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Glycosylated Cationic Porphyrins as Potential Agents in Cancer Phototherapy

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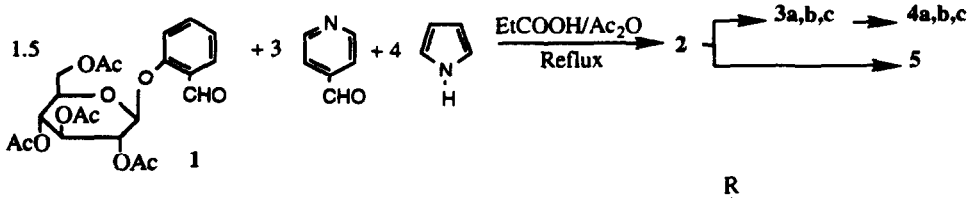
Abstract : New water-soluble cationic porphyrins containing glycosyl group and lipophilic substituents to improve targeting on malignant cells were synthesized in three steps.

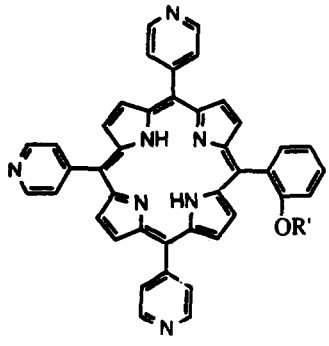
Water soluble porphyrins were recently found to be of great interest due to their affinity for some biomolecules and cancer cells. Cationic porphyrins interact with DNA with the mode of binding depending primarily on the porphyrin geometry. Thus, meso tetrakis (4-(methyl)pyridyl)porphyrin (H_2TMPyP-4) is found to intercalate into DNA[1], whereas meso tetrakis (4-(trimethylammonium) phenyl)porphyrin (H_2TMAPP) and meso tetrakis (4-(trimethylammonium) benzyl)porphyrin (H_2TMABP) induce a strong but non intercalative binding with DNA[2,3]. In the case of cancer phototherapy, their linkages with sugar moieties are of great importance because the sugar increases water solubility, membrane interaction and specific receptor targeting. Some glycosylated porphyrins have been proposed[4]. In connection with our research program on glycosylated porphyrins[5], we report here the synthesis of O-glycosyl cationic porphyrins, **4a, b, c**, with various lipophilic N-substituents such as methyl, isopropyl and n-octyl (Scheme 1). The presence of such substituents could increase the penetrability of the porphyrins across cell membranes.

Salicylaldehyde β-D glucoside was acetylated by acetic anhydride in pyridine at 0°C to obtain **1** (m.p=142°C; $[\alpha]_D$ = -30 (c=0.5 $CHCl_3$)).

The [5-(2-tetraacetyl-β-D-glucopyranosylphenyl)-10,15,20 tris(4-pyridyl)] porphyrine **2** was synthesized by condensation of **1** (1.5 eq) with 4-pyridinecarboxaldehyde (3 eq) and pyrrole (4 eq) in refluxing propionic acid and acetic anhydride (7/1) solution, according to the Adler-Longo method[6].

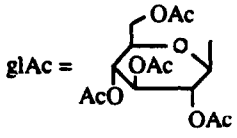
After purification and separation by silica gel chromatography from the other porphyrins, **2** was obtained in an overall 7% yield[7].

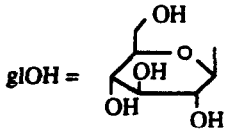


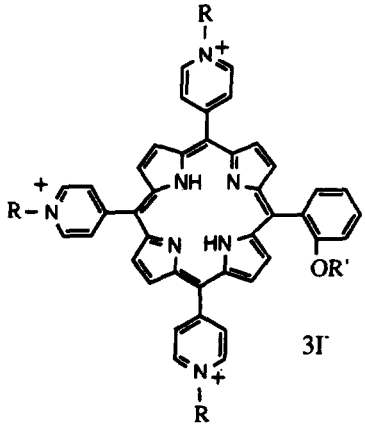


2: R' = glAc

5: R' = glOH







3a: R = Me, R' = glAc

3b: R = iPr, R' = glAc

3c: R = n-Oct, R' = glAc

4a: R = Me, R' = glOH

4b: R = iPr, R' = glOH

4c: R = n-Oct, R' = glOH

Scheme 1

Compound **2** was characterized by secondary ion mass spectrometry (SIMS)[8]. A molecular ion at m/z=963 was detected both in the positive mode ($M^{+\cdot}$) and in the negative mode ($M^{-\cdot}$). Strong peaks corresponding to the loss of one acetylated sugar unit (m/z=632 for **2**-R' and m/z=617 for **2**-OR'+H) were also observed as shown in Figure 1. **3a, b** and **c** were prepared by alkylation of the pyridine nitrogen atoms of **2**. The alkylation reaction was carried out with a large excess of methyl, isopropyl or n-octyl iodide (alkyl iodide - DMF 5/1) in refluxing DMF, giving after purification on PLC (eluents AcOH-MeOH-H_2O 3/2/1), **3a, 3b** and **3c** in 85%, 90% and 75% yields respectively.

Absorption and ^1H NMR spectra (250 MHz) of compounds **3a, b, c** show the expected signals; examination of the coupling constant of anomeric protons of the sugar moiety indicated β configuration for the glycosidic bond[9]. For these cationic compounds, fast atom bombardment mass spectrometry (FAB) was used[9] as no molecular ion was detected by SIMS.

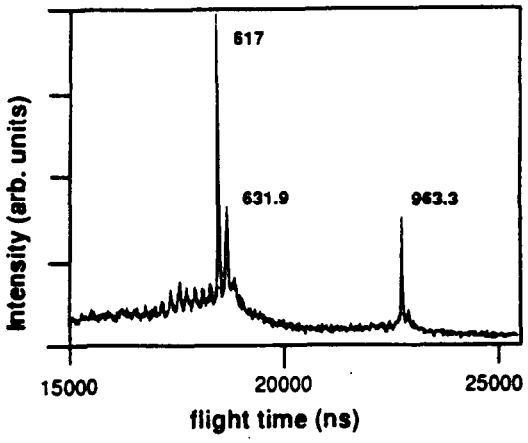


Figure 1 : Partial negative secondary ion mass spectra of **2**

Finally, the protecting groups of **2** and **3a, b, c** were removed by treatment at 0°C with Et_3N-MeOH-H_2O (10/10/1), leading to the expected compounds **5** and **4a, b, c**.

In conclusion, our alkylated glycosylated cationic porphyrins may present better penetration in tissues, and better targeting of some malignant tumors[10]. Biological tests are in progress.

Acknowledgements :

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7. **2** : UV-Visible (acetone) λnm(logε)642(2.78), 586(3.16), 542(3.15), 410(3.6), 414(4.95).
Selected data of ^{1}H nmr ($CDCl_3$) : δ(ppm)=8.97(s,4H,pyr), 8.8(d,2H,J=4.8Hz,β-pyrrole), 8.75(m,8H,pyr).
8.06(dd,6H,J=4.5,1.4Hz, β-pyrrole), 4.89(d,1H,J=7.7Hz,H:β-ose), -2.91(s,2H,N-H).

8. Secondary ion mass spectra of pure electro-sprayed samples on gold substrate were obtained with a time of flight mass spectrometer and a Cs^+ ion primary beam.

9. **3a** : UV-Visible (DMF-H_2O) λnm(logε)644(3.25), 586(3.53), 556(3.6), 518(3.8), 426(4.9).
Selected data of ^{1}H nmr (DMSO) : δ(ppm)=9.46(m,6H,pyr), 9.13(d,4H,J=6.4Hz,β-pyrrole), 8.97(d,6H,J=5.7Hz,pyr).
8.9(m,4H,β-pyrrole), 5.56(d,1H,J=8.1Hz,H:β-ose), 4.7(s,9H,N-Me), -3.05(s,2H,N-H). FAB Mass 1009 (MH^+).
3b : UV-Visible (acetone) λnm(logε)646(2.56), 590(2.95), 554(3.04), 516(3.34), 426(4.31).
Selected data of ^{1}H nmr (DMSO) : δ(ppm)=9.58(d,6H,J=5.6Hz,pyr), 9.45(m,4H,β-pyrrole), 8.95(d,6H,J=5.7Hz,pyr),
8.81(m,4H,β-pyrrole), 5.52(d,1H,J=7.5Hz,H:β-ose),5.37(m,3H,iPr), 1.88(m,18H,iPr), -3.1 (s,2H,N-H). FAB Mass 1094($M+2H^+$).
3c : UV-Visible (acetone) λnm(logε)644(3.1), 588(3.45), 558(3.55), 516(3.72), 426(4.26).
Selected data of ^{1}H nmr(DMSO) : δ(ppm)=9.52(d,6H,J=6.1Hz,pyr), 9.34(m,4H,β-pyrrole), 8.85(d,6H,J=6Hz,pyr).
8.79(m,4H,β-pyrrole), 5.53(d,1H,J=7.9Hz,H:β-ose), 2.68(t,2H,J=1.7Hz,Oct), from 1 to 2.02(m,45H,Oct), -3.02 (s,2H,N-H). FAB Mass 1303(MH^+).

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