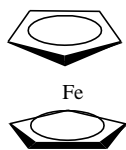


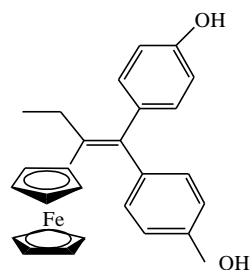
OH-Tamoxifen

OH-Tam



Ferrocene

Fc



Ferrocenyl diphenol compound

Fc-diOH

Figure 1: Chemical formulas of hydroxytamoxifen (OH-Tam), ferrocene (Fc) and 2-ferroceny-1,1-bis(4-hydroxyphenyl)-but-1-ene called ferrocenyl diphenol compound (Fc-diOH).

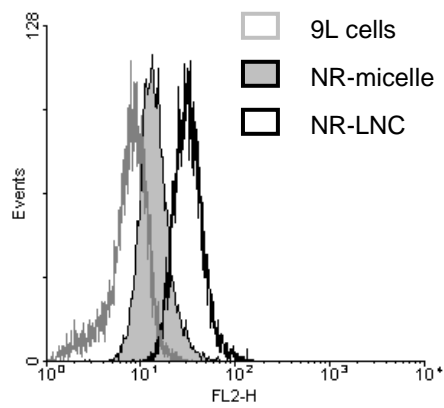
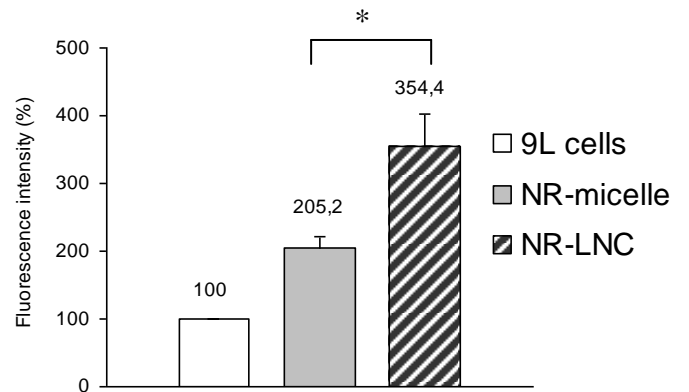
A.**B.**

Figure 2: Evaluation of Nile Red-loaded nanocarrier uptake by 9L cells after 2h of incubation in serum free conditions. (A) represents the fluorescence intensity (FL2-H) as a function of the number of collected cells (events) for control (9L cells), Nile Red loaded micelles (NR-micelle) and Nile Red loaded LNC (NR-LNC). The percentage value given for each histogram indicates the fluorescence intensity (%) \pm SD. No treatment (9L cells) was considered as 100% of fluorescence intensity (B). Note that there is a significant difference between the uptake of NR-LNC and NR-micelle ($p = 0.007$) ($n=3$). “*” means $P < 0.05$ - Student t-test.

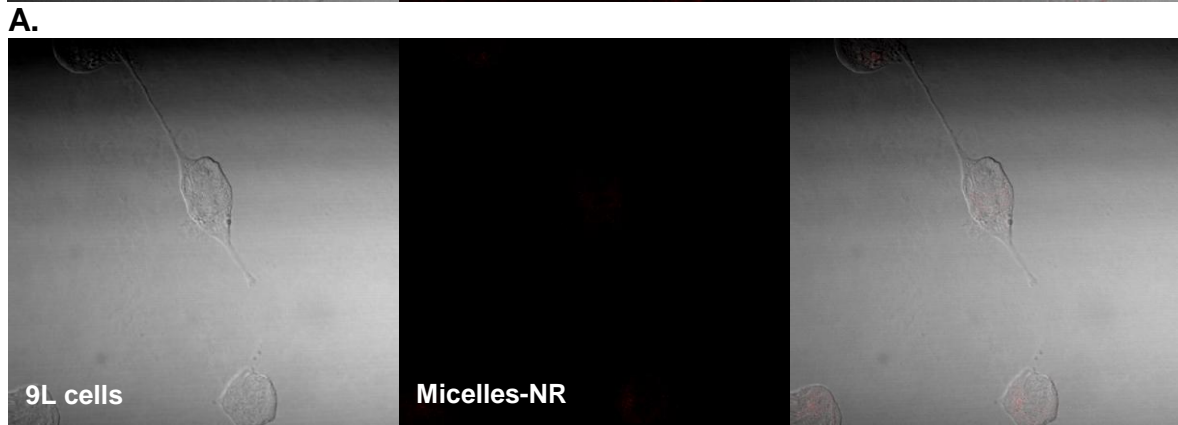
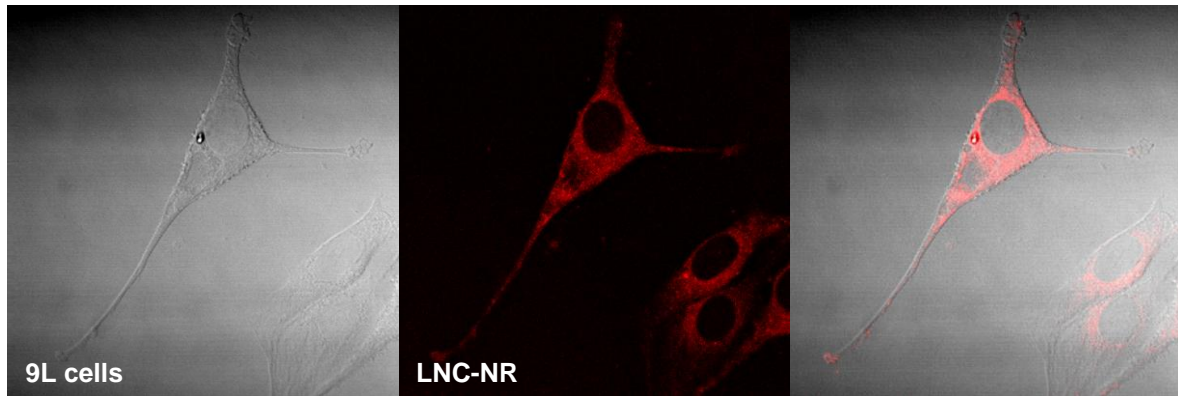


Figure 3: Confocal images of 9L cells after 2h of incubation with fluorescent LNC (LNC-NR) (A) and fluorescent micelles (Micelles-NR) (B) in serum free conditions. Images were taken with a Nomarsky contrast, with a red fluorescence filter and by the superposition of Nomarsky and fluorescent acquisitions. In A, all the fluorescence was found inside the cell, while avoiding the nucleus, demonstrating an uptake of the nanocapsules. On the contrary, a very weak level of fluorescence was observed after the incubation of Nile Red-loaded micelles with 9L cells which means that only a few micelles are able to penetrate the cells (B).

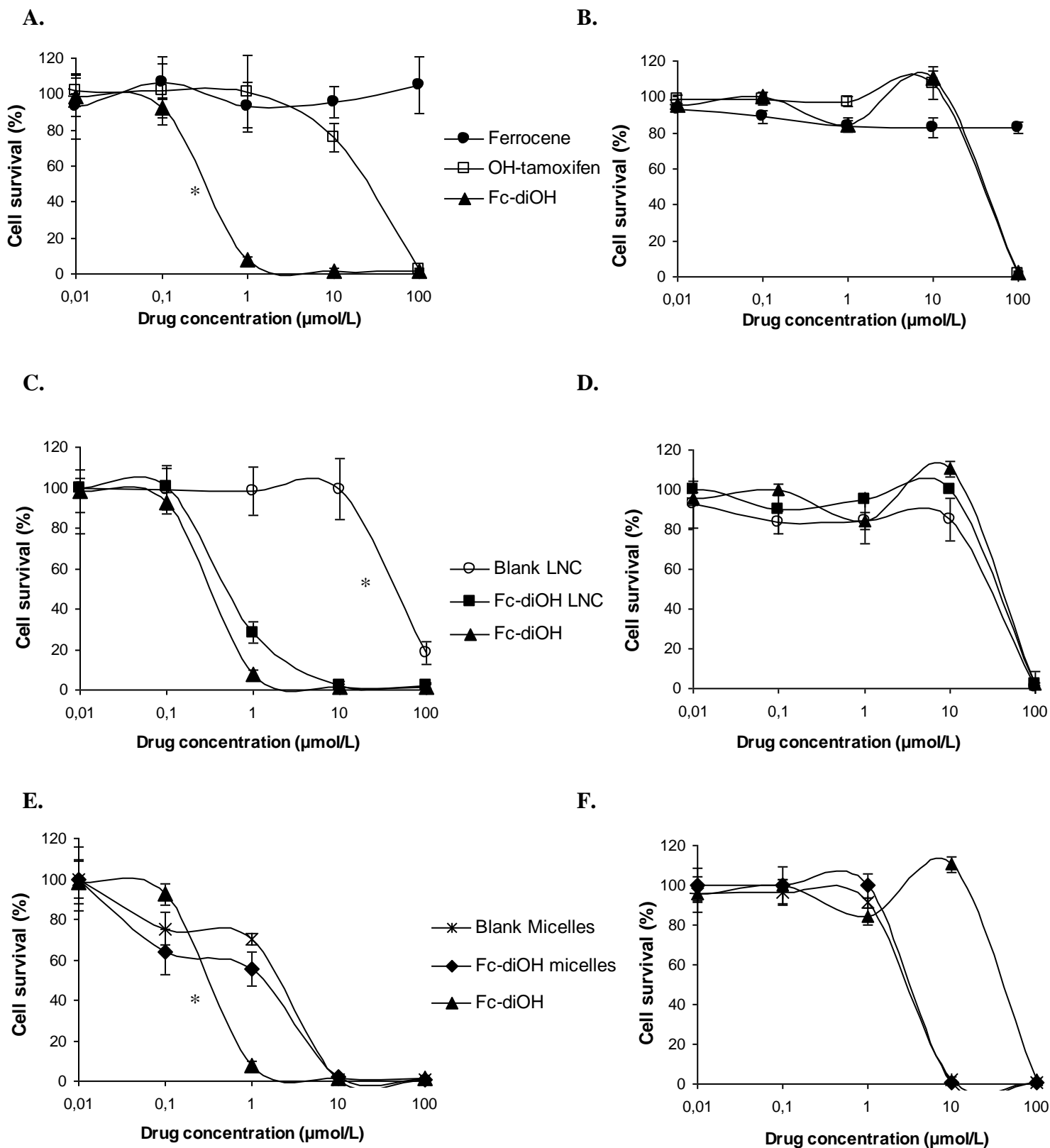
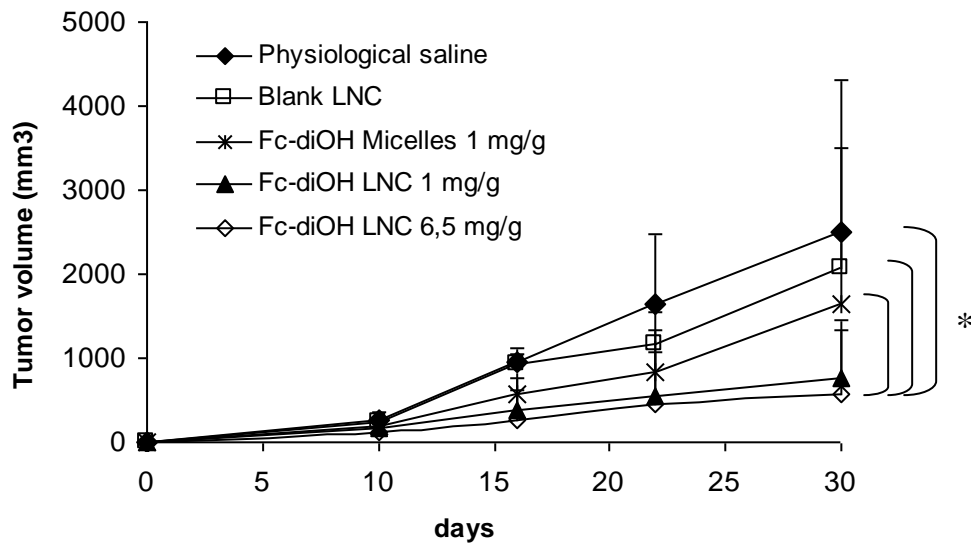


Figure 4: Effects of ferrocene (Fc), hydroxytamoxifen (OH-Tam), ferrocenyl tamoxifen derivatives (Fc-diOH), Fc-diOH-loaded LNC, blank LNC, Fc-diOH-loaded micelles and blank micelles on the proliferation of 9L cells (A, C and E) and astrocytes (B, D and F) after 96h of incubation and at concentrations between 0.01 and 100 µM (MTT assay). Blank nanocarriers are tested with the same excipient concentration than for Fc-diOH loaded LNC. No toxic effect was observed for the ethanol/acetone solutions used to solubilise drugs in solution (data not shown). Data refer to the untreated control and are expressed as the mean of six wells repeated 2 times \pm SD (n=2 in 6 wells). “*” means $f_2 < 50$ compared to the other curves of the same graph - Similarity factor f_2 .

A.



B.

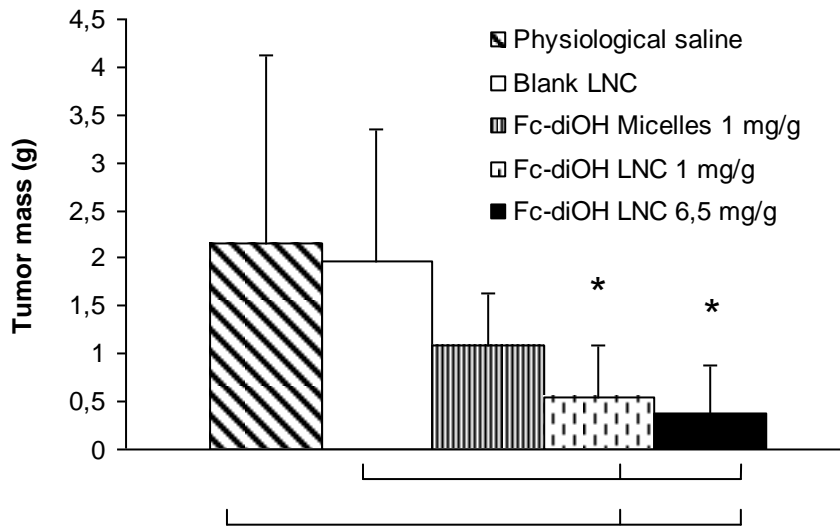


Figure 5: *In vivo* effects of Fc-diOH-loaded nanocarrier treatment on the growth of 9L glioma cells implanted subcutaneously on Fisher rats. Efficacy of the treatments with Fc-diOH-loaded nanocarriers was compared with controls made after a single injection of physiological serum or blank LNC. (A) was an estimation of tumour growth assessed by tumour size measurements \pm SD. Tumours were measured four times a month with callipers and tumour volume was approximated as an ellipsoid. (B) represents values of tumour mass weighted at Day 30 \pm SD. Statistical analysis by pairs show significant differences in A on Day 30 for Fc-diOH LNC treatment (1 and 6.5mg/g) compared to both control injection and to FcdiOH-loaded micelles (1mg/g). Same conclusions were made with tumor mass at Day 30 (B). “*” means $P < 0.05$ - Student t-test.