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PAPER

Gluconjugates of 8-hydroxyquinolines as potential anti-cancer prodrugs†

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8-Hydroxyquinolines are systems of great interest in the field of inorganic and bioinorganic chemistry. They are metal-binding compounds and are known to exhibit a variety of biological activities, such as antibacterial and anticancer activities. Among these systems, clioquinol has been the focus of a renewed interest in recent years. In this scenario, we synthesized and characterized the new clioquinol glucoconjugate, 5-chloro-7-iodo-8-quinolinyl-β-D-glucopyranoside in order to compare this system to that of clioquinol. We also synthesized, 8-quinolinyl-β-D-glucopyranoside, an 8-hydroxyquinoline glucoconjugate. The reason for the development of glucoconjugates is the glucose avidity, and the over-expression of glucose transporters in cancer cells. Here we demonstrate that glycoconjugates are cleaved *in vitro* by β-glucosidase and these systems exhibit antiproliferative activity against different tumor cell lines in the presence of copper(II) ions.

Introduction

8-Hydroxyquinolines (OHQs) are systems of great interest in the field of inorganic and bioinorganic chemistry. They are metal-binding compounds and are known to exhibit a variety of biological activities such as antibacterial[1] and anticancer[2] activities.

Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline, CQ) is the most known member of this family. In the 1950s,[3] it was widely used as an antibiotic for the treatment of diarrhoea and skin infections. In the 1970s, CQ was associated with several thousand cases of subacute myelo-optic neuropathy (SMON) in Japan, leading to its removal from the market.[4] The explanation for neurological side effects among the Japanese is not clear, but many of these cases may have been related to the ability of CQ to function as a 'carrier of heavy metals' to the Central Nervous System (CNS)[5] or to disturb the homeostasis of vitamin B_{12}.[6] Several recent studies have generated renewed interest in CQ as a modulator of metal homeostasis in neurodegenerative disorders such as Alzheimer's disease (AD). A pilot phase II study of oral clioquinol in patients with AD reported that the drug improved the cognition and behaviour of the patients.[7] In this study, one serious adverse event attributed to the CQ was noted in the subjects receiving the drug.

CQ also displays an anticancer effect in *in vitro* and *in vivo* preclinical models. CQ directly induces cell death in malignant cells at low micromolar concentrations.[8] Furthermore, CQ induces apoptosis in cancer cells through a caspase-dependent apoptotic pathway.[8] Currently, CQ is in phase I clinical trial in order to evaluate the tolerance and biological activity of the drug in patients with relapsed or refractory hematologic malignancy, such as Leukemia, Myelodysplasia, non-Hodgkin's and Hodgkin's Lymphoma, and Multiple Myeloma.[9,10] Other OHQ derivatives have also been tested as anticancer compounds.

For CQ and other OHQs it has been reported that the interaction with copper(II) ions is a prerequisite for anticancer activity.[11] Although, the mechanism of action is not completely understood, experimental evidence suggests that OHQ and CQ act as proteasome inhibitors in the presence of copper(II). Even if this mechanism is not fully accepted and a copper-independent proteasome inhibition mechanism has been described, it is widely considered the main action mechanism.[12]

Copper(II) is a co-factor essential for tumor growth and angiogenesis. High levels of copper have consistently been found in many types of human cancers.[13] This datum is fundamental to explain the slight selectivity of CQ towards tumor cells. It has been shown that copper-binding drugs used in the treatment of Wilson's disease have anti-angiogenic effects in cancer models.

Stability constants for CQ with a number of metal ions have recently been reported.[14] For copper(II), the log K1 value is 12.5 and log K2 is about 10.9. Other OHQ derivatives show similar constants depending on the substituent on the phenolic ring.[15]

On the basis of the interest in OHQ derivatives, we synthesized and characterized the new clioquinol glucoconjugate, 5-chloro-7-iodo-8-quinolinyl-β-D-glucopyranoside in order to compare this system to that of CQ (Fig. 1). We also synthesized, 8-quinolinyl-β-D-glucopyranoside, an 8-hydroxyquinoline glucoconjugate.[16] The reason for the development of glucoconjugate is the glucose avidity,[17] the elevated glycolysis of tumour cells and the over-expression of glucose transporters.[18–20] Thus, following the entrapment of glycoconjugates within cancer cells,

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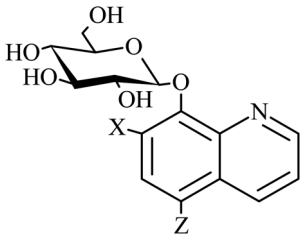

X=Z=H GluOHQ

X=I Z=Cl GluCQ

Fig. 1 Glucoconjugates of OHQ derivatives.

they could be subject to hydrolysis by specific β-glucosidases to liberate the active aglycone, which may exert its anticancer activity as reported for other glycoconjugates.[21] The presence of sugar could eliminate the undesired chelation of systemic metal ions. Moreover, glucoconjugates have also been proposed to impart an elevated uptake to the brain by exploitation of the glucose transport system in the blood–brain barrier.[22]

The glycoconjugation strategy could improve selectivity by targeting drugs to the specific site of action,[23,24] thus preventing side effects of drugs on healthy tissue.

The glycoconjugation approach has been used in an effort to enhance the targeting of analgesics,[25] dopamine derivatives,[26] anti-cancer agents,[27] and chelating agents.[28–33]

To the best of our knowledge this is the first example of glycoconjugation of CQ. In this paper, we report the synthesis of glycoconjugates, cleavage studies with β-glucosidase, and antiproliferative activities of bioconjugates in different cell lines in the presence of zinc(II) and copper(II).

Experimental

General

Commercially available reagents were used directly, unless otherwise noted.

Clioquinol and 8-hydroxyquinoline were purchased from Sigma-Aldrich. TLC was carried out on silica gel plates (Merck 60-F254). β-Glucosidase from almonds was obtained from Sigma-Aldrich.

NMR spectroscopy

^{1}H NMR spectra were recorded at 25 °C with a Varian UNITY PLUS spectrometer at 499.883 MHz. The NMR spectra were obtained by using standard pulse programs from Varian library. In all cases the length of 90° pulse was 7 μs. The 2D experiments (COSY, TOCSY, HSQC) were acquired using 1 K data points, 256 increments and a relaxation delay of 1.2 s.

Mass spectrometry and UV-vis spectroscopy

The ESI-MS measurements were performed on a Finnigan LCQ-Duo ion trap electrospray mass spectrometer. The UV spectra were recorded using an Agilent 8452A diode array spectrophotometer.

General procedure for the synthesis of the glucoconjugates

Quinoline derivative (0.75 mmol) and K_2CO_3 (7.5 mmol) were added to water (30 mL) and methanol (30 mL). Dichloromethane (50 mL) was added to this aqueous solution, followed by acetobromoglucose (1.88 mmol) and tetrabutylammonium bromide (0.75 mmol). The resulting mixture was vigorously stirred for 68 h. The two-phase system was separated, and the aqueous phase was washed repeatedly with dichloromethane.

The combined organic extracts were dried with Na_2SO_4, filtered, and evaporated in vacuum.

The crude product was purified by column chromatography (eluent: AcOEt–hexane = 3 : 2) to obtain the pure peracetylated glucoconjugate.

The removal of the acetyl protecting group was easily achieved in mild conditions. Peracetylated glucoside (0.16 mmol) was dissolved in 8 mL of absolute methanol. To this mixture 2 mL of NaOMe (0.1 N, MeOH solution) was added. After 20 min, a solid precipitated, however the mixture was stirred overnight to complete deacetylation. The product was collected by filtration, washed with cool methanol and dried. As for, 8-quinolinyl β-D-glucopyranoside, the reaction mixture was stirred at r.t. for 24 h and evaporated in vacuum. Ion exchange CM Sephadex (form NH_4^+) was used to remove salts.

8-Quinolinyl-tetra-*O*-acetyl-β-D-glucopyranoside

Yield: 118 mg, 40%

TLC: Rf = 0.20 (AcOEt–*n*-hexane 1 : 1).

ESI-MS: *m*/*z* = 476.00 [GluOHQ + H]$^+$, 498.07 [GluOHQ + Na]$^+$, 950.53 [2GluOHQ + H]$^+$, 972.60 [2GluOHQ + Na]$^+$.

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 9.01 (1H, s, H-2 of OHQ), 8.26 (1H, d, H-4 of OHQ), 7.63 (1H, d, H-6 of OHQ), 7.52 (3H, m, H-3, H-5, H-7 of OHQ), 5.55 (1H, m, H-1 of Glu), 5.47 (1H, m, H-2 of Glu), 5.39 (1H, t, H-3 of Glu), 5.23 (1H, t, H-4 of Glu), 4.27 (1H, dd, H-6 of Glu), 4.21 (1H, dd, H-6 of Glu), 3.88 (1H, ddd, H-5 of Glu), 2.12–2.04 (12H, CH_3).

8-Quinolinyl-β-D-glucopyranoside (GluOHQ)

Yield: 30 mg (65%)

TLC: Rf = 0.36 (PrOH–AcOEt–H_2O–NH_3 4 : 4 : 1 : 1)

ESI-MS: *m*/*z* = 308.00 [GluOHQ + H]$^+$, 330.07 [GluOHQ + Na]$^+$, 636.73 [2GluOHQ + Na]$^+$.

^{1}H NMR (500 MHz, D_2O) δ (ppm): 8.79 (1H, s, H-2 of OHQ), 8.43 (1H, d, H-4 of OHQ), 7.65 (1H, d, H-5 of OHQ), 7.61 (1H, m, H-3 of OHQ), 7.55 (1H, m, H-6 of OHQ), 7.45 (1H, d, H-7 of OHQ) 5.30 (1H, d, $J_{1,2}$ = 7.9 Hz, H-1 of Glu), 3.89 (1H, d, H-3 of Glu), 3.78–3.58 (4H, m, H-2 H-4, H-6 of Glu), 3.50 (1H, m, H-5 of Glu).

UV-vis: (H_2O) λ/nm (ε M^{-1} cm^{-1}) 236 (29734), 298 (3165).

Elemental analysis for $C_{15}H_{17}NO_6 \cdot H_2O$: calc. C 55.36; H 5.89; N 4.31; found C, 55.29; H, 5.94; N, 4.28.

5-Chloro-7-iodo-8-quinolinyl-tetra-*O*-acetyl-β-D-glucopyranoside

Yield: 274 mg, 58%

TLC: Rf = 0.56 (AcOEt–*n*-hexane 1 : 1)

ESI-MS: *m*/*z* = 635.80 [GluCQ + H]$^+$, 657.80 [GluCQ + Na]$^+$, 673.80 [GluCQ + K]$^+$

^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 8.92 (1H, dd, $J_{1,2}$ = 4.1 Hz, $J_{1,3}$ = 1.6 Hz, H-2 of CQ), 8.54 (1H, dd, $J_{1,2}$ = 8.6 Hz, $J_{1,3}$ = 1.6 Hz, H-4 of CQ), 7.99 (1H, s, H-6 of CQ), 7.56 (1H, dd, $J_{1,2}$ = 8.6 Hz, $J_{1,2}$ = 4.1 Hz, H-3 of CQ), 6.28 (1H, d, $J_{1,2}$ = 7.9 Hz, H-1 of Glu), 5.51 (1H, dd, H-2 of Glu) 5.37 (1H, t, H-3 of Glu), 5.27 (1H, t, H-4 of Glu), 4.15 (1H, dd, $J_{1,1}$ = 12.2 Hz, $J_{1,2}$ = 4.9 Hz, H-6 of Glu), 4.02 (1H, dd, $J_{1,1}$ = 12.2 Hz, $J_{1,2}$ = 4.9 Hz, H-6 of Glu), 3.68 (1H, ddd, H-5 of Glu), 2.12 (3H, s, CH_3 of acetyl), 2.07 (3H, s, CH_3 of acetyl), 2.03 (3H, s, CH_3 of acetyl), 1.94 (3H, s, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.7 (C-2 of CQ), 135.4 (C-6 of CQ), 133.4 (C-4 of CQ), 122.1 (C-3 of CQ), 100.7 (C-1 of Glu), 72.9 (C-3 of Glu), 72.2 (C-2 of Glu), 71.8 (C-5 of Glu), 68.6 (C-4 of Glu), 61.7 (C-6 of Glu), 20.9–20.6 (CH_3).

5-Chloro-7-iodo-8-quinolinyl-β-D-glucopyranoside (GluCQ)

Yield: 52 mg, 70%

TLC: Rf = 0.48 (PrOH–AcOEt–H_2O–NH_3 4 : 4 : 1 : 1)

ESI-MS: m/z = 467.87 $[GluCQ+H]^+$, 489.87 $[GluCQ + Na]^+$, 956.40 $[2GluCQ + Na]^+$, 972.40 $[2GluCQ + K]^+$

^{1}H NMR (500 MHz, CD_3OD) δ (ppm): 8.94 (1H, dd, $J_{1,2}$ = 4.2 Hz, $J_{1,3}$ = 1.5 Hz, H-2 of CQ), 8.67 (1H, dd, $J_{1,2}$ = 8.6 Hz, $J_{1,3}$ = 1. 5 Hz, H-4 of CQ), 8.12 (1H, s, H-6 of CQ), 7.73 (1H, dd, $J_{1,2}$ = 8.6 Hz, $J_{1,2}$ = 4.2 Hz, H-3 of CQ), 5.52 (1H, d, $J_{1,2}$ = 7.9 Hz, H-1 of Glu), 3.80–3.72 (2H, m, H-2, H-6 of Glu), 3.69–3.64 (1H, m, H-6 of Glu), 3.51–3.40 (2H, m, H-3, H-4 of Glu), 3.21 (1H, m, H-5 of Glu).

^{13}C NMR (125 MHz, CD_3OD) δ (ppm): 150.1 (C-2 of CQ), 135.6 (C-6 of CQ), 133.8 (C-4 of CQ), 122.6 (C-3 of CQ), 105.3 (C-1 of Glu), 77.0 (C-3 and C-5 of Glu), 74.7 (C-2 of Glu), 69.8 (C-4 of Glu), 61.2 (C-6 of Glu).

UV-vis: (EtOH) λ/nm (ε M^{-1} cm^{-1}) 208 (27326), 248 (33527), 299 (4457).

Elemental analysis for $C_{15}H_{15}ClINO_6 \cdot H_2O$: calc. C 37.08; H 3.53; N 2.88; found C, 37.00; H, 3.57; N, 2.80.

Assessment of enzymatic cleavage of glycoconjugates by β-glucosidase

A screen using almond β-glucosidase was performed to assess the potential of the OHQ glucosides to act as substrates for glucosidases. Glycoconjugates were incubated at 37 °C for 2 h. TLC and ESI-MS monitoring of the glucosidase reactions were used to determine whether the clioquinol glycosides showed any sign of being cleaved by the enzyme. Proligands were stable in aqueous solution for several days.

Enzymatic cleavage was also monitored by UV-vis spectroscopy. All kinetic assays were conducted in 1 cm path length matched quartz cuvettes with an Agilent 8452A diode array spectrophotometer at 37 °C. Unless stated otherwise, β-glucosidase (1×10^{-6} M) was incubated in the assay solution in the presence of the glycoconjugates (6×10^{-5} M) and copper (6×10^{-5} M) or zinc (6×10^{-5} M).

Dilution of glycosides and parent compounds for biological determinations

All glycosides and parent compounds CQ and OHQ were firstly dissolved in 100% dimethylsulfoxide (DMSO) at the concentration of 100 mM and then further diluted in fetal calf serum (FCS, final concentration DMSO 2%).

Determination of antiproliferative activity by the MTT assay

Human cell lines A2780 (ovary, adenocarcinoma), A549 (lung, carcinoma) and MDA-MB-231 (breast, carcinoma) were plated at opportune concentrations in 180 µl into flat-bottomed 96-well microtiter plates. After 6–8 h they were treated with 20 µl containing five 1 : 10 fold concentrations of our compounds (starting from 100 µM) diluted in FCS in the presence or absence of copper(II) and zinc(II) (20 µM $CuCl_2$ and 50 µM $ZnCl_2$) and processed as described elsewhere.[34,35]

IC_{50}s were calculated on the basis of the analysis of single concentration–response curves. For IC_{50}s higher than 120 µM we extrapolated the final mean IC_{50} value using the mean concentration–response curve. Each experiment was repeated 4–6 times.

Statistical analysis

The Mann–Whitney test for non-parametric data was used for the statistical analysis of data.

Results and discussion

Synthetic aspect

In order to synthetize the desired compounds, a modified Michael procedure was utilized. Glycosidic bonds were formed through an SN2 type mechanism under basic conditions using

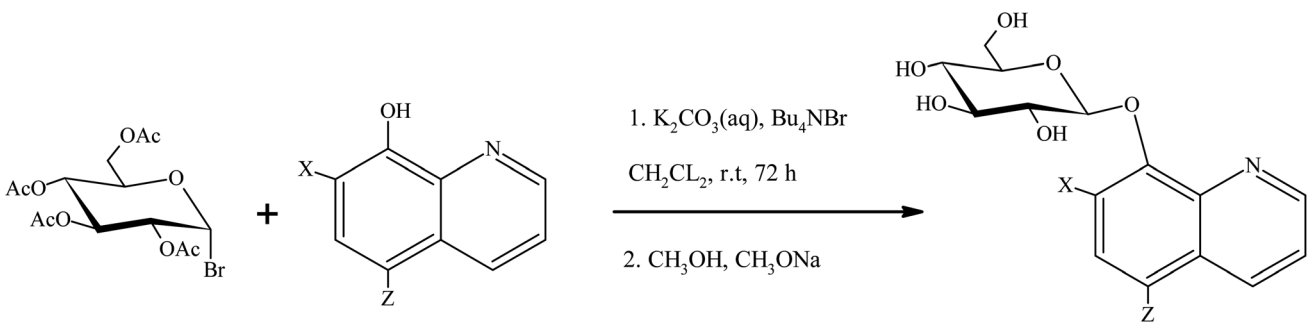

Fig. 2 Synthesis of glucoconjugates.

glycosyl bromides (Fig. 2). Briefly, the glycosyl bromide was dissolved in dichloromethane or chloroform and a water–methanol solution of the base K_2CO_3 was added together with a phase transfer catalyst such as tetrabutylammonium salts. This reaction produced the β-anomer of the CQ glycosides. Then the peracetylated products were deprotected by removing the acetyl protection groups in mild conditions. All novel compounds were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy as well as ESI-MS. NMR spectra, assigned by COSY, TOCSY and HSQC, confirmed the identity of the products. The ^{1}H NMR spectrum of GluCQ is reported in Fig. 3. The protons of the CQ moiety resonate at 8.94, 8.67 and 7.73 ppm and the CQ H-6 resonates as singlet at 8.12 ppm (Fig. 3).

The H-1 of the glucose moiety resonates at 5.5 ppm because of the deshielding effect of the aromatic ring as reported for similar compounds.[36] The $J_{1,2}$ = 7.9 Hz confirms the β configuration of the derivative. The ESI-MS spectra of CQ glycosides show three peaks at 467.87, 489.93, 956.67 *m/z* due to the proton adduct ion $[GalCQ + H]^+$, the sodium adduct ion $[GalCQ + Na]^+$, and the dimeric sodium adduct ion $[2GalCQ + Na]^+$, respectively. Furthermore, the zoom scan spectrum shows a typical isotopic pattern due to the presence of two halogen atoms.

Enzymatic cleavage of clioquinol glycosides

The CQ and OHQ glucosides are not able to strongly complex metal ions. The glucose moiety has to be cleaved before metal chelation. The pyridin ring can complex copper(II) only with a log K1 about 2.6.[15] There are a number of enzymes that cleave β-glycosides in humans, including cytosolic β-glucosidase.[37]

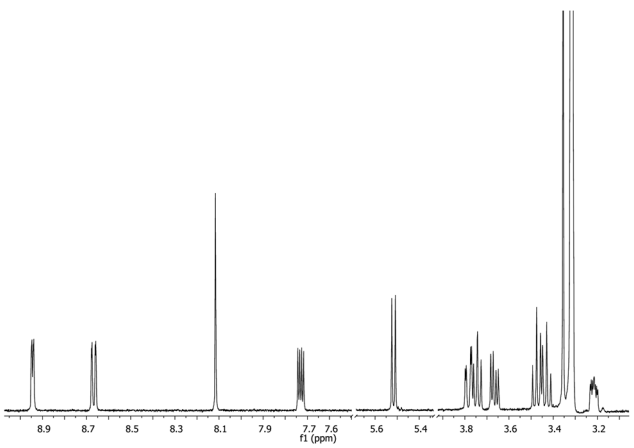

Fig. 3 ^{1}H NMR of GluCQ (500 MHz, CD_3OD).

We tested the potential of the CQ and OHQ glucoconjugates to act as substrates for glucosidases. Almond β-glucosidase was used as the enzyme model. TLC and ESI-MS monitoring of the glucosidase reactions were used to determine whether the clioquinol glycosides were cleaved. Significant cleavage of GluOHQ and GluCQ was observed after 60 min at 37 °C.

Moreover, the enzymatic deglycosylation of glucoconjugates was followed by UV-vis spectroscopy in the presence of metal ions such as copper(II) and zinc(II). The UV-vis spectra were recorded at different points in time (Fig. 4) to follow the hydrolysis. If the glycoconjugates are hydrolized the OHQ moiety is released and the copper(II) and zinc(II) can be bound. The spectra of GluOHQ reported in Fig. 4 provide the first direct temporal link between the kinetics of deglycosylation and the formation of copper(II) complex. In fact, the bands at 235 nm and 298 nm due to ligand transition, were red shifted and decreased in intensity. New bands at 253 nm and 371 nm appear in keeping with the complexation of the copper with OHQ[14] formed by glucosidase. The last spectrum is the same as the OHQ spectrum in the presence of an equimolar concentration of copper. A similar behaviour was found in the presence of zinc (II). For comparison, copper(II) was added to the GluOHQ and no modification of the bands was observed.

Antiproliferative activity of CQ and OHQ glycosides

The antiproliferative activity of glycoconjugates was tested in the absence and in the presence of copper(II) or zinc(II). CQ and OHQ were also tested for comparison (Tables 1 and 2).

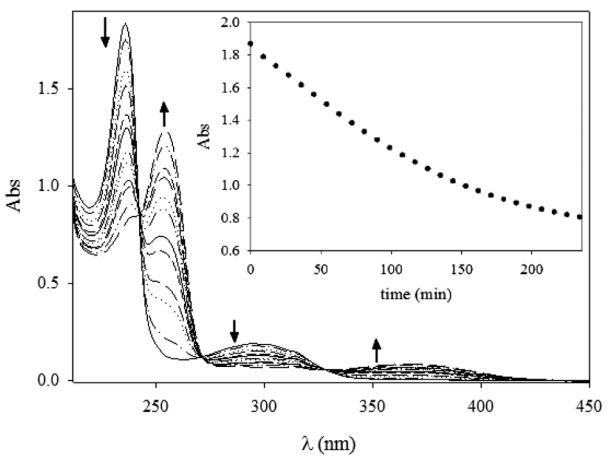

Fig. 4 Enzymatic kinetic assay of GluOHQ in the presence of glucosidase and copper(II) at pH 7.0. UV-vis spectra were recorded every 9 min. Absorbance at 236 nm *versus* time is reported in the inset.

Table 1 Summary of IC_{50}s (μM) of CQ and its glycoside on A2780, A549 and MDA-MB-231 cells

	CQ			GluCQ		
		Cu^{2+}	Zn^{2+}		Cu^{2+}	Zn^{2+}
A2780	55.31 ± 3.23[a]	5.98 ± 0.45	52.91 ± 4.37	119.37 ± 1.22	57.28 ± 12.13	101.18 ± 23.75
A549	65.54 ± 10.77	7.18 ± 0.41	60.33 ± 6.18	79.46 ± 4.48	64.83 ± 4.80	74.45 ± 5.81
MDA-MB-231	52.63 ± 2.00	10.64 ± 5.21	50.00 ± 2.46	106.28 ± 16.71	110.86 ± 17.90	104.10 ± 17.83

[a] Data represent the mean ± SD of 4–6 data.

Table 2 Summary of IC_{50}s (μM) of OHQ and its glycoside on A2780, A549 and MDA-MB-231 cells

	OHQ			GluOHQ		
		Cu^{2+}	Zn^{2+}		Cu^{2+}	Zn^{2+}
A2780	2.17 ± 0.42	0.33 ± 0.10	2.19 ± 0.16	103.10 ± 26.30	5.56 ± 0.36	112.83 ± 12.22
A549	5.28 ± 0.55	0.54 ± 0.03	5.59 ± 0.92	95.72 ± 5.37	6.97 ± 1.13	97.13 ± 4.11
MDA-MB-231	7.77 ± 0.61	0.49 ± 0.02	7.40 ± 2.16	449[a]	49.70 ± 2.81	279[a]

[a] When the value of the IC_{50} in single test were higher than 120 μM the mean IC_{50} was calculated and approximated considering the mean concentration-response curve.

In all cell lines our glycosides, tested in absence of copper(II) and zinc(II), showed IC_{50}s ranging from 79.5 μM to 449 μM with a significant decrease of their mean activity compared to their parent compounds CQ (101.7 ± 16.6 μM *vs.* 57.8 ± 5.6 μM, $p < 0.05$) and OHQ (215.9 ± 164.8 μM *vs.* 5.1 ± 2.3 μM, $p < 0.05$, Table 1).

When copper(II) ions were added, the mean antiproliferative activity for our glucoconjugates increased significantly. In particular for GluOHQ, it increased by 13.8 ± 3.9 times ($p < 0.05$), while for GluCQ the mean antiproliferative activity increased only 1.1 ± 0.85 times. In this case while the antiproliferative activity in the presence of copper(II) was 2.1 ($p = 0.021$) and 1.2 ($p = 0.011$) times higher than that of the controls without copper (II), for A2780 and A549 cells, respectively, in MDA-MD-231 cells GluCQ did not show inhibition of cell proliferation. This behaviour was also observed in the SH-SY5Y cell line, the activity of GluCQ was increased about twice in the presence of copper(II) (data not shown).

Conversely, when zinc(II) ions were added, in no cell lines did we find significant differences in terms of antiproliferative activity compared to controls without ions as reported elsewhere.[2]

A similar behaviour was observed when we tested the parent compounds CQ and OHQ in the presence of copper(II) ions with 7.8 ± 2.0 ($p < 0.05$) and 10.7 ± 3.8 ($p < 0.05$) times increased antiproliferative activity compared to control cultures without ions, respectively. Also in this case zinc(II) ions did not significantly modify the antiproliferative activity of CQ and OHQ. We could hypothesize that glucoconjugates do not have their own antiproliferative activity. A similar behaviour has been reported for O-alkylated derivatives of OHQ and CQ, which are unable to strongly complex copper(II). In all cell lines GluOHQ (Fig. 5) was more active than GluCQ when copper ions were added to the medium culture. This could be due to their hydrolysis in the cells and to the copper(II) complex formation. These data are consistent with the experimental evidence that OHQ has a higher antiproliferative activity than CQ as found by us and others.[2] However, the glucoconjugates are less active than their parent compounds. They are probably not completely hydrolyzed and for this reason IC_{50} values are lower compared to the OHQ and CQ.

Conclusions

Our results suggest that OHQ glycoconjugates are intriguing potential prodrugs. Apart from improving aqueous solubility,

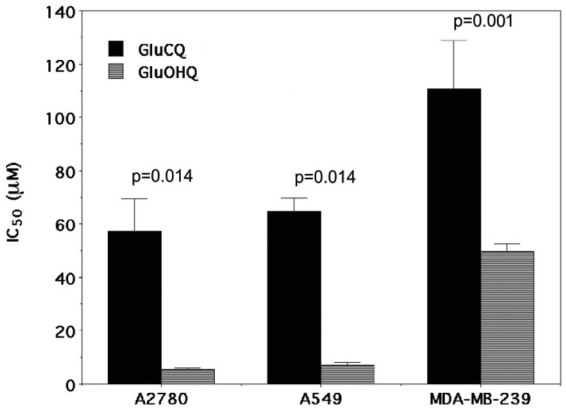

Fig. 5 IC_{50}s values of GluCQ and GluOHQ in three cell lines in the presence of copper(II).

their main advantages are potential targeting and the prevention of side effects owing to systemic chelation. In fact, the chelating function of these compounds is masked and they must be presumably subject to hydrolysis by specific β-glucosidases to liberate the active aglycone in targeted cells. The antiproliferative activity of glucoconjugates is enhanced by the addition of copper(II), up to 18.5 times in the case of GluOHQ. Furthermore, the presence of a glucose moiety could increase the drug uptake of the target cells, exploiting glucose avidity and the overexpression of glucose transporters[38] in cancer cells.

Acknowledgements

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