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Synthesis of benzo analogs of oxoarcyriaflavins and caulersine

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Abstract—In the course of a program aimed at designing new antitumor agents, we were interested in the synthesis of mixed structures of maleimidophenyl carbazoles and natural product caulersine as potential CDK inhibitors. This was performed through an efficient four-step sequence starting from indole or 3-formyl-*N*-Boc indole. 5*H*-Benzocycloheptaindol-6-one derivatives equipped with a fused maleimide (oxophenylarcyriaflavins) or a methyl ester (benzo analog of caulersine) on the central tropone ring were thus obtained.

1. Introduction

Since the isolation and characterization of rebeccamycin **I** in 1985, much attention has been paid by the scientific community to this alkaloid and the whole series of natural or synthetic indolocarbazoles (ICZs).[1] Indeed, rebeccamycin **I** was found to be active against leukemia and melanoma implanted in mice and proved to be a lead compound to develop topoisomerase I inhibitors but aglycones of ICZs exhibit different activities (Fig. 1). For example, natural product arcyriaflavin A **II** is active against HCMV and inhibits CDK4/Cyclin D1 (IC_{50}=140 nM).[2] Interestingly, Cyclin Dependent Kinases (CDKs), as key enzymes for the progression through each stage of the cell division cycle, are major targets to prevent uncontrolled cellular proliferation.[3]

Recently, Zhu and Sanchez-Martinez developed a series of (hetero)arylanalog of arcyriaflavin A **II** endowed with noteworthy CDK4/cyclin D1 inhibitory activities (IC_{50}<100 nM).[4]

As part of our research program aimed at designing modified aglycones of ICZs as potential anticancer agents, we recently evaluated a series of naphtho and phenyl carbazoles **III** and **IV**.[5] Most of these compounds showed good cytotoxic activities (L1210, CEM) and DNA intercalation. Among both series, one derivative (**IV**, R1=OH, R2=H) proved to inhibit a test set of kinases (CDK1 and 5, GSK-3) in the submicromolar range.

Following these preliminary results, we wanted to modulate the biological target of the phenyl carbazole series from DNA intercalation to CDKs' inhibition by a slight modification of the planarity and the addition of a close pair of donor/acceptor hydrogen bonding groups (NH/C=O), well known to be essential to interact with the ATP binding pocket. For this purpose, we chose to increase the size of the central ring from C-6 to C-7, incorporating as well a ketone functionality (**VIII**). This original structure can be related to (i) homoarcyriaflavins (**V**), a patented tyrosine kinase inhibitor,[6] (ii) a natural marine product caulersine[7] (**VI**) for which no biological data are available, and (iii) a suberenone series[8] (**VII**) developed in our laboratory some years ago (Fig. 2). In order to evaluate the indole tropone core on its own, without the additional maleimide moiety, we achieved as well the synthesis of **IX**, a phenyl analog of caulersine.

The retrosynthetic pathway to access type **VIII** and type **IX** compounds is shown in Scheme 1.[9] The tropone central ring would result from an electrophilic cyclization of an acylium

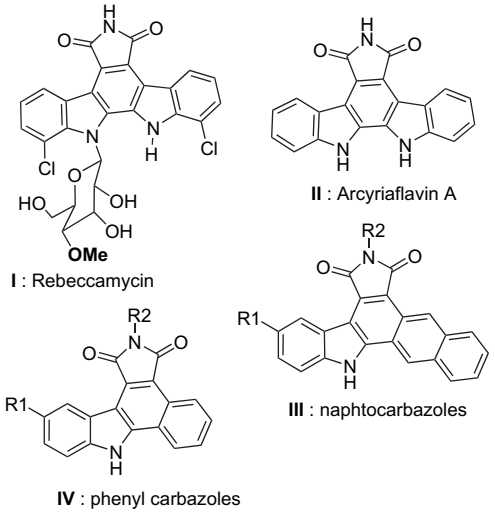

Figure 1. Most representative indolocarbazoles and derivatives.

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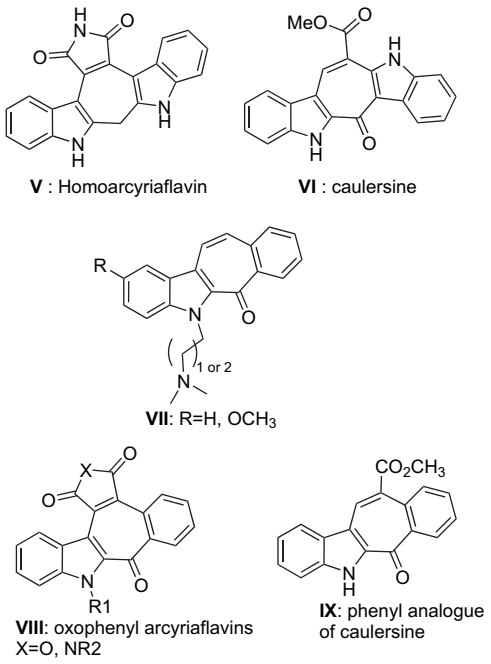
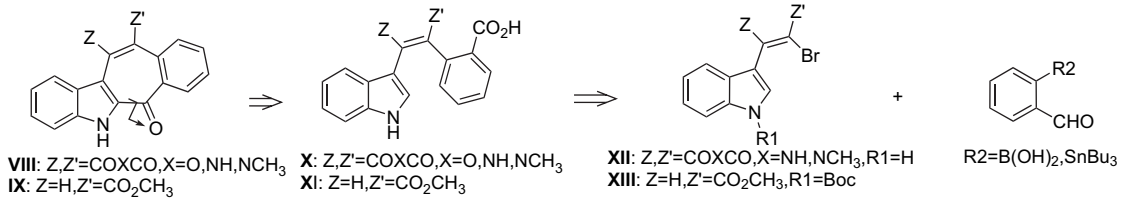


Figure 2. Natural (**VI**) or synthetic (**V**, **VII**) models and targeted compounds (**VIII** and **IX**).

intermediate onto C-2 of the indole moiety. Acid derivatives (**X**, **XI**) would arise from a palladium cross-coupling between 2-formylphenyl boronic acid or a stannylated counterpart and a bromoindolic partner (**XII** or **XIII**), followed by an oxidation step. 3-Bromomaleimide indole **XII** would be formed from indole and 3,4-dibromomaleimide. Meanwhile, 3-bromoacrylate indole **XIII** would result from a Wittig type reaction from 3-formylindole.

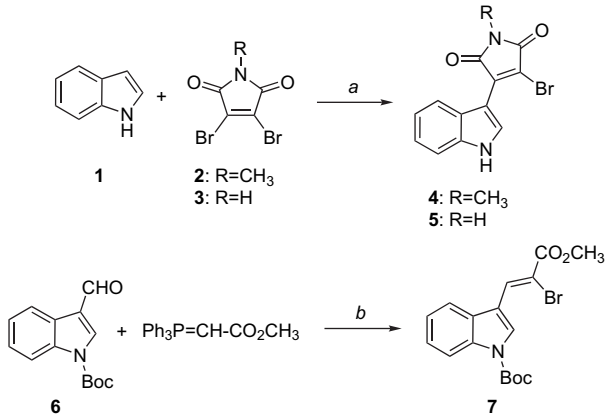


Scheme 1. Retrosynthetic pathway for type **VIII** and type **IX** compounds.

2. Results and discussion

2.1. Access to the bromide derivatives type XII and type XIII

Monoindolyl maleimide bromide **4**[10] was obtained in 91% yield from indole **1** and 3,4-dibromo-*N*-methyl maleimide **2** using a known procedure in the presence of LiHMDS (2.1 equiv) in THF (Scheme 2 and Table 1, entry 1).[11] The access to its demethylated counterpart **5** had briefly been mentioned previously. Faul in 1995 and then Davioud-Charvet in 1998 reported the isolation of **5** or its chloro analog from unprotected 3,4-dibromo(or dichloro)maleimide and 4 equiv of the bromide magnesium salt of indole.[12] Actually, to synthesize **5** from indole and **3**, at least 3 equiv of magnesiated indole salt is required because 1 equiv is consumed by the maleimide nitrogen, 1 equiv is needed for the addition reaction, and the last 1 equiv serves for rearomatization. Indeed, in our hands, the use of 4 equiv of magnesiated indole with 3,4-dibromomaleimide **3** in THF at room temperature afforded the bromomaleimidoindole **5** in a very satisfying 89% yield (Table 1, entry 2). Yet, the need for such an excess of magnesiated indole proved to be a major drawback for this reaction considering the further involvement of more elaborated indolic starting materials. Replacing the Grignard base for LiHMDS appeared as a good alternative in order to reduce the required amount of the indolic derivative. Applying the same procedure (entry 1) but adding one additional equivalent of base for the maleimide nitrogen led to the formation of the desired product **5** in 31% yield (Table 1, entry 3). A further increase of the amount of base (5.3 equiv) and shifting from THF to toluene allowed the isolation of **5** in 84% yield (Table 1, entries 4 and 5).



Scheme 2. (a) See Table 1, entries 1–5. (b) NBS (1.6 equiv), K_2CO_3 (2.5 equiv), CH_2Cl_2, 0 °C to rt, 30 h, 94%.

2.2. Palladium catalyzed cross-couplings

The next step involved a palladium cross-coupling between bromomaleimidoindole **4** or **5** or bromoacrylate indole **7** and commercially available 2-formylphenyl boronic acid **8**.

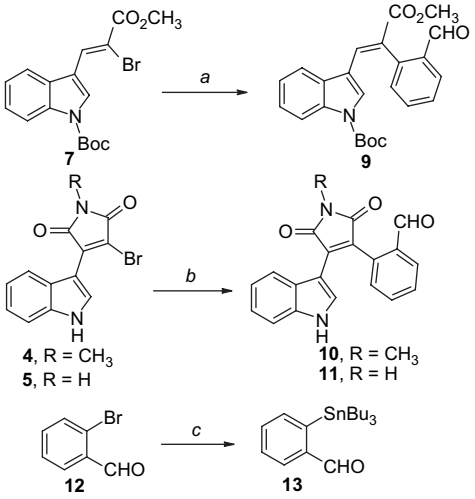
Suzuki coupling between **7** and **8** turned out to be very efficient in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in a mixture of dioxane and water and led to **9** (Scheme 3).

As far as the synthesis of phenyl caulersine is considered, the bromomethyl acrylate functionality of compound **7** could result from a Wittig type reaction from *N*-Boc-3-formylindole **6**[13] and an in situ prepared bromo phosphoylide.[14] The required (*Z*)-isomer could be obtained in an excellent 94% yield after recrystallization from methanol to remove traces of the minor (*E*)-isomer.

Table 1. Experimental conditions for anionic reaction (entries 1–5), Suzuki reactions (entries 6–10), preparation of stannylated benzaldehyde (entries 11–13), and Stille reactions (entry 14)

Entry	Reagent	Conditions	Time	Product (yield,[a] %)
1	**1** (1.0 equiv)	(a) LiHMDS (2.1 equiv), THF, −15 °C (b) **2** (1.0 equiv), THF, −15 to 0 °C	(a) 45 min (b) 1 h	**4** (91)
2	**1** (4.0 equiv)	(a) EtMgBr (4.0 equiv), THF, 60 °C (b) **3** (1.0 equiv), THF, rt	(a) 2 h (b) 1 h	**5** (89)
3	**1** (1.7 equiv)	(a) LiHMDS (3.5 equiv), THF, −15 °C (b) **3** (1.0 equiv), THF, −15 °C, 1 h 30 min and then 0 °C, 30 min	(a) 45 min (b) 2 h	**5** (31)
4	**1** (1.7 equiv)	(a) LiHMDS (5.3 equiv), THF, −15 °C (b) **3** (1.0 equiv), THF, −15 °C, 15 min and then rt, 2 h	(a) 45 min (b) 2 h 15	**5** (76)
5	**1** (1.7 equiv)	(a) LiHMDS (5.3 equiv), toluene, −15 °C (b) **3** (1.0 equiv), THF, −15 °C, 15 min and then rt, 2 h	(a) 1 h (b) 3 h 45 min	**5** (84)
6	**4**	**8** (1.5 equiv), K_2CO_3 (1.8 equiv), $Pd(OAc)_2$ (0.1 equiv), diox/H_2O (85/15), reflux	6 h	**10** (72)
7	**4**	**8** (1.5 equiv), K_2CO_3 (1.8 equiv), $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv), diox/H_2O (85/15), reflux	4 h	**10** (74)
8	**4**	**8** (1.5 equiv), K_2CO_3 (1.8 equiv), $Pd(PPh_3)_4$ (0.1 equiv), diox/H_2O (85/15), reflux	5 h	**10** (59)
9	**5**	**8** (1.5 equiv), K_2CO_3 (1.8 equiv), $Pd(PPh_3)_4$ (0.1 equiv), diox/H_2O (85/15), reflux	3 h 30 min	**11** (27)
10	**5**	**8** (1.5 equiv), K_2CO_3 (1.8 equiv), $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv), diox/H_2O (85/15), reflux	3 h	**11** (33)
11	**12**	Sn_2Bu_6 (1.1 equiv), $PdCl_2(PPh_3)_2$ (0.1 equiv), THF, reflux	48 h	**13** (30)
12	**12**	(a) Sn_2Bu_6 (1.1 equiv), $PdCl_2(PPh_3)_2$ (0.1 equiv), THF, reflux (b) LiCl (0.5 equiv), THF, reflux	(a) 24 h (b) 24 h	**13** (54)
13	**12**	Sn_2Bu_6 (1.1 equiv), $Pd(PPh_3)_4$ (0.1 equiv), toluene, reflux	24 h	**13** (57)
14	**5**	**13** (1.5 equiv), $PdCl_2(PPh_3)_2$ (0.1 equiv), CuI (0.1 equiv), dioxane, reflux	24 h	**11** (54)

[a] Yields are given in isolated products and fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS.



Scheme 3. (a) 2-Formylphenyl boronic acid **8** (2 equiv), K_2CO_3 (4 equiv), $Pd(PPh_3)_4$ (0.1 equiv), diox/H_2O, 70 °C, 2 h, 89%. (b) See Table 1, entries 6–10 and 14. (c) See Table 1, entries 11–13.

In ligandless conditions, previously used by us for a similar coupling,[5] bromo compound **4**, heated in a mixture of dioxane and water in the presence of the boronic acid (1.5 equiv), potassium carbonate (1.8 equiv), and palladium acetate (0.1 equiv), afforded the desired coupled product **10** in 72% yield (Table 1, entry 6). In the presence of triphenylphosphine (0.2 equiv) as a ligand, the yield proved nearly the same (Table 1, entry 7). Changing the catalytic system for palladium tetrakis triphenylphosphine (0.1 equiv) decreased the yield to 59% (Table 1, entry 8).

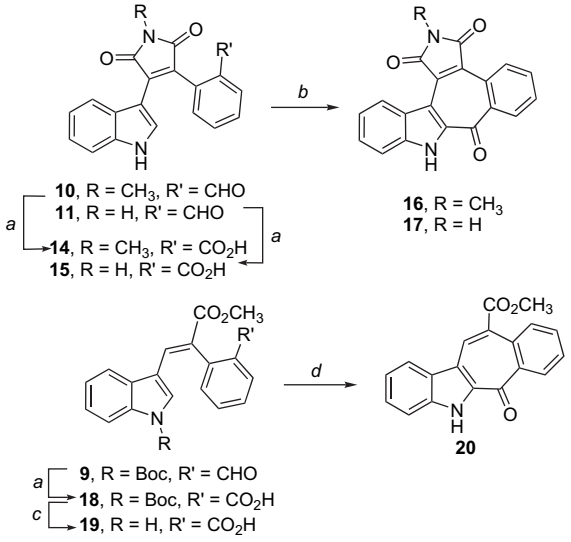
The same coupling starting from demethylated compound **5** proved more challenging. Indeed, whatever Pd[0] catalytic system used, the yield never exceeded 33% (Table 1, entries 9 and 10). In order to optimize the formation of **11**, we shifted from a Suzuki cross-coupling reaction to a Stille coupling involving trialkylstannane **13**. To prepare **13**,[15] we performed a Pd-catalyzed halogen–tin exchange from 2-bromobenzaldehyde **12** using the known procedures. The use of $PdCl_2(PPh_3)_2$ as a catalyst[16] led to a mixture of starting material and stannylated product **13**, the reaction would not evolve further after 48 h (Table 1, entry 11). When lithium chloride (0.5 equiv) was added after 24 h, the stannylated product **13** was obtained in 54% yield (Table 1, entry 12). Using $Pd(PPh_3)_4$ instead of $PdCl_2(PPh_3)_2$, and shifting from THF to toluene, allowed the isolation of **13** in approximately the same yield (57%, Table 1, entry 13).[17] The Stille coupling between **13** and **5** was then performed in standard conditions. Using 1.5 equiv of **13**, 0.2 equiv of $PdCl_2(PPh_3)_2$, and 0.1 equiv of copper(I) iodide in dioxane at room temperature for 24 h allowed the isolation of **11** in 54% yield (Table 1, entry 14). Actually, both routes (Suzuki, one step or Stille, two steps) allowed the synthesis of the unprotected diaryl maleimide **11** from **5** in nearly the same yield (33 and 31%, respectively). Even if the efficiency of either type of coupling is modest, they would not require the use of a protecting group on both nitrogens.

2.3. Electrophilic reaction

The next step was aimed at generating a C-2 indolic carbonyl function. To do so, several useful methods are available from a carboxylic acid function through the generation of an acylium ion, which can undergo a Friedel–Crafts type reaction at electron rich C-2 position of NH indoles via a direct attack or a C-3 attack followed by rearrangement.[8,18]

The oxidation step from aldehydes **9–11** was achieved using sodium chlorite and sulfamic acid in a cold mixture of dioxane and water for a few minutes (Scheme 4).[19] Especially for

the formation of acids **14** and **15**, we noticed that a careful control of both temperature and reaction time is required in order to avoid degradation of the reaction mixture. Acids **14** and **15** were thus obtained in 81 and 62% yield, respectively. Acid **18** was quantitatively generated by the same way without purification.



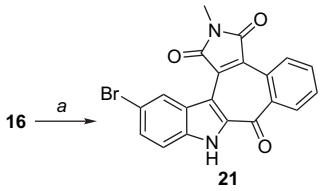
Scheme 4. (a) NH_2SO_3H (8 equiv), $NaClO_2$ (2.2 equiv), dioxane/water, 5 °C, from **10** (1 min): **14**, 81%; from **11** (1 min): **15**, 62%; from **9** (10 min): **18**, quantitative. (b) $BF_3{\cdot}Et_2O$ (40 equiv), DCE, reflux, from **14** (5 h 30 min): **16**, 89%; from **15** (20 h): **17**, 86%. (c) TFA, CH_2Cl_2, r.t., 24 h, **19**, 26%. (d) PPSE (see Section 4), CH_3NO_2, reflux, 10 min, 44% from **18**.

Tropone ring closure was then performed using a large excess of $BF_3{\cdot}Et_2O$ in refluxing dichloroethane from acids **14** and **15**, leading to pentacycles **16** and **17** in 89 and 86% yield, respectively. The same cyclization type reaction from **18** required the preliminary removal of the Boc protective group. This was achieved using trifluoroacetic acid in dichloromethane in a very disappointing 26% yield. Then, the electrophilic cyclization was tried using polyphosphoric acid (PPA) or a mixture of trifluoroacetic anhydride and acid, both conditions resulting in the degradation of the reaction mixture. We assumed that we needed cyclization conditions that could both remove the Boc group and generate the acylium ion in milder conditions. This was performed using trimethylsilyl polyphosphate (PPSE) in nitromethane. Indeed, compound **20** was obtained from **18** in 44% yield.

2.4. Functionalization of compounds 16 and 17

In a related indolocarbazole series, a direct and chemoselective bromination or nitration in *para* position of the indolic nitrogen could be achieved using *N*-bromosuccinimide and nitric acid, respectively.[20] Applied to **16**, the bromination conditions (Scheme 5 and Table 2, entry 1) led to **21** in 55% yield. The position of the bromine atom could be confirmed by 2D NMR experiments (COSY, HMBC). An attempt of electrophilic nitration (HNO_3 in Et_2O) led to an untractable mixture of products.

Having in mind the introduction of solubilizing side chains on the heterocyclic core of **16** and **17**, we envisaged to



Scheme 5. (a) NBS (15 equiv), THF, 0 °C to rt, 4 days, *55%*.

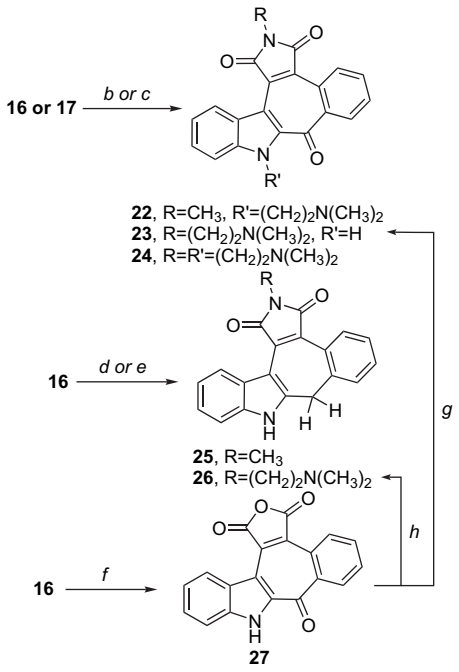
alkylate selectively the indolic or the maleimido nitrogen. Indeed, **16** could be efficiently alkylated on the indolic nitrogen using sodium hydride as a base and 2-dimethylaminoethyl chloride as the electrophilic partner in DMF at 95 °C (Scheme 6). An efficient and selective N-alkylation of the maleimide moiety of **17** proved more problematic. The best conditions found were the use of potassium carbonate as a base in a mixture of DMF and toluene (1/1) at 65 °C. Thus, monoalkylated product **23** was isolated in 34% yield, accompanied with a few amount of dialkylated compound **24** (9% yield). Adding NaI (0.1 equiv) and changing potassium carbonate for sodium hydride led to the same global yield (43%) but decreased the chemoselectively (ratio **23**/**24**=3/7).

In order to selectively introduce the *N*,*N*-dimethylaminoethyl chain on the maleimide nitrogen, we planned to perform a trans-imidification from **16**, by reaction with a large excess of *N*,*N*-dimethylethylene diamine in DMF at 160 °C in a sealed tube. Surprisingly, an unexpected product corresponding to the reduction of the carbonyl function (**25**) was isolated in 41% yield (Table 2, entry 4). When the same reaction was carried out in forcing conditions using the amine as the solvent at reflux for 22 h, product **26** was obtained in 48% yield (Table 2, entry 5). It corresponds to the reduced product with the aminoalkyl chain on the maleimide nitrogen.

We previously observed that the introduction of the aminoalkyl chain on the maleimide nitrogen was more efficient from the cyclic anhydride than from the *N*-methylmaleimide. Anhydride **27** was then generated from **16** using aqueous potassium hydroxide in acetone at room temperature,

Table 2. Reactions performed on **16**, **17**, and **27**

Entry	Reactant	Conditions	Products (yield, %)
1	**16**	NBS (15 equiv), THF, 0 °C to rt, 4 days	**20** (56)
2	**16**	$Cl(CH_2)_2N(CH_3)_2$ (2.5 equiv), NaH (5.1 equiv), DMF 95 °C, 9 h	**22** (84)
3	**17**	$Cl(CH_2)_2N(CH_3)_2$ (2 equiv), K_2CO_3 (1.0 equiv), DMF/toluene 1/1, 65 °C, 24 h	**23** (34), **24** (9)
4	**16**	*N*,*N*-Dimethylethylene diamine (16 equiv), DMF in a sealed tube, 160 °C, 22 h	**25** (41)
5	**16**	*N*,*N*-Dimethylethylene diamine (65 equiv), reflux, 22 h	**26** (48)
6	**16**	Aq KOH (40 equiv), acetone, rt, 24 h and then aq HCl, rt, 12 h	**27** (quant)
7	**27**	*N*,*N*-Dimethylethylene diamine (14 equiv), DMF in a sealed tube, 160 °C, 18 h	**23** (59)
8	**27**	*N*,*N*-Dimethylethylene diamine (114 equiv), reflux, 64 h	**26** (86)



Scheme 6. For reagents and conditions, see Table 2, entries 2–8.

followed by recyclization in acidic medium (Table 2, entry 6). In the same conditions, it appeared that the *N*,*N*-dimethylaminoethyl chain could be introduced on the top part of the molecule affording **23** (Table 2, entry 7). In forcing conditions (Table 2, entry 8), derivative **26**, with a deoxygenated central ring, could be isolated in 86% yield. Indeed, in the case of more electrophilic anhydride compared to *N*-methylmaleimide, the imidification occurs before the reduction.

To our knowledge, this reduction of a cyclic aromatic ketone by an alkyldiamine (primary and tertiary) is unprecedented. We are currently undergoing investigations in order to elucidate a possible mechanism. According to preliminary results, it is noteworthy that the maleimide or anhydride moiety (Michael acceptors) seems necessary for the reduction to occur since neither benzophenone **28**, nor suberenone **29**, nor (1*H*-indol-2-yl)-phenyl-methanone **30**[21] (Fig. 3) can be reduced in the presence of the diamine.

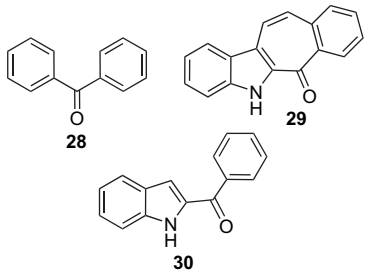


Figure 3.

3. Conclusion

We were able to elaborate an efficient four-step synthetic route to 5*H*-benzocycloheptaindol-6-one derivatives equipped with a fused maleimide or a methyl ester on the central tropone ring. Maleimido pentacycles could be mono- or bis-alkylated with a solubilizing *N*,*N*-dimethyl aminoethyl side chain, while an unexpected reduction of the cyclic ketone was observed in some cases. Further exploration is in progress to elucidate this unusual reactivity.

Preliminary biological results on compounds **16**, **17**, **21**–**26** showed disappointing CDK (1 or 5) inhibitions (>2 μM) meanwhile derivative **23** exhibited a noteworthy micromolar cytotoxicity (F1 epithelial biliary cell line IC_{50} 2 μM after 48 h). New developments on the topic will be reported in due course.

4. Experimental section

4.1. Chemistry

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 250 or 500 instrument using $CDCl_3$ or DMSO-d_6. The chemical shifts are reported in parts per million (δ scale) and all *J* values are in hertz. Melting points are uncorrected. IR absorption spectra were recorded on a Perkin–Elmer FT PARAGON 1000 PC and values were reported in cm^{-1}. MS spectra (Ion Spray) were performed on a Perkin–Elmer SCIEX API 300. HRMS were carried out by the Centre Régional de Mesures Physiques de l'Ouest (CRMPO, Rennes) on a High Resolution Mass Spectrometer with double focalization Varian Mat 311 using Electronic Impact. Monitoring of the reactions was performed using silica gel TLC plates silica Merck 60 F_{254}. Spots were visualized by UV light at 254 and 365 nm. Column chromatographies were performed using silica gel 60 (40–63 μm, Merck). Only the non-available products are described (not found in CAS online).

4.2. 3-Bromo-4-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (5)

Under argon, at room temperature, indole **1** (0.802 g, 6.8 mmol) was dissolved in dry toluene (16 mL). After cooling to −15 °C, a solution of LiHMDS (1 M in hexane, 22 mL, 21.8 mmol,) was added dropwise and then the mixture was stirred for 1 h. A solution of 3,4-dibromomaleimide **3** (1.043 g, 4.1 mmol) in THF (6 mL) was added dropwise at −15 °C. After stirring 15 min at −15 °C, 1 h at 4 °C, and 2 h 30 min at room temperature, the reaction was hydrolyzed with an aqueous hydrochloric acid solution (0.3 N, 50 mL) and the product extracted with EtOAc (50 mL and then 4×20 mL). The combined organic layers were washed with brine (50 mL) and concentrated under reduced pressure. The crude orange residue was precipitated with cooled MeOH (5 mL), the solid was filtered, and dried to afford compound **5** as an orange compound (1.002 g, 84%). R_f (petroleum ether/EtOAc 6/4) 0.42; mp: 160–162 °C (dec); IR (KBr, cm^{-1}) ν 3343, 1772, 1028, 815, 755, 741; ^1H NMR (DMSO-d_6, 250 MHz) δ 7.14 (t, 1H, *J*=7.0 Hz, H_5), 7.22 (t, 1H, *J*=6.8 Hz, H_6), 7.50 (d, 1H, *J*=7.8 Hz, H_7), 7.89 (d, 1H, *J*=8.1 Hz, H_4), 8.03 (d, 1H, *J*=3.0 Hz, H_2), 11.34 (br s, 1H, NH_{mal}), 12.09 (br s, 1H, NH_{indole}); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 103.7 (Cq), 112.3 (CH), 114.6 (Cq), 120.4 (CH), 122.2 (CH), 122.4 (CH), 124.5 (Cq),

131.1 (CH), 136.5 (Cq), 138.0 (Cq), 167.5 (CO), 170.2 (CO); MS (IS) *m/z*: 291–293 $[M+H]^+$, 308–310 $[M+NH_4]^+$.

4.3. 3-(2-Bromo-2-methoxycarbonyl ethenyl)-indole-1-carboxylic acid *tert*-butyl ester (7)

At −20 °C, a solution of methyl(triphenyl phosphoranylidene)acetate (5.45 g, 16.3 mmol) in dry CH_2Cl_2 (100 mL) was treated with recrystallized NBS (3.19 g, 17.9 mmol). After stirring at −20 °C for 30 min, *N*-Boc-3-formylindole (2 g, 8.16 mmol) and K_2CO_3 (3.76 g, 27.2 mmol) were successively added. The reaction mixture was then stirred for 30 h while allowing the temperature to reach the ambient condition. After filtration through a pad of Celite, the filtrate was concentrated in vacuo. The mixture of (*E*)- and (*Z*)-isomer was purified by column chromatography on silica gel (PE/AcOEt, 9.5/0.5). The single (*Z*)-isomer **7** was obtained by recrystallization in hot MeOH as a colorless solid (2.93 g, 94%). R_f (petroleum ether/EtOAc, 9/1) 0.47; mp: 116 °C; IR (KBr, cm^{-1}) ν 1737 (C=O), 1672 (C=O), 1448, 1395, 1354, 1244, 1126, 1097; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.71 (s, 9H, 3×CH_3), 3.93 (s, 3H, OCH_3), 7.33 (dd, 1H, $J=J'=7.2$ Hz, H_{ar}), 7.40 (dd, 1H, $J=J'=7.2$ Hz, H_{ar}), 7.74 (d, 1H, $J=7.2$ Hz, H_{ar}), 8.17 (d, 1H, $J=7.2$ Hz, H_{ar}), 8.50 (s, 1H, =CH), 8.81 (s, 1H, =CH); ^{13}C NMR ($CDCl_3$) δ 28.1 (3×CH_3), 53.5 (OCH_3), 84.9 ($C(CH_3)_3$), 111.6 (Cq), 114.5 (Cq), 115.4 (CH), 118.3 (CH), 123.4 (CH), 125.3 (CH), 128.3 (CH), 129.8 (Cq), 131.3 (CH), 134.6 (Cq), 149.2 (CO), 163.7 (CO). HRMS (EI) calcd for $C_{17}H_{18}NO_4{}^{79}Br$ ($M^{\bullet+}$): 379.04192; found: 379.0424.

4.4. 3-[2-(2-Formyl-phenyl)-2-methoxycarbonyl ethenyl]-indole-1-carboxylic acid *tert*-butyl ester (9)

A solution of **7** (500 mg, 1.3 mmol) in dioxane (25 mL) was treated with 2-formylphenyl boronic acid **8** (394 mg, 2.6 mmol) and K_2CO_3 (724 mg, 5.2 mmol). Water (7.5 mL) was added and the mixture was degassed for 20 min. $Pd(PPh_3)_4$ (151 mg, 10 mol %) was added, the flask was immediately immersed in a pre-heated oil bath, and the reaction mixture was stirred at 70 °C for 2 h. After cooling to room temperature, water was added (25 mL) and the product was extracted with EtOAc (3×20 mL). The organic layer was dried over $MgSO_4$ and the solvents were removed in vacuo. The product was purified by column chromatography on silica gel (petroleum ether/EtOAc, 9/1 and then 8.5/1.5) to afford **9** as a yellow solid (475 mg, 89%). R_f (petroleum ether/EtOAc, 9/1) 0.20; mp: 74 °C; IR (KBr, cm^{-1}) ν 3168 ($C_{sp^2}-H$), 2981 ($C_{sp^3}-H$), 2843 ($C_{sp^3}-H$), 2744 ($C_{sp^2}-H$ aldehyde), 1763–1694 (3×C=O), 1624, 1597, 1569, 1455, 1435, 1150, 1085; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.51 (s, 9H, 3×CH_3), 3.80 (s, 3H, OCH_3), 6.41 (s, 1H, =CH), 7.30–7.39 (m, 3H, H_{ar}), 7.61 (dd, 1H, $J=J'=7.3$ Hz, H_{ar}), 7.69–7.77 (m, 2H, H_{ar}), 8.07–8.11 (m, 2H, H_{ar}), 8.26 (s, 1H, =CH), 10.06 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 27.9 (3×CH_3), 52.4 (OCH_3), 84.2 ($C(CH_3)_3$), 114.7 (Cq), 115.1 (CH), 118.4 (CH), 123.3 (CH), 125.2 (CH), 126.9 (CH), 127.5 (Cq), 128.9 (CH), 129.4 (CH), 129.6 (Cq), 130.8 (CH), 132.0 (CH), 133.9 (Cq), 134.6 (Cq), 134.8 (CH), 140.1 (Cq), 148.6 (CO), 167.1 (CO), 191.2 (CHO). HRMS (EI) calcd for $C_{20}H_{15}NO_5$ ($[M-C_4H_8]^{+\cdot}$): 349.09502; found: 349.0935.

4.5. 3-(2-Formylphenyl)-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione (10)

A solution of compound **4** (201 mg, 0.66 mmol), K_2CO_3 (162 mg, 1.18 mmol), PPh_3 (37 mg, 0.13 mmol), and 2-formylphenyl boronic acid **8** (149 mg, 0.98 mmol) in dioxane/water (5 mL/1 mL) was degassed under argon for 30 min. After addition of $Pd(OAc)_2$ (19 mg, 0.07 mmol), the reaction mixture was immediately placed in a pre-heated oil bath at 100 °C and refluxed for 4 h. After cooling at room temperature and filtration over Celite, the solvents were removed under reduced pressure. The resulting red oil was purified by flash chromatography (petroleum ether/CH_2Cl_2, 1/1 and then petroleum ether/EtOAc/CH_2Cl_2, 1/1/2) to afford compound **10** as an orange solid (162 mg, 74%). R_f (EtOAc/CH_2Cl_2 1/9) 0.38; mp: 225–227 °C; IR (KBr, cm^{-1}) ν 3558, 2774, 1757, 1683, 1388, 750; ^1H NMR (DMSO-d_6, 250 MHz) δ 3.05 (s, 3H, CH_3), 6.21 (d, 1H, $J=8.2$ Hz, H_{7ind}), 6.63 (t, 1H, $J=7.7$ Hz, H_{5ind}), 7.03 (t, 1H, $J=7.7$ Hz, H_{6ind}), 7.32–7.36 (m, 1H, $H_{3\Phi}$), 7.40 (d, 1H, $J=8.0$ Hz, H_{7ind}), 7.61–7.65 (m, 2H, $H_{4/5\Phi}$), 7.93–7.96 (m, 1H, $H_{6\Phi}$), 8.07 (s, 1H, H_{2ind}), 10.00 (s, 1H, CHO), 11.99 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 24.2 (CH_3), 104.2 (Cq), 112.3 (CH), 120.2 (CH), 120.3 (CH), 122.3 (CH), 124.0 (Cq), 126.3 (Cq), 129.0 (CH), 129.4 (CH), 131.4 (CH), 131.9 (CH), 133.1 (Cq), 133.8 (CH), 134.6 (Cq), 134.7 (Cq), 136.6 (Cq), 170.9 $(CO)_{mal}$, 171.1 $(CO)_{mal}$, 191.9 $(CO)_{ald}$; MS (IS) *m/z*: 348.3 $[M+NH_4]^+$.

4.6. 3-(2-Formylphenyl)-4-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (11)

*From **8***: same procedure as described for compound **10**, starting from **5** and **8**. Compound **11** was obtained as an orange solid in 33% yield. *From **13***: a solution containing compound **5** (260 mg, 0.89 mmol), tributylstannylbenzaldehyde **13** (530 mg, 1.34 mmol), and CuI (12 mg, 0.09 mmol) in dioxane (20 mL) was degassed under argon for 30 min. After addition of $PdCl_2(PPh_3)_2$ (13 mg, 0.18 mmol), the reaction mixture was immediately placed in a pre-heated oil bath at 120 °C and refluxed for 8 h. After cooling at room temperature and filtration over Celite, the solvents were removed under reduced pressure. The resulting red oil was purified by flash chromatography (petroleum ether/CH_2Cl_2, 1/1 and then petroleum ether/CH_2Cl_2/EtOAc, 1/1/2). The recovered solid was dissolved in acetonitrile (50 mL) and washed with petroleum ether (5×50 mL) to afford, after removal of the solvents under reduced pressure, compound **11** as an orange solid (152 mg, 54%). R_f (petroleum ether/EtOAc, 1/1) 0.41; mp: 189–193 °C (dec); IR (KBr, cm^{-1}) ν 3431, 3019, 2927, 2855, 1713, 756; ^1H NMR (DMSO-d_6, 250 MHz) δ 6.23 (d, 1H, $J=7.8$ Hz, H_{4ind}), 6.62 (t, 1H, $J=7.8$ Hz, H_{5ind}), 7.02 (t, 1H, $J=7.2$ Hz, H_{6ind}), 7.31–7.34 (m, 1H, $H_{3\Phi}$), 7.39 (d, 1H, $J=8.2$ Hz, H_{7ind}), 7.60–7.63 (m, 2H, $H_{4/5\Phi}$), 7.92–7.96 (m, 1H, $H_{6\Phi}$), 8.02 (d, 1H, $J=3.0$ Hz, H_{2ind}), 10.00 (s, 1H, CHO), 11.15 (br s, 1H, NH maleimide); 11.96 (br s, 1H, NH indole); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 104.1 (Cq), 112.3 (CH), 120.1 (CH), 120.3 (CH), 122.2 (CH), 124.1 (Cq), 127.3 (Cq), 129.2 (CH), 129.4 (CH), 131.4 (CH), 131.7 (CH), 133.0 (Cq), 133.7 (CH), 134.7 (Cq), 134.9 (Cq), 136.5 (Cq), 172.1 $(CO)_{mal}$, 172.2 $(CO)_{mal}$, 191.9 $(CO)_{ald}$; MS (IS) *m/z*: 334.5 $[M+NH_4]^+$, 339.5 $[M+Na]^+$.

4.7. 2-Tributylstannylbenzaldehyde (13)[15]

A solution containing 2-bromobenzaldehyde **12** (500 mg, 2.7 mmol) and hexabutylditin (1.724 g, 2.97 mmol) in dry toluene (10 mL) was degassed under argon for 30 min. After addition of $Pd(PPh_3)_4$ (312 mg, 0.27 mmol), the reaction mixture was immediately placed in a pre-heated oil bath at 100 °C and refluxed for 24 h. After cooling at room temperature, hexane (10 mL) and a saturated aqueous solution of KF (10 mL) were added. After 30 min stirring, a filtration over Celite was carried out, the organic layer was separated, and the solvents were evaporated under reduced pressure. The resulting residue was purified by flash chromatography (petroleum ether/EtOAc, 98/2) to afford compound **13** as a colorless oil (614 mg, 57%). R_f (petroleum ether/EtOAc, 98/2) 0.43; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 0.80 (t, 9H, J=7.2 Hz, CH_3), 0.99 (t, 6H, J=8.0 Hz, CH_2–Sn), 1.19–1.28 (m, 6H, CH_2), 1.38–1.46 (m, 6H, CH_2), 7.56–7.65 (m, 3H, H_{arom}), 7.99 (d, 1H, J=6.4 Hz, H_{arom}), 10.0 (s, 1H, CHO).

4.8. 2-[2,5-Dihydro-4-(1*H*-indol-3-yl)-1-methyl-2,5-dioxo-1*H*-pyrrol-3-yl]benzoic acid (14)

The aldehyde **10** (899 mg, 2.72 mmol) was dissolved in a mixture of dioxane and water (115 mL/30 mL). After cooling to 5 °C, sulfamic acid (2.143 g, 22.07 mmol) was added. A solution of sodium chlorite (151 mg, 6.0 mmol) in water (3 mL) was slowly introduced with accurate control of the temperature. After 1 min, the reaction was quickly quenched with a mixture of water (50 mL), brine (50 mL), and EtOAc (150 mL). The aqueous layer was extracted with EtOAc (3×75 mL). The combined organic layers were washed with water (3×150 mL), dried over magnesium sulfate, and concentrated under reduced pressure. A mixture of EtOAc/CH_2Cl_2 (1/1) was added to the crude brown residue, the precipitate formed was filtered, and washed thoroughly (EtOAc/CH_2Cl_2, 1/1) till a red solid was obtained. The filtrate was evaporated to dryness to afford compound **14** as a brown solid (762 mg, 81%). R_f (EtOAc) 0.27; mp: 135 °C (dec); IR (KBr, cm^{-1}) ν 3323, 1785, 1698, 1385, 747; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.02 (s, 3H, CH_3), 6.43 (d, 1H, J=8.3 Hz, H_{4ind}), 6.65 (t, 1H, J=7.6 Hz, H_{5ind}), 7.02 (t, 1H, J=7.6 Hz, H_{6ind}), 7.07 (d, 1H, J=7.6 Hz, $H_{3\Phi}$), 7.37–7.42 (m, 2H, $H_{4\Phi/7ind}$), 7.50 (t, 1H, J=7.8 Hz, $H_{5\Phi}$), 7.97 (d, 1H, J=2.8 Hz, H_{2ind}), 8.04 (d, 1H, J=7.6 Hz, $H_{6\Phi}$), 11.87 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 24.0 (CH_3), 104.1 (Cq), 112.1 (CH), 119.9 (CH), 120.4 (CH), 122.0 (CH), 124.4 (Cq), 129.0 (CH), 130.0 (Cq), 130.1 (CH), 130.6 (CH), 130.7 (CH), 130.8 (Cq), 131.6 (Cq), 131.7 (CH), 131.9 (Cq), 136.4 (Cq), 168.1 $(CO)_{acid}$, 170.3 $(CO)_{mal}$, 171.5 $(CO)_{mal}$; MS (IS) m/z: 345.3 $[M-H]^-$.

4.9. 2-[2,5-Dihydro-4-(1*H*-indol-3-yl)-2,5-dioxo-1*H*-pyrrol-3-yl]benzoic acid (15)

Compound **15** was obtained as described for compound **14** starting from aldehyde **11** as an orange solid in 62% yield after flash chromatography (petroleum ether/EtOAc, 7/3 and then EtOAc/MeOH, 8/2). R_f (EtOAc) 0.60; mp: 129–132 °C (dec); IR (KBr, cm^{-1}) ν 3386, 1762, 1708, 1624, 745; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 6.56–6.63 (m, 2H, $H_{4/5ind}$), 6.97–7.00 (m, 2H, $H_{6ind/3\Phi}$), 7.28 (t, 1H, J=7.4 Hz, $H_{4\Phi}$), 7.36 (d, 1H, J=8.0 Hz, H_{7ind}), 7.43 (t, 1H, J=7.6 Hz, $H_{5\Phi}$), 7.84 (d, 1H, J=2.1 Hz, H_{2ind}), 8.07 (d, 1H, J=7.8 Hz, $H_{6\Phi}$), 10.87 (br s, 1H, NH), 11.85 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 104.3 (Cq), 111.9 (CH), 119.5 (CH), 120.7 (CH), 121.7 (CH), 124.6 (Cq), 128.5 (CH), 129.4 (Cq), 129.9 (CH), 130.1 (CH), 130.3 (Cq+CH), 130.4 (Cq), 130.5 (CH), 132.0 (Cq), 136.3 (Cq), 169.8 $(CO)_{acid}$, 171.8 $(CO)_{mal}$, 173.0 $(CO)_{mal}$; MS (IS) m/z: 333 $[M+H]^+$, 350 $[M+NH_4]^+$.

4.10. 1*H*-Benzo[5,6]pyrrolo[3′,4′:3,4]cyclohept[1,2-*b*]-indole-2-methyl-1,3,8(2*H*,9*H*)-trione (16)

$BF_3\cdot Et_2O$ (11 mL, 86.62 mmol) was added dropwise to a solution of acid **14** (745 mg, 2.17 mmol) in dichloroethane (120 mL). The mixture was refluxed for 5 h 30 min before quenching with iced water (100 mL). The aqueous layer was extracted three times with CH_2Cl_2 (2×60 mL). The combined organic layers were washed with an aqueous saturated solution of $NaHCO_3$ (120 mL) and then with water (3×120 mL). After drying over $MgSO_4$, the solvents were removed under reduced pressure to yield **16** (626 mg, 89%) as a brown solid. R_f (petroleum ether/EtOAc, 1/1) 0.67; mp 230–233 °C (dec); IR (KBr, cm^{-1}) ν 3272, 1768, 1703, 1388, 750; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.09 (s, 3H, CH_3), 7.32 (t, 1H, J=7.7 Hz, H_{12}), 7.51 (t, 1H, J=7.3 Hz, H_{11}), 7.67 (d, 1H, J=8.3 Hz, H_{10}), 7.84 (d, 1H, J=7.5 Hz, H_6), 7.93 (d, 1H, J=7.7 Hz, H_5), 8.46 (d, 1H, J=8.1 Hz, H_7), 8.72 (d, 1H, J=8.3 Hz, H_{13}), 8.86 (d, 1H, J=8.3 Hz, H_4), 13.04 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 24.1 (CH_3), 111.3 (Cq), 112.8 (CH), 121.8 (CH), 123.8 (Cq), 125.0 (CH), 126.4 (CH), 126.9 (CH), 128.1 (Cq), 129.3 (CH), 130.2 (2CH), 130.9 (Cq), 131.7 (CH), 137.1 (Cq), 138.0 (Cq), 141.1 (Cq), 168.9 $(C{=}O)_{mal}$, 170.1 $(CO)_{mal}$, 179.8 $(CO)_{cycle}$. HRMS (EI) calcd for $C_{20}H_{12}N_2O_3$: 328.08479; found: 328.0855 $(M)^{+\bullet}$.

4.11. 1*H*-Benzo[5,6]pyrrolo[3′,4′:3,4]cyclohept-[1,2-*b*]-indole-1,3,8(2*H*,9*H*)-trione (17)

Same procedure as described for compound **16**, starting from the acid **15**. After 20 h, compound **17** was isolated as an orange solid in 86% yield. R_f (petroleum ether/EtOAc, 6/4) 0.56; mp: 272–275 °C (dec); IR (KBr, cm^{-1}) ν 3274, 1778, 1723, 1582, 1018, 748; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 7.33 (t, 1H, J=7.2 Hz, H_{12}), 7.51 (t, 1H, J=7.2 Hz, H_{11}), 7.67 (d, 1H, J=8.2 Hz, H_{10}), 7.84–7.97 (m, 2H, $H_{5/6}$), 8.52 (d, 1H, J=7.0 Hz, H_4), 8.72 (d, 1H, J=7.7 Hz, H_{13}), 8.87 (d, 1H, J=8.4 Hz, H_7), 11.48 (br s, 1H, $NH_{(2)}$), 13.06 (br s, 1H, $NH_{(9)}$); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 111.5 (Cq), 112.8 (CH), 121.8 (CH), 124.0 (Cq), 126.1 (Cq), 126.5 (CH), 127.0 (CH), 128.5 (Cq), 129.3 (CH), 130.4 (CH), 130.5 (CH), 131.6 (Cq), 131.8 (CH), 137.6 (Cq), 138.0 (Cq), 141.2 (Cq), 170.4 $(CO)_{mal}$, 171.6 $(CO)_{mal}$, 180.3 $(CO)_{cycle}$. HRMS (EI) calcd for $C_{19}H_{10}N_2O_3$: 314.06914; found: 314.0697 $(M)^{+\bullet}$.

4.12. 3-[2-(2-Carboxy-phenyl)-2-methoxycarbonyl-ethynyl]-indole-1-carboxylic acid *tert*-butyl ester (18)

A solution of **9** (500 mg, 1.2 mmol) in a mixture of dioxane (12 mL) and water (4 mL) was treated at 0 °C with

NH_2SO_3H (955 mg, 9.8 mmol) and $NaClO_2$ (279 mg, 3.1 mmol) successively. After 10 min stirring at 0 °C, the reaction mixture was hydrolyzed with water (30 mL) and the product extracted with EtOAc (3×25 mL). The organic layer was washed twice with brine (50 mL), dried over $MgSO_4$, and the solvents were removed in vacuo to afford quantitatively **18** as a cream foamy solid. R_f (petroleum ether/EtOAc, 5/5) 0.42; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.50 (s, 9H, 3×CH_3), 3.75 (s, 3H, OCH_3), 6.43 (s, 1H, =CH), 7.26–7.34 (m, 3H, H_{ar}), 7.52 (ddd, 1H, J=J'=7.6 Hz, J''=1.2 Hz, H_{ar}), 7.62 (ddd, 1H, J=J'=7.4 Hz, J''= 1.5 Hz, H_{ar}), 7.70–7.74 (m, 1H, H_{ar}), 8.02 (s, 1H, =CH), 8.05–8.08 (m, 1H, H_{ar}), 8.23 (dd, 1H, J=7.7 Hz, J'=1.5 Hz, H_{ar}); MS (IS) m/z: 422.5 $[M+H]^{+\bullet}$.

4.13. 2-[2-(1*H*-Indol-3-yl)-1-methoxycarbonyl-ethynyl]-benzoic acid (19)

Compound **18** (55 mg, 126 μmol) in a mixture of CH_2Cl_2 (5 mL) and TFA (1 mL) was stirred at room temperature for 24 h. Water (10 mL) was added and the product was extracted with CH_2Cl_2 (2×10 mL). The organic phase was dried over $MgSO_4$ and the solvents were removed in vacuo. The product was purified by column chromatography on silica gel (3% MeOH in CH_2Cl_2) to afford **19** (11 mg, 26%). R_f (CH_2Cl_2/MeOH, 95/5) 0.40; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 3.51 (s, 3H, OCH_3), 6.18 (d, 1H, J=2.7 Hz, =CH–N), 7.07 (dd, 1H, J=J'=6.7 Hz, H_{ar}), 7.14 (dd, 1H, J=J'=7.9 Hz, H_{ar}), 7.28 (d, 1H, J=7.3 Hz, H_{ar}), 7.35 (d, 1H, J=7.3 Hz, H_{ar}), 7.53–7.59 (m, 3H, H_{ar}), 7.96 (s, 1H, =CH), 8.07 (d, 1H, J=7.3 Hz, H_{ar}), 11.38 (s, 1H, NH), 12.68 (br s, 1H, CO_2H).

4.14. 5,6-Dihydro-benzo[5,6]cyclohept[1,2-*b*]-indole-6-one-11-carboxylic acid methyl ester (20)

A mixture of hexamethyldisiloxane (4.44 mL, 20.9 mmol) and P_2O_5 (1.05 g, 7.4 mmol) in CH_2Cl_2 (40 mL) was refluxed for 45 min. After cooling to room temperature, the volatiles were removed in vacuo. CH_3NO_2 (4 mL) was added to the residue, followed by a solution of **18** (373 mg, 1.2 mmol) in CH_3NO_2 (6 mL). The mixture was heated at reflux for 10 min while the color turned from red to brown. After cooling, CH_3NO_2 was removed at reduced pressure. The residue was partitioned between water (15 mL) and EtOAc (15 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, and the solvents were removed under vacuum. The product crystallized from MeOH to afford a yellow solid (165 mg, 44%). R_f (petroleum ether/EtOAc, 7/3) 0.50; mp: 229 °C; IR (KBr, cm^{-1}) ν 3263 (NH), 1719 (CO), 1705 (CO), 1610, 1572, 1541, 1479, 1380, 1333, 1284; ^{1}H NMR (DMSO-d_6) δ 3.98 (s, 3H, OCH_3), 7.34 (dd, 1H, J=J'=7.1 Hz, H_{ar}), 7.53 (dd, 1H, J=J'=7.5 Hz, H_{ar}), 7.68 (d, 1H, J=8.4 Hz, H_{ar}), 7.75–7.93 (m, 3H, H_{ar}), 8.27 (d, 1H, J=8.1 Hz, H_{ar}), 8.34 (s, 1H, =CH), 8.79 (dd, 1H, J=7.8 Hz, J'=1.9 Hz, H_{ar}); ^{13}C NMR (DMSO-d_6) δ 52.8 (OCH_3), 113.1 (CH), 117.3 (Cq), 121.1 (CH), 121.6 (CH), 124.7 (CH), 126.0 (Cq), 127.3 (CH), 128.9 (CH), 130.4 (CH), 130.5 (Cq), 130.9 (CH), 131.9 (CH), 132.7 (Cq), 135.5 (Cq), 137.6 (Cq), 137.8 (Cq), 170.4 (CO), 177.9 (CO). HRMS (EI) calcd for $C_{19}H_{13}NO_3$ ($M^{+\bullet}$): 303.08954; found: 303.0903.

4.15. 1*H*-Benzo[5,6]pyrrolo[3′,4′:3,4]cyclohept[1,2-*b*]indole-12-bromo-2-methyl-1,3,8(2*H*,9*H*)-trione (21)

To a solution of compound **16** (100 mg, 0.30 mmol) in dry THF (5 mL) at 0 °C was added dropwise a solution of recrystallized NBS (544 mg, 3.05 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature for 3 days. An additional portion of NBS (271 mg, 1.52 mmol) was added and the mixture was stirred for another 24 h. Water (10 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (20 mL) were added. After extractions with EtOAc (3×50 mL), the combined organic layers were washed with water (100 mL) and concentrated under reduced pressure. The crude residue was precipitated with EtOAc (2 mL), to afford, after filtration and drying, compound **21** as an orange solid (69 mg, 55%). R_f (petroleum ether/EtOAc, 8/2) 0.30; mp 316–320 °C (dec); IR (KBr, cm^{-1}) ν 3277, 1765, 1711, 1576, 1479, 1445, 1389, 768; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 3.11 (s, 3H, CH_3), 7.63 (br s, 2H, $H_{10/11}$), 7.84–7.99 (m, 2H, $H_{5/6}$, 8.48 (d, 1H, J=7.6 Hz, H_7), 8.87 (d, 1H, J=7.8 Hz, H_4), 8.94 (s, 1H, H_{13}), 13.22 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 25.0 (CH_3), 110.7 (Cq), 114.4 (Cq), 114.9 (CH), 125.3 (Cq), 126.0 (Cq), 128.4 (Cq), 128.5 (CH), 129.6 (2CH), 130.4 (CH), 130.7 (CH), 132.2 (CH), 136.7 (Cq), 137.4 (Cq), 141.7 (Cq), 169.3 $(CO)_{mal}$, 170.3 $(CO)_{mal}$, 180.2 $(CO)_{cycle}$. HRMS (EI) calcd for $C_{20}H_{11}N_2O_3Br$: 405.99530; found: 405.9939 $(M)^{+\bullet}$.

4.16. 1*H*-Benzo[5,6]pyrrolo[3′,4′:3,4]cyclohept-[1,2-*b*]indole-9-dimethylaminoethyl-2-methyl-1,3,8(2*H*,9*H*)-trione (22)

To a suspension of NaH (8 mg, 0.20 mmol, 60% in oil) in DMF (2 mL) was added dropwise at 0 °C a solution of compound **16** (51 mg, 0.15 mmol) in dry DMF (2 mL). After 30 min, a mixture of NaH (23 mg, 0.58 mmol, 60% in oil) and 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (57 mg, 0.38 mmol) in DMF (1 mL) was added and the reaction mixture was stirred at 95 °C for 9 h. After cooling, iced water (20 mL) was added, the precipitate formed was filtered, and washed with water (2×10 mL). The solid was then dissolved in CH_2Cl_2 and the organic layer was dried over $MgSO_4$. After evaporation of the solvent, compound **22** was isolated as a brown solid (51 mg, 84%). R_f (petroleum ether/EtOAc, 4/6) 0.49; mp: 119–121 °C (dec); IR (KBr, cm^{-1}) ν 2924, 1764, 1706, 1622, 1439, 1385, 744; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 2.06 (s, 6H, CH_3–N), 2.54 (t, 2H, J=6.1 Hz, CH_2–NMe_2), 3.10 (s, 3H, CH_3–N_{mal}), 4.72 (t, 2H, J=5.9 Hz, CH_2–N_{ind}), 7.34 (t, 1H, J=7.6 Hz, H_{12}), 7.54 (t, 1H, J=7.7 Hz, H_{11}), 7.78–7.88 (m, 3H, $H_{5/6/10}$), 8.11 (d, 1H, J=7.8 Hz, H_7), 8.51 (d, 1H, J=8.3 Hz, H_{13}), 8.58 (d, 1H, J=8.0 Hz, H_4); ^{13}C NMR (DMSO-d_6, 125.8 MHz) δ 20.2 (CH_3–N_{mal}), 42.0 (CH_2–N_{ind}), 45.5 ($2CH_3$–NCH_2), 58.8 (CH_2–NMe_2), 111.3 (CH), 112.0 (Cq), 122.0 (CH), 122.6 (Cq), 125.5 (CH), 126.6 (2Cq), 126.7 (CH), 128.8 (CH), 129.0 (CH), 130.5 (CH), 130.6 (Cq), 131.1 (CH), 138.8 (Cq), 140.0 (Cq), 141.1 (Cq), 169.2 $(CO)_{mal}$, 170.1 $(CO)_{mal}$, 184.7 $(CO)_{cycle}$.

HRMS (EI) calcd for $C_{24}H_{21}N_3O_3$: 399.15829; found: 399.1563 $(M)^{+\bullet}$.

4.17. 1*H*-Benzo[5,6]pyrrolo[3′,4′:3,4]cyclohept[1,2-*b*]-indole-2-dimethylaminoethyl-1,3,8(2*H*,9*H*)-trione (23)

From ***17***: 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (46 mg, 0.32 mmol) was stirred in toluene (5 mL) at room temperature in the presence of K_2CO_3 (87 mg, 0.63 mmol) for 15 min. This organic solution was then washed with water (3×5 mL) before drying over $MgSO_4$. This solution was added dropwise at 65 °C to a suspension of **17** (50 mg, 0.16 mmol) and K_2CO_3 (22 mg, 0.16 mmol) in dry DMF (20 mL). The resulting mixture was heated for 24 h at 65 °C. After cooling, water (20 mL) and brine (10 mL) were added. The product was extracted with EtOAc (3×30 mL). The combined organic layers were then washed with water (4×40 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The crude residue was purified by flash chromatography (EtOAc and then EtOAc/MeOH, 8/2) to afford compound **23** as a light brown solid (21 mg, 34%). *From* ***27***: a solution of compound **27** (36 mg, 0.16 mmol), *N*,*N*-dimethylethylenediamine (207 mg, 2.34 mmol), and DMF (0.75 mL) was heated at 160 °C for 18 h in a sealed tube. After cooling, water (5 mL) was added and the pH was adjusted to 1 with a hydrochloric acid solution (1 N, 10 mL). The acidic aqueous medium was washed with EtOAc (2×30 mL) before neutralization (pH 8) with an aqueous solution of $NaHCO_3$ (8 mL). The product was then extracted with EtOAc (5×50 mL). The combined organic layers were washed with water and brine, dried over $MgSO_4$, and the solvent was removed under reduced pressure. Compound **23** was obtained as a light brown solid (26 mg, 59%). R_f (EtOAc/MeOH, 9/1) 0.36; mp: 195–197 °C dec; IR (KBr, cm^{-1}) ν 3448, 2944, 1769, 1702, 1474, 747; ^1H NMR (DMSO-d_6, 250 MHz) δ 2.22 (s, 6H, CH_3–NCH_2), 2.57 (m, 2H, CH_2–NMe_2), 3.76 (t, 2H, J=6.2 Hz, CH_2–N_{mal}), 7.35 (t, 1H, J=7.6 Hz, H_{12}), 7.52 (t, 1H, J=8.5 Hz, H_{11}), 7.68 (d, 1H, J=8.2 Hz, H_{10}), 7.85–7.99 (m, 2H, $H_{5/6}$), 8.52 (d, 1H, J=7.8 Hz, H_4), 8.75 (d, 1H, J=8.7 Hz, H_{13}), 8.89 (d, 1H, J=8.2 Hz, H_7), 13.12 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 36.0 (CH_2–N_{mal}), 45.1 ($2CH_3$–NCH_2), 56.4 (CH_2–NMe_2), 111.4 (Cq), 112.9 (CH), 121.9 (CH), 123.9 (Cq), 125.2 (Cq), 126.4 (CH), 127.1 (CH), 128.3 (Cq), 129.4 (CH), 130.4 (CH), 130.6 (CH), 131.1 (Cq), 132.0 (CH), 137.5 (Cq), 138.1 (Cq), 141.4 (Cq), 169.0 $(CO)_{mal}$, 170.1 $(CO)_{mal}$, 180.2 $(CO)_{cycle}$. HRMS (EI) calcd for $C_{23}H_{19}N_3O_3$: 385.14264; found: 385.1422 $(M)^{+\bullet}$.

4.18. 1*H*-Benzo[5,6]pyrrolo[3′,4′:3,4]cyclohept-[1,2-*b*]indole-2,9-bis(dimethylaminoethyl)-1,3,8-(2*H*,9*H*)-trione (24)

Compound **24** was concomitantly isolated in the reaction leading to **23** from **17**. After the flash chromatography, compound **24** was obtained as an orange solid (9%). R_f (EtOAc/MeOH, 9/1) 0.07; mp: 91–92 °C (dec); IR (KBr, cm^{-1}) ν 3056, 2940, 1765, 1702, 1398, 742; ^1H NMR (DMSO-d_6, 250 MHz) δ 2.06 (s, 6H, CH_3–NCH_{2ind}), 2.23 (s, 6H, CH_3–NCH_{2mal}), 2.50 (m, 4H, CH_2–$NMe_{2(ind+mal)}$), 3.75 (t, 2H, J=6.6 Hz, CH_2–N_{mal}), 4.75 (t, 2H, J=6.6 Hz, CH_2–N_{ind}), 7.36 (t, 1H, J=7.5 Hz, H_{12}), 7.55 (t, 1H, J=8.2 Hz, H_{11}), 7.80–7.88 (m, 3H, $H_{5/6/10}$), 8.13 (d, 1H, J=8.5 Hz, H_4), 8.53 (d, 1H, J=7.5 Hz, H_{13}), 8.59 (d, 1H, J=6.4 Hz, H_7); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 35.9 (CH_2–N_{mal}), 42.1 (CH_2–N_{ind}), 45.0 ($2CH_3$–NCH_{2mal}), 45.5 ($2CH_3$–NCH_{2ind}), 56.3 (CH_2–NMe_{2mal}), 58.8 (CH_2–NMe_{2ind}), 111.4 (CH), 111.9 (Cq), 122.1 (CH), 122.5 (Cq), 125.5 (CH), 126.3 (Cq), 126.5 (Cq), 126.8 (CH), 128.9 (CH), 129.0 (CH), 130.4 (Cq), 130.6 (CH), 131.2 (CH), 138.8 (Cq), 140.2 (Cq), 141.1 (Cq), 168.9 $(CO)_{mal}$, 169.9 $(CO)_{mal}$, 184.7 $(CO)_{cycle}$. HRMS (EI) calcd for $C_{27}H_{28}N_4O_3$: 456.21614; found: 456.2149 $(M)^{+\bullet}$.

4.19. 1*H*-Benzo[5,6]pyrrolo[3′,4′:3,4]cyclohept[1,2-*b*]-indole-2-methyl-1,3(2*H*,9*H*)-dione (25)

In a sealed tube, a solution of **16** (51 mg, 0.14 mmol) and *N*,*N*-dimethylethylenediamine (201 mg, 2.28 mmol) in DMF (0.75 mL) was heated at 160 °C for 22 h. After cooling to room temperature, water was added (15 mL), the pH was adjusted to 8 with 1 N HCl, and the product was extracted with EtOAc (3×30 mL). The combined organic layers were washed with water (3×50 mL) and the solvent was evaporated in vacuo. The product was purified by flash chromatography (petroleum ether/EtOAc, 3/7 and then EtOAc/MeOH, 9/1). Compound **25** was obtained as a red solid (19 mg, 41%). R_f (EtOAc/MeOH, 9/1) 0.91; mp: 94–97 °C (dec); IR (KBr, cm^{-1}) ν 3336, 2925, 1761, 1690, 1587, 1439, 1386, 747; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.09 (s, 3H, CH_3), 3.93 (s, 2H, $CH_{2(cycle)}$), 7.11 (dt, 1H, J=7.5 Hz, J'=1.1 Hz, H_{12}), 7.16 (dt, 1H, J=7.5 Hz, J'=1.1 Hz, H_{11}), 7.36–7.40 (m, 2H, $H_{5/7}$), 7.44 (d, 1H, J=7.9 Hz, H_{10}), 7.51 (dt, 1H, J=7.5 Hz, J'=1.3 Hz, H_6), 7.87 (d, 1H, J=8.1 Hz, H_4), 8.05 (d, 1H, J=7.9 Hz, H_{13}), 12.12 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125.8 MHz) δ 23.8 (CH_3), 33.4 $(CH_2)_{cycle}$, 104.7 (Cq), 111.8 $(CH)_7$, 120.7 (CH), 121.2 (CH), 122.2 (CH), 124.6 (Cq), 126.2 (CH), 127.1 (Cq), 128.6 (CH), 128.7 (CH), 129.1 (Cq), 130.5 (CH), 134.7 (Cq), 135.4 (Cq), 136.6 (Cq), 140.9 (Cq), 170.2 $(CO)_{mal}$, 170.8 $(CO)_{mal}$; MS (IS) *m*/*z*: 332.5 $[M+NH_4]^+$, 337.5 $[M+Na]^+$. HRMS (EI) calcd for $C_{20}H_{14}N_2O_2$: 314.10553; found: 314.1055 $(M)^{+\bullet}$.

4.20. 1*H*-Benzo[5,6]pyrrolo[3′,4′:3,4]cyclohept[1,2-*b*]-indole-2-dimethylaminoethyl-1,3(2*H*,9*H*)-dione (26)

A solution of **27** (100 mg, 0.32 mmol) in *N*,*N*-dimethylethylenediamine (4 mL) was heated at reflux for 64 h. After cooling to room temperature, water was added (10 mL) and the pH was adjusted to 9 by addition of concd HCl (0.5 mL). The product was extracted by EtOAc (5×10 mL). The combined organic layers were washed with water (20 mL). Drying over $MgSO_4$ and removal of the solvents afforded compound **26** (102 mg, 86%) as a brown solid. R_f (petroleum ether/EtOAc, 6/4) 0.26; mp: 165–168 °C (dec); IR (KBr, cm^{-1}) ν 3398, 3050, 2948, 1758, 1694, 1465, 1400, 744; ^1H NMR (DMSO-d_6, 500 MHz) δ 2.22 (s, 6H, CH_3–NCH_2), 2.54 (t, 2H, J=6.6 Hz, CH_2–NMe_2), 3.71 (t, 2H, J=6.6 Hz, CH_2–N_{mal}), 3.94 (s, 2H, $CH_{2(cycle)}$), 7.11 (t, 1H, J=7.5 Hz, H_{12}), 7.16 (t, 1H, J=7.5 Hz, H_{11}), 7.36–7.41 (m, 2H, $H_{5/7}$), 7.44 (d, 1H, J=8.1 Hz, H_{10}), 7.51 (t, 1H, J=7.6 Hz, H_6), 7.87 (d, 1H, J=7.7 Hz, H_4), 8.05 (d, 1H, J=7.9 Hz, H_{13}), 12.15 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6, 125.8 MHz) δ 33.4 $(CH_2)_{cycle}$, 35.7 (CH_2–N_{mal}), 45.2 (2

CH_3–NCH_2), 56.7 (CH_2–NMe_2), 104.7 (Cq), 111.9 (CH), 120.8 (CH), 121.3 (CH), 122.3 (CH), 124.6 (Cq), 126.3 (CH), 126.8 (Cq), 128.7 (2CH), 129.1 (Cq), 130.6 (CH), 134.6 (Cq), 135.5 (Cq), 136.7 (Cq), 141.1 (Cq), 170.1 $(CO)_{mal}$, 170.7 $(CO)_{mal}$; MS (IS) *m/z*: 372.5 $[M+H]^+$. HRMS (EI) calcd for $C_{23}H_{21}N_3O_2$: 371.16338; found: 371.1625 $(M)^{+\bullet}$.

4.21. Benzo[5,6]furo[3′,4′:3,4]cyclohept[1,2-*b*]-indole-1,3,8(9*H*)-trione (27)

A solution of compound **16** (120 mg, 0.37 mmol) and KOH (819 mg, 14.62 mmol) in acetone (3 mL) and water (2 mL) was stirred at room temperature for 24 h. After removal of acetone in vacuo, water was added (10 mL), followed by concentrated hydrochloric acid (2 mL) till pH 1. The solution was stirred 12 h at room temperature. The product was extracted with EtOAc (4×30 mL). The combined organic layers were washed with water (3×40 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Compound **27** was thus obtained quantitatively (117 mg) as a light brown solid. R_f (EtOAc/petroleum ether, 1/1) 0.68; mp: 220–223 °C (dec); IR (KBr, cm^{-1}) ν 3258, 1825, 1755, 1588, 1259, 746; ^1H NMR (DMSO-d_6, 250 MHz, ppm) δ 7.40 (t, 1H, J=7.8 Hz, H_{12}), 7.56 (t, 1H, J=7.6 Hz, H_{11}), 7.72 (d, 1H, J=8.0 Hz, H_{10}), 7.93–8.06 (m, 2H, $H_{5/6}$), 8.57 (d, 1H, J=8.0 Hz, H_4), 8.69 (d, 1H, J=8.4 Hz, H_{13}), 8.85 (d, 1H, J=8.0 Hz, H_7), 13.35 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.9 MHz) δ 110.4 (Cq), 113.3 (CH), 122.6 (CH), 123.7 (Cq), 125.7 (CH), 126.6 (Cq), 127.4 (CH), 127.6 (Cq), 129.8 (CH), 130.1 (CH), 131.5 (CH), 132.5 (Cq), 132.6 (CH), 137.5 (Cq), 138.1 (Cq), 141.7 (Cq), 164.1 $(CO)_{anh}$, 165.0 $(CO)_{anh}$, 179.9 $(CO)_{cycle}$. HRMS (EI) calcd for $C_{19}H_9NO_4$: 315.05316; found: 315.0537 $(M)^{+\bullet}$.

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