Supplementary Material

Development of potent CPP6-gemcitabine conjugates against human prostate cancer cell line (PC-3)

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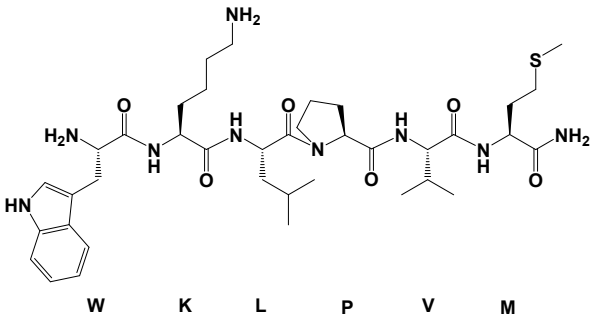

Figure S1- Chemical structure of CPP6-1.

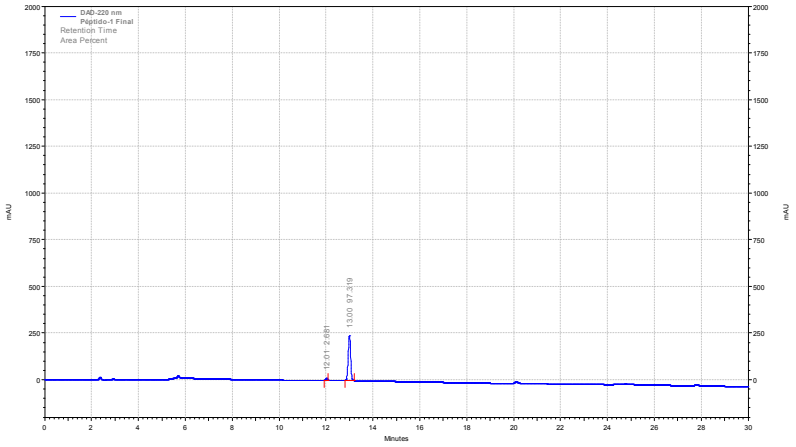

Figure S2- Chromatogram of the CPP6-1 after purification, acquired with a HPLC-DAD system, with a C18 column, using ACN in water with 0.05% TFA as eluent, in gradient mode (0 - 100%), for 30 minutes, at a flow of 1 mL/min and detection at λ = 220 nm.

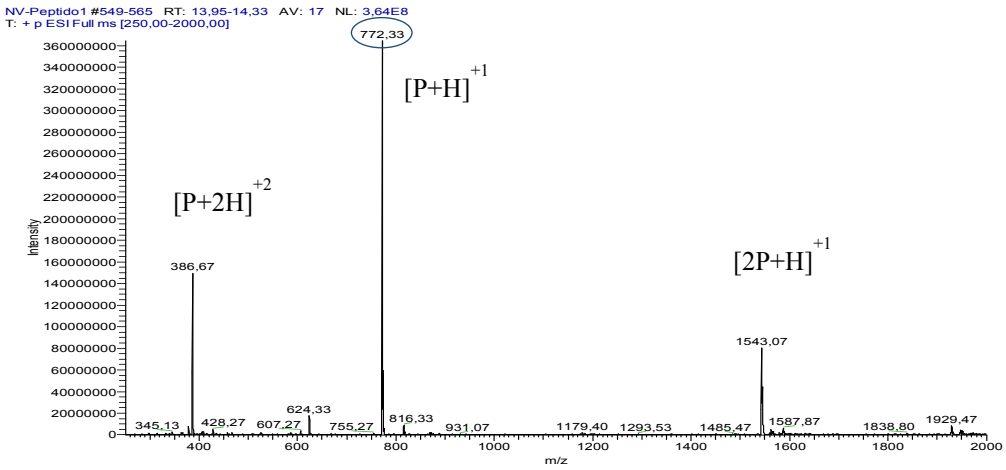

Figure S3- Mass spectrum (LC-ESI/MS Orbitrap, positive mode) of the major peak of the LC-MS chromatogram (data not shown) of CPP6-1.

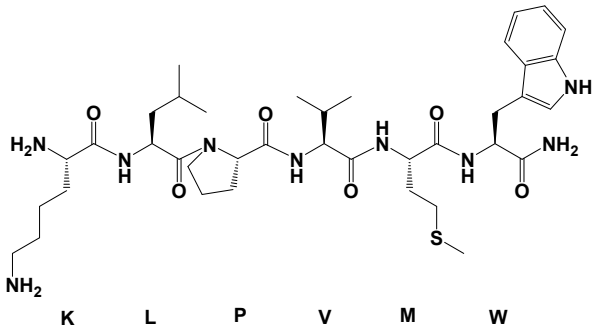

Figure S4- Chemical structure of CPP6-2.

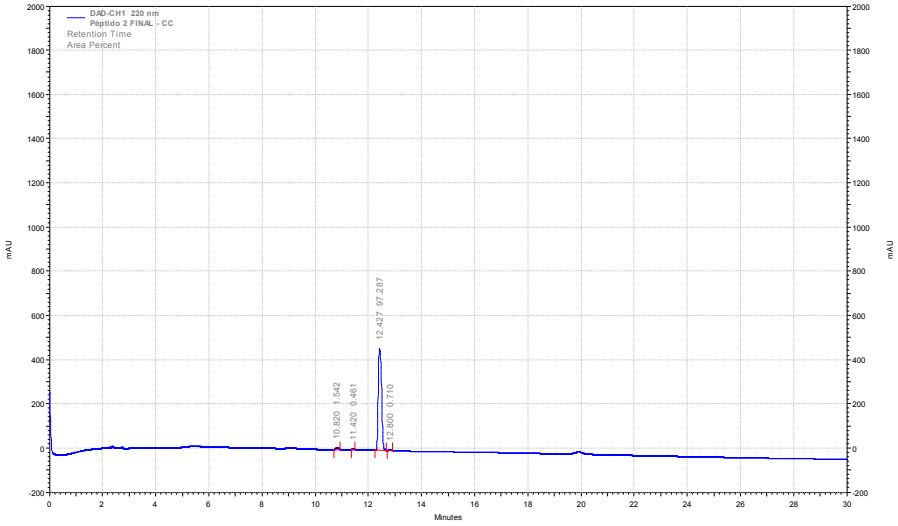

Figure S5 - Chromatogram of the CPP6-2 after purification, acquired with a HPLC-DAD system, with a C18 column, using ACN in water with 0.05% TFA as eluent, in gradient mode (0 - 100%), for 30 minutes, at a flow of 1 mL/min and detection at λ = 220 nm.

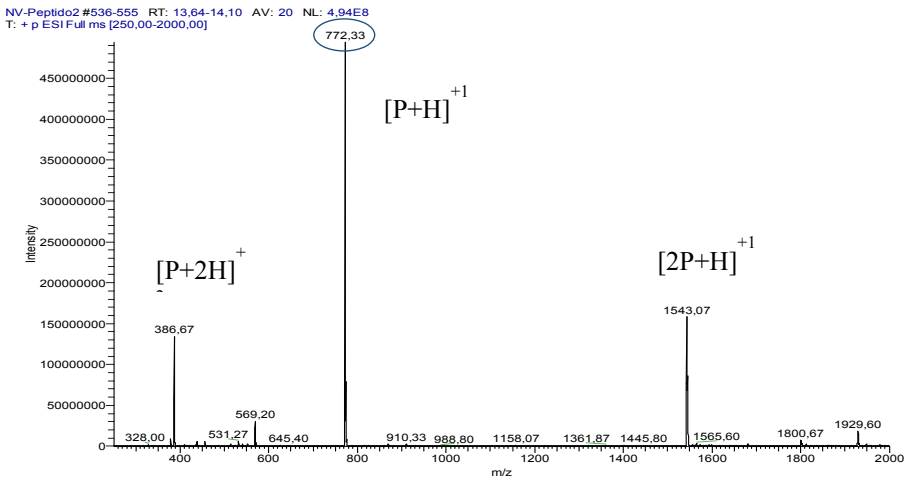

Figure S6 - Mass spectrum (LC-ESI/MS Orbitrap, positive mode) of the major peak of the LC-MS chromatogram (data not shown) of CPP6-2.

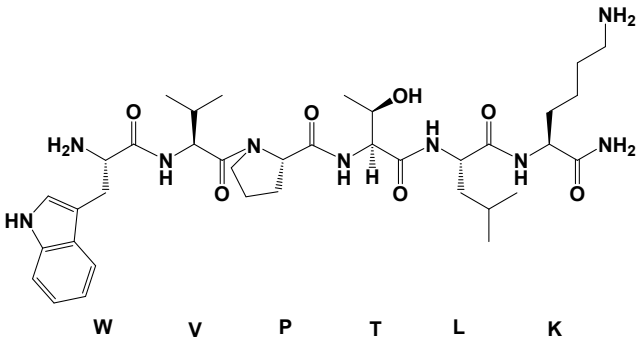

Figure S7- Chemical structure of CPP6-3.

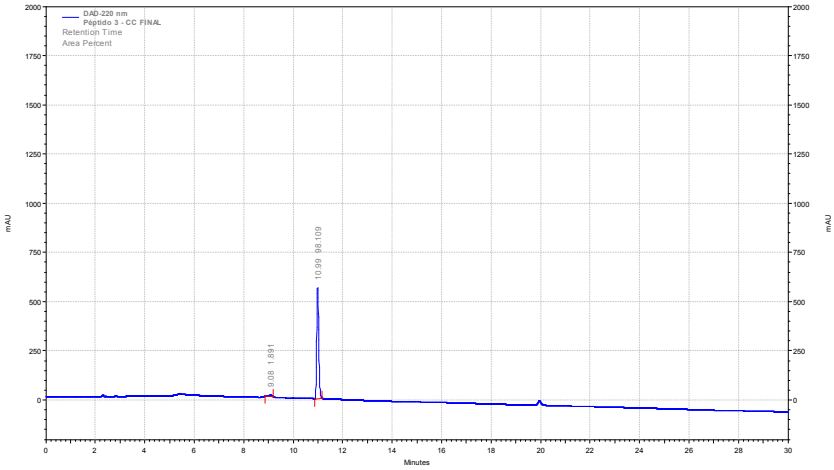

Figure S8 - Chromatogram of the CPP6-3 after purification, acquired with a HPLC-DAD system, with a C18 column, using ACN in water with 0.05% TFA as eluent, in gradient mode (0 - 100%), for 30 minutes, at a flow of 1 mL/min and detection at λ = 220 nm.

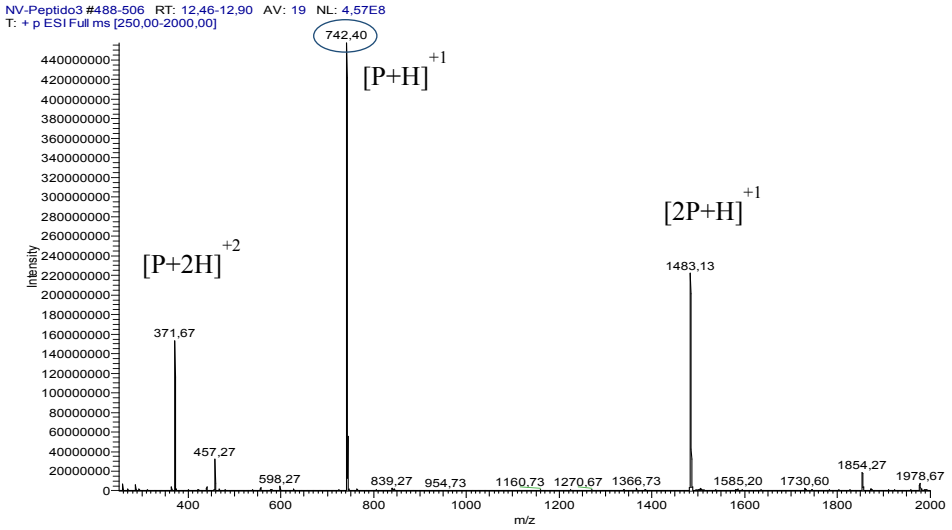

Figure S9 - Mass spectrum (LC-ESI/MS Orbitrap, positive mode) of the major peak of the LC-MS chromatogram (data not shown) of CPP6-3.

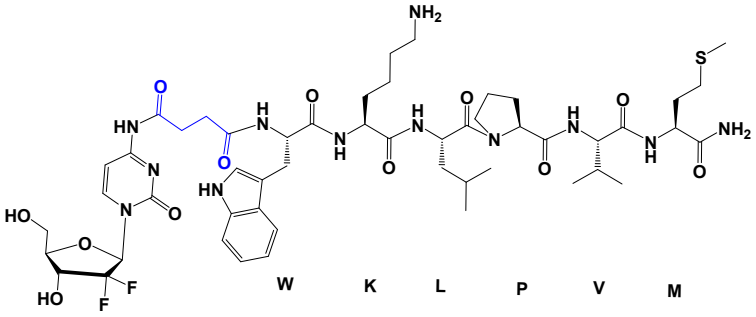

Figure S10 - Chemical structure of Gem-C2-CPP6-1 conjugate.

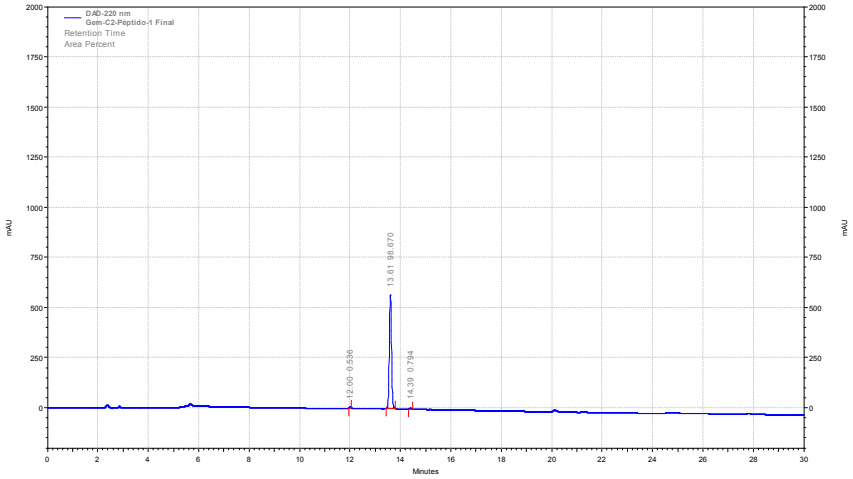

Figure S11 - Chromatogram of the Gem-C2-CPP6-1 conjugate after purification, acquired with a HPLC-DAD system, with a C18 column, using ACN in water with 0.05% TFA as eluent, in gradient mode (0 - 100%), for 30 minutes, at a flow of 1 mL/min and detection at λ = 220 nm.

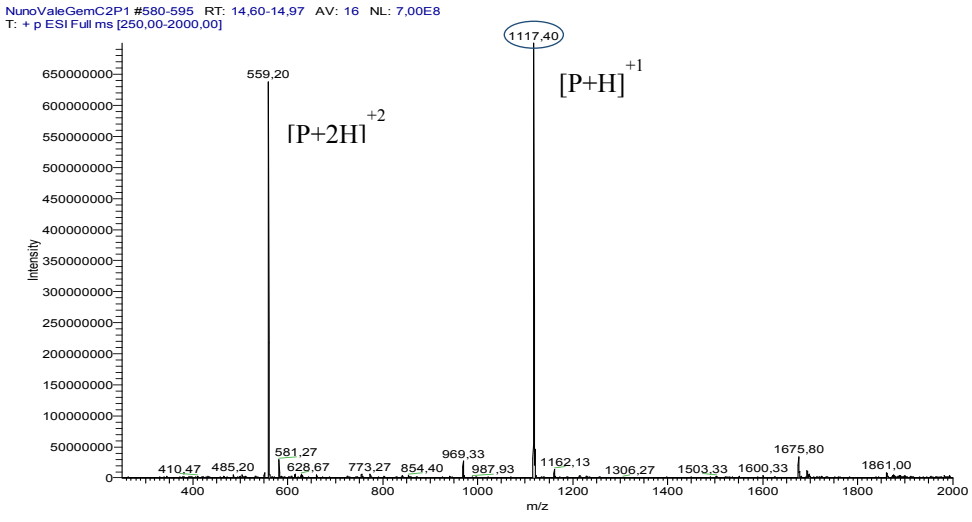

Figure S12 - Mass spectrum (LC-ESI/MS Orbitrap, positive mode) of the major peak of the LC-MS chromatogram (data not shown) of Gem-C2-CPP6-1.

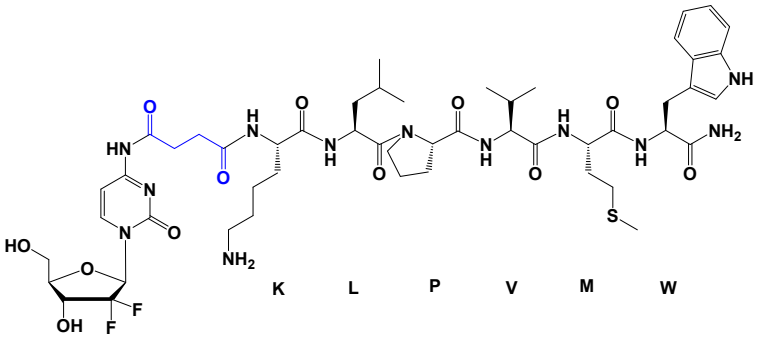

Figure S13 - Chemical structure of Gem-C2-CPP6-2 conjugate.

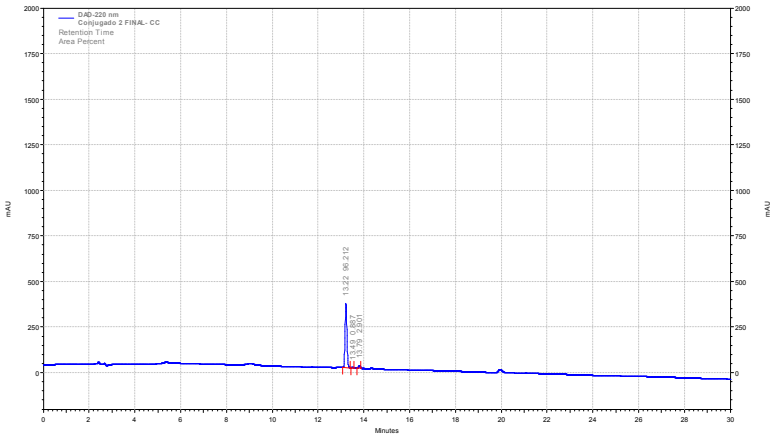

Figure S14 - Chromatogram of the Gem-C2-CPP6-2 conjugate after purification, acquired with a HPLC-DAD system, with a C18 column, using ACN in water with 0.05% TFA as eluent, in gradient mode (0 - 100%), for 30 minutes, at a flow of 1 mL/min and detection at λ = 220 nm.

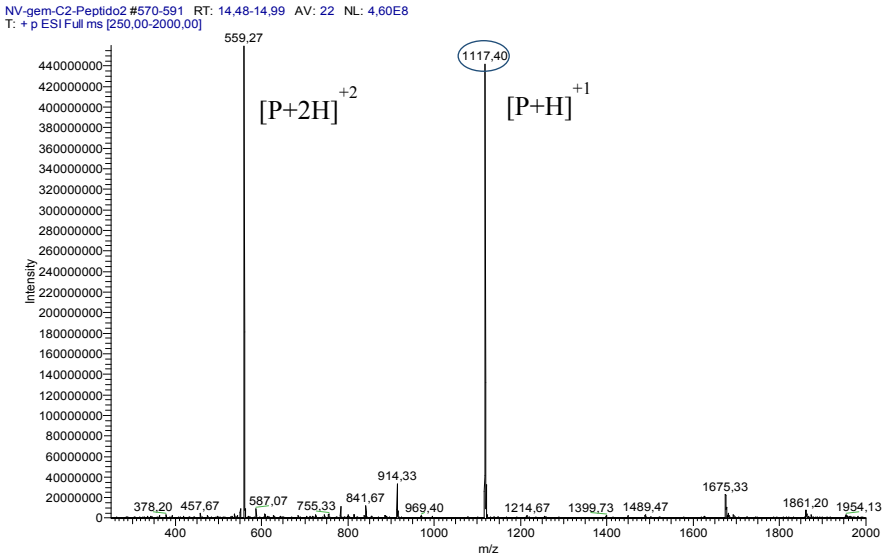

Figure S15 - Mass spectrum (LC-ESI/MS Orbitrap, positive mode) of the major peak of the LC-MS chromatogram (data not shown), of Gem-C2-CPP6-2.

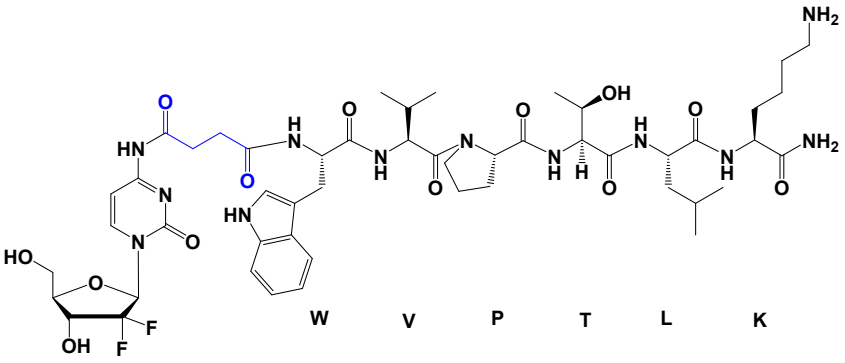

Figure S16 - Chemical structure of Gem-C2-CPP6-2 conjugate.

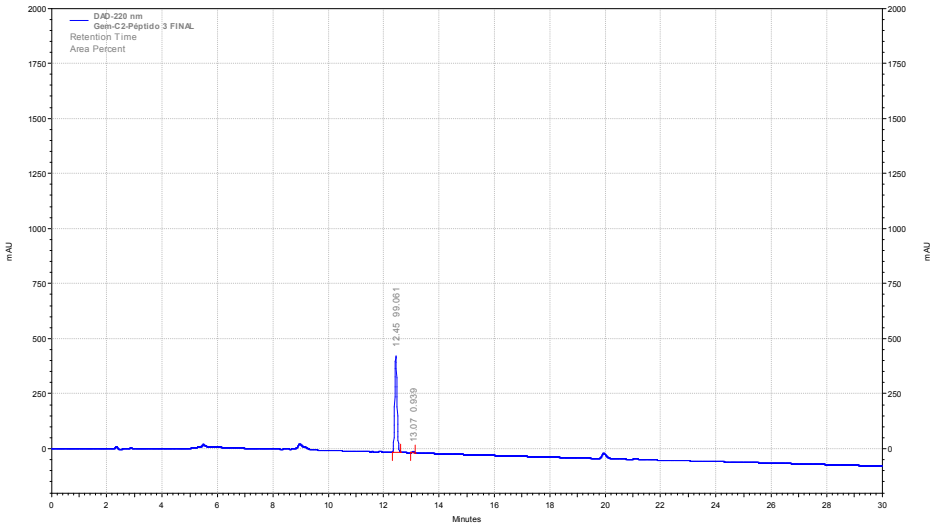

Figure S17 - Chromatogram of the Gem-C2-CPP6-3 conjugate after purification, acquired with a HPLC-DAD system, with a C18 column, using ACN in water with 0.05% TFA as eluent, in gradient mode (0 - 100%), for 30 minutes, at a flow of 1 mL/min and detection at λ = 220 nm.

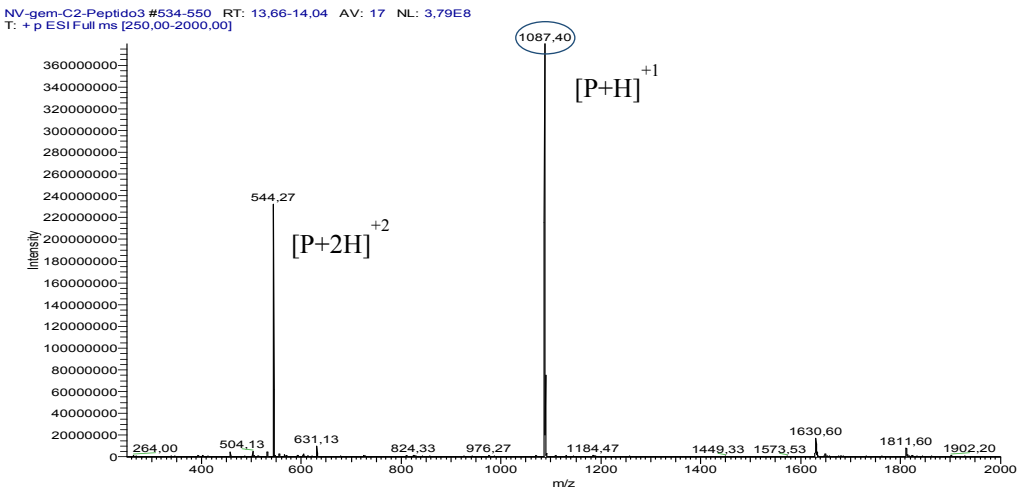

Figure S18 - Mass spectrum (LC-ESI/MS Orbitrap, positive mode) of the major peak of the LC-MS chromatogram (data not shown) of Gem-C2-CPP6-3.

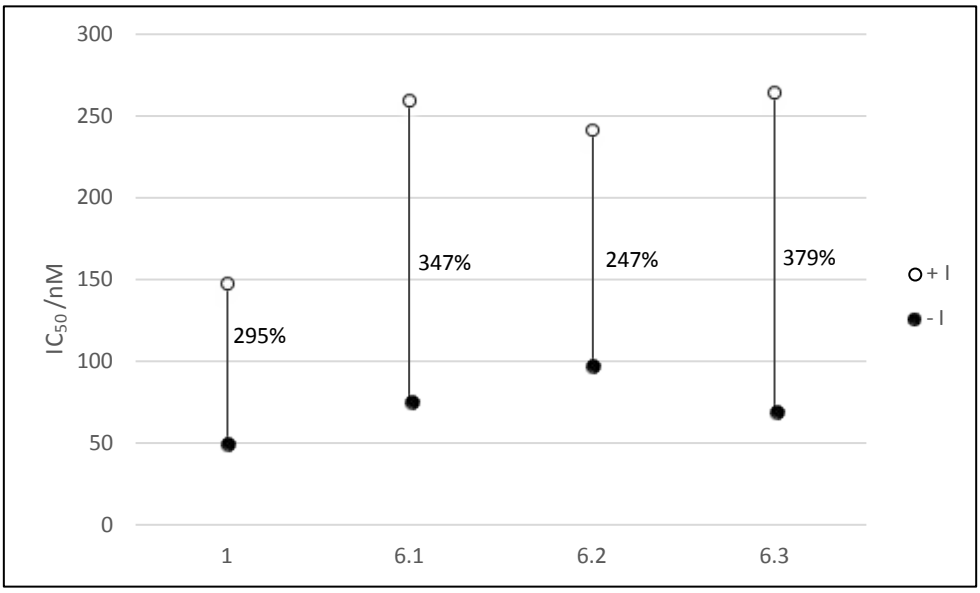

Figure S19. IC_{50} of dFdC and conjugates with or without the presence of the inhibitor NBMPR in BxPC-3cells: percentage of variation between the two values for each compound. +I: with inhibitor; -I: without inhibitor.

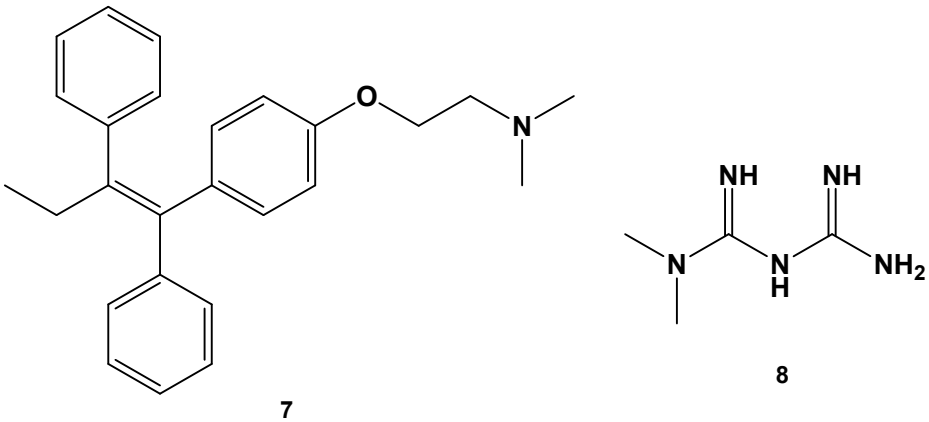

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Figure S20. Chemical structures of drugs tamoxifen (**7**) and metformin (**8**)

Table S1. Molecular properties such as the molecular weight (MW), hydrophobicity parameter logP, lipophilicity parameter logD, and the total polar surface area (TPSA) for peptides **4** and **6**. For all CPP6 and dFdC-CPP6: Number of residue, 6; Extension coefficient ($M^{-1}cm^{-1}$), 5690; isoeletric-point, 14 and net charge at pH 7 is +2 for all peptides **4** and **6**. (Calculated using GastroPlusTM Software)

#	Compound	Sequence	MW/$gmol^{-1}$	logP	logD	T_PSA
4.1	CPP6-1	KLPVMW	772.02	1.94	0.65	247.63
4.2	CPP6-2	KLPVMW	772.02	2.01	0.59	247.63
4.3	CPP6-3	WVPTLK	741.94	1.21	-0.20	267.86
6.1	Gemcitabine-C2-CPP6-1	dFdC-$(CH_2)_2$-WKLPVM	1117.28	2.51	1.51	364.39
6.2	Gemcitabine-C2-CPP6-2	dFdC-$(CH_2)_2$-KLPVMW	1117.28	2.40	1.24	364.39
6.3	Gemcitabine-C2-CPP6-3	dFdC-$(CH_2)_2$-WVPTLK	1087.19	1.84	0.69	384.62