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Synthesis of dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraones bearing a sugar moiety

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Abstract—The synthesis of a series of dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraones, structurally related to the G2 checkpoint inhibitor granulatimide and bearing a sugar moiety, is described. Substitutions were carried out at the 6-position of the glycosyl unit to lead to an amino substituent as observed in many biologically active compounds such as anthracyclins or staurosporines.

1. Introduction

Many antitumor products from natural sources such as anthracyclins, staurosporine and related compounds, contain a heteroaromatic framework to which a sugar moiety is attached (Fig. 1).[1–6] In daunomycin, the prototype anthracyclin antibiotic, the planar chromophore intercalates into the DNA, whereas the amino-sugar lies in the minor groove.[7] In rebeccamycin, the sugar unit is required for a tight interaction with DNA and for topoisomerase I inhibition.[8] In the case of staurosporine, UCN-01 and K-252a, which are kinase inhibitors interacting with the ATP binding site, the sugar unit mimics the ATP ribose.[9,10] An amino function on the carbohydrate moiety is often present. Its amphiphilic properties may facilitate the access to the different cell compartments.

Granulatimide and isogranulatimide (Fig. 1) are natural products, which inhibit the G2 checkpoint of the cell cycle.[11,12] In response to DNA damage, the cell cycle checkpoints are activated. Their role consists in blocking the cell cycle to allow time for DNA repair. G2 checkpoint inhibition has attracted a widespread interest because, in more than 50% of tumors, the G1 checkpoint is lacking. Therefore, the combination of a G2 checkpoint inhibitor with a DNA damaging agent should force selectively cancer cells into a premature and lethal mitosis, due to an accumulation of DNA lesions. The G2 checkpoint is regulated by various kinases and mainly by the Chk1 kinase. Granulatimide and isogranulatimide, as well as staurosporine and UCN-01, are Chk1 inhibitors. Compounds structurally related to granulatimide have been recently synthesized.[13–21]

In this paper, we report the synthesis of bis-imide granulatimide analogue **9** bearing a maleimide moiety instead of the imidazole heterocycle, and a glucosyl unit attached to the indole nitrogen. The sugar moiety was introduced with the aim of improving the biological activity but also to increase the solubility. Indeed, the bis-imide granulatimide analogues previously synthesized in our laboratory proved to be very insoluble that could reduce cell penetration. Moreover, 6′-chloro then 6′-azido substituents were introduced to finally obtain the 6′-amino derivative **13**.

2. Results and discussion

The first steps of the synthesis were perfected with a methyl protective group on the imide nitrogen, which could be removed via an anhydride according to a method described by Brenner et al.,[22] and, in parallel, with a benzyloxymethyl protective group removable at the end of the synthesis[23,24] to give the free imide nitrogen, necessary for kinase inhibition.

Several methods are described in the literature for the glycosylation of indole derivatives. The Koenigs–Knorr

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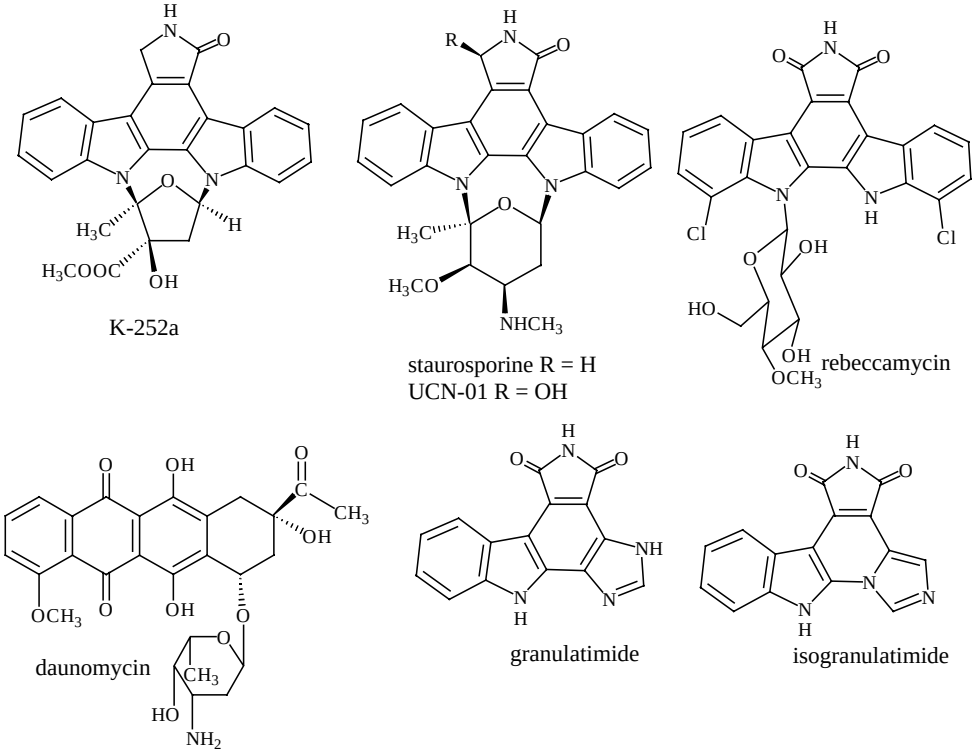


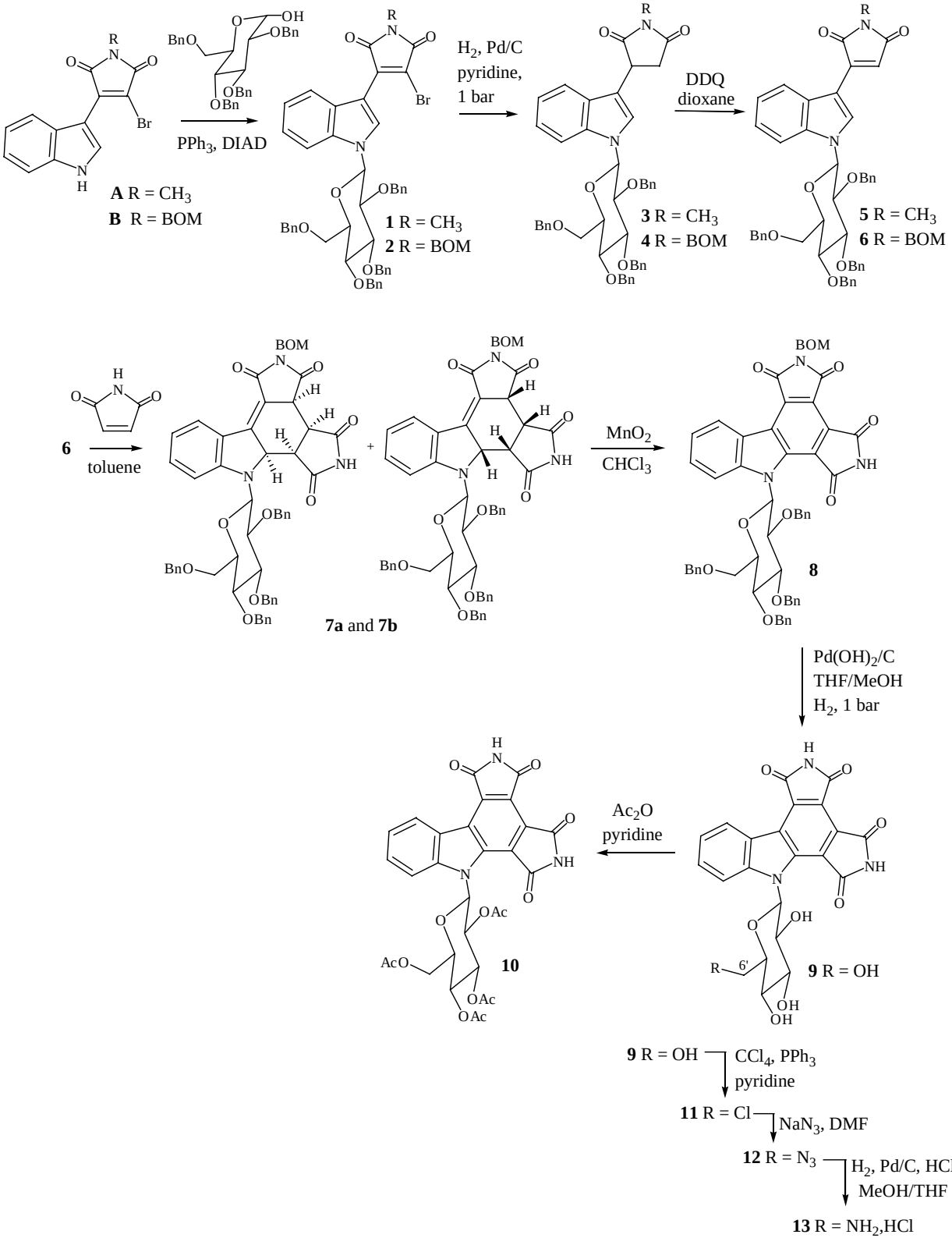
Figure 1. Chemical structures of some natural antitumor compounds.

method was described by Kaneko et al.[25] for the synthesis of rebeccamycin. An anhydrosugar was coupled to a bis-indolylmaleimide or to an indole-3-acetamide in the syntheses of rebeccamycin described by Danishefsky[23] and Faul,[24] respectively. Okhubo et al.[26,27] reported the glycosylation of indolocarbazoles using an α-chlorosugar in a basic heterogeneous medium. A Mitsunobu reaction was performed by Okhubo et al.[28] and Zembower et al.[29] for the glycosylation of bis-indolylmaleimides and indolylbromomaleimides, respectively. For the synthesis of compound **9** (Scheme 1), we chose the Mitsunobu reaction, which was performed on indolylbromomaleimides **A** and **B**. The indolylbromomaleimides **A** and **B**, protected on the imide nitrogen with either a methyl group or benzyloxymethyl substituent, were prepared from the corresponding *N*-protected-dibromomaleimides and indolylmagnesium bromide according to a known procedure.[30]

The glycosylation was carried out using a commercial anomeric mixture of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, leading to bromo-indolylmaleimides **1** and **2** in 94 and 92% yields, respectively. Removal of the bromine atom was performed by hydrogenolysis in the presence of pyridine to avoid the hydrogenolysis of the benzyl groups.[31,32] Succinimides **3** and **4** were obtained in 61 and 58% yields, respectively, as mixtures of diastereoisomers in 0.69:1 and 0.82:1 ratios. The diastereoisomeric ratios were determined from ^{1}H NMR spectra on the signals at 3.47 and 3.50 ppm for compound **3** and at 2.85 and 2.92 ppm for compound **4**. The oxydation step to the corresponding maleimides was carried out using DDQ to give compounds **5** and **6** in 62 and 91% yields, respectively. At this stage, the conversion of *N*-methylmaleimide[22] of compound **5** to an anhydride failed. Therefore, the synthesis was continued only from compound **6**. The Diels–Alder reaction with maleimide gave the cycloadduct **7** from compound **6**, as a mixture of diastereoisomers **7a** and **7b**, which could be separated by chromatography. In a previous work, we observed the isomerization of the Diels–Alder cyclo-adduct from indoline to indole.[19] To get an insight into the structures of compounds **7a** and **7b**, complementary NMR studies were carried out. The indoline structure was proved from ^{1}H–^{13}C long range coupling (^3J) between $H_{1'}$ and two carbons of the indoline, one of them (C_{6b}) bearing a hydrogen (Fig. 2). The Diels–Alder reaction has been performed using various amounts of maleimide and various solvents. The best yield (94%) was obtained in toluene with maleimide (5 equiv). The diastereoisomers **7a** and **7b** were further oxidized using either DDQ or manganese dioxide in various solvents to give compound **8** (Table 1). The best yield (75%) was obtained from the isomer **7b** with MnO_2 in chloroform.

Finally, the BOM and benzyl protective groups were removed by hydrogenolysis using 20% palladium hydroxide on carbon affording compound **9** in 71% yield. Compound **10**, bearing four acetyl groups on the sugar moiety, was also prepared to serve as a possible prodrug, which could be hydrolyzed inside the cells to release compound **9**. This kind of prodrug has been previously successfully used for glycosyl-indigo derivatives.[33,34]

Several substituents were introduced in 6′-position on the sugar moiety. In rebeccamycin series, we had observed that



Scheme 1.

such substituents could modify the biological targets, changing topoisomerase I inhibitors to kinases inhibitors.[35] The chloro-derivative **11** was obtained in 76% yield by treatment of compound **9** by CCl_4 in the presence of triphenylphosphine and pyridine. Nucleophilic substitution using sodium azide led to the azido derivative **12** in 60% yield. Compound **13** was obtained in a quantitative yield by catalytic hydrogenation using 10% Pd/C in methanol/THF/HCl. The hydrochloride was directly formed in the reaction mixture.[36]

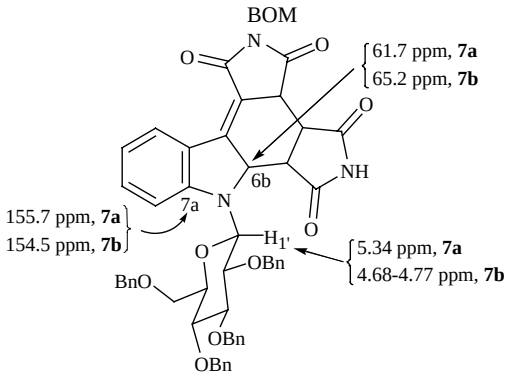


Figure 2.

Table 1. Experimental conditions and yields for the oxidation of **7a** and **7b** to compound **8**

Oxidizing agent	Solvent	Temperature (time of reaction)	Yields
DDQ (2.05 equiv)	Dioxane	Reflux (20 h)	35% from **7a**, 0% from **7b**
DDQ (2.05 equiv)	Toluene	Room temperature (30 h)	47% from **7a**
DDQ (2.5 equiv)	Toluene	Room temperature (24 h) then reflux (1 h)	0% from **7b**
MnO_2 (20 equiv)	CH_2Cl_2	Room temperature (6 h) then 4 days (40 °C)	53% from **7a**
MnO_2 (20 equiv)	$CHCl_3$	Reflux (65 h)	73% from **7a**, 75% from **7b**

3. Conclusion

In conclusion, we have synthesized new bis-imide granulatimide analogues bearing a sugar moiety on the indole nitrogen with the aim of increasing the solubility and the interaction with the target enzyme(s). Moreover, various substituents have been introduced on the sugar unit. The biological activities of these novel granulatimide analogues are under investigation.

4. Experimental

4.1. General

IR spectra were recorded on Perkin-Elmer 881 or Perkin-Elmer Paragon 500 spectrometers (ν in cm^{-1}). NMR spectra were performed on a Bruker AVANCE 400 and AVANCE 500 (chemical shifts δ in ppm, the following abbreviations are used: singlet (s), broad signal (br s), doublet (d), doubled doublet (dd), doubled doubled doublet (ddd), doubled triplet (dt), triplet (t), multiplet (m), tertiary carbons (C *tert*), quaternary carbons (C quat). The signals were assigned from ^1H–^1H COSY and ^{13}C–^1H correlations. Low-resolution mass spectra (ESI+, CI) and HRMS were determined on a Hewlett Packard MS engine. Chromatographic purifications were performed by flash silicagel Geduran SI 60 (Merck) 0.040–0.063 mm column chromatography.

4.1.1. 3-(3-Bromo-2,5-dihydro-1-methyl-2,5-dioxo-pyrrol-4-yl)-1-(1-deoxy-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-y1)-indole (1).

To a mixture of **A** (50 mg, 0.164 mmol), PPh_3 (129 mg, 0.49 mmol) and an anomeric mixture of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (266 mg, 0.49 mmol) in THF (3.2 mL) at −78 °C, DIAD (95 μL) was added dropwise. The mixture was allowed to reach room temperature and stirred for 5 h. 0.2 M HCl (40 mL) was poured into the mixture. After extraction with EtOAc, the organic phase was washed successively with a saturated aqueous $NaHCO_3$ solution and water. The organic phase was dried over $MgSO_4$. The solvent was removed and the residue was purified by flash chromatography (eluent: toluene/EtOAc 50:1) to give **1** as a red solid (128 mg, 0.155 mmol, 94% yield). Mp 55 °C. IR (KBr) $\nu_{C=C}$ 1615 cm^{-1}, $\nu_{C=O}$ 1710, 1770 cm^{-1}. HRMS (FAB+) calcd for $C_{47}H_{43}N_2O_7Br$ $[M]^+$ 826.2254, found 826.2265.

^1H NMR (400 MHz, $CDCl_3$): 3.20 (3H, s), 3.67 (1H, d, J=10.5 Hz), 3.74–3.82 (2H, m), 3.85–3.92 (2H, m), 3.97 (1H, t, J=9.5 Hz), 4.06 (1H, t, J=9.0 Hz), 4.28 (1H, d, J=10.5 Hz), 4.55 (1H, d, J=12.0 Hz), 4.63 (1H, d, J=12.0 Hz), 4.71 (1H, d, J=10.5 Hz), 4.93 (1H, d, J=10.5 Hz), 4.94 (1H, d, J=11.0 Hz), 4.98 (1H, d, J=11.0 Hz), 5.45 (1H, d, J=9.0 Hz), 6.71 (2H, d, J=7.5 Hz), 7.07 (2H, t, J=7.5 Hz), 7.13 (1H, m), 7.23–7.40 (17H, m), 7.67 (1H, m), 8.05–8.09 (2H, m).

^{13}C NMR (100 MHz, $CDCl_3$): 24.9 (CH_3), 68.5, 73.6, 75.1, 75.4, 75.9 (CH_2), 77.5, 78.1, 80.8, 85.5, 86.9 (CH), 112.3, 121.9, 123.4, 123.6, 127.5–128.6, 131.4 (C *tert* arom), 105.6, 115.8, 126.1, 136.1, 136.7, 137.3, 137.9, 138.1, 138.3 (C quat), 166.8, 169.3 (C=O).

4.1.2. 3-(1-Benzyloxymethyl-3-bromo-2,5-dihydro-2,5-dioxo-pyrrol-4-yl)-1-(1-deoxy-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-y1)-indole (2).

Identical procedure as described for **1** was used from **B** (302 mg, 0.73 mmol), PPh_3 (578 mg, 2.20 mmol), 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (1.19 g, 2.20 mmol) and DIAD (427 μL) in THF (13.5 mL) to give after purification by flash chromatography (eluent: toluene/EtOAc 50:1 then 50:2) compound **2** as an orange solid (632 mg, 0.68 mmol, 92% yield). Mp 40 °C. IR (film, NaCl) $\nu_{C=O}$ 1725, 1780 cm^{-1}. Mass (ESI+) 955, 957 $[M+Na]^+$.

^1H NMR (400 MHz, $CDCl_3$): 3.64 (1H, d, J=10.5 Hz), 3.72–3.80 (2H, m), 3.83–3.90 (2H, m), 3.96 (1H, t, J=9.5 Hz), 4.03 (1H, t, J=9.0 Hz), 4.26 (1H, d, J=10.5 Hz), 4.54 (1H, d, J=12.0 Hz), 4.61 (1H, d, J=12.0 Hz), 4.69 (2H, s), 4.69 (1H, d, J=10.5 Hz), 4.89–4.97 (3H, m), 5.19 (2H, s), 5.43 (1H, d, J=9.0 Hz), 6.67–6.71 (2H, m), 7.02–7.13 (3H, m), 7.22–7.40 (22H, m), 7.65 (1H, m), 8.03 (1H, m), 8.04 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$): 67.7, 68.5, 71.9, 73.6, 75.1, 75.4, 75.9 (CH_2), 77.5, 78.1, 80.8, 85.4, 86.8 (CH), 112.4, 122.0, 123.5, 123.7, 127.6–128.7, 131.7 (C *tert* arom), 105.3, 116.1, 126.0, 136.1, 136.6, 137.4, 137.5, 137.9, 138.1, 138.3 (C quat), 166.3, 168.8 (C=O).

4.1.3. 1-(1-Deoxy-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-y1)-3-(1-methyl-2,5-dioxo-pyrrolidin-3-yl)-indole (3).

A solution of compound **1** (344 mg, 0.416 mmol)

in methanol (11.5 mL) and THF (4 mL) was hydrogenated (1 atm) for 3 h in the presence of 10% Pd/C (34 mg) and pyridine (39 μL, 0.48 mmol). After filtration over Celite, the filtrate was evaporated, and the residue was purified by flash chromatography (eluent: cyclohexane/EtOAc 8:2) to give **3** as a pale orange solid (191 mg, 0.254 mmol, 61% yield). Compound **3** was isolated as a mixture of diastereoisomers. IR (KBr) $\nu_{C=O}$ 1705, 1775 cm^{-1}. Mass (ESI+) 751 $[M+H]^+$, 773 $[M+Na]^+$.

^1H NMR (400 MHz, $CDCl_3$): (a: major diastereoisomer; b: minor diastereoisomer) 2.86 ($1H^a$, dd, $J_1=18.5$ Hz, $J_2=5.0$ Hz), 2.92 ($1H^b$, dd, $J_1=18.5$ Hz, $J_2=5.0$ Hz), 3.10 ($3H^b$, s), 3.11 ($3H^a$, s), 3.27 ($1H^b$, dd, $J_1=18.5$ Hz, $J_2=9.5$ Hz), 3.29 ($1H^a$, dd, $J_1=18.5$ Hz, $J_2=9.5$ Hz), 3.47 ($1H^a$, d, $J=10.0$ Hz), 3.50 ($1H^b$, d, $J=10.0$ Hz), 3.69–3.74 ($1H^{a+b}$, m), 3.75–3.87 ($3H^{a+b}$, m), 3.92 ($1H^{a+b}$, t, $J=9.5$ Hz), 3.97 ($1H^b$, t, $J=9.0$ Hz), 3.98 ($1H^a$, t, $J=9.0$ Hz), 4.16 ($1H^b$, d, $J=10.5$ Hz), 4.19 ($1H^a$, d, $J=10.0$ Hz), 4.29–4.35 ($1H^{a+b}$, m), 4.54 ($1H^{a+b}$, d, $J=12.0$ Hz), 4.62 ($1H^a$, d, $J=12.0$ Hz), 4.62 ($1H^b$, d, $J=12.0$ Hz), 4.68 ($1H^{a+b}$, d, $J=10.5$ Hz), 4.88–4.98 ($3H^{a+b}$, m), 5.35 ($1H^{a+b}$, d, $J=9.0$ Hz), 6.69–6.75 ($2H^{a+b}$, m), 7.07–7.38 ($21H^{a+b}$, m), 7.45–7.50 ($1H^{a+b}$, m), 7.59–7.63 ($1H^{a+b}$, m).

^{13}C NMR (100 MHz, $CDCl_3$): 25.2 (CH_3), 36.3, 36.6, 68.6, 73.5, 74.6, 74.7, 75.3, 75.8 (CH_2), 38.0, 38.1, 77.5, 77.9, 81.0, 81.1, 85.4, 86.5 (CH), 112.1, 119.0, 119.1, 120.8, 123.0, 123.8, 123.9, 127.7–128.5 (CH arom), 112.0, 112.1, 127.2, 127.3, 136.3, 136.4, 137.0, 138.0, 138.1, 138.4 (C quat arom), 176.3, 176.4, 177.7, 177.8 (C=O).

4.1.4. 3-(1-Benzyloxymethyl-2,5-dioxo-pyrrolidin-3-yl)-1-(1-deoxy-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-y1)-indole (4).

Identical procedure as for the preparation of **3** was carried out from a mixture of **2** (559 mg, 0.60 mmol) in methanol (16.6 mL) and THF (6 mL) in the presence of Pd/C (56 mg) and pyridine (56 μL, 0.69 mmol), which was hydrogenated for 8 h. Compound **4** was isolated after purification by flash chromatography (eluent: cyclohexane/EtOAc 8:2) as an orange solid (296 mg, 0.345 mmol, 58% yield). Compound **6** was also obtained in mixture with the starting product **2** (117 mg containing 15% of **2** as determined on ^1H NMR spectrum). Compound **4** was isolated as a mixture of diastereoisomers. IR (KBr) $\nu_{C=O}$ 1715, 1780 cm^{-1}. Mass (ESI+) 879 $[M+Na]^+$, 895 $[M+K]^+$.

^1H NMR (400 MHz, $CDCl_3$): (a: major diastereoisomer; b: minor diastereoisomer) 2.85 ($1H^a$, dd, $J_1=18.5$ Hz, $J_2=5.5$ Hz), 2.92 ($1H^b$, dd, $J_1=18.5$ Hz, $J_2=5.5$ Hz), 3.19 ($1H^b$, dd, $J_1=18.5$ Hz, $J_2=9.5$ Hz), 3.21 ($1H^a$, dd, $J_1=18.5$ Hz, $J_2=9.5$ Hz), 3.51 ($1H^a$, d, $J=10.0$ Hz), 3.52 ($1H^b$, d, $J=10.5$ Hz), 3.72–3.77 ($1H^{a+b}$, m), 3.78–3.83 ($1H^{a+b}$, m), 3.84–3.91 ($2H^{a+b}$, m), 3.95 ($1H^{a+b}$, t, $J=9.0$ Hz), 4.00 ($1H^b$, t, $J=9.0$ Hz), 4.01 ($1H^a$, t, $J=9.0$ Hz), 4.16–4.25 ($2H^{a+b}$, m), 4.56 ($1H^a$, d, $J=12.0$ Hz), 4.57 ($1H^b$, d, $J=12.0$ Hz), 4.64 ($1H^a$, d, $J=12.0$ Hz), 4.65 ($1H^b$, d, $J=12.0$ Hz), 4.68–4.75 ($3H^{a+b}$, m), 4.92–5.02 ($3H^{a+b}$, m), 5.15 ($2H^b$, s), 5.16 ($2H^a$, s), 5.37 ($1H^{a+b}$, d, $J=9.0$ Hz), 6.72–6.76 ($2H^{a+b}$, m), 7.10–7.43 ($26H^{a+b}$, m), 7.48–7.52 ($1H^{a+b}$, m), 7.62–7.66 ($1H^{a+b}$, m).

^{13}C NMR (100 MHz, $CDCl_3$): 36.2, 36.4, 68.0, 68.6, 72.3, 73.5, 74.6, 74.7, 75.3, 75.8 (CH_2), 38.0, 38.1, 77.5, 77.9, 81.0, 81.1, 85.4, 86.4 (CH), 112.1, 118.9, 119.0, 120.8, 123.0, 123.9, 124.0, 127.6–128.7 (C *tert* arom), 111.6, 111.7, 127.1, 127.2, 136.3, 136.4, 136.9, 137.6, 138.0, 138.1, 138.4 (C quat arom), 175.9, 176.0, 177.2, 177.3 (C=O).

4.1.5. 1-(1-Deoxy-2,3,4,6-tetra-*O*-benzyl-β-D-gluco-pyranos-1-y1)-3-(2,5-dihydro-1-methyl-2,5-dioxo–pyrrol-3-yl)-indole (5).

A solution of DDQ (21.7 mg, 0.096 mmol) in dioxane (1 mL) was slowly added to a solution of **3** (65.2 mg, 0.087 mmol) in dioxane (1 mL). The mixture was stirred at room temperature overnight, then it was filtered off. After evaporation of the filtrate, the residue was purified by flash chromatography (eluent: cyclohexane/EtOAc 9:1) to give **5** as a yellow solid (40.4 mg, 0.054 mmol, 62% yield). Mp 97–103 °C. IR (KBr) $\nu_{C=C}$ 1617 cm^{-1}, $\nu_{C=O}$ 1703, 1765 cm^{-1}. Mass (ESI+) 749 $[M+H]^+$.

^1H NMR (400 MHz, $CDCl_3$): 3.11 (3H, s), 3.65 (1H, d, $J=10.5$ Hz), 3.72–3.80 (2H, m), 3.83 (1H, dd, $J_1=11.0$ Hz, $J_2=4.0$ Hz), 3.86 (1H, t, $J=9.0$ Hz), 3.93 (1H, t, $J=9.0$ Hz), 4.00 (1H, t, $J=9.0$ Hz), 4.25 (1H, d, $J=10.5$ Hz), 4.54 (1H, d, $J=12.0$ Hz), 4.60 (1H, d, $J=12.0$ Hz), 4.68 (1H, d, $J=10.5$ Hz), 4.89–4.96 (3H, m), 5.42 (1H, d, $J=9.0$ Hz), 6.66–6.70 (3H, m), 7.03 (2H, t, $J=7.5$ Hz), 7.08–7.13 (1H, m), 7.21–7.36 (17H, m), 7.66 (1H, d, $J=8.0$ Hz), 7.80 (1H, d, $J=8.0$ Hz), 8.51 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$): 23.8 (CH_3), 68.6, 73.6, 75.0, 75.4, 75.8, (CH_2), 77.5, 78.1, 80.8, 85.5, 86.8 (CH sugar), 112.8, 116.0, 120.6, 122.7, 123.8, 127.7–128.6, 131.8 (CH), 106.8, 127.2, 136.3, 136.7, 137.9, 138.1, 138.3, 139.0 (C quat), 171.8, 172.3 (C=O).

4.1.6. 3-(1-Benzyloxymethyl-2,5-dihydro-2,5-dioxo-pyrrol-3-yl)-1-(1-deoxy-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-y1)-1*H*-indole (6).

A solution of DDQ (78.2 mg, 0.344 mmol) in dioxane (3.4 mL) was slowly added to a solution of **4** (281 mg, 0.328 mmol) in dioxane (3.4 mL). The mixture was stirred at room temperature for 3 h then it was filtered off. The filtrate was evaporated and the residue was purified by flash chromatography (eluent: cyclohexane/EtOAc 8:2) to give **6** as a yellow solid (254 mg, 0.297 mmol, 91% yield). Mp 47 °C. IR (KBr) $\nu_{C=C}$ 1615 cm^{-1}, $\nu_{C=O}$ 1710, 1770 cm^{-1}. Mass (ESI+) 877 $[M+Na]^+$, 893 $[M+K]^+$.

^1H NMR (400 MHz, $CDCl_3$): 3.65 (1H, d, $J=10.5$ Hz), 3.72–3.80 (2H, m), 3.83 (1H, dd, $J_1=11.0$ Hz, $J_2=4.0$ Hz), 3.86 (1H, t, $J=9.0$ Hz), 3.93 (1H, t, $J=9.0$ Hz), 3.99 (1H, t, $J=9.0$ Hz), 4.26 (1H, d, $J=10.5$ Hz), 4.53 (1H, d, $J=12.0$ Hz), 4.60 (1H, d, $J=12.0$ Hz), 4.66–4.70 (3H, m), 4.89–4.96 (3H, m), 5.13 (2H, s), 5.43 (1H, d, $J=9.0$ Hz), 6.65–6.69 (2H, m), 6.71 (1H, s), 6.98–7.04 (2H, m), 7.07 (1H, m), 7.21–7.41 (22H, m), 7.66 (1H, d, $J=8.0$ Hz), 7.79 (1H, d, $J=7.5$ Hz), 8.52 (1H, s).

^{13}C NMR (100 MHz, $CDCl_3$): 66.6, 68.5, 71.5, 73.5, 75.0, 75.4, 75.8 (CH_2), 77.5, 78.1, 80.8, 85.4, 86.7 (CH), 106.7, 127.1, 136.3, 136.6, 137.6, 137.9, 138.0, 138.3, 139.2

(C quat), 112.8, 116.0, 120.5, 122.8, 124.0, 127.7–128.6, 132.1 (CH), 171.3, 171.6 (C=O).

4.1.7. 2-Benzyloxymethyl-7-(1-deoxy-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-y1)-1,3,3a,3b,4,6,6a,6b-octahydro-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (7a) and (7b). A mixture of **6** (171 mg, 0.20 mmol) and maleimide (97 mg, 1.0 mmol) in toluene (5 mL) was refluxed for 19 h. The solvent was removed and the residue was purified by flash chromatography (eluent: cyclohexane/EtOAc from 7:3 to 4:6) to give **7** (94% yield) as two diasteroisomers **7a** (117 mg, 0.123 mmol) and **7b** (61.4 mg, 0.064 mmol).

Compound **7a**. Mp 95 °C. IR (KBr) $\nu_{C=C}$ 1605 cm^{-1}, $\nu_{C=O}$ 1650, 1710, 1725, 1765 cm^{-1}, ν_{NH} 3150–3550 cm^{-1}. Mass (ESI+) 974 $[M+Na]^+$.

^1H NMR (400 MHz, $CDCl_3$): 2.81 (1H, d, $J=6.5$ Hz), 3.31 (1H, dd, $J_1=8.5$ Hz, $J_2=6.5$ Hz), 3.59–3.66 (2H, m), 3.72–3.89 (6H, m), 4.17 (1H, d, $J=10.5$ Hz), 4.38 (1H, d, $J=12.0$ Hz), 4.45 (1H, d, $J=10.5$ Hz), 4.46 (1H, d, $J=12.0$ Hz), 4.65 (1H, d, $J=12.0$ Hz), 4.66 (1H, d, $J=10.5$ Hz), 4.70 (1H, d, $J=12.0$ Hz), 4.86 (1H, d, $J=11.0$ Hz), 4.87 (1H, d, $J=11.0$ Hz), 4.94 (1H, d, $J=11.0$ Hz), 5.09 (1H, d, $J=10.5$ Hz), 5;15 (1H, d, $J=10.5$ Hz), 5.33 (1H, d, $J=8.5$ Hz), 6.55–6.60 (2H, m), 6.82 (1H, t, $J=7.5$ Hz), 6.93 (1H, d, $J=8.5$ Hz), 7.01–7.09 (3H, m), 7.18–7.35 (19H, m), 7.39 (2H, d, $J=7.5$ Hz), 7.90 (1H, br s, NH), 8.60 (1H, d, $J=7.5$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 38.9, 42.1, 43.7, 61.7, 76.7, 77.4, 77.8, 85.7, 86.2 (CH), 67.5, 68.3, 71.8, 73.4, 74.5, 75.2, 75.7 (CH_2), 110.6, 119.3, 127.6–128.8, 134.9 (CH), 110.3, 120.9, 136.7, 137.7, 137.9 (2C), 138.3, 147.7, 155.7 (C quat), 165.9, 172.1, 173.0, 174.4 (C=O).

Compound **7b**. Mp 94 °C. IR (KBr) $\nu_{C=O}$ 1650, 1705, 1720, 1760 cm^{-1}, ν_{NH} 3200–3550 cm^{-1}. Mass (ESI+) 974 $[M+Na]^+$.

^1H NMR (400 MHz, $CDCl_3$): 2.62 (1H, m), 3.58–3.70 (3H, m), 3.80 (1H, t, $J=9.0$ Hz), 3.86–3.89 (2H, m), 3.91 (1H, t, $J=9.5$ Hz), 4.03 (1H, d, $J=11.0$ Hz), 4.15 (1H, t, $J=9.0$ Hz), 4.52–4.57 (2H, m), 4.65 (1H, d, $J=10.5$ Hz), 4.68–4.77 (5H, m), 4.88 (1H, d, $J=10.5$ Hz), 4.90 (1H, d, $J=11.0$ Hz), 4.98 (1H, d, $J=11.0$ Hz), 5.15 (1H, d, $J=10.5$ Hz), 5.20 (1H, d, $J=10.5$ Hz), 6.87–6.96 (3H, m), 7.08–7.14 (3H, m), 7.22–7.39 (20H, m), 7.44 (2H, d, $J=7.5$ Hz), 7.98 (1H, br s, NH), 8.72 (1H, d, $J=8.0$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 67.5, 68.5, 71.8, 73.3, 75.2, 75.6, 75.7 (CH_2), 39.9, 41.3, 42.1, 65.2, 77.8, 77.9, 79.2, 86.2, 86.8 (CH), 113.3, 120.4, 127.5–128.7; 129.0, 134.7 (CH), 110.8, 122.6, 137.3, 137.7, 138.0, 138.2, 138.4, 147.5, 154.5 (C quat), 165.9, 172.0, 173.4, 174.5 (C=O).

4.1.8. 2-Benzyloxymethyl-7-(1-deoxy-2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranos-1-y1)-1,3,4,6-tetrahydro-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (8). This procedure is also applicable to stereoisomer **7a**.

A mixture of **7b** (84 mg, 0.088 mmol) and MnO_2 (153 mg, 1.76 mmol) in chloroform (4 mL) was refluxed for 60 h. The solvent was removed and the residue was purified by flash chromatography (eluent: cyclohexane/EtOAc 7:3) to give **8** as an orange solid (62.7 mg, 0.066 mmol, 75% yield). Mp 78–80 °C. IR (KBr) $\nu_{C=O}$ 1722, 1781 cm^{-1}, ν_{NH} 3130–3530 cm^{-1}. Mass (ESI+) 970 $[M+Na]^+$.

^1H NMR (400 MHz, $CDCl_3$): 3.20 (1H, d, $J=11.5$ Hz), 3.90–4.03 (5H, m), 4.09–4.14 (1H, m), 4.21 (1H, d, $J=11.5$ Hz), 4.68 (1H, d, $J=12.0$ Hz), 4.71–4.78 (2H, m), 4.79 (2H, s), 4.85 (1H, d, $J=11.0$ Hz), 4.92 (1H, d, $J=11.0$ Hz), 4.98 (1H, d, $J=11.0$ Hz), 5.26 (1H, d, $J=11.0$ Hz), 5.31 (1H, d, $J=11.0$ Hz), 6.15 (2H, d, $J=7.5$ Hz), 6.68 (2H, t, $J=7.5$ Hz), 6.85 (1H, t, $J=7.5$ Hz), 7.23–7.48 (21H, m), 7.53 (1H, t, $J=7.5$ Hz), 7.61 (1H, d, $J=8.5$ Hz), 8,02 (1H, d, $J=8.5$ Hz), 8.67 (1H, br s, NH), 9.13 (1H, d, $J=8.0$ Hz).

^{13}C NMR (100 MHz, $CDCl_3$): 67.3, 69.0, 72.0, 73.3, 74.5, 75.3, 75.9 (CH_2), 77.5, 77.9, 79.8, 85.7, 87.0 (CH), 115.2, 123.5, 126.7–128.6, 130.7 (C *tert* arom), 118.3, 119.3, 121.7, 126.4, 127.2, 130.0, 136.7, 137.5, 137.9 (2C), 138.1, 140.1, 142.1 (C quat arom), 163.9 (2C), 166.6, 166.9 (C=O).

4.1.9. 7-(1-Deoxy-β-D-glucopyranos-1-y1)-1,3,4,6-tetra-hydro-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (9). A solution of **8** (567 mg, 0.60 mmol) in a mixture THF/MeOH 4:1 (44 mL) was hydrogenated (1 atm) for 24 h in the presence of Pearlman catalyst (20% $Pd(OH)_2$/C, 283 mg). THF and MeOH were added, the reaction mixture was stirred at room temperature for 2 h before filtration over Celite. The filtrate was evaporated and the residue was purified by flash chromatography (eluent: THF/cyclohexane 8:2) leading to **9** as an orange solid, which was further washed with CH_2Cl_2 (199 mg, 0.43 mmol, 71% yield). Mp >300 °C. IR (KBr) $\nu_{C=O}$ 1720, 1755, 1770 cm^{-1}, $\nu_{NH,OH}$ 3100–3600 cm^{-1}. HRMS (ESI+) calcd for $C_{22}H_{17}N_3O_9Na$ $[M+Na]^+$490.0862, found 490.0877.

^1H NMR (400 MHz, DMSO-d_6): 3.40–3.52 (2H, m), 3.59–3.73 (2H, m), 3.84–3.94 (2H, m), 4.74 (1H, t, $J=5.5$ Hz, OH), 5.02 (1H, d, $J=5.5$ Hz), 5.19 (1H, d, $J=5.0$ Hz, OH), 5.23 (1H, d, $J=5.0$ Hz, OH), 7.53 (1H, d, $J=9.0$ Hz), 7.54 (1H, t, $J=7.5$ Hz), 7.74 (1H, t, $J=7.5$ Hz), 8.09 (1H, d, $J=7.5$ Hz), 9.28 (1H, d, $J=8.0$ Hz), 11.62–11.91 (2H, br s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 61.0 (CH_2), 69.9, 70.4, 77.4, 80.3, 87.7 (CH), 115.4, 122.5, 126.0, 129.8 (C *tert* arom), 118.5, 120.5, 121.5, 125.2, 127.8, 131.8, 140.2, 141.8 (C quat arom), 165.6, 165.8, 168.3, 169.0 (C=O).

4.1.10. 7-(1-Deoxy-2,3,4,6-tetra-*O*-acetyl-β-D-gluco-pyranos-1-y1)-1,3,4,6-tetrahydro-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (10). Acetic anhydride (101 μL, 1.07 mmol) was added to a mixture of **9** (50 mg, 0.107 mmol) in pyridine (221 μL, 2.73 mmol) at 0 °C. The mixture was stirred at room temperature for 20 h. Water was added. After extraction with EtOAc, the organic phase was dried over $MgSO_4$, and the solvent was removed. The residue was purified by flash chromatography (eluent: cyclohexane/EtOAc from 5:5 to 4:6) to give **10** as a yellow solid (32.6 mg, 0.051 mmol, 48% yield). Mp 176 °C. IR (KBr) $\nu_{C=O}$ 1685–1800 cm^{-1}, ν_{NH} 3100–3550 cm^{-1}.

HRMS (ESI+) calcd for $C_{30}H_{26}N_3O_{13}$ $[M+H]^+$636.1466, found 636.1495.

^{1}H NMR (400 MHz, $CDCl_3$): 1.53 (3H, s), 2.03 (3H, s), 2.17 (3H, s), 2.20 (3H, s), 4.32–4.44 (2H, m), 4.54 (1H, d, J= 11.5 Hz), 5.50 (1H, t, J=9.5 Hz), 5.67 (1H, t, J=9.5 Hz), 5.89 (1H, t, J=9.5 Hz), 7.38 (1H, t, J=7.5 Hz), 7.71 (1H, t, J=8.0 Hz), 7.99 (1H, d, J=8.5 Hz), 8.07 (1H, d, J= 9.0 Hz), 8.82 (1H, br s, NH), 8.96 (1H, d, J=8.0 Hz), 9.06 (1H, br s, NH).

^{13}C NMR (100 MHz, $CDCl_3$): 20.1, 20.6, 20.7, 20.9 (CH_3), 61.8 (CH_2), 68.2, 69.2, 73.5, 74.8, 85.5 (CH), 114.3, 123.7, 127.0, 131.0 (C *tert* arom), 117.7, 121.2, 121.6, 126.9, 127.4, 131.5, 139.8, 141.5 (C quat arom), 164.5, 165.1, 166.9, 167.4, 169.5, 169.8, 170.3, 171.0 (C=O).

4.1.11. 7-(6-Chloro-1,6-dideoxy-β-D-glucopyranos-1-y1)-1,3,4,6-tetrahydro-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (11). PPh_3 (337 mg, 1.28 mmol) then CCl_4 (62 μL, 0.64 mmol) were successively added to a solution of **9** (150 mg; 0.321 mmol) in pyridine (1.6 mL). The mixture was stirred at room temperature for 8 h. The solvent was removed and the residue was dried under vaccum. CH_2Cl_2 was added to the residue and the mixture was filtered off. The solid was purified by flash chromatography (eluent: cyclohexane/THF from 8:2 to 100% THF then THF/methanol 95:5) to give **11** (118 mg, 0.243 mmol, 76% yield) as an orange solid. Mp >300 °C. IR (KBr) $\nu_{C=O}$ 1725, 1780 cm^{-1}, ν_{NH} 3150–3650 cm^{-1}. HRMS (ESI+) calcd for $C_{22}H_{16}N_3O_8NaCl$ $[M+Na]^+$508.0524, found 508.0544.

^{1}H NMR (400 MHz, DMSO-d_6): 3.46 (1H, dt, J_1=9.0 Hz, J_2=5.5 Hz), 3.59 (1H, dt, J_1=9.0 Hz, J_2=6.0 Hz), 3.84–3.90 (1H, m), 3.92 (1H, dt, J_1=9.0 Hz, J_2=6.0 Hz), 4.02 (1H, dd, J_1=12.0 Hz, J_2=5.0 Hz), 4.08 (1H, dd, J_1= 12.0 Hz, J_2=2.5 Hz), 5.13 (1H, d, J=6.0 Hz), 5.33 (1H, d, J=5.5 Hz), 5.58 (1H, d, J=6.0 Hz), 7.55 (1H, ddd, J_1= 8.0 Hz, J_2=7.0 Hz, J_3=1.0 Hz), 7.58 (1H, d, J=9.0 Hz), 7.75 (1H, ddd, J_1=8.5 Hz, J_2=7.0 Hz, J_3=1.5 Hz), 8.08 (1H, d, J=8.5 Hz), 9.28 (1H, ddd, J_1=8.0 Hz, J_2=1.0 Hz, J_3=0.5 Hz), 11.62–11.97 (2H, br s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 45.1 (CH_2), 70.2 (2C), 76.8, 77.8, 87.6 (CH), 115.0, 122.6, 126.1, 129.8 (C *tert* arom), 118.5, 120.7, 121.6, 125.2, 127.7, 131.8, 140.2, 141.6 (C quat arom), 165.5, 165.7, 168.3, 168.8 (C=O).

4.1.12. 7-(6-Azido-1,6-dideoxy-β-D-glucopyranos-1-y1)-1,3,4,6-tetrahydro-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone (12). NaN_3 (95 mg, 1.46 mmol) was added to a solution of compound **11** (71 mg, 0.146 mmol) in anhydrous DMF (3.8 mL). The mixture was heated at 90 °C for 3 days. After evaporation, water was added to the residue. The mixture was filtered off and the solid residue was washed with water. The residue was purified by flash chromatography (eluent: cyclohexane/THF from 8:2). The solid obtained after chromatography was washed with CH_2Cl_2 to give **12** (43.0 mg, 0.087 mmol, 60% yield) as an orange solid. Mp >300 °C. IR (KBr) $\nu_{C=O}$ 1722, 1775 cm^{-1}, ν_{N3} 2104 cm^{-1}, ν_{NH} 3110–3620 cm^{-1}. HRMS (ESI+) calcd for$C_{22}H_{16}N_6O_8Na$ $[M+Na]^+$515.0927, found 515.0934.

^{1}H NMR (400 MHz, DMSO-d_6): 3.40–3.48 (1H, m), 3.50–3.58 (1H, m), 3.65 (1H, dd, J_1=13.0 Hz, J_2=6.0 Hz), 3.76–3.84 (2H, m), 3.93–4.01 (1H, m), 5.13 (1H, d, J=6.0 Hz), 5.33 (1H, d, J=5.5 Hz), 5.52 (1H, d, J=5.5 Hz), 7.52–7.58 (2H, m, $H_{1'}+H_{arom}$), 7.76 (1H, t, J=8.0 Hz), 8.06 (1H, d, J=8.5 Hz), 9.27 (1H, d, J=8.0 Hz), 11.73 (1H, br s, NH), 11.83 (1H, br s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 51.2 (CH_2), 70.1, 70.3, 77.1, 77.9, 87.7 (CH sucre), 114.9, 122.5, 126.0, 128.9 (CH arom), 118.5, 120.7, 121.5, 125.2, 127.7, 131.8, 140.2, 141.5 (C quat arom), 165.4, 165.7, 168.2, 168.8 (C=O).

4.1.13. 7-(6-Amino-1,6-dideoxy-β-D-glucopyranos-1-y1)-1,3,4,6-tetrahydro-dipyrrolo[3,4-*a*:3,4-*c*]carbazole-1,3,4,6-tetraone hydrochloride (13). A solution of **12** (20 mg, 0.041 mmol) in MeOH/THF 2:1 (1.5 mL) was hydrogenated for 5 h in the presence of 10% Pd/C (2 mg) concentrated HCl (4 μL). 10% Pd/C (3 mg) was added and the reaction mixture was hydrogenated for 18 h before filtration over Celite. After evaporation on reduced pressure, compound **13** (20 mg, 0.040 mmol, 98% yield) was obtained as a yellow solid. Mp >235 °C (decomposition). IR (KBr) $\nu_{C=O}$ 1725, 1770 cm^{-1}, ν_{NH} 3100–3650 cm^{-1}. HRMS (ESI+) calcd for $C_{22}H_{19}N_4O_8$ $[M+H]^+$467.1203, found 467.1216.

^{1}H NMR (400 MHz, DMSO-d_6): 3.12–3.21 (1H, m), 3.34–3.41 (1H, m), 3.44–3.58 (2H, m), 3.82–3.89 (1H, m), 3.98–4.05 (1H, m), 5.21 (1H, d, J=5.5 Hz, OH), 5.48 (1H, br s, OH), 5.75 (1H, d, J=4.5 Hz, OH), 7.56 (1H, t, J=7.5 Hz), 7.61 (1H, d, J=9.0 Hz, $H_{1'}$), 7.75 (1H, t, J=7.5 Hz), 8.07 (3H, br s, NH_2, HCl), 8.15 (1H, d, J=8.5 Hz), 9.27 (1H, d, J=8.0 Hz), 11.74 (1H, s, NH), 11.88 (1H, s, NH).

^{13}C NMR (100 MHz, DMSO-d_6): 40.5 (CH_2), 70.0, 71.0, 75.6, 76.8, 87.5 (CH), 115.4, 122.6, 126.0, 129.9 (CH arom), 118.3, 120.8, 121.5, 125.1, 127.7, 131.9, 140.2, 141.5 (C quat arom); 165.5, 165.7, 168.2, 168.8 (C=O).

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