Artificial macrocycles as potent p53-MDM2 inhibitors

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Supporting Information

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1. Experimental Materials and Methods

1.1. Synthesis and analysis

All the reagents and solvents were purchased from Sigma-Aldrich, AK Scientific, Fluorochem, Abcr GmbH, Acros and were used without further purification. All microwave irradiation reactions were carried out in a Biotage Initiator™ Microwave Synthesizer. Thin layer chromatography was performed on Millipore precoated silica gel plates (0.20 mm thick, particle size 25 μm). Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 or 600 spectrometers {^{1}H NMR (500 MHz; 600 MHz), ^{13}C NMR (126 MHz; 151 MHz)}. Chemical shifts for ^{1}H NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, ddd = double doublet of doublets, m = multiplet. Chemical shifts for ^{13}C NMR were reported in ppm relative to the solvent peak. Flash chromatography was performed on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (12 grams). Mass spectra were measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 x 250 mm, 5 μm particle size) or Viridis 2-ethyl pyridine column (4.6 x 250 mm, 5 μm particle size). Analytical chiral SFC was performed on a Reprosil Chiral-IC column (4.6 x 250 mm, 5 μm particle size) and semi-preparative SFC was performed with stacked injector (250 μL injections) on a Reprosil Chiral-IC column (10 x 250 mm, 5 μm particle size) with 25% MeOH/CO_2 as mobile phase. High resolution mass spectra were recorded using a LTQ-Orbitrap-XL (Thermo) at a resolution of 60000@m/z400. Optical rotations were measured in MeOH on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100mL).

1.2. *Protein Expression and Purification*

Fragment of the *N*-terminal domain of human MDM2 (residues 1-118) was cloned into the pET-20 (Novagen) and expressed in E. coli strain BL21-CodonPlus(DE3)-RIL as described previously.[1] In brief, cells were cultured at 37 °C. Protein expression was induced with 1 mM IPTG at OD600 of 0.8 and cultured for additional 5 h at 37 °C. Cells were collected by centrifugation and lysed by sonication. Inclusion bodies were collected by centrifugation, washed with PBS containing 0.05% Triton-X100 and subsequently solubilized in 6 M guanidine hydrochloride in 100 mM Tris-HCl, pH 8.0, containing 1 mM EDTA and 10 mM *β*-mercaptoethanol. The protein was dialyzed against 4 M guanidine hydrochloride pH 3.5 supplemented with 10 mM *β*-mercaptoethanol. Following, the protein was refolded by dropwise addition into 10 mM Tris-HCl, pH 7.0, containing 1 mM EDTA and 10 mM *β*-mercaptoethanol and slow mixing overnight at 4 °C. Ammonium sulfate was added to the final concentration of 1.5 M and the refolded protein was recovered on Butyl Sepharose 4 Fast Flow (GE Healthcare). The protein was eluted using 100 mM Tris-HCl pH 7.2 containing 5 mM β-mercaptoethanol and further purified by gel filtration on HiLoad 16/600 Superdex75 (GE Healthcare) in 50 mM phosphate buffer pH 7.4 containing 150 mM NaCl and 5 mM DTT (FP/NMR buffer).

1.3. Fluorescence Polarization Assay

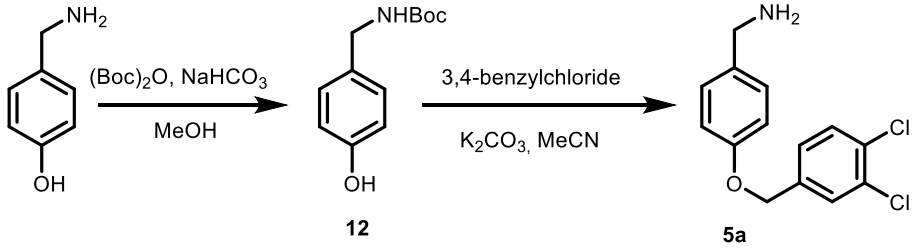
All FP measurements were performed using Tecan Infinite® 200 PRO plate reader. The assay was conducted in 50 mM NaCl, 10 mM Tris pH 8.0, 1 mM EDTA containing 5% DMSO. To determine the optimal concentration of the protein for the competition binding assay, the effective concentration of MDM2 (1-118) was each time ascertained by determining the apparent K_d towards 5'FAM-LTFEHYWAQLTS (P2, 10 nM). Competition assay was performed by contacting serial dilutions of tested compounds with 10 nM P2 at protein concentration yielding $f_0 = 0.8$. Fluorescence polarization was determined at 485 nm excitation and 535 nm emission 15 min after mixing all assay components. All tests were performed using Corning black 96-well NBS assay plates at room temperature.

1.4. NMR Experiments

All NMR spectra were acquired at 300 K using a Bruker Avance 600 MHz spectrometer. Uniform ^{15}N isotope labelling was achieved by expression of the protein in the M9 minimal medium containing $^{15}NH_4Cl$ as the sole nitrogen source. MDM2(1-118) was prepared in 50 mM phosphate buffer pH 7.4 containing 150 mM NaCl and 5 mM DTT. 10% (v/v) of D_2O was added to the samples to provide lock signal. Water suppression was carried out using the WATERGATE sequence.[2] Stock solutions of inhibitors used for titration were prepared in d6-DMSO. Several titration steps (compound/MDM2: 1:5, 1:4, 1:3, 1:2, 1:1, 2:1, 5:1) were performed in order to assess the binding. The spectra were processed with TopSpin 3.2 software. ^{1}H-^{15}N heteronuclear correlations were obtained using the fast HSQC pulse sequence.[3] Assignment of the amide groups of MDM2 was obtained as previously reported.[4]

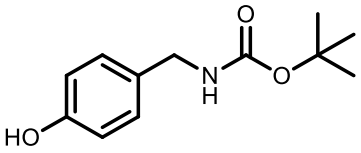
2. Synthetic procedures and analytical data

2.1. Procedure and analytical data for amine 5a



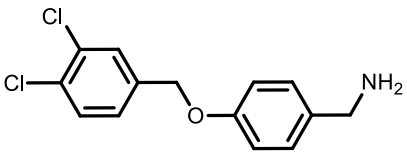
Scheme 1.

2.1.1. Tert-butyl 4-hydroxybenzylcarbamate (12)



4-hydroxybenzylamine (1.0 equiv.), $(Boc)_2O$ (1.1 equiv.) and $NaHCO_3$ (2.1 equiv.) were refluxed in methanol overnight (16 h). Afterwards, the reaction was cooled to rt and methanol was evaporated. To the resulting slurry, water and dichloromethane were added and the aqueous phase was extracted with dichloromethane. Organic layers were collected, washed with water, dried over anhydrous MgSO4 and evaporated, giving crude product as brown oil. The crude product was precipitated and washed with diethyl ether/petroleum ether (approx. 1:1) giving compound **12**; Light brown solid, 99% yield; ^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] 7.10 (d, J = 7.3 Hz, 2H), 6.77 (dt, J = 8.6, 2.0 Hz, 2H), 4.86 (s, 1H), 4.22 (s, 2H), 1.46 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$): δ [ppm] 156.3, 155.5, 130.5, 129.0, 115.6, 79.9, 44.3, 28.6. LC-MS (DAD/ESI): t_R = 5.31 min, Calcd for $C_{12}H_{17}NO_3$ (m/z): $[M-H]^-$ 222.12, found: $[M-H]^-$ 222.10.

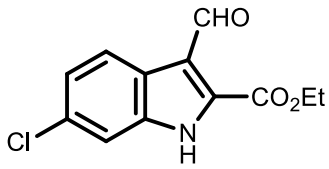
2.1.2. (4-((3,4-dichlorobenzyl)oxy)phenyl)methanamine (5a)



Tert-butyl 4-hydroxybenzylcarbamate **12** (1.0 equiv.), 3,4-benzyl chloride (1.5 equiv.), K_2CO_3 (2.2 equiv.) were refluxed in acetonitrile overnight (16 h). Afterwards, the reaction was cooled to rt and the solvent was evaporated. To the resulting solid, water and dichloromethane were added and the aqueous phase was extracted with dichloromethane. Organic layers were collected washed with water, dried over anhydrous $MgSO_4$ and evaporated, giving crude product as white-yellowish powder. Afterwards the amine was deprotected in presence of trifluoroacetic acid (20 equiv.) and DCM as solvent, the mixture was stirred at rt for 1.5 h. Water was added to stop the reaction and stirred for 5 min more, followed by washing with 2 times with DCM and once with water, to obtain the free amine in the aqueous phase. Further

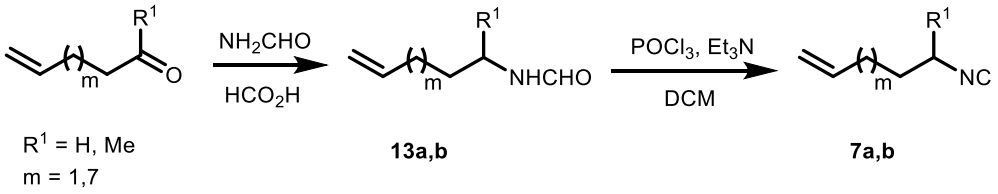
addition of NaOH 1 N and DCM to extract the amine, the organic layer were collected, washed with water, dried over anhydrous $MgSO_4$ and evaporated, giving the final product **5a**; White powder, 67% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.54 (d, J = 2.0 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.29 – 7.22 (m, 3H), 6.95 – 6.88 (m, 2H), 5.01 (s, 2H), 3.81 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 137.5, 136.4, 130.7, 129.3, 128.5, 126.6, 115.0, 68.7, 46.0. HRMS: Calcd for $C_{14}H_{13}Cl_2NO$ (m/z): $[M+H]^-$ 282.0374, found: $[M+H]^-$ 282.0370.

2.2. Procedure and analytical data for ethyl 6-chloro-3-formyl-1H-indole-2-carboxylate (6)



The 6-chloro-1*H*-indole-2-carboxylic acid ethyl ester (1.0 equiv.) and DMF (20 ml) were placed in round-bottom flask equipped with $CaCl_2$ tube. Then, $POCl_3$ (1.2 equiv.) was added dropwise and the reaction mixture was heated overnight (16 h) at 50 ºC. Afterwards, the reaction was cooled to rt, quenched with saturated $NaHCO_3$ solution and extracted with ethyl acetate. Organic layer was collected, washed with water and brine, dried over anhydrous MgSO4 and evaporated. The crude product was washed with diethyl ether giving compound **6**;[5] Light yellow solid, 92% yield; ^{1}H NMR (600 MHz, DMSO-*d6*): δ [ppm] 12.90 (s, 1H), 10.58 (s, 1H), 8.22 (d, J = 8.6 Hz, 1H), 7.56 (d, J = 1.5 Hz, 1H), 7.32 (dd, J = 8.6, 1.9 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C (151 MHz, DMSO-*d6*): δ [ppm] 187.5, 159.9, 136.1, 133.5, 130.4, 124.0, 123.9, 123.4, 118.2, 112.6, 62.0, 14.1; LC-MS (DAD/ESI): t_R = 2.97 min, Calcd for $C_{12}H_{10}ClNO_3$ (m/z): $[M-H]^-$ 250.03, found: $[M-H]^-$ 250.05.

2.3. Procedure and analytical data for isocyanides 7

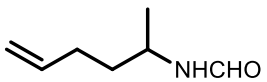


Scheme 2.

2.3.1. General procedure of the modified Leuckart Wallach formamide synthesis

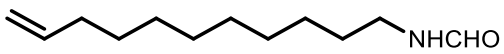
The 10-undecenal or 5-hexen-2-one (1.0 equiv.), formamide (54.0 equiv.) and formic acid (11.5 equiv.) were refluxed at 180 °C for 1 h. Afterwards, the reaction was cooled to rt and extracted with DCM, organic layer was collected, washed with water, dried over anhydrous $MgSO_4$ and evaporated. The products were obtained without further purification.

N-(hex-5-en-2-yl)formamide (13a)



Brown oil, 90% yield; *mixture of rotamers is observed, major rotamer is given*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 8.12 (s, 1H), 6.13 (br s, 1H), 5.86 – 5.72 (m, 1H), 5.12 – 4.90 (m, 2H), 4.08 (dt, J = 14.0, 6.8 Hz, 1H), 2.21 – 2.03 (m, 2H), 1.66 – 1.48 (m, 2H), 1.17 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 160.7, 137.7, 115.0, 43.7, 35.8, 30.0, 20.8. HRMS: Calcd for $C_7H_{13}NO$ (m/z): $[M+H]^-$ 128.0997, found: $[M+H]^-$ 128.010.

N-(undec-10-en-1-yl)formamide (13b)

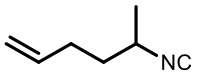


Yellow oil, 92% yield; *mixture of rotamers is observed, major rotamer is given*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 8.16 (s, 1H), 5.84 – 5.77 (m, 1H), 5.00 – 4.92 (m, 2H), 3.29 (q, J = 6.6 Hz, 1H), 2.04 (q, J = 6.9 Hz, 2H), 1.52 (q, J = 6.8 Hz, 2H), 1.33 (d, J = 46.0 Hz, 13H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 161.4, 139.1, 114.1, 41.9, 38.2, 33.8, 29.44, 29.36, 29.2, 29.05, 28.9, 26.83. HRMS: Calcd for $C_{12}H_{23}NO$ (m/z): $[M+H]^-$ 198.1780, found: $[M+H]^-$ 198.1782.

2.3.2. General procedure of the isocyanide synthesis

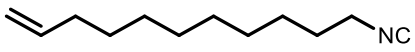
The corresponding formamides **10a** and **10b** (1.0 equiv.), triethylamine (4.0 equiv.) and DCM were put together in a round-bottom flask and cooled to 0 °C. Then $POCl_3$ (1.1 equiv.) was added dropwise and the reaction was stirred at rt for 3-4 h. After the reaction was completed, the products were poured into ice cold solution of $NaHCO_3$ and left to reach rt. The precipitated solid was filtered off and washed with DCM. The remaining water phase was extracted with DCM. Organic layers were collected, washed with water, dried over anhydrous $MgSO_4$ and evaporated. The resulting oils were purified on silica pad with copious amount of DCM, which was then collected and evaporated, giving the pure isocyanides **7a,b**.

5-isocyanohex-1-ene (7a)



Brown oil, 87% yield; *mixture of rotamers is observed, major rotamer is given*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 5.77 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.13 – 4.97 (m, 2H), 3.64 (ddd, J = 8.6, 6.7, 4.9 Hz, 1H), 2.23 (ddq, J = 37.4, 14.9, 7.4, 6.7 Hz, 2H), 1.79 – 1.56 (m, 2H), 1.41 – 1.32 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 154.6, 136.4, 116.1, 49.6, 46.0, 35.8, 29.8, 21.6, 8.6. HRMS: Calcd for $C_7H_{11}N$ (m/z): $[M+H]^-$ 110.0891, found: $[M+H]^-$ 110.0894.

11-isocyanoundec-1-ene (7b)

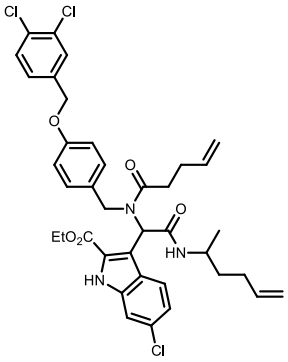


Brown oil, 75% yield; *mixture of rotamers is observed, major rotamer is given*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 5.90 – 5.70 (m, 1H), 5.05 – 4.89 (m, 2H), 3.38 (ddt, J = 6.7, 3.7, 1.8 Hz, 1H), 2.04 (q, J = 6.9 Hz, 2H), 1.68 (ddd, J = 10.0, 4.6, 2.1 Hz, 1H), 1.48 – 1.13 (m, 14H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 154.4, 136.5, 116.1, 49.6, 45.9, 35.8, 31.6, 29.9, 21.6, 8.6. HRMS: Calcd for $C_{12}H_{21}N$ (m/z): $[M+H]^-$ 180.1674, found: $[M+H]^-$ 180.1670.

2.4. General procedure of the Ugi four-component reaction (U-4CR)

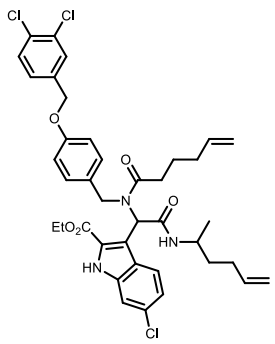
The corresponding amine **5** (1.0 equiv.), aldehyde **6** (1.0 equiv.), isocyanide **7** (1.0 equiv.) and acid **8** (1.0 equiv.) were dissolved in 2,2,2-trifluoroethanol (2 mL) and placed into a microwave vial which irradiated at 120 ºC for 60 min. Afterwards, the solvent was evaporated and the crude mixture was purified by flash chromatography (hexane-ethyl acetate) giving the corresponding compounds **4** (yields 15-60%) as yellow oils.

Ethyl 6-chloro-3-(1-(*N*-(4-((3,4-dichlorobenzyl)oxy)benzyl)pent-4-enamido)-2-(hex-5-en-2-ylamino)-2-oxoethyl)-1*H*-indole-2-carboxylate (4a)



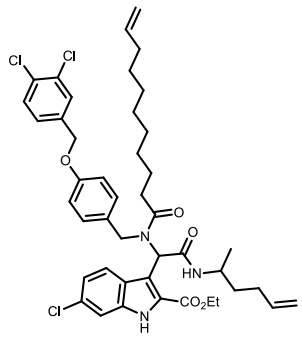
15% yield; *mixture of rotamers and diastereomers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.30 (s, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.29 – 7.14 (m, 4H), 7.08 (dd, J = 14.5, 8.6 Hz, 1H), 6.97 – 6.84 (m, 2H), 6.53 (dt, J = 20.4, 9.6 Hz, 4H), 5.82 (ddt, J = 16.7, 12.5, 6.1 Hz, 1H), 5.58 (dd, J = 13.4, 7.5 Hz, 1H), 5.09 – 4.90 (m, 5H), 4.91 – 4.61 (m, 4H), 4.48 – 4.26 (m, 4H), 4.05 (dd, J = 13.5, 6.8 Hz, 1H), 3.47 (s, 1H), 2.57 (dd, J = 13.2, 7.5 Hz, 1H), 2.44 (ddt, J = 25.2, 13.9, 6.8 Hz, 4H), 2.30 (t, J = 7.4 Hz, 1H), 2.07 (d, J = 7.3 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.80 (q, J = 7.0 Hz, 1H), 1.43 (dt, J = 12.5, 7.2 Hz, 1H), 1.36 (q, J = 9.0, 8.0 Hz, 3H), 1.30 – 1.21 (m, 1H), 1.11 (d, J = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 173.5, 172.2, 169.3, 162.8, 160.9, 157.6, 156.8, 137.8, 137.5, 137.0, 135.8, 132.6, 131.8, 131.6, 131.2, 130.8, 130.5, 130.3, 130.0, 129.2, 129.2, 129.0, 128.0, 127.2, 126.5, 126.4, 126.3, 125.7, 122.9, 122.4, 115.7, 115.3, 115.0, 114.7, 114.3, 111.8, 100.0, 77.3, 77.1, 76.8, 68.5, 68.4, 61.6, 54.4, 50.2, 49.1, 45.5, 43.9, 43.0, 35.8, 35.5, 33.1, 30.2, 29.9, 29.6, 29.4, 20.5, 14.4; LC-MS (DAD/ESI): t_R = 3.22 min, Calcd for $C_{38}H_{40}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 722.20, found: $[M-H]^-$ 722.13.

Ethyl 6-chloro-3-(1-(*N*-(4-((3,4-dichlorobenzyl)oxy)benzyl)hex-5-enamido)-2-(hex-5-en-2-ylamino)-2-oxoethyl)-1*H*-indole-2-carboxylate (4b)



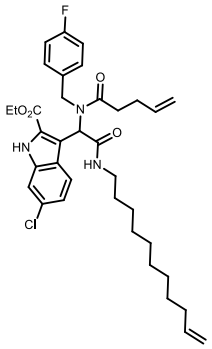
21% yield; *mixture of rotamers and diastereomers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.30 (s, 1H), 7.85 (dd, *J* = 8.7, 4.9 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.50 – 7.41 (m, 3H), 7.31 – 7.15 (m, 5H), 7.10 (d, *J* = 8.6 Hz, 1H), 6.93 – 6.86 (m, 2H), 6.62 – 6.44 (m, 3H), 5.76 (ddtd, *J* = 18.0, 14.6, 10.3, 7.3 Hz, 3H), 5.14 – 4.89 (m, 8H), 4.90 – 4.63 (m, 4H), 4.51 – 4.34 (m, 4H), 4.32 – 4.22 (m, 2H), 4.12 – 3.98 (m, 1H), 2.37 – 2.24 (m, 2H), 2.24 – 2.15 (m, 2H), 2.08 (tt, *J* = 14.3, 7.3 Hz, 4H), 1.86 – 1.65 (m, 4H), 1.59 – 1.39 (m, 3H), 1.41 – 1.27 (m, 4H), 1.28 – 1.15 (m, 1H), 1.11 (dd, *J* = 15.5, 6.5 Hz, 2H), 0.95 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 190.8, 177.3, 174.1, 172.8, 169.3, 161.0, 157.7, 156.8, 138.1, 138.0, 137.8, 137.7, 137.3, 137.2, 135.9, 132.7, 132.6, 132.1, 131.9, 131.8, 131.7, 131.2, 130.9, 130.7, 130.6, 130.5, 129.3, 129.2, 129.0, 127.1, 126.5, 126.4, 126.3, 125.8, 124.7, 123.0, 122.8, 122.4, 115.4, 115.4, 115.1, 115.0, 114.9, 114.7, 114.2, 112.2, 111.8, 77.3, 77.1, 76.8, 68.7, 68.5, 68.4, 61.7, 54.4, 49.1, 45.5, 45.4, 43.9, 43.0, 35.9, 35.4, 33.3, 33.2, 33.1, 33.0, 33.0, 30.2, 29.9, 24.8, 24.5, 24.0, 20.6, 20.5, 14.4; LC-MS (DAD/ESI): t_R = 3.21 min, Calcd for $C_{39}H_{42}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 736.22, found: $[M-H]^-$ 736.15.

Ethyl 6-chloro-3-(1-(*N*-(4-((3,4-dichlorobenzyl)oxy)benzyl)undec-10-enamido)-2-(hex-5-en-2-ylamino)-2-oxoethyl)-1*H*-indole-2-carboxylate (4c)



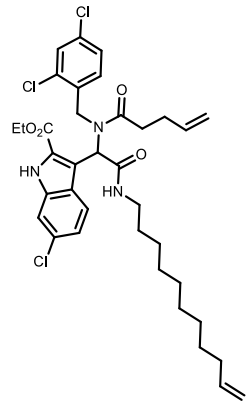
18% yield; *mixture of rotamers and diastereomers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.64 (d, *J* = 9.4 Hz, 1H), 7.92 – 7.81 (m, 1H), 7.57 – 7.38 (m, 4H), 7.37 – 7.06 (m, 5H), 6.99 (d, *J* = 5.9 Hz, 1H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.66 – 6.44 (m, 3H), 5.86 – 5.69 (m, 3H), 5.28 (s, 1H), 5.14 – 4.88 (m, 6H), 4.84 (d, *J* = 15.4 Hz, 2H), 4.80 – 4.67 (m, 1H), 4.45 (dd, *J* = 17.5, 8.0 Hz, 1H), 4.36 (t, *J* = 7.8 Hz, 1H), 4.31 – 4.21 (m, 1H), 4.11 – 4.00 (m, 1H), 2.52 – 2.39 (m, 1H), 2.31 (dt, *J* = 11.7, 6.8 Hz, 1H), 2.20 (t, *J* = 7.6 Hz, 1H), 2.02 (dq, *J* = 14.5, 7.7, 7.1 Hz, 4H), 1.79 (q, *J* = 7.1 Hz, 1H), 1.75 – 1.52 (m, 3H), 1.52 – 1.16 (m, 21H), 1.17 – 1.02 (m, 3H), 0.95 (d, *J* = 6.5 Hz, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 177.5, 174.4, 174.4, 173.3, 169.5, 169.4, 161.1, 160.2, 157.6, 156.8, 139.2, 139.2, 139.1, 138.0, 137.8, 137.3, 137.2, 136.0, 132.7, 132.6, 131.9, 131.8, 131.5, 131.3, 130.9, 130.5, 130.5, 129.2, 129.1, 129.0, 128.1, 127.7, 127.2, 126.5, 126.4, 126.3, 125.7, 122.9, 122.8, 122.3, 121.7, 115.3, 115.1, 115.0, 115.0, 114.9, 114.7, 114.6, 114.2, 114.2, 114.2, 114.1, 113.9, 112.3, 111.9, 77.4, 77.1, 76.9, 68.5, 68.4, 61.6, 61.3, 57.2, 56.9, 54.5, 54.3, 53.5, 49.2, 49.1, 46.3, 45.7, 45.5, 45.4, 43.0, 36.8, 35.9, 35.4, 34.1, 33.8, 30.2, 29.9, 29.6, 29.4, 29.4, 29.3, 29.3, 29.2, 29.2, 29.1, 28.9, 25.8, 25.4, 24.9, 20.6, 20.5, 14.3; LC-MS (DAD/ESI): t_R = 3.14 min, Calcd for $C_{44}H_{52}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 806.30, found: $[M-H]^-$ 806.32.

Ethyl 6-chloro-3-(1-(*N*-(4-fluorobenzyl)pent-4-enamido)-2-oxo-2-(undec-10-en-1-ylamino)ethyl)-1*H*-indole-2-carboxylate (4d)



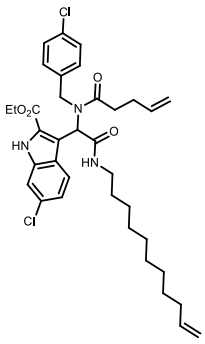
23% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.50 (d, J = 8.5 Hz, 1H), 7.13 (t, J = 9.5 Hz, 2H), 6.35 (s, 3H), 6.13 (s, 1H), 5.70 (s, 3H), 5.14 (d, J = 16.6 Hz, 3H), 4.75 (d, J = 17.8 Hz, 2H), 4.46 (d, J = 17.7 Hz, 2H), 7.82 (d, J = 8.8 Hz, 3H), 7.01 (d, J = 17.0 Hz, 1H), 6.62 (dt, J = 21.6, 8.1 Hz, 4H), 6.53 (s, 1H), 5.82 (tdd, J = 16.7, 10.3, 4.3 Hz, 3H), 5.08 – 4.98 (m, 3H), 4.94 (dd, J = 16.4, 10.6 Hz, 4H), 4.38 (dt, J = 14.3, 7.2 Hz, 1H), 4.32 (dt, J = 14.4, 7.1 Hz, 2H), 3.82 (d, J = 15.2 Hz, 1H), 3.29 (dt, J = 13.1, 6.5 Hz, 1H), 3.21 (dt, J = 13.9, 6.7 Hz, 1H), 2.57 (dq, J = 17.0, 10.8, 9.2 Hz, 2H), 2.47 (dt, J = 13.6, 7.1 Hz, 3H), 2.36 (tt, J = 13.5, 8.0 Hz, 2H), 2.02 (q, J = 6.6 Hz, 3H), 1.48 (d, J = 24.1 Hz, 1H), 1.35 (dq, J = 15.6, 8.4, 7.7 Hz, 11H), 1.17 (d, J = 18.6 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 173.4, 169.8, 160.8, 160.4, 139.2, 137.4, 135.8, 133.6, 131.7, 127.6, 127.2, 126.5, 126.5, 125.7, 122.6, 121.6, 115.5, 115.3, 114.7, 114.6, 114.1, 113.9, 112.3, 111.9, 77.3, 77.1, 76.8, 61.7, 61.4, 56.4, 54.1, 49.1, 46.8, 40.0, 33.8, 33.1, 32.5, 29.4, 29.4, 29.2, 29.1, 28.9, 26.9, 14.4; LC-MS (DAD/ESI): t_R = 2.82 min, Calcd for $C_{36}H_{45}Cl_FN_3O_4$ (m/z): $[M-H]^-$ 636.31, found: $[M-H]^-$ 636.31.

Ethyl 6-chloro-3-(1-(*N*-(2,4-dichlorobenzyl)pent-4-enamido)-2-oxo-2-(undec-10-en-1-ylamino)ethyl)-1*H*-indole-2-carboxylate (4e)



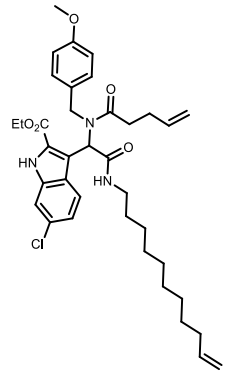
26% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.40 (s, 2H), 9.25 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.14 – 7.07 (m, 2H), 7.00 (d, J = 12.4 Hz, 2H), 6.64 (s, 1H), 5.82 (tdt, J = 16.8, 9.9, 6.4 Hz, 3H), 5.66 (t, J = 5.5 Hz, 3H), 5.11 – 5.03 (m, 1H), 5.02 – 4.89 (m, 5H), 4.68 (s, 2H), 4.44 – 4.32 (m, 3H), 3.29 (tt, J = 12.4, 6.2 Hz, 1H), 3.21 (dq, J = 12.8, 6.9 Hz, 1H), 3.10 – 2.99 (m, 1H), 2.89 – 2.81 (m, 1H), 2.53 – 2.35 (m, 5H), 2.26 – 2.16 (m, 1H), 2.02 (q, J = 7.0 Hz, 3H), 1.38 (dtt, J = 22.7, 15.1, 7.4 Hz, 9H), 1.15 (t, J = 12.4 Hz, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 173.5, 173.5, 169.4, 169.4, 160.9, 160.9, 139.2, 139.2, 137.2, 137.2, 137.1, 137.1, 136.8, 135.8, 135.8, 133.8, 133.8, 132.8, 132.8, 132.3, 132.3, 132.0, 132.0, 131.1, 131.1, 129.3, 129.3, 128.8, 128.8, 128.0, 128.0, 127.5, 127.5, 127.3, 127.3, 126.9, 126.9, 126.4, 126.4, 125.8, 125.8, 125.5, 125.5, 122.8, 122.8, 121.8, 121.8, 115.8, 115.8, 115.5, 115.5, 115.3, 115.3, 115.2, 115.2, 114.3, 114.3, 114.1, 114.1, 112.1, 112.1, 111.9, 111.9, 77.3, 77.3, 77.0, 77.0, 76.8, 76.8, 61.9, 61.9, 61.6, 61.6, 56.3, 54.2, 54.2, 47.3, 47.3, 45.3, 40.9, 40.9, 40.3, 40.3, 40.1, 40.1, 35.7, 35.7, 33.8, 33.8, 32.8, 32.8, 32.4, 32.4, 29.5, 29.5, 29.4, 29.4, 29.4, 29.4, 29.2, 29.2, 29.2, 29.2, 29.1, 29.1, 28.9, 28.9, 27.0, 27.0, 26.9, 26.9, 23.4, 23.4, 14.5, 14.5, 14.3, 14.3; LC-MS (DAD/ESI): t_R = 2.86 min, Calcd for $C_{36}H_{44}Cl_3N_3O_4$ (m/z): $[M-H]^-$ 686.24, found: $[M-H]^-$ 686.23.

Ethyl 6-chloro-3-(1-(*N*-(4-chlorobenzyl)pent-4-enamido)-2-oxo-2-(undec-10-en-1-ylamino)ethyl)-1*H*-indole-2-carboxylate (4f)



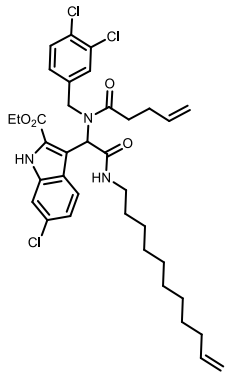
25% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.49 (s, 1H), 9.37 (s, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.31 – 7.20 (m, 1H), 7.11 (d, *J* = 8.9 Hz, 1H), 7.00 (s, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.31 (d, *J* = 7.7 Hz, 1H), 6.15 (s, 1H), 5.79 (tdd, *J* = 24.4, 12.6, 6.7 Hz, 2H), 5.14 (d, *J* = 17.4 Hz, 1H), 4.99 (dd, *J* = 17.5, 11.2 Hz, 2H), 4.92 (d, *J* = 11.3 Hz, 1H), 4.74 (d, *J* = 18.0 Hz, 1H), 4.46 (d, *J* = 18.1 Hz, 1H), 4.34 (dtdd, *J* = 23.8, 19.8, 11.5, 7.0 Hz, 2H), 3.79 (d, *J* = 15.6 Hz, 1H), 3.42 – 3.34 (m, 1H), 3.30 (dq, *J* = 13.1, 6.7 Hz, 1H), 3.20 (dq, *J* = 13.0, 6.8 Hz, 1H), 2.56 (dt, *J* = 14.4, 6.5 Hz, 1H), 2.51 – 2.42 (m, 1H), 2.40 (dd, *J* = 10.3, 5.9 Hz, 1H), 2.38 – 2.29 (m, 1H), 2.03 (p, *J* = 7.5, 6.6 Hz, 2H), 1.49 (s, 1H), 1.44 – 1.32 (m, 6H), 1.23 (d, *J* = 35.4 Hz, 7H), 1.15 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 173.9, 173.4, 169.9, 160.8, 139.2, 137.6, 137.3, 136.5, 135.9, 132.2, 131.7, 129.0, 127.9, 127.4, 127.4, 127.2, 126.4, 125.6, 124.9, 122.6, 122.5, 121.5, 115.4, 115.1, 114.4, 114.1, 112.4, 112.0, 77.3, 77.1, 76.8, 61.7, 61.4, 56.4, 54.2, 51.6, 49.1, 46.9, 40.2, 40.0, 33.8, 33.1, 32.5, 29.4, 29.4, 29.2, 29.1, 28.9, 27.1, 27.0, 26.9, 23.6, 14.4; LC-MS (DAD/ESI): t_R = 2.89 min, Calcd for $C_{36}H_{45}Cl_2N_3O_4$ (m/z): $[M-H]^-$ 652.28, found: $[M-H]^-$ 652.31.

Ethyl 6-chloro-3-(1-(*N*-(4-methoxybenzyl)pent-4-enamido)-2-oxo-2-(undec-10-en-1-ylamino)ethyl)-1*H*-indole-2-carboxylate (4g)



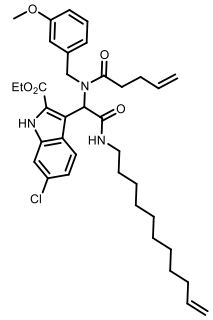
25% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.17 (s, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.26 (d, *J* = 6.0 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.98 (s, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 2H), 6.43 (d, *J* = 11.5 Hz, 1H), 5.89 – 5.74 (m, 2H), 5.69 (s, 1H), 5.05 – 4.98 (m, 2H), 4.98 – 4.89 (m, 2H), 4.72 (d, *J* = 17.6 Hz, 1H), 4.42 – 4.35 (m, 1H), 4.32 (dt, *J* = 10.7, 7.0 Hz, 1H), 3.66 (s, 3H), 3.30 (dt, *J* = 13.2, 6.7 Hz, 1H), 3.25 – 3.19 (m, 1H), 2.58 (dd, *J* = 13.3, 7.5 Hz, 1H), 2.53 – 2.43 (m, 2H), 2.39 (dt, *J* = 11.2, 6.3 Hz, 2H), 2.02 (q, *J* = 6.5 Hz, 2H), 1.49 – 1.31 (m, *J* = 8.0, 7.4 Hz, 7H), 1.23 (d, *J* = 33.7 Hz, 6H), 1.16 (s, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 169.9, 139.2, 139.2, 137.5, 137.5, 135.8, 135.8, 131.6, 131.6, 129.9, 129.2, 129.2, 126.2, 126.2, 122.8, 122.8, 122.5, 122.5, 115.5, 115.2, 115.2, 114.1, 114.1, 114.1, 114.1, 113.3, 113.3, 111.8, 111.8, 77.3, 77.3, 77.0, 77.0, 76.8, 76.8, 61.7, 61.7, 55.2, 55.2, 54.3, 54.3, 49.1, 49.1, 43.1, 40.0, 40.0, 33.8, 33.8, 33.1, 33.1, 29.4, 29.4, 29.4, 29.4, 29.2, 29.2, 29.1, 29.1, 28.9, 28.9, 26.9, 26.9, 14.4, 14.4; LC-MS (DAD/ESI): t_R = 3.03 min, Calcd for $C_{37}H_{48}ClN_3O_5$ (m/z): $[M-H]^-$ 648.33, found: $[M-H]^-$ 648.28.

Ethyl 6-chloro-3-(1-(*N*-(3,4-dichlorobenzyl)pent-4-enamido)-2-oxo-2-(undec-10-en-1-ylamino)ethyl)-1*H*-indole-2-carboxylate (4h)



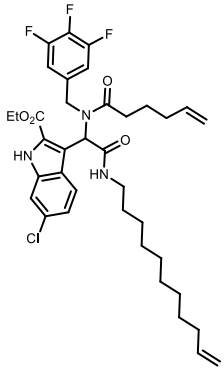
25% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.66 (s, 1H), 9.46 (s, 1H), 7.79 (d, *J* = 8.8 Hz, 1H), 7.35 – 7.27 (m, 1H), 7.14 (dd, *J* = 17.6, 8.6 Hz, 1H), 7.08 – 6.97 (m, 1H), 6.75 (s, 1H), 6.44 (d, *J* = 8.1 Hz, 1H), 6.21 (d, *J* = 8.1 Hz, 1H), 5.94 (dd, *J* = 16.7, 10.2 Hz, 1H), 5.89 – 5.74 (m, 3H), 5.24 (d, *J* = 15.7 Hz, 1H), 5.14 (d, *J* = 17.4 Hz, 1H), 5.07 – 5.02 (m, 1H), 5.00 (s, 1H), 4.99 – 4.95 (m, 1H), 4.92 (d, *J* = 10.0 Hz, 1H), 4.74 (d, *J* = 18.1 Hz, 1H), 4.42 – 4.37 (m, 1H), 4.32 (dq, *J* = 12.5, 6.4, 5.6 Hz, 1H), 3.69 (d, *J* = 15.6 Hz, 1H), 3.39 (s, 1H), 3.30 (dq, *J* = 13.3, 6.9 Hz, 1H), 3.19 (dq, *J* = 21.5, 7.8, 7.2 Hz, 1H), 2.99 (dd, *J* = 12.8, 6.6 Hz, 2H), 2.94 – 2.84 (m, 1H), 2.42 (dtdd, *J* = 58.9, 36.3, 16.5, 9.6 Hz, 6H), 2.09 – 1.98 (m, 3H), 1.61 (d, *J* = 10.3 Hz, 1H), 1.51 (s, 2H), 1.38 (ddq, *J* = 23.2, 16.5, 9.4, 7.6 Hz, 8H), 1.31 – 1.18 (m, 10H), 1.18 – 1.04 (m, 4H), 0.93 – 0.81 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 173.4, 169.9, 160.8, 139.2, 139.2, 138.5, 137.2, 137.2, 131.8, 131.8, 129.7, 129.7, 129.1, 129.1, 127.8, 127.8, 127.0, 127.0, 125.4, 125.4, 124.4, 124.4, 122.7, 122.7, 122.2, 122.2, 115.6, 115.6, 115.3, 115.3, 114.1, 114.1, 112.5, 112.5, 112.2, 112.2, 77.3, 77.3, 77.1, 77.1, 76.8, 76.8, 61.9, 61.9, 61.6, 61.6, 56.1, 54.1, 54.1, 48.8, 48.8, 46.7, 40.1, 40.1, 33.8, 33.8, 33.0, 33.0, 32.4, 32.4, 29.4, 29.4, 29.1, 29.1, 28.9, 28.9, 26.9, 26.9, 14.3; LC-MS (DAD/ESI): t_R = 2.94 min, Calcd for $C_{36}H_{44}Cl_3N_3O_4$ (m/z): [M-H]- 686.24, found: [M-H]-686.23.

Ethyl 6-chloro-3-(1-(*N*-(3-methoxybenzyl)pent-4-enamido)-2-oxo-2-(undec-10-en-1-ylamino)ethyl)-1*H*-indole-2-carboxylate (4i)



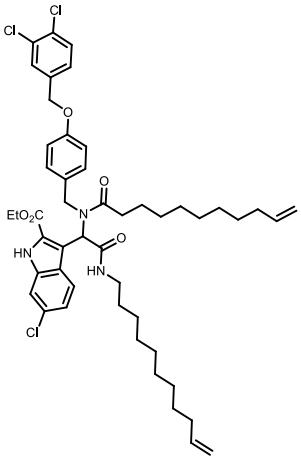
31% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.80 (s, 1H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.27 (s, 1H), 7.10 (d, *J* = 8.8 Hz, 1H), 7.04 (s, 1H), 6.86 (dt, *J* = 14.7, 7.9 Hz, 1H), 6.51 – 6.40 (m, 1H), 6.27 (d, *J* = 7.4 Hz, 1H), 6.10 (s, 1H), 5.95 (t, *J* = 12.4 Hz, 1H), 5.82 (ddq, *J* = 25.5, 16.1, 9.0, 8.0 Hz, 2H), 5.25 – 5.11 (m, 1H), 5.01 (s, 1H), 4.97 (d, *J* = 4.6 Hz, 1H), 4.93 (t, *J* = 8.7 Hz, 1H), 4.75 (d, *J* = 17.8 Hz, 1H), 4.54 – 4.41 (m, 2H), 4.33 (dt, *J* = 14.4, 7.2 Hz, 1H), 4.24 (dt, *J* = 17.5, 6.9 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 1H), 3.77 (d, *J* = 12.6 Hz, 1H), 3.46 (s, 2H), 3.29 (dt, *J* = 12.8, 6.5 Hz, 1H), 3.21 (dt, *J* = 13.0, 6.3 Hz, 1H), 2.55 (ddd, *J* = 22.3, 16.2, 5.7 Hz, 1H), 2.44 (dt, *J* = 12.7, 7.6 Hz, 2H), 2.41 – 2.30 (m, 1H), 2.03 (q, *J* = 7.1 Hz, 2H), 1.49 (s, 1H), 1.35 (p, *J* = 11.6, 10.2 Hz, 6H), 1.24 (dd, *J* = 13.8, 6.5 Hz, 6H), 1.15 (s, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 173.7, 170.1, 161.1, 159.3, 139.7, 139.2, 137.4, 136.8, 136.1, 131.5, 128.9, 127.4, 125.9, 122.5, 122.4, 117.4, 115.4, 115.3, 114.3, 114.1, 112.5, 112.1, 110.3, 77.4, 77.1, 76.9, 61.7, 56.8, 55.2, 54.8, 54.3, 49.7, 47.4, 40.0, 35.8, 33.8, 33.1, 29.4, 29.4, 29.3, 29.2, 29.1, 28.9, 28.8, 26.9, 21.0, 14.2. LC-MS (DAD/ESI): t_R = 4.55 min, Calcd for $C_{37}H_{48}ClN_3O_5$ (m/z): $[M-H]^-$ 648.33, found: $[M-H]^-$ 648.39.

Ethyl 6-chloro-3-(2-oxo-1-(*N*-(3,4,5-trifluorobenzyl)hex-5-enamido)-2-(undec-10-en-1-ylamino)ethyl)-1*H*-indole-2-carboxylate (4j)



45% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.02 (s, 1H), 8.84 (d, *J* = 13.8 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.30 (d, *J* = 35.6 Hz, 3H), 7.17 (dd, *J* = 21.2, 8.4 Hz, 2H), 6.98 (s, 1H), 6.32 (s, 1H), 5.99 (s, 1H), 5.85 – 5.71 (m, 4H), 5.57 (s, 1H), 5.28 (d, *J* = 16.4 Hz, 1H), 4.99 (td, *J* = 27.4, 26.7, 14.3 Hz, 8H), 4.77 – 4.67 (m, 1H), 4.42 (dd, *J* = 29.8, 11.1 Hz, 5H), 4.07 (s, 1H), 3.68 (d, *J* = 16.0 Hz, 1H), 3.33 – 3.26 (m, 1H), 3.23 (d, *J* = 5.5 Hz, 1H), 2.46 – 2.34 (m, 2H), 2.20 (s, 3H), 2.11 (dq, *J* = 12.9, 6.8 Hz, 4H), 2.05 – 2.00 (m, 6H), 1.95 – 1.57 (m, 5H), 1.55 – 0.97 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 174.4, 173.8, 169.7, 169.5, 160.7, 139.2, 138.2, 137.9, 135.8, 132.1, 127.1, 125.5, 124.8, 123.0, 123.0, 122.3, 121.4, 115.4, 115.3, 115.1, 114.1, 112.3, 112.0, 109.8, 109.6, 109.1, 109.0, 77.3, 77.0, 76.8, 62.0, 61.7, 55.9, 54.0, 48.7, 46.8, 40.2, 40.1, 33.8, 33.3, 33.0, 33.0, 32.8, 32.6, 32.2, 29.5, 29.4, 29.4, 29.2, 29.1, 28.9, 26.9, 26.8, 24.2, 23.9, 23.8, 14.3; LC-MS (DAD/ESI): t_R = 3.47 min, Calcd for $C_{37}H_{45}ClF_3N_3O_4$ (m/z): $[M-H]^-$ 686.31, found: $[M-H]^-$ 686.10.

Ethyl 6-chloro-3-(1-(*N*-(4-((3,4-dichlorobenzyl)oxy)benzyl)undec-10-enamido)-2-oxo-2-(undec-10-en-1-ylamino)ethyl)-1*H*-indole-2-carboxylate (4k)

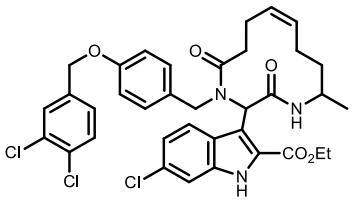


17% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 8.99 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.24 – 7.16 (m, 2H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.96 (s, 2H), 6.53 (d, *J* = 9.5 Hz, 3H), 6.49 – 6.29 (m, 1H), 5.80 (ddd, *J* = 14.7, 10.4, 4.2 Hz, 2H), 5.62 (s, 1H), 5.04 – 4.89 (m, 5H), 4.87 (s, 2H), 4.71 (d, *J* = 17.5 Hz, 1H), 4.47 – 4.36 (m, 2H), 4.35 – 4.26 (m, 1H), 3.25 (dt, *J* = 37.4, 6.9 Hz, 4H), 2.46 (d, *J* = 8.7 Hz, 1H), 2.31 (dd, *J* = 15.6, 7.7 Hz, 1H), 2.12 – 1.96 (m, 5H), 1.87 – 1.66 (m, 2H), 1.37 (dq, *J* = 14.9, 8.3, 5.8 Hz, 13H), 1.32 – 1.20 (m, 15H), 1.20 – 1.04 (m, 7H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 174.2, 169.9, 160.9, 156.7, 139.2, 139.2, 137.3, 135.8, 132.7, 131.9, 131.7, 130.9, 130.6, 129.3, 129.0, 127.6, 127.1, 126.4, 126.3, 125.8, 122.9, 122.5, 121.8, 115.1, 115.0, 114.9, 114.2, 114.1, 113.9, 112.1, 111.7, 77.3, 77.0, 76.8, 68.6, 68.4, 61.7, 61.3, 56.7, 54.1, 49.1, 46.6, 43.0, 40.0, 33.8, 33.8, 33.3, 29.4, 29.4, 29.3, 29.2, 29.1, 28.9, 26.9, 25.4, 24.9, 24.8, 14.4, 14.2; LC-MS (DAD/ESI): t_R = 3.41 min, Calcd for $C_{49}H_{62}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 876.38, found: $[M-H]^-$ 876.27.

2.5. General procedure for the ring-closure metathesis (RCM) reaction

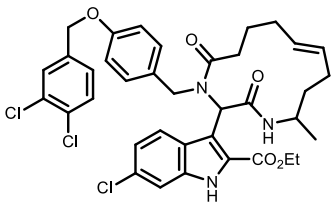
The corresponding U-4CR compound **4** (1.0 equiv.) was dissolved in dry DCM and the second generation Grubbs catalyst (0.08 equiv.) was added under N_2 atmosphere. The reaction mixture was refluxed for 3 d. The solvent was evaporated and the crude mixture was purified by flash chromatography (hexane-ethyl acetate) giving the corresponding compounds **3** (yields 10-96%) as green-brown powders.

Ethyl 6-chloro-3-(1-(4-((3,4-dichlorobenzyl)oxy)benzyl)-5-methyl-3,12-dioxo-1,4-diazacyclododec-8-en-2-yl)-1*H*-indole-2-carboxylate (3a)



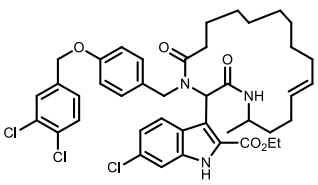
89% yield; *mixture of rotamers and diastereomers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.71 (d, J = 7.2 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.48 – 7.40 (m, 2H), 7.40 – 7.31 (m, 1H), 7.29 – 7.20 (m, 1H), 7.20 – 7.12 (m, 1H), 7.12 – 7.05 (m, 1H), 7.04 – 6.97 (m, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.67 (d, J = 8.6 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 6.35 (dd, J = 12.5, 8.6 Hz, 1H), 5.85 (s, 1H), 4.94 (d, J = 12.2 Hz, 1H), 4.81 (t, J = 10.6 Hz, 2H), 4.68 (dd, J = 17.1, 7.3 Hz, 1H), 4.35 – 4.18 (m, 3H), 2.72 – 2.65 (m, 1H), 2.59 (dd, J = 12.8, 6.0 Hz, 1H), 2.55 – 2.39 (m, 1H), 2.33 (s, 2H), 2.02 (dq, J = 42.6, 13.5, 12.9 Hz, 2H), 1.77 – 1.62 (m, 1H), 1.45 (d, J = 6.6 Hz, 1H), 1.42 – 1.30 (m, 4H), 1.27 (d, J = 13.6 Hz, 4H), 1.06 (d, J = 6.1 Hz, 1H), 0.87 (q, J = 10.6, 8.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 176.4, 173.6, 169.5, 168.9, 160.3, 160.1, 157.2, 156.9, 139.0, 137.3, 137.1, 135.9, 135.1, 132.6, 132.5, 131.9, 131.1, 130.6, 130.5, 130.3, 129.5, 129.1, 129.1, 127.7, 127.0, 126.9, 126.5, 125.8, 125.7, 124.9, 124.5, 124.0, 121.5, 121.4, 121.1, 115.6, 114.4, 114.2, 114.1, 113.6, 112.7, 112.3, 77.3, 77.1, 76.8, 68.4, 61.3, 61.2, 58.8, 54.6, 48.2, 46.8, 46.2, 45.7, 34.5, 33.6, 33.1, 32.8, 31.9, 31.4, 31.3, 30.2, 29.8, 29.7, 29.5, 29.4, 27.1, 26.7, 22.7, 21.8, 20.5, 18.2, 14.3, 14.2; LC-MS (DAD/ESI): t_R = 5.52 min, Calcd for $C_{36}H_{36}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 694.17, found: $[M-H]^-$ 694.15.

Ethyl 6-chloro-3-(1-(4-((3,4-dichlorobenzyl)oxy)benzyl)-5-methyl 3,13-dioxo-1,4-diazacyclododec-8-en-2-yl)-1*H*-indole-2-carboxylate (3b)



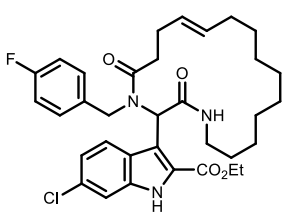
29% yield; *mixture of rotamers and diastereomers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.52 (s, 1H), 7.50 – 7.42 (m, 1H), 7.35 – 7.22 (m, 2H), 7.06 (q, *J* = 6.2, 5.1 Hz, 1H), 6.88 (dd, *J* = 12.2, 8.8 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.53 (s, 1H), 6.22 (d, *J* = 6.7 Hz, 1H), 5.87 – 5.67 (m, 1H), 5.31 (d, *J* = 13.0 Hz, 1H), 4.99 (q, *J* = 10.8, 10.0 Hz, 2H), 4.37 (d, *J* = 5.6 Hz, 1H), 4.28 (ddt, *J* = 18.0, 10.7, 5.4 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 3H), 2.92 (d, *J* = 16.8 Hz, 1H), 2.43 (ddd, *J* = 34.3, 25.7, 13.1 Hz, 1H), 2.34 – 2.15 (m, 2H), 2.05 (s, 5H), 1.76 (dt, *J* = 14.8, 7.4 Hz, 1H), 1.71 – 1.56 (m, 1H), 1.33 (q, *J* = 8.0, 7.5 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 4H), 1.12 (d, *J* = 6.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 174.1, 171.2, 169.7, 160.0, 157.3, 137.3, 135.9, 132.5, 131.9, 131.4, 130.6, 130.5, 129.7, 129.3, 129.2, 129.1, 126.7, 126.5, 124.9, 121.9, 121.5, 115.8, 115.3, 115.0, 114.5, 112.6, 77.3, 77.0, 76.8, 68.6, 68.4, 61.2, 60.4, 57.8, 48.6, 45.0, 43.0, 35.9, 34.8, 33.1, 30.8, 30.2, 30.0, 24.7, 22.5, 22.2, 21.1, 14.3, 14.2; LC-MS (DAD/ESI): t_R = 3.50 min, Calcd for $C_{37}H_{38}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 708.19, found: $[M-H]^-$ 708.30.

Ethyl 6-chloro-3-(1-(4-((3,4-dichlorobenzyl)oxy)benzyl)-5-methyl-3,18-dioxo-1,4-diazacyclooctadec-8-en-2-yl)-1*H*-indole-2-carboxylate (3c)



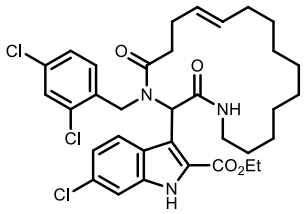
26% yield; *mixture of rotamers and diastereomers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.98 (d, *J* = 8.7 Hz, 1H), 7.77 – 7.67 (m, 1H), 7.60 – 7.40 (m, 4H), 7.39 – 7.22 (m, 2H), 7.17 (dd, *J* = 16.9, 7.7 Hz, 2H), 7.07 (dd, *J* = 19.4, 8.4 Hz, 1H), 6.56 (d, *J* = 16.8 Hz, 4H), 5.45 – 5.25 (m, 2H), 4.94 – 4.88 (m, 1H), 4.83 (d, *J* = 9.1 Hz, 2H), 4.46 – 4.34 (m, 1H), 4.33 – 4.18 (m, 2H), 4.11 (dt, *J* = 13.3, 6.9 Hz, 1H), 2.15 – 1.97 (m, 3H), 1.94 (s, 1H), 1.86 (s, 1H), 1.60 – 1.11 (m, 23H), 1.09 – 1.03 (m, 1H), 0.91 (dq, *J* = 22.1, 8.6, 7.0 Hz, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 174.4, 169.6, 161.1, 157.1, 156.7, 137.3, 135.9, 132.6, 131.8, 131.6, 131.5, 130.8, 130.5, 130.2, 129.4, 129.1, 129.0, 128.6, 127.2, 126.4, 126.4, 125.9, 123.3, 122.3, 122.0, 114.9, 114.2, 113.6, 111.8, 77.3, 77.1, 76.8, 68.4, 61.6, 61.3, 54.5, 49.2, 45.8, 45.2, 44.1, 38.0, 36.9, 33.6, 33.2, 31.8, 30.9, 30.2, 29.7, 29.4, 28.8, 28.5, 28.4, 28.1, 27.5, 27.2, 26.9, 26.5, 25.8, 25.6, 24.5, 20.7, 20.6, 19.5, 14.4; LC-MS (DAD/ESI): t_R = 3.53 min, Calcd for $C_{42}H_{48}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 778.27, found: $[M-H]^-$ 781.52.

Ethyl 6-chloro-3-(1-(4-fluorobenzyl)-3,18-dioxo-1,4-diazacyclooctadec-14-en-2-yl)-1*H*-indole-2-carboxylate (3d)



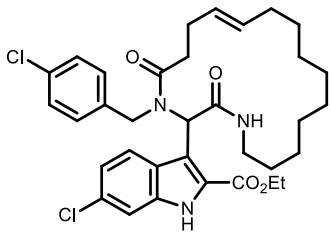
68% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.23 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.19 (s, 1H), 7.10 (dd, J = 25.5, 8.9 Hz, 2H), 6.66 (d, J = 7.8 Hz, 2H), 6.56 – 6.46 (m, 3H), 6.36 – 6.25 (m, 2H), 6.07 (t, J = 5.3 Hz, 1H), 5.59 – 5.43 (m, 3H), 5.16 (d, J = 15.4 Hz, 1H), 4.38 – 4.18 (m, 3H), 3.74 (d, J = 15.5 Hz, 1H), 3.57 (dt, J = 12.0, 6.4 Hz, 1H), 3.19 (d, J = 5.4 Hz, 1H), 3.00 (tt, J = 15.8, 6.1 Hz, 1H), 2.67 – 2.53 (m, 1H), 2.52 – 2.43 (m, 2H), 2.31 (td, J = 17.0, 16.6, 8.3 Hz, 2H), 2.26 – 2.11 (m, 1H), 2.11 – 1.98 (m, 3H), 1.94 (s, 1H), 1.56 (dd, J = 16.1, 9.6 Hz, 2H), 1.51 – 1.32 (m, 16H), 1.31 – 1.19 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 174.0, 170.2, 170.1, 162.2, 160.2, 160.0, 135.8, 134.8, 131.7, 131.5, 130.2, 129.4, 128.7, 127.6, 127.6, 127.0, 126.7, 125.0, 122.8, 122.7, 122.4, 121.4, 114.9, 114.6, 114.0, 113.9, 112.3, 112.0, 77.4, 77.1, 76.8, 61.3, 56.1, 55.9, 54.6, 49.1, 46.9, 40.0, 39.7, 39.5, 34.3, 33.7, 33.4, 31.7, 31.5, 31.3, 29.8, 29.4, 28.6, 28.5, 28.1, 28.0, 27.9, 27.8, 27.5, 27.1, 27.0, 26.8, 26.7, 26.2, 25.9, 25.8, 24.9, 14.4; LC-MS (DAD/ESI): t_R = 3.32 min, Calcd for $C_{34}H_{41}ClFN_3O_4$ (m/z): $[M-H]^-$ 608.28, found: $[M-H]^-$ 608.28.

Ethyl 6-chloro-3-(1-(2,4-dichlorobenzyl)-3,18-dioxo-1,4-diazacyclooctadec-14-en-2-yl)-1*H*-indole-2-carboxylate (3e)



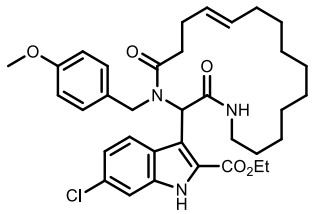
72% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 10.51 – 10.27 (m, 3H), 7.88 (dd, J = 26.7, 8.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 2.8 Hz, 2H), 7.06 (d, J = 8.8 Hz, 1H), 6.98 – 6.90 (m, 1H), 6.84 (dq, J = 24.1, 8.4 Hz, 3H), 6.62 – 6.52 (m, 1H), 6.26 (d, J = 5.4 Hz, 1H), 6.04 (dd, J = 36.3, 30.0 Hz, 1H), 5.52 (tt, J = 15.6, 7.4 Hz, 2H), 5.45 – 5.35 (m, 1H), 5.16 – 4.98 (m, 2H), 4.81 – 4.56 (m, 2H), 4.47 – 4.38 (m, 2H), 4.20 (d, J = 17.1 Hz, 1H), 3.71 (dt, J = 12.3, 6.3 Hz, 2H), 3.57 – 3.41 (m, 1H), 3.03 – 2.89 (m, 2H), 2.48 (dt, J = 15.3, 8.7 Hz, 2H), 2.40 (dd, J = 9.8, 6.0 Hz, 1H), 2.35 (s, 8H), 2.21 – 2.13 (m, 1H), 2.05 (dt, J = 14.8, 6.3 Hz, 2H), 1.68 – 1.56 (m, 1H), 1.47 (q, J = 10.6, 7.1 Hz, 6H), 1.42 – 1.31 (m, 10H), 1.28 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 174.0, 170.1, 136.1, 134.7, 132.2, 131.5, 131.2, 129.5, 128.4, 127.8, 126.7, 125.7, 124.7, 122.6, 121.7, 114.0, 112.3, 77.4, 77.1, 76.9, 61.3, 56.0, 45.4, 40.0, 33.6, 31.7, 29.2, 28.3, 28.1, 27.8, 27.7, 27.6, 27.5, 27.0, 26.2, 24.9, 14.6; LC-MS (DAD/ESI): t_R = 3.47 min, Calcd for $C_{34}H_{40}Cl_3N_3O_4$ (m/z): $[M-H]^-$ 658.21, found: $[M-H]^-$ 658.44.

Ethyl 6-chloro-3-(1-(4-chlorobenzyl)-3,18-dioxo-1,4-diazacyclooctadec-14-en-2-yl)-1*H*-indole-2-carboxylate (3f)



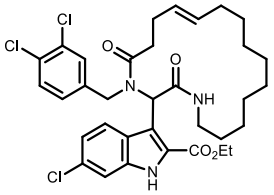
41% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 8.99 (s, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.26 (d, J = 5.9 Hz, 1H), 7.18 – 7.13 (m, 1H), 6.98 – 6.90 (m, 1H), 6.80 (d, J = 8.3 Hz, 2H), 6.63 (d, J = 7.8 Hz, 1H), 6.53 – 6.42 (m, 1H), 6.29 (t, J = 7.9 Hz, 2H), 5.92 (s, 1H), 5.60 – 5.45 (m, 2H), 5.22 (d, J = 15.6 Hz, 1H), 4.29 (dddd, J = 18.2, 10.7, 7.1, 3.5 Hz, 2H), 3.71 (dd, J = 15.6, 7.2 Hz, 3H), 3.67 – 3.55 (m, 1H), 3.14 (td, J = 12.5, 4.9 Hz, 1H), 3.00 (ddt, J = 31.4, 15.8, 6.7 Hz, 1H), 2.55 – 2.45 (m, 1H), 2.32 (tt, J = 16.9, 8.3 Hz, 1H), 2.05 (dd, J = 11.2, 6.3 Hz, 2H), 1.78 (s, 2H), 1.65 – 1.53 (m, 1H), 1.52 – 1.33 (m, 11H), 1.33 – 1.17 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 173.9, 170.1, 159.9, 137.7, 135.6, 131.9, 131.6, 131.5, 129.4, 128.1, 127.4, 127.3, 127.2, 126.9, 126.5, 125.0, 122.8, 121.5, 114.7, 112.2, 77.3, 77.0, 76.8, 61.4, 56.0, 47.0, 40.0, 33.6, 31.7, 29.8, 29.3, 28.6, 28.1, 28.0, 27.9, 27.7, 27.4, 27.0, 26.1, 25.8, 14.4; LC-MS (DAD/ESI): t_R = 3.41 min, Calcd for $C_{34}H_{41}Cl_2N_3O_4$ (m/z): $[M-H]^-$ 624.25, found: $[M-H]^-$ 624.47.

Ethyl 6-chloro-3-(1-(4-methoxybenzyl)-3,18-dioxo-1,4-diazacyclooctadec-14-en-2-yl)-1*H*-indole-2-carboxylate (3g)



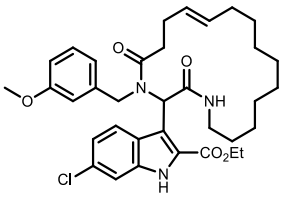
96% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.34 (s, 1H), 7.43 (d, J = 8.7 Hz, 1H), 7.15 (s, 1H), 7.08 (dd, J = 22.4, 9.0 Hz, 1H), 6.99 (d, J = 27.8 Hz, 1H), 6.60 (t, J = 10.0 Hz, 1H), 6.53 (d, J = 8.0 Hz, 1H), 6.43 (dd, J = 14.7, 7.5 Hz, 2H), 6.36 (d, J = 8.4 Hz, 1H), 6.19 (d, J = 5.3 Hz, 1H), 5.54 (d, J = 17.8 Hz, 2H), 4.88 (d, J = 15.2 Hz, 1H), 4.32 – 4.21 (m, 2H), 3.93 – 3.86 (m, 1H), 3.65 (d, J = 7.1 Hz, 3H), 3.41 (dd, J = 12.6, 6.2 Hz, 1H), 3.35 – 3.26 (m, 1H), 3.02 (td, J = 9.7, 9.3, 4.6 Hz, 1H), 2.51 (ddt, J = 47.5, 28.3, 12.5 Hz, 2H), 2.39 – 2.23 (m, 1H), 2.21 – 2.11 (m, 1H), 2.09 – 1.93 (m, 3H), 1.61 – 1.11 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 174.0, 170.4, 160.1, 158.0, 135.8, 131.5, 131.5, 131.2, 129.4, 128.8, 127.8, 127.6, 127.0, 126.5, 125.0, 122.8, 122.3, 122.2, 121.5, 114.7, 113.4, 113.0, 112.9, 112.3, 112.0, 77.3, 77.1, 76.8, 61.5, 61.2, 56.6, 55.2, 54.8, 49.1, 46.7, 39.9, 39.4, 33.7, 33.5, 31.7, 31.2, 29.4, 29.2, 28.4, 27.9, 27.7, 27.4, 27.3, 27.0, 26.9, 26.7, 26.5, 26.1, 25.8, 24.9, 23.6, 14.4; LC-MS (DAD/ESI): t_R = 3.50 min, Calcd for $C_{35}H_{44}ClN_3O_5$ (m/z): $[M-H]^-$ 620.30, found: $[M-H]^-$ 620.42.

Ethyl 6-chloro-3-(1-(3,4-dichlorobenzyl)-3,18-dioxo-1,4-diazacyclooctadec-14-en-2-yl)-1*H*-indole-2-carboxylate (3h)



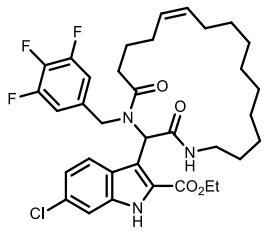
20% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.17 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.28 (d, *J* = 10.1 Hz, 1H), 7.18 – 7.14 (m, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.49 (d, *J* = 16.5 Hz, 1H), 6.31 (s, 1H), 6.25 – 6.17 (m, 1H), 5.96 (t, *J* = 5.3 Hz, 2H), 5.50 (q, *J* = 5.5 Hz, 1H), 5.31 – 5.18 (m, 2H), 4.32 (td, *J* = 12.2, 10.6, 5.4 Hz, 2H), 3.69 (dd, *J* = 8.3, 5.0 Hz, 1H), 3.67 – 3.63 (m, 1H), 3.63 – 3.56 (m, 1H), 3.04 (dt, *J* = 20.1, 10.0 Hz, 1H), 2.95 (ddd, *J* = 15.9, 10.4, 5.2 Hz, 1H), 2.52 – 2.37 (m, 2H), 2.30 (ddd, *J* = 16.2, 10.6, 5.6 Hz, 1H), 2.11 – 1.97 (m, 2H), 1.58 (dq, *J* = 21.6, 6.7, 6.0 Hz, 1H), 1.51 – 1.13 (m, 20H), 0.89 (dt, *J* = 15.1, 7.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 173.9, 170.0, 160.0, 139.6, 135.7, 131.9, 131.4, 131.1, 129.6, 129.4, 129.0, 127.8, 126.9, 125.5, 124.9, 123.0, 121.3, 114.5, 112.4, 77.3, 77.1, 76.8, 70.6, 70.0, 69.1, 63.7, 61.6, 55.8, 46.8, 40.1, 33.6, 31.7, 29.3, 28.7, 28.2, 28.0, 27.8, 27.7, 27.5, 27.1, 26.2, 14.4; LC-MS (DAD/ESI): t_R = 3.5 min, Calcd for $C_{34}H_{40}Cl_3N_3O_4$ (m/z): $[M-H]^-$ 658.21, found: $[M-H]^-$ 658.17.

Ethyl 6-chloro-3-(1-(3-methoxybenzyl)-3,18-dioxo-1,4-diazacyclooctadec-14-en-2-yl)-1*H*-indole-2-carboxylate (3i)



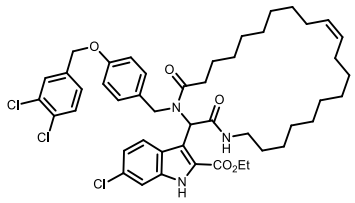
11% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.14 – 9.02 (m, 1H), 8.94 (d, *J* = 17.6 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.45 – 7.30 (m, 2H), 7.21 (d, *J* = 9.1 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 4H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.92 (t, *J* = 7.8 Hz, 1H), 6.80 – 6.74 (m, 1H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.47 (d, *J* = 3.9 Hz, 1H), 6.31 (dd, *J* = 14.6, 7.7 Hz, 1H), 6.03 (dd, *J* = 16.9, 6.3 Hz, 1H), 5.88 (d, *J* = 20.3 Hz, 1H), 5.54 (tt, *J* = 15.5, 8.1 Hz, 2H), 5.11 (d, *J* = 15.4 Hz, 1H), 4.76 (d, *J* = 17.8 Hz, 1H), 4.73 – 4.56 (m, 1H), 4.49 (dd, *J* = 17.7, 7.0 Hz, 1H), 4.42 – 4.35 (m, 1H), 4.31 (dd, *J* = 8.9, 4.9 Hz, 2H), 3.90 – 3.78 (m, 1H), 3.70 (td, *J* = 23.5, 7.7 Hz, 2H), 3.57 (dd, *J* = 13.0, 7.1 Hz, 1H), 3.49 (d, *J* = 7.2 Hz, 4H), 3.31 – 3.21 (m, 1H), 3.04 (ddd, *J* = 21.6, 11.4, 6.8 Hz, 1H), 2.63 – 2.49 (m, 2H), 2.48 – 2.39 (m, 1H), 2.35 (ddd, *J* = 16.2, 9.9, 6.5 Hz, 1H), 2.27 (dd, *J* = 17.1, 10.3 Hz, 1H), 2.16 (d, *J* = 7.2 Hz, 1H), 2.10 – 1.97 (m, 2H), 1.74 (s, 1H), 1.55 (s, 1H), 1.53 – 1.14 (m, 21H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 173.9, 170.2, 160.0, 158.8, 140.6, 135.7, 131.6, 131.5, 131.3, 129.5, 129.0, 128.7, 128.4, 127.2, 125.2, 123.0, 122.6, 122.4, 121.7, 118.5, 117.5, 114.8, 112.5, 112.4, 112.1, 111.8, 110.9, 110.6, 77.3, 77.0, 76.8, 61.7, 61.4, 56.3, 54.8, 54.7, 49.7, 47.4, 39.9, 39.4, 33.7, 33.4, 31.7, 31.3, 29.4, 28.4, 28.0, 27.9, 27.7, 27.4, 27.1, 26.9, 26.7, 26.1, 25.8, 24.9, 14.4, 14.3; LC-MS (DAD/ESI): t_R = 3.47 min, Calcd for $C_{35}H_{44}ClN_3O_5$ (m/z): $[M-H]^-$ 620.30, found: $[M-H]^-$ 620.26.

Ethyl 6-chloro-3-(3,19-dioxo-1-(3,4,5-trifluorobenzyl)-1,4-diazacyclononadec-14-en-2-yl)-1*H*-indole-2-carboxylate (3j)



18% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 8.94 (s, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.28 (d, J = 16.6 Hz, 2H), 7.25 – 7.10 (m, 1H), 6.51 (d, J = 15.5 Hz, 2H), 5.99 (d, J = 6.7 Hz, 1H), 5.85 (d, J = 28.1 Hz, 1H), 5.56 – 5.46 (m, 1H), 5.42 (dd, J = 13.0, 6.5 Hz, 1H), 5.26 (q, J = 16.1, 15.2 Hz, 1H), 4.47 – 4.30 (m, 2H), 3.75 – 3.54 (m, 1H), 3.21 (dd, J = 48.3, 7.1 Hz, 1H), 2.87 – 2.69 (m, 1H), 2.61 – 2.46 (m, 1H), 2.44 – 2.29 (m, 1H), 2.03 (dd, J = 26.6, 9.6 Hz, 2H), 1.93 (d, J = 5.4 Hz, 1H), 1.85 (d, J = 4.9 Hz, 1H), 1.66 (d, J = 17.0 Hz, 1H), 1.60 – 1.44 (m, 2H), 1.45 – 1.12 (m, 14H), 0.97 – 0.82 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 174.7, 169.8, 169.5, 159.9, 135.5, 132.2, 131.7, 131.6, 131.4, 130.0, 129.5, 129.4, 129.1, 126.9, 124.9, 123.2, 121.3, 112.2, 109.7, 77.3, 77.2, 77.0, 76.8, 61.8, 56.0, 46.8, 46.7, 40.0, 39.8, 33.4, 31.9, 31.6, 31.4, 29.3, 28.8, 28.4, 28.3, 28.0, 27.7, 27.4, 27.3, 27.0, 26.9, 26.6, 26.3, 26.2, 25.5, 25.2, 25.1, 25.0, 24.8, 14.3; LC-MS (DAD/ESI): t_R = 3.25 min, Calcd for $C_{35}H_{41}ClF_3N_3O_4$ (m/z): $[M+H]^-$ 660.27, found: $[M-H]^-$ 660.24.

Ethyl 6-chloro-3-(1-(4-((3,4-dichlorobenzyl)oxy)benzyl)-3,24-dioxo-1,4-diazacyclotetracos-14-en-2-yl)-1*H*-indole-2-carboxylate (3k)

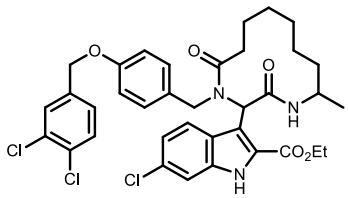


30% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 8.95 (d, J = 20.1 Hz, 2H), 8.21 (d, J = 14.1 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H), 7.46 (d, J = 9.4 Hz, 2H), 7.36 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.16 – 7.04 (m, 2H), 6.99 (s, 1H), 6.52 (d, J = 9.9 Hz, 2H), 6.46 (d, J = 7.7 Hz, 1H), 6.39 (s, 2H), 6.21 (s, 1H), 6.07 (s, 1H), 5.40 – 5.28 (m, 2H), 4.88 (s, 2H), 4.67 (d, J = 17.8 Hz, 1H), 4.44 – 4.25 (m, 5H), 4.12 (q, J = 7.1 Hz, 1H), 3.93 (d, J = 14.9 Hz, 1H), 3.49 (s, 2H), 2.52 (d, J = 36.2 Hz, 1H), 2.04 (q, J = 9.2, 5.2 Hz, 4H), 1.90 – 1.58 (m, 3H), 1.58 – 1.44 (m, 2H), 1.44 – 1.08 (m, 26H), 0.90 (dt, J = 14.6, 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 174.9, 170.1, 162.5, 159.9, 156.9, 156.6, 137.5, 135.7, 132.7, 131.6, 130.8, 130.6, 130.4, 130.0, 129.3, 129.0, 127.7, 127.0, 126.4, 126.3, 125.0, 123.0, 122.4, 122.2, 121.6, 115.0, 114.3, 114.0, 112.1, 111.7, 77.3, 77.2, 77.0, 76.8, 68.3, 61.5, 61.3, 60.4, 57.1, 54.6, 50.9, 49.1, 46.4, 39.9, 33.9, 33.8, 33.6, 32.2, 32.0, 29.7, 29.6, 29.5, 29.4, 29.2, 29.2, 29.0, 28.9, 28.7, 28.3, 28.1, 27.9, 27.2, 27.0, 26.9, 26.1, 25.5, 14.4, 14.2. LC-MS (DAD/ESI): t_R = 3.53 min, Calcd for $C_{47}H_{58}Cl_3N_3O_5$ (m/z): $[M+Na+H]^-$ 873.55, found: $[M+Na+H]^+$ 873.55.

2.6. General procedure for the hydrogenation reactions

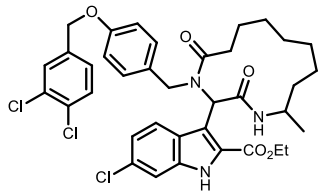
The corresponding RCM adduct **3** (1.0 equiv.) was stirred in methanol in a two-neck flask with a H_2 and N_2 supply. The solution was bubbled with N_2 to remove the remaining oxygen, 10% palladium on activated charcoal (1.0 equiv.) was added slowly and dissolved in methanol. The N_2 was removed and the H_2 was released and let flow for 1 h through the mixture. The crude reaction was filtrated over celite, the solvent was evaporated, giving the corresponding compounds **2** (yields 70-99%) as brown powders.

Ethyl 6-chloro-3-(1-(4-((3,4-dichlorobenzyl)oxy)benzyl)-5-methyl-3,12-dioxo-1,4-diazacyclododecan-2-yl)-1*H*-indole-2-carboxylate (2a)



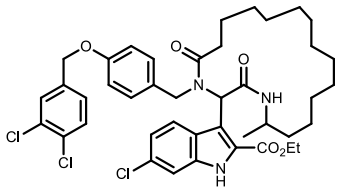
99% yield; *mixture of rotamers and diastereomers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.53 – 7.44 (m, 1H), 7.24 (d, *J* = 21.4 Hz, 4H), 7.11 (dd, *J* = 8.7, 1.5 Hz, 1H), 6.66 (dd, *J* = 27.4, 9.0 Hz, 4H), 6.20 (d, *J* = 8.9 Hz, 1H), 4.95 (s, 1H), 4.32 (p, *J* = 6.8 Hz, 2H), 4.05 (d, *J* = 6.5 Hz, 1H), 3.49 (s, 1H), 3.03 (t, *J* = 12.5 Hz, 1H), 2.53 – 2.43 (m, 1H), 2.36 (s, 1H), 1.56 (d, *J* = 40.5 Hz, 9H), 1.45 – 1.38 (m, 1H), 1.38 – 1.31 (m, 3H), 1.27 (d, *J* = 15.1 Hz, 14H), 1.22 – 1.09 (m, 3H), 1.04 (d, *J* = 6.1 Hz, 4H), 0.91 – 0.77 (m, 6H). 7.47 (d, *J* = 8.2 Hz, 1H), 7.26 (s, 2H), 7.22 (s, 1H), 7.11 (dd, *J* = 8.7, 1.5 Hz, 1H), 6.69 (d, *J* = 9.9 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.20 (d, *J* = 8.9 Hz, 1H), 4.95 (s, 1H), 4.32 (p, *J* = 6.8 Hz, 1H), 4.20 (s, 1H), 4.05 (d, *J* = 6.5 Hz, 1H), 3.49 (s, 1H), 1.60 (s, 5H), 1.52 (s, 2H), 1.45 – 1.39 (m, 1H), 1.38 – 1.32 (m, 2H), 1.27 (d, *J* = 15.1 Hz, 11H), 1.21 (s, 1H), 1.18 – 1.10 (m, 1H), 1.04 (d, *J* = 6.1 Hz, 3H), 0.87 (dq, *J* = 17.6, 9.3, 6.1 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 175.8, 169.2, 160.0, 157.2, 137.3, 135.7, 131.7, 130.6, 129.1, 126.4, 122.1, 115.5, 114.5, 112.2, 77.3, 77.0, 76.8, 68.4, 61.3, 58.4, 47.0, 45.7, 32.4, 31.9, 29.8, 29.7, 29.4, 26.9, 25.1, 24.4, 24.2, 22.9, 22.7, 14.5, 14.1; LC-MS (DAD/ESI): t_R = 3.48 min, Calcd for $C_{36}H_{38}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 696.19, found: $[M-H]^-$ 696.35.

Ethyl 6-chloro-3-(1-(4-((3,4-dichlorobenzyl)oxy)benzyl)-5-methyl-3,13-dioxo-1,4-diazacyclotridecan-2-yl)-1*H*-indole-2-carboxylate (2b)



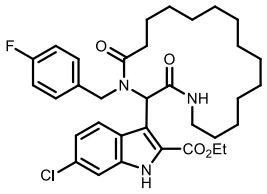
99% yield; *mixture of rotamers and diastereomers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.90 (s, 1H), 7.58 – 7.48 (m, 2H), 7.44 (s, 2H), 7.32 – 7.14 (m, 5H), 7.03 (s, 2H), 6.84 (d, *J* = 40.8 Hz, 2H), 6.68 (s, 2H), 4.95 (d, *J* = 20.5 Hz, 2H), 4.36 (s, 1H), 4.25 (s, 3H), 2.78 (s, 1H), 2.19 (s, 2H), 1.59 (d, *J* = 37.4 Hz, 2H), 1.51 – 1.38 (m, 5H), 1.28 (d, *J* = 20.0 Hz, 12H), 1.11 (s, 3H), 0.90 (d, *J* = 22.0 Hz, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 175.0, 170.3, 160.0, 157.5, 137.2, 136.0, 132.1, 131.3, 130.6, 129.6, 129.2, 129.2, 129.1, 126.5, 121.7, 121.4, 115.0, 114.7, 114.5, 112.7, 77.3, 77.1, 76.8, 68.5, 68.4, 61.3, 58.5, 45.4, 44.4, 43.0, 36.8, 32.8, 31.6, 31.5, 29.7, 26.0, 25.5, 24.5, 23.4, 22.4, 19.9, 19.0, 14.3; LC-MS (DAD/ESI): t_R = 3.42 min, Calcd for $C_{37}H_{40}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 710.20, found: $[M-H]^-$ 710.14.

Ethyl 6-chloro-3-(1-(4-((3,4-dichlorobenzyl)oxy)benzyl)-5-methyl-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1*H*-indole-2-carboxylate (2c)



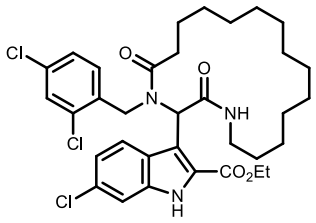
98% yield; *mixture of rotamers and diastereomers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.61 (d, *J* = 7.8 Hz, 1H), 7.45 (q, *J* = 11.0, 10.5 Hz, 3H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 14.4, 5.2 Hz, 3H), 7.09 (dt, *J* = 23.5, 11.5 Hz, 2H), 6.54 (d, *J* = 21.2 Hz, 3H), 4.87 (d, *J* = 27.2 Hz, 2H), 4.47 – 4.35 (m, 1H), 4.28 (dt, *J* = 16.4, 8.3 Hz, 1H), 4.18 – 4.06 (m, 1H), 3.90 (t, *J* = 6.1 Hz, 1H), 3.03 (t, *J* = 6.3 Hz, 1H), 1.83 (s, 1H), 1.52 – 1.13 (m, 28H), 1.09 (dd, *J* = 17.4, 6.3 Hz, 2H), 0.90 (dt, *J* = 17.2, 8.4 Hz, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 174.4, 169.6, 161.0, 156.7, 137.3, 136.5, 135.8, 131.8, 131.5, 131.4, 130.5, 129.0, 127.4, 127.0, 126.4, 126.3, 125.9, 123.0, 122.6, 122.4, 122.1, 119.4, 118.8, 114.5, 114.4, 114.2, 113.6, 111.7, 111.3, 77.3, 77.1, 76.8, 68.4, 62.6, 61.6, 57.7, 54.2, 49.2, 45.9, 45.0, 37.1, 36.7, 33.8, 33.5, 29.7, 28.8, 28.1, 28.0, 27.6, 27.5, 27.4, 27.2, 27.0, 26.8, 26.4, 26.1, 25.9, 25.5, 25.3, 24.9, 24.4, 22.7, 20.9, 20.6, 14.4, 14.1; LC-MS (DAD/ESI): t_R = 3.44 min, Calcd for $C_{42}H_{50}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 780.28, found: $[M-H]^-$ 780.27.

Ethyl 6-chloro-3-(1-(4-fluorobenzyl)-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1*H*-indole-2-carboxylate (2d)



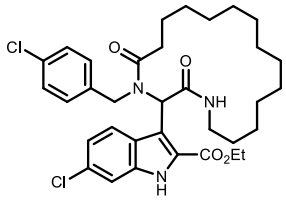
70% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.41 (s, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.41 (d, *J* = 8.9 Hz, 1H), 7.15 (s, 1H), 7.09 (dt, *J* = 14.9, 9.1 Hz, 2H), 7.03 – 6.95 (m, 1H), 6.91 (d, *J* = 13.3 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 3H), 6.51 (s, 3H), 6.35 (d, *J* = 21.7 Hz, 2H), 6.01 (s, 1H), 5.09 (d, *J* = 15.3 Hz, 1H), 4.73 (d, *J* = 17.3 Hz, 1H), 4.40 (d, *J* = 17.7 Hz, 1H), 4.35 – 4.17 (m, 3H), 3.79 (d, *J* = 15.4 Hz, 1H), 3.68 (ddd, *J* = 25.7, 13.0, 6.2 Hz, 1H), 3.48 (td, *J* = 15.4, 14.7, 7.7 Hz, 2H), 3.36 (d, *J* = 6.4 Hz, 1H), 3.08 (d, *J* = 6.7 Hz, 1H), 2.83 (dd, *J* = 15.8, 7.5 Hz, 1H), 2.54 – 2.43 (m, 2H), 2.33 – 2.22 (m, 1H), 1.87 – 1.77 (m, 3H), 1.63 – 1.45 (m, 7H), 1.46 – 1.19 (m, 34H), 0.94 – 0.83 (m, 1H); ^{13}C NMR (126 MHz, CDCl3) δ [ppm]. 174.8, 174.2, 170.3, 170.0, 160.0, 135.8, 134.5, 133.6, 131.5, 127.7, 127.0, 126.6, 124.9, 122.8, 122.3, 121.2, 114.8, 114.6, 114.1, 114.0, 112.4, 112.0, 100.0, 77.3, 77.1, 76.8, 61.5, 61.2, 56.6, 54.9, 49.2, 46.6, 40.1, 39.5, 33.5, 33.4, 29.6, 29.0, 28.5, 28.0, 27.8, 27.6, 27.4, 27.1, 27.0, 26.7, 26.4, 26.2, 26.1, 25.5, 25.1, 24.4, 14.3; LC-MS (DAD/ESI): t_R = 3.18 min, Calcd for $C_{34}H_{43}ClFN_3O_4$ (m/z): $[M-H]^-$ 610.29, found: $[M-H]^-$ 610.24.

Ethyl 6-chloro-3-(1-(2,4-dichlorobenzyl)-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1*H*-indole-2-carboxylate (2e)



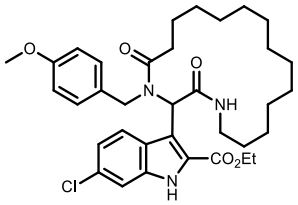
92% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.34 (d, *J* = 24.1 Hz, 1H), 9.13 (d, *J* = 11.7 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.47 (dq, *J* = 36.4, 13.9, 11.4 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.27 (d, *J* = 6.3 Hz, 1H), 7.19 (d, *J* = 9.7 Hz, 1H), 7.14 (d, *J* = 10.9 Hz, 1H), 7.06 (dd, *J* = 14.0, 7.5 Hz, 3H), 6.97 – 6.90 (m, 1H), 6.83 (s, 1H), 6.77 (dd, *J* = 20.0, 7.1 Hz, 1H), 5.91 (s, 1H), 5.10 – 4.96 (m, 1H), 4.66 (t, *J* = 15.9 Hz, 1H), 4.45 – 4.22 (m, 3H), 4.13 (d, *J* = 16.8 Hz, 1H), 3.53 – 3.43 (m, 1H), 3.43 – 3.29 (m, 1H), 3.15 – 3.06 (m, 1H), 2.14 (dt, *J* = 16.4, 9.7 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.80 (s, 1H), 1.63 – 1.05 (m, 27H), 0.92 – 0.79 (m, 1H); ^{13}C NMR (126 MHz, CDCl3) δ [ppm] 174.1, 169.5, 160.9, 160.3, 136.0, 135.7, 133.8, 133.0, 132.3, 132.1, 131.9, 131.5, 129.4, 128.8, 128.2, 128.0, 127.8, 126.9, 126.7, 125.8, 125.3, 124.7, 123.3, 122.8, 122.6, 121.5, 114.8, 112.1, 111.9, 77.3, 77.1, 76.8, 61.7, 61.5, 56.5, 55.1, 47.5, 45.2, 45.1, 40.2, 40.1, 39.6, 33.7, 33.2, 33.1, 31.7, 29.7, 29.6, 29.4, 29.0, 28.6, 28.2, 28.0, 27.9, 27.8, 27.5, 27.5, 27.4, 27.2, 27.2, 27.1, 27.0, 26.9, 26.7, 26.4, 26.2, 26.1, 25.6, 24.8, 24.3, 14.5, 14.2; LC-MS (DAD/ESI): t_R = 4.42 min, Calcd for $C_{34}H_{42}Cl_3N_3O_4$ (m/z): $[M-H]^-$ 660.22, found: $[M-H]^-$ 660.01.

Ethyl 6-chloro-3-(1-(4-chlorobenzyl)-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1*H*-indole-2-carboxylate (2f)



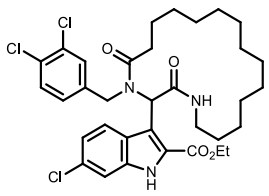
99% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 10.60 (d, *J* = 10.3 Hz, 1H), 10.53 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.55 (t, *J* = 9.0 Hz, 1H), 7.33 – 7.21 (m, 2H), 7.09 (d, *J* = 8.7 Hz, 1H), 7.05 – 6.99 (m, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 14.2 Hz, 1H), 6.79 (dd, *J* = 8.2, 3.6 Hz, 2H), 6.64 (dd, *J* = 17.3, 8.0 Hz, 2H), 6.47 (d, *J* = 12.7 Hz, 1H), 6.30 (d, *J* = 8.1 Hz, 2H), 6.24 (s, 1H), 5.22 (d, *J* = 15.6 Hz, 1H), 4.28 (dt, *J* = 18.1, 9.0 Hz, 2H), 3.79 – 3.72 (m, 1H), 3.56 (dq, *J* = 19.8, 6.5, 6.0 Hz, 1H), 3.13 (dd, *J* = 12.7, 6.1 Hz, 1H), 2.97 (dd, *J* = 12.0, 5.0 Hz, 1H), 2.75 (dt, *J* = 15.1, 6.4 Hz, 1H), 2.47 (dq, *J* = 22.3, 14.3, 11.4 Hz, 2H), 2.25 – 2.15 (m, 1H), 1.86 – 1.75 (m, 2H), 1.62 – 1.14 (m, 38H), 0.94 – 0.80 (m, 1H).; ^{13}C NMR (126 MHz, CDCl3) δ [ppm] 174.4, 173.9, 170.3, 170.1, 161.0, 160.3, 138.0, 137.0, 136.2, 132.0, 131.2, 131.0, 127.9, 127.5, 127.3, 127.1, 127.1, 126.6, 125.4, 124.9, 122.7, 122.2, 122.0, 121.3, 114.3, 114.1, 112.5, 112.2, 77.5, 77.2, 77.0, 61.2, 61.0, 56.2, 56.0, 54.8, 49.2, 47.1, 47.0, 40.1, 40.0, 40.0, 39.8, 39.5, 39.3, 33.3, 33.1, 32.4, 29.6, 29.4, 28.9, 28.6, 28.0, 27.7, 27.5, 27.4, 27.3, 27.2, 27.1, 27.0, 26.9, 26.7, 26.4, 26.1, 26.1, 25.5, 25.3, 25.0, 24.4, 23.7, 14.5, 14.3; LC-MS (DAD/ESI): t_R = 3.26 min, Calcd for $C_{34}H_{43}Cl_2N_3O_4$ (m/z): $[M-H]^-$ 626.26 found: $[M-H]^-$ 626.42.

Ethyl 6-chloro-3-(1-(4-methoxybenzyl)-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1H-indole-2-carboxylate (2g)



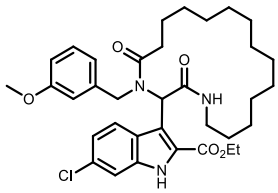
89% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.36 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.21 – 7.01 (m, 2H), 6.96 (d, *J* = 22.9 Hz, 1H), 6.61 (d, *J* = 7.3 Hz, 1H), 6.52 (t, *J* = 12.1 Hz, 2H), 6.44 (s, 2H), 4.68 (d, *J* = 17.6 Hz, 1H), 4.45 – 4.20 (m, 3H), 3.66 (s, 3H), 3.57 – 3.43 (m, 1H), 2.56 – 2.43 (m, 1H), 2.33 – 2.22 (m, 1H), 1.82 (s, 2H), 1.57 (s, 1H), 1.48 (s, 3H), 1.45 – 1.27 (m, 22H), 1.26 (s, 1H); ^{13}C NMR (126 MHz, CDCl3) δ [ppm] 174.8, 174.3, 170.5, 170.1, 160.9, 158.3, 135.9, 131.4, 129.8, 127.9, 127.1, 126.4, 125.7, 123.1, 122.1, 121.5, 114.9, 113.4, 113.1, 112.4, 111.9, 77.3, 77.1, 76.8, 61.5, 61.2, 57.1, 55.2, 55.0, 49.2, 46.3, 40.0, 39.5, 33.6, 29.4, 29.0, 28.6, 28.0, 27.8, 27.6, 27.5, 27.3, 27.0, 26.9, 26.6, 26.4, 26.2, 26.1, 25.6, 25.1, 24.5, 14.3; LC-MS (DAD/ESI): t_R = 3.33 min, Calcd for $C_{35}H_{46}ClN_3O_5$ (m/z): $[M-H]^-$ 622.31, found: $[M-H]^-$ 622.35.

Ethyl 6-chloro-3-(1-(3,4-dichlorobenzyl)-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1H-indole-2-carboxylate (2h)



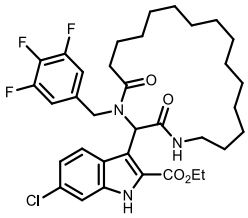
99% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.12 (s, 1H), 8.97 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.49 (d, *J* = 15.9 Hz, 1H), 6.32 (s, 1H), 6.23 (d, *J* = 7.6 Hz, 1H), 6.04 (s, 1H), 5.86 (s, 1H), 5.28 (d, *J* = 15.7 Hz, 1H), 4.75 (d, *J* = 17.7 Hz, 1H), 4.50 – 4.38 (m, 1H), 4.32 (p, *J* = 7.4, 6.9 Hz, 2H), 3.65 (dd, *J* = 5.7, 3.3 Hz, 1H), 3.53 (dd, *J* = 13.1, 6.3 Hz, 1H), 3.29 (dd, *J* = 13.0, 6.3 Hz, 2H), 3.02 – 2.87 (m, 1H), 2.80 (dt, *J* = 15.0, 8.0 Hz, 1H), 2.48 (dq, *J* = 19.3, 10.9, 9.3 Hz, 1H), 2.30 – 2.21 (m, 2H), 2.07 (s, 1H), 1.89 – 1.75 (m, 2H), 1.65 – 1.46 (m, 4H), 1.46 – 1.27 (m, 21H), 1.25 (d, *J* = 6.1 Hz, 1H), 0.90 (dt, *J* = 16.5, 7.1 Hz, 1H); ^{13}C NMR (126 MHz, CDCl3) δ [ppm] 174.9, 170.1, 160.0, 139.5, 135.8, 132.1, 131.3, 130.0, 129.3, 128.0, 127.3, 125.8, 125.1, 124.7, 123.2, 122.9, 121.5, 115.0, 112.5, 112.1, 77.5, 77.2, 77.0, 70.8, 70.2, 69.3, 63.9, 62.0, 61.8, 56.4, 54.8, 49.1, 46.8, 40.4, 39.7, 33.6, 33.4, 31.9, 29.9, 29.7, 29.2, 28.8, 28.2, 28.0, 27.8, 27.5, 27.4, 27.3, 27.1, 26.9, 26.7, 26.4, 26.3, 25.6, 25.3, 24.6, 14.6. LC-MS (DAD/ESI): t_R = 3.34 min, Calcd for $C_{34}H_{42}Cl_3N_3O_4$ (m/z): $[M-H]^-$ 660.22, found: $[M-H]^-$ 660.15.

Ethyl 6-chloro-3-(1-(3-methoxybenzyl)-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1*H*-indole-2-carboxylate (2i)



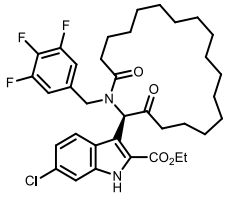
91% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.27 – 9.12 (m, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.41 (dd, *J* = 19.7, 8.6 Hz, 1H), 7.16 (d, *J* = 15.9 Hz, 1H), 7.09 (t, *J* = 8.7 Hz, 1H), 6.98 (s, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.62 – 6.45 (m, 2H), 6.30 (dd, *J* = 13.6, 6.6 Hz, 1H), 6.15 (d, *J* = 12.3 Hz, 1H), 6.08 (d, *J* = 7.2 Hz, 1H), 5.97 (s, 1H), 4.93 (d, *J* = 14.4 Hz, 1H), 4.74 (d, *J* = 17.5 Hz, 1H), 4.44 (d, *J* = 17.6 Hz, 1H), 4.39 – 4.24 (m, 2H), 3.97 (d, *J* = 14.9 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.72 (dd, *J* = 13.1, 5.8 Hz, 2H), 3.64 – 3.57 (m, 1H), 3.47 (d, *J* = 24.1 Hz, 4H), 3.34 – 3.21 (m, 1H), 3.07 (dd, *J* = 12.2, 5.8 Hz, 1H), 2.92 – 2.78 (m, 1H), 2.56 – 2.46 (m, 1H), 2.25 (dd, *J* = 14.7, 6.3 Hz, 1H), 1.83 (s, 2H), 1.63 – 1.19 (m, 29H), 0.90 (dt, *J* = 20.8, 7.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 174.3, 170.0, 160.9, 159.4, 139.7, 135.9, 131.4, 129.0, 128.6, 123.1, 122.3, 118.7, 117.5, 114.8, 112.7, 112.4, 111.8, 111.1, 110.5, 77.3, 77.1, 76.8, 61.6, 61.3, 56.9, 54.9, 54.7, 49.8, 47.1, 40.0, 39.5, 33.6, 29.4, 29.0, 28.6, 28.0, 27.8, 27.6, 27.4, 27.1, 27.0, 26.6, 26.4, 26.2, 26.1, 25.5, 25.1, 24.6, 14.4, 14.3; LC-MS (DAD/ESI): t_R = 3.31 min, Calcd for $C_{35}H_{46}ClN_3O_5$ (m/z): $[M-H]^-$ 622.31, found: $[M-H]^-$ 622.17.

Ethyl 6-chloro-3-(3,19-dioxo-1-(3,4,5-trifluorobenzyl)-1,4-diazacyclononadecan-2-yl)-1*H*-indole-2-carboxylate (2j)



87% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, CDCl3) δ [ppm] 9.27 – 9.12 (m, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.41 (dd, *J* = 19.7, 8.6 Hz, 1H), 7.16 (d, *J* = 15.9 Hz, 1H), 7.09 (t, *J* = 8.7 Hz, 1H), 6.98 (s, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.62 – 6.45 (m, 2H), 6.30 (dd, *J* = 13.6, 6.6 Hz, 1H), 6.15 (d, *J* = 12.3 Hz, 1H), 6.08 (d, *J* = 7.2 Hz, 1H), 5.97 (s, 1H), 4.93 (d, *J* = 14.4 Hz, 1H), 4.74 (d, *J* = 17.5 Hz, 1H), 4.44 (d, *J* = 17.6 Hz, 1H), 4.39 – 4.24 (m, 2H), 3.97 (d, *J* = 14.9 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.72 (dd, *J* = 13.1, 5.8 Hz, 2H), 3.64 – 3.57 (m, 1H), 3.47 (d, *J* = 24.1 Hz, 4H), 3.34 – 3.21 (m, 1H), 3.07 (dd, *J* = 12.2, 5.8 Hz, 1H), 2.92 – 2.78 (m, 1H), 2.56 – 2.46 (m, 1H), 2.25 (dd, *J* = 14.7, 6.3 Hz, 1H), 1.83 (s, 2H), 1.63 – 1.19 (m, 29H), 0.90 (dt, *J* = 20.8, 7.2 Hz, 1H); ^{13}C NMR (126 MHz, CDCl3) δ [ppm] 174.6, 169.7, 160.0, 135.5, 132.2, 126.9, 124.9, 123.2, 121.3, 114.8, 112.2, 109.9, 109.7, 77.0, 76.8, 61.7, 55.9, 54.7, 46.7, 40.2, 33.1, 29.4, 28.4, 28.2, 27.8, 27.6, 26.9, 26.8, 26.6, 26.2, 26.2, 25.8, 24.6, 14.3; LC-MS (DAD/ESI): t_R = 3.16 min, Calcd for $C_{35}H_{43}ClF_3N_3O_4$ (m/z): $[M+2-H]^-$ 662.29, found: $[M+2-H]^-$ 662.29.

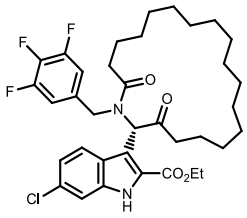
(+)-ethyl 6-chloro-3-(3,19-dioxo-1-(3,4,5-trifluorobenzyl)azacyclononadecan-2-yl)-1*H*-indole-2-carboxylate (2ja)



Chiral column t_R = 12.84 min, HRMS: Calcd for $C_{35}H_{43}ClF_3N_3O_4$ (m/z): $[M+2-H]^-$ 662.2942, found: $[M+2-H]^-$ 662.2967.

$[\alpha]_D^{20}$= + 31.5° (c = 0.67, MeOH)

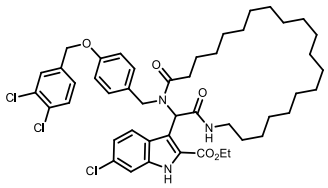
(-)-ethyl 6-chloro-3-(3,19-dioxo-1-(3,4,5-trifluorobenzyl)azacyclononadecan-2-yl)-1*H*-indole-2-carboxylate (2jb)



Chiral column t_R = 17.83 min, HRMS: Calcd for $C_{35}H_{43}ClF_3N_3O_4$ (m/z): $[M+2-H]^-$ 662.2942, found: $[M+2-H]^-$ 662.2968.

$[\alpha]_D^{20}$= - 32.9° (c = 1.47, MeOH)

Ethyl 6-chloro-3-(1-(4-((3,4-dichlorobenzyl)oxy)benzyl)-3,24-dioxo-1,4-diazacyclotetracosan-2-yl)-1*H*-indole-2-carboxylate (2k)

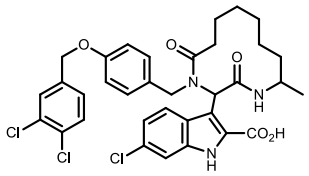


95% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.89 (d, J = 8.7 Hz, 1H), 7.78 (dd, J = 24.4, 8.8 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.42 (d, J = 26.5 Hz, 3H), 7.35 (dd, J = 18.8, 5.7 Hz, 1H), 7.27 (d, J = 8.2 Hz, 2H), 7.23 – 7.15 (m, 2H), 7.15 – 7.04 (m, 2H), 6.99 (dd, J = 16.2, 6.0 Hz, 1H), 6.94 – 6.87 (m, 1H), 6.53 (s, 2H), 6.46 (d, J = 7.4 Hz, 1H), 6.38 (s, 1H), 5.43 – 5.28 (m, 2H), 5.07 – 4.92 (m, 2H), 4.89 (d, J = 21.3 Hz, 2H), 4.70 (s, 1H), 4.42 (d, J = 15.2 Hz, 1H), 4.38 – 4.23 (m, 2H), 4.00 (d, J = 9.4 Hz, 1H), 3.80 (d, J = 8.7 Hz, 1H), 3.52 – 3.42 (m, 1H), 2.44 (s, 1H), 2.32 (td, J = 14.8, 13.9, 9.4 Hz, 2H), 2.04 (d, J = 29.8 Hz, 4H), 1.55 – 1.11 (m, 36H), 0.87 (q, J = 11.1, 8.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 136.2, 130.8, 130.5, 130.0, 129.2, 129.0, 129.0, 127.7, 126.5, 126.4, 126.3, 124.7, 124.5, 124.0, 123.2, 123.2, 122.4, 115.1, 114.3, 113.9, 112.4, 112.1, 111.7, 77.3, 77.3, 77.0, 76.8, 68.6, 68.4, 61.3, 49.1, 40.0, 32.0, 31.9, 31.4, 30.2, 29.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.4, 28.9, 28.3, 28.1, 27.9, 27.2, 26.8, 26.7, 26.3, 26.1, 25.5, 22.7, 14.4, 14.1; LC-MS (DAD/ESI): t_R = 3.46 min, HRMS Calcd for $C_{47}H_{60}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 850.36, found: $[M-H]^-$ 850.51.

2.7. General procedure for the hydrolysis reaction

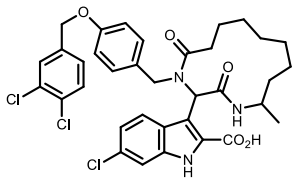
To a stirred solution of the corresponding compound **2** (1.0 equiv.) in ethanol-water (1:1), LiOH (10.0 equiv.) was added and the reaction mixture stirred at rt for 3 days. Afterwards, pH was adjusted to approximately 6 with the addition of 1 N HCl and then the reaction mixture extracted with DCM. The organic layer was separated, washed with water, dried over anhydrous $MgSO_4$ and evaporated, affording the corresponding compounds **1** (yields 11-70%) as a yellow-brown oils.

6-chloro-3-(1-(4-((3,4-dichlorobenzyl)oxy)benzyl)-5-methyl-3,12-dioxo-1,4-diazacyclododecan-2-yl)-1*H*-indole-2-carboxylic acid (1a)



70% yield; *mixture of rotamers and diastereomers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.49 (d, J = 20.5 Hz, 2H), 7.39 – 7.20 (m, 3H), 6.67 (d, J = 29.0 Hz, 2H), 6.21 (s, 1H), 4.95 (s, 2H), 4.51 – 3.97 (m, 2H), 1.58 (d, J = 70.1 Hz, 6H), 1.30 (d, J = 42.1 Hz, 12H), 1.04 (s, 2H), 0.86 (d, J = 16.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 169.3, 169.2, 160.0, 130.6, 129.1, 126.4, 122.1, 114.5, 112.2, 77.3, 77.0, 76.8, 68.4, 61.3, 47.0, 45.7, 29.7, 26.9, 24.2, 22.9, 14.5; LC-MS (DAD/ESI): t_R = 4.83 min, HRMS: Calcd for $C_{34}H_{34}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 668.1564, found: $[M-H]^-$ 668.1567.

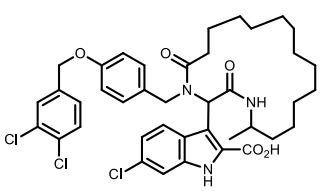
6-chloro-3-(1-(4-((3,4-dichlorobenzyl)oxy)benzyl)-5-methyl-3,13-dioxo-1,4-diazacyclotridecan-2-yl)-1*H*-indole-2-carboxylic acid (1b)



66% yield; *mixture of rotamers and diastereomers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 9.73 (s, 1H), 7.51 (d, J = 9.4 Hz, 1H), 7.44 (q, J = 10.2, 9.3 Hz, 2H), 7.33 – 7.14 (m, 4H), 7.13 – 7.02 (m, 2H), 6.91 (dd, J = 18.4, 8.7 Hz, 1H), 6.80 (d, J = 6.9 Hz, 1H), 6.69 (dd, J = 18.2, 8.3 Hz, 2H), 6.32 (d, J = 8.0 Hz, 2H), 4.98 (dd, J = 20.7, 13.0 Hz, 2H), 4.37 (d, J = 4.9 Hz, 1H), 4.24 (dd, J = 16.7, 7.0 Hz, 2H), 2.78 (s, 1H), 2.28 – 2.14 (m, 2H), 1.75 – 1.52 (m, 2H), 1.52 – 1.37 (m, 2H), 1.35 – 1.15 (m, 9H), 1.14 – 1.01 (m, 2H), 0.93 (d, J = 5.9 Hz, 1H), 0.87 (td, J = 12.4, 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 175.0, 170.3, 160.0, 157.5, 137.2, 136.0, 132.8, 132.1, 132.0, 131.5, 130.6, 129.6, 129.3, 129.2, 129.1, 127.9, 127.0, 126.5, 124.8, 121.9, 121.6, 115.0, 114.9, 114.7, 112.6, 77.3, 77.1, 76.8, 68.6, 68.4, 61.3, 58.4, 45.4, 44.4, 43.0, 36.8, 32.8, 31.6, 31.5, 29.7, 26.1, 25.5, 24.5, 23.4, 22.4, 19.9, 19.0, 14.3, 14.0; LC-MS (DAD/ESI): t_R = 4.27 min, HRMS: Calcd for $C_{35}H_{36}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 682.1721, found: $[M-H]^-$ 682.1723.

.

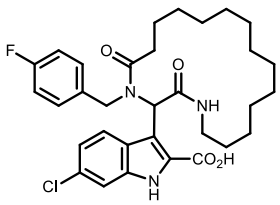
6-chloro-3-(1-(4-((3,4-dichlorobenzyl)oxy)benzyl)-5-methyl-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1*H*-indole-2-carboxylic acid (1c)



58% yield; *mixture of rotamers and diastereomers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 8.28 (s, 1H), 7.79 (s, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.47 (ddd, J = 33.2, 16.7, 9.2 Hz, 2H), 7.40 – 7.33 (m, 3H), 7.24 – 7.14 (m, 5H), 7.10 (dd, J = 16.7, 9.2 Hz, 4H), 6.68 (d, J = 35.9 Hz, 1H), 6.60 – 6.46 (m, 4H), 4.89 (d, J = 17.1 Hz, 1H), 4.79 (d, J = 17.4 Hz, 2H), 4.72 (s, 1H), 4.48 (d, J = 17.6 Hz, 1H), 4.11 (dq, J = 14.8, 6.9 Hz, 2H), 3.91 (t, J = 6.3 Hz, 1H), 3.03 (t, J = 6.3 Hz, 1H), 2.04 (s, 1H), 1.57 – 1.29 (m, 22H), 1.26 (q, J = 7.1, 6.5 Hz, 9H), 1.09 (td, J = 17.4, 16.6, 7.7 Hz, 2H), 1.02 – 0.80 (m, 5H); ^{13}C NMR (126 MHz, CDCl3) δ [ppm] 175.9, 156.9, 137.1, 136.5, 135.8, 131.5, 130.5, 129.1, 127.4, 126.4, 126.3, 122.6, 122.4, 122.1, 119.4, 118.8, 114.4, 112.1, 111.9, 111.3, 77.3, 77.0, 76.8, 68.4, 62.6, 60.5, 54.6, 49.5, 36.4, 33.6, 29.7, 28.6, 28.1, 27.9, 27.4, 27.3, 27.1, 26.8, 26.3, 25.3, 24.9, 20.7, 14.2; LC-MS (DAD/ESI): t_R = 3.69 min, HRMS: Calcd for $C_{40}H_{46}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 752.2503, found: $[M-H]^-$ 752.2508.

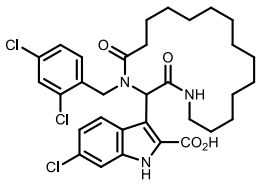
.

6-chloro-3-(1-(4-fluorobenzyl)-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1*H*-indole-2-carboxylic acid (1d)



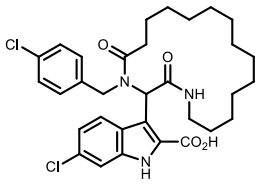
82% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]. 7.24 (s, 7H), 7.06 – 6.89 (m, 11H), 6.86 – 6.53 (m, 1H), 4.34 (d, J = 21.7 Hz, 6H), 3.47 – 3.34 (m, 1H), 3.14 (d, J = 5.5 Hz, 1H), 2.58 (s, 1H), 2.28 (t, J = 7.4 Hz, 2H), 2.20 (s, 6H), 1.62 (s, 9H), 1.48 (dd, J = 16.3, 9.6 Hz, 3H), 1.25 (s, 50H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]. 173.4, 134.7, 129.3, 115.3, 115.2, 77.4, 77.2, 76.9, 42.5, 40.4, 40.2, 40.0, 39.9, 39.7, 36.5, 34.2, 30.3, 29.4, 29.3, 26.9, 25.8, 24.9, 15.0; LC-MS (DAD/ESI): t_R = 4.03 min, Calcd for $C_{32}H_{39}ClFN_3O_4$ (m/z): $[M-H]^-$ 582.26 found: $[M-H]^-$ 582.29.

6-chloro-3-(1-(2,4-dichlorobenzyl)-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1*H*-indole-2-carboxylic acid (1e)



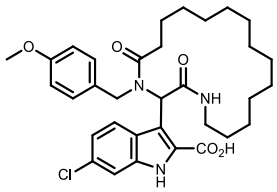
24% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]. 10.66 (s, 1H), 7.56 (d, J = 6.4 Hz, 1H), 7.49 (s, 1H), 7.31 (d, J = 26.5 Hz, 2H), 7.17 (d, J = 15.3 Hz, 2H), 7.05 (d, J = 7.1 Hz, 1H), 6.81 – 6.66 (m, 1H), 6.55 (d, J = 7.3 Hz, 1H), 5.36 (s, 1H), 4.43 (s, 1H), 3.40 (s, 1H), 2.61 (d, J = 16.6 Hz, 1H), 2.30 (d, J = 13.9 Hz, 1H), 2.23 (s, 1H), 1.94 (s, 1H), 1.62 (s, 2H), 1.47 (d, J = 15.8 Hz, 1H), 1.41 (s, 1H), 1.20 (d, J = 53.8 Hz, 15H), 0.88 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm]. 163.6, 137.5, 133.2, 130.3, 129.0, 127.1, 125.8, 123.1, 121.1, 116.0, 115.7, 112.1, 108.2, 77.5, 77.3, 77.0, 68.0, 40.5, 40.1, 40.0, 39.8, 39.6, 39.4, 36.3, 31.8, 29.6, 29.4, 29.2, 25.7, 14.1; LC-MS (DAD/ESI): t_R = 4.87 min, Calcd for $C_{32}H_{38}Cl_3N_3O_4$ (m/z): $[M-H]^-$ 632.19, found: $[M-H]^-$ 632.10.

6-chloro-3-(1-(4-chlorobenzyl)-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1*H*-indole-2-carboxylic acid (1f)



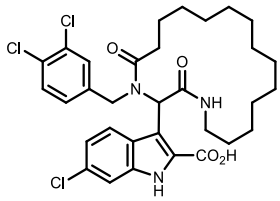
31% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 8.14 (d, J = 8.6 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 20.2 Hz, 1H), 7.24 (dd, J = 15.0, 6.4 Hz, 3H), 7.18 (dd, J = 11.9, 7.3 Hz, 3H), 7.08 (dt, J = 18.4, 9.9 Hz, 1H), 6.68 (d, J = 17.7 Hz, 1H), 4.43 – 4.37 (m, 1H), 4.33 (d, J = 9.8 Hz, 2H), 3.54 (d, J = 6.7 Hz, 1H), 3.38 (d, J = 6.1 Hz, 1H), 3.11 (d, J = 6.8 Hz, 1H), 2.31 (t, J = 7.3 Hz, 1H), 2.20 (dt, J = 12.5, 7.4 Hz, 3H), 2.06 – 1.98 (m, 1H), 1.73 – 1.51 (m, 5H), 1.50 – 1.40 (m, 1H), 1.38 – 1.00 (m, 32H), 0.93 – 0.81 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 170.2, 158.9, 137.1, 133.4, 130.9, 129.0, 128.8, 128.7, 128.7, 128.6, 123.4, 121.5, 116.6, 115.8, 111.9, 110.5, 108.8, 77.3, 77.3, 77.1, 76.8, 43.6, 42.8, 42.7, 40.7, 40.3, 38.7, 36.7, 36.6, 34.1, 30.0, 29.7, 29.4, 29.3, 29.3, 29.2, 29.1, 29.0, 28.8, 26.8, 26.7, 25.8, 24.9, 24.8, 15.2, 15.0; LC-MS (DAD/ESI): t_R = 4.10 min, Calcd for $C_{32}H_{39}Cl_2N_3O_4$ (m/z): $[M-H]^-$ 598.23, found: $[M-H]^-$ 598.21.

6-chloro-3-(1-(4-methoxybenzyl)-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1*H*-indole-2-carboxylic acid (1g)



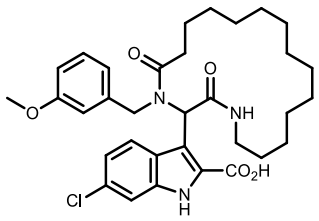
54% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.86 – 7.79 (m, 1H), 7.48 (d, J = 12.2 Hz, 1H), 7.33 (d, J = 26.8 Hz, 1H), 7.19 (d, J = 8.2 Hz, 3H), 7.08 – 6.98 (m, 1H), 6.95 – 6.88 (m, 1H), 6.87 – 6.79 (m, 2H), 6.66 (s, 1H), 6.65 – 6.54 (m, 2H), 6.50 (s, 1H), 4.40 – 4.30 (m, 2H), 3.77 (d, J = 6.4 Hz, 3H), 3.58 (s, 2H), 3.28 (s, 1H), 2.35 (dd, J = 12.9, 5.4 Hz, 1H), 2.20 (s, 2H), 1.62 (s, 3H), 1.51 (d, J = 7.2 Hz, 1H), 1.46 – 1.02 (m, 34H), 0.88 (dt, J = 17.8, 11.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 176.0, 173.9, 171.6, 159.4, 158.7, 152.1, 152.1, 145.2, 143.7, 141.1, 141.1, 133.9, 130.7, 129.6, 129.6, 128.2, 126.9, 123.4, 122.6, 117.2, 116.4, 114.5, 114.5, 114.0, 111.1, 109.1, 77.7, 77.7, 77.5, 77.2, 55.7, 55.6, 49.9, 43.6, 40.3, 37.2, 37.2, 34.1, 32.4, 30.1, 30.1, 29.9, 29.7, 29.7, 29.5, 28.5, 28.4, 28.3, 27.8, 27.4, 27.2, 26.8, 26.2, 26.0, 25.3, 23.1, 21.2, 14.6; LC-MS (DAD/ESI): t_R = 4.79 min, HRMS: Calcd for $C_{33}H_{42}ClN_3O_5$ (m/z): $[M-H]^-$ 594.2813, found: $[M-H]^-$ 594.2810.

6-chloro-3-(1-(3,4-dichlorobenzyl)-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1*H*-indole-2-carboxylic acid (1h)



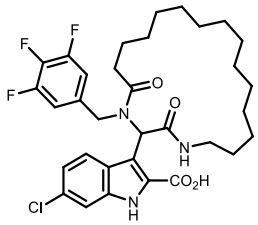
20% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.31 (s, 1H), 7.05 (s, 1H), 6.70 – 6.52 (m, 1H), 6.39 (d, J = 29.2 Hz, 1H), 4.32 (d, J = 32.3 Hz, 2H), 3.75 (s, 1H), 3.70 – 3.56 (m, 3H), 3.48 (s, 1H), 2.46 (s, 1H), 2.33 (s, 1H), 2.22 (s, 1H), 1.86 (s, 2H), 1.82 – 1.18 (m, 26H), 0.96 – 0.78 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 143.2, 130.6, 129.4, 127.0, 77.3, 77.0, 76.8, 68.0, 42.4, 36.6, 31.9, 29.7, 29.4, 29.2, 27.4, 26.9, 25.7, 25.6, 14.9, 14.1; LC-MS (DAD/ESI): t_R = 4.77 min, HRMS: Calcd for $C_{32}H_{38}Cl_3N_3O_4$ (m/z): $[M-H]^-$ 632.1928, found: $[M-H]^-$ 632.1928.

6-chloro-3-(1-(3-methoxybenzyl)-3,18-dioxo-1,4-diazacyclooctadecan-2-yl)-1*H*-indole-2-carboxylic acid (1i)



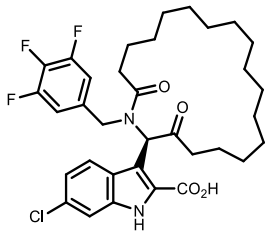
26% yield; *mixture of rotamers observed*; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.82 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.23 (dd, *J* = 10.7, 5.7 Hz, 3H), 7.13 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.05 – 6.98 (m, 2H), 6.94 (d, *J* = 6.7 Hz, 1H), 6.88 (d, *J* = 11.3 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 2H), 6.80 (d, *J* = 6.1 Hz, 4H), 6.68 – 6.63 (m, 1H), 6.63 – 6.57 (m, 1H), 6.50 (s, 1H), 5.93 (s, 1H), 4.40 (d, *J* = 5.6 Hz, 3H), 3.85 (d, *J* = 6.1 Hz, 1H), 3.78 (qd, *J* = 9.5, 8.6, 4.8 Hz, 6H), 3.65 (dd, *J* = 15.3, 8.6 Hz, 1H), 3.56 – 3.50 (m, 1H), 3.46 (s, 1H), 3.40 (d, *J* = 13.3 Hz, 2H), 3.09 (t, *J* = 6.9 Hz, 1H), 2.34 (q, *J* = 6.9 Hz, 1H), 2.27 – 2.18 (m, 3H), 1.63 (d, *J* = 7.0 Hz, 6H), 1.55 – 1.51 (m, 1H), 1.50 – 1.43 (m, 2H), 1.41 (s, 1H), 1.28 (ddd, *J* = 28.1, 21.4, 14.5 Hz, 56H), 0.98 – 0.92 (m, 1H), 0.87 (q, *J* = 11.5, 9.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 159.9, 133.5, 129.7, 120.0, 116.8, 116.0, 113.4, 112.9, 77.3, 77.0, 76.8, 55.2, 43.6, 39.6, 36.8, 34.0, 29.7, 29.4, 29.3, 29.1, 29.0, 26.9, 25.8, 24.7, 15.2; LC-MS (DAD/ESI): t_R = 4.78 min, HRMS: Calcd for $C_{33}H_{42}ClN_3O_5$ (m/z): $[M-H]^-$ 594.2813, found: $[M-H]^-$ 594.2817.

6-chloro-3-(3,19-dioxo-1-(3,4,5-trifluorobenzyl)-1,4-diazacyclononadecan-2-yl)-1*H*-indole-2-carboxylic acid (1j)



Racemic mixture: 45% yield; ^{1}H NMR (500 MHz DMSO-d_6) δ [ppm] 11.83 (d, *J* = 6.2 Hz, 1H), 7.63 (dt, *J* = 15.1, 9.5 Hz, 1H), 7.39 (dd, *J* = 24.6, 2.0 Hz, 1H), 7.26 (q, *J* = 6.1, 4.7 Hz, 1H), 7.22 – 7.02 (m, 3H), 6.24 – 6.17 (m, 1H), 6.12 (t, *J* = 7.9 Hz, 1H), 5.05 (dd, *J* = 20.6, 16.1 Hz, 1H), 4.35 (p, *J* = 7.3, 6.8 Hz, 1H), 4.23 (d, *J* = 5.9 Hz, 1H), 3.94 – 2.95 (m, 36H), 2.72 (s, 1H), 2.51 (d, *J* = 2.3 Hz, 8H), 2.18 – 2.07 (m, 1H), 1.63 (s, 2H), 1.61 – 1.40 (m, 3H), 1.33 (d, *J* = 4.7 Hz, 4H), 1.29 (s, 23H), 1.24 – 1.15 (m, 8H), 0.83 (s, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ [ppm] 174.9, 173.4, 173.0, 170.3, 170.0, 164.0, 162.6, 160.8, 153.0, 150.5, 148.5, 142.6, 137.8, 137.4, 136.5, 136.4, 136.3, 131.2, 130.0, 129.4, 128.7, 128.6, 127.5, 126.0, 125.8, 125.3, 125.1, 124.9, 122.2, 121.8, 114.8, 112.4, 111.9, 111.7, 110.7, 110.0, 90.7, 68.5, 61.4, 55.5, 47.2, 41.4, 40.5, 40.4, 40.3, 40.2, 40.2, 40.1, 40.0, 39.9, 39.8, 39.7, 39.6, 39.4, 39.3, 38.5, 35.7, 35.6, 35.5, 34.1, 34.1, 32.8, 31.2, 29.9, 29.5, 29.2, 28.7, 28.5, 28.3, 27.7, 27.4, 26.9, 26.2, 25.6, 24.8, 18.4; LC-MS (DAD/ESI): t_R = 3.96 min, HRMS: Calcd for $C_{33}H_{39}ClF_3N_3O_4$ (m/z): $[M-H]^-$ 632.2581, found: $[M-H]^-$ 632.2582.

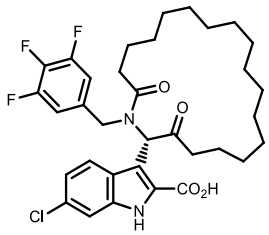
(+)-6-chloro-3-(3,19-dioxo-1-(3,4,5-trifluorobenzyl)azacyclononadecan-2-yl)-1*H*-indole-2-carboxylic acid (1ja)



68% yield; HRMS: Calcd for $C_{33}H_{39}ClF_3N_3O_4$ (m/z): $[M-H+2]^-$ 632.2629, found: $[M-H+2]^-$ 634.26563.

$[\alpha]_D^{20}$= + 36.6° (c = 1.00, MeOH)

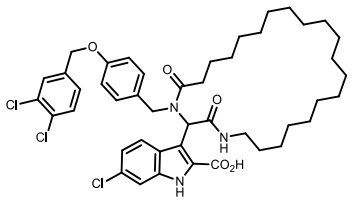
(-)-6-chloro-3-(3,19-dioxo-1-(3,4,5-trifluorobenzyl)azacyclononadecan-2-yl)-1*H*-indole-2-carboxylic acid (1jb)



66% yield; HRMS: Calcd for $C_{33}H_{39}ClF_3N_3O_4$ (m/z): $[M-H+2]^-$ 632.2629, found: $[M-H+2]^-$ 634.26563.

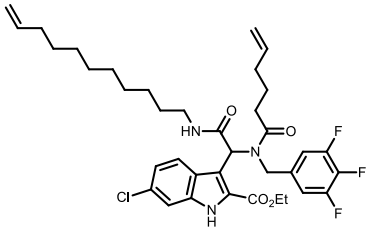
$[\alpha]_D^{20}$= - 29.62° (c = 1.08, MeOH)

6-chloro-3-(1-(4-((3,4-dichlorobenzyl)oxy)benzyl)-3,24-dioxo-1,4-diazacyclotetracosan-2-yl)-1*H*-indole-2-carboxylic acid (1k)

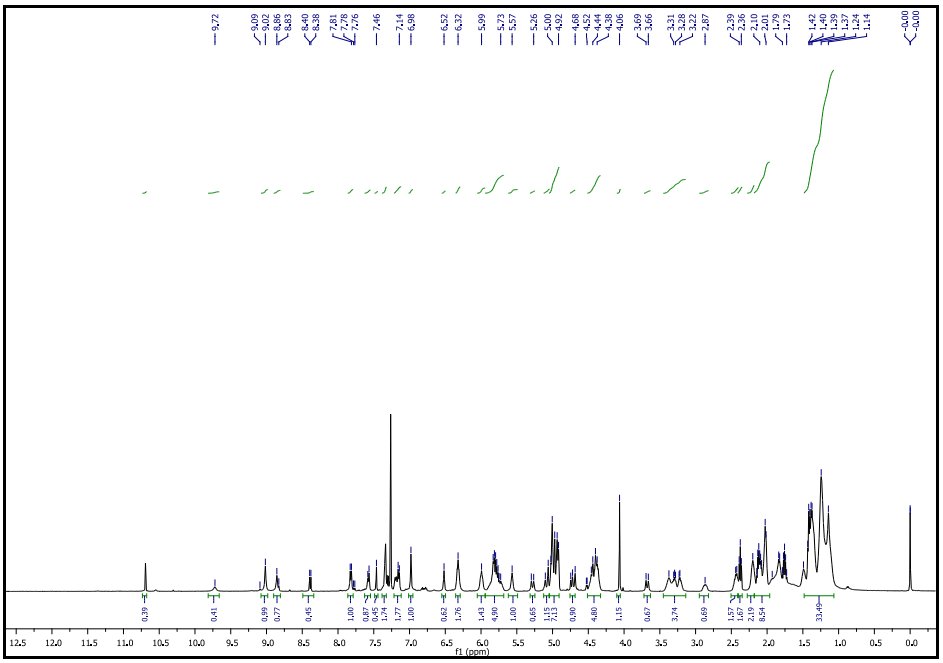


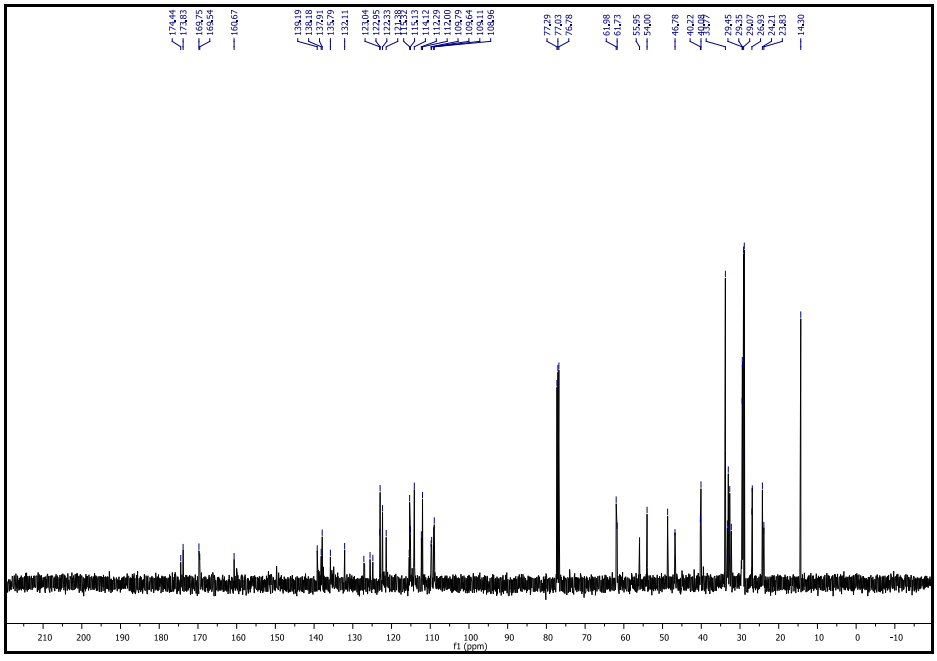
99% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.51 (s, 9H), 7.44 (s, 3H), 7.35 (d, *J* = 16.6 Hz, 2H), 7.14 (dd, *J* = 81.5, 42.4 Hz, 11H), 6.54 (s, 4H), 6.41 (d, *J* = 42.3 Hz, 1H), 4.91 (d, *J* = 58.1 Hz, 8H), 4.31 (d, *J* = 41.2 Hz, 3H), 2.26 (d, *J* = 68.1 Hz, 12H), 1.98 (d, *J* = 28.9 Hz, 6H), 1.73 – 1.04 (m, 43H), 0.88 (s, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ [ppm] 170.2, 160.0, 157.6, 156.6, 137.2, 135.7, 130.8, 130.5, 129.2, 129.0, 128.4, 126.4, 124.5, 115.0, 114.3, 113.9, 77.5, 77.3, 77.3, 77.0, 76.8, 68.5, 68.4, 61.3, 57.1, 52.1, 49.2, 46.5, 43.0, 40.0, 36.8, 33.8, 32.5, 32.0, 31.4, 30.2, 29.7, 29.6, 29.4, 28.9, 28.1, 27.2, 26.9, 26.8, 26.2, 25.6, 24.9, 22.7, 14.4, 14.1; LC-MS (DAD/ESI): t_R = 4.92 min, Calcd for $C_{45}H_{56}Cl_3N_3O_5$ (m/z): $[M-H]^-$ 822.23, found: $[M-H]^-$ 822.32.

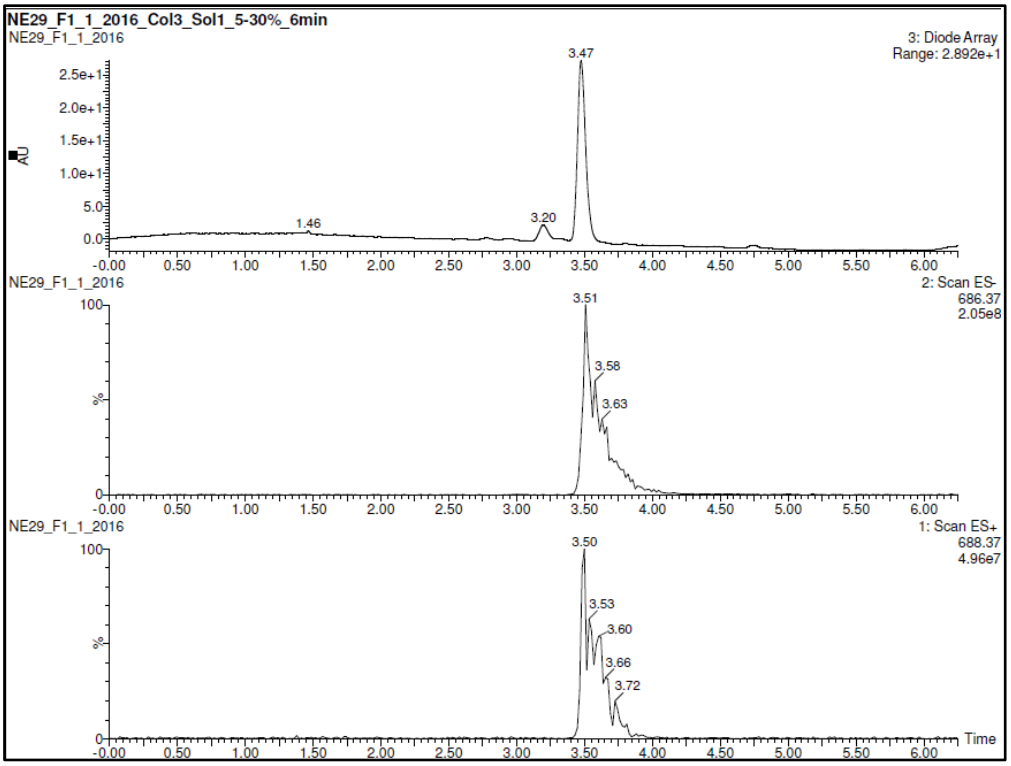
3. Exemplary copies of NMR and MS data of final compounds

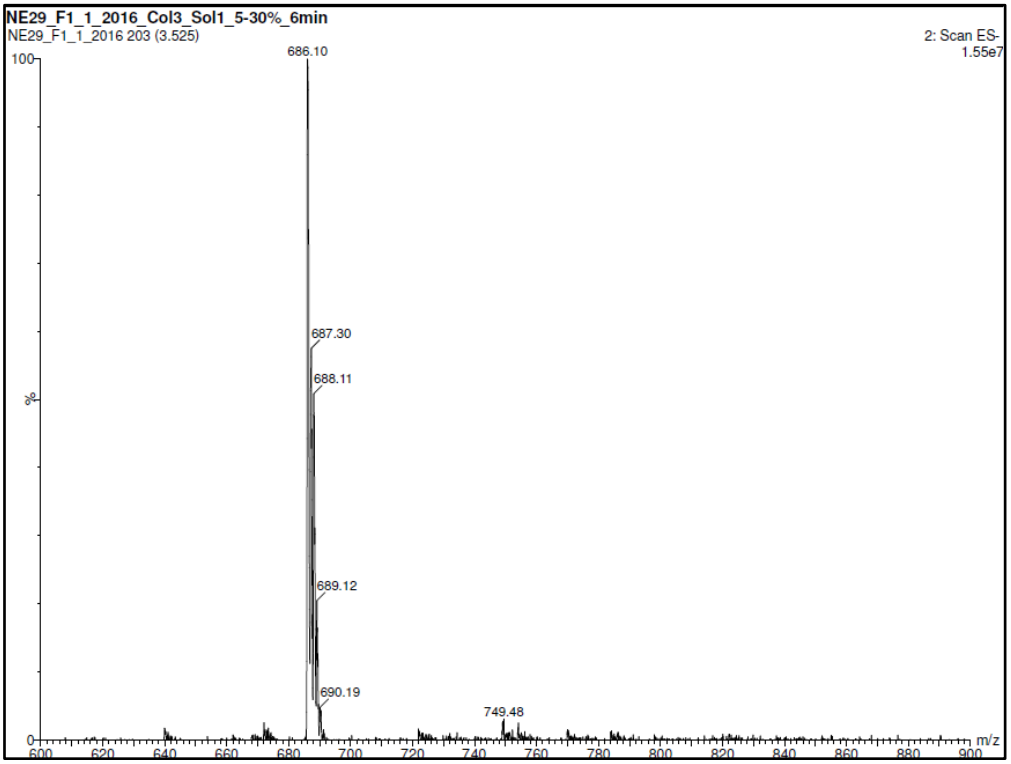


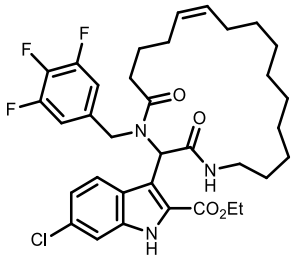
4j



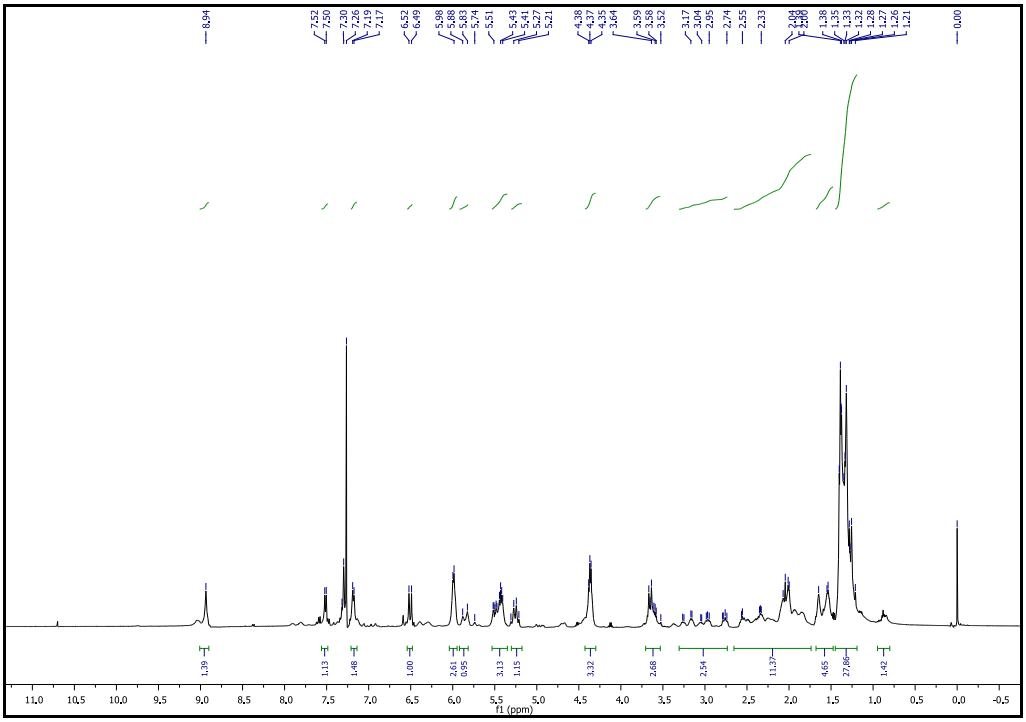


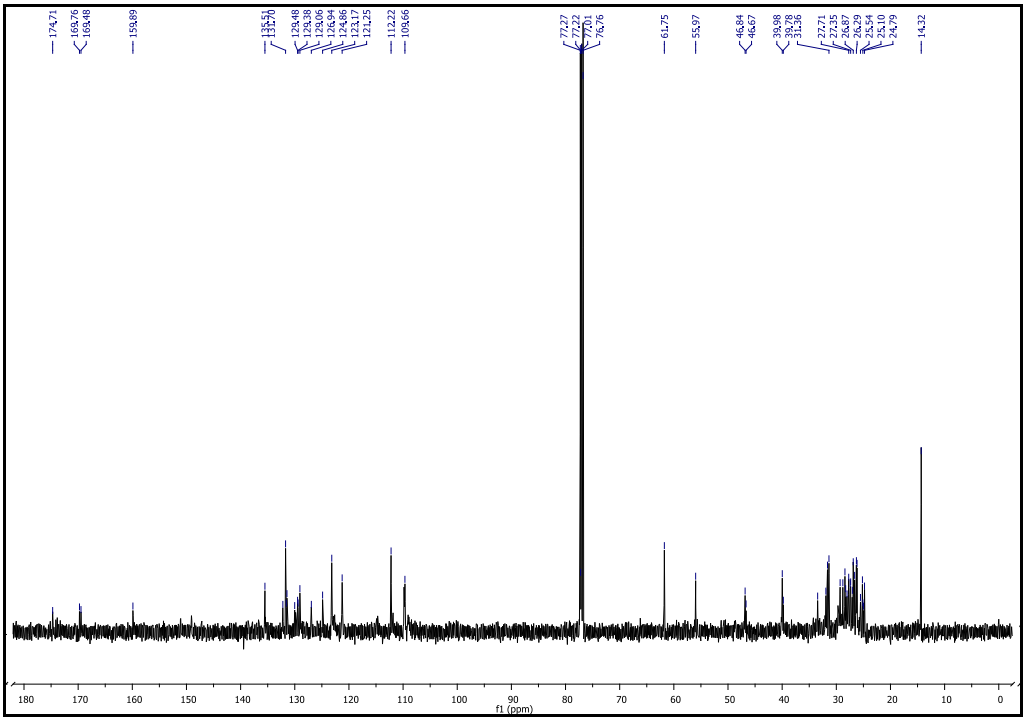

NE29_F1_1_2016_Col3_Sol1_5-30%_6min
NE29_F1_1_2016
3: Diode Array
Range: 2.892e+1
AU
3.47
3.20
1.46
NE29_F1_1_2016
2: Scan ES-
686.37
2.05e8
%
3.51
3.58
3.63
NE29_F1_1_2016
1: Scan ES+
688.37
4.96e7
%
3.50
3.53
3.60
3.66
3.72
Time

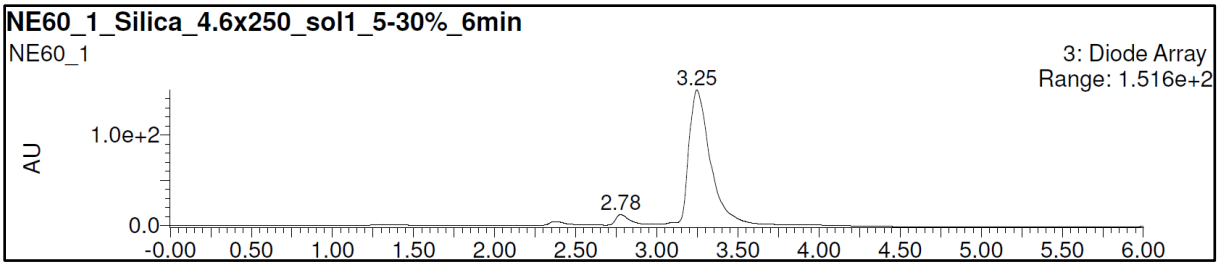

NE29_F1_1_2016_Col3_Sol1_5-30%_6min
NE29_F1_1_2016 203 (3.525)
2: Scan ES-
1.55e7
%
686.10
687.30
688.11
689.12
690.19
749.48
m/z

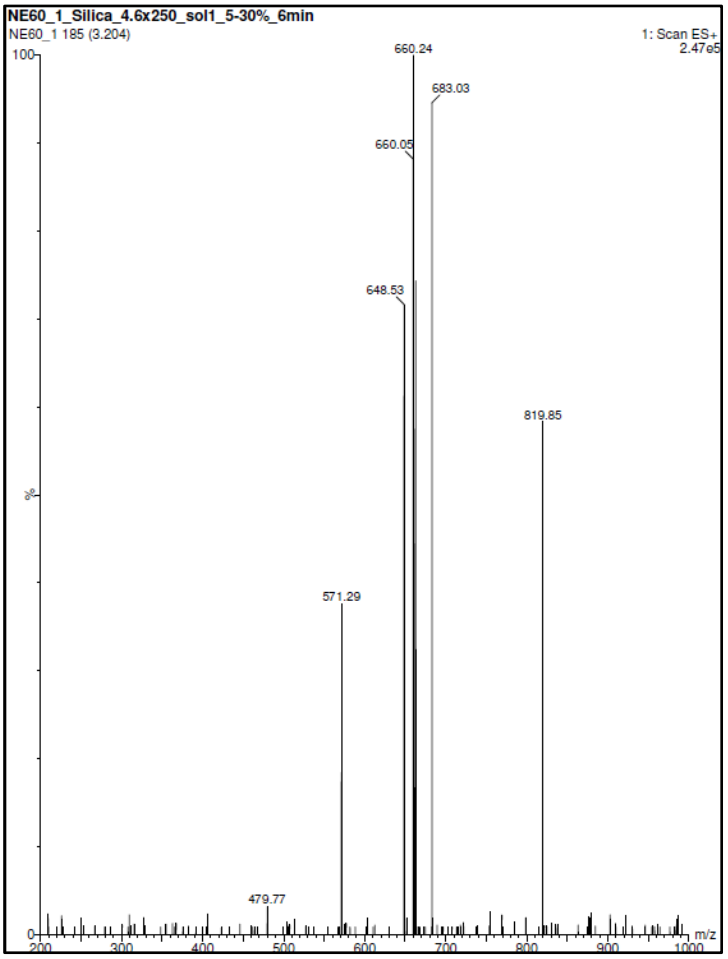


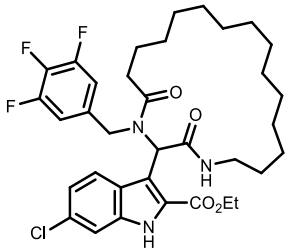
3j



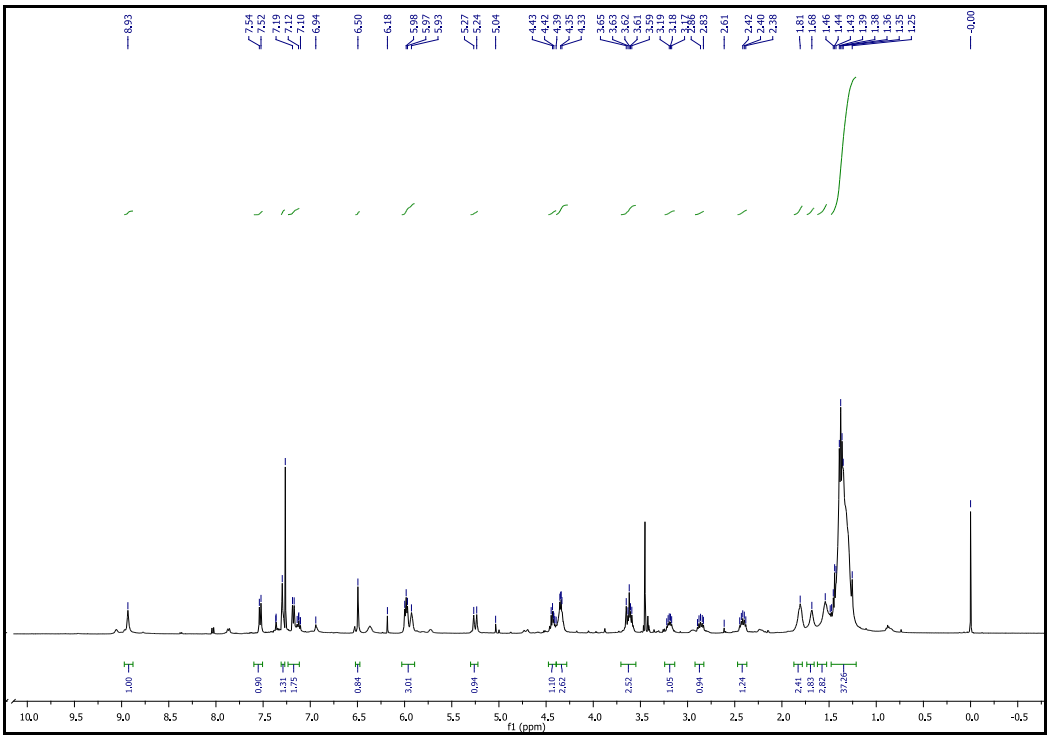


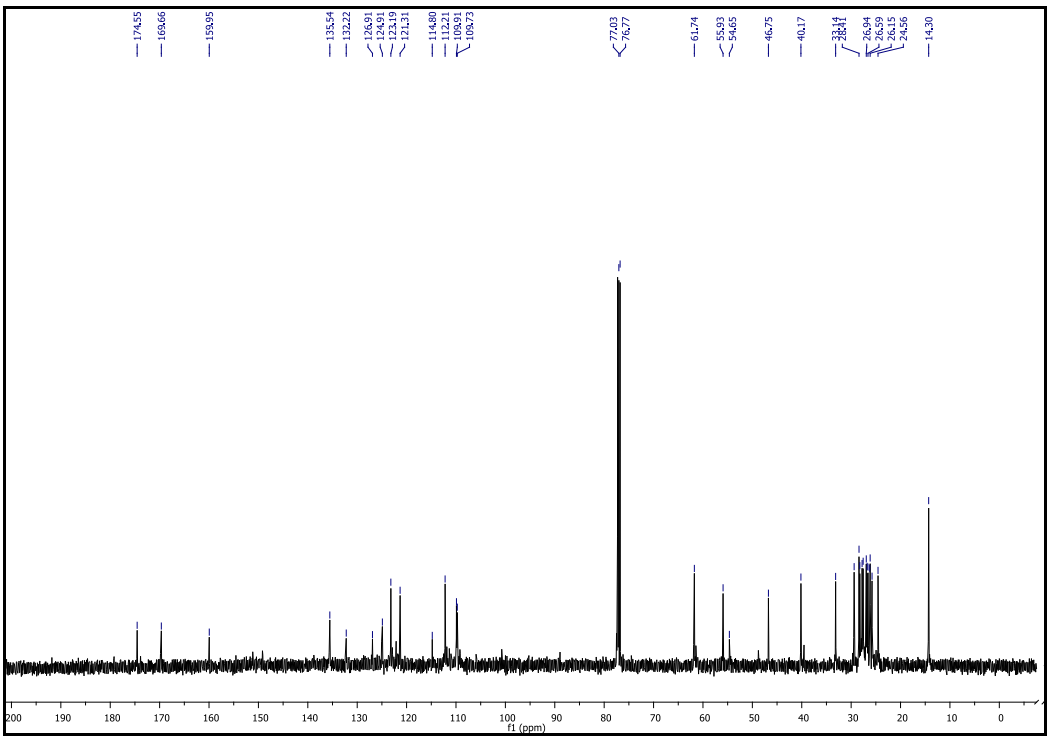

NE60_1_Silica_4.6x250_sol1_5-30%_6min
NE60_1
3: Diode Array
Range: 1.516e+2
AU
1.0e+2
0.0
3.25
2.78
-0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00

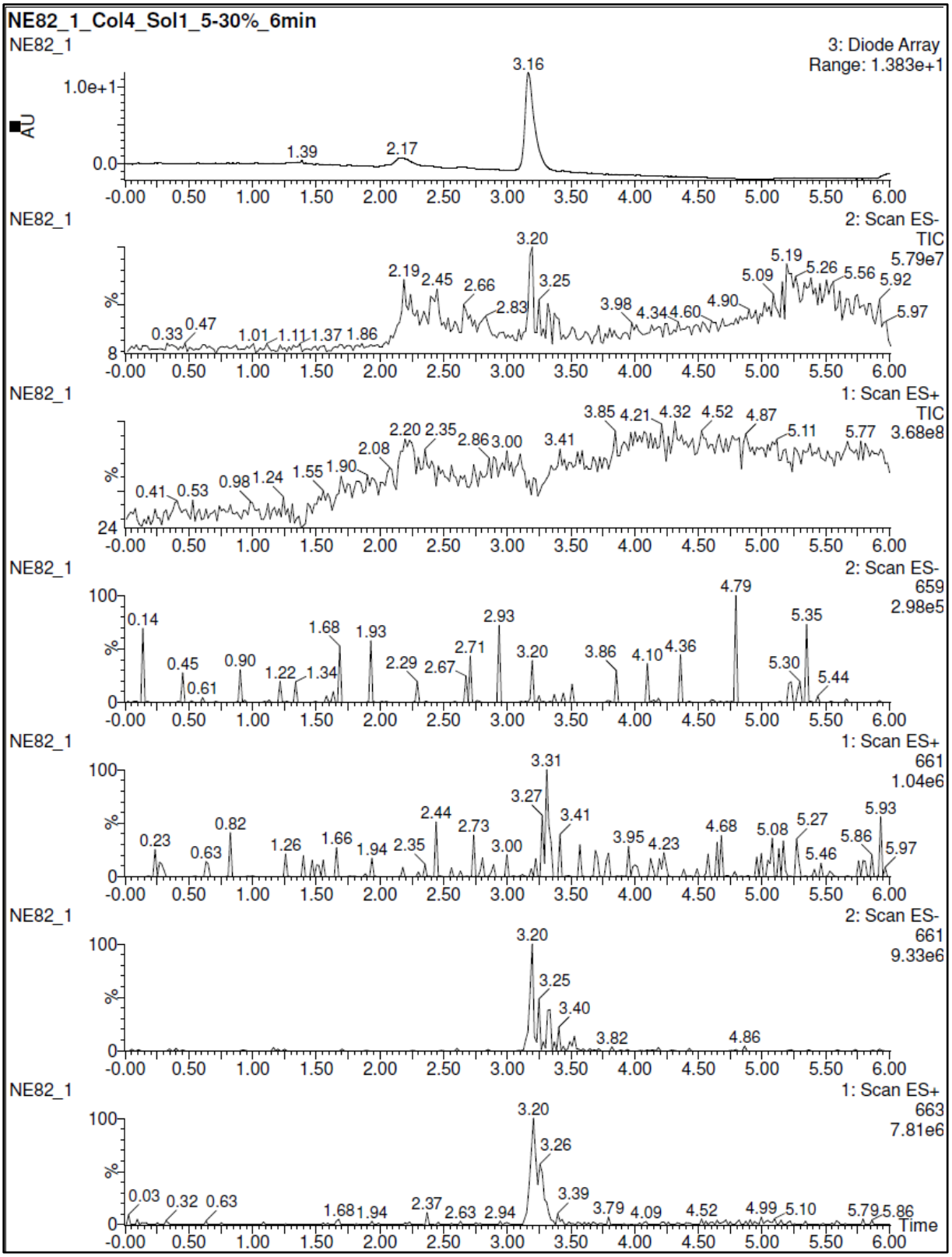

NE60_1_Silica_4.6x250_sol1_5-30%_6min
NE60_1 185 (3.204)
1: Scan ES+
2.47e5
100
%
0
660.24
683.03
660.05
648.53
819.85
571.29
479.77
200
300
400
500
600
700
800
900
1000
m/z

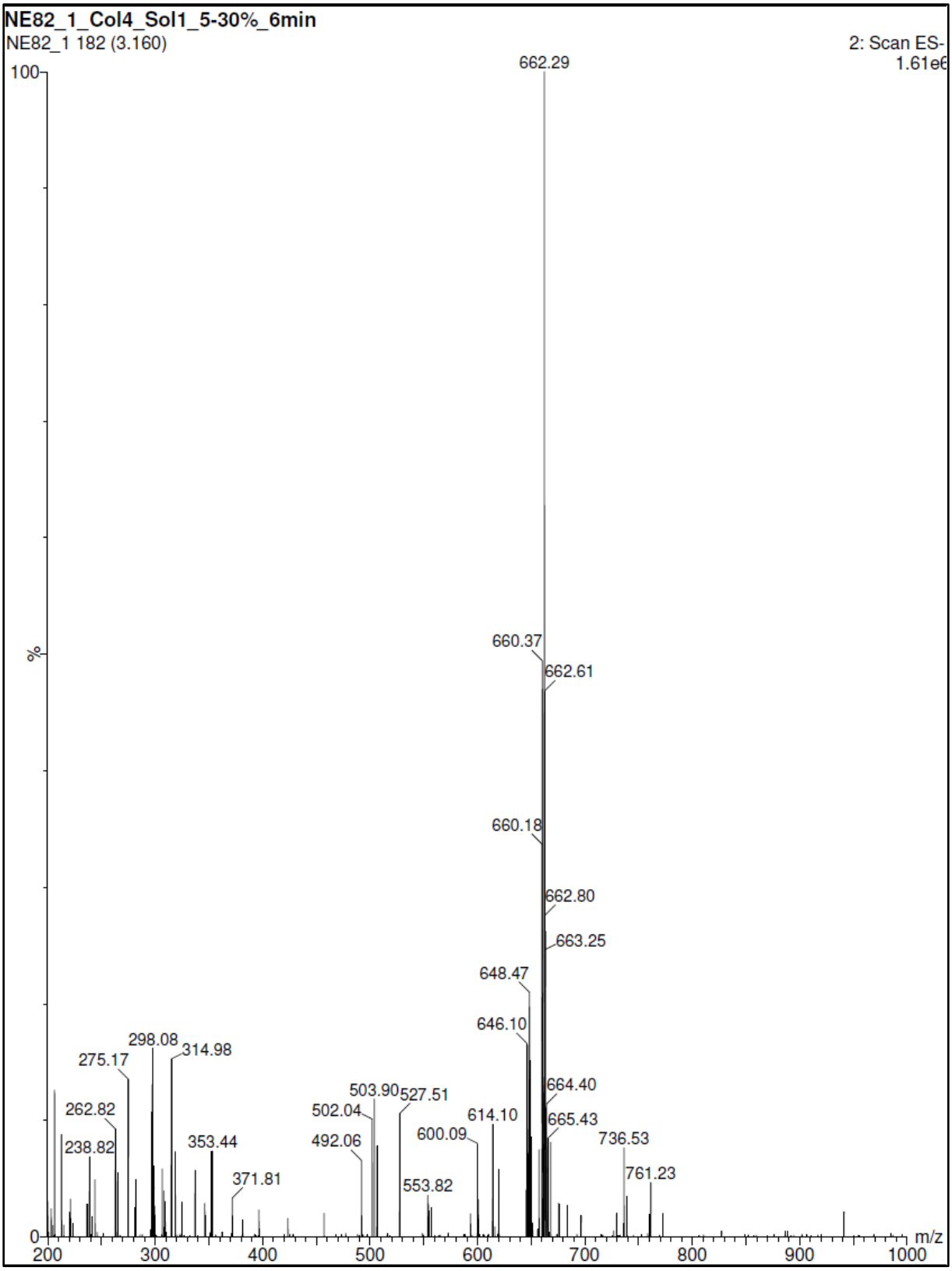

F
F
F
O
N
O
N
H
CO2Et
N
H
Cl

2j


8.93
7.54
7.52
7.19
7.12
7.10
6.94
6.50
6.18
5.98
5.97
5.93
5.27
5.24
5.04
4.43
4.42
4.39
4.35
4.33
3.65
3.63
3.62
3.61
3.59
3.19
3.18
3.17
2.86
2.83
2.61
2.42
2.40
2.38
1.81
1.68
1.46
1.44
1.43
1.39
1.38
1.36
1.35
1.25
0.00
1.00
0.90
1.31
1.75
0.84
3.01
0.94
1.10
2.62
2.52
1.05
0.94
1.24
2.41
1.83
2.82
37.26
f1 (ppm)

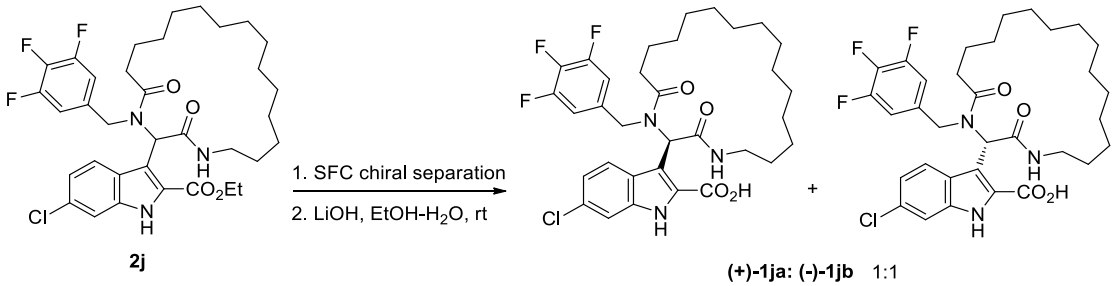

174.55
169.66
159.95
135.54
132.22
126.91
124.91
123.19
121.31
114.80
112.21
110.91
109.73
77.03
76.77
61.74
55.93
54.65
46.75
40.17
33.14
28.41
26.94
26.59
26.15
24.56
14.30
f1 (ppm)

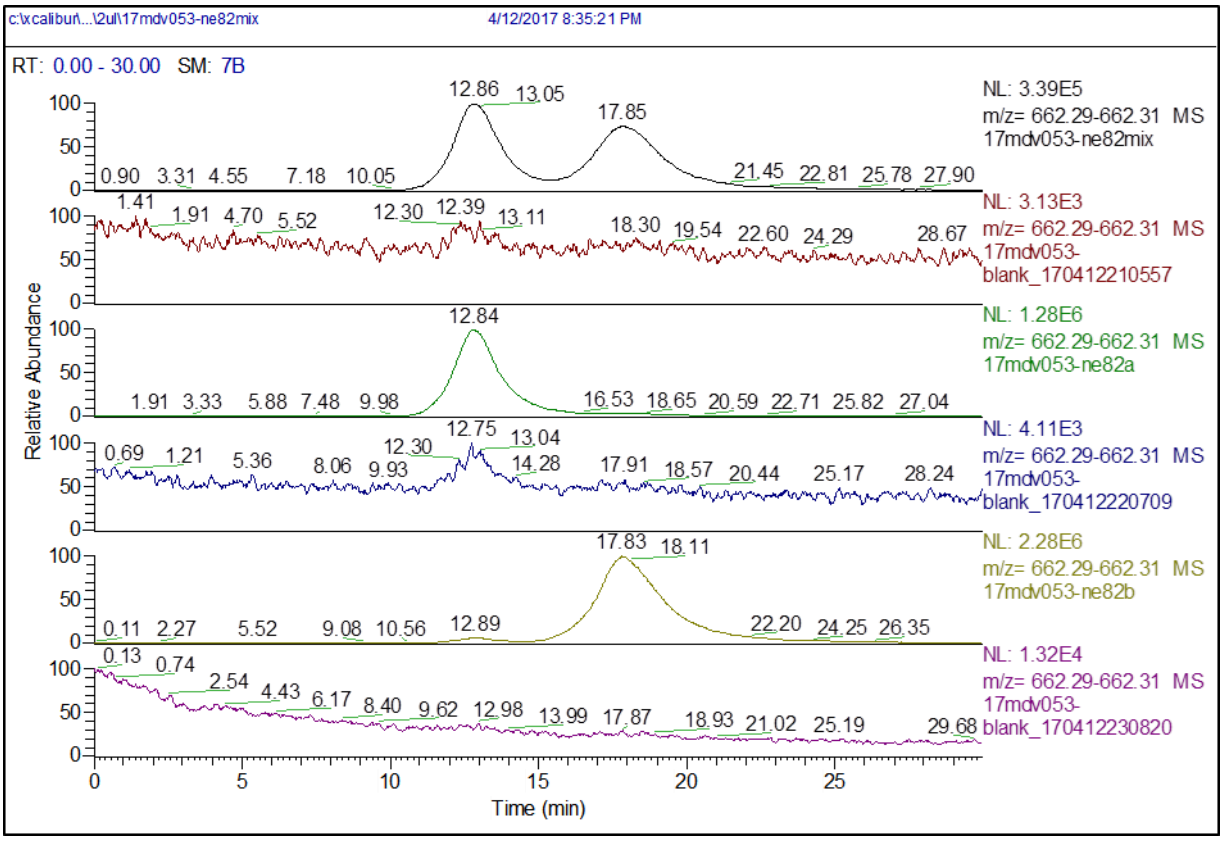

NE82_1_Col4_Sol1_5-30%_6min
NE82_1
3: Diode Array
Range: 1.383e+1
AU
1.0e+1
0.0
3.16
1.39
2.17
NE82_1
2: Scan ES-
TIC
5.79e7
%
8
3.20
2.19
2.45
2.66
3.25
2.83
3.98
4.34
4.60
4.90
5.19
5.09
5.26
5.56
5.92
5.97
0.33
0.47
1.01
1.11
1.37
1.86
NE82_1
1: Scan ES+
TIC
3.68e8
%
24
3.85
4.21
4.32
4.52
4.87
5.11
5.77
2.20
2.35
2.86
3.00
3.41
2.08
1.90
1.55
1.24
0.98
0.53
0.41
NE82_1
2: Scan ES-
659
2.98e5
100
%
0
4.79
0.14
1.68
1.93
2.93
5.35
0.45
0.90
1.22
1.34
2.29
2.67
2.71
3.20
3.86
4.10
4.36
5.30
5.44
0.61
NE82_1
1: Scan ES+
661
1.04e6
100
%
0
3.31
3.27
3.41
2.44
2.73
0.82
5.93
0.23
0.63
1.26
1.66
1.94
2.35
3.00
3.95
4.23
4.68
5.08
5.27
5.86
5.46
5.97
NE82_1
2: Scan ES-
661
9.33e6
100
%
0
3.20
3.25
3.40
3.82
4.86
NE82_1
1: Scan ES+
663
7.81e6
100
%
0
3.20
3.26
0.03
0.32
0.63
1.68
1.94
2.37
2.63
2.94
3.39
3.79
4.09
4.52
4.99
5.10
5.79
5.86
Time
-0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
4.50
5.00
5.50
6.00

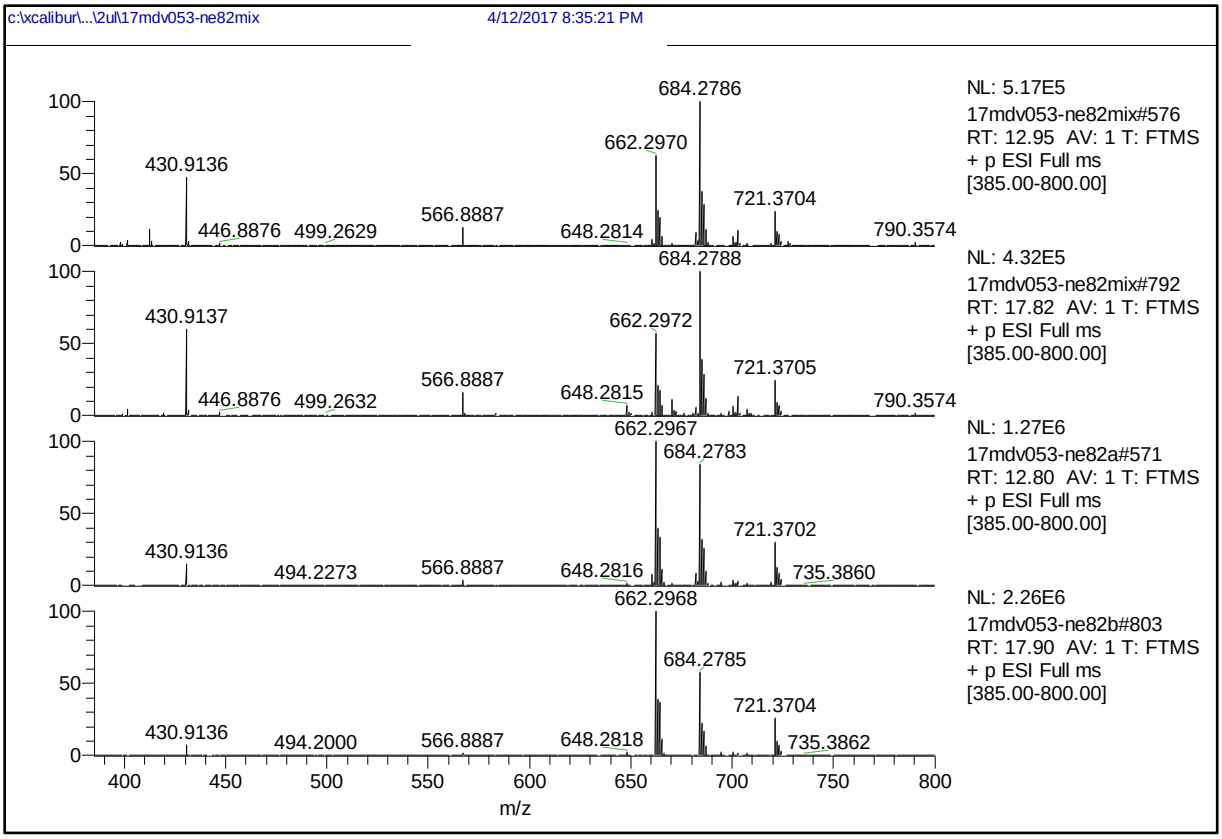

NE82_1_Col4_Sol1_5-30%_6min
NE82_1 182 (3.160)
2: Scan ES-
1.61e6
100
%
0
662.29
660.37
662.61
660.18
662.80
663.25
648.47
646.10
298.08
314.98
275.17
503.90
527.51
664.40
262.82
502.04
614.10
665.43
600.09
736.53
238.82
353.44
492.06
761.23
371.81
553.82
200
300
400
500
600
700
800
900
1000
m/z

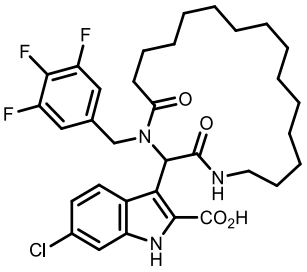
Enantioseparation of compound **2j**

Enantiomeric fractions of the racemic mixture **2j** were separated in a semi-preparative SFC performed with stacked injector (250 µL injections) on a Chiral-IC column with 25% MeOH/CO_2 as mobile phase. Each fraction was evaporated, affording the corresponding pure enantiomers **2ja** and **2jb.** Afterwards, each enantiomer was subjected to hydrolysis giving the corresponding acids **1ja** and **1jb**. The optical rotation of all the four adducts was measured to determine the purity of the enantiomers.

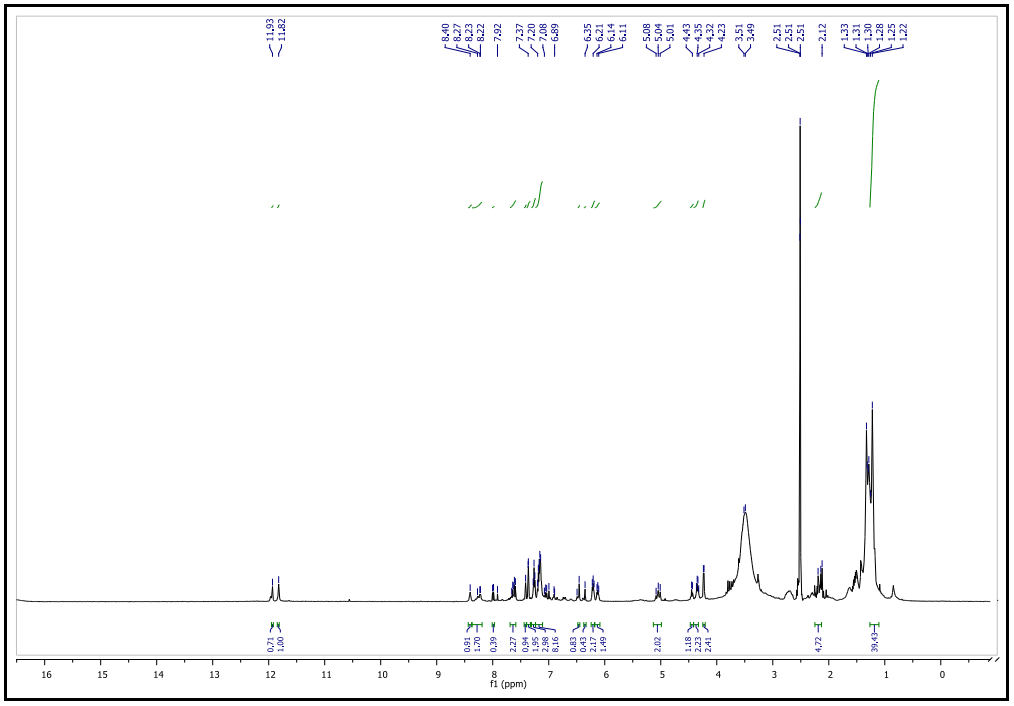


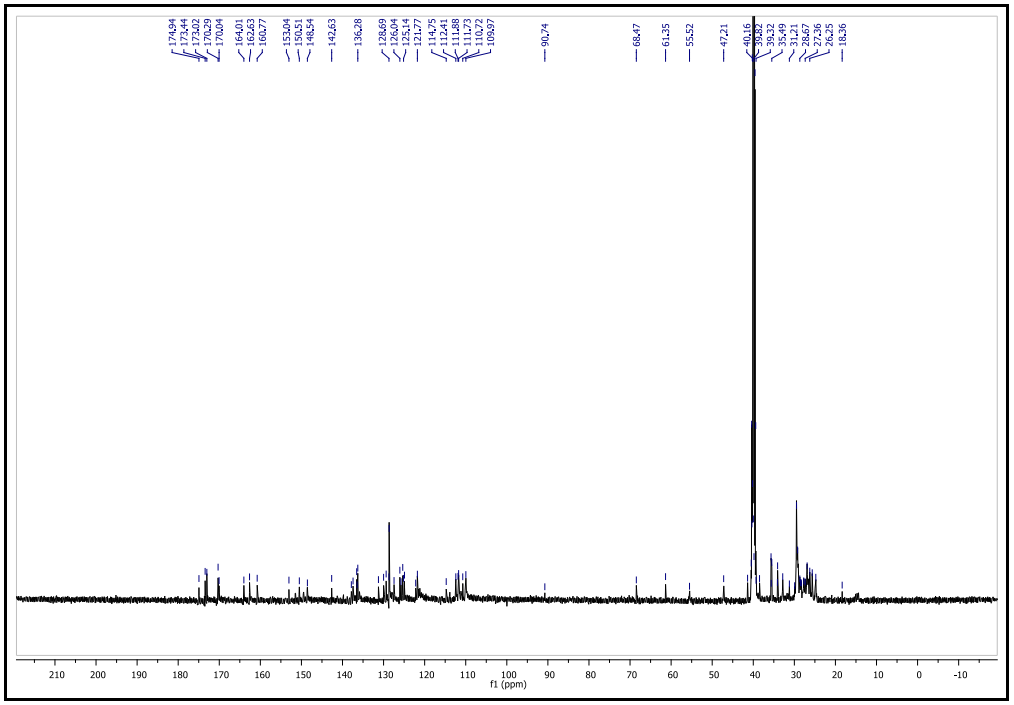



c:\xcalibur\...\2ul\17mdv053-ne82mix
4/12/2017 8:35:21 PM
684.2786
662.2970
430.9136
721.3704
446.8876
499.2629
566.8887
648.2814
790.3574
NL: 5.17E5
17mdv053-ne82mix#576
RT: 12.95 AV: 1 T: FTMS
+ p ESI Full ms
[385.00-800.00]
684.2788
430.9137
662.2972
721.3705
446.8876
499.2632
566.8887
648.2815
790.3574
NL: 4.32E5
17mdv053-ne82mix#792
RT: 17.82 AV: 1 T: FTMS
+ p ESI Full ms
[385.00-800.00]
662.2967
684.2783
430.9136
721.3702
494.2273
566.8887
648.2816
735.3860
NL: 1.27E6
17mdv053-ne82a#571
RT: 12.80 AV: 1 T: FTMS
+ p ESI Full ms
[385.00-800.00]
662.2968
684.2785
430.9136
721.3704
494.2000
566.8887
648.2818
735.3862
NL: 2.26E6
17mdv053-ne82b#803
RT: 17.90 AV: 1 T: FTMS
+ p ESI Full ms
[385.00-800.00]
100
50
0
400
450
500
550
600
650
700
750
800
m/z


F
F
F
O
N
O
N
H
CO2H
Cl
N
H

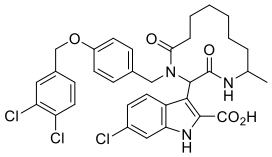
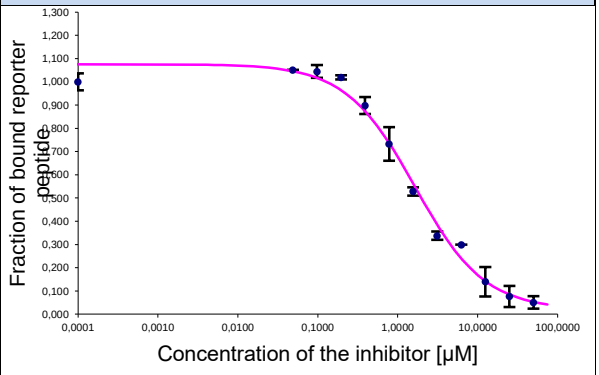
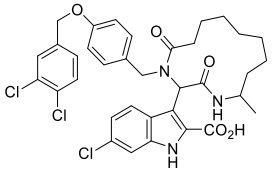
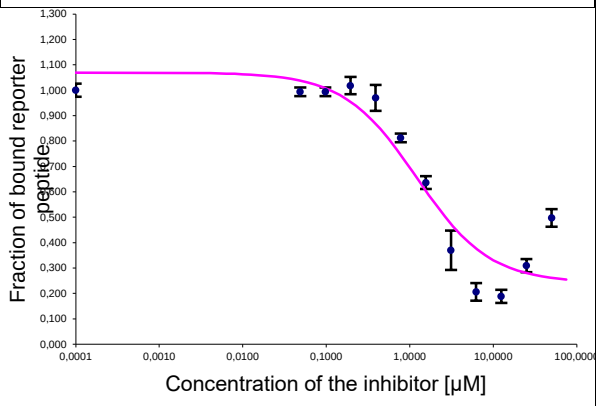
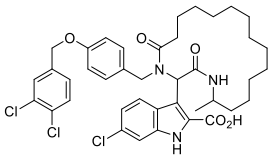
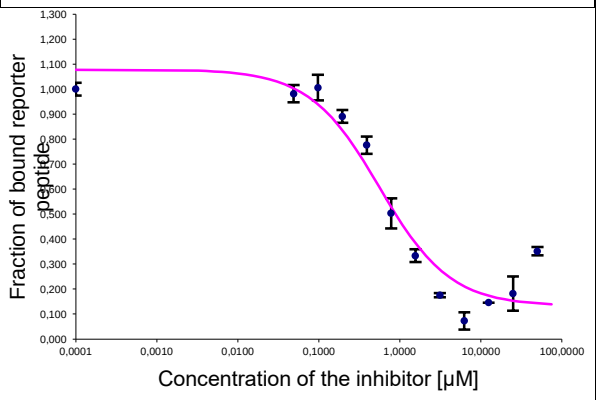
1j

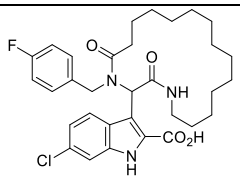
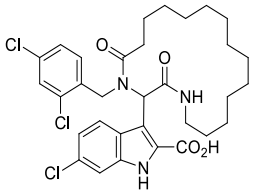
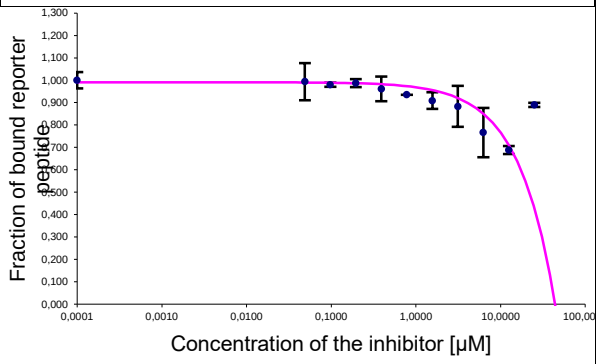
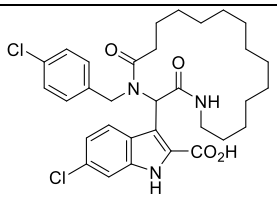
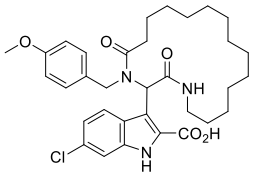
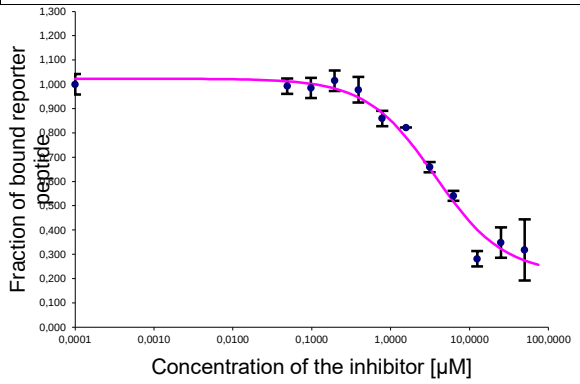

11.93
11.82
8.40
8.27
8.23
8.22
7.92
7.37
7.20
7.08
6.89
6.35
6.21
6.14
6.11
5.08
5.04
5.01
4.43
4.35
4.32
4.23
3.51
3.49
2.51
2.51
2.51
2.12
1.33
1.31
1.30
1.28
1.25
1.22
0.71
1.00
0.91
1.70
0.39
2.27
0.84
1.95
2.98
8.16
0.83
0.43
2.17
1.49
2.02
1.18
2.23
2.41
4.72
39.49
f1 (ppm)

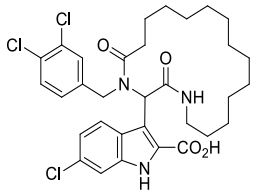
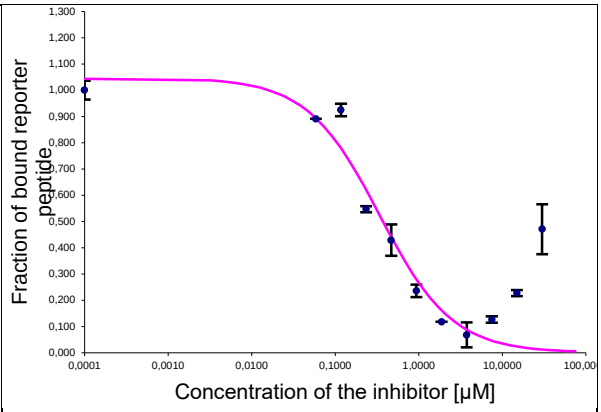
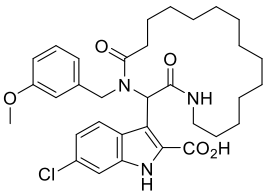
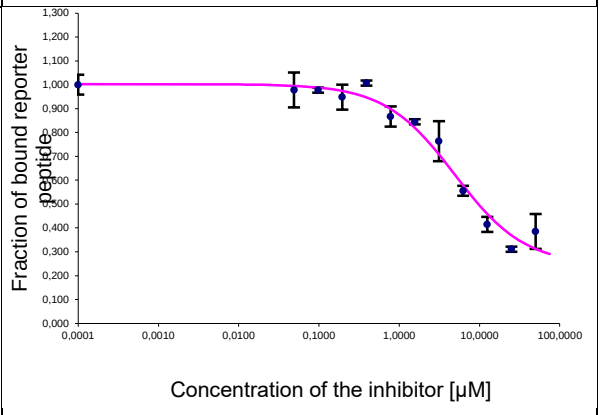
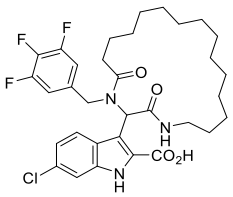
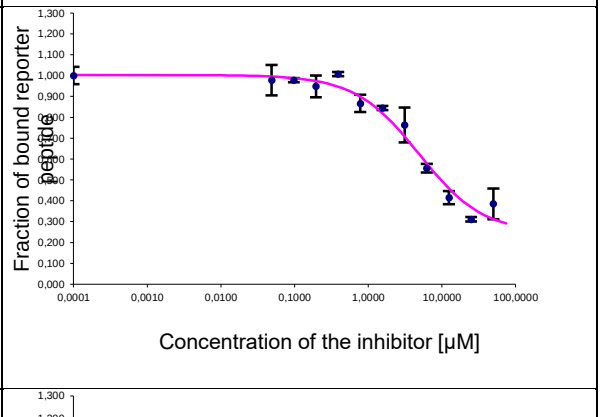
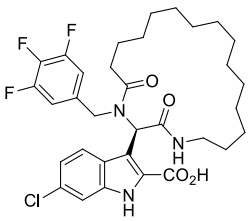
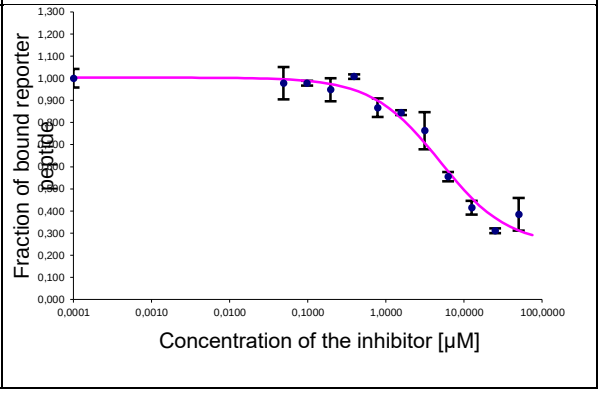

174.94
173.44
173.02
170.29
170.04
164.01
162.63
160.77
153.04
150.51
148.54
142.63
136.28
128.69
126.04
125.14
121.77
114.75
112.41
111.98
111.73
110.72
109.97
90.74
68.47
61.35
55.52
47.21
40.16
39.22
39.32
35.49
31.21
28.67
22.36
26.25
18.36
f1 (ppm)

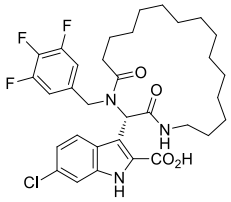
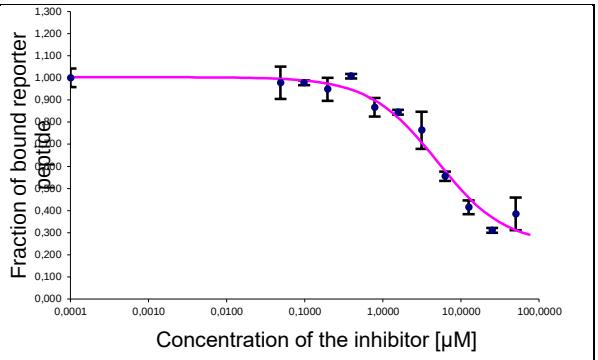
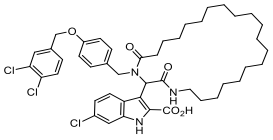
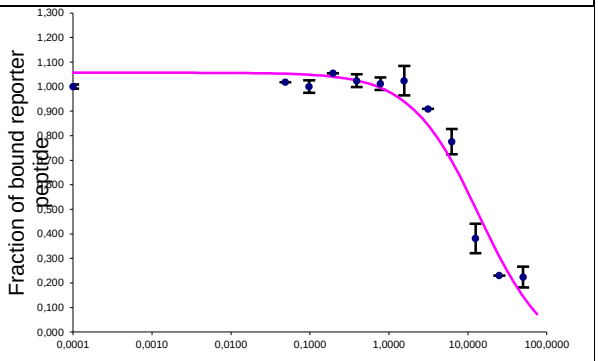
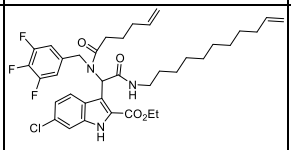
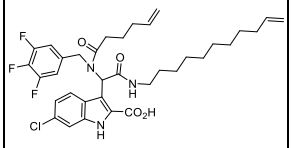
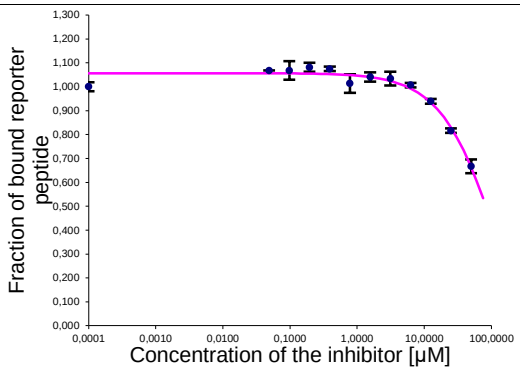
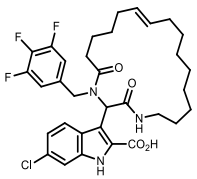
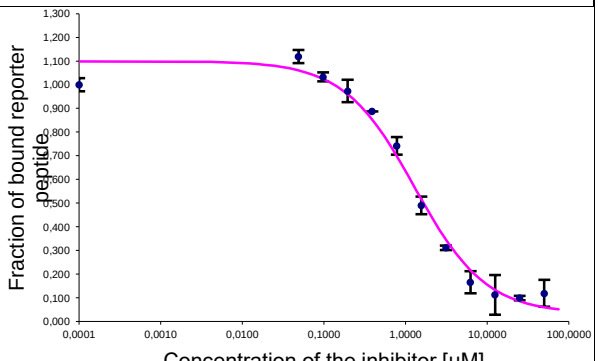
4. Activities of macrocyclic inhibitors of p53-MDM2 interaction

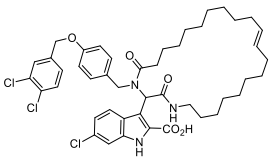
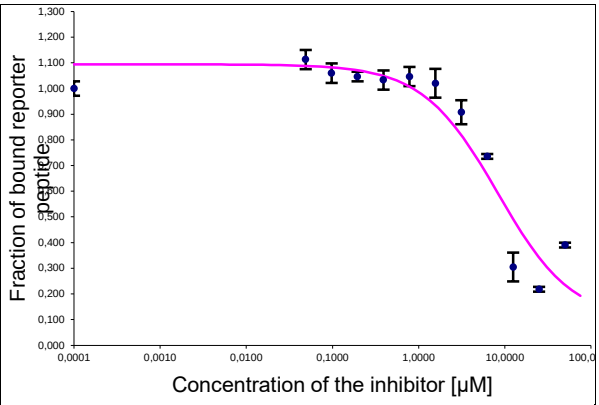
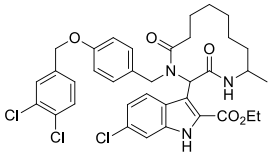
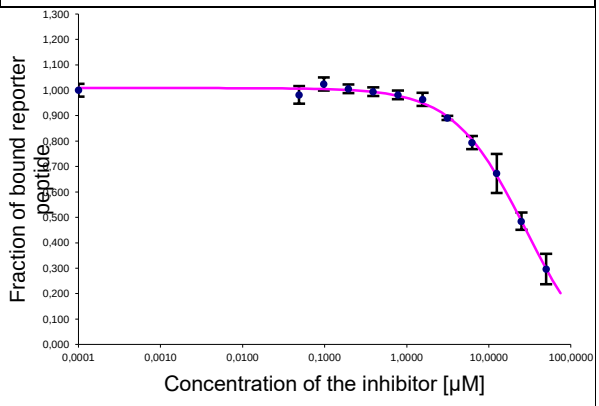
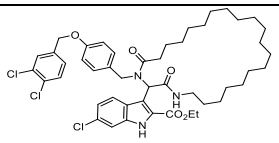
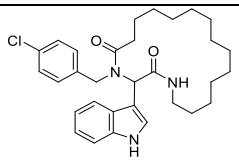
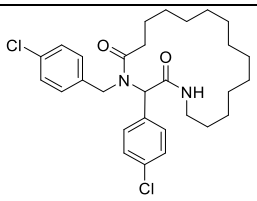
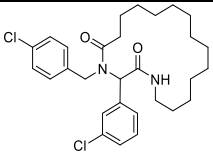
Table S1. Results of the evaluation of inhibitory activity (K_i values) of the compounds towards MDM2 using FP assay.

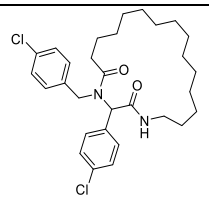
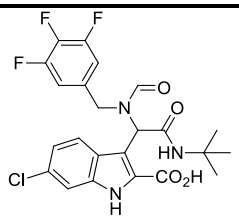
Entry	Number	Structure	K_i MDM2 [μM]	Plot (MDM2)
1	**1a**		0.354	
3	**1b**		0.320	
4	**1c**		0.098	

5	**1d**		*not active*	-
6	**1e**		5.250	
7	**1f**		*not active*	-
8	**1g**		1.260	

9	**1h**		0.082	
10	**1i**		1.780	
11	**1j**		0.139	
12	**1ja**		0.093	

13	**1jb**		0.700	
14	**1k**		1.910	
15	**4j-ester**		*not active*	-
	4j-acid		14.26	
16	**3j**		0.340	

17	**3k**		2.53	
18	**2a**		2.98	
19	**2k**		*not active*	-
20	**10**		*not active*	-
21	**11**		*not active*	-
22	**14**		*not active*	-

23	**15**		*not active*	-
24	**9**		0.100	

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