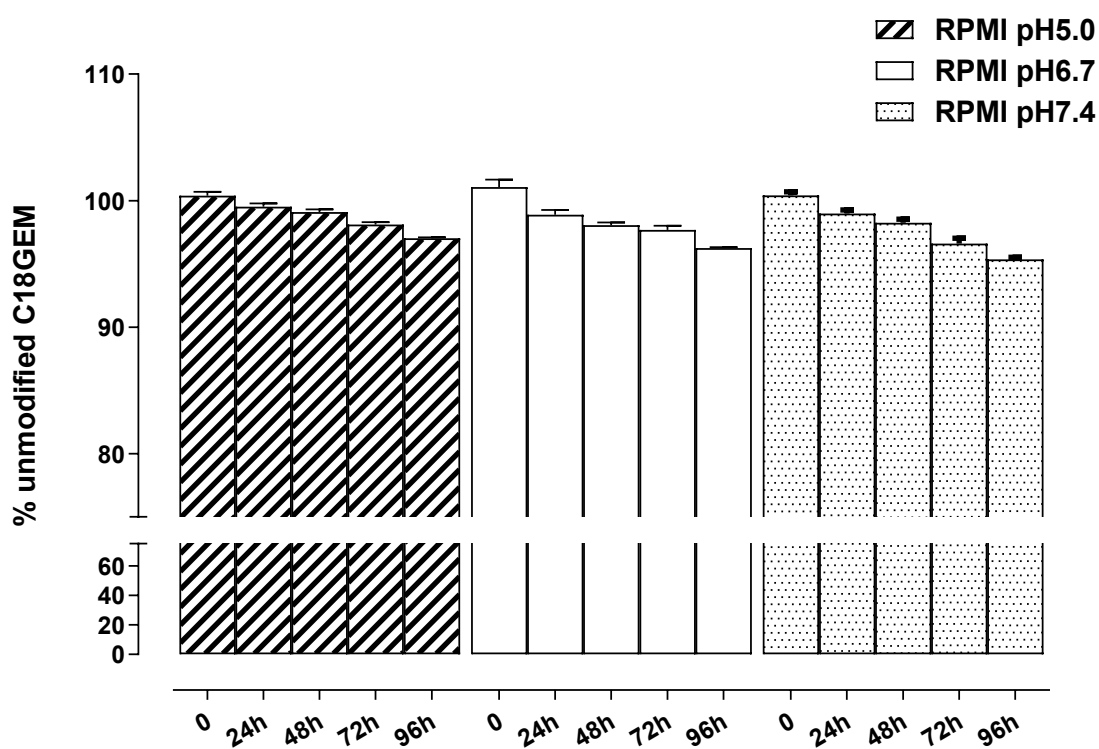
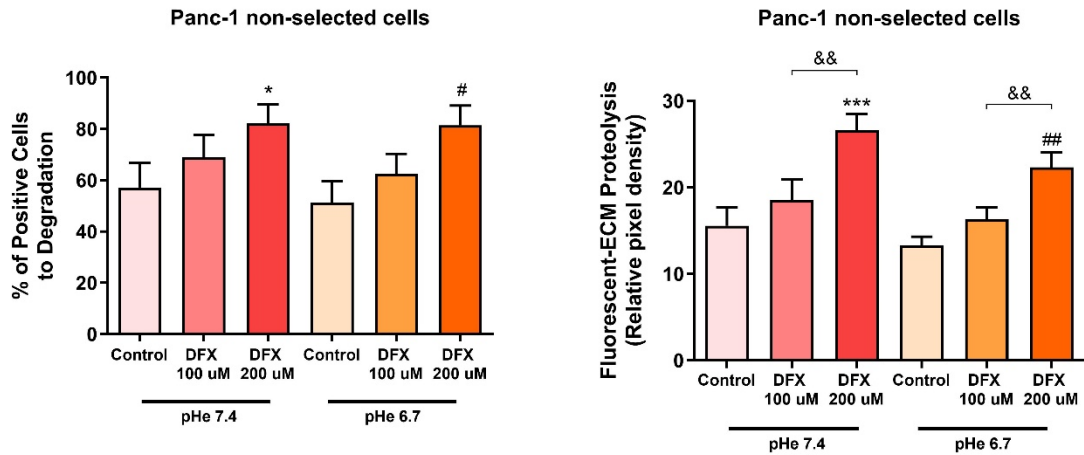


Figure S1A. Stability of GEM in RMPI 1640 at pH 5,0, 6,7, 7,4 over 96 hours. % of unmodified compound vs time (hours).



S1B. Stability of C18GEM prodrug in RMPI 1640 at pH 5,0, 6,7, 7,4 over 96 hours. % of unmodified compound vs time (hours).

A



B

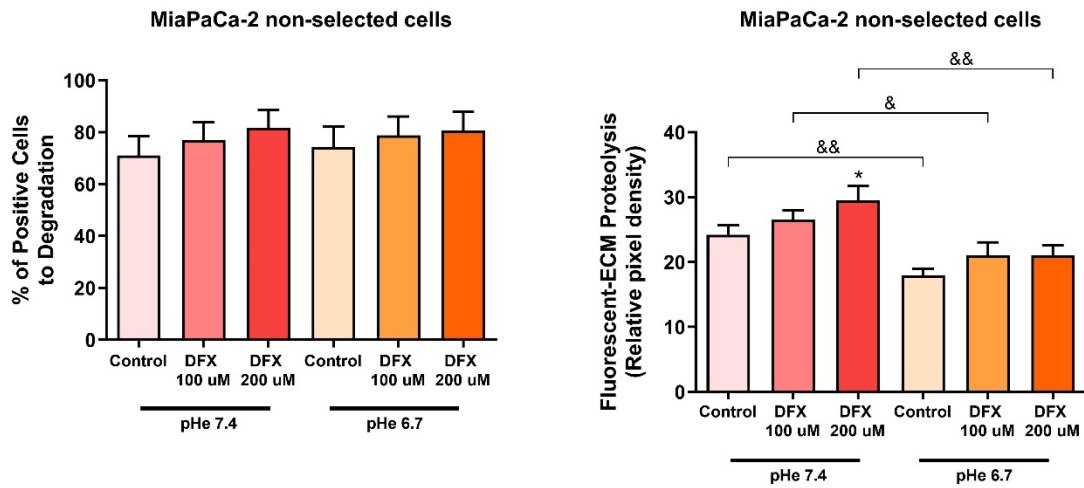
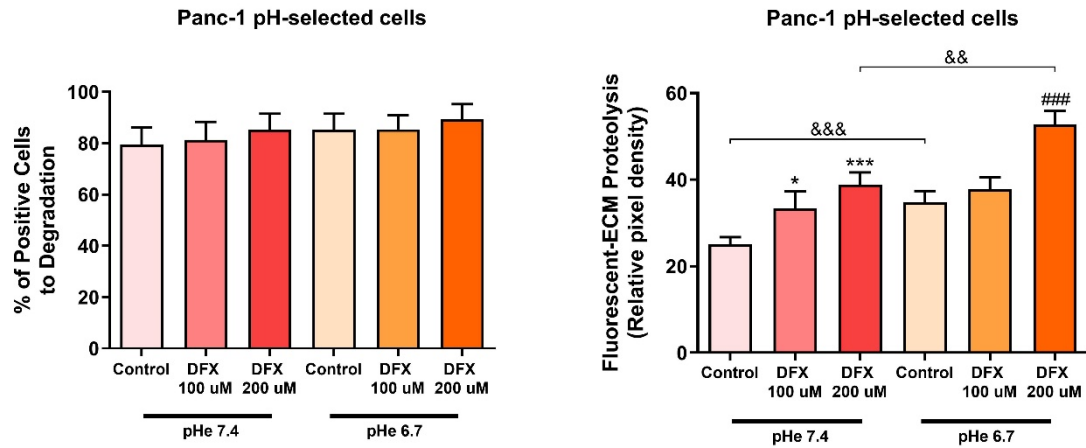


Figure S2. Effect of both hypoxia and acidic pH_e on the number of invadopodia-positive cells and their ECM-proteolytic activity/cell in non acid selected Panc-1 cells (A) and MiaPaCa-2 cells (B). The percentage of cells that formed invadopodia and mean ECM degradation/cell was determined by fluorescence microscopy. Error bars indicate mean \pm S.E.M (n=3). * p<0.05; *** p<0.001 when compared with control pH_e 7.4; # p<0.05; ## p<0.01 when compared with control pH_e 6.7; & p<0.05; && p<0.01 when compared within the same treatment between the two different pH_e.

A



B

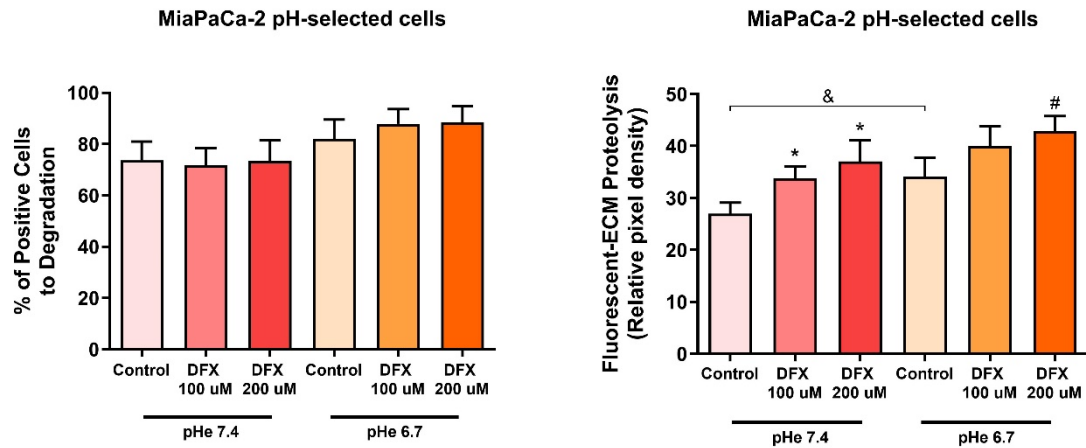
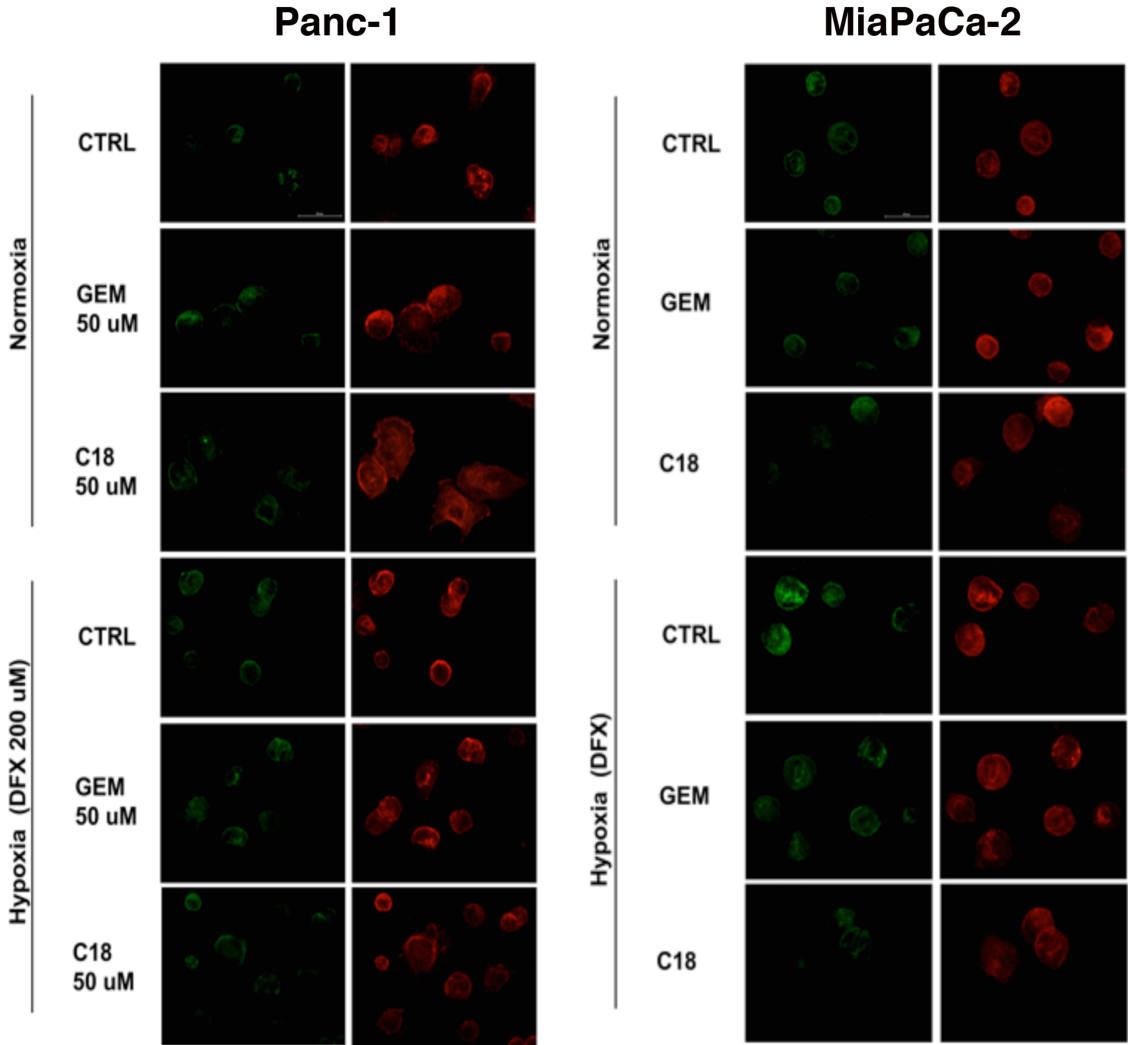
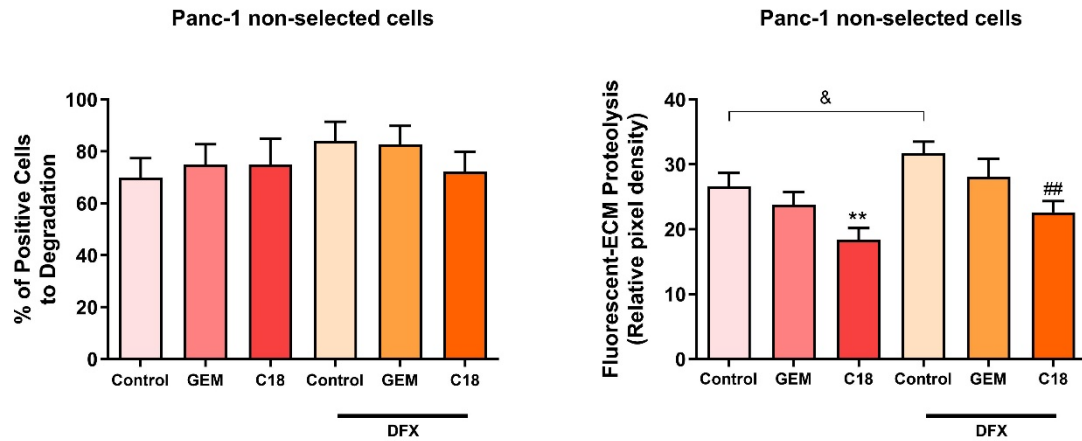


Figure S3. Effect of both hypoxia and acidic pH_e on the number of invadopodia-positive cells and their ECM-proteolytic activity/cell in Panc-1 pH-selected cells (A) and MiaPaCa-2 pH-selected cells (B). The percentage of invadopodia positive cells and their mean ECM degradation/cell was determined by fluorescence microscopy. Error bars indicate mean \pm S.E.M (n=3). * p<0.05; *** p<0.001 when compared with control pH_e 7.4; # p<0.05; ### p<0.001 when compared with control pH_e 6.7; & p<0.05 && p<0.01 when compared within the same treatment between the two different pH_e.

Figure S4. Effect of GEM and C18 on Invadopodia in normoxia and hypoxia. These panels show typical images related to the experiments of Figure 5 of proteolytic digestion in green and actin in red. The white bar in the upper right (CTRL) panel of each cell line represents 50µm.



A



B

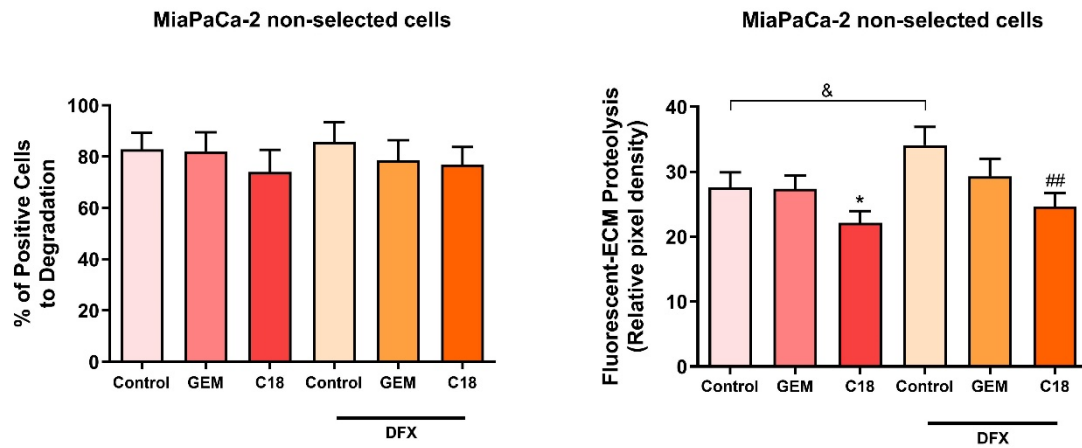
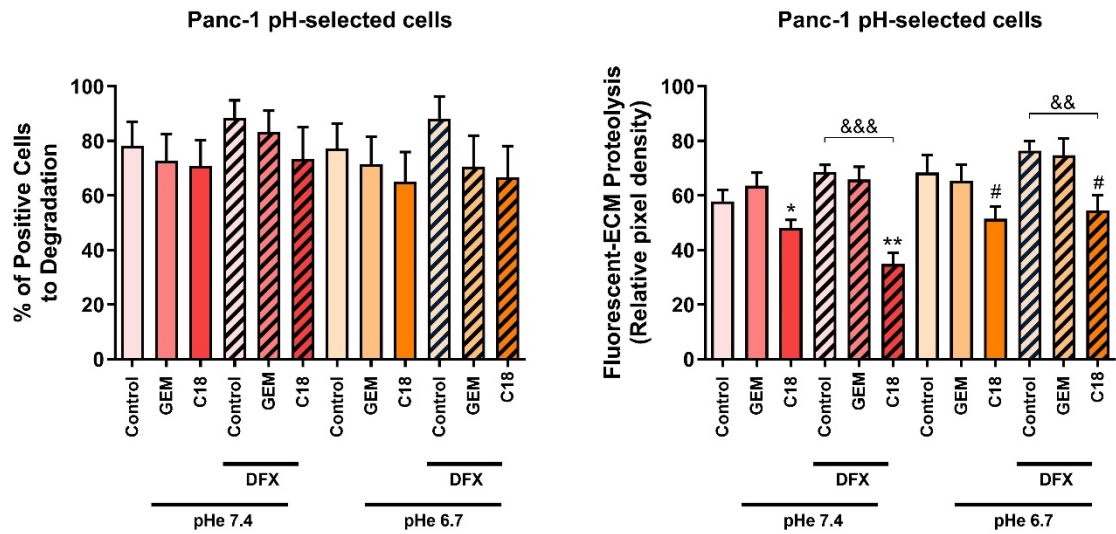


Figure S5. Effect of GEM and C18 on the number of invadopodia-positive cells and their ECM-proteolytic activity/cell in non pH-selected Panc-1 cells (A) and MiaPaCa-2 cells (B) in normoxic and hypoxic conditions. The percentage of invadopodia positive cells and their mean ECM degradation/cell was determined by fluorescence microscopy. Error bars indicate mean \pm S.E.M (n=3). * $p < 0.05$; ** $p < 0.01$ when compared with control; ## $p < 0.01$ when compared with DFX group; & $p < 0.05$ when compared within the same treatment between the presence or absence of hypoxia.

A



B

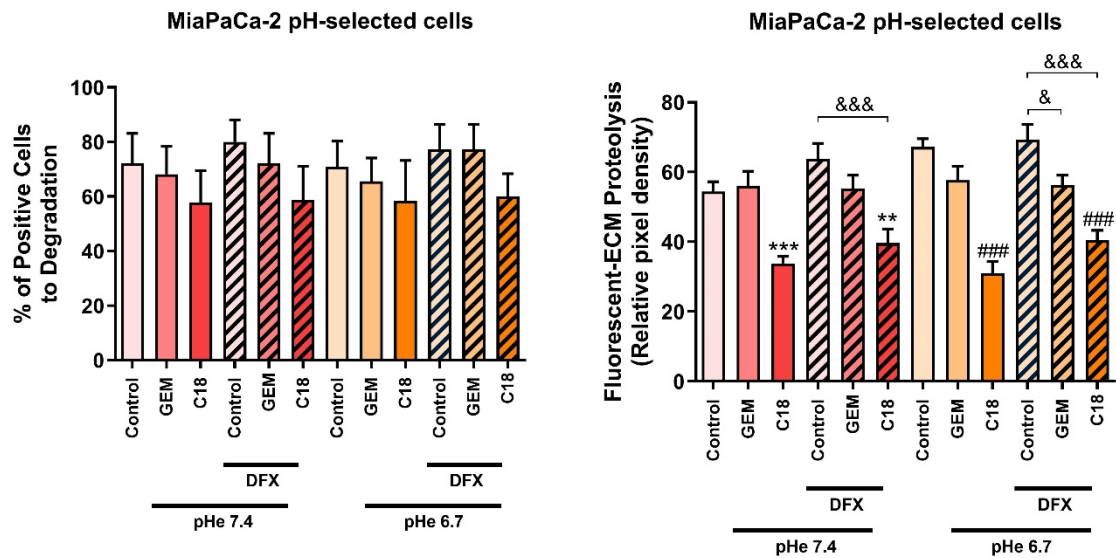


Figure S6. Effect of both GEM and C18 on the number of invadopodia-positive cells and their ECM-proteolytic activity/cell in Panc-1 pH-selected cells (A) and MiaPaCa-2 pH-selected cells (B) in normoxic and DFX (200 μ M)-induced hypoxic conditions. The percentage of cells forming invadopodia and their ECM degradation were determined by fluorescence microscopy. Error bars indicate mean \pm S.E.M (n=3). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ when compared with control pH_e 7.4; # $p < 0.05$; ### $p < 0.001$ when compared with control pH_e 6.7; & $p < 0.05$; && $p < 0.001$; &&& $p < 0.001$ when compared within the same pH_e between normoxic and hypoxic condition.