Expedited Synthesis of Substituted Dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraones Structurally Related to Granulatimide

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Abstract: Dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraones can be considered as granulatimide analogues. In view of structure–activity relationship studies in these series, a parallel liquid-phase microwave-assisted synthesis was developed to generate a small library of compounds bearing various substituents at positions 8, 9, 10, or 11 on the aromatic framework.

Key words: parallel synthesis, granulatimide, antitumor agents, dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone

Granulatimide and isogranulatimide (Figure 1), natural compounds isolated from the ascidian *Didemnum granulatum*, have triggered considerable interest since the discovery in 1998 of their inhibitory properties toward the G2 checkpoint of the cell cycle.[1–4] The G2 checkpoint represents a promising target for the development of anticancer drugs. Indeed, because of the inefficiency of the G1 checkpoint in more than 60% of cancer cells, combining DNA damaging agents with G2 checkpoint inhibitors should force cancer cells selectively into a premature and lethal mitosis.[5–7] In connection with this, phase I and II clinical trials are reported with UCN-01, a G2 checkpoint inhibitor (Figure 1), in combination with topotecan in ovarian cancers and in combination with cisplatin or carboplatin in patients with advanced refractory solid tumors.[8–10] To improve the biological activities of granulatimide and isogranulatimide, structure–activity relationship studies have been carried out.[11–18] In particular, analogues have been synthesized in which the imidazole moiety has been replaced by a pyrrole or in which the indole unit has been replaced by a 7-azaindole. In another family of granulatimide analogues, the imidazole heterocycle has been replaced by a maleimide moiety (Figure 1).[16–18]

In this paper, we report a more efficient synthetic method to prepare new bis-imide analogues substituted at posi-

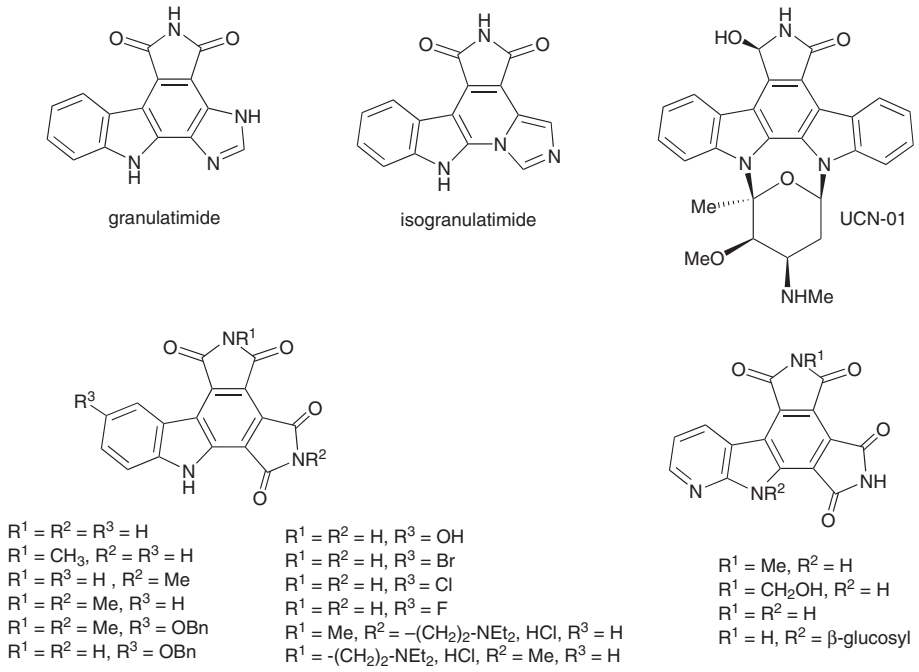

Figure 1 Chemical structures of granulatimide, isogranulatimide, UCN-01, and bis-imide analogues previously synthesized.

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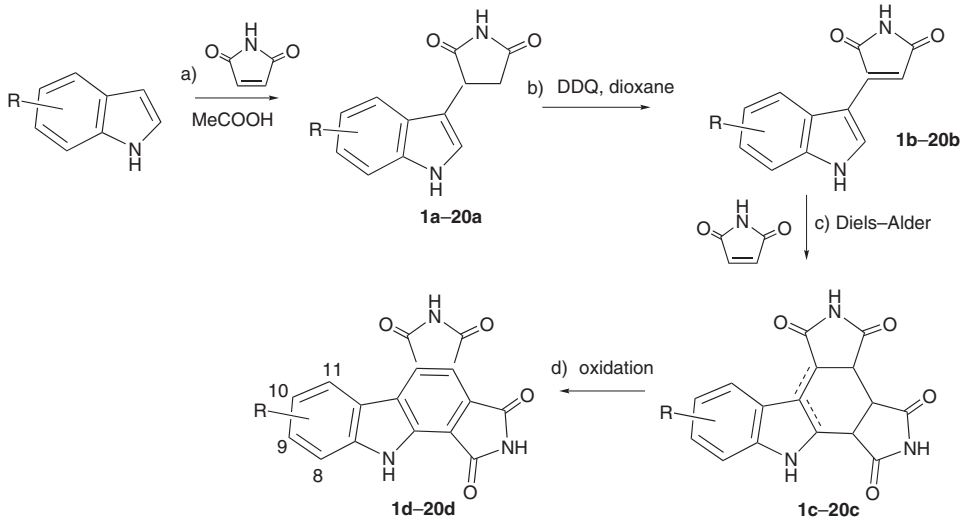

Scheme 1 Synthetic scheme for bis-imide analogues.

tions 8, 9, 10, or 11 of the indole heterocycle (Tables 1 . The general synthetic scheme for the bis-imide analogues (**1d**–**20d**) required four steps from the corresponding substituted indoles (Scheme 1). Compared with the previously described procedures, the efficiency of the syntheses was greatly improved by using a parallel solution-phase method for step b and microwave irradiation for two steps: the Michael addition (step a) and the Diels–Alder cycloaddition (step c), and in some cases for the last oxidation step (step d).

The typical method for the synthesis of the bis-imide granulatimide analogues was carried out as follows. For the first step (step a), commercially available substituted indoles and maleimide (three equivalents) in glacial acetic acid were heated in sealed tubes at 190 °C in a CEM Explorer microwave oven (200 W, no cooling). With several compounds, additional amounts of maleimide were required for complete disappearance of the indoles to be observed (HPLC). The mixtures were then poured into water and purified by solid phase extraction (SPE) on Waters Oasis HLB cartridges.[19] The yields for step a varied from 37–99%. The reactivity is dependant on the nature of the substituent and on its position on the indole moiety (Table 1). Several substitutions on the indoles are not compatible with the AcOH/microwave method. For example, nitro substituents induced only degradation/polymerization, cyano substituents were transformed into the corresponding primary amides, CF_3 substituents were hydrolyzed to COOH groups, and unprotected anilines were rapidly acetylated.

Hydroxymethyl and formyl groups in positions 5 or 6 induced polymerization. For the synthesis of compound **1d**, the hydroxyl group had to be protected first with a benzyl group. As expected, the Michael reaction proceeded smoothly with the benzyl ether. The benzyl group was then removed at this stage of the synthesis by catalytic hydrogenation.

The oxidation step (step b) was carried out in parallel on a Büchi Syncore reactor using 0.2 M DDQ in dioxane at room temperature for one hour. The reaction mixtures were then centrifuged in Whatman filtration tubes. It was necessary to perform the centrifugation rapidly when the required products were formed to avoid a further addition reaction of DDQ-2H to the maleimides followed by re-oxidation leading to compounds **A** (Figure 2).

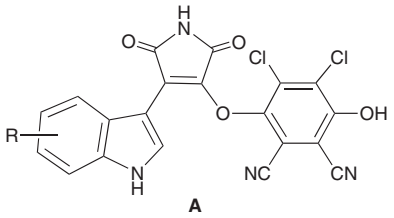

Figure 2

After centrifugation, the solid (DDQ-2H) was washed with dioxane and the filtrates were lyophilized. For the Diels–Alder reaction (step c), a mixture of the crude compounds obtained in step b, and maleimide (three equivalents) in dioxane were heated in sealed tubes in a microwave oven (200 W, CEM) at 170 °C for one hour. After concentration, water was added, and the mixtures were filtered in Whatman tubes. The precipitates were dissolved in dioxane and freeze-dried. It was observed from LC/MS analysis that the final bis-imide products were in some cases obtained directly after step c (Table 1). The Diels–Alder adducts were then oxidized (step d) using DDQ (2.1 equivalents) or in the presence of TFA in dioxane for various reaction times and at various temperatures. Alternatively, these mixtures can be heated via microwave irradiation in sealed tubes at 170 °C (200 W, no cooling). After evaporation, water was added to the residues, the mixtures were filtered, and the solid residues were washed with water then with ethyl actetate to give the bis-imides **1d**–**20d**. The yields for step d varied from

Table 1 New Bis-imides **1d–20d**

Compd	C-8	C-9	C-10	C-11	Step a **1a–20a**		Step b **1b–20b**	Step c **1c–20c**		Step d **1d–20d**		
					Heating time (h)	Yield (%)	Yield (%)[b]	Heating time (h)	Yield[c]	Conditions[d]	Yield (%)	Purity[e]
1	H	OH	H	H	1[a]	89[a]	nd	1	nd	reflux, 60 h	33	nd
2	OMe	H	H	H	2	75	nd	1	nd	MW, 1 h	56	>99
3	H	OMe	H	H	2	99	26	1	63	45 °C, 3 d	28	97
4	H	H	OMe	H	1	69	65	1	70	80 °C, 55 h	38	>99
5	H	H	H	OMe	1.5	84	nd	5	21	reflux, 60 h	65	nd
6	F	H	H	H	3	68	nd	2	nd	MW, 2 h	24	97
7	H	F	H	H	3.3	78	nd	1	52	reflux, 60 h	23	nd
8	H	F	F	H	3	66	nd	2	nd	MW, 1 h	27	98
9	Cl	H	H	H	20	49	10	1	19	45 °C, 3 d	15	86
10	H	Cl	H	H	4	50	nd	1	82	reflux, 60 h	51	nd
11	H	Br	H	H	3	92	nd	2	nd	MW, 30 min	27	96
12	CH_3	H	H	H	1	67	nd	1	51	reflux, 3 d	27	nd
13	H	CH_3	H	H	1	89	nd	1	80	r.t., 24 h	31	nd
14	H	COOH	H	H	4	37	nd	2	nd	MW, 1 h	42	91
15	H	H	COOH	H	5	43	nd	5	nd	40 °C, 24 h	23	99
16	H	H	H	COOH	5	45	7	1	nd	MW, 1 h	38	92
17	H	COOMe	H	H	3	66	nd	2	nd	MW, 1 h	15	85
18	H	H	COOMe	H	7	73	nd	1	88	reflux, 60 h	31	nd
19	H	H	H	COOMe	8	81	16	4	**19d**[f]	MW, 30 min	5	99
20	H	-OCH_2O-		H	1	84	65	1	nd	80 °C, 55 h	59	99

[a] Step a performed with benzyl protecting group.
[b] The yield was not determined (nd) when the required product formed as a mixture with DDQ-H2 and/or with the starting material.
[c] For step c, the yield was not determined when the required product formed as a mixture with the final product, generally obtained after step d.
[d] DDQ used as the oxidant except for compound **12**, where TFA (13 equiv) and dioxane were employed.
[e] Determined by HPLC (210 nm).
[f] Major product.

5–65% (Table 1). The melting points of **1d–20d** were found to be >300 °C. Due to the insolubility of some compounds, their ^{13}C NMR spectra could not be recorded.

In conclusion, we have synthesized a series of granulatimide and isogranulatimide bis-imides analogues **1d–20d** bearing various substituents on positions 8, 9, 10, and 11 of the aromatic framework. The method differs from the procedure previously described by the use of parallel synthesis for step b. Moreover, the microwave-assisted reactions allowed a reduction in the reaction times from at least two days to about one hour. The biological activities of these compounds are currently under investigation.

IR spectra were recorded on a Perkin-Elmer 881, Perkin-Elmer Paragon 500 or Bruker Vector 22 spectrometer. NMR spectra were performed on a Bruker AVANCE 400 or Bruker AVANCE 200 DPX. Low resolution mass spectra (ESI+ and APCI+) and HRMS were determined on a MS Hewlett Packard engine or Q-TOF 2 Micromass. Due to the insolubility of some compounds, their ^{13}C NMR spectra could not be recorded.

9-Hydroxy-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (1d)

IR (KBr): 1604 (C=C), 1650–1840 (C=O), 3100–3650 (=NH) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6–D_2O): δ = 6.91 (1 H, dd, *J* = 8.5, 2.0 Hz), 7.13 (1 H, d, *J* = 2.0 Hz), 8.77 (1 H, d, *J* = 8.5 Hz).

HRMS (ESI+): *m*/*z* calcd for $C_{16}H_7N_3NaO_5$ [M + Na]$^+$: 344.0283; found: 344.0288.

8-Methoxy-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (2d)
IR (ATR): 1706, 1768 (C=O), 3180, 3276, 3459 (NH) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.00 (3 H, s, CH_3), 7.22 (1 H, d, *J* = 7.5 Hz), 7.32 (1 H, t, *J* = 7.5 Hz), 8.55 (1 H, d, *J* = 7.5 Hz), 11.45 (1 H, s, NH), 11.50 (1 H, s, NH), 12.18 (1 H, s, NH).

MS (EI): *m*/*z* = 335 [M]$^+$.

9-Methoxy-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (3d)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.90 (3 H, s, CH_3), 7.00 (1 H, dd, *J* = 8.5, 1.5 Hz), 7.20 (1 H, d, *J* = 1.5 Hz), 8.80 (1 H, d, *J* = 8.5 Hz), 11.60 (2 H, br, NH).

MS (EI): *m*/*z* = 335 [M]$^+$.

10-Methoxy-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (4d)
IR (ATR): 1709, 1775 (C=O), 3174, 3367 (NH) cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.90 (3 H, s, CH_3), 7.28 (1 H, dd), 7.61 (1 H, d), 8.48 (1 H, d), 11.5 (2 H, 2 s, NH), 12.5 (1 H, s, NH).

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_9N_3NaO_5$ [M + Na]$^+$: 358.0440; found: 358.0474.

11-Methoxy-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (5d)
IR (KBr): 1717, 1771 (C=O), 3344, 3100–3400 (NH) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.04 (3 H, s, CH_3), 6.91 (1 H, d, *J* = 8.0 Hz), 7.37 (1 H, d, *J* = 8.0 Hz), 7.64 (1 H, t, *J* = 8.0 Hz), 11.31 (1 H, s, NH), 11.51 (1 H, s, NH), 12.73 (1 H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.2 (CH_3), 102.8, 104.8, 131.6 (Ar-CH), 110.0, 117.3, 121.1, 121.8, 124.9, 130.7, 137.0, 146.0, 156.5 (Ar-C), 165.8, 166.2, 166.6, 168.6 (C=O).

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_9N_3NaO_5$ [M + Na]$^+$: 358.0440; found: 358.0439.

8-Fluoro-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (6d)
IR (ATR): 1702, 1784 (C=O), 3100–3350 (NH) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.40 (1 H, m), 7.55 (1 H, dd), 8.90 (1 H, d), 11.60 (2 H, 2 s, NH), 13.15 (1 H, s, NH).

HRMS (ESI+): *m*/*z* calcd for $C_{16}H_7FN_3O_4$ [M + H]$^+$: 324.0421; found: 324.0452.

9-Fluoro-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7d)
IR (KBr): 1700, 1735, 1780 (C=O), 3100–3600 (NH) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.31 (1 H, pseudo dt, *J* = 9.5, 2.0 Hz), 7.46 (1 H, dd, *J* = 9.5, 2.0 Hz), 8.98 (1 H, dd, *J* = 9.0, 5.5 Hz), 11.60 (1 H, s, NH), 11.62 (1 H, s, NH), 12.82 (1 H, s, NH).

HRMS (ESI+): *m*/*z* calcd for $C_{16}H_7FN_3O_4$ [M + H]$^+$: 324.0421; found: 324.0424.

9,10-Difluoro-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (8d)
IR (ATR): 1714, 1759 (C=O), 3100–3380 (NH) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.55 (1 H, t), 8.69 (1 H, t), 11.60 (2 H, 2 s, NH), 12.75 (1 H, s, NH).

HRMS (ESI+): *m*/*z* calcd for $C_{16}H_6F_2N_3O_4$ [M + H]$^+$: 342.0326; found: 342.0353.

8-Chloro-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (9d)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.40 (1 H, br), 7.70 (1 H, d), 9.00 (1 H, d), 11.50 (3 H, br, NH).

MS (ESI): *m*/*z* = 340 [M + H]$^+$.

9-Chloro-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (10d)
IR (KBr): 1604 (C=C), 1723, 1761 (C=O), 3110–3390 (NH) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.45 (1 H, d, *J* = 8.5 Hz), 7.70 (1 H, s), 8.89 (1 H, d, *J* = 8.5 Hz), 11.61 (1 H, s, NH), 11.63 (1 H, s, NH), 12.77 (1 H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 112.3, 121.9, 126.8 (Ar-CH), 118.2, 118.3, 120.0, 123.4, 126.0, 131.5, 134.3, 137.0, 144.5 (Ar-C), 166.2 (2 C), 168.4, 169.0 (C=O).

HRMS (ESI+): *m*/*z* calcd for $C_{16}H_6ClN_3NaO_4$ [M + Na]$^+$: 361.9945; found: 361.9964.

9-Bromo-1,3,4,6-tetrahydro-1,3,4,6-tetraoxo-7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole (11d)
IR (KBr): 1600 (C=C), 1720, 1760 (C=O), 3100–3380 (NH) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.62 (1 H, dd, *J* = 8.5, 1.5 Hz), 7.91 (1 H, d, *J* = 1.5 Hz), 8.88 (1 H, d, *J* = 8.5 Hz), 11.63 (1 H, s, NH), 11.65 (1 H, s, NH), 12.83 (1 H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 115.4, 124.6, 127.0 (Ar-CH), 118.4, 118.5, 120.1, 122.9, 123.5, 126.2, 131.7, 136.9, 144.8 (Ar-C), 166.2, 166.3, 168.4, 169.1 (C=O).

HRMS (ESI+): *m*/*z* calcd for $C_{16}H_6BrN_3NaO_4$ [M + Na]$^+$: 405.9439; found: 405.9424.

8-Methyl-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (12d)
IR (KBr): 1715, 1770 (C=O), 3254, 3307 (NH) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.75 (3 H, s, CH_3), 7.38 (1 H, pseudo t, *J* = 7.5 Hz), 7.52 (1 H, d, *J* = 7.0 Hz), 8.95 (1 H, d, *J* = 8.0 Hz), 11.58 (1 H, s, NH), 11.60 (1 H, s, NH), 12.36 (1 H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.5 (CH_3), 121.7, 123.0, 130.9 (Ar-CH), 118.1, 119.5, 119.8, 122.5, 125.0, 125.8, 131.3; 137.1, 143.1 (Ar-C), 166.2 (2 C), 168.2, 169.1 (C=O).

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_9N_3NaO_4$ [M + Na]$^+$: 342.0491; found: 342.0501.

9-Methyl-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (13d)
IR (KBr): 1720, 1765 (C=O), 3100–3400 (NH) cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.56 (3 H, s, CH_3), 7.26 (1 H, d, *J* = 8.5 Hz), 7.54 (1 H, s), 8.82 (1 H, d, *J* = 8.0 Hz), 11.53 (1 H, s, NH), 11.54 (1 H, s, NH), 12.62 (1 H, br, NH).

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_9N_3NaO_4$ [M + Na]$^+$: 342.0491; found: 342.0494.

1,3,4,6-Tetrahydro-1,3,4,6-tetraone-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-9-carboxylic Acid (14d)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.95 (1 H, d, *J* = 8.5 Hz), 8.30 (1 H, s), 8.95 (1 H, dd, *J* = 8.5, 1.0 Hz), 11.50 (3 H, br s), 12.80 (1 H, br).

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_7N_3NaO_6$ [M + Na]$^+$: 372.0233; found: 372.0247.

1,3,4,6-Tetrahydro-1,3,4,6-tetraone-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-10-carboxylic Acid (15d)
IR (ATR): 1710, 1770 (C=O), 3100–3500 (NH) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.80 (1 H, d, *J* = 8.5 Hz), 8.25 (1 H, dd, *J* = 8.5, 1.0 Hz), 9.15 (1 H, s), 11.6 and 13.0 (4 H, br).

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_7N_3NaO_6$ [M + Na]$^+$: 372.0233; found: 372.0246.

1,3,4,6-Tetrahydro-1,3,4,6-tetraone-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-11-carboxylic Acid (16d)
^1H NMR (400 MHz, DMSO-d_6): δ = 7.65 (1 H, d, *J* = 8.0 Hz), 7.70 (1 H, t, *J* = 8.0 Hz), 7.95 (1 H, d, *J* = 8.0 Hz), 11.4 (1 H, s), 11.6 (1 H, s), 13.0 (1 H, br s).

HRMS (ESI+): *m*/*z* calcd for $C_{17}H_7N_3NaO_6$ [M + Na]$^+$: 372.0233; found: 372.0237.

9-Methoxycarbonyl-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (17d)
IR (ATR): 1708, 1760 (C=O), 3100–3680 (NH) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.98 (3 H, s), 8.00 (1 H, d, *J* = 8.5 Hz), 8.35 (1 H, s), 9.05 (1 H, d, *J* = 8.5 Hz), 11.65 (2 H, 2 s, NH), 13.0 (1 H, s, NH).

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_9N_3NaO_6$ [M + Na]$^+$: 386.0389; found: 386.0418.

10-Methoxycarbonyl-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (18d)
IR (KBr): 1715, 1774 (C=O), 3100–3400 (NH) cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.97 (3 H, s, CH_3), 7.88 (1 H, d, *J* = 9.0 Hz), 8.31 (1 H, dd, *J* = 8.5, 1.5 Hz), 9.72 (1 H, d, *J* = 1.5 Hz), 11.68 (1 H, s, NH), 11.72 (1 H, s, NH), 13.15 (1 H, s, NH).

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_9N_3NaO_6$ [M + Na]$^+$: 386.0389; found: 386.0396.

11-Methoxycarbonyl-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (19d)
^1H NMR (400 MHz, DMSO-d_6): δ = 3.80 (3 H, s), 7.65 (1 H, d, *J* = 8.0 Hz), 7.75 (1 H, t, *J* = 8.0 Hz), 8.00 (1 H, d, *J* = 8.0 Hz).

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_9N_3O_6$ [M]$^+$: 363.0491; found: 363.0482.

9,10-Methylenedioxy-1,3,4,6-tetrahydro-2*H*,5*H*,7*H*-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (20d)
IR (ATR): 1627 (C=C), 1706, 1753 (C=O), 3248 (NH) cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 6.20 (2 H, s), 7.05 (1 H, s), 8.18 (1 H, s), 11.4 (2 H, s, NH), 12.4 (1 H, s, NH).

MS (EI+): *m*/*z* = 349 [M]$^+$.

References

(1) Berlinck, R. G. S.; Britton, R.; Piers, E.; Lim, L.; Roberge, M.; Moreira da Rocha, R.; Andersen, R. J. *J. Org. Chem.* **1998**, *63*, 9850.
(2) Roberge, M.; Berlinck, R. G. S.; Xu, L.; Andersen, H. J.; Lim, L. Y.; Curman, D.; Stringer, C. M.; Friend, S. H.; Davies, P.; Vincent, I.; Haggarty, S. J.; Kelly, M. T.; Britton, R.; Piers, E.; Anderson, R. J. *Cancer Res.* **1998**, *58*, 5701.
(3) Andersen, R. J.; Roberge, M.; Sanghera, J.; Leung, D. International Patent WO99/47522, **1999**; *Chem. Abstr.* **1999**, *131*, 243451.
(4) Jiang, X.; Zhao, B.; Britton, R.; Lim, L. Y.; Leong, D.; Sanghera, J. S.; Zhou, B. B.; Piers, E.; Andersen, R. J.; Roberge, M. *Mol. Cancer Ther.* **2004**, *3*, 1221.
(5) Kawabe, T. *Mol. Cancer Ther.* **2004**, *3*, 513.
(6) Prudhomme, M. *Curr. Med. Chem: Anti-Cancer Agents* **2004**, *4*, 435.
(7) Zhou, B. B.; Bartek, J. *Nat. Rev. Cancer* **2004**, *4*, 216.
(8) Dancey, J.; Sausville, E. A. *Nat. Rev. Drug Discovery* **2003**, *2*, 296.
(9) Senderowicz, A. M. *Cancer Biol. Ther.* **2003**, *2*, S84.
(10) Sausville, E. A.; Elsayed, Y.; Monga, M.; Kim, G. *Annu. Rev. Pharmacol. Toxicol.* **2003**, *43*, 199.
(11) Piers, E.; Britton, R.; Andersen, R. J. *J. Org. Chem.* **2000**, *65*, 530.
(12) Yoshida, T.; Nishiyachi, M.; Nakashima, N.; Murase, M.; Kotani, E. *Chem. Pharm. Bull.* **2002**, *50*, 872.
(13) Terpin, A.; Winklhofer, C.; Schumann, S.; Steglich, W. *Tetrahedron* **1998**, *54*, 1745.
(14) Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, *44*, 3927.
(15) Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, *44*, 4607.
(16) Hugon, B.; Pfeiffer, B.; Renard, P.; Prudhomme, M. *Tetrahedron Lett.* **2003**, 44 3935.
(17) Ator, M. A.; Bihovsky, R.; Chatterjee, S.; Dunn, D.; Hudkins, R. L. International Patent WO01/85686 A2, **2001**; *Chem. Abstr.* **2001**, *135*, 371989.
(18) Hénon, H.; Messaoudi, S.; Hugon, B.; Anizon, F.; Pfeiffer, B.; Prudhomme, M. *Tetrahedron* **2005**, *61*, 5599.
(19) For SPE purifications, Waters Oasis HLB extraction cartridges (6 g) were used with the following eluents: H_2O, then H_2O–MeCN (80:20), and then MeCN. For some compounds a gradient performed with Jones Flash master II was necessary. After evaporation, Et_2O was added to the solid residues, the compounds were filtered and dried.