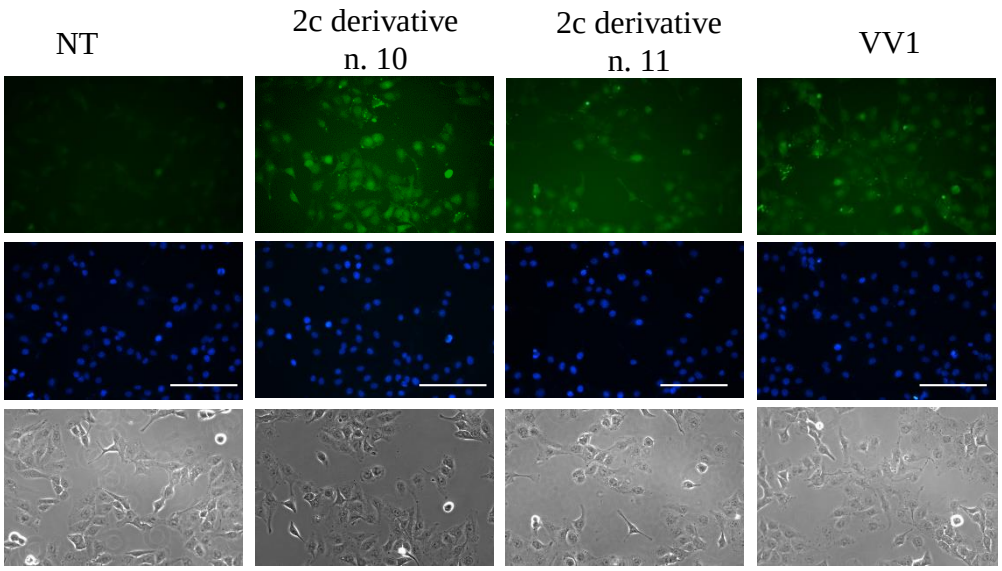
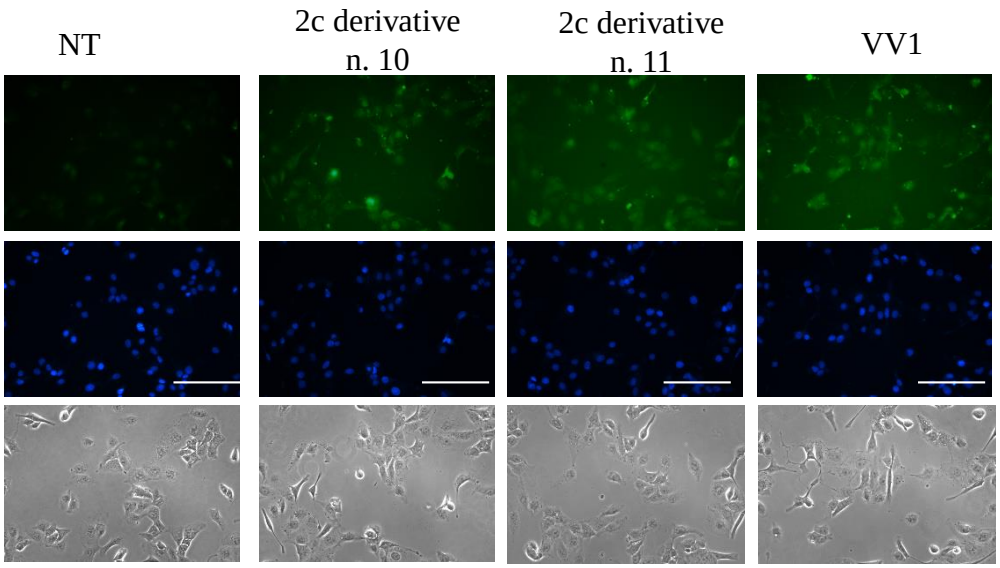
Figure S1. *Representative imagines of the uptake of 2c derivatives n10/11 and VV1 fluorescently labelled in Kuramochi and OVCAR3 cell lines*

A) Kuramochi

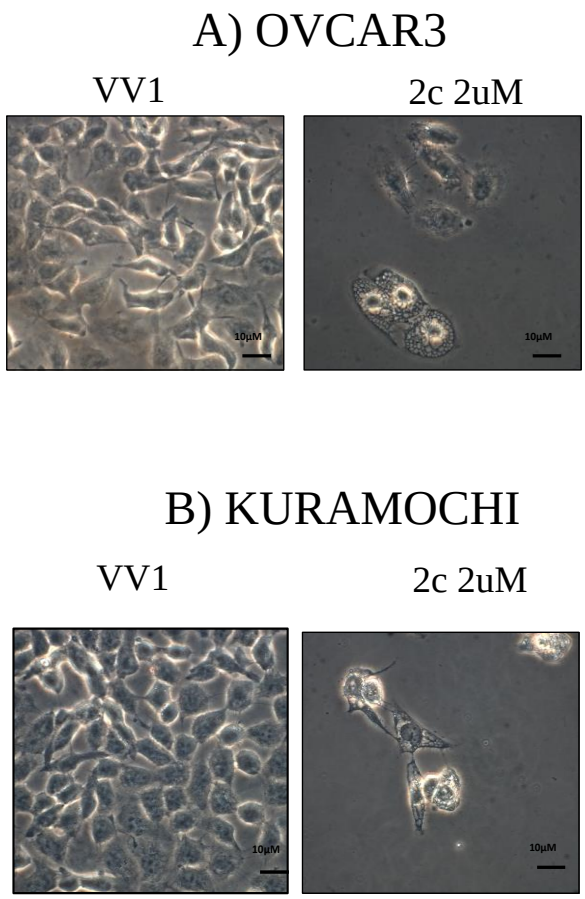


B) OVCAR3



A) and B) Representative images of Kuramochi and OVCAR3, respectively, treated by the 2c-derivatives n10, n11 (see table 1) or VV1 (2 μM) conjugated with fluorescein; images were taken 24 hours after drug administration; scale bar: 100 μm, magnification 20x; nuclei have been labelled by DAPI (blue); images were taken with a Leica DM2000 fluorescence microscope.

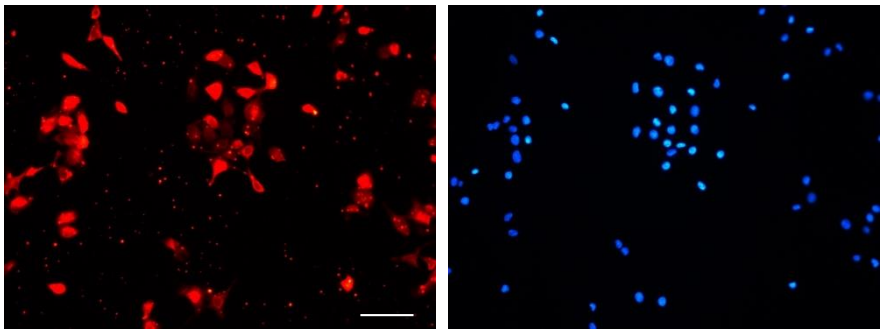
Figure S2. *Representative imagines of the morphology of OVCAR3 and Kuramochi cell lines following 2c administration*



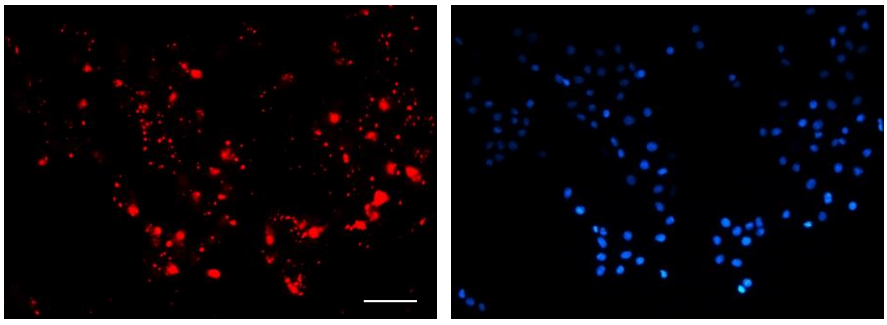
Representative imagines of the morphology of OVCAR3 (A) and Kuramochi (B) cell lines, analysed with a Leica DM 2000 phase contrast microscope, 24 hours after treatment with the 2c and the VV1 control, at a concentration of 2µM. (40/63x objective, Bar: 10µm).

Figure S3. *Trilencer siRNA uptake in OVCAR3 and Kuramochi*

OVCAR3



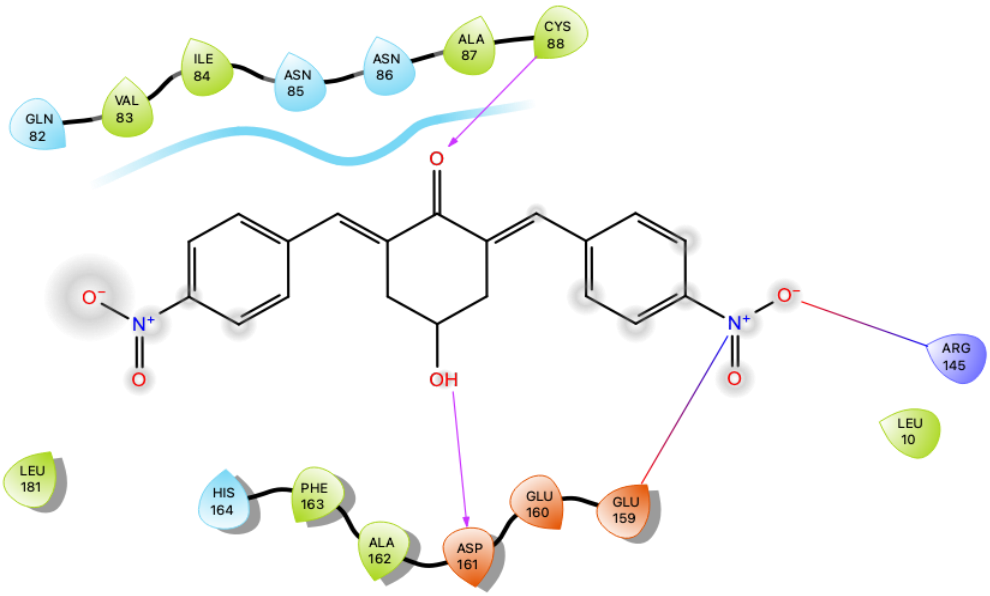
Kuramochi



OVCAR3/Kuramochi were seeded at the density of 7,2*10^4 cells/well in six well plate on collagen I coated slide; transfection was carried 24 hours later for 4 hours using the red fluorescent Trilencer siRNA complexed with lipofectamine 2000. Imagines were taken immdediately after the end of transfection. Scale bar: 100 μm, magnification 20x; nuclei have been labelled by DAPI (blue); images were taken with a Leica DM2000 fluorescence microscope

Figure S4. *In silico docking of 2c to deubiquitinase UCHL5: molecular details*

A) Ligand interaction map for the "in" complex. Green: hydrophobic; cyan: polar; red: negatively charged.



B) Ligand interaction map for the "out" complex. Green: hydrophobic; cyan: polar; red: negatively charged; violet: positively charged.

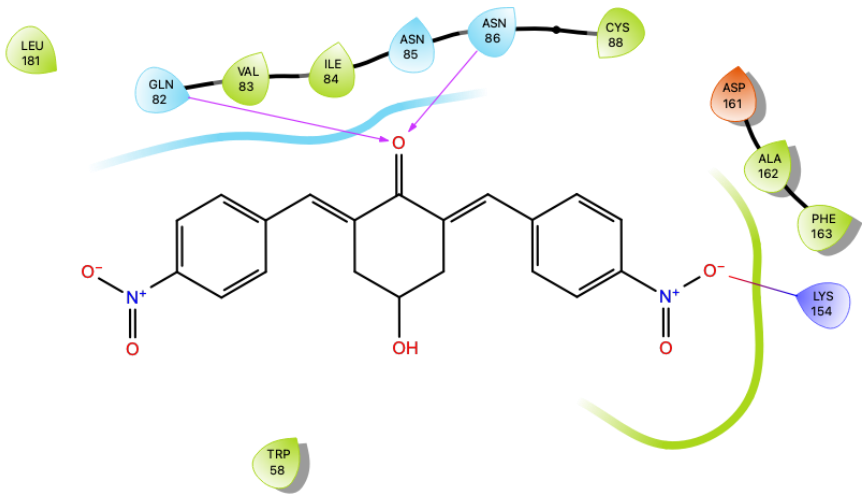
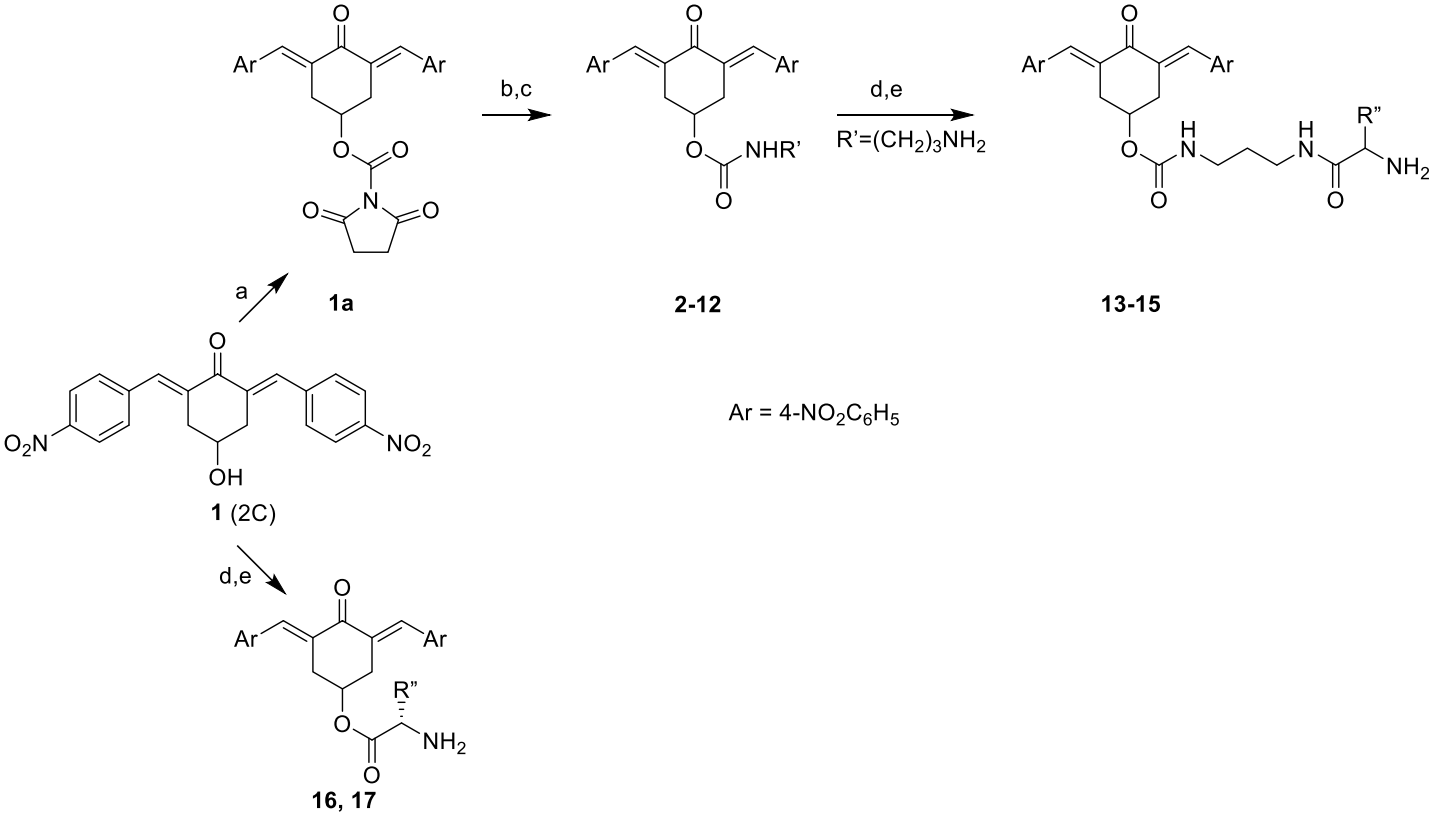


Figure S5. *Conjugation of the secondary alcohol group of 2c to primary amines and to carboxylic acids*



Reagents and conditions: a) N,N'-disuccinidimyl carbonate; b) R-NH_2, CH_2Cl_2, TEA, rt 12 h, 52-85%. c) for R=$(CH_2)_3$NHBoc and R=$(CH_2)_5$NHBoc: 10% TFA in DCM, rt, 12h; 82-85% overall. d) (L)-BocNHPhe or (L)-BocNHLeu, EDC, HOBt, CH_2Cl_2, TEA, 25 °C, 12h. e) 10% TFA in CH_2Cl_2, 25 °C, 12h, 62-70% overall.