzo[*b*]carbaole derivatives related to the ellipticines whose cytotoxic activity was evaluated in the NCI's in vitro anticancer screening panel consisting of 60 human cancer cell lines. The results obtained from this assay indicated that the extent of activity was largely linked to both a *p*-quinonoid moiety in ring C and a hydroxyl group at position 2 of the heterocycle. The introduction of a *N*-(2-dimethylaminoethyl)-carboxamide side chain at position 1 led to the highly active derivatives **12**. Among them, the *N*-2-phenethyl substituted compound **12k** displayed selective activity against the melanoma panel of cell lines. This selective activity is the reason why this compound is now being reviewed by the NCI for further testing. Furthermore, the derivatives **9d** and **9e** showed high selective activity against the leukemia panel of cell lines which is related to the *N*-methoxybenzyl substitution. The highest activity over all cell lines among our compounds was obtained for the *p*-quinone methide **15c**. Its in vitro cytotoxicity was comparable to those of well established anticancer drugs such as amsacrine or mitomycin C. COMPARE analysis as well as UV experiments with increasing DNA concentrations indicated a novel mechanism of action which is in contrast to the elliptines independent of interaction with DNA. Only for the quinone methide **15c** we observed an interaction with DNA, which seemed to be different from the classical intercalation mode. However, even if its precise mechanism of action and DNA binding mode have yet to be elucidated, its DNA interacting properties may represent an explanation for the high activity of this compound. The quinone methide structure in **15c** can be considered as an alkylating function. However, we do not assume a covalent binding of **15c** to DNA since chemically we were not able to obtain an addition prod-

uct with simple nucleophiles (e.g., morpholine). As a prolongation of our work it will be interesting to see if a 5*H*-benzo[*b*]carbazole derivative containing both a *N*-(2-dimethylaminoethyl)-carboxamide side chain at position 1 and a *p*-quinone methide moiety in ring C exhibits an increased activity.

4. Experimental section

Melting points were determined using a Gallenkamp apparatus and are uncorrected. NMR spectra were obtained on Bruker AC 200 and Varian VXR 300 spectrometers in DMSO-d_6, $CDCl_3$ or pyridine-d_5 using tetramethylsilane (TMS) as an internal standard. The chemical shifts are reported in ppm, in units. Mass spectra were recorded on Finnigan MAT 4000, Incos 50 Finnigan MAT instruments. Elemental analyses were performed with a Perkin Elmer PE 2400 CHN elemental analysator. Commercially available solvents and reagents were used without further purification unless otherwise mentioned.

4.1. 2-Hydroxymethylene-1-indanone (2)

Compound **2** was synthesized similarly to Ruhemann and Levy:[12] To a stirred suspension of sodium methylate (1.70 g, 31.47 mmol) in 60 mL dry diethyl ether was added methyl formiate (2.40 g, 39.97 mmol). Then 1-indanone **1** (3.30 g, 24.97 mmol) dissolved in diethyl ether was added by portions, and the reaction mixture was stirred for 2 h at room temperature. Afterwards, the mixture was poured into 100 mL ice water, and diethyl ether was removed by air. The remaining aqueous solution was neutralized with diluted acetic acid and extracted three times with diethyl ether (45 mL). The organic layer was then dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was recrystallized from ethanol/water to give **2** as a pile yellow powder (mp 125 °C) in 58% yield.

4.2. 2-Dimethylaminomethylene-1-indanone (3)

Compound **3** was prepared according to the method prescribed by Wagner and Lutz.[13]

4.3. General procedures for the preparation of the secondary aminomethyleneindanones (4)

4.3.1. Route A. To a stirred solution of 2-hydroxymethylene-1-indanone **2** in chloroform were added the appropriate amine and catalytic amounts of *p*-toluenesulfonic acid. The mixture was refluxed for 1 h. After cooling, the solvent was removed in vacuo and the residue was recrystallized. In this manner the aminomethyleneindanones **4a-u** were obtained.

4.3.2. Route B. To a stirred solution of 2-dimethylaminomethylene-1-indanone **3** in ethanol were added the appropriate amine and catalytic amounts of *p*-toluenesulfonic acid. The mixture was refluxed for 4 h. After cooling, the reaction mixture was concentrated in vacuo and put for 10 h into the refrigerator. The precipitate formed was then filtered and recrystallized. In this manner the aminomethyleneindanones **4a-n** were obtained.

Compound data of the aminomethyleneindanones **4** are listed in Table 2.

4.4. General procedure for the preparation of the 2-hydroxy-5*H*-benzo[*b*]carbazole-6,11-diones (6)

To a stirred solution of the appropriate aminomethyleneindanone **4** in glacial acetic acid was added

Table 2. Compound data of the aminomethyleneindanones **4**[a]

Compound	Method	Yield	Mp[b]	Mol. weight		Anal. Calcd for	Found
4a	A/B	89%/81%	200[c]	173.21	$C_{11}H_{11}NO$	C: 76.28, H: 6.40, N: 8.09	C: 76.24, H: 6.38, N: 8.16
4b	A/B	89%/79%	119	187.24	$C_{12}H_{13}NO$	C: 76.98, H: 7.00, N: 7.48	C: 77.09, H: 6.90, N: 7.47
4c	A/B	94%/77%	133[d]	249.31	$C_{17}H_{15}NO$	C: 81.90, H: 6.06, N: 5.62	C: 81.74, H: 6.18, N: 5.54
4d	A/B	96%/67%	115	279.33	$C_{18}H_{17}NO_2$	C: 77.40, H: 6.13, N: 5.01	C: 77.19, H: 6.22, N: 5.01
4e	A/B	98%/68%	127	279.33	$C_{18}H_{17}NO_2$	C: 77.40, H: 6.13, N: 5.01	C: 77.16, H: 6.12, N: 4.96
4f	A/B	96%/74%	140	309.36	$C_{19}H_{19}NO_3$	C: 73.77, H: 6.19, N: 4.53	C: 73.63, H: 6.30, N: 4.43
4g	A/B	97%/78%	141	263.33	$C_{18}H_{17}NO$	C: 82.10, H: 6.51, N: 5.32	C: 82.08, H: 6.70, N: 5.18
4h	A/B	94%/68%	161	283.76	$C_{17}H_{14}NO_2Cl$	C: 71.96, H: 4.97, N: 4.94	C: 71.87, H: 4.73, N: 4.86
4i	A/B	68%/68%	168	317.21	$C_{17}H_{12}NO_2Cl_2$	C: 64.37, H: 3.81, N: 4.41	C: 64.15, H: 3.98, N: 4.33
4k	A/B	93%/68%	141	263.33	$C_{18}H_{17}NO$	C: 82.10, H: 6.51, N: 5.32	C: 82.19, H: 6.64, N: 5.25
4l	A/B	81%/73%	124	323.40	$C_{20}H_{21}NO_3$	C: 74.28, H: 6.55, N: 4.33	C: 73.98, H: 6.51, N: 4.34
4m	A/B	92%/66%	130	277.36	$C_{19}H_{19}NO$	C: 82.28, H: 6.90, N: 5.05	C: 82.08, H: 7.04, N: 5.04
4n	A/B	66%/49%	128	250.29	$C_{16}H_{14}N_2O$	C: 76.78, H: 5.64, N: 11.19	C: 76.50, H: 5.65, N: 11.03
4o	A	94%	227	235.28	$C_{16}H_{13}NO$	C: 81.68, H: 5.57, N: 5.95	C: 81.74, H: 5.74, N: 5.86
4p	A	97%	205	265.31	$C_{17}H_{15}NO$	C: 76.96, H: 5.70, N: 5.28	C: 76.94, H: 5.28, N: 5.02
4q	A	86%	224	341.40	$C_{23}H_{19}NO_2$	C: 80.92, H: 5.61, N: 4.10	C: 80.79, H: 5.56, N: 4.04
4r	A	67%	226	269.73	$C_{16}H_{12}NOCl$	C: 71.25, H: 4.48, N: 5.19	C: 69.74, H: 4.35, N: 5.10
4s	A	82%	273	277.32	$C_{18}H_{15}NO_2$	C: 77.96, H: 5.45, N: 5.05	C: 78.14, H: 5.51, N: 5.05
4t	A	94%	254	260.30	$C_{17}H_{12}N_2O$	C: 78.44, H: 4.65, N: 10.76	C: 78.24, H: 4.58, N: 10.61
4u	A	89%	291	280.28	$C_{16}H_{12}N_2O_3$	C: 68.57, H: 4.32, N: 9.99	C: 68.32, H: 4.27, N: 9.84

[a] Additional MS, IR and NMR data are available.
[b] Melting points are in °C and uncorrected.
[c] Ref. 7: 195 °C.
[d] Ref. 7: 118 °C.

1,4-benzoquinone **5a** by portions. The reaction mixture was stirred for 16 h at room temperature, then filtered and the precipitate was recrystallized.

4.4.1. 5-Benzyl-2-hydroxy-5*H*-benzo[*b*]carbazole-6,11-dione (6c). 1000 mg (4.01 mmol) **4c**, 1550 mg (14.34 mmol) **5a**, 8 mL acetic acid, 430 mg (30%), mp 298 °C (red powder from toluene), ^{1}H NMR and MS data were consistent with the reference spectra,[7] Anal. Calcd for $C_{23}H_{15}NO_3$ (353.38): C, 78.17; H, 4.28; N, 3.96. Found: C, 78.40; H, 4.40; N, 4.23.

4.4.2. 2-Hydroxy-5-(2-metoxybenzyl)-5*H*-benzo[*b*]carbazole-6,11-dione (6d). 1100 mg (3.94 mmol) **4d**, 1520 mg (14.06 mmol) **5a**, 8 mL acetic acid, 410 mg (31%), mp 289 °C (red powder from toluene), ^{1}H NMR (DMSO-d_6) δ 9.72 (s, 1H, OH-2), 8.13–8.02 (m, 2H, H-7, H-10), 7.89–7.75 (m, 2H, H-8, H-9), 7.67 (d, J = 2.2 Hz, 1H, H-1), 7.43 (d, J = 9.0 Hz, 1H, H-4), 7.30–7.13 (m, 1H, H-4′), 7.07 ('d', 1H, H-6′), 6.97 (dd, J = 2.2 Hz, J = 9.0 Hz, 1H, H-3), 6.74 ('t', 1H, H-5′), 6.44 ('d', 1H, H-3′), 5.92 (s, 2H, N–CH_2), 3.90 (s, 3H, OCH_3), MS (EI) m/z 383 (M^+), Anal. Calcd for $C_{24}H_{17}NO_4$ (383.40): C, 75.19; H, 4.47; N, 3.65. Found: C, 74.96; H, 4.56; N, 3.64.

4.4.3. 2-Hydroxy-5-(3,5-dimethoxymetoxybenzyl)-5*H*-benzo[*b*]carbazole-6,11-dione (6f). 2200 mg (7.11 mmol) **4f**, 2910 mg (26.92 mmol) **5a**, 15 mL acetic acid, 920 mg (31%), mp 308 °C (red powder from toluene), ^{1}H NMR (DMSO-d_6) δ 9.74 (s, 1H, OH-2), 8.12–8.05 (m, 2H, H-7, H-10), 7.89–7.79 (m, 2H, H-8, H-9), 7.66 (d, J = 2.3 Hz, 1H, H-1), 7.57 (d, J = 9.1 Hz, 1H, H-4), 7.00 (dd, J = 2.3 Hz, J = 9.1 Hz, 1H, H-3), 6.39 (d, J = 2.2 Hz, 1H, H-4′), 6.33 (d, J = 2.2 Hz, 2H, H-2′, H-6′), 5.90 (s, 2H, N–CH_2), 3.66 (s, 6H, 2 × OCH_3), MS (EI) m/z 413 (M^+), Anal. Calcd for $C_{25}H_{19}NO_5$ (413.42): C, 72.63; H, 4.63; N, 3.39. Found: C, 72.64; H, 4.86; N, 3.21.

4.4.4. 2-Hydroxy-5-(3-methylbenzyl)-5*H*-benzo[*b*]carbazole-6,11-dione (6g). 1150 mg (4.37 mmol) **4g**, 1890 mg (17.49 mmol) **5a**, 8 mL acetic acid, 350 mg (23%), mp 291 °C (red powder from toluene), ^{1}H NMR (DMSO-d_6) δ 9.73 (s, 1H, OH-2), 8.13–8.07 (m, 2H, H-7, H-10), 7.89–7,80 (m, 2H, H-8, H-9), 7.67 (d, J = 2.3 Hz, 1H, H-1), 7.58 (d, J = 9.1 Hz, 1H, H-4), 7.16 (dd, J = 2.3 Hz, J = 9.1 Hz, 1H, H-3), 7.09–6.95 (m, 4H, H-2′, H-4′, H-5′ and H-6′), 5.95 (s, 2H, N–CH_2), 2.23 (s, 3H, CH_3), MS (EI) m/z 367 (M^+), Anal. Calcd for $C_{24}H_{17}NO_3$ (367.40): C, 78.46; H, 4.66; N, 3.81. Found: C, 78.07; H, 4.98; N, 3.71.

4.4.5. 5-(2-Chlorobenzyl)-2-hydroxy-5*H*-benzo[*b*]carbazole-6,11-dione (6h). 340 mg (1.20 mmol) **4h**, 420 mg (3.89 mmol) **5a**, 5 mL acetic acid, 80 mg (18%), mp 293 °C (red powder from ethanol), ^{1}H NMR (DMSO-d_6) δ 9.77 (s, 1H, OH-2), 8.14–8.00 (m, 2H, H-7, H-10), 7.89–7.73 (m, 2H, H-8, H-9), 7.71 (d, J = 2.1 Hz, 1H, H-1), 7.59–7.55 (m, 1H, H-3′), 7.51 (d, J = 9.1 Hz, 1H, H-4), 7.33–7.29 (m, 2H, H-4′, H-5′), 7.01 (dd, J = 2.1 Hz, J = 9.1 Hz, 1H, H-3), 6.40 ('d', 1H, H-6′), 6.03 (s, 2H, N–CH_2), MS (EI) m/z 387 (M^+), Anal. Calcd for $C_{23}H_{14}NO_3Cl$ (387.83): C, 71.23; H, 3.64; N, 3.61. Found: C, 71.26; H, 3.47; N, 3.49.

4.4.6. 5-(2,4-Dichlorobenzyl)-2-hydroxy-5*H*-benzo[*b*]carbazole-6,11-dione (6i). 940 mg (2.95 mmol) **4i**, 1200 mg (11.10 mmol) **5a**, 10 mL acetic acid, 365 mg (29%), mp 337 °C (red powder from ethanol), ^{1}H NMR (DMSO-d_6) δ 9.78 (s, 1H, OH-2), 8.13–8.08 (m, 2H, H-7, H-10), 7.88–7.78 (m, 2H, H-8, H-9), 7.75 (d, J = 2.1 Hz, 1H, H-3′), 7.69 (d, J = 2.3 Hz, 1H, H-1), 7.52 (d, J = 9.1 Hz, 1H, H-4), 7.20 (dd, J = 2.1 Hz, J = 8.5 Hz, 1H, H-5′), 7.01 (dd, J = 2.3 Hz, J = 9.1 Hz, 1H, H-3), 6.40 (d, J = 8.5 Hz, 1H, H-6′), 5.97 (s, 2H, N–CH_2), MS (EI) m/z 422 (M^+), Anal. Calcd. for $C_{23}H_{13}NO_3Cl_2$ (422.26): C, 65.42; H, 3.10; N, 3.22. Found: C, 65.24; H, 3.10; N, 3.18.

4.4.7. 2-Hydroxy-5-(2-phenethyl)-5*H*-benzo[*b*]carbazole-6,11-dione (6k). 1140 mg (4.33 mmol) **4k**, 1560 mg (14.43 mmol) **5a**, 4 mL acetic acid, 370 mg (23%), mp 216 °C (red powder from toluene), ^{1}H NMR (DMSO-d_6) δ 9.64 (s, 1H, OH-2), 8.10–8.06 (m, 2H, H-7, H-10), 7.86–7.79 (m, 2H, H-8, H-9), 7.62 (d, J = 2.1 Hz, 1H, H-1), 7.54 (d, J = 9.1 Hz, 1H, H-4), 7.36–7.16 (m, 5H, aromat. H's), 6.96 (dd, J = 2.1 Hz, J = 9.1 Hz, 1H, H-3), 4.88–4.78 (m, 2H, N–CH_2–CH_2), 3.10–3.04 (m, 2H, N–CH_2–CH_2), MS (EI) m/z 367 (M^+), Anal. Calcd for $C_{24}H_{17}NO_3$ (367.40): C, 78.46; H, 4.66; N, 3.81. Found: C, 78.44; H, 4.59; N, 3.67.

4.4.8. 2-Hydroxy-5-(3-phenylpropyl)-5*H*-benzo[*b*]carbazole-6,11-dione (6m). 600 mg (2.16 mmol) **4m**, 900 mg (8.33 mmol) **5a**, 4 mL acetic acid, 170 mg (20%), mp 227 °C (red powder from toluene), ^{1}H NMR (DMSO-d_6) δ 9.62 (s, 1H, OH-2), 8.10–8.03 (m, 2H, H-7, H-10), 7.88–7.72 (m, 2H, H-8, H-9), 7.63 (d, J = 2.2 Hz, 1H, H-1), 7.56 (d, J = 9.1 Hz, 1H, H-4), 7.33–7.06 (m, 5H, aromat. H's), 7.01 (dd, J = 2.2 Hz, J = 9.1 Hz, 1H, H-3), 4.71 (t, 2H, N–CH_2–CH_2–CH_2), 2.69 (t, 2H, N–CH_2–CH_2–CH_2), 2.23–2.03 (m, 2H, N–CH_2–CH_2–CH_2), MS (EI) m/z 381 (M^+), Anal. Calcd for $C_{25}H_{19}NO_3$ (381.43): C, 78.72; H, 5.02; N, 3.67. Found: C, 78.46; H, 5.11; N, 3.43.

4.4.9. 2-Hydroxy-5-(4-metoxyphenyl)-5*H*-benzo[*b*]carbazole-6,11-dione (6p). 1100 mg (4.15 mmol) **4p**, 1600 mg (14.80 mmol) **5a**, 12 mL acetic acid, 325 mg (21%), mp 335 °C (red powder from ethanol), ^{1}H NMR (DMSO-d_6) δ 9.70 (s, 1H, OH-2), 8.14–8.09 (m, 1H, H-10), 7.98–7.93 (m, 1H, H-7), 7.88–7.74 (m, 2H, H-8, H-9), 7.70 (s, br s, 1H, H-1), 7.49–7.43 (m, 2H, H-2′, H-6′), 7.18–7.10 (m, 2H, H-3′, H-5′), 7.04–6.94 (m, 2H, H-3, H-4), 3.89 (s, 3H, OCH_3); MS (EI) m/z 369 (M^+), Anal. Calcd for $C_{23}H_{15}NO_4$ (369.38): C, 74.79; H, 4.09; N, 3.79. Found: C, 74.40; H, 4.09; N, 3.49.

4.4.10. 5-(2-Benzyloxyphenyl)-2-hydroxy-5*H*-benzo[*b*]-carbazole-6,11-dione (6q). 2200 mg (7.11 mmol) **4q**, 2910 mg (26.92 mmol) **5a**, 15 mL acetic acid, 920 mg (31%), mp 281 °C (red powder from toluene), ^{1}H NMR (DMSO-d_6) δ 9.74 (s, 1H, OH-2), 8.20–8.10 (m, 1H, H-10), 7.98–7.94 (m, 1H, H-7), 7.88–7.79 (m, 2H,

H-8, H-9), 7.66 (s, br s, 1H, H-1), 7.61–7.33 (m, 7H, aromat. H's), 7.24–7.20 (m, 2H, H-3′, H-5′), 7.05–6.96 (m, 2H, H-3, H-4), 5.22 (s, 2H, –CH_2–); MS (EI) *m/z* 446 (M^++1), Anal. Calcd for $C_{29}H_{19}NO_4$ (445.48): C, 78.19; H, 4.30; N, 3.14. Found: C, 78.24; H, 4.66; N, 3.41.

4.5. General procedure for the preparation of the 5*H*-benzo[*b*]carbazole-2,6-diols (7)

To a stirred solution of the appropriate aminomethyleneindanone **4** in glacial acetic acid was added 1,4-benzoquinone **5a** by portions. The reaction mixture was stirred for 30 min at room temperature under argon atmosphere, then filtered and the precipitate was washed with ethanol and recrystallized.

4.5.1. 5-(4-Methoxyphenyl)-5*H*-benzo[*b*]carbazole-2,6-diol (7p). 420 mg (1.58 mmol) **4p**, 180 mg (1.67 mmol) **5a**, 5 mL acetic acid, 320 mg (56%), mp 159 °C (yellow powder from acetone), ^{1}H NMR (DMSO-d_6) (after 24 h in solution: 6-hydroxyl tautomer) δ 9.18 and 9.05 (2 × s, 2 × 1H, OH-2, OH-6), 8.23 (s, 1H, H-11), 8.21–8.16 (m, 1H, H-7 or H-10), 8.04–7.99 (m, 1H, H-7 or H-10), 7.60 (d, J = 1.1 Hz, 1H, H-1), 7.42–7.38 (m, 2H, H-2′, H-6′), 7.36–7.31 (m, 2H, H-8, H-9), 7.12–7.06 (H-3′, H-5′), 6.97 (d, J = 9.1 Hz, 1H, H-4), 6.91 (dd, J = 1.1, J = 9.1 Hz, 1H, H-3), 3.86 (s, 3H, OCH_3), MS (EI) *m/z* 355 (M^+), Anal. Calcd for $C_{23}H_{17}NO_3$ (355.39): C, 77.73; H, 4.82; N, 3.94. Found: C, 77.33; H, 4.98; N, 3.71.

4.5.2. 5-(4-Benzyloxyphenyl)-5*H*-benzo[*b*]carbazole-2,6-diol (7q). 1000 mg (2.93 mmol) **4q**, 330 mg (3.05 mmol) **5a**, 7 mL acetic acid, 320 mg (56%), mp 188 °C (yellow powder from acetone), ^{1}H NMR (DMSO-d_6) (after 24 h in solution: 6-hydroxyl tautomer) δ 9.16 and 9.06 (2 × s, 2 × 1H, OH-2, OH-6), 8.23 (s, 1H, H-11), 8.20–8.16 (m, 1H, H-7 or H-10), 8.04–7.99 (m, 1H, H-7 or H-10), 7.60 (d, J = 1.1 Hz, 1H, H-1), 7.42–7.38 (m, 2H, H-2′, H-6′), 7.56–7.30 (m, 9H, aromat. H's), 7.19–7.14 (m, 2H, H-3′, H-5′),6.97–6.89 (m, 2H, H-3, H-4), 5.20 (s, 2H, –CH_2–), MS (EI) *m/z* 431 (M^+), Anal. Calcd for $C_{29}H_{21}NO_3$ (431.49): C, 80.72; H, 4.91; N, 3.25. Found: C, 80.16; H, 5.13; N, 3.24.

4.6. General procedure for the preparation of the methyl 2,6-dihydroxy-5*H*-benzo[*b*]carbazole-1-carboxylates (8)

To a stirred solution of the appropriate aminomethyleneindanone **4** in glacial acetic acid was added 2-methoxycarbonyl-1,4-benzoquinone **5b** by portions. The reaction mixture was stirred for 15 min at room temperature, then filtered and the precipitate was washed with isopropanol and recrystallized.

4.6.1. Methyl 2,6-dihydroxy-5-methyl-5*H*-benzo[*b*]carbazole-1-carboxylate (8a). 220 mg (1.27 mmol) **4a**, 270 mg (1.63 mmol) **5b**, 4 mL acetic acid, 265 mg (65%), mp 188 °C (yellow powder from acetone), ^{1}H NMR (DMSO-d_6) (after 24 h in solution: 6-hydroxyl tautomer) δ 9.59 and 9.49 (2 × s, 2 × 1H, OH-2, OH-6), 8.29 ('d', 1H, H-7), 7.99 ('d', 1H, H-10), 7.87 (s, 1H, H-11), 7.52 (d, J = 8.9 Hz, 1H, H-4), 7.47–7.29 (m, 2H, H-8, H-9), 7.17 (d, J = 8.9 Hz, 1H, H-3), 4.19 (s, 3H, N–CH_3), 4.08 (s, 3H, $COOCH_3$), MS (EI) *m/z* 321 (M^+), Anal. Calcd for $C_{19}H_{15}NO_4$ (321.33): C, 71.02; H, 4.71; N, 4.36. Found: C, 71.30; H, 4.68; N, 4.15.

4.6.2. Methyl 5-ethyl-2,6-dihydroxy-5*H*-benzo[*b*]carbazole-1-carboxylate (8b). 120 mg (0.64 mmol) **4b**, 110 mg (0.66 mmol) **5b**, 1 mL acetic acid, 125 mg (58%), mp 172 °C (yellow powder from toluene), ^{1}H NMR (DMSO-d_6) (after 24 h in solution: 6-hydroxyl tautomer) δ 9.57 and 9.54 (2 × s, 2 × 1H, OH-2, OH-6), 8.29 ('d', 1H, H-7), 7.99 ('d', 1H, H-10), 7.85 (s, 1H, H-11), 7.52 (d, J = 8.9 Hz, 1H, H-4), 7.49–7.29 (m, 2H, H-8, H-9), 7.15 (d, J = 8.9 Hz, 1H, H-3), 4.77 (quart., J = 6.8 Hz, 2H, N-CH_2–CH_3), 4.07 (s, 3H, $COOCH_3$), 1.30 (t, J = 6.8 Hz, 3H, N–CH_2–CH_3), MS (EI) *m/z* 335 (M^+), Anal. Calcd for $C_{20}H_{17}NO_4$ (335.36): C, 71.63; H, 5.11; N, 4.18. Found: C, 71.64; H, 5.22; N, 4.03.

4.6.3. Methyl 5-benzyl-2,6-dihydroxy-5*H*-benzo[*b*]carbazole-1-carboxylate (8c). 190 mg (0.76 mmol) **4c**, 140 mg (0.84 mmol) **5b**, 2 mL acetic acid, 190 mg (63%), mp 234 °C (yellow powder from toluene), ^{1}H NMR (DMSO-d_6) (after 24 h in solution: 6-hydroxyl tautomer) δ 9.63 and 9.54 (2 × s, 2 × 1H, OH-2, OH-6), 8.27 ('d', 1H, H-7), 8.00 ('d', 1H, H-10), 7.88 (s, 1H, H-11), 7.50 (d, J = 8.6 Hz, 1H, H-4), 7.43–7.30 (m, 2H, H-8, H-9), 7.27–7.11 (m, 5H, aromat. H's), 7.09 (d, J = 8.6 Hz, 1H, H-3), 6.03 (s, 2H, N–CH_2), 4.07 (s, 3H, $COOCH_3$), MS (EI) *m/z* 397 (M^+), Anal. Calcd for $C_{25}H_{19}NO_4$ (397.43): C, 75.55; H, 4.82; N, 3.52. Found: C, 75.30; H, 4.83; N, 3.31.

4.6.4. Methyl 2,6-dihydroxy-5-(2-methoxybenzyl)-5*H*-benzo[*b*]carbazole-1-carboxylate (8d). 600 mg (2.15 mmol) **4d**, 400 mg (2.41 mmol) **5b**, 8 mL acetic acid, 610 mg (67%), mp 210 °C (yellow powder from toluene), ^{1}H NMR (DMSO-d_6) (directly after dissolving: 6-keto tautomer) δ 10.05 (s, 1H, OH-2), 8.14 ('d', 1H, H-7), 7.73–7.62 (m, 2H, H-8, H-9), 7.55–7.46 (m, 2H, H-4, H-10), 7.22–7.02 (m, 3H, H-3, H-4′ and H-6′), 6.66 (m, 1H, H-5′), 6.10 ('d', 1H, H-3′), 5.99 (s, 2H, N–CH_2), 4.38 (s, 2H, CH_2-11), 4.05 (s, 3H, $COOCH_3$), 3.92 (s, 3H, OCH_3) MS (EI) *m/z* 427 (M^+), Anal. Calcd for $C_{26}H_{21}NO_5$ (427.45): C, 73.06; H, 4.95; N, 3.28. Found: C, 73.21; H, 5.08; N, 3.28.

4.6.5. Methyl 2,6-dihydroxy-5-(4-methoxybenzyl)-5*H*-benzo[*b*]carbazole-1-carboxylate (8e). 170 mg (0.61 mmol) **4e**, 110 mg (0.66 mmol) **5b**, 2 mL acetic acid, 145 mg (56%), mp 200 °C (yellow powder from toluene), ^{1}H NMR (DMSO-d_6) (after 24 h in solution: 6-hydroxyl tautomer) δ 9.63 and 9.51 (2 × s, 2 × 1H, OH-2, OH-6), 8.29 ('d', 1H, H-7), 7.98 ('d', 1H, H-10), 7.88 (s, 1H, H-11), 7.50 (d, J = 8.6 Hz, 1H, H-4), 7.43–7.30 (m, 2H, H-8, H-9), 7.27–7.11 (m, 5H, aromat. H's), 7.09 (d, J = 8.6 Hz, 1H, H-3), 7.09–7.05 (m, 2H, H-2′, H-6′), 6.82–6.78 (m, 2H, H-3′, H-5′), 5.94 (s, 2H, N–CH_2), 4.07 (s, 3H, $COOCH_3$), 3.63 (s, 3H, OCH3), MS (EI) *m/z* 427 (M^+), Anal. Calcd for $C_{26}H_{21}NO_5$ (427.26): C, 73.06; H, 4.95; N, 3.28. Found: C, 73.25; H, 5.08; N, 3.18.

4.6.6. Methyl 2,6-dihydroxy-5-(3,5-dimethoxybenzyl)-5*H*-benzo[*b*]carbazole-1-carboxylate (8f). 400 mg (1.29 mmol) **4f**, 250 mg (1.51 mmol) **5b**, 5 mL acetic acid, 395 mg (67%), mp 218 °C (yellow powder from toluene), ^{1}H NMR (DMSO-d_6) (after 24 h in solution: 6-hydroxyl tautomer) δ 9.68 and 9.60 (2 × s, 2 × 1H, OH-2, OH-6), 8.21 ('d', 1H, H-7), 8.01 ('d', 1H, H-10), 7.88 (s, 1H, H-11), 7.50 (d, J = 8.9 Hz, 1H, H-4), 7.44–7.31 (m, 2H, H-8, H-9), 7.10 (d, J = 8.9 Hz, 1H, H-3), 6.31 (d, J = 2.1 Hz, 1H, H-4′), 6.26 (d, J = 2.1 Hz, 2H, H-2′, H-6′), 5.94 (s, 2H, N–CH_2), 4.08 (s, 3H, $COOCH_3$), 3.60 (s, 6H, 2 × OCH_3); MS (EI) m/z 457 (M^+), Anal. Calcd for $C_{27}H_{23}NO_6$ (457.48): C, 70.89; H, 5.07; N, 3.06. Found: C, 70.83; H, 5.13; N, 3.01.

4.6.7. Methyl 2,6-dihydroxy-5-(3-methylbenzyl)-5*H*-benzo[*b*]carbazole-1-carboxylate (8g). 110 mg (0.42 mmol) **4g**, 90 mg (0.54 mmol) **5b**, 3 mL acetic acid, 115 mg (67%), mp 191 °C (yellow crystals from toluene), ^{1}H NMR (DMSO-d_6) (directly after dissolving: 6-keto tautomer) δ 10.05 (s, 1H, OH-2), 8.19 ('d', 1H, H-7), 7.70–7.65 (m, 3H, H,4, H-8 and H-9), 7.55–7.47 (m, 1H, H-10), 7.16–7.08 (m, 2H, H-3, H-5′), 7.02–6.97 (m, 2H, H-2′, H-4′), 6.79 ('d', 1H, H-6′), 6.01 (s, 2H, N–CH_2), 4.35 (s, 2H, CH_2-11), 4.04 (s, 3H, $COOCH_3$), 2.20 (s, 3H, CH_3) MS (EI) m/z 411 (M^+), Anal. Calcd for $C_{26}H_{21}NO_4$ (411.46): C, 75.90; H, 5.14; N, 3.40. Found: C, 75.76; H, 5.40; N, 3.33.

4.6.8. Methyl 5-(2-chlorobenzyl)-2,6-dihydroxy-5*H*-benzo-[*b*]carbazole-1-carboxylate (8h). 400 mg (1.41 mmol) **4h**, 300 mg (1.81 mmol) **5b**, 2 mL acetic acid, 380 mg (62%), mp 192 °C (yellow powder from toluene), ^{1}H NMR (DMSO-d_6) (after 24 h in solution: 6-hydroxyl tautomer) δ 9.65 and 9.59 (2 × s, 2 × 1H, OH-2, OH-6), 8.22–8.18 (m, 1H, H-7), 8.04–8.00 (m, 1H, H-10), 7.91 (s, 1H, H-11), 7.55–7.51 (m, 1H, H-3′), 7.44–7.30 (m, 3H, H-4, H-8 and H-9), 7.26–7.18 (m, 1H, H-5′), 7.15–6.99 (m, 2H, H-3, H-4′), 6.20 ('d', 1H, H-6′), 6.09 (s, 2H, N–CH_2), 4.10 (s, 3H, $COOCH_3$), MS (EI) m/z 431 (M^+), Anal. Calcd for $C_{25}H_{28}NO_4Cl$ (431.88): C, 69.53; H, 4.20; N, 3.24. Found: C, 69.34; H, 4.13; N, 3.21.

4.6.9. Methyl 5-(2,4-dichlorobenzyl)-2,6-dihydroxy-5*H*-benzo[*b*]carbazole-1-carboxylate (8i). 500 mg (1.57 mmol) **4i**, 300 mg (1.81 mmol) **5b**, 8 mL acetic acid, 465 mg (64%), mp 230 °C (yellow powder from toluene), ^{1}H NMR (pyridine-d_5) δ ~11.80 ('s', br s, 2H, OH-2, OH-6), 8.79–8.72 (m, 2H, H-7, H-10), 8.24–8.20 (m, 1H, H-10), 6.86 (dd, J = 2.1 Hz, J = 8.3 Hz, 1H, H-5′), 6.57 (d, J = 8.3 Hz, 1H, H-6′), 6.31 (s, 2H, N–CH_2), 4.26 (s, 3H, $COOCH_3$), MS (EI) m/z 466 (M^+), Anal. Calcd for $C_{25}H_{17}NO_4Cl_2$ (466.32): C, 64.39; H, 3.67; N, 3.00. Found: C, 64.64; H, 3.67; N, 3.25.

4.6.10. Methyl 2,6-dihydroxy-5-(2-phenethyl)-5*H*-benzo-[*b*]carbazole-1-carboxylate (8k). 340 mg (1.29 mmol) **4k**, 300 mg (1.81 mmol) **5b**, 3 mL acetic acid, 360 mg (68%), mp 185 °C (yellow needles from acetone), ^{1}H NMR (DMSO-d_6) (after 24 h in solution: 6-hydroxyl tautomer) δ 9.64 and 9.56 (2 × s, 2 × 1H, OH-2, OH-6), 8.34 ('d', 1H, H-7), 8.00 ('d', 1H, H-10), 7.85 (s, 1H, H-11), 7.54 (d, J = 8.9 Hz, 1H, H-4), 7.49–7.19 (m, 7H, aromat. H's), 7.12 (d, J = 8.9 Hz, 1H, H-3), 4.89 (t, J = 7.7 Hz, 2H, N-CH_2–CH_2), 4.08 (s, 3H, $COOCH_3$), 3.03 (t, J = 7.7 Hz, 2H, N–CH_2–CH_2), MS (EI) m/z 411 (M^+), Anal. Calcd for $C_{26}H_{21}NO_4$ (411.45): C, 75.90; H, 5.14; N, 3.40. Found: C, 75.72; H, 5.06; N, 3.47.

4.6.11. Methyl 2,6-dihydroxy-5-[2-(3,4-dimethoxyphenyl)ethyl]-5*H*-benzo[*b*]carbazole-1-carboxylate (8l). 770 mg (2.38 mmol) **4l**, 500 mg (3.01 mmol) **5b**, 2 mL acetic acid, 715 mg (64%), mp 155 °C (yellow needles from acetone), ^{1}H NMR (DMSO-d_6) (after 24 h in solution: 6-hydroxyl tautomer) δ 9.62 and 9.55 (2 × s, 2 × 1H, OH-2, OH-6), 8.33 ('d', 1H, H-7), 8.00 ('d', 1H, H-10), 7.87 (s, 1H, H-11), 7.53 (d, J = 8.8 Hz, 1H, H-4), 7.53–7.35 (m, 2H, H-8, H-9), 7.10 (d, J = 8.8 Hz, 1H, H-3), 6.85–6.78 (m, 3H, H-2′, H-5′ and H-6′), 4.87 (t, 2H, N-CH_2–CH_2), 4.07 (s, 3H, $COOCH_3$), 3.69 (s, 6H, 2 × OCH_3), 2.97 (t, 2H, N–CH_2–CH_2) MS (EI) m/z 471 (M^+), Anal. Calcd for $C_{28}H_{25}NO_6$ (471.51): C, 71.33; H, 5.34; N, 2.97. Found: C, 71.13; H, 5.38; N, 2.97.

4.6.12. Methyl 2,6-dihydroxy-5-(3-phenylpropyl)-5*H*-benzo[*b*]carbazole-1-carboxylate (8m). 700 mg (2.52 mmol) **4m**, 450 mg (2.71 mmol) **5b**, 7 mL acetic acid, 725 mg (68%), mp 162 °C (yellow powder from toluene), ^{1}H NMR (DMSO-d_6) (directly after dissolving: 6-hydroxyl tautomer) δ 9.53 and 9.49 (2 × s, 2 × 1H, OH-2, OH-6), 8.29 ('d', 1H, H-7), 7.98 ('d', 1H, H-10), 7.87 (s, 1H, H-11), 7.47 (d, J = 9.1 Hz, 1H, H-4), 7.43–7.18 (m, 7H, aromat. H's), 7.13 (d, J = 9.1 Hz, 1H, H-3), 4.80–4.73 (m, 2H, N–CH_2–CH_2–CH_2), 4.07 (s, 3H, $COOCH_3$), 2.70–2.62 (m, 2H, N–CH_2–CH_2–CH_2), 2.16–2.01 (m, 2H, N–CH_2–CH_2–CH_2) MS (EI) m/z 425 (M^+), Anal. Calcd for $C_{27}H_{23}NO_4$ (425.49): C, 76.22; H, 5.45; N, 3.29. Found: C, 76.37; H, 5.62; N, 3.17.

4.6.13. Methyl 2,6-dihydroxy-5-pyridine-2-ylmethyl-5*H*-benzo[*b*]carbazole-1-carboxylate (8n). 370 mg (1.48 mmol) **4n**, 260 mg (1.57 mmol) **5b**, 4 mL acetic acid, 355 mg (60%), mp 185 °C (yellow powder from isopropanol), ^{1}H NMR (DMSO-d_6) (directly after dissolving: 6-hydroxyl tautomer) δ 10.32 and 9.58 (2 × s, 2 × 1H, OH-2, OH-6), 8.56–8.53 (m, 1H, H-3′), 8.29 ('d', 1H, H-7), 8.00 ('d', 1H, H-10), 7.88 (s, 1H, H-11), 7.71 ('dt', 1H, H-5′), 7.57 (d, J = 8.6 Hz, 1H, H-4), 7.47–7.24 (m, 3H, H-8, H-9 and H-4′), 7.11 (d, J = 8.6 Hz, 1H, H-3), 7.08 ('d', 1H, H-6′), 6.03 (s, 2H, N–CH_2), 4.08 (s, 3H, $COOCH_3$), MS (EI) m/z 398 (M^+), Anal. Calcd for $C_{24}H_{18}N_2O_4$ (425.49): C, 72.35; H, 4.55; N, 7.03. Found: C, 72.15; H, 4.67; N, 6.82.

4.6.14. Methyl 2,6-dihydroxy-5-(4-methoxyphenyl)-5*H*-benzo[*b*]carbazole-1-carboxylate (8p). 420 mg (1.58 mmol) **4p**, 300 mg (1.81 mmol) **5b**, 8 mL acetic acid, 180 mg (28%), mp 219 °C (green crystals from toluene), ^{1}H NMR (DMSO-d_6) (directly after dissolving: 6-hydroxyl tautomer) δ 9.65 and 9.17 (2 × s, 2 × 1H, OH-2, OH-6), 8.20–8.15 (m, 1H, H-7), 8.04–8.00 (m, 1H, H-10), 7.89 (s, 1H, H-11), 7.42–7.30 (m, 4H, H-8, H-9, H-2′ and H-6′), 7.12–7.05 (m, 4H, H-3, H-4, H-3′ and H-5′), 4.10 (s, 3H, $COOCH_3$), 3.86 (s, 3H, OCH_3), MS

(EI) *m/z* 413 (M^+), Anal. Calcd for $C_{25}H_{19}NO_5$ (413.43): C, 72.63; H, 4.63; N, 3.39. Found: C, 72.42; H, 4.61; N, 3.30.

4.7. General procedure for the preparation of the methyl 2-hydroxy-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylates (9)

The appropriate compound **8** was dissolved in a mixture of acetone 5/NaOH (5% (m/v)). After stirring for 24 h at room temperature in the presence of air, the solution was neutralized with diluted HCl and concentrated in vacuo. The aqueous layer was extracted three times with methylene chloride. Then the organic layer was washed with water, dried over $MgSO_4$ and evaporated to dryness. The residue was recrystallized.

4.7.1. Methyl 2-hydroxy-5-methyl-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (9a). 160 mg (0.50 mmol) **8a**, 124 mg (74%), mp 245 °C (orange needles from isopropanol), ^{1}H NMR (DMSO-d_6) δ 9.99 (s, 1H, OH-2), 8.09–8.03 (m, 2H, H-7, H-10), 7.87–7.78 (m, 2H, H-8, H-9), 7.72 (d, J = 9.1 Hz, 1H, H-4), 7.15 (d, J = 9.1 Hz, 1H, H-3), 4.19 (s, 3H, $COOCH_3$), 3.93 (s, 3H, N–CH_3), MS (EI) *m/z* 335 (M^+), Anal. Calcd for $C_{19}H_{13}NO_5$ (335.31): C, 68.06; H, 3.91; N, 4.18. Found: C, 67.85; H, 4.11; N, 4.18.

4.7.2. Methyl 5-ethyl-2-hydroxy-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (9b). 70 mg (0.21 mmol) **8b**, 58 mg (81%), mp 215 °C (red needles from isopropanol), ^{1}H NMR (DMSO-d_6) δ 10.01 (s, 1H, OH-2), 8.11–8.03 (m, 2H, H-7, H-10), 7.87–7.79 (m, 2H, H-8, H-9), 7.78 (d, J = 9.0 Hz, 1H, H-4), 7.13 (d, J = 9.0 Hz, 1H, H-3), 4.75 (quart, J = 6.9 Hz, 2H, N–CH_2–CH_3), 3.92 (s, 3H, $COOCH_3$), 1.38 (t, J = 6.9 Hz, 3H, N–CH_2–CH_3), MS (EI) *m/z* 349 (M^+), Anal. Calcd for $C_{20}H_{15}NO_5$ (349.35): C, 68.75; H, 4.33; N, 4.01. Found: C, 68.49; H, 4.49; N, 3.96.

4.7.3. Methyl 5-benzyl-2-hydroxy-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (9c). 100 mg (0.25 mmol) **8c**, 80 mg (80%), mp 250 °C (orange needles from ethanol), ^{1}H NMR (DMSO-d_6) δ 9.98 (s, 1H, OH-2), 8.10–8.05 (m, 2H, H-7, H-10), 7.89–7.76 (m, 2H, H-8, H-9), 7.69 (d, J = 9.1 Hz, 1H, H-4), 7.35–7.17 (m, 5H, aromat. H's), 7.13 (d, J = 9.1 Hz, 1H, H-3), 6.04 (s, 2H, N–CH_2), 3.94 (s, 3H, $COOCH_3$), MS (EI) *m/z* 411 (M^+), Anal. Calcd for $C_{25}H_{17}NO_5$ (411.42): C, 72.99; H, 4.16; N, 3.40. Found: C, 72.78; H, 4.22; N, 3.33.

4.7.4. Methyl 2-hydroxy-5-(2-methoxybenzyl)-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (9d). 100 mg (0.23 mmol) **8d**, 82 mg (83%), mp 260 °C (orange needles from ethanol), ^{1}H NMR (DMSO-d_6) δ 9.96 (s, 1H, OH-2), 8.10–8.01 (m, 2H, H-7, H-10), 7.87–7.78 (m, 2H, H-8, H-9), 7.65 (d, J = 9.1 Hz, 1H, H-4), 7.26–7.18 (m, 1H, H-4′), 7.09 (d, J = 9.1 Hz, 1H, H-3), 7.08–7.04 (m, 1H, H-6′), 6.77–6.69 (m, 1H, H-5′), 6.43 ('d', 1H, H-3′), 5.96 (s, 2H, N–CH_2), 3.94 (s, 3H, $COOCH_3$), 3.89 (s, 3H, OCH_3), MS (EI) *m/z* 441 (M^+), Anal. Calcd for $C_{26}H_{19}NO_6$ (441.44): C, 70.74; H, 4.34; N, 3.17. Found: C, 70.49; H, 4.54; N, 3.17.

4.7.5. Methyl 2-hydroxy-5-(4-methoxybenzyl)-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (9e). 100 mg (0.23 mmol) **8e**, 76 mg (74%), mp 211 °C (orange crystals from isopropanol), ^{1}H NMR (DMSO-d_6) δ 10.02 (s, 1H, OH-2), 8.12–8.05 (m, 2H, H-7, H-10), 7.89–7.81 (m, 2H, H-8, H-9), 7.74 (d, J = 9.1 Hz, 1H, H-4), 7.21–7.17 (m, 2H, H-2′, H-6′), 7.14 (d, J = 9.1 Hz, 1H, H-3), 6.87–6.83 (m, 2H, H-3′, H-5′), 5.97 (s, 2H, N–CH_2), 3.93 (s, 3H, $COOCH_3$), 3.68 (s, 3H, OCH_3), MS (EI) *m/z* 441 (M^+), Anal. Calcd for $C_{26}H_{19}NO_6$ (441.44): C, 70.74; H, 4.34; N, 3.17. Found: C, 70.46; H, 4.43; N, 3.10.

4.7.6. Methyl 2-hydroxy-5-(3,5-dimethoxybenzyl)-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (9f). 50 mg (0.11 mmol) **8f**, 35 mg (64%), mp 178 °C (orange powder from toluene), ^{1}H NMR (DMSO-d_6) 10.02 (s, 1H, OH-2), 8.10–8.05 (m, 2H, H-7, H-10), 7.88–7.80 (m, 2H, H-8, H-9), 7.67 (d, J = 9.1 Hz, 1H, H-4), 7.14 (d, J = 9.1 Hz, 1H, H-3), 6.39 (d, J = 2.1 Hz, 1H, H-4′), 6.32 (d, J = 2.1 Hz, 2H, H-2′, H-6′), 5.96 (s, 2H, N–CH_2), 3.93 (s, 3H, $COOCH_3$), 3.66 (s, 6H, 2 × OCH_3); MS (EI) *m/z* 471 (M^+), Anal. Calcd for $C_{27}H_{21}NO_7$ (471.47): C, 68.78; H, 4.49; N, 2.97. Found: C, 68.51; H, 4.79; N, 2.83.

4.7.7. Methyl 2-hydroxy-5-(3-methylbenzyl)-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (9g). 100 mg (0.24 mmol) **8g**, 75 mg (75%), mp 200 °C (orange powder from isopropanol), ^{1}H NMR (DMSO-d_6) δ 10.01 (s, 1H, OH-2), 8.09–8.03 (m, 2H, H-7, H-10), 7.84–7.77 (m, 2H, H-8, H-9), 7.65 (d, J = 9.1 Hz, 1H, H-4), 7.21–6.91 (m, 4H, aromat. H's), 7.13 (d, J = 9.1 Hz, 1H, H-3), 5.98 (s, 2H, N–CH_2), 3.95 (s, 3H, $COOCH_3$), 3.68 (s, 3H, OCH_3), MS (EI) *m/z* 425 (M^+), Anal. Calcd for $C_{26}H_{19}NO_5$ (425.45): C, 73.40; H, 4.50; N, 3.29. Found: C, 73.15; H, 4.49; N, 3.20.

4.7.8. Methyl 5-(2-chlorobenzyl)-2-hydroxy-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (9h). 150 mg (0.35 mmol) **8h**, 115 mg (74%), mp 235 °C (orange powder from isopropanol), ^{1}H NMR (DMSO-d_6) δ 10.08 (s, 1H, OH-2), 8.11–8.07 (m, 1H, H-7 or H-10), 8.04–7.99 (m, 1H, H-7 or H-10), 7.89–7.76 (m, 2H, H-8, H-9), 7.62 (d, J = 9.1 Hz, 1H, H-4), 7.57 ('d', 1H, H-3′), 7.34–7.25 ('dt', 1H, H-5′), 7.14 (d, J = 9.1 Hz, 1H, H-3), 7.13–7.09 (m, 1H, H-4′), 6.40–6.36 ('dd', 1H, H-6′), 6.06 (s, 2H, N–CH_2), 3.96 (s, 3H, $COOCH_3$), MS (EI) *m/z* 445 (M^+), Anal. Calcd for $C_{25}H_{16}NO_5Cl$ (445.86): C, 67.35; H, 3.62; N, 3.14. Found: C, 67.18; H, 3.82; N, 3.08.

4.7.9. Methyl 5-(2,4-dichlorobenzyl)-2-hydroxy-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (9i). 100 mg (0.22 mmol) **8i**, 77 mg (73%), mp 225 °C (orange needles from ethanol), ^{1}H NMR (DMSO-d_6) δ 10.02 (s, 1H, OH-2), 8.11–8.06 (m, 2H, H-7, H-10), 7.89–7.78 (m, 2H, H-8, H-9), 7.74 (d, J = 2.1 Hz, 1H, H-3′), 7.63 (d, J = 9.1 Hz, 1H, H-4), 7.20 (dd, J = 2.1 Hz, J = 8.4 Hz, 1H, H-5′), 7.15 (d, J = 9.1 Hz, 1H, H-3), 6.41 (d, J = 8.4 Hz, 1H, H-6′), 6.02 (s, 2H, N–CH_2), 3.96 (s, 3H, $COOCH_3$), MS (EI) *m/z* 480 (M^+), Anal. Calcd for $C_{25}H_{15}NO_5Cl_2$ (480.31): C, 62.52; H, 3.15; N, 2.92. Found: C, 62.41; H, 3.33; N, 2.97.

4.7.10. Methyl 2-hydroxy-6,11-dioxo-5-(2-phenethyl)-5*H*-benzo[*b*]carbazole-1-carboxylate (9k). 100 mg (0.24 mmol) **8k**, 91 mg (88%), mp 210 °C (orange crystals from isopropanol), ^{1}H NMR (DMSO-d_6) δ 9.97 (s, 1H, OH-2), 8.12–8.04 (m, 2H, H-7, H-10), 7.88–7.77 (m, 2H, H-8, H-9), 7.66 (d, J = 9.2 Hz, 1H, H-4), 7.28–7.15 (m, 5H, aromat. H's), 7.09 (d, J = 9.2 Hz, 1H, H-3), 4.92 (t, 2H, N–CH_2–CH$_2$), 3.94 (s, 3H, COOCH$_3$), 3.08 (t, 3H, N–CH$_2$–CH_2), MS (EI) m/z 425 (M$^+$), Anal. Calcd for $C_{26}H_{19}NO_5$ (425.44): C, 73.40; H, 4.50; N, 3.29. Found: C, 73.22; H, 4.34; N, 3.33.

4.7.11. Methyl 2-hydroxy-5-[2-(3,4-dimethoxyphenyl)-ethyl]-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (9l). 72 mg (0.15 mmol) **8l**, 52 mg (73%), mp 158 °C (orange powder from isopropanol), ^{1}H NMR (DMSO-d_6) δ 9.96 (s, 1H, OH-2), 8.10–8.03 (m, 2H, H-7, H-10), 7.85–7.80 (m, 2H, H-8, H-9), 7.66 (d, J = 9.1 Hz, 1H, H-4), 7.09 (d, J = 9.1 Hz, 1H, H-3), 6.81–6.67 (m, 3H, aromat. H's), 4.95–4.89 (m, 2H, N–CH_2–CH$_2$), 3.92 (s, 3H, COOCH$_3$), 3.65 and 3.63 (2 × s, 2 × 3H, OCH$_3$-4′, OCH$_3$-6′), 3.03–2.97 (m, 2H, N–CH$_2$–CH_2), MS (EI) m/z 485 (M$^+$), Anal. Calcd for $C_{28}H_{23}NO_7$ (485.50): C, 69.27; H, 4.78; N, 2.89. Found: C, 69.01; H, 4.86; N, 2.65.

4.7.12. Methyl 2-hydroxy-6,11-dioxo-5-(2-phenylpropyl)-5*H*-benzo[*b*]carbazole-1-carboxylate (9m). 220 mg (0.52 mmol) **8m**, 185 mg (81%), mp 142 °C (red powder from isopropanol), ^{1}H NMR (DMSO-d_6) δ 10.03 (s, 1H, OH-2), 8.10–8.02 (m, 2H, H-7, H-10), 7.83–7.78 (m, 2H, H-8, H-9), 7.71 (d, J = 9.1 Hz, 1H, H-4), 7.29–7.13 (m, 6H, aromat. H's), 4.75 (t, J = 7.2 Hz, 2H, N–CH_2–CH$_2$–CH$_2$), 3.93 (s, 3H, COOCH$_3$), 2.68 (t, J = 7.2 Hz, 2H, N–CH$_2$–CH$_2$–CH_2), 2.13–2.06 (m, 2H, N–CH$_2$–CH_2–CH$_2$), MS (EI) m/z 439 (M$^+$), Anal. Calcd for $C_{27}H_{21}NO_5$ (439.47): C, 73.79; H, 4.82; N, 3.19. Found: C, 73.68; H, 4.92; N, 3.15.

4.7.13. Methyl 2-hydroxy-6,11-dioxo-5-(2-pyridylmethyl)-5*H*-benzo[*b*]carbazole-1-carboxylate (9n). 110 mg (0.28 mmol) **8n**, 72 mg (64%), mp 270 °C (red powder from ethanol), ^{1}H NMR (DMSO-d_6) δ 9.95 (s, 1H, OH-2), 8.10–8.00 (m, 2H, H-7, H-10), 7.88–7.78 (m, 2H, H-8, H-9), 7.74–7.73 (m, 2H, aromat. H's), 7.68 (d, J = 9.1 Hz, 1H, H-4), 7.28–7.21 (m, 2H, aromat. H's), 7.12 (d, J = 9.1 Hz, 1H, H-3), 6.11 (s, 2H, N–CH$_2$), 3.95 (s, 3H, COOCH$_3$), MS (EI) m/z 412 (M$^+$), Anal. Calcd for $C_{24}H_{16}N_2O_5$ (412.41): C, 69.90; H, 3.91; N, 6.79. Found: C, 69.62; H, 4.07; N, 6.55.

4.7.14. Methyl 2-hydroxy-5-(4-methoxyphenyl)-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (9p). 30 mg (0.07 mmol) **8p**, 18 mg (57%), mp 263 °C (orange powder from isopropanol), ^{1}H NMR (DMSO-d_6) δ 10.03 (s, 1H, OH-2), 8.12–8.08 (m, 1H, H-10), 7.97–7.93 (m, 1H, H-7), 7.89–7.78 (m, 2H, H-8, H-9), 7.50–7.44 (m, 2H, H-2′, H-6′), 7.17–7.11 (m, 3H, H-3 or H-4 and H-3′, H-5′), 7.68 (d, J = 9.1 Hz, 1H, H-4), 7.28–7.21 (m, 2H, aromat. H's), 7.06 (d, J = 9.1 Hz, 1H, H-3 or H-4), 3.96 (s, 3H, COOCH$_3$), 3.89 (s, 3H, OCH$_3$), MS (EI) m/z 427 (M$^+$), Anal. Calcd for $C_{25}H_{17}NO_6$ (427.42): C, 70.25; H, 4.01; N, 3.28. Found: C, 70.07; H, 3.76; N, 3.26.

4.7.15. Methyl 2-anilino-5-hydroxy-1′-oxospiro[benzofuran-3(2H),2′-indan]-4-carboxylate (10o). Compound **4o** (320 mg, 1.36 mmol) was dissolved in 7 mL warm acetic acid (40 °C). Then 2-methoxycarbonyl-1,4-benzoquinone **5b** (260 mg, 1.57 mmol) was added, and the reaction mixture was stirred for 15 min at room temperature and then put for 6 h in the refrigerator. The formed precipitate was filtered and recrystallized from toluene to give **10o** as white powder (mp 195 °C) in 36% yield: ^{1}H NMR (DMSO-d_6) δ 9.90 (s, 1H, OH-5), 7.78–7.72 (m, 2H, aromat. indanone protons), 7.63 ('d', 1H, aromat. indanone proton), 7.50 ('t', 1H, aromat. indanone proton), 7.22–7.00 (m, 3H, 2 aromat. phenyl protons and H-7), 6.89–6.82 (m, 3H, 2 aromat. phenyl protons and H-6), 6.71 ('t', 1H, aromat. phenyl proton), 6.28 (d, J = 11.5 Hz, 1H, H-2), 5.80 (d, J = 11.5 Hz, 1H, NH), 3.74 (d, J = 17.1 Hz, 1H, CH$_2$-3′), 3.54 (d, J = 17.1 Hz, 1H, CH$_2$-3′), 3.04 (s, 3H, COOCH$_3$), MS (EI) m/z 401 (M$^+$), Anal. Calcd for $C_{24}H_{19}NO_5$ (401.42): C, 71.81; H, 4.77; N, 3.49. Found: C, 71.30; H, 4.68; N, 4.15.

4.7.16. Methyl 5-hydroxy-2-(4-methoxyanilino)-1′-oxospiro[benzofuran-3(2H),2′-indan]-4-carboxylate (10p). This compound was obtained from the preparation of **8p**. The precipitate formed after 8 h was filtered and recrystallized: 100 mg (15%), mp 195 °C (white crystals from toluene), ^{1}H NMR (DMSO-d_6) 9.91 (s, 1H, OH-5), 7.80–7.72 (m, 2H, aromat. indanone protons), 7.63 ('d', 1H, aromat. indanone proton), 7.51 ('t', 1H, aromat. indanone proton), 7.00 (d, J = 9.1 Hz, 1H, H-7), 6.86 (d, J = 9.1 Hz, 1H, H-6), 6.83–6.77 (m, 2H, H-2′, H-6′), 6.74–6.68 (m, 3H, H-3′, H-5′), 6.20 (d, J = 12.0 Hz, 1H, H-2), 5.49 (d, J = 12.0 Hz, 1H, NH), 3.71 (d, J = 17.4 Hz, 1H, CH$_2$-3′), 3.63 (s, 3H, OCH$_3$-4″), 3.54 (d, J = 17.4 Hz, 1H, CH$_2$-3′), 3.02 (s, 3H, COOCH$_3$), ^{13}C NMR (50 MHz, DMSO-d_6) 202.5 (s, 1′-C=O), 167.0 (s, *C*OOCH$_3$), 153.1, 152.9, 152.5, 151.7, 138.59, 136.2, 135.2, 128.8, 128.1, 128.0, 127.7, 126.6, 125.2, 123.5, 117.8, 116.4, 116.0, 114.2, 111.9, 97.0 (d, J = 169.4 Hz, C-2), 61.8 (s, C-3 (=spiro-C)), 55.2 (quart, J = 143.6 Hz, OCH$_3$-4″), 50.9 (quart, J = 148.3 Hz, COO*C*H$_3$), 41.6 (t, br s, $J \sim$ 136.5 Hz, C-3′), MS (EI) m/z 431 (M$^+$), Anal. Calcd for $C_{25}H_{21}NO_6$ (431.45): C, 69.60; H, 4.91; N, 3.25. Found: C, 69.53; H, 5.07; N, 3.01.

4.7.17. Methyl 2-(4-chloroanilino)-5-hydroxy-1′-oxospiro[benzofuran-3(2H),2′-indan]-4-carboxylate (10r). Contrary to the above prescribed method for **10o**, compound **10r** was prepared by heating the reaction mixture for 30 min at 80 °C and then for 2 h at room temperature. After adding isopropanol, the formed precipitate was filtered and recrystallized: 300 mg (1.11 mmol) **4r**, 200 mg (1.20 mmol) **5b**, 3 mL acetic acid, 185 mg (38%), mp 210 °C (white powder from toluene), MS (EI) m/z 435 (M$^+$), Anal. Calcd for $C_{24}H_{18}NO_5Cl$ (435.87): C, 66.14; H, 4.16; N, 3.21. Found: C, 66.33; H, 4.22; N, 3.05.

4.7.18. Methyl 2-(4-acetylanilino)-5-hydroxy-1′-oxospiro[benzofuran-3(2H),2′-indan]-4-carboxylate (10s). Contrary to the above prescribed method for **10o**, compound **10s** was prepared by heating the reaction mixture for 5 min at 80 °C and then for 2 h at room temperature.

After adding isopropanol, the formed precipitate was filtered and recrystallized: 115 mg (0.41 mmol) **4s**, 70 mg (0.42 mmol) **5b**, 3 mL acetic acid, 80 mg (44%), mp 241 °C (white powder from toluene), MS (EI) *m/z* 444 (M^++1), Anal. Calcd for $C_{26}H_{21}NO_6$ (443.46): C, 70.42; H, 4.77; N, 3.16. Found: C, 70.33; H, 4.70; N, 3.03.

4.7.19. Methyl 2-(4-cyananilino)-5-hydroxy-1′-oxospiro[benzofuran-3(2H),2′-indan]-4-carboxylate (10t). Contrary to the above prescribed method for **10o**, compound **10t** was prepared by heating the reaction mixture for 5 min at 80 °C and then for 2 h at room temperature. After adding isopropanol, the formed precipitate was filtered and recrystallized: 200 mg (0.77 mmol) **4t**, 160 mg (0.96 mmol) **5b**, 8 mL acetic acid, 140 mg (43%), mp 237 °C (white powder from toluene), MS (EI) *m/z* 426 (M^+), Anal. Calcd for $C_{25}H_{18}N_2O_5$ (426.43): C, 70.42; H, 4.25; N, 6.57. Found: C, 70.34; H, 4.26; N, 6.40.

4.7.20. Methyl 5-hydroxy-2-(4-nitranilino)-1′-oxospiro[benzofuran-3(2H),2′-indan]-4-carboxylate (10u). Contrary to the above prescribed method for **10o**, compound **10u** was prepared by heating the reaction mixture for 1 h at reflux. After adding isopropanol, the formed precipitate was filtered and recrystallized: 200 mg (0.71 mmol) **4u**, 140 mg (0.84 mmol) **5b**, 8 mL acetic acid, 75 mg (24%), mp 220 °C (yellow powder from toluene), MS (EI) *m/z* 446 (M^+), Anal. Calcd for $C_{24}H_{18}N_2O_7$ (446.42): C, 64.57; H, 4.06; N, 6.28. Found: C, 64.72; H, 3.99; N, 6.00.

4.8. General procedures for the preparation of the methyl 2-hydroxy-5*H*-benzo[*b*]carbazole-1-carboxylates (11)

4.8.1. Route A. The appropriate compound **8** was refluxed with 4 equiv zinc in about 10 mL glacial acetic acid for 6 h. The hot solution was poured into 50 mL water and then extracted three times with methylene chloride (30 mL). The organic layer was washed with water, dried over $NaSO_4$ and evaporated to dryness. The residue was recrystallized.

4.8.2. Route B. Instead of compounds **8** we employed their quinonoid counterparts **9** and heated for 12 h at reflux.

4.8.3. Methyl 2-hydroxy-5-methyl-5*H*-benzo[*b*]carbazole-1-carboxylate (11a). Route A: 50 mg (0.16 mmol) **8a**, 30 mg (63%), route B: 75 mg (0.22 mmol) **9a**, 40 mg (59%), mp 171 °C (yellow crystals from isopropanol), ^{1}H NMR (DMSO-d_6) δ 9.68 (s, 1H, OH-2), 8.35 (s, 1H, H-6 or H-11), 8.08 ('d', 1H, H-7 or H-10), 8.00 ('d', 1H, H-7 or H-10), 7.93 (s, 1H, H-6 or H-11), 7.60 (d, J = 8.8 Hz, 1H, H-4), 7.52–7.44 (m, 1H, H-8 or H-9), 7.40–7.32 (m, 1H, H-8 or H-9), 7.19 (d, J = 8.8 Hz, 1H, H-3), 4.10 (s, 3H, $COOCH_3$), 3.89 (s, 3H, N–CH_3), MS (EI) *m/z* 305 (M^+), Anal. Calcd for $C_{19}H_{15}NO_3$ (305.34): C, 74.74; H, 4.95; N, 4.59. Found: C, 74.63; H, 5.16; N, 4.38.

4.8.4. Methyl 5-benzyl-2-hydroxy-5*H*-benzo[*b*]carbazole-1-carboxylate (11c). Route A: 70 mg (0.18 mmol) **8c**, 50 mg (72%), route B: 100 mg (0.27 mmol) **9c**, 65 mg (63%), mp 171 °C (yellow crystals from ethanol), ^{1}H NMR (DMSO-d_6) δ 9.72 (s, 1H, OH-2), 8.37 (s, 1H, H-6 or H-11), 8.09 ('d', 1H, H-7 or H-10), 8.00 (s, 1H, H-6 or H-11), 7.95 ('d', 1H, H-7 or H-10), 7.59 (d, J = 8.8 Hz, 1H, H-4), 7.51–7.33 (m, 2H, H-8, H-9), 7.30–7.16 (m, 5H, aromat. H's), 7.15 (d, J = 8.8 Hz, 1H, H-3), 5.70 (s, 2H, N–CH_2), 4.11 (s, 3H, $COOCH_3$), MS (EI) *m/z* 381 (M^+), Anal. Calcd for $C_{25}H_{19}NO_3$ (381.44): C, 78.72; H, 5.02; N, 3.67. Found: C, 78.57; H, 5.24; N, 3.61.

4.8.5. Methyl 2-hydroxy-5-(3,5-dimethoxybenzyl)-5*H*-benzo[*b*]carbazole-1-carboxylate (11f). Route A: 100 mg (0.22 mmol) **8f**, 70 mg (73%), route B: 100 mg (0.21 mmol) **9f**, 60 mg (67%), mp 141 °C (yellow crystals from isopropanol), ^{1}H NMR (DMSO-d_6) 9.71 (s, 1H, OH-2), 8.36 (s, 1H, H-6 or H-11), 8.09 ('d', 1H, H-7 or H-10), 7.98 (s, 1H, H-6 or H-11), 7.96 ('d', 1H, H-7 or H-10), 7.58 (d, J = 8.8 Hz, 1H, H-4), 7.51–7.33 (m, 2H, H-8, H-9), 7.15 (d, J = 8.8 Hz, 1H, H-3), 6.36 (d, J = 2.1 Hz, 1H, H-4′), 6.29 (d, J = 2.1 Hz, 2H, H-2′, H-6′), 5.60 (s, 2H, N–CH_2), 4.11 (s, 3H, $COOCH_3$), 3.62 (s, 6H, 2 × OCH_3); MS (EI) *m/z* 441 (M^+), Anal. Calcd for $C_{27}H_{23}NO_5$ (441.49): C, 73.46; H, 5.25; N, 3.17. Found: C, 73.25; H, 5.21; N, 3.14.

4.8.6. Methyl 2-hydroxy-5-(3-methylbenzyl)-5*H*-benzo-[*b*]carbazole-1-carboxylate (11g). Route A: 100 mg (0.24 mmol) **8g**, 70 mg (75%), route B: 100 mg (0.24 mmol) **9g**, 55 mg (54%), mp 145 °C (yellow crystals from isopropanol), ^{1}H NMR (3DMSO-d_6) δ 9.70 (s, 1H, OH-2), 8.37 (s, 1H, H-6 or H-11), 8.09 ('d', 1H, H-7 or H-10), 7.97 (s, 1H, H-6 or H-11), 7.95 ('d', 1H, H-7 or H-10), 7.57 (d, J = 8.9 Hz, 1H, H-4), 7.52–7.33 (m, 2H, H-8, H-9), 7.15 (d, J = 8.9 Hz, 1H, H-3), 7.14–7.10 (m, 1H, H-5′), 7.05–7.01 (m, 2H, H-4′, H-6′), 6.94–6.90 (m, 1H, H-2′), 5.68 (s, 2H, N–CH_2), 4.11 (s, 3H, $COOCH_3$), 2.19 (s, 3H, CH_3), MS (EI) *m/z* 395 (M^+), Anal. Calcd for $C_{26}H_{21}NO_3$ (395.46): C, 78.97; H, 5.35; N, 3.54. Found: C, 78.75; H, 5.34; N, 3.38.

4.8.7. Methyl 2-hydroxy-5-[2-(3,4-dimethoxyphenyl)-ethyl]-5*H*-benzo[*b*]carbazole-1-carboxylate (11l). Route A: 85 mg (0.18 mmol) **8l**, 55 mg (67%), route B: 100 mg (0.21 mmol) **9l**, 60 mg (62%), mp 140 °C (yellow crystals from isopropanol), ^{1}H NMR (DMSO-d_6) δ 9.76 (s, 1H, OH-2), 8.31 (s, 1H, H-6 or H-11), 8.06 ('d', 1H, H-7 or H-10), 7.98 ('d', 1H, H-7 or H-10), 7.94 (s, 1H, H-6 or H-11), 7.52 (d, J = 8.9 Hz, 1H, H-4), 7.51–7.32 (m, 2H, H-8, H-9), 7.11 (d, J = 8.9 Hz, 1H, H-3), 6.80–6.77 (m, 3H, H-2′, H-5′and H-6′), 4.61 (t, 2H, N–CH_2–CH_2), 4.11 (s, 3H, $COOCH_3$), 3.65 and 3.63 (2 × s, 2 × 3H, OCH_3-3′, OCH_3-4′), 3.01 (t, 2H, N–CH_2–CH_2), MS (EI) *m/z* 455 (M^+), Anal. Calcd for $C_{28}H_{25}NO_5$ (455.52): C, 73.83; H, 5.53; N, 3.07. Found: C, 73.59; H, 5.30; N, 2.90.

4.9. General procedure for the preparation of the 2-hydroxy-*N*-(2-dimethylaminomethyl)-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxamide hydrochlorides (12)

The appropriate quinone **9** was dissolved in 5 mL *N*,*N*-dimethylenediamine and heated at reflux for 2 h.

Afterwards the reaction mixture was cooled down to room temperature, acidified to pH = 1 with concd HCl and put in the refrigerator. After 24 h the precipitate was filtered, washed with water and recrystallized.

4.9.1. 2-Hydroxy-5-methyl-*N*-(2-dimethylaminomethyl)-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxamide hydrochloride (12a). 100 mg (0.26 mmol) **9a**, 48 mg (40%), mp 271 °C (red powder from toluene), ^{1}H NMR (DMSO-d_6) δ 9.94 (s, 1H, OH-2), 9.46 (s, br s, 1H, N*H*$(CH_3)_2$), 8.45 (t, 1H, CONH), 8.11–8.05 (m, 2H, H-7, H-10), 7.86–7.83 (m, 2H, H-8, H-9), 7.74 (d, J = 9.1 Hz, 1H, H-4), 7.21 (d, J = 9.1 Hz, 1H, H-3), 4.23 (s, 3H, N–CH_3), 3.70–3.65 (m, 2H, NHCH_2CH_2NH$(CH_3)_2$), 3,51–3.45 (m, 2H, NHCH_2CH_2NH$(CH_3)_2$), 3.00 (s, 6H, NH(CH_3)$_2$), MS (EI) *m*/*z* 391 (M(base)$^+$), Anal. Calcd for $C_{22}H_{21}N_3O_4 \times$ HCl (427.89): C, 61.76; H, 5.18; N, 9.82. Found: C, 61.74; H, 5.51; N, 10.09.

4.9.2. 2-Hydroxy-5-(2-methoxybenzyl)-*N*-(2-dimethylaminomethyl)-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxamide hydrochloride (12d). 105 mg (0.26 mmol) **9d**, 58 mg (46%), mp 299 °C (red powder from ethanol), ^{1}H NMR (DMSO-d_6) δ 9.97 (s, 1H, OH-2), 9.77 (s, br s, 1H, N*H*$(CH_3)_2$), 8.47 (t, 1H, CONH), 8.13–8.03 (m, 2H, H-7, H-10), 7.90–7.77 (m, 2H, H-8, H-9), 7.53 (d, J = 9.1 Hz, 1H, H-4), 7.27–7.06 (m, 2H, H-4′, H-6′), 7.16 (d, J = 9.1 Hz, 1H, H-3), 6.77–6.70 (m, 1H, H-5′), 6.37 ('d', 1H, H-3′), 5.99 (s, 2H, N_5–CH_2), 3.91 (s, 3H, OCH_3), 3.70 (t, 2H, NHCH_2CH_2NH$(CH_3)_2$), 3,53–3.48 (m, 2H, NHCH_2CH_2NH$(CH_3)_2$), 2.98 (s, 6H, NH(CH_3)$_2$), MS (EI) *m*/*z* 497 (M(base)$^+$), Anal. Calcd for $C_{29}H_{27}N_3O_5 \times$ HCl (534.01): C, 65.23; H, 5.29; N, 7.87. Found: C, 65.31; H, 5.41; N, 7.26.

4.9.3. 2-Hydroxy-5-(3,5-dimethoxybenzyl)-*N*-(2-dimethylaminomethyl)-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxamide hydrochloride (12f). 120 mg (0.25 mmol) **9f**, 62 mg (44%), mp 272 °C (red powder from ethanol), ^{1}H NMR (DMSO-d_6) δ ~10.1–9.5 (m, br s, 2H, OH-2, N*H*$(CH_3)_2$), 8.44 (t, 1H, CONH), 8.11–8.07 (m, 2H, H-7, H-10), 7.90–7.79 (m, 2H, H-8, H-9), 7.67 (d, J = 9.1 Hz, 1H, H-4), 7.19 (d, J = 9.1 Hz, 1H, H-3), 6.40 (d, J = 2.1 Hz, 1H, H-4′), 6.29 (d, J = 2.1 Hz, H-2′, H-6′), 5.98 (s, br s, 2H, N_5–CH_2), 3.67 ('s', 8H, 2 × OCH_3, NHCH_2CH_2NH$(CH_3)_2$), 3,52–3.46 (m, 2H, NHCH_2CH_2NH$(CH_3)_2$), 2.98 (s, 6H, NH(CH_3)$_2$), MS (EI) *m*/*z* 527 (M(base)$^+$), Anal. Calcd for $C_{29}H_{27}N_3O_5 \times$ HCl (564.05): C, 63.88; H, 5.36; N, 7.45. Found: C, 63.78; H, 5.80; N, 7.08.

4.9.4. 2-Hydroxy-*N*-(2-dimethylaminomethyl)-6,11-dioxo-5-(2-phenethyl)-5*H*-benzo[*b*]carbazole-1-carboxamide hydrochloride (12k). 110 mg (0.26 mmol) **9k**, 52 mg (39%), mp 293 °C (red powder from toluene), ^{1}H NMR (DMSO-d_6) δ 9.96 (s, 1H, OH-2), 9.76 (s, br s, 1H, N*H*$(CH_3)_2$), 8.43 (t, 1H, CONH), 8.12–8.06 (m, 2H, H-7, H-10), 7.86–7.82 (m, 2H, H-8, H-9), 7.70 (d, J = 9.1 Hz, 1H, H-4), 7.31–7.28 (m, 5H, aromat. H's), 7.18 (d, J = 9.1 Hz, 1H, H-3), 4.94 (t, 2H, N_5–CH_2–CH_2), ~3.69 (m, 2H, NHCH_2 CH_2NH$(CH_3)_2$), ~3,49 (m, 2H, NHCH_2CH_2NH$(CH_3)_2$), 3.08 (t, 2H, N_5–CH_2–CH_2), 2.99 (s, 6H, NH(CH_3)$_2$), MS (EI) *m*/*z* 481 (M(base)$^+$), Anal. Calcd for $C_{29}H_{27}N_3O_4 \times$ HCl (518.01): C, 67.24; H, 5.45; N, 8.11. Found: C, 67.40; H, 5.77; N, 8.06.

4.10. General procedure for the preparation of the 2-hydroxy-1-dimethylaminomethyl-5*H*-benzo[*b*]carbazole-6,11-diones (13)

The appropriate quinone **6**, bisdimethylaminomethane and catalytic amounts of acetic acid were heated in ~30 mL dioxane at reflux for 2 h. After cooling, the solvent was removed in vacuo. The residue was recrystallized.

4.10.1. 2-Hydroxy-5-(2-methoxybenzyl)-1-dimethylaminomethyl-5*H*-benzo[*b*]carbazole-6,11-dione (13d). 120 mg (0.31 mmol) **6d**, 600 mg (5.87 mmol) bisdimethylaminomethane, 80 mg (58%), mp 131 °C (dark red crystals from isopropanol), ^{1}H NMR ($CDCl_3$) δ 8.23 (m, 1H, H-10), 8.11 (m, 1H, H-7), 7.69 (m, 2H, H-8, H-9), 7.30 (d, J = 9.1 Hz, 1H, H-4), 7.22 ('d', 1H, H-6′), 7.09 (d, J = 9.1 Hz, 1H, H-3), 6.93 ('d', 1H, H-4′), 6.74 ('t', 1H, H-3′), 6.03 (s, 2H, N_5–CH_2), 5.11 (s, 2H, CH_2-1), 3.96 (s, 3H, OCH_3), 2.67 (s, 6H, $N(CH_3))_2$, MS (DCI) *m*/*z* 441 (M^++1), Anal. Calcd for $C_{27}H_{24}N_2O_4$ (440.50): C, 73.62; H, 5.49; N, 6.36. Found: C, 73.53; H, 5.44; N, 6.56.

4.11. Hydroxy-5-(3,5-dimethoxybenzyl)-1-dimethylaminomethyl-5*H*-benzo[*b*]carbazole-6,11-dione (13f)

230 mg (0.56 mmol) **6f**, 1000 mg (9.78 mmol) bisdimethylaminomethane, 120 mg (46%), mp 238 °C (dark red powder from isopropanol), ^{1}H NMR ($CDCl_3$) δ 8.23 (m, 1H, H-10), 8.11 (m, 1H, H-7), 7.69 (m, 2H, H-8, H-9), 7.26 (d, J = 9.0 Hz, 1H, H-4), 7.02 (d, J = 9.0 Hz, 1H, H-3), 6.32 (d, J = 2.1 Hz, 1H, H-4′), 6.27 (d, J = 2.1 Hz, 2H, H-4′, H-6′), 5.95 (s, 2H, N_5–CH_2), 4.80 (s, 2H, CH_2-1), 3.72 (s, 6H, 2 × OCH_3), 2.48 (s, 6H, $N(CH_3)_2$), MS (DCI) *m*/*z* 471 (M^++1), Anal. Calcd for $C_{28}H_{26}N_2O_5$ (470.53): C, 71.48; H, 5.57; N, 5.95. Found: C, 71.44; H, 5.42; N, 5.59.

4.11.1. 5-(2,4-Dichlorobenzyl)-2-hydroxy-1-dimethylaminomethyl-5*H*-benzo[*b*]carbazole-6,11-dione (13i). 150 mg (0.36 mmol) **6i**, 640 mg (6.26 mmol) bisdimethylaminomethane, 80 mg (47%), mp 252 °C (red crystals from toluene), ^{1}H NMR ($CDCl_3$) δ 8.24 (m, 1H, H-10), 8.08 (m, 1H, H-7), 7.70 (m, 2H, H-8, H-9), 7.49 (d, J = 2.1 Hz, 1H, H-3′), 7.21 (dd, J = 2.1 Hz, J = 8.3 Hz, 1H, H-5′), 7.12 (d, J = 9.1 Hz, 1H, H-4), 7.02 (d, J = 9.1 Hz, 1H, H-3), 6.36 (d, J = 8.3 Hz, 1H, H-6′), 6.02 (s, 2H, N_5–CH_2), 4.81 (s, 2H, CH_2-1), 2.49 (s, 6H, $N(CH_3)_2$), MS (DCI) *m*/*z* 479 (M^+), Anal. Calcd for $C_{26}H_{20}N_2O_3Cl_2$ (479.36): C, 65.15; H, 4.21; N, 5.84. Found: C, 65.57; H, 4.43; N, 5.98.

4.11.2. 2-Hydroxy-5-(4-methoxyphenyl)-1-dimethylaminomethyl-5*H*-benzo[*b*]carbazole-6,11-dione (13p). 180 mg (0.49 mmol) **6p**, 850 mg (8.32 mmol) bisdimethylaminomethane, 95 mg (45%), mp 223 °C (dark red powder from ethyl acetate), ^{1}H NMR ($CDCl_3$) δ 8.25 (m, 1H, H-10), 8.01 (m, 1H, H-7), 7.68 (m, 2H, H-8, H-9), 7.33–7.26 (m, 2H, H-3′, H-5′), 7.15–7.05 (m, 2H, H-2′,

H-6′), 7.01 (d, J = 8.9 Hz, 1H, H-4), 6.92 (d, J = 8.9 Hz, 1H, H-3), 4.88 (s, 2H, CH_2-1), 3.93 (s, 3H, OCH_3), 2.53 (s, 6H, $N(CH_3)_2$), MS (EI) m/z 383, 368 Anal. Calcd for $C_{26}H_{22}N_2O_4$ (426.47): C, 73.23; H, 5.20; N, 6.57. Found: C, 73.28; H, 5.34; N, 6.45.

4.12. General procedure for the preparation of the methyl 2-hydroxy-11-methylene-6-oxo-5*H*-benzo[*b*]carbazole-1-carboxylates (15)

The appropriate compound **8**, bisdimethylaminomethane and catalytic amounts of acetic acid were heated in dioxane at reflux under argon atmosphere for 6 h. After cooling, the reaction mixture was concentrated in vacuo. The precipitate was filtered and recrystallized under argon atmosphere.

4.12.1. Methyl 2-hydroxy-5-methyl-11-methylene-6-oxo-5*H*-benzo[*b*]carbazole-1-carboxylate (15a). 500 mg (1.56 mmol) **8a**, 3180 mg (31.13 mmol) bisdimethylaminomethane, 15 mL dioxane, 190 mg (37%), mp 221 °C (orange powder from ethanol), ^{1}H NMR ($CDCl_3$) δ 10.30–10.01 (s, br s, 1H, OH-2), 8.31 ('dd', 1H, H-7), 7.97 (m, 1H, H-10), 7.68–7.49 (m, 2H, H-8, H-9), 7.59 (d, J = 9.1 Hz, 1H, H-4), 7.17 (d, J = 9.1 Hz, 1H, H-3), 6.24 (s, 1H, $=CH_2$), 5.49 (s, 1H, $=CH_2$), 4.29 (s, 3H, N–CH_3), 3.92 (s, 3H, $COOCH_3$), MS (EI) m/z 333 (M^+), Anal. Calcd for $C_{20}H_{15}NO_4$ (333.35): C, 72.06; H, 4.54; N, 4.20. Found: C, 72.09; H, 4.10; N, 4.28.

4.12.2. Methyl 5-benzyl-2-hydroxy-11-methylene-6-oxo-5*H*-benzo[*b*]carbazole-1-carboxylate (15c). 300 mg (0.76 mmol) **8c**, 1500 mg (14.68 mmol) bisdimethylaminomethane, 10 mL dioxane, 110 mg (36%), mp 228 °C (orange powder from ethanol), ^{1}H NMR ($CDCl_3$) δ 10.18 (s, 1H, OH-2), 8.31 (m, 1H, H-7), 8.00 (m, 1H, H-10), 7.69–7.49 (m, 2H, H-8, H-9), 7.58 (d, J = 9.1 Hz, 1H, H-4), 7.32–7.12 (m, 5H, aromat. H's), 7.12 (d, J = 9.1 Hz, 1H, H-3), 6.30 (s, 1H, $=CH_2$), 6.11 (s, 2H, N–CH_2), 5.57 (s, 1H, $=CH_2$), 3.94 (s, 3H, $COOCH_3$), ^{13}C NMR (50 MHz, DMSO-d_6) δ 177.0 (m, 6-C=O), 168.0 (m, $COOCH_3$), 151.4 (dd, J = 1.6 Hz, J = 9.4 Hz), 138.0, 137.1, 134.3, 134.0, 132.5, 130.8, 129.9, 128.5, 128.3, 127.1, 126.4, 125.7 and 124.2 (2 × m, C-7 and C-10), 122.0, 118.2 (d, J = 162.0 Hz, C-3), 116.8 (t, J = 160.8 Hz, $=CH_2$), 115.2 (d, J = 163.5 Hz, C-4), 111.9, 51.8 (q, J = 147.5 Hz, $COOCH_3$), 47.1 Hz (t, J = 141.4 Hz, N–CH_2), MS (EI) m/z 409 (M^+), Anal. Calcd for $C_{26}H_{19}NO_4$ (409.45): C, 76.27; H, 4.68; N, 3.42. Found: C, 76.26; H, 4.89; N, 3.37.

4.13. Crystal structure determination of compound 15c

Crystals of **15c** suitable for X-ray study were selected by means of a polarization microscope. They were investigated on a Stoe imaging plate diffraction system using graphite monochromatized MoKα radiation (λ = 0.71073 Å). Unit cell parameters were determined by a least-squares refinement on the positions of 3491 strong reflections, distributed equally in reciprocal space. An anorthic lattice was found compatible with space groups $P1$ and $\overline{P1}$. The latter was confirmed in the course of the structure refinement. Crystal data: $M_r(C_{26}H_{19}NO_4)$ = 409.42, a = 8.7308(11) Å, b = 10.4832(11) Å, c = 10.8491(6) Å, α = 89.449(13)°, β = 80.557(14)°, γ = 79.309(14), V = 962.30(19) Å^3, Z = 2, D_x = 1.413 g cm^{-3}, μ = 0.096 mm^{-1}, T = 291 K, yellow crystal of dimensions 0.4 × 0.2 × 0.1 mm. Intensity data (12,025) (Θ_{min} = 1.98°, Θ_{max} = 25.95°) were collected and Lp corrections were applied. The structure was solved by direct methods[26] and approximate positions of all the hydrogen atoms were found via difference Fourier synthesis. Refinement (356 parameters, all of 3504 unique reflections used) by full-matrix least-squares calculations on F^2,[27] converged to the following final indicators: $R_1[F_o^2 > 2\sigma(F_o^2)] = 0.037$, $wR_2 = 0.052$ (all data), $w = 1/[\sigma^2(F_o^2) + (0.01P)^2 + 0.5P]$ where $P = (F_o^2 + 2F_c^2)/3$, $S = 0.665$,[27] largest peak and hole in the final difference map are 0.105 e/Å^2 and −0.118 e/Å^2, respectively. Anisotropic displacement parameters were used for all nonhydrogen atoms. H atoms coordinates and isotropic displacement parameters refined to physically reasonable values within the limits of experimental error. Scattering factors, dispersion corrections and absorption coefficients were taken from International Tables for Crystallography (1992, Vol. C, Tables 6.114, 4.268 and 4.2.4.2).

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 242621. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.13.1. Methyl 2-hydroxy-5-(2-methoxybenzyl)-11-methylene-6-oxo-5*H*-benzo[*b*]carbazole-1-carboxylate (15d). 150 mg (0.35 mmol) **8d**, 700 mg (6.85 mmol) bisdimethylaminomethane, 10 mL dioxane, 45 mg (29%), mp 158 °C (orange powder from ethanol), ^{1}H NMR ($CDCl_3$) δ 10.25–10.15 (s, br s, 1H, OH-2), 8.29 ('dd', 1H, H-7), 8.00 ('dd', 1H, H-10), 7.71–7.54 (m, 3H, H-4, H-8 and H-9), 7.22–7.04 (m, 2H, H-3, H-4′), 6.90 ('d', 1H, H-6′), 6.69 ('t', 1H, H-5′), 6.50 ('d', 1H, H-3′), 6.29 (s, 1H, $=CH_2$), 6.10 (s, 2H, N–CH_2), 5.57 (s, 1H, $=CH_2$), 3.94 ('s', 6H, $COOCH_3 + OCH_3$), MS (EI) m/z 439 (M^+), Anal. Calcd for $C_{27}H_{21}NO_5$ (439.47): C, 73.79; H, 4.82; N, 3.19. Found: C, 73.80; H, 4.72; N, 2.90.

4.13.2. Methyl 2-hydroxy-5-(3-methylbenzyl)-11-methylene-6-oxo-5*H*-benzo[*b*]carbazole-1-carboxylate (15g). 610 mg (1.48 mmol) **8g**, 3000 mg mg (29.36 mmol) bisdimethylaminomethane, 20 mL dioxane, 235 mg (38%), mp 189 °C (orange powder from isopropanol), ^{1}H NMR ($CDCl_3$) δ 10.18 (s, 1H, OH-2), 8.32 ('dd', 1H, H-7), 8.00 ('dd', 1H, H-10), 7.66–7.50 (m, 2H, H-8, H-9), 7.58 (d, J = 9.1 Hz, 1H, H-4), 7.19–6.90 (m, 4H, aromat. H's), 7.12 (d, J = 9.1 Hz, 1H, H-3), 6.30 (s, 1H, $=CH_2$), 6.08 (s, 2H, N–CH_2), 5.58 (s, 1H, $=CH_2$), 3.94 (s, 3H, $COOCH_3$), 2.21 (s, 3H, CH_3), MS (EI) m/z 423 (M^+), Anal. Calcd for $C_{27}H_{21}NO_4$ (423.47): C, 76.58; H, 5.00; N, 3.31. Found: C, 76.33; H, 5.21; N, 3.28.

4.14. General procedure for the preparation of the methyl 2-methoxy-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylates (16)

The appropriate quinone **9** was dissolved in NaOH (10% (m/V)). The solution was cooled, and dimethylsulfate was added by portions and then heated at reflux for 30 min. After cooling, the precipitate was filtered and recrystallized from isopropanol.

4.14.1. Methyl 2-methoxy-5-methyl-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (16a). 100 mg (0.30 mmol) **9a**, 40 mg (0.35 mmol) dimethylsulfate, 3 mL NaOH, 65 mg (63%), mp 239 °C (orange powder from isopropanol), ^{1}H NMR (DMSO-d_6) δ 8.11–8.04 (m, 2H, H-7, H-10), 7.90 (d, J = 9.3 Hz, 1H, H-4), 7.85–7.81 (m, 2H, H-8, H-9), 7.44 (d, J = 9.3 Hz, 1H, H-3), 4.23 (s, 3H, N–CH_3), 3.95 (s, 3H, $COOCH_3$, 3.88 (s, 3H, OCH_3),), MS (EI) m/z 349 (M^+), Anal. Calcd for $C_{20}H_{15}NO_5$ (349.35): C, 68.76; H, 4.33; N, 4.01. Found: C, 68.56; H, 4.60; N, 3.91.

4.14.2. Methyl 5-benzyl-2-methoxy-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (16c). 170 mg (0.41 mmol) **9c**, 55 mg (0.44 mmol) dimethylsulfate, 4 mL NaOH, 135 mg (78%), mp 215 °C (red powder from isopropanol), ^{1}H NMR (DMSO-d_6) δ 8.11–8.05 (m, 2H, H-7, H-10), 7.89–7.81 (m, 3H, H-4, H-8, H-9), 7.41 (d, J = 9.3 Hz, 1H, H-3), 7.31–7.18 (m, 5H, H-2′, H-3′, H-4′, H-5′ and H-6′), 6.08 (s, 2H, N–CH_2), 3.97 (s, 3H, $COOCH_3$), 3.86 (s, 3H, OCH_3-2), MS (EI) m/z 425 (M^+) Anal. Calcd for $C_{26}H_{19}NO_5$ (425.45): C, 73.40; H, 4.50; N, 3.29. Found: C, 73.15; H, 4.52; N, 3.18.

4.15. General procedure for the preparation of the methyl 2-acetoxy-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylates (17) and the methyl 2,6-diacetoxy-5*H*-benzo[*b*]carbazole-1-carboxylates (18)

The appropriate starting compound **8/9** was heated in acetic anhydride and catalytic amounts of pyridine at reflux for 2 h. After cooling, the solvent was removed in vacuo, and the residue was recrystallized.

4.15.1. Methyl 2-acetoxy-5-methyl-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (17a). 100 mg (0.30 mmol) **9a**, 10 mL acetic anhydride, 70 mg (63%), mp 226 °C (yellow crystals from isopropanol), ^{1}H NMR (DMSO-d_6) δ 8.13–8.03 (m, 2H, H-7, H-10), 7.98 (d, J = 9.1 Hz, 1H, H-4), 7.89–7.78 (m, 2H, H-8, H-9), 7.41 (d, J = 9.1 Hz, 1H, H-3), 4.26 (s, 3H, N–CH_3), 3.96 (s, 3H, $COOCH_3$), 2.28 (s, 3H, $OCOCH_3$), MS (EI) m/z 377 (M^+), Anal. Calcd for $C_{21}H_{15}NO_6$ (377.36): C, 66.84; H, 4.01; N, 3.71. Found: C, 66.64; H, 4.14; N, 3.59.

4.15.2. Methyl 2-acetoxy-5-benzyl-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (17c). 100 mg (0.24 mmol) **9c**, 10 mL acetic anhydride, 65 mg (71%), mp 231 °C (yellow crystals from isopropanol), ^{1}H NMR (DMSO-d_6) δ 8.12–8.06 (m, 2H, H-7, H-10), 7.92 (d, J = 9.1 Hz, 1H, H-4), 7.92–7.80 (m, 2H, H-8, H-9), 7.41 (d, J = 9.1 Hz, 1H, H-3), 7.33–7.21 (m, 5H, aromat. H's), 6.11 (s, 2H, N–CH_2), 3.97 (s, 3H, $COOCH_3$), 2.27 (s, 3H, $OCOCH_3$), MS (EI) m/z 453 (M^+), Anal. Calcd for $C_{27}H_{19}NO_6$ (453.46): C, 71.52; H, 4.22; N, 3.09. Found: C, 71.25; H, 4.46; N, 2.84.

4.15.3. Methyl 2-acetoxy-5-(3,5-dimethoxybenzyl)-6,11-dioxo-5*H*-benzo[*b*]carbazole-1-carboxylate (17f). 50 mg (0.11 mmol) **9f**, 7 mL acetic anhydride, 30 mg (55%), mp 193 °C (yellow powder from isopropanol), ^{1}H NMR (DMSO-d_6) δ 8.14–8.08 (m, 2H, H-7, H-10), 7.90 (d, J = 9.1 Hz, 1H, H-4), 7.89–7.81 (m, 2H, H-8, H-9), 7.38 (d, J = 9.1 Hz, 1H, H-3), 6.42–6.37 (m, 3H, H-2′, H-4′ and H-6′), 6.03 (s, 2H, N–CH_2), 3.97 (s, 3H, $COOCH_3$), 3.67 (s, 6H, OCH_3-3′, OCH_3-5′), 2.28 (s, 3H, $OCOCH_3$), MS (EI) m/z 513 (M^+), Anal. Calcd for $C_{29}H_{23}NO_8$ (513.51): C, 67.83; H, 4.51; N, 2.73. Found: C, 67.80; H, 4.65; N, 2.85.

4.15.4. Methyl 2,6-diacetoxy-5-methyl-5*H*-benzo[*b*]carbazole-1-carboxlate (18a). 100 mg (0.31 mmol) **8a**, 10 mL acetic anhydride, 80 mg (65%), mp 218 °C (yellow needles from isopropanol), ^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H, H-11), 8.06–8.02 (m, 1H, H-7), 7.84–7.79 (m, 1H, H-10), 7.57–7.37 (m, 2H, H-8, H-9), 7.43 (d, J = 8.6 Hz, 1H, H-4), 7.30 (d, J = 8.6 Hz, 1H, H-3), 4.15 (s, 3H, $COOCH_3$), 4.01 (s, 3H, N–CH_3), 2.59 and 2.35 (2 × s, 2 × 3H, 2 × $OCOCH_3$), MS (EI) m/z 405 (M^+), Anal. Calcd for $C_{23}H_{19}NO_6$ (405.41): C, 68.14; H, 4.72; N, 3.45. Found: C, 67.92; H, 4.72; N, 3.42.

4.15.5. Methyl 2,6-diacetoxy-5-benzyl-5*H*-benzo[*b*]carbazole-1-carboxlate (18c). 80 mg (0.20 mmol) **8c**, 10 mL acetic anhydride, 65 mg (70%), mp 215 °C (yellow powder from isopropanol), ^{1}H NMR ($CDCl_3$) δ 8.53 (s, 1H, H-11), 8.06–8.02 (m, 1H, H-7), 7.70–7.66 (m, 1H, H-10), 7.55–7.37 (m, 2H, H-8, H-9), 7.34–7.12 (m, 5H, aromat. H's), 7.33 (d, J = 8.8 Hz, 1H, H-4), 7.22 (d, J = 8.8 Hz, 1H, H-3), ~5.7 (s, br s, 2H, N–CH_2), 4.17 (s, 3H, $COOCH_3$), 4.01 (s, 3H, N–CH_3), 2.35 and 2.10 (2 × s, 2 × 3H, 2 × $OCOCH_3$), MS (EI) m/z 481 (M^+), Anal. Calcd for $C_{29}H_{23}NO_6$ (481.51): C, 72.34; H, 4.81; N, 2.91. Found: C, 72.16; H, 4.85; N, 2.86.

4.15.6. Methyl 2,6-diacetoxy-5-(3,5-dimethoxybenzyl)-5*H*-benzo[*b*]carbazole-1-carboxlate (18f). 100 mg (0.22 mmol) **8f**, 10 mL acetic anhydride, 85 mg (73%), mp 191 °C (yellow powder from isopropanol), ^{1}H NMR ($CDCl_3$) 8.53 (s, 1H, H-11), 8.05–8,02 (m, 1H, H-7), 7.72–7.67 (m, 1H, H-10), 7.56–7.38 (m, 2H, H-8, H-9), 7.32 (d, J = 8.9 Hz, 1H, H-4), 7.22 (d, J = 8.9 Hz, 1H, H-3), 6.37–6.35 (m, 3H, H-2′, H-4′ and H-6′), ~5.6 (s, br s, 2H, N-CH_2), 4.17 (s, 3H, $COOCH_3$), 3.67 (s, 6H, OCH_3-3′, OCH_3-5′), 2.35 and 2.13 (2 × s, 2 × 3H, 2 × $OCOCH_3$), MS (EI) m/z 541 (M^+), Anal. Calcd for $C_{31}H_{27}NO_8$ (481.51): C, 68.75; H, 5.03; N, 2.59. Found: C, 68.54; H, 4.78; N, 2.43.

4.16. General procedure for the preparation of the 5*H*-benzo[*b*]carbazole-6,11-diones (21)

Compound **3** was dissolved in isopropanol. A solution of the appropriate phenylhydrazine **19** dissolved in 2 M HCl was added under stirring. The reaction mixture was heated at reflux for 3 h. After cooling, the precipi-

tate was filtered and dissolved in a mixture of 15 mL methylene chloride and 15 mL acetone. After adding of $KMnO_4$, the reaction was stirred at room temperature for 12 h. The mixture was then diluted with 100 mL water and extracted three times with methylene chloride (30 mL). The organic layer was washed with water, dried over $NaSO_4$ and evaporated to dryness in vacuo. The residue was recrystallized.

4.16.1. 5-Methyl-5*H*-benzo[*b*]carbazole-6,11-dione (21a). 750 mg (4.01 mmol) **3**, 600 mg (4.91 mmol) **19a**, 10 mL isopropanol, 10 mL 2 M HCl, 1600 mg (10.13 mmol) $KMnO_4$, 520 mg (50%), mp 209 °C (orange powder from toluene), ^{1}H NMR ($CDCl_3$) 8.48–8.44 (m, 1H, H-1), 8.24–8.15 (m, 2H, H-7, H-10), 7.78–7.65 (m, 2H, H-8, H-9), 7.50–7.36 (m, 3H, H-2, H-3 and H-4), 4.27 (s, 3H, N–CH_3), MS (EI) *m*/*z* 261 (M^+), Anal. Calcd for $C_{17}H_{11}NO_2$ (261.28): C, 78.15; H, 4.24; N, 5.36. Found: C, 77.92; H, 4.26; N, 5.27.

4.16.2. 5-Benzyl-5*H*-benzo[*b*]carbazole-6,11-dione (21c). 2150 mg (11.48 mmol) **3**, 2700 mg (11.50 mmol) **19c**, 30 mL isopropanol, 20 mL 2 M HCl, 2500 mg (15.82 mmol) $KMnO_4$, 1800 mg (48%), mp 180 °C (orange needles from isopropanol), ^{1}H NMR ($CDCl_3$) 8.54–8.47 (m, 1H, H-1), 8.26–8.21 (m, 1H, H-7 or H-10), 8.18–8.13 (m, 1H, H-7 or H-10), 7.78–7.64 (m, 2H, H-8, H-9), 7.49–7.36 (m, 3H, H-2, H-3 and H-4), 7.34–7.17 (m, 5H, aromat. H's), 6.02 (s, 2H, N–CH_2); MS (EI) *m*/*z* 337 (M^+), Anal. Calcd for $C_{23}H_{15}NO_2$ (337.38): C, 81.88; H, 4.48; N, 4.15. Found: C, 81.71; H, 4.52; N, 4.00.

4.17. Interaction with DNA

Absorption spectra were measured with a Perkin–Elmer Lambda 16 UV–vis spectrometer. Stock solutions of compounds **6p**, **9c**, **9d**, **9k**, **11c**, **12d** and **15c** were prepared with a concentration of 5×10^{-3} M. The final concentration of 5×10^{-4} M was reached by diluting 300 μL of the stock solutions with the appropriate volume of buffer (TRIS buffer, 50 mM NaCl, 5 mM tromethamol, pH 7.2) and DNA solution, respectively, in the cuvette (final volume: 3.0 mL).

Ethidium bromide was purchased from Sigma–Aldrich. A 10^{-3} M stock solution of the drug was prepared. The final concentration for the experiments was 1.7×10^{-4} M and reached by diluting 500 μL stock solution with the appropriate volume of buffer and DNA solution, respectively, in the cuvette (final volume: 3 mL).

Calf thymus DNA (high polymerized Na-salt, type I) was purchased from Sigma–Aldrich and used without further purification. The DNA solution was prepared by dissolving 120 mg calf thymus DNA in 250.0 mL buffer.

Titrations of the drugs were performed at 25 °C by adding three different volumes of DNA solution (250, 500 and 750 μL) to 300 μL 5×10^{-3} M drug solution or to 500 μL 10^{-3} M ethidium bromide solution. The final volume of 3.0 mL in the cuvette was reached by diluting these solutions with buffer. The incubation time was 5 min. In the case of the time dependent experiment of **15c** UV spectra were recorded after 5 min incubation time up to 30 min incubation time.

Acknowledgements

We wish to thank Dr. Narayanan from the NCI (Bethesda, MD, USA) for the in vitro testing of our compounds.

References and notes

1. Goodwin, S.; Smith, A. F.; Horning, E. C. *J. Am. Chem. Soc.* **1959**, *81*, 1903.
2. Juret, P.; Heron, J. F.; Couette, J. E.; Delozier, T.; Le Talaer, J. Y. *Cancer Treat. Rep.* **1982**, *66*, 1909.
3. Clarysse, A.; Brugarolas, A.; Siegenthaler, P.; Abele, R.; Cavalli, F.; de Jager, R.; Renard, G.; Rozencweig, M.; Hansen, H. H. *Eur. J. Cancer Clin. Oncol.* **1984**, *20*, 243.
4. Taatjes, D. J.; Gaudino, G.; Koch, T. H. *Chem. Res. Toxicol.* **1997**, *10*, 953.
5. Hargreaves, R. H. J.; Hartley, J. A.; Butler, J. *Front. Biosci.* **2001**, *5*, 172.
6. Rehn, C.; Pindur, U. *Monatsh. Chem.* **1996**, *127*, 645.
7. Kucklaender, U.; Pitzler, H.; Kuna, K. *Arch. Pharm. (Weinheim)* **1994**, *327*, 137.
8. Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A. *J. Natl. Cancer Inst.* **1991**, *83*, 757–766.
9. Boyd, M. R.; Paull, K. D. *Drug Dev. Res.* **1995**, *34*, 91.
10. Kreul, J. D. Ph.D. Dissertation, Heinrich-Heine-Universitaet Duesseldorf, Germany, 1997.
11. Nenitzescu, C. D. *Bull. Soc. Chim. Romania* **1929**, *11*, 37.
12. Ruhemann, S.; Levy, S. I. *J. Chem. Soc.* **1912**, *101*, 2542.
13. Wagner, R. M.; Lutz, C. *Chem. Ber.* **1971**, *104*, 2975.
14. Martin, J. C.; Barton, K. R.; Gott, P. G.; Meen, R. H. *J. Org. Chem.* **1966**, *31*, 943.
15. Allen, G. R., Jr.; Weiss, M. J. *J. Org. Chem.* **1968**, *33*, 198.
16. Denny, W. A.; Atwell, G. J.; Rewcastle, G. W.; Baguley, B. C. *J. Med. Chem.* **1987**, *30*, 658.
17. Palmer, B. D.; Rewcastle, G. W.; Atwell, G. J.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1988**, *31*, 707.
18. Troxler, F.; Bormann, G.; Seemann, F. *Helv. Chim. Acta* **1968**, *51*, 1203.
19. Cummings, J.; Spanswick, V. J.; Smith, J. F. *Eur. J. Cancer* **1995**, *31A*, 1928.
20. Meunier, G.; De Montauzon, D.; Bernadou, J.; Grassy, G.; Bonnafous, M.; Cros, S.; Meunier, B. *Lab. Pharmacol. Toxicol. Fond* **1988**, *33*, 93.
21. Meunier, G.; Meunier, B. *J. Biol. Chem.* **1985**, *260*, 10576.
22. Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241.
23. Paull, K. D.; Shoemaker, R. H.; Hodes, L.; Monks, A.; Scudiero, D. A.; Rubinstein, L.; Plowman, J.; Boyd, M. R. *J. Natl. Cancer Inst.* **1989**, *81*, 1088.
24. Gormley, P. E.; Sethi, V. S.; Sysyk, R. L. *Cancer Res.* **1978**, *38*, 1300.
25. Chaires, J. B.; Dattagupta, N.; Crothers, D. M. *Biochemistry* **1982**, *21*, 3933.
26. Sheldrick, G. M. SHELXS86. Program for the Solution of Crystal Structures, University of Göttingen, 1985.
27. Sheldrick, G. M. SHELXL97. Program for the Refinement of Crystal Structures, University of Göttingen, 1997.