Synthesis, radiosynthesis and biological evaluation of new proteasome inhibitors in a tumor targeting approach

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Contents of S.I.:

S1. Ratio of injected dose of **[^{125}I]-12** in B16 tumor to that in blood.

S2. Aldehyde derivatives synthesized.

S3. Main fragmentations of $[M+H]^+$ ions from electrospray of aldehyde **12** [a].

S4. Synthesis of radiolabelled compound **[^{125}I]-12.** [a]

S5. Experimental section

S6. Acknowledgments

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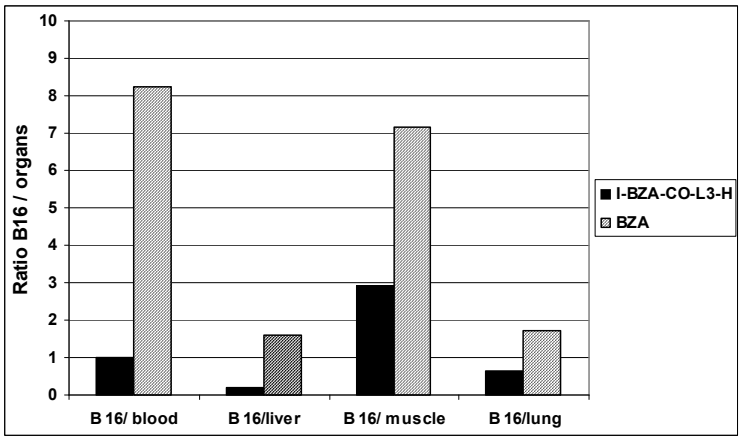
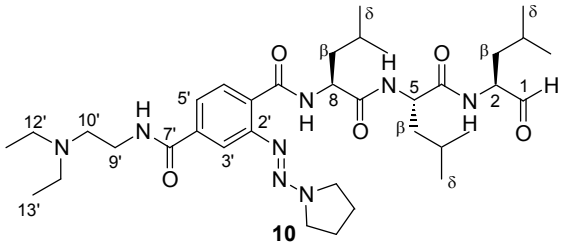
S1. Ratio of injected dose of [^{125}**I**]-**12** in B16 tumor to that in blood.



S2. Aldehyde derivatives synthesized.



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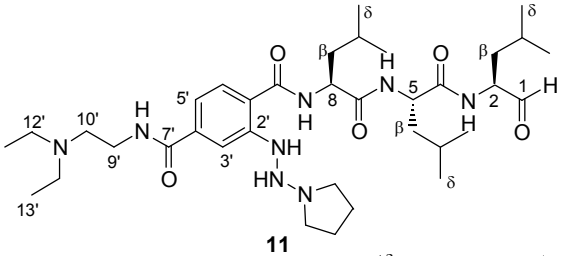

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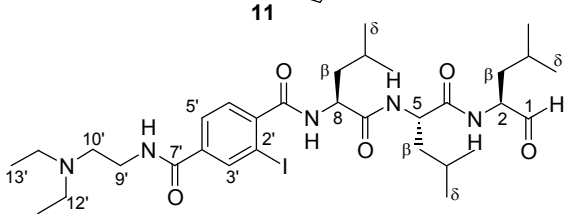

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Figure 1. Main fragmentations of $[M+H]^+$ ions

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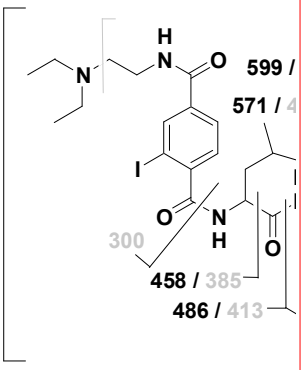

12: $[M + H]^+$ m

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[a] **ESI** mass spectra were obtained on an ESQUIRE-LC ion trap spectrometer (see E

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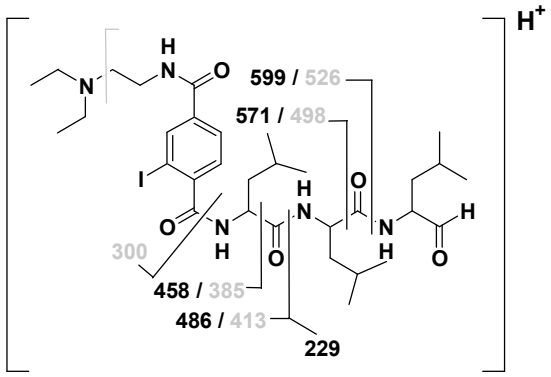
S3. Main fragmentations of $[M+H]^+$ ions from electrospray of aldehyde **12** [a].



12: $[M + H]^+$ m/z 714

[a] **ESI** mass spectra were obtained on an ESQUIRE-LC ion trap spectrometer (see Experimental Section).

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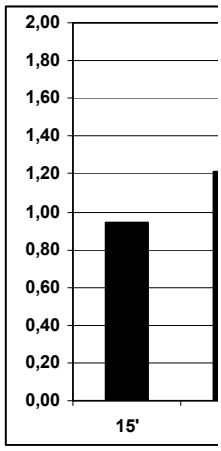

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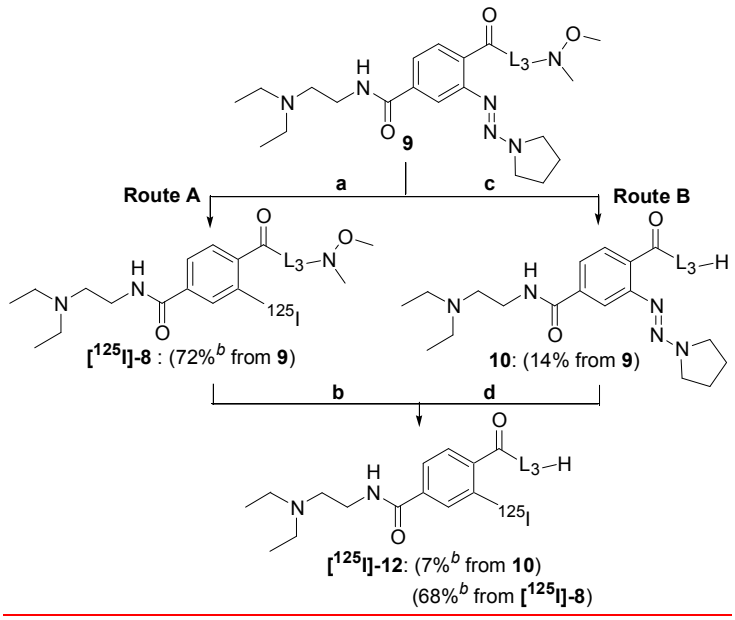
S4. Synthesis of radiolabelled compound **[^{125}I]-12.** [a]



[a]Reagents: (a) [^{125}I]-NaI, CH_3CN, CF_3COOH (b) $AlLiH_4$, THF, -80 °C; (c) $AlLiH_4$, THF, -80 °C; (d) [^{125}I]-NaI, CH_3CN, CH_3SO_3H. [b]Yield of incoporation of 125-iodine

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S5. Experimental Section

Chemistry

All reagents and solvents were from commercial suppliers and were used with no further purification. Tetrahydrofuran (THF) was distilled over sodium-benzophenone. All the other reaction solvents were anhydrous or commercial HPLC grade (Carlo Erba Reagenti, Milan, Italy). Iodine-125 in NaOH pH = 7-11, free from reducing agents was from Amersham Biosciences. Purity was checked by TLC on precoated silica gel plates (plastic sheet 60 F_{254}, layer thickness 0.25 mm, SDS, Pepin, France), aluminium oxide plates (60 F_{254}, neutral type E, layer thickness 0.20 nm, Merk, Darmstadt, Germany) or RP-18 plates (RP-18 F_{254S}, Merk). Solvent mixture A: DCM/MeOH (98/2%). Solvent mixture B: H_2O/CH_3CN/TFA (40/60/0.1%). Melting points were determined on a Reichert-Jung Koffler apparatus. Infrared spectra were recorded in KBr pellets or in CCl_4 on an FT Vector 22 instrument (ν expressed in cm^{-1}; Bruker, Bremen, Germany, developed in supporting information). Proton and carbon nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker AM 200 (4.7 T), or Bruker DRX 500 (11.7 T) spectrometer. Chemical shifts (δ) are reported in parts per million relative to the internal standard $(CH_3)_3Si$ or relative to solvent signals ($CDCl_3$, δ = 7.26 ppm for ^1H NMR and δ = 77.0 ppm for ^{13}C NMR or DMSO-d_6, δ = 2.49 ppm for ^1H NMR and δ = 39.0 ppm for ^{13}C NMR). Electrospray ionization mass spectra (ESI-MS) were obtained on an ESQUIRE-LC spectrometer in positive mode (solvent: CH_3CN or CH_3CN/H_2O 1:1; Bruker). Main fragmentations of $[M+H]^+$ ions from electrospray of synthesized derivatives were determined. HPLC chromatograms were obtained on a Hewlett Packard series 1100 instrument; RP18 column, solvent A: H_2O, NH_4OH 0.2 %, solvent B: MeOH, NH_4OH 0.2%, method: gradient 30% of B (5 min) to 80% of B (15 min), flow rate 0.5 mL/min, detection at 254 nm or by flow scintillation analyzer (FLO-ONE; Packard).

The amino acids required for the preparation of inhibitors **8**, **9**, **10**, **11** and **12** were synthesized by standard peptide chemistry methods and (or) literature synthesis.

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General method A

(E)-dimethyl 2-(pyrrolidin-1-yldiazenyl)terephthalate (2)

^{1}H NMR ($CDCl_3$, 200 MHz): 2.01 (ma, 4H, H8), 3.66 (ma, 2H, H7), 3.87 (s, 3H, CH_3), 3.9 (m, 5H, H7 and CH_3), 7.61 (d, 1H, J = 8 Hz, H6), 7.77 (dd, 1H, J = 8 Hz and J = 2 Hz, H5), 8.07 (d, 1H, J = 2 Hz, H3); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 23.48 (C8), 46.49, 51.09 (C7), 52.09, 52.22 (CH_3), 120.28 (C3), 124.99 (C5), 129.11 (C6), 129.84 (C1), 132.65 (C4), 150.13 (C2), 166.49, 168 (C=O); SM m/z = 292.22 $[M+H]^+$; anal. ($C_{14}H_{17}N_3O_4$) C,H,N.

General method B

(E)-methyl 4-((2-(diethylamino)ethyl)carbamoyl)-2-(pyrrolidin-1-yldiazenyl)benzoate (3)

; ^{1}H NMR ($CDCl_3$, 200 MHz): 0.98 (t; 6H; J = 7 Hz; H13); 2.11 (m; 4H; H pyrrolidine); 2.56 (q; 4H; J = 6 Hz; H12); 2.65 (t; 2H; J = 8 Hz; H10); 3.58 (q; 2H; J = 8 Hz; H9); 3.76 (t, 2H; J = 6 Hz; N-CH_2 pyrrolidine); 3.92 (s; 3H; OCH_3); 4.05 (t, 2H; J = 6 Hz; N-CH_2 pyrrolidine); 7.82 (d; 1H; J = 8 Hz; H5); 8.23 (s; 1H; H3); 8.37 (d; 1H; J = 8 Hz; H6); 9.59 (ma; 1H; H8); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 11.4 (C13); 23.6 and 23.9 (C pyrrolidine); 37.9 (C9), 46.8 and 47.3 (C12); 48.33 (N-CH_2 pyrrolidine); 51.3 (N-CH_2 pyrrolidine); 52.5 (C10); 52.9 (OCH_3); 112.0 (C2); 118.3 (C3); 120.5 (C1); 125.3 (C5); 129.9 (C4); 131.5 (C6); 166.0 and 167.0 (C7 and C=O); SM m/z = 376.24 $[M+H]^+$; anal. ($C_{19}H_{29}N_5O_3$) C,H,N.

General method C

Methyl 4-((2-(diethylamino)ethyl)carbamoyl)-2-iodobenzoate (4)

^{1}H NMR ($CDCl_3$, 200 MHz): 1.08 (t, 6H, J = 8 Hz, H13), 2.66 (q, 4H, J = 8 Hz, H12), 2.76 (t, 2H, J = 6 Hz, H10), 3.56 (q, 2H, J = 6 Hz, H9), 3.91 (s, 3H, CH_3), 6.92 (ma, 1H, H8), 7.44 (d, 1H, J = 8 Hz, H6); 8,01 (dd, 1H, J = 8 Hz et J = 2 Hz, H5); 8.48 (d, 1H, J = 2 Hz, H3); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 11.08 (C13), 36.9 (C9), 46.74 (C12), 51.31 (C10); 52.51 (CH_3), 92.13 (C2), 127.97 (C6), 129.25 (C5), 132.26 (C4), 140.78 (C3), 145.97 (C1), 164.88 (C7), 168.67 (C=O); SM m/z = 405.25 $[M+H]^+$.

General method D

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Lithium 4-((2-(diethylamino)ethyl)carbamoyl)-2-iodobenzoate (5)

^{1}H NMR ($CDCl_3$, 200 MHz): 1.08 (t, 6H, *J* = 8 Hz, H13), 2.66 (m, 4H, H12), 2.76 (m, 6H, H10, H9), 6.92 (ma, 1H, H8), 7,2 (d, 1H, *J* = 8 Hz, H6); 7,8 (d, 1H, *J* = 8 Hz, H5); 8.29 (s, 1H, H3); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 11.0 (C13), 36.9 (C9), 46.9 (C12), 51.4 (C10); 93.1 (C2), 131.9 (C6), 130.1 (C5), 141.3 (C4), 140.78 (C3), 147.3 (C1), 165.5 (C7), 168.8 (C=O); IR (KBr); ν_{NH} 3422 cm^{-1}, ν_{CH} 2972 cm^{-1}, ν_{CO} 1608 cm^{-1}; SM *m/z* = 391.24 $[M+H]^+$.

Lithium (E)-4-((2-(diethylamino)ethyl)carbamoyl)-2-(pyrrolidin-1-yldiazenyl)benzoate (6)

The lithium salt **6** was synthesized according to method **D** with compound **3** (1 eq; 5.6 mmol; 2.09 g) in THF (100 mL). The reaction mixture was then evaporated under reduced pressure and the crude product was washed with acetone and diethylether to give 2.05 g of compound **6** (yield: 100%): white solid; mp > 200°C, TLC Rf: 0.6 (RP-18, H_2O/CH_3CN/TFA 40:60:0.1 %); ^{1}H NMR ($CDCl_3$, 200 MHz): 0.89 (t, 6H, *J* = 8 Hz, H13), 2.05 (ma, 4H, H pyrrolidine); 2.49 (m, 6H, H11 and H12); 3.41 (m, 2H, H9); 3.72 (ma, 2H, N-CH_2 pyrrolidine); 4.01 (ma, 2H, N-CH_2 pyrrolidine); 7.65 (d, 1H, *J* = 8 Hz, H); 7.96 (d, 1H, *J* = 8 Hz, H); 8.02 (s, 1H, H3), 9.43 (ma, H8); ^{13}C NMR ($CDCl_3$, 50.3 MHz): 9.72 (C13); 21.51 and 21.97 (C pyrrolidine); 35.85 (C9), 44.76 and 45.53 (C12); 49.69 (N-CH_2 pyrrolidine); 50.31 (N-CH_2 pyrrolidine); 51.50 (C10); 115.84 (C2); 123.69 (C3); 123.91 (C1); 127.86 (C5); 142.34 (C4); 146.13 (C6); 163.92 and 166.6 (C7 and C=O); IR (KBr); ν_{NH} 3235 cm^{-1}, ν_{CH} 2965 cm^{-1}, ν_{CO} 1632 cm^{-1}; SM *m/z* = 362.14 $[M+H]^+$; anal. ($C_{18}H_{26}LiN_5O_3$, 1.3 H_2O) C,H,N.

N^4-(2-(diethylamino)ethyl)-2-iodo-N^1-(1-(1-(1-(methoxy(methyl)amino)-4-methyl-1-oxopentan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-4-methyl-1-oxopentan-2-yl)terephthalamide (8)

^{1}H NMR ($CDCl_3$; 500 MHz) δ: 0.9 (m, 12H, Hδ); 1.41 (t, *J* = 6.9 Hz, 6H, H13'); 1.52 (m, 6H, Hγ and Hβ); 3.16 (s, 3H, NCH_3); 2.21 (m, 4H, H12'); 2.31 (m, 2H, H10'); 3.79 (s, 3H, OCH_3); 3.87 (m, 2H, H9'); 4.77 (m, 2H, H5 and H8); 5.11 (m, 1H, H2); 7.26 (m, 1H, H3); 7.40 (d, 1H, *J* = 8.0 Hz, H6'); 7.77 (d, *J* = 8 Hz, 1H, H5'); 8.13 (m, 1H, H6); 8.22 (s, 1H, H3'), 8.62 (ma, 1H, H9); ^{13}C NMR ($CDCl_3$; 50.3

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MHz): 9,33 (C13'), 21,88; 22,33; 22,57; 22,69; 22,84; 23,31 (Cδ), 24,68; 24,84; 24,90 (Cγ), 32,29 (NCH3), 35,71 (C9'), 41,08, 41,49 (Cβ), 47,5 (C12'), 47,5 (C2), 51,72 (C5 or C8), 52,72 (C5 or C8), 53,42 (C10'), 61,76 (OCH_3), 92,58 (C2'); 127,44 (C5'), 128,07 (C6'), 136,66 (C4'), 139,07 (C3'), 143,23 (C1'), 165,06, 169,16 (C1, C4 and C7), 171,71, 172,87 (C10 and C7'); IR (KBr): ν_{NH} 3295 cm^{-1}, ν_{CH} 2958 cm^{-1} ν_{CO} 1641 cm^{-1}; SM *m/z* = 773,4 $[M+H]^+$; anal. ($C_{34}H_{57}IN_6O_6$) C,H,N.

General method E

(E)-N^4-(2-(diethylamino)ethyl)-N^1-(1-(1-(1-(methoxy(methyl)amino)-4-methyl-1-oxopentan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-4-methyl-1-oxopentan-2-yl)-2-(pyrrolidin-1-yldiazenyl)terephthalamide (9)

To a solution of acid salt **5** (2,2 mmol; 793,60 mg) in CH_2Cl_2 at 0 °C were added successively hydroxybenzotriazole (HOBt, 0.1 g, 0.66 mmol, 0.3 eq), dicyclocarbodiimide (DCC, 0.52 g, 2.53 mmol, 1.15 eq) and triethylamine (0.5 mL, 5.5 mmol, 2.5 eq). The mixture was stirred at 0 °C for 1 h. A solution of compound **7** (1,9 mmol; 940,02 mg) in CH_2Cl_2 was added dropwise at 0°C and the reaction mixture was stirred overnight at room temperature. A white precipitate of dicyclohexylurea (DCU) was eliminated by filtration and the filtrate was washed with saturated aqueous sodium bicarbonate solution (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by flash chromatography (silica gel, CH_2Cl_2/gradient of MeOH 0 up to 4 %) to give 504,2 mg of **8** (yield: 34%): yellow solid; mp 118 ± 1 °C; TLC Rf: 0,2 (silica, CH_2Cl_2 / MeOH 9:1), 0,5 (alumina, CH_2Cl_2 / MeOH 95:5), 0,4 (RP-18, H_2O/CH_3CN/TFA 40:60:0,1 %); ^1H NMR ($CDCl_3$; 200 MHz): 0,89 (m, 18H, Hγ), 1,08 (t, 6H, *J* = 6 Hz, H13'), 1,6 (m, 9H, Hβ and Hγ), 2,11, (m, 4H, Hpyrr); 2,72 (m, 6H, H10' and H12'), 3,17 (s, 3H, NCH_3), 3,72 (m, 4H, Hpyrr), 3,78 (s, 3H, OCH_3), 4,02 (m, 2H, H9'), 4,53 (q, 1H, *J* = 8 Hz, H8), 4,69 (q, 1H, *J* = 8 Hz, H5), 5,05 (q, 1H, *J* = 8 Hz, H2), 6,56 (d, 1H, *J* = 8 Hz, H9), 6,91 (d, 1H, *J* = 8 Hz, H3), 6,98 (d, 1H, *J* = 8 Hz, H6), 7,57 (dd, 1H, *J* = 8 Hz and *J* = 2 Hz, H5'), 8,00 (d, 1H, *J* = 2 Hz, H3'), 8,32 (d, 1H, *J* = 8 Hz, H6'), 9,71 (ma, 1H, H8'); ^{13}C NMR

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(CDCl$_3$; 50.3 MHz): 10.71 (C13'), 21.60, 22.01, 22.33, 22.78, 22.83, 23.30 (Cδ), 23.93, 23.57 (C12'), 24.62, 24.78, 24.84 (Cγ), 32.18 (NCH3), 37.46 (Cpyrr), 41.06, 41.79 (Cβ), 46.9 (C10'), 47.4 (Cpyrr), 47.55 (C2), 51.8 (C9'), 51.88 (C5 or C8), 51.9 (C12'), 51.98 (C5 or C8), 61.58 (OCH$_3$), 116.03 (C3'), 122.75 (C5'), 127.87 (C2'), 131.62 (C6'), 136.51 (C1'), 149.04 (C4'), 166.08, 166.98 (C1, C4 and C7), 171.45, 171.77 (C10 and C7'); IR (KBr): ν_{NH} 3286 cm^{-1}, ν_{CH} 2957 cm^{-1} ν_{CO} 1638 cm^{-1}; M.S. *m/z* = 744.61 [M+H]$^+$; anal. ($C_{38}H_{65}N_9O_6$, 0.1 H_2O) C,H,N.

General method F

(E)-N^4-(2-(diethylamino)ethyl)-N^1-(4-methyl-1-(4-methyl-1-(4-methyl-1-oxopentan-2-ylamino)-1-oxopentan-2-ylamino)-1-oxopentan-2-yl)-2-(pyrrolidin-1-yldiazenyl)terephthalamide (10)

A solution of lithium aluminium hydride in ether (1M/THF, 1.1 eq, 2.2 mmol) was added dropwise at – 80 °C under a nitrogen atmosphere to a solution of **9** (1 eq, 2.01 mmol, 1.49 g) in anhydrous THF (5 mL). The mixture was stirred for 90 min and was then allowed to warm to 0 °C. The reaction was quenched by adding water (20 mL) and excess lithium aluminium hydride was eliminated by the Mihailovic method. The resulting crude reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, concentrated under vacuum and purified by flash chromatography (aluminium oxide, CH_2Cl_2/gradient of MeOH 2 up to 5 %) to give 942.6 mg of **10** (yield: 68%): white solid; TLC Rf: 0.4 (alumina, CH_2Cl_2 / MeOH 95:5); ^{1}H NMR (CDCl$_3$; 200 MHz): 0.84 (m, 18H, Hγ), 0.95 (t, 6H, *J* = 8 Hz, H13'), 1.43 (m, 3H, H8β and H8γ); 1.51 (m, 3H, H5β and H5γ), 1.69 (m, 3H, H2β and H2γ), 2.03 (m, 4H, Hpyrr); 2.52 (q, *J*= 6 Hz, 4H, H12'), 2.60 (t, *J* = 6 Hz, 4H, H10'), 3.52 (m, 2H, H9'), 3.67 (m, 2H, Hpyrr), 3.89 (m, 2H, Hpyrr), 4.32 (m, 1H, H8), 4.64 (m, 1H, H5), 4.84 (m, 1H, H2), 7.62 (m, 1H, H3), 7.69 (m, 1H, H6), 7.70 (m, 1H, H9), 7.58 (d, 1H, *J* = 8 Hz, H5'), 7.98 (s, 1H, H3'), 8.25 (d, 1H, *J* = 8 Hz, H6'), 9.43 (s, 1H, H1); 9.56 (ma, 1H, H8'); ^{13}NMR (CDCl$_3$; 50.3 MHz): 10.84 (C13'), 21.61, 21.63, 21.91, 22.18, 22.28, 22.61 (Cδ), 22.73, 23.01 (C12'), 23.49, 23.87, 24.60 (Cγ), 37.21 (Cpyrr), 40.63, 40.86 (Cβ), 46.88 (C10'), 47.31 (CPyrr), 51.65 (C2),

51.79 (C9'), 51.92 (C5 or C8), 51.98 (C5 or C8), 57.21 (C12'), 116.33 (C3'); 122.70 (C5'); 127.91 (C6'); 131.37 (C1'); 136.31 (C4'); 148.83 (C2'); 165.73, 167.11 (C10 and C7'), 172.19 (C4); 172.38 (C7), 200.05 (C1); IR (KBr); ν_{NH} 3450 cm^{-1}, ν_{CH} 2965 cm^{-1} ν_{CO} 1630 cm^{-1}; SM *m/z* = 785.7 $[M+H]^+$; anal. ($C_{36}H_{60}N_8O_5$, 0.7 H_2O) C,H,N.

N^4-(2-(diethylamino)ethyl)-N^1-(4-methyl-1-(4-methyl-1-(4-methyl-1-oxopentan-2-ylamino)-1-oxopentan-2-ylamino)-1-oxopentan-2-yl)-2-(pyrrolidin-1-yl-hydrazino)terephthalamide (11)

The reduction of Weinreb amide **8** (1 eq, 1.38 mmol, 1.03 g) was achieved using method **F**. The reaction was quenched by adding water (20 mL) and excess lithium aluminium hydride was eliminated by the Mihailovic method. The resulting crude reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the product was isolated by recrystallization from diethyl ether to give 0.67 g of **11** (yield: 70%): yellow solid; TLC Rf: 0.3 (alumina, CH_2Cl_2 / MeOH 95:5); ^1H NMR ($CDCl_3$; 200 MHz): 0.9 (m, 24H, Hγ and H13'), 1.6 (m, 9H, Hβ and Hγ); 2.05 (m, 4H, Hpyrr); 2.54 (q, *J* = 6 Hz, 4H, H12'), 2.61 (t, *J* = 6 Hz, 4H, H10'), 3.60 (m, 2H, H9'), 3.71 (m, 2H, Hpyrr), 3.90 (m, 2H, Hpyrr), 4.31 (m, 1H, H8), 4.66 (m, 1H, H5), 4.91 (m, 1H, H2), 7.70 (m, 1H, H3), 7.80 (m, 1H, H6), 7.85 (m, 1H, H9), 7.88 (d, 1H, *J* = 8 Hz, H5'), 8.01 (s, 1H, H3'), 8.25 (d, 1H, *J* = 8 Hz, H6'), 9.60 (s, 1H, H1); 9.65 (ma, 1H, H8'); ^{13}C NMR ($CDCl_3$; 50.3 MHz): 8.44 (C13'), 21.57, 21.80, 21.96, 22.25, 22.32, 22.84 (Cδ), 23.09 (C12'), 23.88, 24.78, 24.87 (Cγ), 37.61 (Cpyrr), 40.83, 41.19, 41.75 (Cβ), 47.24 (C10'), 47.68 (Cpyrr), 48.03 (C2), 50.79 (C9'), 51.80 (C5 or C8), 52.18 (C5 or C8), 57.27 (C12'), 115.86 (C3'); 122.63 (C5'); 126.91 (C6'); 131.31 (C1'); 137.08 (C4'); 149.31 (C2'); 166.78, 167.18 (C10 and C7'), 171.47 (C4); 172.17 (C7), 199.53 (C1); IR (KBr); ν_{NH} 3470 cm^{-1}, ν_{CH} 2950 cm^{-1} ν_{CO} 1645 cm^{-1}; SM *m/z* = 687.49 $[M+H]^+$; anal. ($C_{36}H_{62}N_8O_5$, 2.5 HCl, 3.5 H_2O) C,H,N.

N^4-(2-(diethylamino)ethyl)-2-iodo-N^1-(4-methyl-1-(4-methyl-1-(4-methyl-1-oxopentan-2-ylamino)-1-oxopentan-2-ylamino)-1-oxopentan-2-yl)terephthalamide (12)

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^{1}H NMR ($CDCl_3$; 500 MHz) δ: 0.90 (m, 12H, Hδ); 1.19 (t, *J* = 8 Hz, 6H, H13'); 1.68 (m, 6H, Hγ and Hβ); 2.86 (m, 4H, H12'); 2.96 (m, 2H, H10'); 3.62 (m, 2H, H9'); 4.37 (m, 1H, H8); 4.57 (m, 1H, H5); 4.79 (m, 1H, H2); 7.34 (m, 1H, H6'); 7.41 (m, 1H, H9); 7.52 (m, 1H, H6); 7.69 (d, *J* = 8 Hz, 1H, H5'); 7.79 (m, 1H, H3); 8.16 (s, 1H, H3'); 9.48 (s, 1H, H1); ^{13}C NMR ($CDCl_3$; 50.3 MHz): 10.43 (C13'), 21.66, 21.79, 22.10, 22.20, 22.74, 23.02 (Cδ), 24.64, 24.79, 24.94 (Cγ), 37.31 (C9'), 40.76, 40.9, 41.5 (Cβ), 47.51 (C12'), 51.24 (C5 or C8), 52.59 (C5 or C8), 53.37 (C10'), 57.33 (C2), 92.61 (C2'), 127.09 (C5'), 127.51 (C6'), 128.03 (C3'), 136.30 (C4'), 138.83 (C1'), 165.52, 168.99 (C1, C4 and C7), 172.28, 172.37 (C10 and C7'); SM *m/z* = 714.3 $[M+H]^+$; anal. ($C_{32}H_{52}IN_5O_5$, HCl, 1 H_2O) C,H,N.

N^4-(2-(diethylamino)ethyl)-2-iodo-N^1-(1-(1-(1-(methoxy(methyl)amino)-4-methyl-1-oxopentan-2-ylamino)-4-methyl-1-oxopentan-2-ylamino)-4-methyl-1-oxopentan-2-yl)terephthalamide ([^{125}I]-8)

To a solution of compound **9** (10 µmol, 7.4 mg) in acetonitrile (CH_3CN; 50 µL) at – 10°C was added a solution of 0.1 N sodium iodide (50 µL) and 160 µCi de $Na^{125}I$, and then a solution of trifluoroacetic acid (10 µL). The reaction mixture was stirred at room temperature and made alkaline with 100 µL of a saturated solution of $NaHCO_3$ to give **[^{125}I]-8** (radiochemical yield: 69 %): TLC Rf: 0.5 (alumina, CH_2Cl_2 / MeOH 95:5); HPLC Rt: 27.1 min.

Cytotoxicity assay. Attached human ocular melanoma IPC227F and murin B16 cells were seeded in 96-well plates and incubated for 24 h at 37 °C in a humidified atmosphere under 5% CO_2 with standard medium (DMEM + 10% calf fetal serum). After addition of fresh medium containing increasing concentrations of drugs previously prepared in DMSO (final concentration 0.025%), cells were incubated for 48 h for the determination of IC_{50}, washed with 1X PBS buffer and then frozen at – 80 °C. After thawing at room temperature, cells were incubated for 1 h at room temperature with 0.01%

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SDS solution, frozen again at - 80 °C, and then thawed again at room temperature. The Hoechst dye 33342 solution was added to each sample (final concentration 15 µg/ml) and plates were incubated for 1 h at room temperature on a plate shaker in the dark. Fluorescence was measured using a fluorescence microplate reader at 360/460 nm (Fluoroskan Ascent FL; Labsystems, Farnborough, Hampshire) and cell survival rates (percent cell survival relative to untreated control) were calculated. The cytotoxic activity of drugs was expressed as the concentration inhibiting cell growth by 50% (IC_{50}) calculated from the survival curves.

Drug biodistribution

The specific activity of **[^{125}I]-12** was 1.875 Ci/µM. It was injected IV at a concentration of 0.07 µM/mouse (3.7 10^{-3} mmol/kg) as 32.7 µCi (43.5 × 10^{6} cpm). The drug biodistribution was examined at eight times with two mice per time: 15 min, 30 min, 1 h, 3 h, 6 h, 24 h, 48 h and 72 h post-injection. Mice were sacrified, embedded in carboxymethylcellulose and frozen in liquid nitrogen. Sagittal cryodried sections 40 µ thick were quantified. The radioactivity was detected using an AMBIS® counter (acquisition time 1000 min)

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S6. Acknowledgments.

We thank Dr M. Borel for the proton and carbon nuclear magnetic resonance spectra recorded on a Bruker DRX 500 instrument, M. Bayle for the synthesis of several intermediates and Dr J. Helfenbein and Dr M.-F. Moreau for many helpful discussions throughout the course of this work.

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S7. Appendix

Elemental analysis

Formula	Calculated (%)	Found (%)
2: ($C_{14}H_{17}N_3O_4$)	**C** 57.72	**C** 57.55
	H 5.88	**H** 5.94
	N 14.42	**N** 14.54
3: ($C_{19}H_{29}N_5O_3$)	**C** 60.78	**C** 60.57
	H 7.79	**H** 7.61
	N 18.65	**N** 18.41
6: ($C_{18}H_{26}LiN_5O_3$, 1.3 H_2O)	**C** 55.32	**C** 55.40
	H 7.38	**H** 7.13
	N 17.92	**N** 17.77
8: ($C_{34}H_{57}IN_6O_6$)	**C** 52.84	**C** 52.55
	H 7.43	**H** 7.50
	N 10.88	**N** 10.89
9: ($C_{38}H_{65}N_9O_6$, 0.1 H_2O)	**C** 61.20	**C** 60.99
	H 8.81	**H** 8.87
	N 16.90	**N** 16.55
10: ($C_{36}H_{60}N_8O_5$, 0.7 H_2O)	**C** 61.99	**C** 61.86
	H 8.87	**H** 8.83
	N 16.06	**N** 16.11
11: ($C_{36}H_{62}N_8O_5$, 2.5 HCl, 3.5 H_2O)	**C** 51.41	**C** 51.23

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	H 8.57	**H** 8.29
	N 13.32	N 13.05
12: ($C_{32}H_{52}IN_5O_5$, HCl, 1 H_2O)	**C** 50.03	**C** 50.00
	H 7.22	**H** 7.32
	N 9.12	**N** 8.98

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Radiochemical purity of [^{125}I]-12: > 99.3% (detection with Flow Scintillation Analyser (FLO-ONE ; Packard)).

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To a solution of dimethyl aminoterephthalate (1) (1 eq

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90 g) in water (100 mL) was added a solution of HCl 37% to obtain a red suspension, and the mixture was vigorously stirred

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for 30 min. at 0 °C under a nitrogen atmosphere. To the reaction mixture was added dropwise a

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56 g) in 20 mL of water at 0 °C. T

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he mixture was stirred for 45 min. and

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7 mmol) and 12 mL of 1N potassium hydroxi

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at 0°C were then added. The reaction mixture was stirred for 3 h at room temperature

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made alkaline to pH = 12 with NaOH and extracted with CH_2Cl_2 (3 ×

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100 mL). The organic layer was dried over $MgSO_4$ and concentrated in part under vacuum to obtain 17.

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To a solution of lithium hydroxide monohydrate (0.13 g, 3.18 mmol, 1.5 eq) in water (3.5 mL) was added dropwise a solution of compound **4** (2.

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1 mg) in THF (3.5 mL) at 0 °C. The mixture was allowed to reach room temperature and then stirred for 1 h. The reaction mixture was evaporated under reduced pressure and the crude product was washed with acetone and dried to

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give 842 mg of **5** (yield: 100%): white solid; mp > 200 ± 1 °C, TLC Rf

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51 mmol, 380 mg) was achieved

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using method **C**.

The crude product was purified by flash chromatography (aluminium oxide, CH_2Cl_2/gradient of MeOH 0 up to 2 %) to

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give 290 mg of 11 (yield: 73%): beige solid; mp 120 ± 1 °C; TLC

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A solution of lithium aluminium hydride in ether (1M/THF, 1.

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2 mmol) was added dropwise at – 90 °C under a nitrogen atmosphere to a solution of **8**

(1 eq, 0.

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17 mmol, 130 mg) in anhydrous THF (5 mL). The mixture was stirred for 2 h 30 min

and then

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to 0 °C. The reaction was quenched by

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lithium aluminium hydride was eliminated by the Mihailovic method. The resulting crude reaction mixture was extracted with CH_2Cl_2 (2 ×

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50 mL). The combined organic layers were dried over $MgSO_4$, concentrated under vacuum and

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purified by flash chromatography (aluminium oxide, CH_2Cl_2/gradient of MeOH 2 up to 3 %) to

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1 mg of **12** (yield: 48%): yellow solid; mp > 200°C

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