Supporting Information

A systematic investigation of the permeability of androgen receptor PROTACs

Duncan E. Scott, Timothy P.C. Rooney, Elliott D. Bayle,[†,‡] Tashfina Mirza, Henriette M.G. Willems, Jonathan H. Clarke, Stephen P. Andrews, John Skidmore[*]

ALBORADA Drug Discovery Institute, University of Cambridge, Island Research Building, Cambridge Biomedical Campus, Hills Road, Cambridge, CB2 0AH, United Kingdom

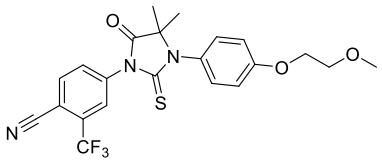
[†]Alzheimer's Research UK UCL Drug Discovery Institute, The Cruciform Building, University College London, Gower Street, London, WC1E 6BT, United Kingdom

[‡]The Francis Crick Institute, 1 Midland Road, Kings Cross, London, NW1 1AT, United Kingdom

*** Corresponding Author**

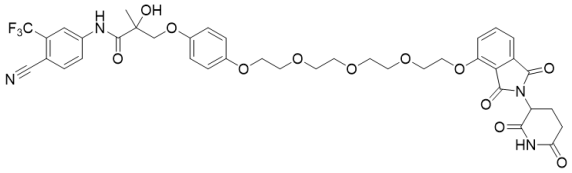
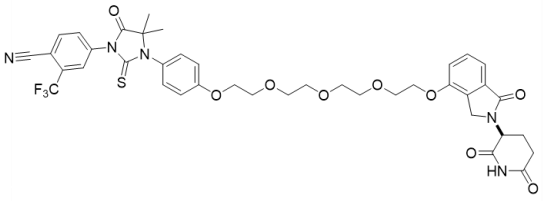
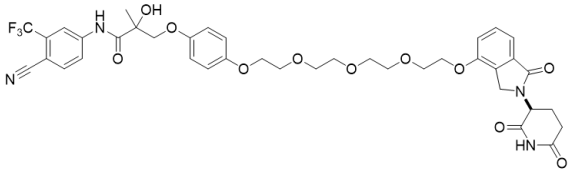
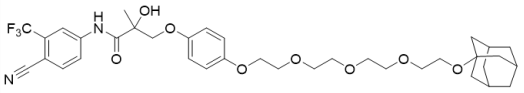
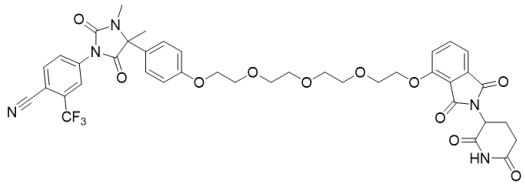
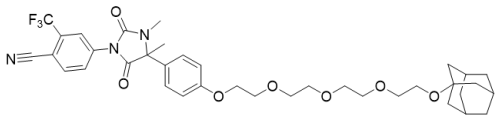
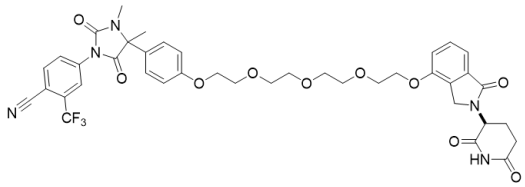
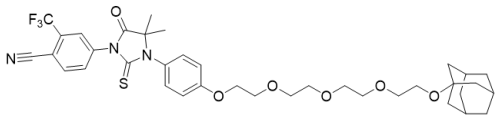
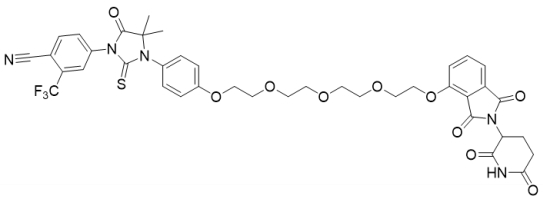
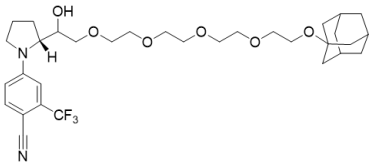
John Skidmore js930@cam.ac.uk

Table of Contents

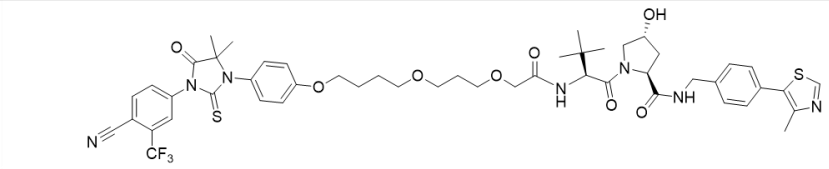
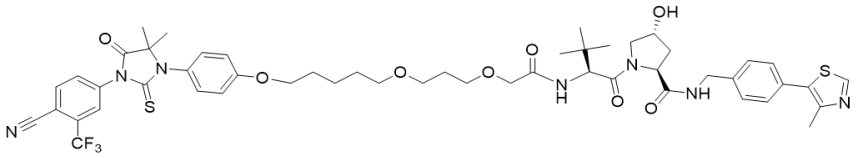
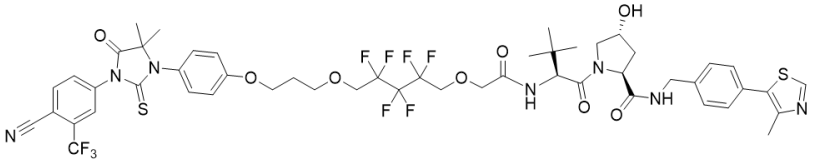
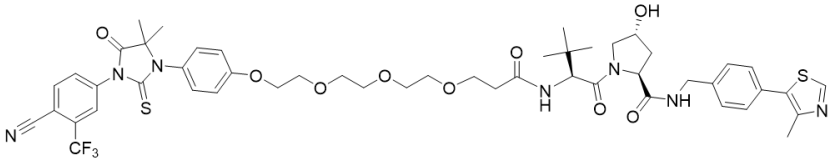
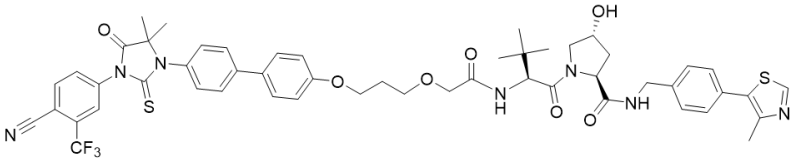
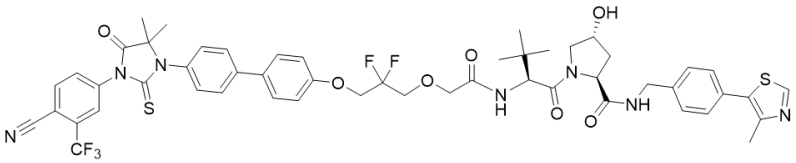
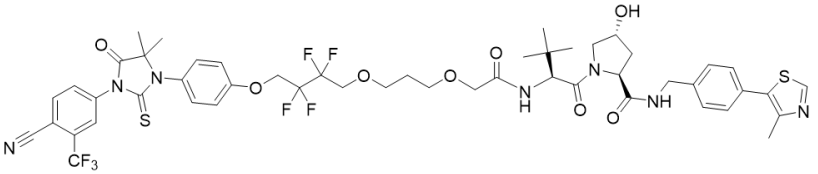
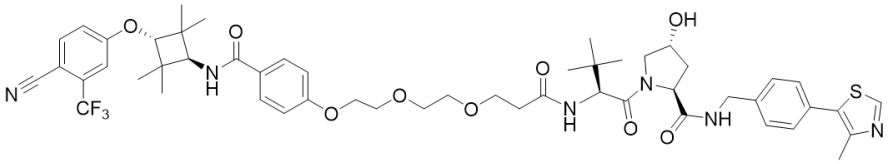
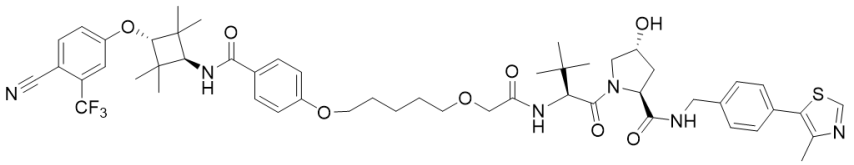


3b

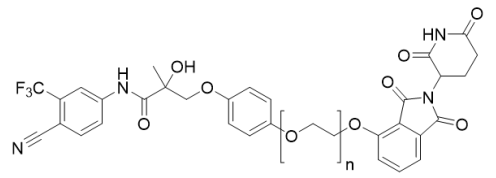
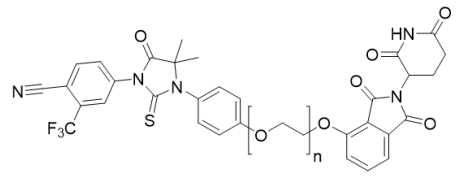
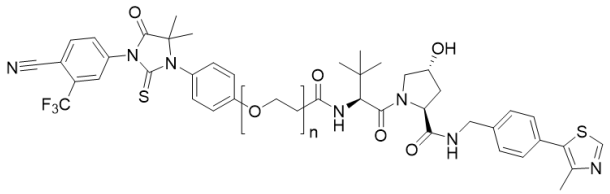
Supporting Figure S1: Structure of compound **3b**, used to model the exit vectors from AR of an attachment to the SARM ligand.

ID	Structure	ID	Structure
10		**15**	
11		**16**	
12		**17**	
13		**18**	
14		**19**	

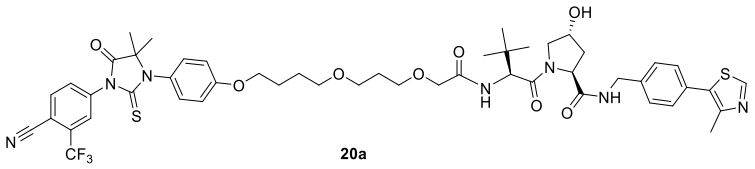
Supporting Figure S2: Full structures of PROTAC Set 1, as reported in Figure 3.

ID	Structure
20a	
20b	
20c	
20d	
20e	
20f	
20g	
20h	
20i	

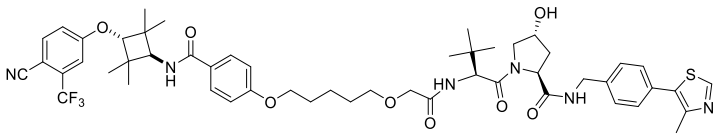
Supporting Figure S3: Full structures of PROTAC Set 2, as reported in Table 1.

Structure	calc_LogD [pH = 7.4]*	
	n = 0	n = 4
	2.80	2.96
	4.33	4.48
	5.25	5.49

Supporting Figure S4: Effect of a PEG-linker on the calculated logD of linked AR and E3 ligase ligands. Addition of 4 ethylene glycol units results in a small predicted overall logD change of between 0.14 to 0.16. * calc_LogD [pH = 7.4] was calculated using cxcalc (ChemAxon).



20a



20i

Compound	AR binding	
	K_I	IC_{50}
20a	11 nM	25 nM
20i	5 nM	11 nM

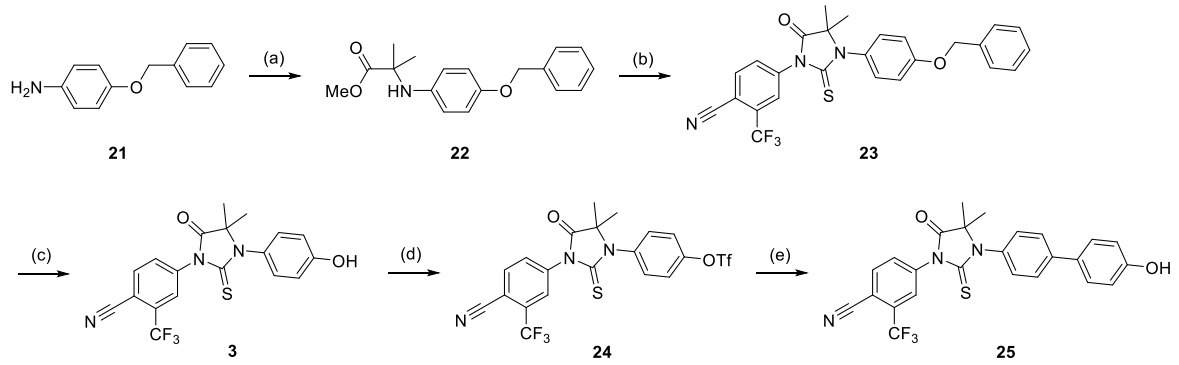
Supporting Figure S5: AR affinity data for PROTACs **20a** and **20i.**

Accompanying text for synthetic routes:

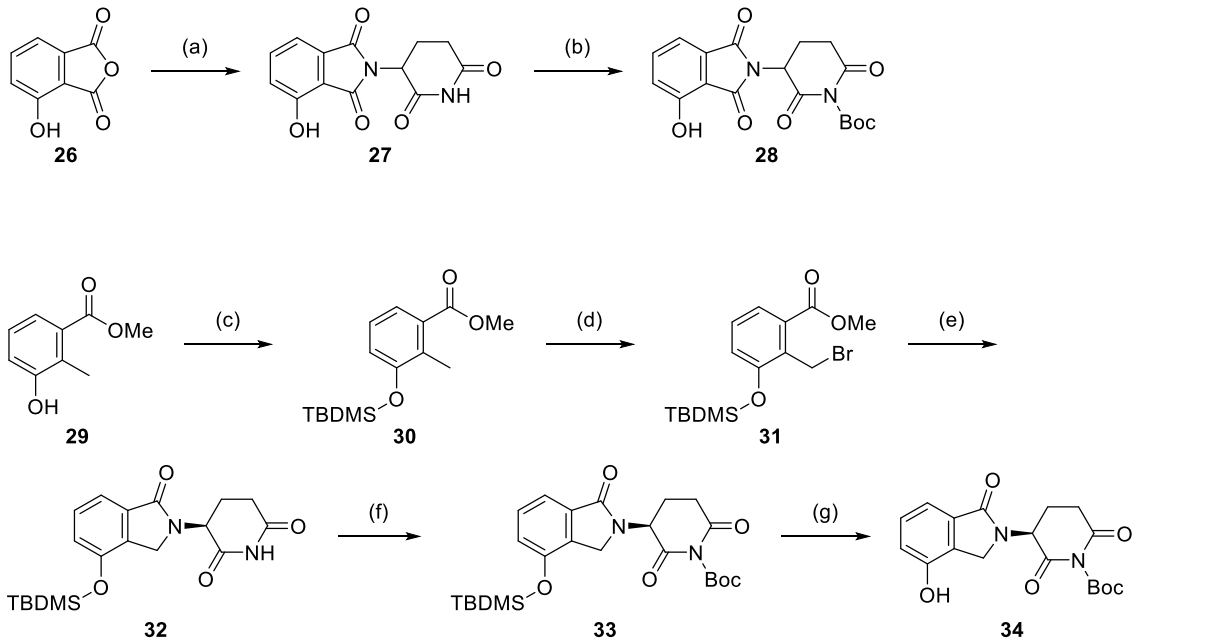
Molecules **10**-**19** of PROTAC Set 1 were constructed from the AR ligands **1**-**4**, and E3 ligase ligands **6, 7** and **8**, linked by a PEG chain (Figure 3A, Figure S2). Gustafson *et al.* have previously reported compounds SARD033 and SARD279 as cell-active molecules capable of removing the AR through a hydrophobic tagging strategy.[1] As such, the adamantyl group **8** was combined into PROTACs with a wider selection of AR ligands to give PROTACs **16**-**19** (Figure 3A, Figure S2). The Cereblon-targeting PROTACs **10**-**15** were constructed by alkylating the AR ligand with a suitable di-tosylated linker to afford intermediates **37**, **38** and **39** (Scheme S3). The remaining tosylate group was displaced with the thalidomide derivatives **28** or **34** protected on the piperidinedione nitrogen with a Boc group (Scheme S2). Boc-deprotection was achieved either under the alkylation conditions or following treatment with TFA to furnish the desired PROTACs **10**-**15**. The final alkylation with the thalidomide derivatives **28** and **34** did not proceed under the expected mild conditions but often required microwave heating between 110-120 °C, leading to competitive degradation of the starting material and product in some cases. This was particularly an issue with thalidomide-derived AR PROTACs.

To access the adamantyl-containing degrons **16**-**18** the requisite phenols **1**, **2** and **3** were alkylated with a functionalised adamantyl group **42** (Scheme S4).[1] The first step to access the Ligandrol-based compounds was an S_NAr reaction of L-prolinol with aryl fluoride **43**. Oxidation to the aldehyde **45** was achieved with a Parikh-Doering oxidation, followed by conversion to epoxide **46** with a Johnson-Corey-Chaykovsky reaction. Epoxide **46** was ring-opened with PEG-adamantyl alcohol **41** affording the Ligandrol-based hydrophobic degron **19**.

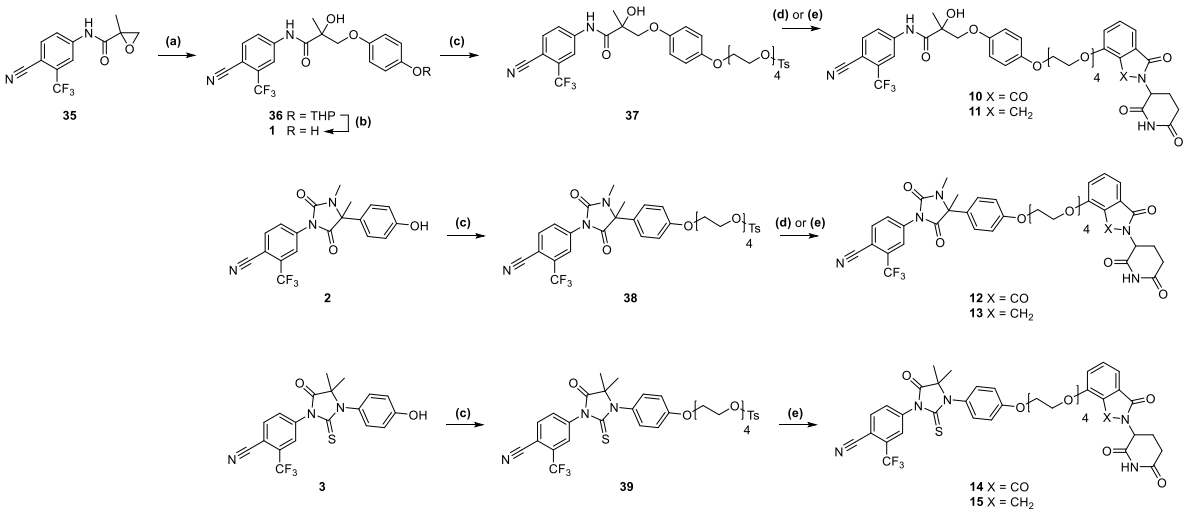
A second set of PROTACs was synthesised, all incorporating the VHL ligand **9**, a variety of linkers, and AR ligands **3** and **5** (Table 1). In terms of chemical tractability, alkylation of the phenol with tosyl-activated linkers proceeded reasonably well to furnish carbon-oxygen based linkers. Gem-difluorine groups in the vicinal position to the linker tosylate group however gave relatively poor yields of this transformation, although the use of a triflate rather than a tosylate in the synthesis of **20g** proceeded in reasonable yield (Scheme S6). The fluorination of PROTAC linkers may open up new linker options for future study. The AR-ligand-linkers were typically protected as tert-butyl esters, which were removed with TFA and coupled to the VHL ligand to give VHL PROTACs **20a**-**g**.



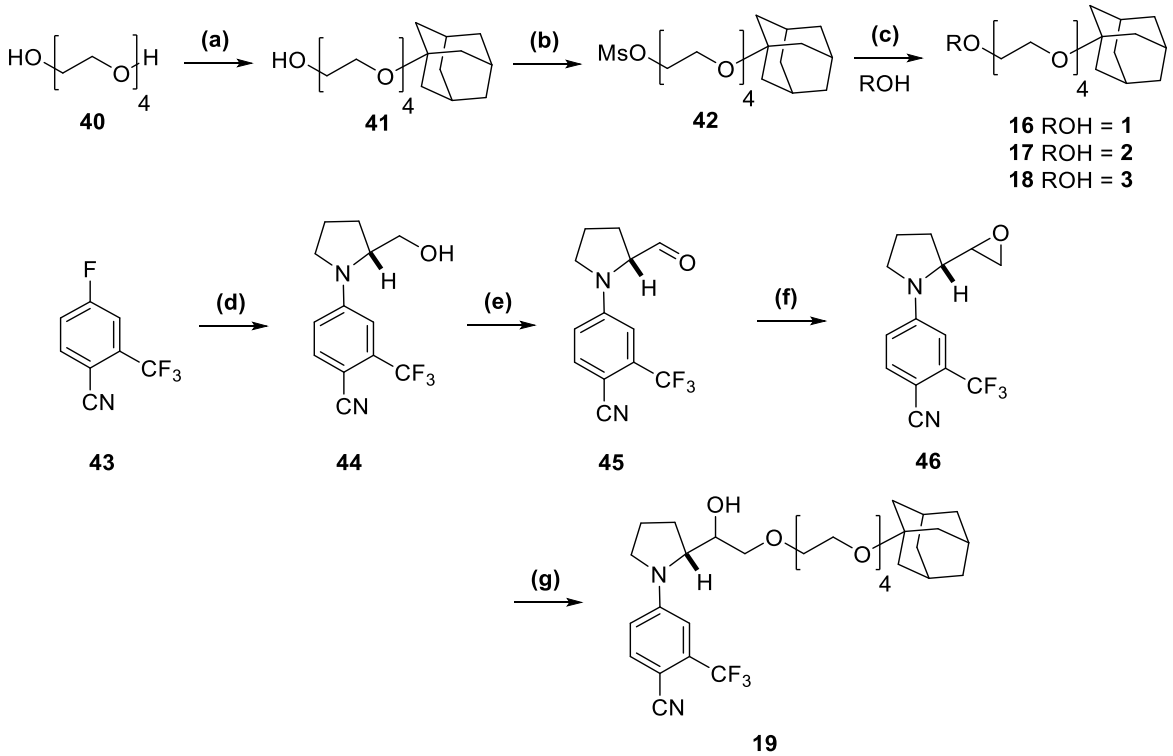
Supporting Scheme S1: Synthesis of thiohydantoin based SARMs **3** and **25**. (a) methyl α-bromoisobutyrate, $NaHCO_3$, 150 °C. (b) 4-cyano-3-(trifluoromethyl)phenylisothiocyanate, DMSO, IPA, 82 °C, 84%. (c) BBr_3, CH_2Cl_2, -78 °C, 92%. (d) Tf_2O, Et_3N, CH_2Cl_2, 0 °C, quant. (e) (4-hydroxyphenyl)boronic acid, K_3PO_4, $Pd(PPh_3)_4$, 1,4-dioxane, 130 °C, 87%.



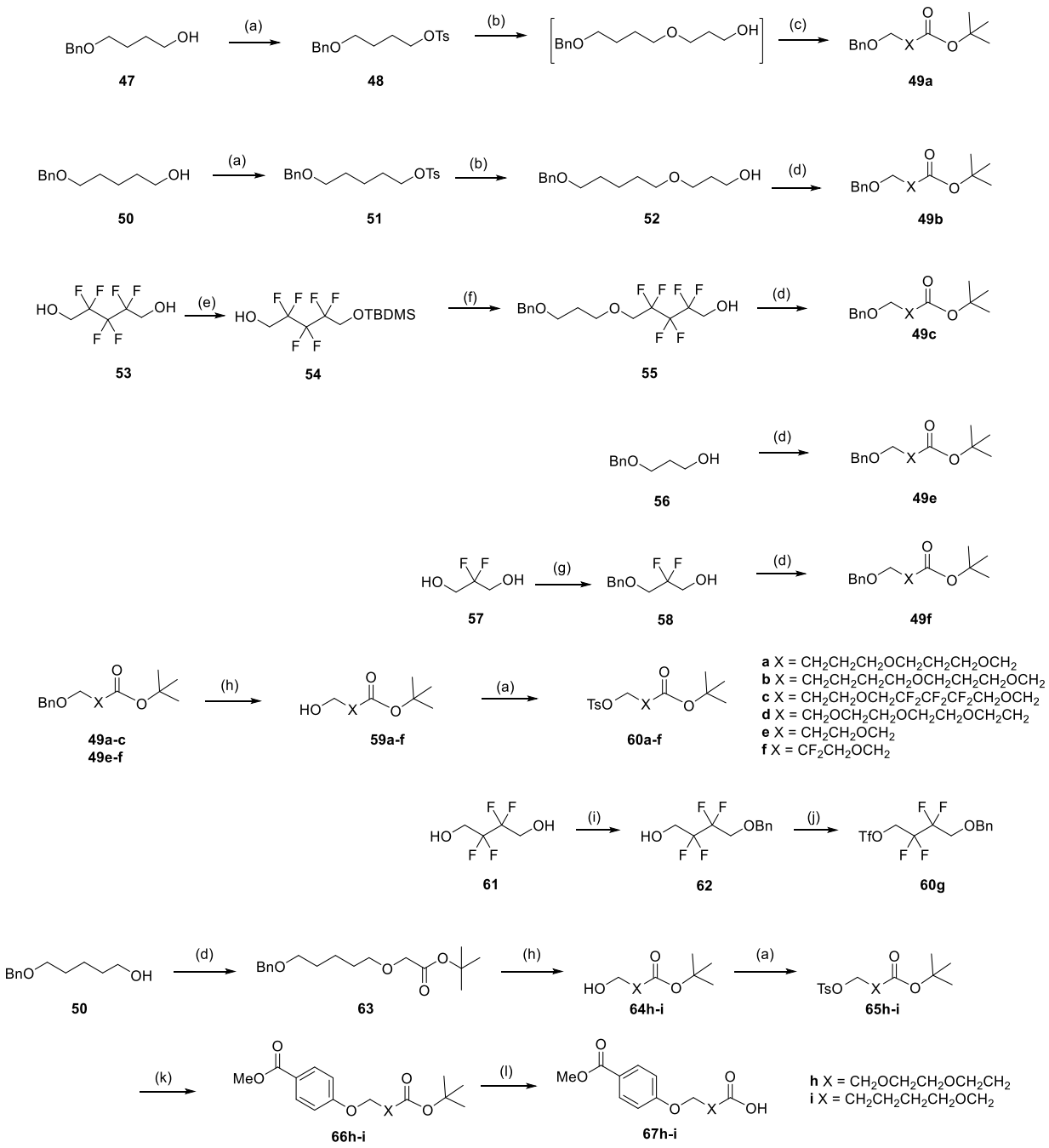
Supporting Scheme S2: Synthesis of **28** and **34**. (a) 3-aminopiperidine-2,6-dione hydrochloride, DCC, Et_3N, THF, 80 °C, 90%. (b) Boc_2O, piperidine, DMAP, 1,4-dioxane, 71%. (c) TBDMSCl, imidazole, DMF, 85%. (d) ABCN, NBS, $CHCl_3$, 70 °C, 91%. (e) (3*S*)-3-aminopiperidine-2,6-dione hydrobromide, Et_3N, THF, 75 °C, 33%. (f) Boc_2O, Et_3N, DMAP, THF, 65%. (g) TBAF, THF, -40 °C to rt, 93%.



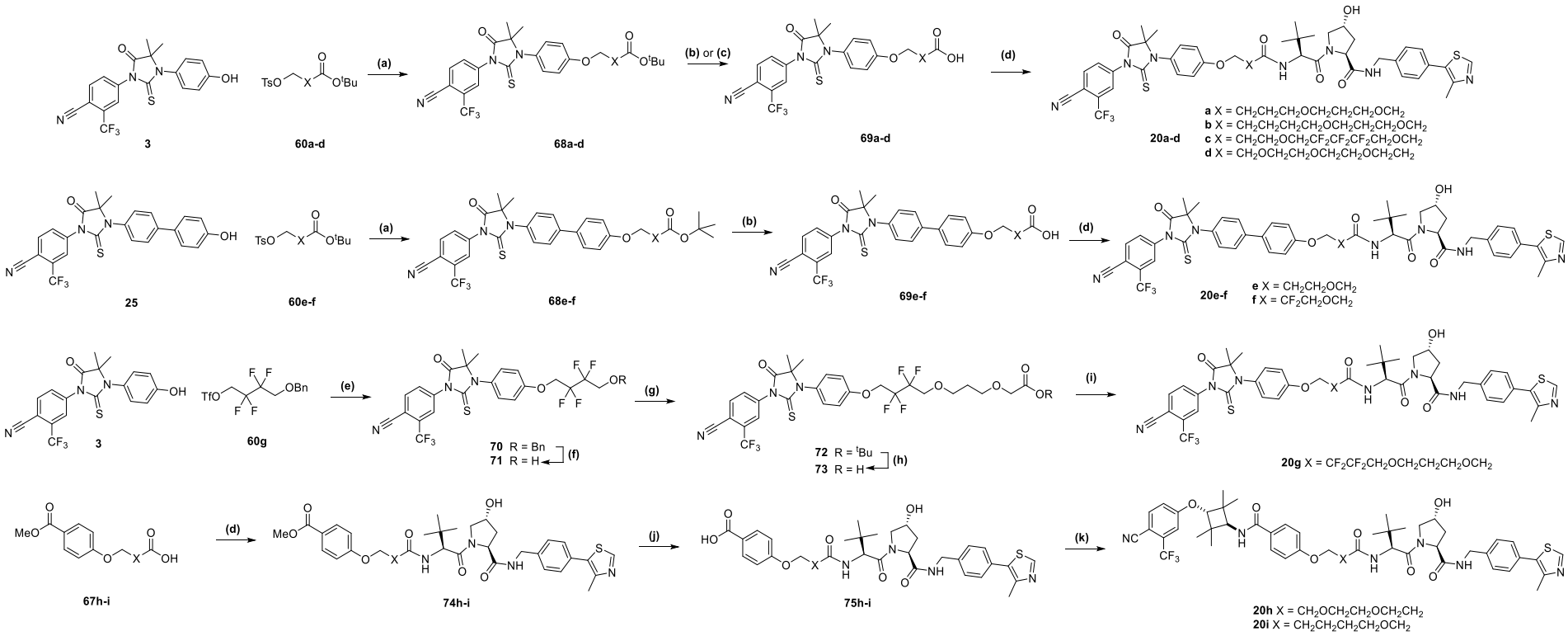
Supporting Scheme S3: Synthesis of cereblon-binding AR PROTACs **10**-**15**. Reagents and conditions: (a) 4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenol, K_2CO_3, rt, 91%. (b) HCl, 1,4-dioxane, MeOH, 4 °C, 84%. (c) tetraethylene glycol di(*p*-toluenesulfonate), K_2CO_3, acetone, 110-120 °C, 32-48%, (d) i) *tert*-butyl 3-(4-hydroxy-1,3-dioxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate **28** or *tert*-butyl (3*S*)-3-(4-hydroxy-1-oxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate **34**, K_2CO_3, acetone, 100-110 °C ii) TFA, CH_2Cl_2, 0 °C, 11-27% (2 steps); (e) *tert*-butyl 3-(4-hydroxy-1,3-dioxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate **28** or *tert*-butyl (3*S*)-3-(4-hydroxy-1-oxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate **34**, K_2CO_3, acetone, 100-120 °C, 6-30%.



Supporting Scheme S4: Synthesis of adamantyl-based AR hydrophobic degrons **16**-**19**. Reagents and conditions: (a) 1-Bromoadamantane, NEt_3, DBU, 110 °C, 85%[1] (b) MsCl, NEt_3, CH_2Cl_2, rt, quant. yield[1] (c) **1** or **2** or **3**, K_2CO_3, acetone, 110-120 °C, 11-75%; (d) (R)-pyrrolidin-2-ylmethanol, NEt_3, THF, 50 °C, 63%; (e) SO_3.pyridine, NEt_3, CH_2Cl_2, DMSO, 0 °C; (f) NaH, trimethylsulfoxonium iodide, DMSO, THF, rt, 22% (2 steps); (g) **41**, NaH, THF, 110 °C, 26%.



Supporting Scheme S5: Synthesis of linker group intermediates. (a) TsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C to rt. (b) 1,3-propanediol, NaH, DMF, 0 °C to rt. (c) *tert*-butyl bromoacetate, NaH, DMF, 0 °C to rt. (d) *tert*-butyl bromoacetate, Bu_4NCl or Bu_4NBr, NaOH, CH_2Cl_2 or toluene, H_2O. (e) TBDMSCl, imidazole, DMF, 0 °C to rt. (f) 3-benzyloxypropyl 4-methylbenzenesulfonate, NaH, DMF, 0 °C to rt. (g) BnBr, NaH, THF, rt – reflux. (h) Pd/C, H_2, H_2O, MeOH or EtOH. (i) BnBr, K_2CO_3, MeCN, 85 °C. (j) Tf_2O, pyridine, CH_2Cl_2. (k) methyl 4-hydroxybenzoate, K_2CO_3, MeCN, 50 °C. (l) TFA, CH_2Cl_2, 0°C to rt.



Supporting Scheme S6: Synthesis of VHL ligand PROTACs **20a**-**i**. Reagents and conditions (a) Cs_2CO_3, DMF, 90 °C, 9-96%; (b) HCl, dioxane rt; (c) TFA, CH_2Cl_2, rt; (d) **9**, HATU, DIPEA, DMF, rt, 12-91%; (e) Cs_2CO_3, DMF, 100 °C, 88%; (f) BBr_3, CH_2Cl_2, -78 °C, 86%; (g) *tert*-butyl 2-(3-(tosyloxy)propoxy)acetate, NaH, DMF, 0 °C to rt; (h) CH_2Cl_2, TFA, rt,; (i) **9**, HATU, DIPEA, DMF, rt, 13% (3 steps); (j) LiOH, THF, H_2O, 35 °C 91% - quant. yield; (k) 4-(*trans*-3-amino-2,2,4,4-tetramethylcyclobutoxy)-2-(trifluoromethyl)benzonitrile hydrochloride, HATU, DIPEA, DMF, rt, 55-70%.

Compound	PAMPA[a]	HSA[b]	LogD[c]
1	1.4 ± 0.6	ND	4.0
2	8.3 ± 1.1	11	4.4
3	4.6 ± 3.0	9	5.0
25	ND	4	5.8
6	2.0	26	0.4
7	<0.2	64	0.2
9	ND	24	1.4

Supporting Table S1: Additional logD and HSA %free data for compounds in this study. ND denotes not determined. [a] PAMPA permeability / 10^{-6} cm s^{-1}. [b] HSA % free, determined by HPLC method. [c] chromLogD$_{7.4}$, determined by HPLC method

Compound	**PAMPA assay C_0 / µM**	**Papp / 10^{-6} cm s^{-1}**	**% Recovery**
1	200	1.4 ± 0.6	86
2	200	8.3 ± 1.1	90
3	100	4.6 ± 3.0	59
4	200	13.3 ± 3.3	59
6	200	2.0 ± 1.3	78
7	200	BLQ	112
10	200	0.3 ± 0.03	79
11	200	0.4 ± 0.2	73
12	100	BLQ	82
13	200	0.3 ± 0.08	55
14	200	BLQ	112
15	25	BLQ	38
16	100	BLQ	12
17	50	BLQ	71
18	50	BLQ	66
19	100	2.3 ± 0.9	33
20a	25	BLQ	41
20b	25	BLQ	48
20c	25	BLQ	43
20d	25	BLQ	21
20e	25	BLQ	52
20f	31	BLQ	43
20g	25	BLQ	32
20h	12.5	BLQ	61
20i	25	BLQ	47

Supporting Table S2: PAMPA summary table. Papp values are the average of three experiments / 10^{-6} cm s^{-1}. BLQ denotes Below Limit of Quantification.

Compound	A2B Papp	A2B % Recovery	B2A Papp	B2A% Recovery
14	1.7 ± 0.20	83	14.1 ± 1.02	87
18	0.15 ± 0.03	63	0.22 ± 0.12	59
20a	< 2.7	71	1.4 ± 0.04	60
20b	0.35 (n = 1)	65	0.24 ± 0.07	57
20c	0.26 (n = 1)	80	< 0.79	82
20d	< 0.69	69	8.6 ± 2.10	67
20g	< 0.11	101	0.33 (n = 1)	95

Supporting Table S3: Caco-2 summary table. Papp values are the average of two experiments unless stated otherwise. A2B and B2A permeability in units of 10^{-6} cm s^{-1}.

Computational Methods:

An antagonist model of the androgen receptor (AR) was created by remodelling Leu880 to Val903 of the AR into an antagonist binding mode. Residues Met528 to Ala551 of a crystal structure of the estrogen receptor (ER) bound to antagonist tamoxifen (PDB ID: 3ERT) were used as a template for the antagonist androgen receptor model.

AR crystal structure 2PNU was used as the main model for the homology model, but residues 528 to 551 of 3ERT (helix 12 to C-terminal) were used to model an open conformation of helix 12 in MOE.[2] The 2PNU ligand was used to maintain the binding pocket. Geometry checks on the resulting homology model did not indicate any clashes or areas of high strain energy.

Compound **3b** was placed into the AR homology model by superposing it onto the ligand of the AR crystal structure with the most similar ligand, PDB ID:3V49. The protein-ligand complex was then refined in Maestro (FF: OPLS3E; VSGB solvation).[3] The resulting complex was used to set up docking runs in Glide.[3]

'cxcalc' was used for the calculation of calc_LogD [pH = 7.4] values, cxcalc, ChemAxon (https://www.chemaxon.com).

Biological Methods:

PAMPA permeability: Passive permeability was assessed using a PAMPA (parallel artificial membrane permeability) assay (Corning GenTest Cat. No. #353015). Briefly, compounds were loaded into the donor wells of a 96-well PAMPA plate, then incubated at room temperature for 5 hours with 5% DMSO in ammonium acetate buffer pH 7.4. The concentration of compound either side of the membrane was then determined using UV or mass spec analysis, then converted to an apparent permeability coefficient P_{app} in 10^{-6} cm s^{-1}. PAMPA permeability was calculated with the following equations:

PAMPA P_{app} (10^{-6} cm s^{-1}) = $\{-\ln[1-C_A(t)/C_{eq}]\}/[A*(1/V_D + 1/V_A)*t]$
$C_{eq} = [C_D(t)*V_D + C_A(t)*V_A]/(V_D+V_A)$
$C_A(t)$ = Acceptor well compound concentration at time t
$C_D(t)$ = Donor well compound concentration at time t
A = filter area (0.3 cm^2)
V_D = Donor well volume (0.3 mL)
V_A = Acceptor well volume (0.2 mL)
t = incubation time (seconds). Compounds were incubated for 5 hours (18,000 seconds).
The percent recovery of compounds in the PAMPA assay were calculated according to the following equation:
% recovery = $[C_D(t) * V_D + C_A(t)*V_A] / (C_0 * V_D)$
C_0 = Initial concentration of compound in donor well.

Each compound was performed in triplicate, and standard deviations are given in the text. Three compounds were used in each plate as controls and each gave the expected permeability values. Papp / 10^{-6} cm s^{-1}: Caffeine = 7.8 ± 1.6 (lit. Papp = 9.6 ± 0.6), Propanolol = 5.2 ± 2.5 (lit. Papp = 8.6 ± 0.3), Sulfasalazine = BLQ (lit. Papp = 0.2 ± 0.04). BLQ = Below Limit of Quantification.

Caco-2 permeability: Caco-2 permeability was performed by Cyprotex ("Caco-2 Permeability Bi-drirectional"). Briefly, compounds were administered at 10 µM (1% final DMSO concentration) to the apical or basolateral side of a polarised Caco-2 cell monolayer, then incubated for 120 minutes before

appearance on the opposite side of the monolayer was determined. The efflux ratio (ER) is calculated from the ratio of B-A to A-B permeabilities. Each compound was tested in duplicate and standard deviations are given in the text. Three compounds were used in each experiment as controls and each gave the expected permeability values. A-B Papp / 10^{-6} cm s^{-1}: Atenolol = 0.20 ± 0.009, Propanolol = 34.8 ± 0.89, Talinolol = 0.15 ± 0.014.

Western blotting: Response curves for changes in cellular levels of AR in LNCaP cells (relative to control untreated cells) were generated for each PROTAC using an in-cell Western blot technique. Cells were grown in serum-depleted medium for 24 hours and then transferred to a 96-well plate for a further 16 hours. PROTACs were added to appropriate final concentrations (0-10 μM) in a total volume of 100 μL and incubated for 6 hours. Cells were then washed and fixed before permeabilisation with 0.1% Triton X-100 in PBS. After blocking, cells were incubated with anti-AR antibody (Abcam ab9474) overnight at 4 °C. After washing, fluorescent anti-mouse secondary antibody and DRAQ5 (used as a counterstain to control for variance in cell proliferation) were added to the cells for 45 minutes. Further wash steps were performed before reading the plate at the appropriate fluorescence wavelengths in a Typhoon (GE-Healthcare). Data presentation and statistical analysis was carried out using Prism (Graphpad).

Androgen Receptor binding assay: Androgen receptor binding was assessed using a radio-ligand displacement assay performed by Eurofins Cerep ("In Vitro Pharmacology: Human AR (h) (agonist radio-ligand) Receptor Binding Assay"). Briefly, displacement of 1 nM of [3H]methyltrienolone by PROTAC compounds from AR protein isolated from LNCaP cells was measured. PROTAC compounds were titrated over a range of concentrations (0.1 nM – 10 μM) in the presence of AR protein for 24hr at 4 °C.

Biophysical Methods:

ChromLogD: Chromatographic logD values were determined from the chromatographic hydrophobicity index (CHI) using the equation $chromLogD_{7.4} = 0.0857\ CHI_{7.4} - 2$.[4] The CHI value of individual compounds was measured on a Waters Aquity UPLC system, XSelect HSS C18 5 μm 4.6x150 mm HPLC column, 5-100% gradient of MeCN in 50mM NH_4OAc in H_2O adjusted to pH 7.4. Retention times of standards with known CHI were used to establish the linear regression expression for use on the test compounds. The calibration compounds were as follows; Phenyltetrazole, Benzimidazole, Acetanilide, Phenol, Acetophenone, Indol, Nitrobenzene, Propiophenone, Anisole, Benzofuran, Butyrophenone, Valerophenone.[5]

ChromHSA: The % free fraction from binding to human serum albumin (HSA) was determined from the retention times of the compounds on a CHIRALPAK® HSA 50x3 mm column. A 0-30% gradient of IPA in 50mM NH_4OAc in H_2O adjusted to pH 7.4 was applied on a Waters Aquity UPLC system. The retention times of known samples, with a range of % free fractions, were used to calculate the HSA binding, as reported previously.[6] The calibration compounds were as follows; Warfarin = 5.1 ± 0.4% (lit. = 2%), Nizatidine = 65 ± 4.4% (lit. = 65%), Bromazepam = 21 ± 0.8% (lit. = 40%), Carbamazepine = 18 ± 1.6% (lit. = 25%), Budesonide = 16 ± 1.1% (lit. = 12%), Piroxicam = 5.0 ± 0.1% (lit. = 5.5%), Nicardipine = 10 ± 1.7% (lit. = 5%), Ketoprofen = 1.6 ± 0.1% (lit. = 1.3%), Indomethacine = -0.1 ± 0.1% (lit. = 1%), Diclofenac = 0.7 ± 0.1% (lit. = 0.2%).

Synthetic Methods:

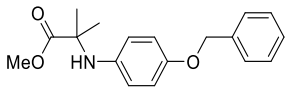
General Experiment and Information: Reagents and solvents were of commercially available reagent grade quality and used without further purification. Compound **2** was synthesised as described previously.[7] Compound **9** was synthesised as described previously.[8] 4-(trans-3-amino-2,2,4,4-tetramethyl-cyclobutoxy)-2-(trifluoromethyl)benzonitrile hydrochloride was synthesised as described previously.[9] Reactions requiring anhydrous conditions were carried out in oven dried glassware under an atmosphere of N_2. Microwave heated reactions were carried out sealed flasks using a Biotage Initiator8+ with the power varied to achieve the stated temperature. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F_{254} aluminium or glass supported sheets, or by liquid chromatography-mass spectrometry (LCMS). Flash column chromatography was carried out on a Biotage Isolera One system using either normal phase (SiO_2) or reverse phase (C18) cartridges. Compounds were loaded in solution or adsorbed onto Celite® 545 or ISOLUTE® HM-N, and eluted using a linear gradient of the specified solvents. Purification by C18 reverse phase HPLC was carried using an Agilent 1260 Infinity machine and a Waters XBridge BEH C18 OBD column (130 Å, 5 µm, 30 mm × 100 mm) with a linear gradient of H_2O (with 0.1% NH_3) and MeCN (with 0.1% NH_3). LCMS and low resolution mass spectrometry (LRMS) analysis was performed on a Waters Aquity HClass UPLC system with a Aquity QDa for mass detection. High-resolution mass spectra (HRMS) were measured on a XEVO G2S QTOF or VION IMS QTOF spectrometer at the Department of Chemistry, University of Cambridge. NMR spectra were recorded on a Bruker Advance III (^{1}H = 300 MHz, ^{19}F = 282 MHz, ^{13}C = 75 MHz) spectrometer using the requisite solvent as a reference for internal deuterium lock. The chemical shift data for each signal are given as δ chemical shift (multiplicity, *J* values in Hz, integration) in units of parts per million (ppm) relative to tetramethylsilane (TMS) where δH (TMS) = 0.00 ppm. The multiplicity of each signal is indicated by: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), or m (multiplet). Signals from exchangeable protons are not always detected. UPLC analysis of final compounds was performed on a Waters Aquity HClass UPLC system and is reported as method name, retention time, UV % purity. The method parameters are as follows;

Method	Column	Additive	Flow rate	Gradient (time, %MeCN in H_2O)
A	BEH C18 (130 Å, 1.7 µm, 2.1 mm × 50 mm)	10 mM NH_3	0.6 mL/min	0 min, 5%; 0.8 min, 5%; 3.3 min, 95%; 4.3 min, 95%; 4.5 min, 5%; 5.5 min, 5%.
B	HSS C18 (100 Å, 1.8 µm, 2.1 mm × 50 mm)	0.1% HCO_2H	0.6 mL/min	0 min, 5%; 0.8 min, 5%; 3.3 min, 95%; 4.3 min, 95%; 4.5 min, 5%; 5.5 min, 5%.
C	BEH C18 (130 Å, 1.7 µm, 2.1 mm × 50 mm)	10 mM NH_3	0.6 mL/min	0 min, 5%; 0.8 min, 5%; 8.3 min, 95%; 9.3 min, 95%; 9.5 min, 5%; 10.5 min, 5%.
D	HSS C18 (100 Å, 1.8 µm, 2.1 mm × 50 mm)	0.1% HCO_2H	0.6 mL/min	0 min, 5%; 0.8 min, 5%; 8.3 min, 95%; 9.3 min, 95%; 9.5 min, 5%; 10.5 min, 5%.

Abbreviations: ABCN: 1,1'-azobis(cyclohexanecarbonitrile, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA: *N*,*N*-diisopropylethylamine, DMF: *N,N*-dimethylformamide, HATU: *N*-[(dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide, HRMS: high resolution mass spectrometry, LCMS: liquid chromatography-mass spectrometry, LRMS: low resolution mass spectrometry, IPA: isopropyl alcohol, NBS: *N*-bromosuccinimide, TBDMS: *tert*-butyldimethylsilyl, TFA: trifluoroacetic acid, THF: tetrahydrofuran.

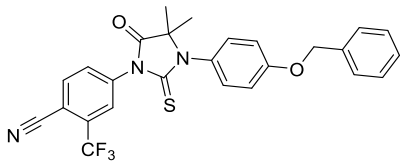
Scheme S1 Experimental:

Methyl 2-(4-benzyloxyanilino)-2-methyl-propanoate 22



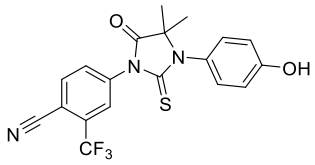
An oven-dried 100 mL flask with stirrer was charged with 4-benzyloxyaniline **21** (1820 mg, 9.13 mmol), methyl α-bromoisobutyrate (3.00 mL, 23.2 mmol) and sodium hydrogen carbonate (1950 mg, 23.2 mmol). The flask was sealed with a suba, evacuated and back-filled with nitrogen (×3). The heterogenous mixture was slowly stirred and heated without solvent at 150 °C. After 5 h, the brown viscous solution was allowed to cool to rt overnight. TLC of the crude mixture shows complete consumption of the starting material. Accordingly, the reaction mixture was partitioned between H_2O (30 mL) and diethyl ether (30 mL). The aqueous phase was further extracted with diethyl ether (2 × 30 mL), the combined organics washed with H_2O (100 mL) and brine (100 mL), then dried (Na_2SO_4). The mixture was filtered and the filtrate concentrated *in vacuo* to give a brown residue that was purified by flash chromatography (50g SiO_2, EtOAc:Hexane, 0-20%) to give methyl 2-(4-benzyloxyanilino)-2-methyl-propanoate **22** (2370 mg, 7.92 mmol, 87% yield) as an orange oil that solidified on standing overnight. MS (ESI): *m/z* $[M+H]^+$ calcd $[C18H22NO3]^+$ 300.2, found 300. ^1H NMR (300 MHz, Chloroform-*d*) δ 7.48 - 7.32 (m, 5H), 6.90 - 6.80 (m, 2H), 6.70 - 6.60 (m, 2H), 5.01 (s, 2H), 3.89 (br. s, 1H), 3.75 - 3.70 (m, 3H), 1.49 - 1.56 (m, 6H).

4-[3-(4-Benzyloxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile 23



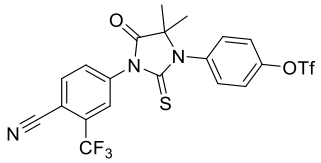
An oven-dried 100 mL flask with stirrer was charged with methyl 2-(4-benzyloxyanilino)-2-methyl-propanoate **22** (1687 mg, 5.64 mmol) and 4-cyano-3-(trifluoromethyl)phenylisothiocyanate (1873 mg, 8.21 mmol). The flask was sealed with a suba, evacuated and back-filled with nitrogen (x3). Anhydrous DMSO (18 mL) and isopropyl acetate (18 mL) were added and a 10 cm Vigreux column fitted. The reaction mixture stirred at 25 °C for 2hr before heating the mixture to 82 °C and heating for a further 16 h. TLC analysis showed complete consumption of SM. Accordingly, the reaction mixture was cooled to rt, quenched with sat. aq. $NaHCO_3$ (10 mL), stirred for 10 min and then further diluted with H_2O (100 mL), extracted with EtOAc (3 × 100 mL), the organics combined and rewashed with H_2O (3 × 100 mL) and brine (100 mL). The organic phases were dried (Na_2SO_4), filtered, and the filtrate concentrated *in vacuo*. The crude residue was purified flash column chromatography (50g SiO_2, EtOAc:Hexane, 0-30%) to give 4-[3-(4-benzyloxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **23** (2356 mg, 4.75 mmol, 84% yield) as an off-white solid. MS (ESI): *m/z* $[M+H]^+$ calcd $[C26H21F3N3O2S]^+$ 496.1, found 496. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.04 - 7.96 (m, 2H), 7.90 - 7.82 (m, 1H), 7.51 - 7.36 (m, 5H), 7.27 - 7.21 (m, 2H), 7.17 - 7.11 (m, 2H), 5.13 (s, 2H), 1.60 (s, 6H). ^{19}F NMR (282 MHz, Chloroform-d) δ -61.97.

4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile 3



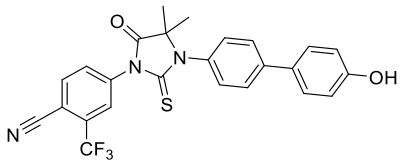
An oven-dried 250 mL flask with stirrer was charged with 4-[3-(4-benzyloxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **23** (2145 mg, 4.33 mmol). The flask was sealed with a suba, evacuated and back-filled with nitrogen (X3). Anhydrous CH_2Cl_2 (20 mL) was added and the reaction mixture cooled to -78 °C. Boron tribromide (1M in CH_2Cl_2, 8.66 mL, 8.66 mmol) was added in a single portion. The reaction mixture was stirred at -78 °C for 1.5 h. TLC analysis showed complete consumption of SM. Accordingly sat. aq. sodium bicarbonate solution (5 mL) was added and the mixture stirred rapidly for 5 min. The crude mixture was then diluted with CH_2Cl_2 (100 mL) and H_2O (100 mL) and warmed to rt. The phases were separated and the aqueous phase re-extracted with CH_2Cl_2 (2 x 100 mL), the organics were combined, washed with H_2O (100 mL) and brine (100 mL), then dried (Na_2SO_4). The solution was filtered and the filtrate concentrated *in vacuo* to give the crude product as an orange residue. The crude residue was purified by flash column chromatography (SiO_2, EtOAc:Hexane, 0-50%) to give an iridescent foam. The material was freeze-dried to give 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **3** (1615 mg, 3.98 mmol, 92% yield) as an off-white powder. MS (ESI): *m/z* $[M-H]^-$ calcd $[C19H13F3N3O2S]^-$ 404.1, found 404. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.04 - 7.96 (m, 2H), 7.91 - 7.82 (m, 1H), 7.22 - 7.15 (m, 2H), 7.03 - 6.94 (m, 2H), 5.31 (br. s, 1H), 1.63 - 1.56 (m, 6H). ^{19}F NMR (282 MHz, Chloroform-d) δ -61.95. These data are in accordance with the literature.[10]

[4-[3-[4-cyano-3-(Trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenyl] trifluoromethanesulfonate 24



4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **3** (100 mg, 0.250 mmol) was dissolved in CH_2Cl_2 (2 mL) in an ice bath, followed by addition of triethylamine (0.1 mL, 0.74 mmol) and triflic anhydride (0.050 mL, 0.30 mmol) and the reaction mixture was stirred under N_2 for 1 hour. The reaction was quenched with H_2O (20 mL) and washed with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with brine and dried (hydrophobic frit). The organic solvent was removed *in vacuo* and the crude product [4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenyl] trifluoromethanesulfonate **24** (132 mg, 0.246 mmol, quant.), a brown oil, was used in the next reaction without further purification.

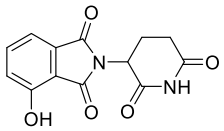
4-[3-[4-(4-Hydroxyphenyl)phenyl]-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile 25



[4-[3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenyl] trifluoromethanesulfonate **24** (132 mg, 0.250 mmol), tetrakis(triphenylphosphine)palladium (29 mg, 0.020 mmol) and tripotassium phosphate monohydrate (170 mg, 0.740 mmol) were heated at 90 °C for 1 hour in 1,4-Dioxane (2 mL) under microwave irradiation. Then H_2O (10 mL) was added to the reaction mixture and washed with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and dried (hydrophobic frit) and the solvent removed *in vacuo*. The residue was purified by silica gel chromatography (SiO_2, gradient elution 10 to 100% EtOAc in petrol) to give 4-[3-[4-(4-hydroxyphenyl)phenyl]-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **25** (104 mg, 0.216 mmol, 87% yield) as a pale yellow oil. MS (ESI): *m/z* $[M-H]^-$ calcd $[C25H17F3N3O2S]^-$ 480.1, found 480.3. 1H NMR (300 MHz, Chloroform-d) δ 8.01 (d, *J* = 1.7 Hz, 1H), 7.99 (s, 1H), 7.88 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.75 – 7.67 (m, *J* =8.1 Hz, 2H), 7.56 – 7.48 (m, *J* = 8.4 Hz, 2H), 7.40 – 7.32 (mF, *J* = 8.6 Hz, 2H), 6.98 – 6.90 (m, *J* = 8.6 Hz, 2H), 5.40 (bs, 1H), 1.65 (s, 6H).

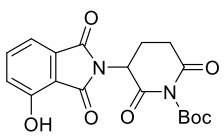
Scheme S2 experimental:

2-(2,6-Dioxo-3-piperidyl)-4-hydroxy-isoindoline-1,3-dione 27



A dry 25 mL flask was charged with 4-hydroxyisobenzofuran-1,3-dione **26** (220 mg, 1.34 mmol) , 3-aminopiperidine-2,6-dione hydrochloride (243 mg, 1.47 mmol) and THF (5mL), then triethylamine (0.560 mL, 4.02 mmol) was added and the reaction heated at 80 °C for 4 hours. After this period a solution of *N*,*N*'-dicyclohexylcarbodiimide (332 mg, 1.61 mmol) and 4-dimethylaminopyridine (16 mg, 0.13 mmol) was added and the reaction mixture was stirred at 80 °C for a further 20 hours. Upon completion the reaction mixture was cooled to 0 °C, filtered (eluent THF), and concentrated *in vacuo*. Purification via silica gel chromatography (gradient elution 1 to 20% MeOH in CH_2Cl_2) yielded 2-(2,6-dioxo-3-piperidyl)-4-hydroxy-isoindoline-1,3-dione **27** (332 mg, 1.21 mmol, 90% yield) as a pale yellow solid. MS (ESI): *m/z* $[M-H]^-$ calcd $[C13H9N2O5]^-$ 273.1, found 273.1. 1H NMR (300 MHz, Chloroform-d) δ 8.26 (s, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 5.05 – 4.86 (m, 1H), 3.06 – 2.68 (m, 3H), 2.28 – 2.13 (m, 1H).

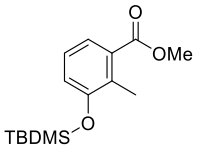
***Tert*-butyl 3-(4-hydroxy-1,3-dioxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate 28**



2-(2,6-dioxo-3-piperidyl)-4-hydroxy-isoindoline-1,3-dione **27** (320 mg, 1.17 mmol), di-*t*-butyl-dicarbonate (535 mg, 2.45 mmol) and 4-dimethylaminopyridine (143 mg, 1.17 mmol) were stirred at r.t. in 1,4-dioxane (10 mL). After stirring for 3 hours piperidine (0.120 mL, 1.17 mmol) was added and

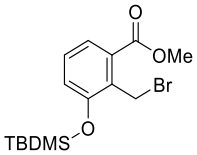
stirred for a further hour at room temperature, then water (20 mL) and CH_2Cl_2 (20 mL) was added. The aqueous layer was further washed with CH_2Cl_2 (20 mL) and the organic layers combined, dried through a hydrophobic frit and the solvent removed *in vacuo*. Purification via silica gel chromatography (gradient elution 1 to 10% MeOH in CH_2Cl_2) yielded *tert*-butyl 3-(4-hydroxy-1,3-dioxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate **28** (311 mg, 0.831 mmol, 71% yield) as a yellow solid. MS (ESI): *m/z* $[M-H]^-$ calcd $[C18H17N2O7]^-$ 373.1, found 373.1. 1H NMR (300 MHz, DMSO-d6) δ 7.62 (t, *J* = 7.8 Hz, 1H), 7.23 (dd, *J* = 17.4, 7.8 Hz, 2H), 5.33 (dd, *J* = 12.9, 5.3 Hz, 1H), 3.10 (ddd, *J* = 17.5, 13.8, 5.5 Hz, 1H), 2.78 (ddd, *J* = 17.6, 4.5, 2.4 Hz, 1H), 2.62 (td, *J* = 13.2, 4.4 Hz, 1H), 2.18 - 1.98 (m, 1H), 1.49 (s, 9H).

Methyl 3-[*tert*-butyl(dimethyl)silyl]oxy-2-methyl-benzoate 30



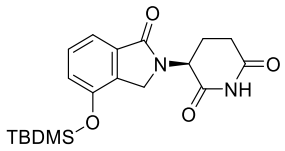
To a solution of methyl 3-hydroxy-2-methyl-benzoate **29** (1.00 g, 6.02 mmol) and imidazole (819 mg, 12.0 mmol) in anhydrous DMF (6.0 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (998 mg, 6.62 mmol) portionwise over 5 mins. The reaction mixture was allowed to warm to rt and stirred for 17.5 hrs. Upon completion the reaction mixture was concentrated *in vacuo*, resuspended in EtOAc (50 mL), washed with $NaHCO_3$ (2 × 50 mL) and brine (50 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification via silica gel chromatography (gradient elution 2 to 30% EtOAc in petroleum ether) yielded methyl 3-[*tert*-butyl(dimethyl)silyl]oxy-2-methyl-benzoate **30** (1440 mg, 5.13 mmol, 85% yield) as a colourless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.15 – 7.03 (m, 1H), 6.93 (ddd, *J* = 8.1, 1.3, 0.4 Hz, 1H), 3.88 (s, 3H), 2.42 (d, *J* = 0.5 Hz, 3H), 1.02 (s, 9H), 0.22 (s, 6H).

Methyl 2-(bromomethyl)-3-[*tert*-butyl(dimethyl)silyl]oxy-benzoate 31



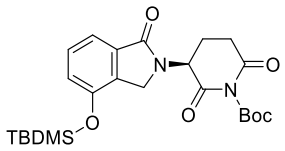
To a solution of methyl 3-[*tert*-butyl(dimethyl)silyl]oxy-2-methyl-benzoate **30** (1500 mg, 5.35 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (157 mg, 0.640 mmol) in chloroform (13 mL) was added *N*-bromosuccinimide (1142 mg, 6.42 mmol) over 5 mins. The reaction mixture was heated at 70 °C for 4 hrs, then cooled, washed with Na_2SO_3 (50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification via silica gel chromatography (gradient elution 2 to 20% EtOAc in petroleum ether) yielded methyl 2-(bromomethyl)-3-[*tert*-butyl(dimethyl)silyl]oxy-benzoate **31** (1751 mg, 4.87 mmol, 91% yield) as a colourless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.54 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.02 (dd, *J* = 8.2, 1.3 Hz, 1H), 5.05 (s, 2H), 3.95 (s, 3H), 1.09 (s, 9H), 0.33 (s, 6H).

(3*S*)-3-[4-[*Tert*-butyl(dimethyl)silyl]oxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione 32



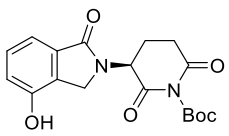
To a mixture of methyl 2-(bromomethyl)-3-[*tert*-butyl(dimethyl)silyl]oxy-benzoate **31** (406 mg, 1.13 mmol) and (3*S*)-3-aminopiperidine-2,6-dione hydrobromide (260 mg, 1.24 mmol) in THF (9.4 mL) was added triethylamine (0.36 mL, 2.6 mmol) at the reaction mixture heated at 75 °C for 18 hrs. After this period the reaction mixture was cooled to rt, concentrated *in vacuo*, resuspended in CH_2Cl_2 (50 mL), washed with H_2O (2 × 50 mL) and brine (50 mL), then dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (gradient elution 20 to 100% EtOAc in petroleum ether) yielded (3*S*)-3-[4-[*tert*-butyl(dimethyl)silyl]oxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione **32** (139 mg, 0.371 mmol, 33% yield) as a white solid. MS (ESI): *m/z* $[M+H]^+$ calcd $[C19H27N2O4Si]^+$ 375.2, found 375.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.94 (s, 1H), 7.52 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.44 – 7.33 (m, 1H), 7.00 (dd, *J* = 8.0, 0.9 Hz, 1H), 5.24 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.42 (d, *J* = 16.2 Hz, 1H), 4.27 (d, *J* = 16.1 Hz, 1H), 3.02 – 2.76 (m, 2H), 2.43 (qd, *J* = 12.9, 5.4 Hz, 1H), 2.24 (dtd, *J* = 13.0, 5.2, 2.7 Hz, 1H), 1.03 (s, 9H), 0.29 (s, 6H).

Tert-butyl (3*S*)-3-[4-[*tert*-butyl(dimethyl)silyl]oxy-1-oxo-isoindolin-2-yl]-2,6-dioxo-piperidine-1-carboxylate 33



To a solution of (3*S*)-3-[4-[*tert*-butyl(dimethyl)silyl]oxy-1-oxo-isoindolin-2-yl]piperidine-2,6-dione **32** (50 mg, 0.13 mmol) and triethylamine (0.04 mL, 0.29 mmol) in THF (1.3 mL) was added di-*t*-butyl-dicarbonate (64 mg, 0.29 mmol) and 4-dimethylaminopyridine (3.3 mg, 0.030 mmol) as a solution in THF (0.5 mL) and the reaction mixture was stirred at rt for 1.5 hrs. After this time the reaction was queched with H_2O (25 mL), extracted with CH_2Cl_2 (2 × 25 mL) and the combined organics were washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (12g SiO_2, gradient elution 6 to 80% EtOAc in petroleum ether) yielded *tert*-butyl (3*S*)-3-[4-[*tert*-butyl(dimethyl)silyl]oxy-1-oxo-isoindolin-2-yl]-2,6-dioxo-piperidine-1-carboxylate **33** (41 mg, 0.086 mmol, 65% yield) as a white solid. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C24H38N3O6Si]^+$ 492.3, found 492.1. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.52 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 6.99 (dd, *J* = 8.0, 0.9 Hz, 1H), 5.32 (dd, *J* = 13.5, 5.1 Hz, 1H), 4.40 (d, *J* = 16.1 Hz, 1H), 4.25 (d, *J* = 16.1 Hz, 1H), 3.09 – 2.82 (m, 2H), 2.44 (qd, *J* = 13.0, 5.4 Hz, 1H), 2.21 (dtd, *J* = 13.0, 5.2, 2.7 Hz, 1H), 1.58 (s, 9H), 1.03 (s, 9H), 0.29 (d, *J* = 0.9 Hz, 6H).

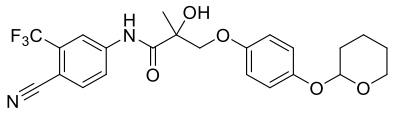
Tert-butyl (3*S*)-3-(4-hydroxy-1-oxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate 34



To a solution of *tert*-butyl (3*S*)-3-[4-[*tert*-butyl(dimethyl)silyl]oxy-1-oxo-isoindolin-2-yl]-2,6-dioxo-piperidine-1-carboxylate **33** (95 mg, 0.20 mmol) in THF (4 mL) at -40 °C was added tetrabutylammonium fluoride (1M THF solution) (0.22 mL, 0.220 mmol) and the reaction mixture stirred at -40 °C for 15 mins. Then the reaction mixture was warmed to rt, quenched with sat. aq. NH_4Cl (25 mL), extracted with EtOAc (2 × 25 mL), and the combined organics were washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (12g SiO_2, gradient elution 20 to 100% EtOAc in petroleum ether) yielded *tert*-butyl (3*S*)-3-(4-hydroxy-1-oxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate **34** (67 mg, 0.19 mmol, 93% yield) as a white solid. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C18H24N3O6]^+$ 378.2, found 378.1 (50%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.45 (d, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.01 (dd, *J* = 7.9, 1.1 Hz, 1H), 5.29 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.47 (d, *J* = 16.3 Hz, 1H), 4.33 (d, *J* = 16.4 Hz, 1H), 3.07 – 2.81 (m, 2H), 2.38 (qd, *J* = 13.0, 5.3 Hz, 1H), 2.20 (dtd, *J* = 12.9, 5.1, 2.7 Hz, 1H), 1.58 (s, 9H).

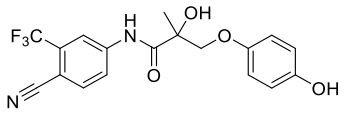
Scheme S3 experimental:

_N_-(4-Cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-2-methyl-3-(4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenoxy)propanamide 36



N-(4-Cyano-3-(trifluoromethyl)phenyl)-2-methyloxirane-2-carboxamide **35** (300 mg, 1.11mmol), 4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenol (280 mg, 1.44mmol) and potassium carbonate (307 mg, 2.22 mmol) were stirred in isopropyl alcohol (20 mL) at room temperature and the reaction solution heated to reflux for 3 hours. The solvent was removed under reduced pressure and the residue taken up in EtOAc (40 mL) and H_2O (40 mL). The organic layer was dried *in vacuo* and purified by flash column chromatography (SiO_2, EtOAc:Hexane, 10-100%) to give *N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methyl-3-(4-tetrahydropyran-2-yloxyphenoxy)propanamide **36** (468 mg, 1.01 mmol, 91% yield) as a white foam. MS (ESI): *m/z* $[M-H]^-$ calcd $[C23H22F3N2O5]^-$ 463.1, found 463.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.16 (s, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 7.97 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.05 – 6.96 (m, 2H), 6.89 – 6.82 (m, 2H), 5.31 (t, *J* = 3.3 Hz, 1H), 4.43 (d, *J* = 9.1 Hz, 1H), 3.95 (d, *J* = 9.1 Hz, 1H), 3.93 – 3.87 (m, 1H), 3.60 (dtd, *J* = 11.3, 4.2, 1.5 Hz, 1H), 2.06 – 1.63 (m, 6H), 1.59 (s, 3H).

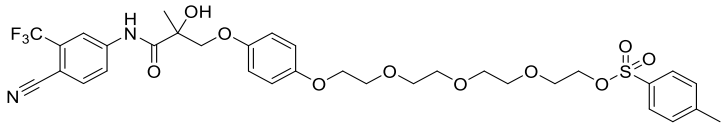
_N_-(4-Cyano-3-(trifluoromethyl)phenyl)-2-hydroxy-3-(4-hydroxyphenoxy)-2-methylpropanamide 1



Hydrogen chloride (2.0 mL, 8.0 mmol, 4.0 M in 1,4-dioxane) was added to a solution of *N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methyl-3-(4-tetrahydropyran-2-yloxyphenoxy)propanamide **36** (470 mg, 1.01 mmol) in methanol (8 mL) and stirred at 4 °C for 1.5 hours. The solvent was removed *in vacuo* and EtOAc (20 mL) and H_2O (20 mL) were added. The organic layer was dried by passing through a hydrophobic-frit phase separator and the solvent removed *in vacuo*. The residue was purified by silica gel chromatography (10-100% EtOAc in hexane) to give *N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-3-(4-hydroxyphenoxy)-2-methyl-propanamide **1** (323 mg, 0.850

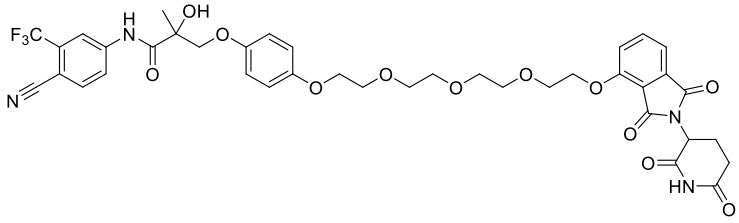
mmol, 84% yield) as a white foam. MS (ESI): *m/z* $[M-H]^-$ calcd $[C18H14F3N2O4]^-$ 379.1, found 379.1. ^1H NMR (300 MHz, Chloroform-*d*) δ 9.15 (s, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 7.98 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 6.88 – 6.71 (m, 4H), 4.70 (s, 1H), 4.42 (d, *J* = 9.1 Hz, 1H), 3.94 (d, *J* = 9.1 Hz, 1H), 3.48 (s, 1H), 1.59 (s, 3H).

2-(2-(2-(2-(4-(3-((4-Cyano-3-(trifluoromethyl)phenyl)amino)-2-hydroxy-2-methyl-3-oxopropoxy)phenoxy)ethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate 37



A flask was charged with *N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-3-(4-hydroxyphenoxy)-2-methyl-propanamide **1** (100 mg, 0.260 mmol), tetraethylene glycol di(p-toluenesulfonate) (397 mg, 0.790 mmol), potassium carbonate (40 mg, 0.290 mmol) in acetone (25mL). The reaction mixture was heated to reflux and stirred for 48 hours, then heated under microwave irradiation at 120 °C for 2 hours. The reaction mixture was cooled to room temperature, the solvent removed *in vacuo* and the residue purified by silica gel chromatography (10-100% EtOAc: pet ether 40-60) to give the product with some starting material impurity. The almost-pure material was taken in MeCN and purified by preparatory HPLC (5 to 95% MeCN in H_2O with 0.1% NH_3) to give 2-[2-[2-[2-[4-[3-[4-cyano-3-(trifluoromethyl)anilino]-2-hydroxy-2-methyl-3-oxo-propoxy]phenoxy]ethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate **37** (60 mg, 0.085 mmol, 32% yield) as a clear oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C33H41F3N3O10S]^+$ 728.2, found 728.2. ^1H NMR (300 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 8.13 (d, *J* = 2.1 Hz, 1H), 7.97 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.80 (dd, *J* = 8.5, 2.3 Hz, 3H), 7.34 (dt, *J* = 8.0, 0.7 Hz, 2H), 6.86 (s, 4H), 4.43 (d, *J* = 9.1 Hz, 1H), 4.19 – 4.11 (m, 2H), 4.11 – 4.04 (m, 2H), 3.95 (d, *J* = 9.1 Hz, 1H), 3.88 – 3.78 (m, 2H), 3.77 – 3.63 (m, 6H), 3.63 – 3.55 (m, 4H), 2.46 (s, 3H), 1.59 (s, 3H).

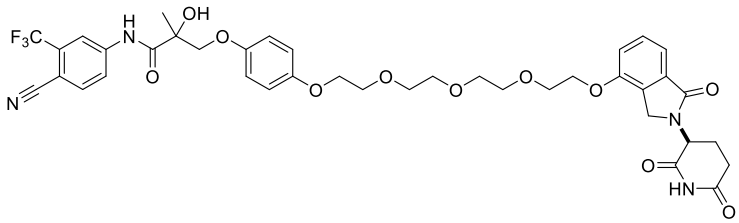
***N*-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenoxy)-2-hydroxy-2-methylpropanamide 10**



A flask was charged with 2-[2-[2-[2-[4-[3-[4-cyano-3-(trifluoromethyl)anilino]-2-hydroxy-2-methyl-3-oxo-propoxy]phenoxy]ethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate **37** (25 mg, 0.040 mmol), *tert*-butyl 3-(4-hydroxy-1,3-dioxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate (13 mg, 0.040 mmol) and potassium carbonate (5.0 mg, 0.040 mmol) in acetone (2 mL). The reaction mixture was heated to reflux and stirred for 20 hours and then heated under microwave irradiation at 100 °C for 1 hour. The reaction mixture was cooled to room temperature, the solvent removed *in vacuo* and the residue purified by preparatory HPLC (5 to 95% MeCN in H_2O with 0.1% NH_3) to give Boc-protected intermediate (29 mg, 0.032 mmol) as a clear oil. This was taken up in CH_2Cl_2 (2 mL), TFA (1 mL) was added dropwise at 0 °C, and allowed to warm to room temperature. After stirring for 1 hour, LCMS

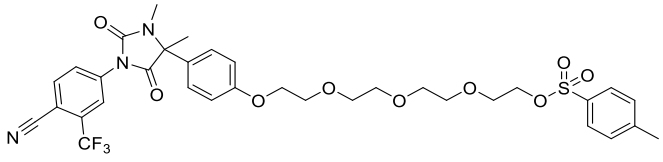
indicated that the reaction had gone to completion, the solvent was removed *in vacuo* and the product was purified by preparatory HPLC (5 to 95% MeCN in H_2O with 0.1% NH_3) to give *N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[4-[2-[2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]phenoxy]-2-hydroxy-2-methyl-propanamide **10** (2.8 mg, 0.003 mmol, 11% yield) as a clear oil. MS (ESI): *m/z* $[M-H]^-$ calcd $[C39H38F3N4O12]^-$ 811.2, found 811.2. ^1H NMR (300 MHz, Methanol-d_4) δ 8.38 (d, *J* = 2.2 Hz, 1H), 8.15 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.81 – 7.67 (m, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 6.89 – 6.81 (m, 5H), 5.19 – 5.01 (m, 1H), 4.42 – 4.32 (m, 2H), 4.26 (d, *J* = 9.5 Hz, 1H), 4.17 (t, *J* = 4.6 Hz, 1H), 4.10 – 3.87 (m, 5H), 3.84 – 3.71 (m, 3H), 3.72 – 3.61 (m, 6H), 2.93 – 2.64 (m, 3H), 2.21 – 2.06 (m, 1H), 1.52 (s, 3H). UPLC analysis (method C), 5.30 min, 88%.

_N_-(4-cyano-3-(trifluoromethyl)phenyl)-3-(4-(2-(2-(2-(2-((2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenoxy)-2-hydroxy-2-methylpropanamide 11



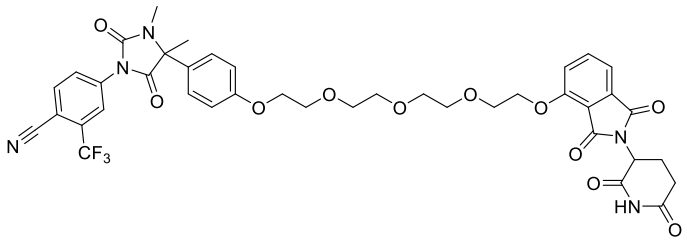
To a microwave flask containing *tert*-butyl (3*S*)-3-(4-hydroxy-1-oxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate (23 mg, 0.070 mmol) and potassium carbonate (17 mg, 0.12 mmol) was added a solution of 2-[2-[2-[2-[4-[3-[4-cyano-3-(trifluoromethyl)anilino]-2-hydroxy-2-methyl-3-oxo-propoxy]phenoxy]ethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate **37** (44 mg, 0.060 mmol) in anhydrous acetone (1.2 mL). The reaction mixture was heated under microwave irradiation at 120 °C for 1 hr, then stirred at rt for 20 hrs. Then the reaction mixture was diluted with EtOAc (25 mL), washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo*. Purification by reverse phase chromatography (12g C18, gradient elution 10 to 80% MeCN in H_2O) yielded the de-Boc product *N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[4-[2-[2-[2-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-4-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]phenoxy]-2-hydroxy-2-methyl-propanamide **11** (7.0 mg, 0.009 mmol, 14% yield) as a white solid (colourless oil once concentrated from CDCl3). MS (ESI): *m/z* $[M-H]^-$ calcd $[C39H40F3N4O11]^-$ 797.3, found 797. ^1H NMR (300 MHz, Chloroform-*d*) δ 9.31 (d, *J* = 7.2 Hz, 1H), 8.28 (s, 1H), 8.22 – 8.08 (m, 1H), 8.06 – 7.92 (m, 1H), 7.79 (dd, *J* = 8.5, 3.9 Hz, 1H), 7.49 – 7.32 (m, 2H), 7.09 – 6.95 (m, 1H), 6.86 – 6.63 (m, 4H), 5.23 – 5.07 (m, 1H), 4.42 – 3.58 (m, 21H), 2.95 – 2.70 (m, 2H), 2.37 – 2.06 (m, 2H), 1.54 (s, 3H). UPLC analysis (method B), 2.99 min, >98%.

2-(2-(2-(2-(4-(1-(4-cyano-3-(trifluoromethyl)phenyl)-3,4-dimethyl-2,5-dioxoimidazolidin-4-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate 38



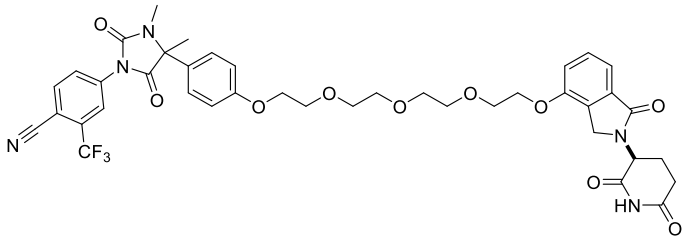
To a microwave vial containing 4-[4-(4-hydroxyphenyl)-3,4-dimethyl-2,5-dioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **2** (42 mg, 0.11 mmol) and potassium carbonate (18 mg, 0.13 mmol) was added a solution of tetraethylene glycol di(p-toluenesulfonate) (163 mg, 0.32 mmol) in acetone (1 mL) and the reaction mixture was heated at 110 °C under microwave irradiation for 1 hr. After this period the reaction mixture was diluted with EtOAc (25 mL), washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (24 g SiO_2, gradient elution 5 to 60% EtOAc in CH_2Cl_2) yielded 2-[2-[2-[2-[4-[1-[4-cyano-3-(trifluoromethyl)phenyl]-3,4-dimethyl-2,5-dioxo-imidazolidin-4-yl]phenoxy]ethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate **38** (38 mg, 0.052 mmol, 48% yield) as a colourless oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C34H40F3N4O9S]^+$ 737.2, found 737.3. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.16 (d, *J* = 2.0 Hz, 1H), 8.01 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.83 – 7.75 (m, 2H), 7.38 – 7.31 (m, 2H), 7.31 – 7.22 (m, 2H), 7.04 – 6.95 (m, 2H), 4.19 – 4.13 (m, 4H), 3.87 (dd, *J* = 5.7, 3.9 Hz, 2H), 3.76 – 3.54 (m, 10H), 2.94 (s, 3H), 2.45 (s, 3H), 1.94 (s, 3H).

4-(4-(4-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)-3,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile 12



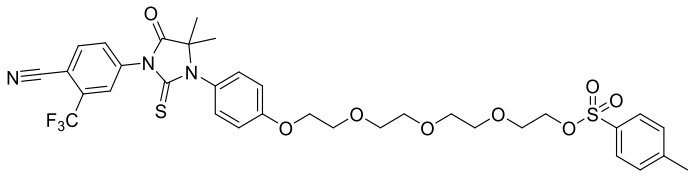
To a microwave vial charged with 2-[2-[2-[2-[4-[1-[4-cyano-3-(trifluoromethyl)phenyl]-3,4-dimethyl-2,5-dioxo-imidazolidin-4-yl]phenoxy]ethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate **38** (15 mg, 0.020 mmol) and potassium carbonate (17.3 mg, 0.130 mmol) was added a solution of *tert*-butyl 3-(4-hydroxy-1,3-dioxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate (12 mg, 0.030 mmol) in acetone (1mL) and the reaction mixture was heated at 110 °C under microwave irradiation for 2 hrs. Then the reaction was diluted with EtOAc (25 mL), washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (12 g SiO_2, gradient elution 10 to 100% EtOAc in petroleum ether, then 0 to 10% MeOH added), followed by resuspension in H_2O:MeCN (1:1, 25 mL) and lyophilisation yielded the Boc-protected intermediate (6.4 mg, 0.007 mmol, 33% yield) as a white solid. This was redissolved in CH_2Cl_2 (1mL), cooled to 0 °C, then trifluoroacetic acid (0.050 mL, 0.71 mmol) was added and the reaction mixture was stirred at 0 °C for 7 hrs. After this time the reaction was concentrated *in vacuo*, resuspended in CH_2Cl_2 (15 mL), washed with 10% citric acid (10 mL) and brine (10 mL) then dried (hydrophobic frit) and concentrated *in vacuo* to give 4-[4-[4-[2-[2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]phenyl]-3,4-dimethyl-2,5-dioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **12** (4.8 mg, 0.006 mmol, 27% yield) as a colourless oil. MS (ESI): *m/z* $[M-H]^-$ calcd $[C40H37F3N5O11]^-$ 820.2, found 820. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 2.0 Hz, 1H), 8.02 (s, 1H), 7.92 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.60 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.23 – 7.12 (m, 3H), 6.94 – 6.86 (m, 2H), 4.86 (dd, *J* = 12.1, 5.4 Hz, 1H), 4.32 – 4.23 (m, 2H), 4.11 – 4.00 (m, 2H), 3.91 – 3.83 (m, 2H), 3.82 – 3.75 (m, 2H), 3.75 – 3.68 (m, 2H), 3.68 – 3.54 (m, 6H), 3.16 – 3.02 (m, 1H), 2.85 (s, 3H), 2.80 – 2.61 (m, 2H), 2.07 – 1.97 (m, 1H), 1.85 (s, 3H). UPLC analysis (method B), 3.13 min, >98%.

4-(4-(4-(2-(2-(2-(2-((2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)-3,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile 13



To a microwave vial charged with 2-[2-[2-[2-[4-[1-[4-cyano-3-(trifluoromethyl)phenyl]-3,4-dimethyl-2,5-dioxo-imidazolidin-4-yl]phenoxy]ethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate **38** (15 mg, 0.020 mmol) and potassium carbonate (6.0 mg, 0.040 mmol) was added a solution of *tert*-butyl (3S)-3-(4-hydroxy-1-oxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate (7.9 mg, 0.020 mmol) in acetone (0.4 mL) and the reaction mixture was heated at 110 °C under microwave irradiation for 2 hours. Upon completion the reaction was diluted with EtOAc (25 mL), washed with brine (25 mL), dried (hyrophobic frit) and concentrated *in vacuo*. Purification via reverse phase chromatography (12 g C18, gradient elution 10 to 80% MeCN in H_2O) yielded only the Boc-deprotected product 4-[4-[4-[2-[2-[2-[2-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-4-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]phenyl]-3,4-dimethyl-2,5-dioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **13** (3.4 mg, 0.004 mmol, 20% yield) as a white solid after lyophilisation. MS (ESI): *m/z* $[M-H]^-$ calcd $[C40H39F3N5O10]^-$ 806.3, found 806. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.19 – 8.12 (m, 1H), 8.07 – 7.88 (m, 3H), 7.55 – 7.39 (m, 2H), 7.29 – 7.16 (m, 2H), 7.06 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.03 – 6.92 (m, 2H), 5.22 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.51 – 4.10 (m, 6H), 3.92 – 3.82 (m, 3H), 3.78 – 3.57 (m, 8H), 2.94 (s, 3H), 2.92 – 2.76 (m, 2H), 2.45 – 2.14 (m, 3H), 1.94 (s, 3H). UPLC analysis (method D), 5.40 min, >98%.

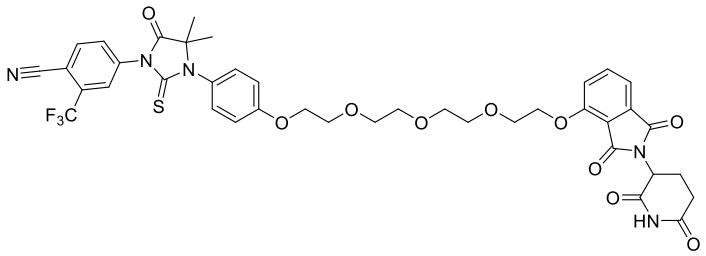
2-(2-(2-(2-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)ethoxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate 39



To a microwave vial containing 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **3** (87 mg, 0.21 mmol) and potassium carbonate (44 mg, 0.32 mmol) was added a solution of tetraethylene glycol di(p-toluenesulfonate) (0.26 mL, 0.64 mmol) in acetone (2 mL) and the reaction mixture was heated at 110 °C under microwave irradiation for 1 hr. After this period the reaction was diluted with EtOAc (25 mL), washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (30g SiO_2, gradient elution 10 to 100% EtOAc in petroleum ether; then 30g SiO_2, gradient elution 5 to 60% EtOAc in CH_2Cl_2) followed by purification via reverse phase silica gel chromatography (12g C18, gradient elution 10 to 100% MeOH in H_2O) yielded 2-[2-[2-[2-[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenoxy]ethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate **39** (50

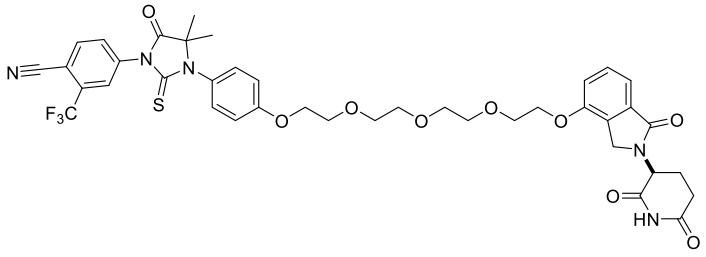
mg, 0.068 mmol, 32% yield) which was obtained as a white solid after lyophilisation. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C34H40F3N4O8S2]^+$ 753.2, found 753. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.04 – 7.95 (m, 2H), 7.87 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.84 – 7.76 (m, 2H), 7.40 – 7.31 (m, 2H), 7.27 – 7.17 (m, 2H), 7.13 – 7.01 (m, 2H), 4.26 – 4.12 (m, 4H), 3.94 – 3.86 (m, 2H), 3.78 – 3.65 (m, 6H), 3.64 – 3.57 (m, 4H), 2.46 (s, 3H), 1.59 (s, 6H) ^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.94.

4-(3-(4-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile 14



To a microwave vial containing a suspension of 2-[2-[2-[2-[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenoxy]ethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate **39** (29 mg, 0.040 mmol) and potassium carbonate (27 mg, 0.20 mmol) was added a solution of *tert*-butyl 3-(4-hydroxy-1,3-dioxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate (22 mg, 0.060 mmol) in acetone (1mL) and the reaction heated under microwave irradiation at 110 °C for 2 hrs. Upon completion the reaction was concentrated *in vacuo*, resuspended in EtOAc (25 mL), washed with brine (25 mL) dried (hydrophobic frit) and concentrated *in vacuo*. Purification via reverse phase chromatography (12g C18, gradient elution 10 to 100% MeCN in H_2O) yielded only the Boc-deprotected product 4-[3-[4-[2-[2-[2-[2-[2-(2,6-dioxo-3-piperidyl)-1,3-dioxo-isoindolin-4-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]phenyl]-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **14** (9.9 mg, 0.012 mmol, 30% yield) as a white solid after lypholisation. MS (ESI): *m/z* $[M-H]^-$ calcd $[C40H37F3N5O10S]^-$ 836.2, found 836. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.08 – 7.95 (m, 3H), 7.91 – 7.82 (m, 1H), 7.69 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.49 (dd, *J* = 7.3, 0.7 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.26 – 7.16 (m, 2H), 7.12 – 7.01 (m, 2H), 4.96 (dd, *J* = 12.1, 5.4 Hz, 1H), 4.42 – 4.33 (m, 2H), 4.24 – 4.15 (m, 2H), 4.02 – 3.86 (m, 4H), 3.86 – 3.77 (m, 2H), 3.81 – 3.62 (m, 6H), 2.97 – 2.67 (m, 3H), 2.22 – 2.08 (m, 1H), 1.59 (s, 6H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.96. UPLC analysis (method C), 5.74 min, 91%.

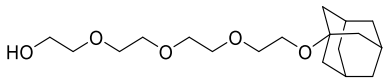
(S)-4-(3-(4-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile 15



To a microwave vial containing a suspension of 2-[2-[2-[2-[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenoxy]ethoxy]ethoxy]ethoxy]ethyl 4-methylbenzenesulfonate **39** (32 mg, 0.040 mmol) and cesium carbonate (43 mg, 0.13 mmol) was added a solution of *tert*-butyl (3*S*)-3-(4-hydroxy-1-oxo-isoindolin-2-yl)-2,6-dioxo-piperidine-1-carboxylate (17 mg, 0.050 mmol) in DMF (1 mL) and the reaction heated under microwave irradiation at 100 °C for 1 hr. After this time the reaction mixture was concentrated, resuspended in EtOAc (25 mL), washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo*. Purification via preparatory HPLC (30 to 75% MeCN in H_2O with 0.1% NH_3) yielded the Boc-deprotected product 4-[3-[4-[2-[2-[2-[2-[2-[(3S)-2,6-dioxo-3-piperidyl]-1-oxo-isoindolin-4-yl]oxyethoxy]ethoxy]ethoxy]ethoxy]phenyl]-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **15** (2.0 mg, 0.002 mmol, 6% yield) as a white solid after lyophilisation. MS (ESI): *m/z* $[M-H]^-$ calcd $[C40H39F3N5O9S]^-$ 822.2, found 822. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.04 – 7.93 (m, 2H), 7.86 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.25 – 7.17 (m, 2H), 7.10 – 6.98 (m, 3H), 5.23 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.51 – 4.14 (m, 6H), 3.94 – 3.85 (m, 3H), 3.79 – 3.58 (m, 7H), 3.00 – 2.75 (m, 3H), 2.47 – 2.18 (m, 3H), 1.56 (s, 6H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.97. UPLC analysis (method C), 5.61 min, 91%.

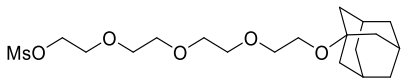
Scheme S4 Experimental:

2-(2-(2-(2-(((3s,5s,7s)-Adamantan-1-yl)oxy)ethoxy)ethoxy)ethoxy)ethan-1-ol 41



A round-bottom flask was charged with tetraethylene glycol **40** (4577 mg, 23.6 mmol), 1-bromoadamantane 99% (1000 mg, 4.65 mmol), triethylamine (2.09 mL, 15.0 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mL, 0.23 mmol). Upon stirring at 110 °C for 18 h the reaction was diluted with 25 mL 1 M aq. HCl and extracted with CH_2Cl_2 (2 x 25 mL). The organic layer was washed with H_2O (2 x 25 mL) and dried with Na_2SO_4 to yield a crude oil. Column chromatography (4:1 Hex:EtOAc to 100% EtOAc) gave the product **41** (1.30 g, 3.95 mmol, 85% yield) as a colourless oil. MS (ESI): *m/z* $[M+H]^+$ calcd $[C18H33O5]^+$ 329.2, found 329.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.78 – 3.72 (m, 2H), 3.69 (d, *J* = 3.1 Hz, 8H), 3.65 – 3.58 (m, 6H), 2.16 (s, 3H), 1.77 (d, *J* = 3.0 Hz, 6H), 1.71 – 1.55 (m, 6H). These data are in agreement with the literature.[1]

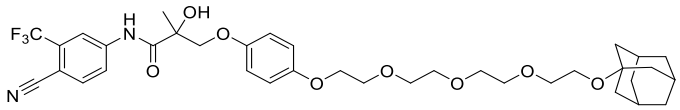
2-(2-(2-(2-(((3s,5s,7s)-Adamantan-1-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl methanesulfonate42



A round-bottom flask was charged 2-[2-[2-[2-(1-adamantyloxy)ethoxy]ethoxy]ethoxy]ethanol **41** (200 mg, 0.61 mmol), methanesulfonyl chloride (0.07 mL, 0.910 mmol) and triethylamine (0.25 mL, 1.83 mmol). Upon stirring at room temperature for 18 h, the reaction was diluted with 5 mL 1M aq. HCl and extracted with CH_2Cl_2 (2 x 5 mL). The organic layer was washed with H_2O (2 x 10 mL) and dried with Na_2SO_4. Purification by silica gel chromatography (SiO_2, gradient elution 25 to 100% EtOAc in petroleum ether) gave 2-(2-(2-(2-(((3s,5s,7s)-adamantan-1-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl methanesulfonate **42** (252 mg, 0.620 mmol, quant. yield) as a clear oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd

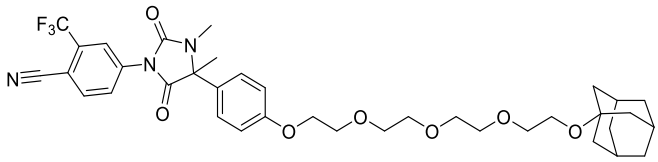
[C19H38NO7S]$^+$ 424.2, found 424.4. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.45 – 4.36 (m, 2H), 3.83 – 3.75 (m, 2H), 3.75 – 3.53 (m, 12H), 3.11 (s, 3H), 2.16 (s, 3H), 1.80 – 1.73 (m, 6H), 1.67 – 1.54 (m, 6H).

3-[4-[2-[2-[2-[2-(1-Adamantyloxy)ethoxy]ethoxy]ethoxy]ethoxy]phenoxy]-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methyl-propanamide 16



N-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-3-(4-hydroxyphenoxy)-2-methyl-propanamide **1** (42 mg, 0.11 mmol), 2-[2-[2-[2-(1-adamantyloxy)ethoxy]ethoxy]ethoxy]ethyl methanesulfonate **42** (50 mg, 0.120 mmol) and potassium carbonate (17 mg, 0.12 mmol) in acetone (1 mL) were heated at 120 °C for 2 hours under microwave irradiation. After cooling to room temperature, EtOAc (20 mL) and H_2O (20 mL) were added and the layers separated. The aqueous layer was further washed with EtOAc (20 mL). The combined organic layers were combined and dried (hydrophobic frit) and the product purified by preparatory HPLC (5 to 95% MeCN in H_2O with 0.1% NH_3). Further purification by reverse-phase chromatography (12g C18 gradient elution 5 to 80% MeCN in H_2O) to give 3-[4-[2-[2-[2-[2-(1-adamantyloxy)ethoxy]ethoxy]ethoxy]ethoxy]phenoxy]-*N*-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methyl-propanamide **16** (57 mg, 0.083 mmol, 75% yield) as a clear oil. MS (ESI): *m/z* [M-H]$^-$ calcd [C36H44F3N2O8]$^-$ 689.3, found 689.4. ^{1}H NMR (300 MHz, Chloroform-d) δ 9.22 (s, 1H), 8.15 (d, *J* = 2.1 Hz, 1H), 7.99 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 6.84 (s, 4H), 4.42 (d, *J* = 9.1 Hz, 1H), 4.11 – 4.05 (m, 2H), 3.94 (d, *J* = 9.1 Hz, 1H), 3.88 – 3.81 (m, 2H), 3.75 – 3.67 (m, 4H), 3.67 (s, 4H), 3.60 (dt, *J* = 3.4, 1.6 Hz, 4H), 2.15 (s, 3H), 1.77 – 1.72 (m, 6H), 1.61 (m, 9H). UPLC analysis (method A), 3.57 min, >98%.

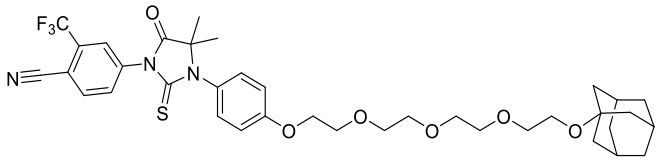
4-(4-(4-(2-(2-(2-(2-(((3*s*,5*s*,7*s*)-adamantan-1-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)-3,4-dimethyl-2,5-dioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile 17



4-[4-(4-hydroxyphenyl)-3,4-dimethyl-2,5-dioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **2** (28 mg, 0.070 mmol), 2-[2-[2-[2-(1-adamantyloxy)ethoxy]ethoxy]ethoxy]ethyl methanesulfonate **42** (32 mg, 0.080 mmol) and potassium carbonate (11 mg, 0.080 mmol) in acetone (1mL) were heated at 120 °C for 2 hours under microwave irradiation. After cooling to room temperature, EtOAc (20 mL) and H_2O (20 mL) was added and the layers separated. The aqueous layer was further washed with EtOAc (20 mL). The combined organic layers were combined and dried through a phase separator and the product purified by silica gel chromatography (SiO_2, gradient elution 10 to 100% EtOAc in petroleum ether) to give the product 4-[4-[4-[2-[2-[2-[2-(1-adamantyloxy)ethoxy]ethoxy]ethoxy]ethoxy]phenyl]-3,4-dimethyl-2,5-dioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **17** (17.4 mg, 0.025 mmol, 35% yield) as a clear oil. MS (ESI): *m/z* [M+NH4]$^+$ calcd [C37H48F3N4O7]$^+$ 717.3, found 717.6. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.16 (d, *J* = 2.0 Hz, 1H), 8.01 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.31 – 7.22 (m, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 4.16 (dd, *J* = 5.7, 4.0 Hz, 2H), 3.88 (dd, *J* = 5.7, 4.0 Hz, 2H), 3.79 – 3.64 (m, 8H), 3.64 – 3.57 (m,

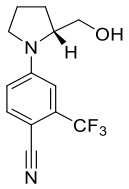
4H), 2.95 (s, 3H), 2.15 (s, 3H), 1.76 (d, *J* = 3.0 Hz, 6H), 1.72 – 1.56 (m, 9H). UPLC analysis (method A), 3.66 min, >98%.

4-(3-(4-(2-(2-(2-(2-(((3*s*,5*s*,7*s*)-adamantan-1-yl)oxy)ethoxy)ethoxy)ethoxy)ethoxy)phenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile 18



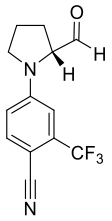
A 2mL microwave vial containing a mixture of 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **3** (40 mg, 0.10 mmol), 2-[2-[2-[2-(1-adamantyloxy)ethoxy]ethoxy]ethoxy]ethyl methanesulfonate **42** (40 mg, 0.10 mmol) and potassium carbonate (14 mg, 0.10 mmol) in acetone (1 mL) was heated for 2 hrs under microwave irradiation at 80 °C. LCMS indicated starting material was still present so the reaction was heated at 110 °C for a further 1 hr. After cooling to rt, the reaction was diluted with EtOAc (25 mL), washed with H_2O (25 mL) and brine (25 mL), then dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (12g C18, gradient elution 10 to 100% MeCN in H_2O) yielded 4-[3-[4-[2-[2-[2-[2-(1-adamantyloxy)ethoxy]ethoxy]ethoxy]ethoxy]phenyl]-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **18** (7.7 mg, 0.011 mmol, 11% yield) as a white solid after lypholisation. MS (ESI): *m/z* $[M+Na]^+$ calcd $[C37H44F3N3NaO6S]^+$ 738.3, found 738. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.04 – 7.95 (m, 2H), 7.91 – 7.82 (m, 1H), 7.26 – 7.16 (m, 2H), 7.12 – 7.03 (m, 2H), 4.25 – 4.16 (m, 2H), 3.96 – 3.87 (m, 2H), 3.80 – 3.67 (m, 8H), 3.66 – 3.54 (m, 4H), 2.16 (s, 3H), 1.76 (d, *J* = 2.9 Hz, 6H), 1.69 – 1.54 (m, 12H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.97. UPLC analysis (method C), 7.40 min, >98%.

4-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile 44



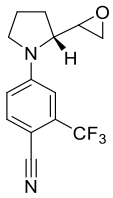
A 20mL microwave flask was charged with (*R*)-pyrrolidin-2-ylmethanol (0.49 mL, 4.9 mmol), 4-Fluoro-2-(trifluoromethyl)benzonitrile **43** (1120 mg, 5.93 mmol), triethylamine (0.76 mL, 5.4 mmol) and anhydrous THF (10 mL), then sealed and heated at 50 °C for 18 hrs. Upon completion the reaction mixture was concentrated *in vacuo*, resuspended in CH_2Cl_2 (50 mL), washed with NH_4Cl (2 x 50 mL) and brine (50 mL), then dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (gradient elution 8 to 66% EtOAc in petroleum ether) yielded 4-[(2*R*)-2-(hydroxymethyl)pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile **44** (843 mg, 3.12 mmol, 63% yield) as a white solid. MS (ESI): *m/z* $[M-H]^-$ calcd $[C13H12F3N2O]^-$ 269.1, found 269. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.56 (dd, *J* = 8.8, 0.8 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.79 (dd, *J* = 8.8, 2.6 Hz, 1H), 4.08 – 3.96 (m, 1H), 3.73 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.66 (dd, *J* = 11.0, 6.7 Hz, 1H), 3.61 – 3.49 (m, 1H), 3.37 – 3.22 (m, 1H), 2.29 – 1.99 (m, 4H).

4-[(2*R*)-2-formylpyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile 45



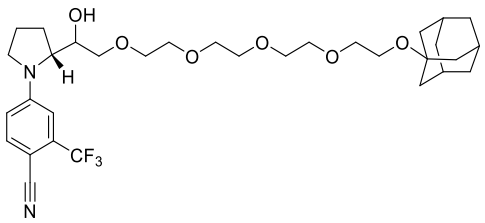
To a solution of 4-[(2R)-2-(hydroxymethyl)pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile **44** (819 mg, 3.03 mmol) in CH_2Cl_2 (15.2 mL) and DMSO (3.8 mL) at 0 °C was added triethylamine (4.22 mL, 30.3 mmol) followed by sulfur trioxide pyridine complex (1929 mg, 12.1 mmol) and the reaction mixture was stirred at 0 °C for 2 hrs. After this time the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL), followed by H_2O (25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), then the combined organics were washed with brine (25 mL) and 10% LiCl (5 × 25 mL), dried (hydrophobic frit) and concentrated *in vacuo*. The crude material was redissolved in CH_2Cl_2 (50 mL), washed with sat aq $NaHCO_3$ (2 × 50 mL), then dried (hydrophobic frit) and concentrated *in vacuo*. The product 4-[(2*R*)-2-formylpyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile **45** (618 mg, 2.30 mmol, 76% yield) was isolated as a yellow oil and used immediately in the following reaction. MS (ESI): *m/z* $[M-H]^-$ calcd $[C13H10F3N2O]^-$ 267.1, found 267.

4-((2*R*)-2-(oxiran-2-yl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile 46



To a dry 25 mL flask containing a solution of sodium hydride (60% dispersion in mineral oil, 101 mg, 2.53 mmol) in DMSO (2.3 mL) was added trimethylsulfoxonium iodide (558 mg, 2.53 mmol) and the mixture stirred for 5 mins. When gas evolution had stopped, a solution of 4-[(2*R*)-2-formylpyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile **45** (618 mg, 2.3 mmol) in THF (2.3 mL) was added and the reaction mixture was stirred at rt for 60 mins. Upon completion the reaction mixture was concentrated *in vacuo* to remove the THF then partitioned between H_2O (25 mL) and EtOAc (25 mL). The aqueous phase was further extracted with EtOAc (25 mL), and the combined organics were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification via silica gel chromatography (30g SiO_2, gradient elution 6 to 80% EtOAc in petroleum ether) yielded 4-[(2*R*)-2-(oxiran-2-yl)pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile **46** (188 mg, 0.666 mmol, 29% yield) as a pale yellow oil. MS (ESI): *m/z* $[M+H]^+$ calcd $[C14H14F3N2O]^+$ 283.1, found 283. ^1H NMR (300 MHz, Chloroform-*d*) δ 7.66 – 7.54 (m, 1H), 7.05 (d, *J* = 2.6 Hz, 0.2H), 6.95 (d, *J* = 2.6 Hz, 0.8H), 6.88 (dd, *J* = 8.8, 2.5 Hz, 0.2H), 6.79 (dd, *J* = 8.8, 2.6 Hz, 0.8H), 4.10 – 4.00 (m, 0.8H), 3.77 – 3.67 (m, 0.2H), 3.62 – 3.51 (m, 1H), 3.40 – 3.23 (m, 1H), 3.14 – 2.99 (m, 1H), 2.86 (dd, *J* = 4.8, 3.8 Hz, 0.8H), 2.80 (dd, *J* = 4.7, 4.0 Hz, 0.2H), 2.66 (dd, *J* = 4.9, 2.6 Hz, 0.8H), 2.52 (dd, *J* = 4.7, 2.7 Hz, 0.2H), 2.31 – 1.99 (m, 4H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -62.33 (s, 0.6F), -62.39 (s, 2.4F).

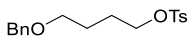
4-((2*R*)-2-(14-(((3*s*,5*s*,7*s*)-adamantan-1-yl)oxy)-1-hydroxy-3,6,9,12-tetraoxatetradecyl)pyrrolidin-1-yl)-2-(trifluoromethyl)benzonitrile 19



Sodium hydride (60% dispersion in mineral oil, 8.5 mg, 0.210 mmol) was added to a solution of 2-[2-[2-[2-(1-adamantyloxy)ethoxy]ethoxy]ethoxy]ethanol **41** (58 mg, 0.180 mmol) in THF (1mL) and stirred for 30 mins at room temperature. A solution of 4-[(2*R*)-2-(oxiran-2-yl)pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile **46** (50 mg, 0.180 mmol) in THF (0.5 mL) was added and the reaction mixture was stirred at rt for 10 mins then heated to 110 °C under microwave radiation for 2 hours. After cooling to room temperature, H_2O (20 mL) was added and the mixture extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo*. The crude residue was purified by silica gel chromatography (SiO_2, gradient elution 10 to 100% EtOAc in petroleum ether). Further purification by reverse-phase chromatography (C18, gradient elution 5 to 80% MeCN in H_2O) to give the product 4-[(2*R*)-2-[2-[2-[2-[2-[2-(1-adamantyloxy)ethoxy]ethoxy]ethoxy]ethoxy]-1-hydroxy-ethyl]pyrrolidin-1-yl]-2-(trifluoromethyl)benzonitrile **19** (28 mg, 0.046 mmol, 26% yield). MS (ESI): *m/z* $[M-H]^-$ calcd $[C32H44F3N2O6]^-$ 609.3, found 609.3. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.63 – 7.55 (m, 1H), 7.04 (d, *J* = 2.5 Hz, 0.15 H), 6.99 (d, *J* = 2.5 Hz, 0.85 H), 6.89 (dd, *J* = 8.9, 2.6 Hz, 0.15H), 6.82 (dd, *J* = 8.8, 2.6 Hz, 0.85H), 4.10 (t, *J* = 7.2 Hz, 0.15H), 4.05 – 3.95 (m, 0.85H), 3.92 (dd, *J* = 6.9, 3.1 Hz, 0.15H), 3.85 (q, *J* = 5.2 Hz, 0.85H), 3.74 – 3.50 (m, 18H), 3.42 (dd, *J* = 9.9, 5.4 Hz, 1H), 3.35 – 3.22 (m, 1H), 2.40 – 1.80 (m, 9H), 1.75 (m, *J* = 2.9 Hz, 5H), 1.70 – 1.54 (m, 5H). UPLC analysis (method A), 3.61 min, >98%.

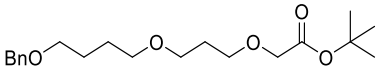
Scheme S5 experimental:

4-(Benzyloxy)butyl 4-methylbenzenesulfonate 48



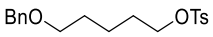
A 100 mL flask with stirrer was charged p-toluenesulfonyl chloride (3330 mg, 17.5 mmol) and 4-dimethylaminopyridine (203 mg, 1.66 mmol). The flask was sparrged with nitrogen and anhydrous CH_2Cl_2 (20 mL) added. The mixture was cooled in an ice-bath and 4-benzyloxybutan-1-ol **47** (2.93 mL, 16.64 mmol) and triethylamine (2.55 mL, 18.3 mmol) added. The reaction mixture was allowed to warm to RT overnight. Reaction diluted with H_2O (40 mL), stirred for 5 min and then passed through a hydrophobic frit. The organic phase was concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography (50 g SiO_2, linear gradient 5-40% EtOAc in hexanes) gave 4-(benzyloxy)butyl 4-methylbenzenesulfonate **48** (4700 mg, 14.1 mmol, 84%) as a clear oil. MS (ESI): *m/z* $[M+H]^+$ calcd $[C18H23O4S]^+$ 335.1, found 335.1. ^{1}H NMR (300 MHz, Chlorofrom-*d*) δ 7.91 - 7.73 (m, 2H), 7.46 - 7.22 (m, 7H), 4.47 (s, 2H), 4.08 (t, *J* = 6.42 Hz, 2H), 3.45 (t, *J* = 6.10 Hz, 2H), 2.46 (s, 3H), 1.87 - 1.73 (m, 2H), 1.73 - 1.60 (m, 2H).

***Tert*-butyl 2-(3-(4-(benzyloxy)butoxy)propoxy)acetate 49a**



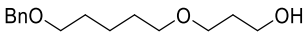
An oven-dried 100 mL flask with stirrer was charged with sodium hydride (60% dispersion in mineral oil, 556 mg, 13.9 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous DMF (40 mL) was added followed by1,3-propanediol (1.06 mL, 14.6 mmol) and the reaction mixture stirred at 0 °C for 1 hr. 4-benzyloxybutyl 4-methylbenzenesulfonate **48** (4650 mg, 13.9 mmol) was added and the reaction mixture allowed to warm to RT and stirred overnight. The reaction mixture was then cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 556 mg, 13.9 mmol) was added and the reaction mixture stirred for 15 min. *Tert*-butyl bromoacetate (2.05 mL, 13.9 mmol) was added and the reaction mixture allowed to warm to RT and stirred for 36 h. Then the reaction was quenched with saturated ammonium chloride (10 mL) and concentrated *in vacuo*. The crude residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL) and the biphasic mixture passed through a phase separator. The aqueous phase was reshaken with CH_2Cl_2 (100 mL) and passed through a phase separator. The combined organic phase was concentrated *in vacuo* then was purified by flash chromatography (50 g SiO_2, linear gradient 0-10% EtOAc in hexanes) to give *tert*-butyl 2-(3-(4-(benzyloxy)butoxy)propoxy)acetate **49a** (3040 mg, 8.62 mmol) as a mixture with impurities that was used in the next step without further purification. MS (ESI): *m/z* $[M+Na]^+$ calcd $[C20H32NaO5]^+$ 375.2, found 375.3.

5-(Benzyloxy)pentyl 4-methylbenzenesulfonate 51



A 100 mL flask with stirrer was charged p-toluenesulfonyl chloride (1660 mg, 8.76 mmol) and 4-dimethylaminopyridine (102 mg, 0.830 mmol). The flask was sparged with nitrogen and anhydrous CH_2Cl_2 (30mL) added. The mixture was cooled in an ice-bath and 5-(benzyloxy)pentan-1-ol **50** (1.50 mL, 8.34 mmol) added. The reaction mixture was allowed to warm to RT overnight. The reaction mixture was diluted with H_2O (40 mL), stirred for 5 min and then passed through a 75 mL phase separator. The organic phase was concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography (50 g SiO_2, linear gradient 5-50% EtOAc in hexanes) gave 5-(benzyloxy)pentyl 4-methylbenzenesulfonate **51** (2330 mg, 6.69 mmol, 80% yield) as a clear oil. MS (ESI): *m/z* $[M+H]^+$ calcd $[C19H25O4S]^+$ 349.1, found 349.1. ^1H NMR (300 MHz, Chlorofrom-*d*) δ 7.86 - 7.75 - (m, 2H), 7.43 - 7.24 (m, 7H), 4.50 (s, 2H), 4.05 (t, *J* = 6.42 Hz, 2H), 3.45 (t, *J* = 6.33 Hz, 2H), 2.46 (s, 3H), 1.76 - 1.37 (m,6H).

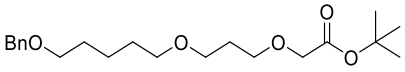
3-((5-(Benzyloxy)pentyl)oxy)propan-1-ol 52



An oven-dried 100 mL flask with stirrer was charged with sodium hydride (60% dispersion in mineral oil, 290 mg, 7.26 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous DMF (20 mL) followed by 1,3-propanediol (0.53 mL, 7.26 mmol) were added and the reaction mixture stirred at 25 °C for 0.5 hr. To the cloudy solution was added a solution of 5-benzyloxypentyl 4-methylbenzenesulfonate **51** (2300 mg, 6.60 mmol) in anhydrous DMF (10 mL). The solution was stirred at 25 °C for 15 min and then warmed to 50 °C and stirred for a further 4 hr. The reaction mixture was cooled to RT then concentrated *in vacuo*. The residue was partitioned between H_2O (40 mL) and CH_2Cl_2 (40 mL) and passed through a hydrophobic frit. The aqueous phase was extracted with CH_2Cl_2 (40 mL) and passed through a hydrophobic frit twice more and then the organic

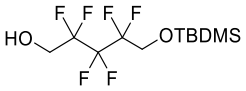
phases were combined and concentrated *in vacuo*. The crude yellow oil was then purified by flash chromatography (50 g SiO_2, linear gradient 5-100% EtOAc in hexanes) to give 3-((5-(benzyloxy)pentyl)oxy)propan-1-ol **52** (1258 mg, 4.99mmol, 76% yield) as a viscous oil. MS (ESI): *m/z* $[M+H]^+$ calcd $[C15H25O3]^+$ 253.2, found 253.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.41 - 7.29 (m, 5H), 4.52 (s, 2H), 3.80 (q, *J* = 5.4 Hz, 2H), 3.66 - 3.60 (m, 2H), 3.48 (td, *J* =11.0, 6.5 Hz, 4H), 2.48 (t, *J* = 5.2 Hz, 1H), 1.85 (td, *J* = 11.2, 5.7 Hz, 2H), 1.72 - 1.56 (m, 4H), 1.51 - 1.38 (m, 2H).

Tert-butyl 2-(3-((5-(benzyloxy)pentyl)oxy)propoxy)acetate 49b



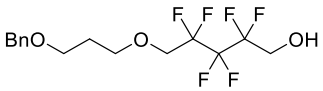
An oven-dried 100 mL flask with stirrer was charged with 3-(5-benzyloxypentoxy)propan-1-ol **52** (440 mg, 1.74 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). CH_2Cl_2 (3 mL) was added followed by *tert*-butyl bromoacetate (1.03 mL, 6.97 mmol) and tetrabutylammonium chloride (533 mg, 1.92 mmol). A solution of sodium hydroxide (1.10 g, 10.2 mmol) in H_2O (3 ml) was added and the biphasic mixture stirred rapidly at RT for 24 hr. The crude reaction mixture was passed through a hydrophobic frit and the organic phase concentrated *in vacuo* to give a crude orange residue. This was purified by flash chromatography (25 g SiO_2, linear gradient 5-50% EtOAc in hexanes) to give *tert*-butyl 2-[3-(5-benzyloxypentoxy)propoxy]acetate **49b** (277 mg, 0.76 mmol, 43% yield) as a clear oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C21H38NO5]^+$ 384.3, found 384.3. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.39 - 7.29 (m, 5H), 4.52 (s, 2H), 3.97 (s, 2H), 3.66 - 3.39 (m, 8H), 1.90 (t, *J* = 6.4 Hz, 2H), 1.72 - 1.56 (m, 6H), 1.52 - 1.48 (m, 9H).

5-((_Tert_-butyldimethylsilyl)oxy)-2,2,3,3,4,4-hexafluoropentan-1-ol 54



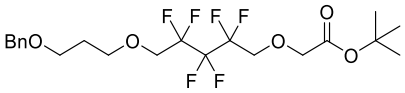
An oven-dried 100 mL flask fitted with a pressure-equalising dropping funnel and with stirrer was charged with 2,2,3,3,4,4-hexafluoropentane-1,5-diol **53** (1000 mg, 4.71 mmol) and imidazole (353 mg, 5.19 mmol). The flask was placed under a blanket of nitrogen and anhydrous DMF (30 mL) was added and the reaction mixture cooled to 0 °C. During this time, a solution of *tert*-butyldimethylsilyl chloride (781 mg, 5.19 mmol) in anhydrous DMF (5 mL) was prepared in the dropping funnel and then added dropwise over 0.5 hr. The solution was allowed to warm to RT and stirred overnight. The reaction was quenched with sat. aq. $NaHCO_3$ (15 mL) and extracted with ether (3 x 50 mL), washed with H_2O (100 mL), 10% lithium chloride soln. (100 mL) and brine (100 mL), then dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo* to give a crude oil. This was purified by flash chromatography (45 g SiO_2, linear gradient 0-30% EtOAc in hexanes) to give **54** 5-[*tert*-butyl(dimethyl)silyl]oxy-2,2,3,3,4,4-hexafluoro-pentan-1-ol (692 mg, 2.12 mmol, 45% yield) as an oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 4.00 - 4.19 (m, 4H), 0.91 - 0.96 (m, 9H), 0.11 - 0.15 (m, 6H).

5-(3-(Benzyloxy)propoxy)-2,2,3,3,4,4-hexafluoropentan-1-ol 55



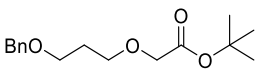
An oven-dried 50 mL flask with stirrer was charged with 5-[*tert*-butyl(dimethyl)silyl]oxy-2,2,3,3,4,4-hexafluoro-pentan-1-ol **54** (345 mg, 1.06 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous DMF (5 mL) was added and the reaction mixture cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 47 mg, 1.2 mmol) was added in a single portion and the mixture stirred for 15 min. 3-Benzyloxypropyl 4-methylbenzenesulfonate (339 mg, 1.06 mmol) was added and the reaction allowed to warm to RT and stirred for a further 48 hr. The reaction mixture was quenched with sat. aq. ammonium chloride (1 mL), diluted with H_2O (30 mL) and then partitioned with EtOAc (30 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 x 30 mL). Organic phases were combined, washed with H_2O (100 mL), 10% aq. lithium chloride (100 mL) and brine (100 mL), then dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo* to give a crude residue. This was purified by flash chromatography (10 g SiO_2, linear gradient 0-30% EtOAc in hexanes) to give 5-(3-(benzyloxypropoxy)-2,2,3,3,4,4-hexafluoro-pentan-1-ol **55** (168 mg, 0.466 mmol, 44% yield) as an oil. MS (ESI): *m/z* $[M-H]^-$ calcd $[C15H17F6O3]^-$ 359.1, found 359.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.42 - 7.29 (m, 5H), 4.53 (s, 2H), 4.07 (t, *J* = 14.31 Hz, 2H), 4.00 - 3.85 (m, 2H), 3.74 (t, *J* = 6.2 Hz, 2H), 3.60 (t, *J* = 6.1 Hz, 2H), 2.05 (br. s, 1H), 1.93 (quin, *J* = 6.2 Hz, 2H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -120.04 (m, 2F), -122.69 (m, 2F), -126.26 (s, 2F).

Tert-butyl 2-((5-(3-(benzyloxy)propoxy)-2,2,3,3,4,4-hexafluoropentyl)oxy)acetate 49c



A 25 mL flask with stirrer was charged with 5-(3-benzyloxypropoxy)-2,2,3,3,4,4-hexafluoro-pentan-1-ol **55** (164 mg, 0.460 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Tetrabutylammonium chloride (1267 mg, 0.460 mmol) and *tert*-butyl bromoacetate (0.27 mL, 1.82 mmol) were added followed by 35% aq. sodium hydroxide (2 mL) and the reaction mixture stirred rapidly overnight. The phases were separated and the organic phase diluted with toluene (5 mL), washed with H_2O (5 mL) and brine (5 mL) then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography) (10 g SiO_2, linear gradient 0-30% EtOAc in hexanes) to give *tert*-butyl 2-((5-(3-(benzyloxy)propoxy)-2,2,3,3,4,4-hexafluoropentyl)oxy)acetate **49c** (58 mg, 0.122 mmol, 27%)as a clear oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C21H32F6NO5]^+$ 492.2, found 492.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 - 7.29 (m, 5H), 4.52 (s, 2H), 4.17 - 4.03 (m, 4H), 3.92 (s, 2H), 3.73 (t, *J* = 6.2 Hz, 2H), 3.59 (t, *J* = 6.1 Hz, 2H), 1.93 (t, *J* = 6.2 Hz, 2H), 1.51 (s, 9H). ^{19}F NMR (282 MHz, Chloroform-*d*): -120.08 (m, 2F), -120.48 (m, 2F), -126.13 (s, 2F).

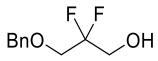
Tert-butyl 2-(3-(benzyloxy)propoxy)acetate 49e



A 100 mL flask with stirrer was charged with 3-(benzyloxy)-1-propanol **56** (1870 mg, 11.3 mmol) and tetrabutylammonium chloride (3126 mg, 11.3 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Toluene (30mL) and 35% aq. sodium hydroxide (15 mL) was added and the reaction mixture cooled to 5 °C in an ice-water bath. *Tert*-butyl bromoacetate (6.65 mL, 45 mmol) was added and the reaction mixture stirred rapidly overnight. Stirring was stopped and the phases allowed to separate. The organic phase was collected, washed with brine (50 mL), then dried

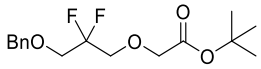
(Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (40 g SiO_2, linear gradient 0-20% EtOAc in hexanes) to give *tert*-butyl 2-(3-(benzyloxy)propoxy)acetate **49e** (1610 mg, 5.74 mmol, 51% yield). MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C16H28NO4]^+$ 298.2, found 298.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 - 7.29 (m, 5H), 4.53 (s, 2H), 3.97 (s, 2H), 3.64 (m, 4H), 1.96 (t, *J* = 6.3 Hz, 2H), 1.53 - 1.47 (m, 9H).

3-(Benzyloxy)-2,2-difluoropropan-1-ol 58



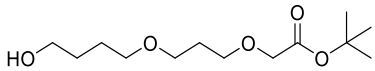
A suspension of sodium hydride (60% dispersion in mineral oil, 357 mg, 8.92 mmol) in THF (2 mL) was treated dropwise with 2,2-difluoropropane-1,3-diol **57** (0.95 mL, 8.92 mmol) and the mixture was stirred at room temperature for 45 mins. Benzylbromide (1373 mg, 8.03 mmol) and tetrabutylammonium iodide (102 mg, 0.28 mmol) was added, and the mixture was stirred at room temperature for 30 mins and then heated to reflux for 2 hours. The reaction was quenched with 10% potassium carbonate (20 mL) and extracted with EtOAc (3 x 20 mL). The organic extracts were washed with brine (20 mL), dried through a phase separator and the solvent removed *in vacuo* to give 3-(benzyloxy)-2,2-difluoropropan-1-ol **58** (489 mg, 2.42 mmol, 27%) as a clear oil. MS (ESI): *m/z* $[M-H]^-$ calcd $[C10H11F2O2]^-$ 201.1, found 201.1. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.50 – 7.29 (m, 5H), 4.66 (s, 2H), 3.92 (td, *J* = 12.8, 7.1 Hz, 2H), 3.80 (t, *J* = 12.4 Hz, 2H), 1.95 (tt, *J* = 7.1, 0.9 Hz, 1H).

***Tert*-butyl 2-(3-(benzyloxy)-2,2-difluoropropoxy)acetate 49f**



A flask was charged with **58** (489 mg, 2.42 mmol) and tetrabutylammonium chloride (672 mg, 2.42 mmol). Toluene (30 mL) and 35% aq. sodium hydroxide (3.23 mL, 28.22 mmol) was added and the reaction mixture was cooled to 4 °C in an ice-water bath. *Tert*-butyl bromoacetate (1.43 mL, 9.67 mmol) was added and the reaction mixture stirred rapidly overnight. When TLC indicated consumption of the starting material, stirring was stopped and the phases allowed to separate. The organic phase was collected, washed with brine (50 mL), then dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, EtOAc:pet ether 40-60) to give *tert*-butyl 2-(3-(benzyloxy)-2,2-difluoropropoxy)acetate **49f** (614 mg, 1.94 mmol, 80%) as a clear oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C16H26F2NO4]^+$ 334.2, found 334.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.46 – 7.31 (m, 5H), 4.66 (s, 2H), 4.08 (s, 2H), 3.90 (t, *J* = 12.5 Hz, 2H), 3.79 (t, *J* = 12.8 Hz, 2H), 1.50 (s, 9H).

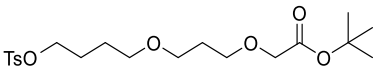
***Tert*-butyl 2-(3-(4-hydroxybutoxy)propoxy)acetate 59a**



An oven-dried 100 mL flask with stirrer was charged with *tert*-butyl 2-[3-(4-benzyloxybutoxy)propoxy]acetate **49a** (3040 mg, 8.62 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Palladium (10% w/w on carbon, 918 mg, 0.86 mmol) was added and wetted with H_2O (5 mL), followed by ethanol (45 mL) and acetic acid (3 mL). The

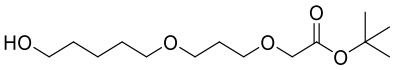
heterogeneous solution was evacuated and back-filled with nitrogen (x3) and then the process was repeated with hydrogen gas (x5). The reaction mixture was stirred at 25 °C overnight. The reaction was purged with nitrogen and then dry ice before filtering through a pad of celite, eluting with EtOAc (2 x 25 mL). The solvent was removed *in vacuo* and the crude residue purified by flash chromatography (50 g SiO_2, linear gradient 0-50% EtOAc in hexanes) to give *tert*-butyl 2-[3-(4-hydroxybutoxy)propoxy]acetate **59a** (276 mg, 1.05mmol, 12% yield) as a viscous oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.97 (s, 2H), 3.66 (br. s., 1H), 3.65 - 3.47 (m, 8H), 1.91 (t, *J* = 6.33 Hz, 2H), 1.73 - 1.66 (m, 4H), 1.52 - 1.49 (m, 9H).

Tert-butyl 2-(3-(4-(tosyloxy)butoxy)propoxy)acetate 60a



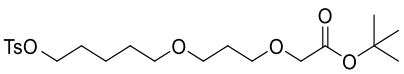
An oven-dried 100 mL flask with stirrer was charged with *tert*-butyl 2-[3-(4-hydroxybutoxy)propoxy]acetate **59a** (200 mg, 0.760 mmol) and p-toluenesulfonyl chloride (160 mg, 0.840 mmol) . The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous CH_2Cl_2 (7 mL) was added followed by triethylamine (62 µL, 0.840 mmol) and 4-dimethylaminopyridine (9.0 mg, 0.080 mmol) and the reaction mixture stirred at 25 °C for 48 hr. Upon completion the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 1M HCl (10 mL) and brine (10 mL), then passed through a hydrophobic frit and concentrated *in vacuo*. The residue was purified by flash chromatography (10 g SiO_2, linear gradient 0-50% EtOAc in hexanes to give *tert*-butyl 2-(3-(4-(tosyloxy)butoxy)propoxy)acetate **60a** (140 mg, 0.34 mmol, 44%) as a clear oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.25 Hz, 2H), 7.37 (dd, *J* =8.62, 0.73 Hz, 2H), 4.07 (t, *J* = 6.42 Hz, 2H), 3.96 (s, 2H), 3.59 (t, *J* = 6.33 Hz, 2H), 3.49 (t, *J* = 6.33 Hz, 2H), 3.39 (t, *J* = 6.05 Hz, 2H), 2.47 (s, 3H), 1.86 (t, *J* = 6.33 Hz, 6H), 1.45 - 1.52 (m, 9H).

Tert-butyl 2-(3-((5-hydroxypentyl)oxy)propoxy)acetate 59b



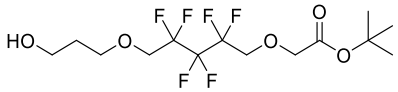
An oven-dried 25 mL flask with stirrer was charged with *tert*-butyl 2-[3-(5-benzyloxypentoxy)propoxy]acetate **49b** (250 mg, 0.68 mmol) and palladium (10% w/w on carbon, 73 mg, 0.07 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Ethanol (3 mL) was added and the flask evacuated and back-filled with hydrogen (x5).The heterogeneous reaction mixture was rapidly stirred at 25 °C overnight. After 16.5 hr the flask was flushed with nitrogen gas, diluted with EtOAc (10 mL) and passed through a 2.5 g Celite plug eluting with EtOAc. The solution was concentrated *in vacuo* to give *tert*-butyl 2-(3-((5-hydroxypentyl)oxy)propoxy)acetate **59b** (189 mg, 0.68 mmol, 100%) that was used without further purification. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.97 (s, 2H), 3.73 - 3.59 (m, 4H), 3.54 (t, *J* = 6.4 Hz, 2H), 3.45 (t, *J* = 6.4 Hz, 2H), 1.91 (t, *J* = 6.3 Hz, 2H), 1.69 - 1.56 (m, 5H), 1.53 - 1.38 (m, 11H).

Tert-butyl 2-(3-((5-(tosyloxy)pentyl)oxy)propoxy)acetate 60b



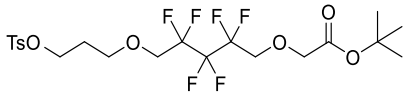
An oven-dried 50 mL flask with stirrer was charged with *tert*-butyl 2-[3-(5-hydroxypentoxy)propoxy]acetate **59b** (185 mg, 0.67 mmol), *N*,*N*-dimethylpyridin-4-amine (8.0 mg, 0.07 mmol) and 4-methylbenzenesulfonyl chloride (153 mg, 0.80 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous CH_2Cl_2 (4 mL) was added followed by triethylamine (0.11 mL, 0.80 mmol) and the reaction mixture stirred at 25 °C for 2 hr. The reaction was quenched with H_2O and the phases separated. The aqueous phase was washed twice with CH_2Cl_2 (2 x 5 mL) and the organic phases combined and passed through a hydrophobic frit and then concentrated *in vacuo* to give a crude gum. This was purified by flash chromatography (10 g SiO_2, linear gradient 0-30% EtOAc in hexanes) to give *tert*-butyl 2-(3-((5-(tosyloxy)pentyl)oxy)propoxy)acetate **60b** (214 mg, 0.50 mmol, 74% yield) as an oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C21H38NO7S]^+$ 448.2, found 448.3. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.40 - 7.33 (m, 2H), 4.04 (t, *J* = 6.5 Hz, 2H), 3.96 (s, 2H), 3.60 (t, *J* = 6.3 Hz, 2H), 3.50 (t, *J* = 6.4 Hz, 2H), 3.38 (t, *J* = 6.3 Hz, 2H), 2.47 (s, 3H), 1.88 (t, *J* = 6.4 Hz, 2H), 1.63 (m, 3H), 1.57 - 1.33 (m, 12H).

Tert-butyl 2-((2,2,3,3,4,4-hexafluoro-5-(3-hydroxypropoxy)pentyl)oxy)acetate 59c



An oven-dried 100 mL flask with stirrer was charged with *tert*-butyl 2-[5-(3-benzyloxypropoxy)-2,2,3,3,4,4-hexafluoro-pentoxy]acetate **49c** (58 mg, 0.120 mmol) and palladium (10% w/w on carbon, 13 mg, 0.010 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Methanol (1 mL) was added and the reaction mixture re-evacuated and back-filled with hydrogen gas (x5). The reaction mixture was stirred under a balloon of hydrogen at 25 °C for 24 h then purged with nitrogen gas and filtered through a plug of celite (2 g) eluting with EtOAc (10 mL). The filtrate was concentrated *in vacuo* to give a crude *tert*-butyl 2-((2,2,3,3,4,4-hexafluoro-5-(3-hydroxypropoxy)pentyl)oxy)acetate **59c** (48 mg, 0.120 mmol, quant.) that was used without further purification.

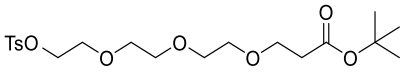
Tert-butyl 2-((2,2,3,3,4,4-hexafluoro-5-(3-(tosyloxy)propoxy)pentyl)oxy)acetate 60c



An oven-dried 50 mL flask with stirrer was charged with *tert*-butyl 2-[2,2,3,3,4,4-hexafluoro-5-(3-hydroxypropoxy)pentoxy]acetate **59c** (48 mg, 0.120 mmol) and 4-methylbenzenesulfonyl chloride (26 mg, 0.140 mmol).The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous CH_2Cl_2 (1mL) was added followed by *N*,*N*-diethylethanamine (19 uL, 0.140 mmol) and *N*,*N*-dimethylpyridin-4-amine (1.5 mg, 0.010 mmol) and the reaction mixture stirred at 25 °C overnight. The reaction was then diluted with CH_2Cl_2 (5 mL) and washed with 1 M aq. HCl (aq). The biphasic mixture was passed through a hydrophobic frit and the organic phase concentrated *in vacuo* to give a crude oil. This was purified by flash chromatography (10 g SiO_2, linear gradient 0-30% EtOAc in hexanes) to give *tert*-butyl 2-[2,2,3,3,4,4-hexafluoro-5-[3-(p-tolylsulfonyloxy)propoxy]pentoxy]acetate **60c** (31 mg, 0.058 mmol, 46% yield). MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C21H32F6NO7S]^+$ 556.2, found 556.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.6 Hz, 2H), 7.37 (dd, *J* = 8.6, 0.7 Hz, 2H), 4.19 - 4.01 (m, 6H), 3.82 (s, 2H), 3.64 (t, *J* = 5.8 Hz, 2H), 2.47

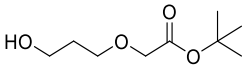
(s, 3H), 2.02 - 1.90 (m, 2H), 1.51 (s, 9H). ^{19}F NMR (282 MHz, Chloroform-*d*) Shift -120.15 (m, 2F), -120.48 (m, 2F), -126.13 (s, 2F).

Tert-butyl 3-(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)propanoate 60d



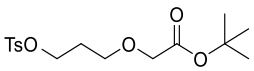
p-Toluenesulfonyl chloride (360 mg, 1.90 mmol) was added to a solution of 4-dimethylaminopyridine (22 mg, 0.18 mmol), triethylamine (275 µL, 1.98 mmol) and *tert*-butyl 3-(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)propanoate **59d** (500 mg, 1.80 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. After consumption of the starting alcohol, H_2O (6 mL) was added, stirred for 5 mins, and the mixture passed through a fritted phase separator. The organic phase was concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography (SiO_2, 10-100% EtOAc:pet ether 40-60) to give *tert*-butyl 3-(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)propanoate **60d** as a clear oil (732 mg, 1.69 mmol, 94%). MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C20H36NO8S]^+$ 450.2, found 450.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.82 (dt, *J* = 8.2, 2.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.22 – 4.13 (m, 2H), 3.76 – 3.66 (m, 4H), 3.61 (s, 4H), 3.60 (s, 4H), 2.51 (t, *J* = 6.6 Hz, 2H), 2.47 (s, 3H), 1.46 (s, 9H).

Tert-butyl 2-(3-hydroxypropoxy)acetate 59e



An oven-dried 100 mL flask with stirrer was charged with *tert*-butyl 2-(3-benzyloxypropoxy)acetate **49e** (1500 mg, 5.35 mmol) and palladium (10% w/w on carbon, 569 mg, 0.540 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Ethanol (25 mL) was added and the reaction mixture purged with nitrogen. The flask was re-evacuated and back-filled with hydrogen (x5) and the reaction mixture stirred at 20 °C for 22 hr. The reaction mixture was purged with nitrogen and then blanketed with dry ice. The mixture was filtered through a 10 g pad of celite and concentrated *in vacuo* to give *tert*-butyl 2-(3-hydroxypropoxy)acetate **59e** as a viscous oil that was used without further purification. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.99 (s, 2H), 3.84 (d, *J* = 5.5 Hz, 2H), 3.71 (t, *J* = 5.7 Hz, 2H), 2.94 (t, *J* = 6.8 Hz, 1H), 1.91 - 1.78 (m, 2H), 1.56 - 1.45 (m, 9H).

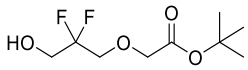
Tert-butyl 2-(3-(tosyloxy)propoxy)acetate 60e



p-Toluenesulfonyl chloride (316 mg, 1.66 mmol) was added to a solution of 4-dimethylaminopyridine (19 mg, 0.16 mmol), triethylamine (242 µL, 1.73 mmol) and *tert*-butyl 2-(3-hydroxypropoxy)acetate **59e** (300 mg, 1.58 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. After consumption of the starting alcohol, H_2O (6 mL) was added, stirred for 5 mins, and the mixture passed through a fritted phase separator. The organic phase was concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography (SiO_2, 10-100% EtOAc:pet ether 40-60) to give *tert*-butyl 2-(3-(tosyloxy)propoxy)acetate **60e** as a clear oil (390 mg,

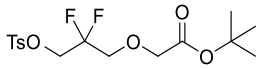
1.13 mmol, 72%). MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C16H28NO6S]^+$ 362.2, found 362.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.19 (t, *J* = 6.3 Hz, 2H), 3.88 (s, 2H), 3.57 (t, *J* = 6.0 Hz, 2H), 2.47 (s, 3H), 1.97 (quin, *J* = 6.1 Hz, 2H), 1.49 (s, 9H).

Tert-butyl 2-(2,2-difluoro-3-hydroxypropoxy)acetate 59f



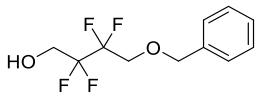
To a flask containing *tert*-butyl 2-(3-(benzyloxy)-2,2-difluoropropoxy)acetate **49f** (610 mg, 1.93 mmol) was added palladium (10% w/w on carbon, 205 mg, 0.193 mmol) and the flask filled with nitrogen. Anhydrous methanol (9 mL) was added, and a balloon of hydrogen gas was bubbled through and the reaction stirred at room temperature for 3 hours. The reaction mixture was filtered through celite and the celite plug washed with EtOAc (30 mL). The solvent was removed *in vacuo* to give *tert*-butyl 2-(2,2-difluoro-3-hydroxypropoxy)acetate **59f** (436 mg, 1.93 mmol, 100%) as a clear oil, which was used without further purification.

Tert-butyl 2-(2,2-difluoro-3-(tosyloxy)propoxy)acetate 60f



p-Toluenesulfonyl chloride (386 mg, 2.03 mmol) was added to a solution of 4-dimethylaminopyridine (24 mg, 0.19 mmol), triethylamine (296 µL, 2.12 mmol) and *tert*-butyl 2-(3-hydroxypropoxy)acetate **59f** (437 mg, 1.93 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. After consumption of the starting alcohol, H_2O (6 mL) was added, stirred for 5 mins, and the mixture passed through a phase separator. The organic phase was concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography (SiO_2, 10-100% EtOAc:pet ether 40-60) to give *tert*-butyl 2-(2,2-difluoro-3-(tosyloxy)propoxy)acetate **60f** (410 mg, 1.08 mmol, 56%) as a clear oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C16H26F2NO6S]^+$ 398.1, found 398.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.89 – 7.78 (m, 2H), 7.46 – 7.32 (m, 2H), 4.31 (t, *J* = 12.0 Hz, 2H), 4.01 (s, 2H), 3.83 (t, *J* = 12.1 Hz, 2H), 2.48 (s, 3H), 1.50 (s, 9H).

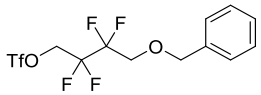
4-(benzyloxy)-2,2,3,3-tetrafluorobutan-1-ol 62



An oven-dried 100 mL flask with stirrer fitted with water-less condenser was charged with 2,2,3,3-tetrafluoro-1,4-butanediol **61** (1000 mg, 6.17 mmol) and potassium carbonate (1705 mg, 12.3 mmol). The flask was purged under a blanket of nitrogen. Anhydrous MeCN (20 mL) and benzyl bromide (0.73 mL, 6.17 mmol) were added and the reaction mixture stirred under reflux conditions overnight. After 16 hr, the reaction mixture was cooled to RT and filtered through a small pad of celite (eluting with MeCN). The filtrated was concentrated *in vacuo* to give a crude oil. This was purified by flash chromatography (12g SiO_2, linear gradient 0-30% EtOAc in hexanes) to give 4-(benzyloxy)-2,2,3,3-tetrafluorobutan-1-ol **62** (1445 mg, 5.73 mmol, 93 % yield) as an oil. ^{1}H NMR (300 MHz, Chloroform-

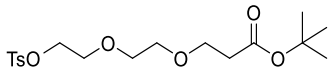
d) δ 7.31 - 7.45 (m, 5H), 4.70 (s, 2H), 3.86 - 4.10 (m, 4H), 2.52 - 2.44 (m, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) Shift -121.95 (m, 2F), -124.58 (m, 2F).

4-(benzyloxy)-2,2,3,3-tetrafluorobutyl trifluoromethanesulfonate 60g



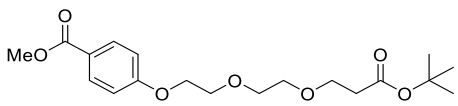
An oven-dried 25 mL flask with stirrer was charged with 4-benzyloxy-2,2,3,3-tetrafluoro-butan-1-ol **62** (100 mg, 0.40 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous CH_2Cl_2 (6 mL) and anhydrous pyridine (60 µL, 0.790 mmol) was added and the reaction mixture stirred at 25 °C for 5 min. Trifluoromethanesulfonic anhydride (70 µL, 0.40 mmol) was added and the solution stirred for 3 hr, then the mixture was diluted with H_2O (6 mL), stirred rapidly for 5 min and then passed through a hydrophobic frit. The organic phase was concentrated *in vacuo* to give a yellow oil that was used immediately in the next reaction without further purification.

***Tert*-butyl 3-(2-(2-(tosyloxy)ethoxy)ethoxy)propanoate 65h**



To a solution of p-toluenesulfonyl chloride (427 mg, 2.24 mmol) and 4-dimethylaminopyridine (26 mg, 0.21 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added triethylamine (237 mg, 2.35 mmol) and 2-methyl-2-propanyl 3-[2-(2-hydroxyethoxy)ethoxy]propanoate **64h** (500 mg, 2.13 mmol). The reaction mixture was warmed to rt and stirred for 24 hrs. Upon completion the reaction mixture was washed with H_2O (50 mL), then passed through a hydrophobic frit (eluent CH_2Cl_2) and concentrated *in vacuo*. Purification via silica gel chromatography (25 g SiO_2, gradient elution 2 to 40% EtOAc in petroleum ether) yielded *tert*-butyl 3-[2-[2-(p-tolylsulfonyloxy)ethoxy]ethoxy]propanoate **65h** (657 mg, 1.69 mmol, 79% yield) as a colourless oil. MS (ESI): *m/z* $[M+H]^+$ calcd $[C18H29O7S]^+$ 389.2, found 411. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.87 – 7.76 (m, 2H), 7.41 – 7.31 (m, 2H), 4.20 – 4.14 (m, 2H), 3.74 – 3.65 (m, 4H), 3.62 – 3.51 (m, 4H), 2.50 (t, *J* = 6.5 Hz, 2H), 2.47 (s, 3H), 1.46 (s, 9H).

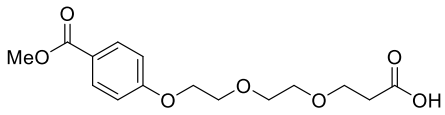
Methyl 4-(2-(2-(3-(*tert*-butoxy)-3-oxopropoxy)ethoxy)ethoxy)benzoate 66h



To a 20 mL microwave flask containing Methyl 4-hydroxybenzoate (255 mg, 1.68 mmol) and potassium carbonate (347 mg, 2.51 mmol) was added a solution of *tert*-butyl 3-[2-[2-(p-tolylsulfonyloxy)ethoxy]ethoxy]propanoate **65h** (652 mg, 1.68 mmol) in anhydrous MeCN (8 mL). The reaction mixture was heated at 50 °C for 23 hrs. Upon completion the reaction mixture was concentrated *in vacuo*, then resuspended between CH_2Cl_2 (50 mL) and H_2O (50 mL). The organic layer was washed with brine (50 mL), then dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (45g SiO_2, gradient elution 5 to 40% EtOAc in petroleum ether) yielded methyl 4-[2-[2-(3-*tert*-butoxy-3-oxo-propoxy)ethoxy]ethoxy]benzoate **66h** (346 mg, 0.939 mmol, 56% yield) as a colourless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.05 – 7.95 (m, 2H), 7.00 – 6.90 (m, 2H),

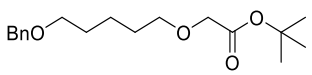
4.24 – 4.16 (m, 2H), 3.90 (s, 3H), 3.94 – 3.85 (m, 2H), 3.80 – 3.55 (m, 6H), 2.53 (t, *J* = 6.5 Hz, 2H), 1.46 (s, 9H).

3-(2-(2-(4-(Methoxycarbonyl)phenoxy)ethoxy)ethoxy)propanoic acid 67h



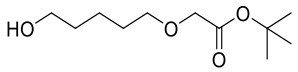
To a solution of methyl 4-[2-[2-(3-*tert*-butoxy-3-oxo-propoxy)ethoxy]ethoxy]benzoate **66h** (240 mg, 0.650 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added trifluoroacetic acid (0.50 mL, 6.51 mmol). The reaction mixture was warmed to rt and stirred for a further 3 hrs. Upon completion the reaction was concentrated *in vacuo*, resuspended in Et_2O (10 mL), then the solvent was decanted to afford 3-[2-[2-(4-methoxycarbonylphenoxy)ethoxy]ethoxy]propanoic acid **67h** (144 mg, 0.461 mmol, 71% yield) as a white solid. MS (ESI): *m/z* $[M-H]^-$ calcd $[C15H19O7]^-$ 311.1, found 311. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.72 (s, 1H), 8.05 – 7.95 (m, 2H), 7.00 – 6.90 (m, 2H), 4.25 – 4.16 (m, 2H), 3.91 (s, 3H), 3.98 – 3.56 (m, 8H), 2.68 (t, *J* = 6.1 Hz, 2H).

***Tert*-butyl 2-((5-(benzyloxy)pentyl)oxy)acetate 63**



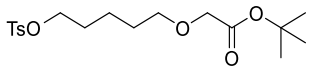
To a solution of 5-(benzyloxy)pentan-1-ol (1.00 g, 5.15mmol), *tert*-butyl bromoacetate (1.52 mL, 10.3 mmol) and *N*,*N*,*N*-tributylbutan-1-aminium bromide (497 mg, 1.54 mmol) in toluene (26 mL) was added an aqueous solution of sodium hydroxide (35%) (74 mL, 226 mmol). Then the reaction mixture was stirred rapidly for 26 hrs. After this time stirring was stopped, the phases allowed to separate, the organic phase was diluted with toluene (50 mL) then washed with brine (50 mL), dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (45 g SiO2, gradient elution 2 to 20% EtOAc in petroleum ether) yielded *tert*-butyl 2-(5-benzyloxypentoxy)acetate **63** (1.19 g, 3.86 mmol, 75% yield) as a colourless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) 7.41 – 7.29 (m, 5H), 4.52 (s, 2H), 3.96 (s, 2H), 3.51 (dt, *J* = 10.7, 6.5 Hz, 4H), 1.74 – 1.60 (m, 4H), 1.54 – 1.41 (m, 11H).

***Tert*-butyl 2-((5-hydroxypentyl)oxy)acetate 64i**



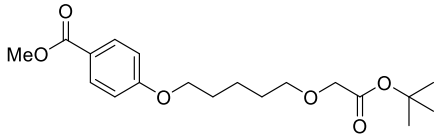
A 100 mL flask was charged with *tert*-butyl 2-(5-benzyloxypentoxy)acetate **63** (1.18 g, 3.85 mmol), placed under an N2 atmosphere and ethanol (25.67mL) was added. Palladium (10% w/w on carbon, 204 mg, 0.190 mmol) was added and the N2 atmosphere re-established. Then the flask was flushed with a balloon of hydrogen gas and stirred at rt for 23 hrs. Upon completion the flask was flushed with N2, then diluted with EtOAc (50 mL), filtered through a plug of celite (eluent EtOAc) and concentrated *in vacuo* to give *tert*-butyl 2-(5-hydroxypentoxy)acetate **64i** (894 mg, 4.10 mmol, quant.) as a colourless oil. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 3.97 (s, 2H), 3.67 (t, *J* = 6.4 Hz, 2H), 3.54 (t, *J* = 6.4 Hz, 2H), 1.74 – 1.56 (m, 4H), 1.50 (s, 9H), 1.54 – 1.40 (m, 2H).

Tert-butyl 2-((5-(tosyloxy)pentyl)oxy)acetate 65i



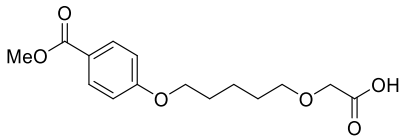
To a solution of *tert*-butyl 2-(5-hydroxypentyl)oxy)acetate **64i** (886 mg, 4.06 mmol) and 4-dimethylaminopyridine (50 mg, 0.41 mmol) in CH_2Cl_2 (14 mL) at 0 °C was added triethylamine (0.62 mL, 4.46 mmol) and p-toluenesulfonyl chloride (813 mg, 4.26 mmol). The reaction mixture was warmed to rt and stirred for 18 hrs. Upon completion the reaction mixture was washed with H_2O (50 mL), then passed through a hydrophobic frit (eluent CH_2Cl_2) and concentrated *in vacuo*. Purification via silica gel chromatography (45 g SiO_2, gradient elution 2 to 30% EtOAc in petroleum ether) yielded *tert*-butyl 2-[5-(p-tolylsulfonyloxy)pentoxy]acetate **65i** (1.23 g, 3.30 mmol, 81% yield) as a colourless oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C18H32NO6S]^+$ 390.2, found 390. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.87 – 7.75 (m, 2H), 7.41 – 7.32 (m, 2H), 4.04 (t, *J* = 6.5 Hz, 2H), 3.93 (s, 2H), 3.48 (t, *J* = 6.3 Hz, 2H), 2.47 (s, 3H), 1.76 – 1.53 (m, 4H), 1.51 (s, 9H), 1.47 – 1.35 (m, 2H).

Methyl 4-((5-(2-(*tert*-butoxy)-2-oxoethoxy)pentyl)oxy)benzoate 66i



To a 20 mL microwave flask containing methyl 4-hydroxybenzoate (408 mg, 2.68 mmol) and potassium carbonate (557 mg, 4.03 mmol) was added a solution of *tert*-butyl 2-[5-(p-tolylsulfonyloxy)pentoxy]acetate (1.00 g, 2.68 mmol) in anhydrous MeCN (13 mL). The reaction mixture was heated at 50 oC for 17 hrs, then heated at 80 °C for a further 5.5 hrs. Upon completion the reaction mixture was concentrated *in vacuo*, then resuspended between EtOAc (50 mL) and H_2O (50 mL). The organic layer was washed with brine (50 mL) then dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (45g SiO_2, gradient elution 1 to 60% EtOAc in petroleum ether) yielded methyl 4-[5-(2-*tert*-butoxy-2-oxo-ethoxy)pentoxy]benzoate **66i** (585 mg, 1.66 mmol, 62% yield) as a colourless oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C19H32NO6]^+$ 370.2, found 370. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.04 – 7.94 (m, 2H), 6.96 – 6.86 (m, 2H), 4.04 (t, *J* = 6.4 Hz, 2H), 3.98 (s, 2H), 3.90 (s, 3H), 3.57 (t, *J* = 6.3 Hz, 2H), 1.86 (dt, *J* = 13.9, 6.6 Hz, 2H), 1.79 – 1.66 (m, 2H), 1.66 – 1.55 (m, 2H), 1.49 (s, 9H).

2-((5-(4-(Methoxycarbonyl)phenoxy)pentyl)oxy)acetic acid 67i

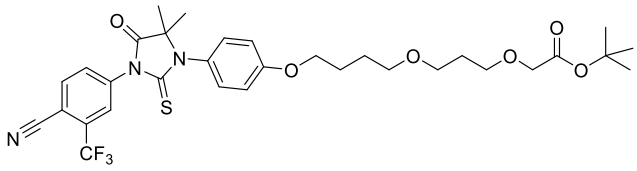


To a solution of methyl 4-[5-(2-*tert*-butoxy-2-oxo-ethoxy)pentoxy]benzoate **66i** (309 mg, 0.880 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added trifluoroacetic acid (0.670 mL, 8.77 mmol). The reaction mixture was warmed to rt and stirred for a further 3 hrs. Upon completion the reaction was concentrated *in vacuo*, resuspended in Et2O (10 mL), but solid didn't precipitate so solvent was removed *in vacuo*. The crude material was asiotroped with toluene (3 × 15 mL) to afford 2-[5-(4-methoxycarbonylphenoxy)pentoxy]acetic acid **67i** (231 mg, 0.780 mmol, 89% yield) as a white solid.

MS (ESI): *m/z* $[M-H]^-$ calcd $[C15H19O6]^-$ 295.1, found 295. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.05 – 7.95 (m, 2H), 6.97 – 6.86 (m, 2H), 4.14 (s, 2H), 4.05 (t, *J* = 6.3 Hz, 2H), 3.91 (s, 3H), 3.63 (t, *J* = 6.4 Hz, 2H), 1.94 – 1.51 (m, 6H).

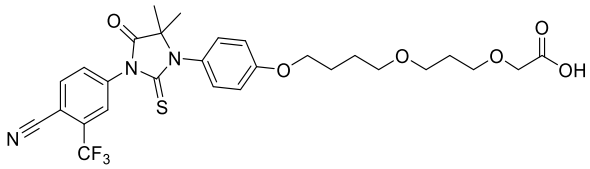
Scheme S6 Experimental:

Tert-butyl 2-(3-(4-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)butoxy)propoxy)acetate 68a



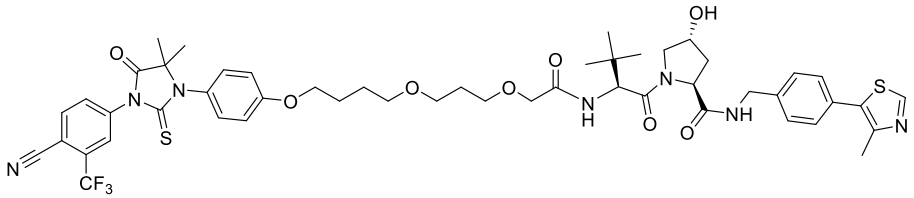
An oven-dried 5 mL microwave tube with stirrer was charged with 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **60a** (97 mg, 0.24 mmol), caesium carbonate (94 mg, 0.29 mmol) and *tert*-butyl 2-[3-[4-(p-tolylsulfonyloxy)butoxy]propoxy]acetate **3** (100 mg, 0.24 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous DMF (1.5 mL) was added, the septum removed and the tube capped with a Teflon lined lid. The homogenous reaction mixture was heated under microwave irradiation at 90 °C for 80 min. The solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), the aqueous phase was extracted with CH_2Cl_2 (3x 10 ml) and washed with brine, before being passed through a hydrophobic frit. The organic phase was concentrated *in vacuo* and the crude residue purified by flash chromatography (12g SiO_2, linear gradient 0-30% EtOAc in hexanes) to give *tert*-butyl 2-(3-(4-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)butoxy)propoxy)acetate **68a** (100 mg, 0.15 mmol, 64%) as a clear oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C32H42F3N4O6S]^+$ 667.3, found 667.3. ^1H NMR (300 MHz, Chloroform-*d*) δ 7.95 - 8.03 (m, 2H), 7.87 (dd, *J* = 1.93, 8.34 Hz, 1H), 7.17 - 7.26 (m, *J* = 8.8 Hz, 2H), 6.99 - 7.08 (m, *J* = 9.0 Hz, 2H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.97 (s, 2H), 3.47 - 3.67 (m, 6H), 1.86 - 2.00 (m, 4H), 1.78 (dd, J = 5.3, 9.0 Hz, 2H), 1.59 (s, 6H), 1.50 (s, 9H).

2-(3-(4-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)butoxy)propoxy)acetic acid 69a



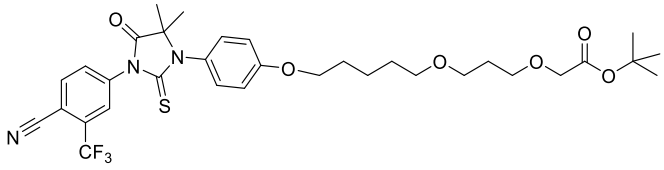
An oven-dried 25 mL flask with stirrer was charged with *tert*-butyl 2-[3-[4-[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenoxy]butoxy]propoxy]acetate **68a** (24 mg, 0.040 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous 1,4-Dioxane (1.0 mL) followed by hydrogen chloride in dioxane (4 M, 0.5mL, 1.0 mmol) and then the reaction mixture stirred at 80 °C for 3 hr. The reaction mixture was concentrated *in vacuo* and the residue used in the next step without further purification. MS (ESI): *m/z* $[M+H]^+$ calcd $[C28H31F3N3O6S]^+$ 594.2, found 594.2.

(2*S*,4*R*)-1-((S)-2-(2-(3-(4-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)butoxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide 20a



An oven-dried flask with stirrer was charged with 2-[3-[4-[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenoxy]butoxy]propoxy]acetic acid **69a** (39 mg, 0.07 mmol) and (2*S*,4*R*)-1-[(2*S*)-2-amino-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride **9** (31 mg, 0.07 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous DMF (0.80 mL) was added followed by diisopropylethylamine (20 µL, 0.140 mmol) and the reaction mixture stirred for 5 min. HATU (28 mg, 0.070 mmol) was added and the reaction mixture stirred at 25 °C for 12 h. The mixture was next diluted with EtOAc (10 mL), partitioned with H_2O (20 mL) and the phases separated. The aqueous phase was further extracted with EtOAc (3 x 20 mL) and the organics combined, washed with H_2O (50 mL), 10% aq. lithium chloride solution (50 mL) and brine (100 mL) then dried (Na_2SO_4), filtered and concentrated i*n vacuo* to give a crude residue that was purified by reverse-phase HPLC (5 to 95% MeCN in H_2O with 0.1% NH_3) to give (2*S*,4*R*)-1-((*S*)-2-(2-(3-(4-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)butoxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **20a** (8.0 mg, 0.010 mmol, 12%) as a white solid after freeze-drying. MS (ESI): *m/z* $[M+H]^+$ calcd $[C50H59N7O8F3S2]^+$ 1006.4, found 1006.5. HRMS *m/z* (ES+) calcd. for $[C50H59N7O8F3S2]^+$ 1006.3813 $[M+H]^+$, found 1006.3838. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.04 – 7.95 (m, 2H), 7.87 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.45 – 7.29 (m, 5H), 7.24 – 7.14 (m, 3H), 7.03 (d, *J* = 8.9 Hz, 2H), 4.77 (t, *J* = 7.9 Hz, 1H), 4.65 – 4.54 (m, 2H), 4.49 (d, *J* = 8.6 Hz, 1H), 4.36 (dd, *J* = 14.8, 5.2 Hz, 1H), 4.16 (d, *J* = 11.5 Hz, 1H), 4.04 (t, *J* = 6.2 Hz, 2H), 3.96 (d, *J* = 2.4 Hz, 2H), 3.68 – 3.58 (m, 3H), 3.53 (dt, *J* = 9.3, 6.2 Hz, 4H), 2.73 – 2.58 (m, 2H), 2.54 (s, 3H), 2.18 – 2.08 (m, 1H), 1.96 – 1.72 (m, 6H), 1.60 (s, 6H), 0.97 (s, 9H). UPLC analysis (method C), 6.32 min, 96%.

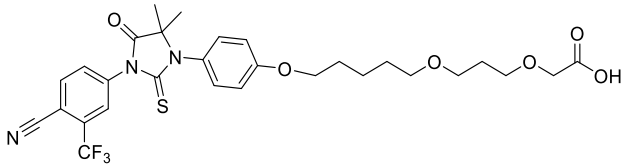
***Tert*-butyl 2-(3-((5-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)pentyl)oxy)propoxy)acetate 68b**



An oven-dried 5 mL microwave tube with stirrer was charged with 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **3** (90 mg, 0.22 mmol), cesium carbonate (87 mg, 0.27 mmol) and *tert*-butyl 2-[3-[5-(p-tolylsulfonyloxy)pentoxy]propoxy]acetate **60b** (96 mg, 0.22 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous DMF (1.2 mL) was added, the septum

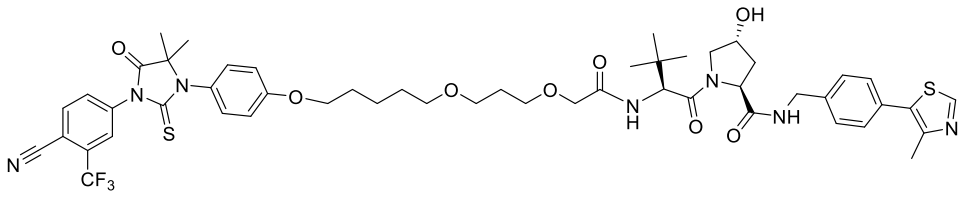
removed and the tube capped with a teflon-lined lid. The homogenous reaction mixture was heated under microwave irradiation at 90 °C for 90 min. The solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL), the aqueous phase was extracted with CH_2Cl_2 (3x 10 ml) and washed with brine, before being passed through a hydrophobic frit. The organic phase was concentrated *in vacuo* and the crude residue purified by flash chromatography (12g SiO_2, linear gradient 0-30% EtOAc in hexanes) to give *tert*-butyl 2-(3-((5-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)pentyl)oxy)propoxy)acetate **68b** (133 mg, 0.20 mmol, 90%) as a clear oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C33H44F3N4O6S]^+$ 681.3, found 681.4. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.04 - 7.96 (m, 2H), 7.89 - 7.85 (m, 1H), 7.25 - 7.17 (m, 2H), 7.09 - 7.00 (m, 2H), 4.08 - 3.99 (m, 2H), 3.98 (s, 2H), 3.63 (t, *J* = 6.3 Hz, 2H), 3.56 (t, *J* = 6.4 Hz, 2H), 3.48 (t, *J* = 6.3 Hz, 2H), 1.96 - 1.81 (m, 4H), 1.71 - 1.51 (m, 10H), 1.50 (s, 9H).

2-(3-((5-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)pentyl)oxy)propoxy)acetic acid 69b



A 10 mL flask with stirrer was charged with *tert*-butyl 2-[3-[5-[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenoxy]pentoxy]propoxy]acetate **68b** (120 mg, 0.18 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous HCl (4M in 1,4-dioxane, 2.0 mL, 2.0 mM) and H_2O (0.5 mL) were added and the reaction mixture stirred at 80 °C for 3 hr. The reaction mixture was then cooled to RT and concentrated *in vacuo*. The crude product was used directly in the next reaction without further purification. MS (ESI): *m/z* $[M+H]^+$ calcd $[C29H33F3N3O6S]^+$ 608.2, found 608.2.

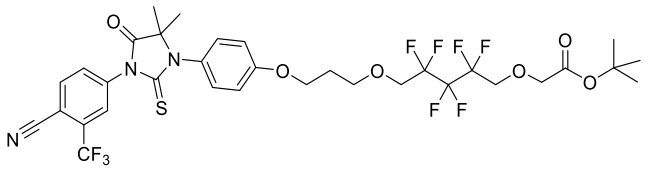
(2*S*,4*R*)-1-((*S*)-2-(2-(3-((5-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)pentyl)oxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide 20b



An oven-dried 25 mL flask with stirrer was charged with 2-[3-[5-[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenoxy]pentoxy]propoxy]acetic acid **69b** (44 mg, 0.070 mmol) and (2*S*,4*R*)-1-[(2*S*)-2-amino-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride **9** (34 mg, 0.070 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous DMF (1.0 mL) and *N*,*N*-diisopropylethylamine (30 µL, 0.180 mmol) were added and the reaction mixture stirred at 25 °C for 5 min. HATU (28 mg, 0.070 mmol) was added in a single portion and reaction mixture stirred for 1 hr. The reaction mixture was quenched with H_2O, stirred for 5 min and then partitioned between EtOAc (15 mL) and H_2O (30 mL). The phases were

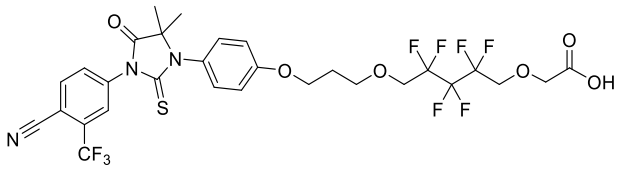
separated and the aqueous phase re-extracted with EtOAc (4 x 15 mL), the organic phases were combined, washed with H_2O (50 mL), brine (50 mL), passed through a hydrophobic frit and the organics concentrated *in vacuo* to give a crude oil. This was purified by preparatory HPLC (5 to 95% MeCN in H_2O with 0.1% NH_3) to give (2*S*,4*R*)-1-((*S*)-2-(2-(3-((5-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)pentyl)oxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **20b** (36 mg, 0.035 mmol, 49% yield) as a white amorphous solid. MS (ESI): *m/z* $[M+H]^+$ calcd $[C51H61N7O8F3S2]^+$ 1020.4, found 1020.5. HRMS *m/z* (ES+) calcd. for $C51H61N7O8F3S2^+$ 1020.3975 $[M+H]^+$, found 1020.4009. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.03 - 7.96 (m, 2H), 7.90 - 7.82 (m, 1H), 7.42 - 7.29 (m, 5H), 7.25 - 7.16 (m, 3H), 7.07 - 6.99 (m, 2H), 4.76 (t, *J* = 8.0 Hz, 1H), 4.65 - 4.48 (m, 3H), 4.36 (dd, *J* = 15.0, 5.2 Hz, 1H), 4.14 (d, *J* = 11.6 Hz, 1H), 4.06 - 3.98 (m, 2H), 3.95 (d, *J* = 1.8 Hz, 2H), 3.68 - 3.58 (m, 3H), 3.53 (t, *J* = 6.3 Hz, 2H), 3.46 (t, *J* = 6.2 Hz, 2H), 3.05 (br. s, 1H), 2.67 - 2.56 (m, 1H), 2.56 - 2.51 (m, 3H), 2.18 - 2.09 (m, 1H), 1.97 - 1.79 (m, 5H), 1.62 - 1.50 (m, 9H), 0.97 (s, 9H). UPLC analysis (method C), 6.44 min, >98%.

Tert-butyl 2-((5-(3-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)propoxy)-2,2,3,3,4,4-hexafluoropentyl)oxy)acetate 68c



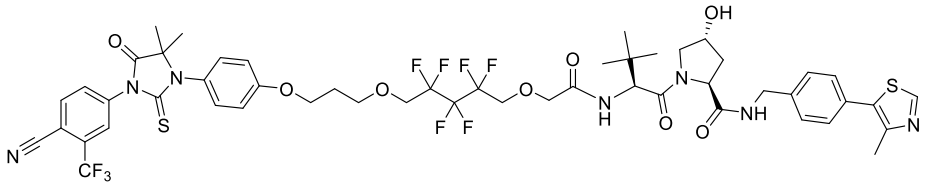
A 5 mL microwave tube with stirrer was charged with 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **3** (23 mg, 0.060 mmol), *tert*-butyl 2-[2,2,3,3,4,4-hexafluoro-5-[3-(p-tolylsulfonyloxy)propoxy]pentoxy]acetate **60c** (30 mg, 0.060 mmol) and cesium carbonate (22 mg, 0.070 mmol) . The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous DMF (1.0 mL) was added and the vial capped with a Teflon lined lid. The reaction mixture was heated under microwave irradiation at 95 °C for 1.5 hr. The reaction mixture was then quenched with sat. aq. ammonium chloride (1 mL) and partitioned between EtOAc (5 mL) and H_2O (5 mL). The aqueous phase was extracted with EtOAc (2 x 5 mL) and the combined organics washed with 10% aq. lithium chloride solution (10 mL) and brine (10 mL), then dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo* to give a crude residue. This was purified by flash chromatography (12g SiO_2, linear gradient 5-100% EtOAc in hexanes) to give *tert*-butyl 2-((5-(3-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)propoxy)-2,2,3,3,4,4-hexafluoropentyl)oxy)acetate **68c** (31 mg, 0.040 mmol, 72% yield) as a foam. MS (ESI): *m/z* $[M+H]^+$ calcd $[C33H35F9N3O6S]^+$ 772.2, found 773.2. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.94 - 7.86 (m, 2H), 7.80 - 7.75 (m, 1H), 7.13 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 4.10 - 3.94 (m, 6H), 3.87 (s, 2H), 3.73 (t, *J* = 6.0 Hz, 2H), 2.04 (s, 2H), 1.55 - 1.46 (m, 6H), 1.41 (s, 9H); ^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.96 (s, 3F), -120.04 (m, 2F), -120.45 (m, 2F), -126.07 (s, 2F).

Tert-butyl 2-((5-(3-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)propoxy)-2,2,3,3,4,4-hexafluoropentyl)oxy)acetate 69c



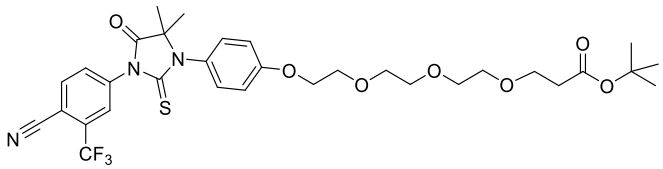
An oven-dried 10 mL flask with stirrer was charged with *tert*-butyl 2-[5-[3-[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenoxy]propoxy]-2,2,3,3,4,4-hexafluoro-pentoxy]acetate **68c** (31 mg, 0.040 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous CH_2Cl_2 (0.25 mL) and trifluoroacetic acid (0.23 mL, 3.1 mmol) were added and the reaction mixture stirred at 25 °C for 2 hr. The solvent was removed *in vacuo* and the crude acid used directly in the next step.

(2*S*,4*R*)-1-((*S*)-2-(2-((5-(3-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)propoxy)-2,2,3,3,4,4-hexafluoropentyl)oxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide 20c



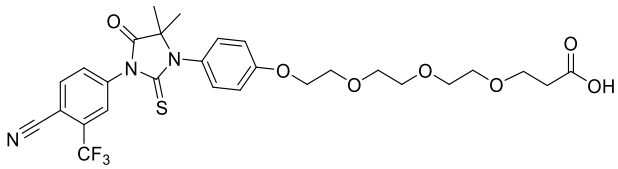
An oven-dried 25 mL flask with stirrer was charged with 2-[5-[3-[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenoxy]propoxy]-2,2,3,3,4,4-hexafluoro-pentoxy]acetic acid **69c** (28 mg, 0.040 mmol), and (2*S*,4*R*)-1-[(2*S*)-2-amino-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride **9** (20 mg, 0.040 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous DMF (0.5 mL) and *N*-ethyl-*N*-isopropyl-propan-2-amine (100 µL, 0.080 mmol) were added and the reaction mixture stirred at 25 °C for 5 min. HATU (16 mg, 0.040 mmol) was added in a single portion and the reaction mixture stirred overnight at 25 °C. The reaction mixture was then partitioned between H_2O (5 mL) and EtOAc (5 mL). The aqueous phase was further extracted with EtOAc (4 x 5 mL) and the organic phases were combined, washed with 10% aq. lithium chloride (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo* to give a crude residue. This was purified preparatory HPLC (5 to 95% MeCN in H_2O with 0.1% NH_3) to give (2*S*,4*R*)-1-((*S*)-2-(2-((5-(3-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)propoxy)-2,2,3,3,4,4-hexafluoropentyl)oxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **20c** (13 mg, 0.010 mmol, 29%) as an amorphous solid. MS (ESI): *m/z* $[M+H]^+$ calcd $[C51H55F9N7O8S2]^+$ 1128.3, found 1128.5. ^{1}H NMR (300 MHz, Chlorform-*d*) δ 8.70 (s, 1H), 8.04 - 7.96 (m, 2H), 7.90 - 7.83 (m, 1H), 7.42 - 7.33 (m, 4H), 7.26 - 7.17 (m, 3H), 7.11 (d, *J* = 9.0 Hz, 1H), 7.07 - 7.01 (m, 2H), 4.79 - 4.71 (m, 1H), 4.64 - 4.54 (m, 2H), 4.48 (d, *J* = 8.4 Hz, 1H), 4.35 (dd, *J* = 15.0, 5.1 Hz, 1H), 4.19 - 4.04 (m, 6H), 4.03 - 3.89 (m, 4H), 3.81 (t, *J* = 6.0 Hz, 2H), 3.64 (dd, *J* = 11.4, 3.7 Hz, 1H), 2.62 - 2.51 (m, 4H), 2.17 - 2.07 (m, 3H), 1.59 (s, 6H), 0.96 (s, 9H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.96 (s, 3F), -119.98 (m, 2F), -120.03 (m, 2F) -125.73 (s, 2F). UPLC analysis (method C), 6.45 min, 94%.

***Tert*-butyl 3-(2-(2-(2-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)ethoxy)ethoxy)ethoxy)propanoate 68d**



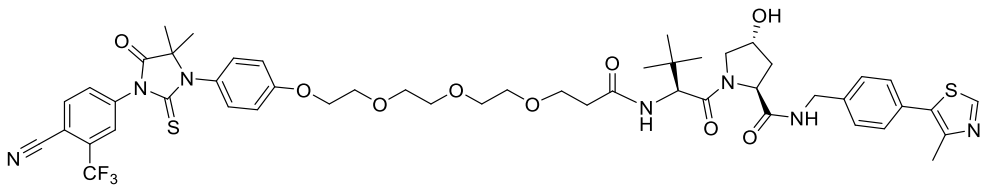
Caesium carbonate (32 mg, 0.10 mmol) was added to a solution of 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **3** (40 mg, 0.10 mmol) and *tert*-butyl 3-(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)propanoate **60d** (43 mg, 0.10 mmol) in DMF (1 mL). The reaction mixture was heated at 90 °C under microwave irradiation for 1 hour. After cooling to room temperature, the reaction was diluted with EtOAc (25 mL), washed with H_2O (25 mL). The organic layer was dried by passing through a phase separating frit and the solvent removed *in vacuo*. The crude residue was purified by silica gel chromatography (SiO_2, gradient elution 10 to 100% EtOAc in petrol) to give *tert*-butyl 3-(2-(2-(2-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)ethoxy)ethoxy)ethoxy)propanoate **68d** (63 mg, 96%) as a clear oil. MS (ESI): *m/z* $[M+NH4]^+$ calcd $[C32H42F3N4O7S]^+$ 683.3, found 683.4. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.03 – 7.95 (m, 2H), 7.86 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.26 – 7.17 (m, 2H), 7.13 – 7.02 (m, 2H), 4.20 (dd, *J* = 5.6, 4.2 Hz, 2H), 3.95 – 3.85 (m, 2H), 3.78 – 3.58 (m, 10H), 2.52 (t, *J* = 6.6 Hz, 2H), 1.59 (s, 6H), 1.46 (s, 9H).

3-(2-(2-(2-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)ethoxy)ethoxy)ethoxy)propanoic acid 69d



Trifluoroacetic acid (1 mL) was added to a stirred solution of *tert*-butyl 3-(2-(2-(2-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)ethoxy)ethoxy)ethoxy)propanoate **68d** (63 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) at room temperature and stirred for 2 hours. The reaction mixture was then concentrated under reduced pressure to give a crude material which was used directly in the next step without further purification. MS (ESI): *m/z* $[M-H]^-$ calcd $[C28H29F3N3O7S]^-$ 608.2, found 608.3.

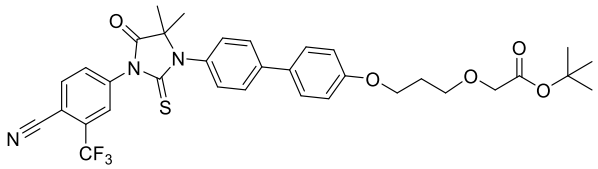
(2*S*,4*R*)-1-((*S*)-14-(*Tert*-butyl)-1-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)-12-oxo-3,6,9-trioxa-13-azapentadecan-15-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide 20d



To a stirred solution of 3-(2-(2-(2-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)ethoxy)ethoxy)ethoxy)propanoic acid **69d** (60 mg, 0.10 mmol), (2*S*,4*R*)-1-[(2*S*)-2-amino-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-

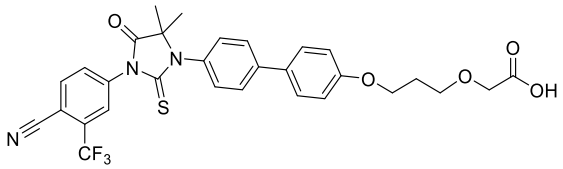
yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride **9** (42 mg, 0.10 mmol) and diisopropylethylamine (70 µL, 0.39 mmol) in DMF (1 mL) was added HATU (41 mg, 0.11 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 30 mins. Then H_2O (20 mL) and EtOAc (50 mL) were added and the organic layer dried through a phase separator frit. The solvent was removed *in vacuo*, and the residue was purified by silica gel chromatography (SiO_2, gradient elution 1 to 15% MeOH in CH_2Cl_2), followed by reverse-phase chromatography (C18, gradient elution 5-80% MeCN in H_2O) to give (2*S*,4*R*)-1-((*S*)-14-(*tert*-butyl)-1-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)-12-oxo-3,6,9-trioxa-13-azapentadecan-15-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **20d** (45 mg, 0.044 mmol, 45%). MS (ESI): *m/z* $[M+H]^+$ calcd $[C50H59F3N7O9S2]^+$ 1022.4, found 1022.5. HRMS *m/z* (ES+) calcd. for $[C50H58N7O9F3S2]^+$ 1022.3762 $[M+H]^+$, found 1022.3781. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.05 – 7.96 (m, 2H), 7.86 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.43 – 7.33 (m, 5H), 7.27 – 7.17 (m, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 7.00 (d, *J* = 7.9 Hz, 1H), 4.77 (t, *J* = 8.0 Hz, 1H), 4.60 (dd, *J* = 14.9, 6.7 Hz, 1H), 4.52 (s, 1H), 4.44 (d, *J* = 8.1 Hz, 1H), 4.35 (dd, *J* = 14.9, 5.2 Hz, 1H), 4.22 – 4.12 (m, 3H), 3.93 – 3.84 (m, 2H), 3.74 (dd, *J* = 6.6, 4.1 Hz, 4H), 3.69 (d, *J* = 5.1 Hz, 6H), 3.57 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.04 (s, 1H), 2.68 – 2.44 (m, 6H), 2.15 (dt, *J* = 13.5, 7.1 Hz, 1H), 1.59 (s, 6H), 0.95 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.15 (CS), 175.11 (CO), 172.18 (CO), 171.74 (CO), 170.92 (CO), 159.50 (C_q), 150.52 (CH), 148.00 (C_q), 138.37 (C_q), 137.18 (C_q), 135.22 (CH), 133.53 (q, *J* = 33.4 Hz, C_q), 132.24 (CH), 131.89 (C_q), 130.64 (CH), 129.47 (CH), 128.13 (CH), 127.54 (C_q), 127.15 (q, *J* = 4.8 Hz, CH), 121 (q, J = 274.3 Hz, CF_3), 115.65 (CH), 114.84 (C_q), 110.14 (C_q), 70.79 (CH_2), 70.54 (CH_2), 70.49 (CH_2), 70.46 (CH_2), 70.06 (CH), 69.53 (CH_2), 67.69 (CH_2), 67.12 (CH_2), 66.34 (C_q), 58.50 (CH), 57.78 (CH), 56.71 (CH_2), 43.17 (CH_2), 36.66 (CH_2), 36.03 (CH_2), 34.85 (C_q), 26.42 (CH_3), 23.64 (CH_3), 15.88 (CH_3). One quaternary carbon peak not distinguishable. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.94. UPLC analysis (method C), 3.18 min, 95%.

Tert-butyl 2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)propoxy)acetate 68e



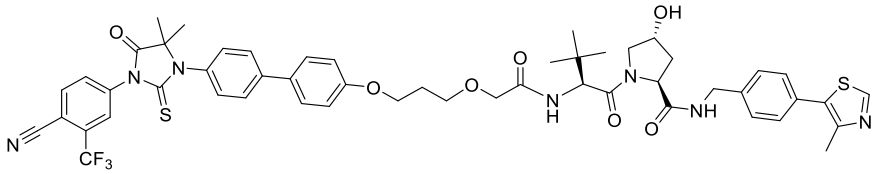
Caesium carbonate (23 mg, 0.07 mmol) was added to a solution of 4-[3-[4-(4-hydroxyphenyl)phenyl]-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **25** (33 mg, 0.07 mmol) and *tert*-butyl 2-(3-(tosyloxy)propoxy)acetate **60e** (24 mg, 0.07 mmol) in DMF (1 mL). The reaction mixture was heated at 90 °C under microwave irradiation for 1 hour. After cooling to room temperature, the reaction was diluted with EtOAc (25 mL) and washed with H_2O (25 mL). The organic layer was dried by passing through a phase separating frit and the solvent removed *in vacuo*. The crude residue was purified by silica gel chromatography (SiO_2, gradient elution 10 to 100% EtOAc in petrol) to give *tert*-butyl 2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)propoxy)acetate **68e** as a clear oil (34 mg, 74%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.05 – 7.97 (m, 2H), 7.89 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 4.18 (t, *J* = 6.2 Hz, 2H), 4.01 (s, 2H), 3.75 (t, *J* = 6.1 Hz, 2H), 2.16 (quin, *J* = 6.2 Hz, 2H), 1.65 (s, 6H), 1.50 (s, 9H).

2-(3-((4'-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)propoxy)acetic acid 69e



Trifluoroacetic acid (0.5 mL) was added to a stirred solution of *tert*-butyl 2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)propoxy)acetate **68e** (34 mg, 0.052 mmol) in CH_2Cl_2 (2 mL) at room temperature and stirred for 2 hours. The reaction mixture was then concentrated under reduced pressure to give 2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)propoxy)acetic acid **69e** which was used directly in the next step without further purification. MS (ESI): *m/z* $[M-H]^-$ calcd $[C30H25F3N3O5S]^-$ 596.1, found 596.2.

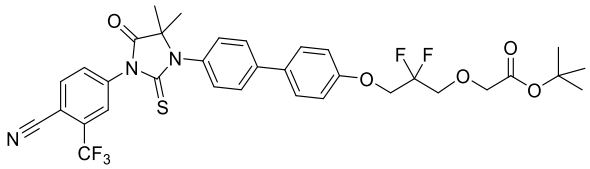
(2*S*,4*R*)-1-((*S*)-2-(2-(3-((4'-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide 20e



To a stirred solution of 2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)propoxy)acetic acid **69e** (30 mg, 0.051 mmol), (2*S*,4*R*)-1-[(2*S*)-2-amino-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride **9** (22 mg, 0.051 mmol) and diisopropylethylamine (36 µL, 0.20 mmol) in DMF (1 mL) was added HATU (21 mg, 0.060 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 30 mins. Then H_2O (20 mL) and EtOAc (50 mL) were added, the organic layer was separated, dried (hydrophobic frit) and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (SiO_2, gradient elution 1 to 15% MeOH in CH_2Cl_2), followed by reverse-phase chromatography (C18, gradient elution 5 to 80% MeCN in H_2O) to give (2*S*,4*R*)-1-((*S*)-2-(2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **20e** (24 mg, 0.024 mmol, 47%). MS (ESI): *m/z* $[M+H]^+$ calcd $[C52H5N7O7F3S2]^+$ 1010.4, found 1010.4. HRMS *m/z* (ES+) calcd. for $[C52H55N7O7F3S2]^+$ 1010.3551 $[M+H]^+$, found 1010.3555. ^1H NMR (300 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.63 (t, *J* = 6.0 Hz, 1H), 8.41 (d, *J* = 8.3 Hz, 1H), 8.33 (d, *J* = 1.9 Hz, 1H), 8.11 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.85 – 7.72 (m, 2H), 7.66 (d, *J* = 8.7 Hz, 2H), 7.51 – 7.20 (m, 7H), 7.07 (d, *J* = 8.7 Hz, 2H), 5.18 (d, *J* = 3.5 Hz, 1H), 4.58 (d, *J* = 9.5 Hz, 1H), 4.52 – 4.33 (m, 3H), 4.26 (dd, *J* = 15.7, 5.6 Hz, 1H), 4.14 (t, *J* = 6.3 Hz, 2H), 3.99 (s, 2H), 3.75 – 3.57 (m, 4H), 2.44 – 2.40 (m, 2H), 2.14 – 1.98 (m, 3H), 1.91 (ddd, *J* = 12.9, 8.9, 4.3 Hz, 1H), 1.54 (s, 6H), 0.95 (s, 9H). ^{13}C NMR (75 MHz, DMSO) δ 180.37 (CS), 175.48 (CO), 172.22 (CO), 169.64 (CO), 168.91 (CO), 158.99 (C_q), 151.92 (C_q), 148.19 (C_q), 140.98 (C_q), 139.88 (C_q), 138.61 (CH), 136.66 (CH), 134.54 (C_q), 134.40 (CH), 131.75 (C_q), 131.59 (C_q), 130.61 (CH), 130.15 (C_q), 129.15 (CH), 128.61 (CH), 128.48 (CH),

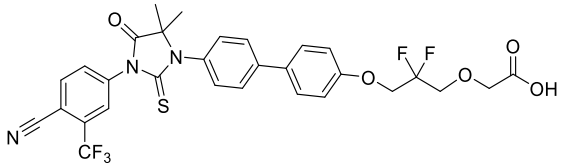
127.91 (CH), 127.57 (CH), 115.46 (CH), 109.03 (C_q), 69.96 (CH_2), 69.35 (CH), 68.14 (CH_2), 66.84 (C_q), 65.11 (CH_2), 59.23 (CH), 57.10 (CH_2), 56.17 (CH), 42.12 (CH_2), 38.38 (CH_2), 36.33 (C_q), 29.47 (CH_2), 26.67 (CH_3), 23.44 (CH_3), 16.37 (CH_3). 3 quaternary carbons (including *C*F_3) not distinguishable. ^{19}F NMR (282 MHz, DMSO-d_6) δ -60.72. UPLC analysis (method A), 3.40 min, 93%.

Tert-butyl 2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)-2,2-difluoropropoxy)acetate 68f



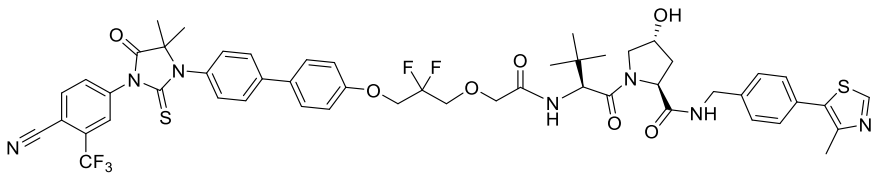
Caesium carbonate (26 mg, 0.08 mmol) was added to a solution of 4-[3-[4-(4-hydroxyphenyl)phenyl]-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **25** (39 mg, 0.08 mmol) and *tert*-butyl 2-(2,2-difluoro-3-(tosyloxy)propoxy)acetate **60f** (30 mg, 0.08 mmol) in DMF (1 mL). The reaction mixture was heated at 90 °C under microwave irradiation for 1 hour. After cooling to room temperature, the reaction was diluted with EtOAc (25 mL), washed with H_2O (25 mL). The organic layer was dried by passing through a phase separating frit and the solvent removed *in vacuo*. The crude residue was purified by FCC (SiO_2, 10-100% EtOAc:pet ether 40-60) to give *tert*-butyl 2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)-2,2-difluoropropoxy)acetate **68f** as a clear oil (5.0 mg, 9%). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.05 – 7.98 (m, 2H), 7.89 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.11 – 7.03 (m, 2H), 4.38 (t, *J* = 12.0 Hz, 2H), 4.11 (s, 2H), 4.02 (t, *J* = 12.3 Hz, 2H), 1.65 (s, 6H), 1.50 (s, 9H).

2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)-2,2-difluoropropoxy)acetic acid 69f



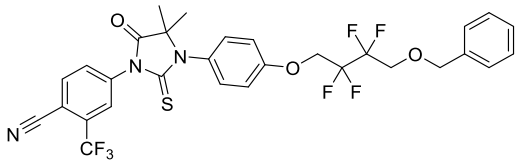
Trifluoroacetic acid (0.5 mL) was added to a stirred solution of *tert*-butyl 2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)-2,2-difluoropropoxy)acetate **68f** (5.0 mg, 0.007 mmol) in CH_2Cl_2 (2 mL) at room temperature and stirred for 2 hours. The reaction mixture was then concentrated under reduced pressure to give a crude material which was used directly in the next step without further purification. MS (ESI): *m/z* $[M-H]^-$ calcd $[C30H23F5N3O5S]^-$ 632.1, found 632.3.

(2*S*,4*R*)-1-((*S*)-2-(2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)-2,2-difluoropropoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide 20f



To a stirred solution of 2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)-2,2-difluoropropoxy)acetic acid **69f** (4.0 mg, 0.006 mmol), (2*S*,4*R*)-1-[(2*S*)-2-amino-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride **9** (3.0 mg, 0.006 mmol) and diisopropylethylamine (4 µL, 0.025 mmol) in DMF (1 mL) was added HATU (3.0 mg, 0.007 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 30 mins. Then H_2O (20 mL) and EtOAc (50 mL) were added and the organic layer dried through a phase separator frit. The solvent was removed *in vacuo*, and the residue was purified by FCC (SiO_2, MeOH: CH_2Cl_2 1-15%) to give (2*S*,4*R*)-1-((*S*)-2-(2-(3-((4'-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-[1,1'-biphenyl]-4-yl)oxy)-2,2-difluoropropoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **20f** (2.4 mg, 0.002 mmol, 36%). MS (ESI): *m/z* $[M+H]^+$ calcd $[C52H53F5N7O7S2]^+$ 1046.3, found 1046.4. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 8.06 – 7.99 (m, 2H), 7.93 – 7.85 (m, 1H), 7.75 – 7.68 (m, 2H), 7.63 – 7.54 (m, 2H), 7.44 – 7.32 (m, 5H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 4.76 (t, *J* = 7.9 Hz, 1H), 4.60 (dd, *J* = 15.0, 6.6 Hz, 2H), 4.49 (d, *J* = 8.5 Hz, 1H), 4.42 – 4.26 (m, 3H), 4.12 (d, *J* = 9.1 Hz, 2H), 4.00 (td, *J* = 12.2, 8.5 Hz, 2H), 3.74 – 3.59 (m, 2H), 2.62 (ddd, *J* = 12.7, 7.6, 4.6 Hz, 1H), 2.53 (s, 3H), 2.22 – 2.00 (m, 1H), 1.65 (s, 6H), 0.95 (s, 9H). UPLC analysis (method A), 3.40 min, 96%.

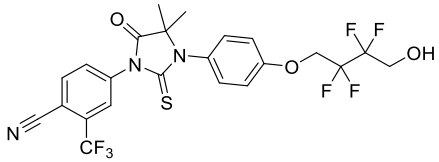
4-(3-(4-(4-(Benzyloxy)-2,2,3,3-tetrafluorobutoxy)phenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile 70



An oven-dried 5 mL microwave vial was charged with (4-benzyloxy-2,2,3,3-tetrafluoro-butyl) trifluoromethanesulfonate **60g** (75 mg, 0.20 mmol), cesium carbonate (76 mg, 0.2 mmol) and 4-[3-(4-hydroxyphenyl)-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **3** (79 mg, 0.20 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous DMF (2 mL) was added, the reaction vessel capped with a Teflon lined metal lid and heated under microwave irradiation for 2 hr at 100 °C. LCMS showed ca 80% conversion. Reaction reheated under microwave irradiation for 2 hr at 100 °C. The crude mixture was quenched with sat. aq. ammonium chloride (1 mL) and then partitioned with H_2O (5 mL) and EtOAc (5 mL). The aqueous phase was further extracted with EtOAc (3 x 5 mL) and the organic phase combined washed with 10% aq. lithium chloride solution (10 mL) and brine (10 mL), then dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo* to give 4-(3-(4-(4-(benzyloxy)-2,2,3,3-tetrafluorobutoxy)phenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile **70** (110 mg, 0.172 mmol, 88%) as a solid. MS (ESI): *m/z* $[M+H]^+$ calcd $[C30H25F7N3O3S]^+$ 640.1, found 640.3. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.06 - 7.95 (m, 2H), 7.91 - 7.83 (m, 1H), 7.44 - 7.31 (m, 5H), 7.27 - 7.22 (m, 2H), 7.10 - 7.04 (m, 2H), 4.70 (s, 2H), 4.52 (t, *J* = 13.85 Hz, 2H), 4.06 - 3.93 (m, 2H), 1.65 - 1.55 (m, 6H). ^{19}F NMR

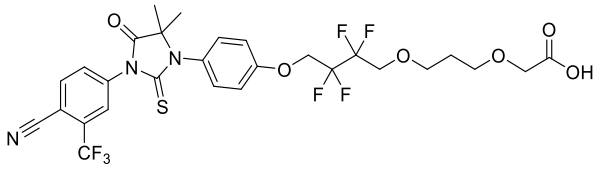
(282 MHz, Chloroform-*d*) δ -61.96 (s, 3F), -121.09 (app. t, *J* = 27.8 Hz, 2F), -121.88 (app. t, *J* = 29.4 Hz, 2F).

4-(4,4-Dimethyl-5-oxo-3-(4-(2,2,3,3-tetrafluoro-4-hydroxybutoxy)phenyl)-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile 71



An oven-dried 25 mL flask with stirrer was charged with 4-[3-[4-(4-benzyloxy-2,2,3,3-tetrafluoro-butoxy)phenyl]-4,4-dimethyl-5-oxo-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **70** (110 mg, 0.170 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous CH_2Cl_2 (1.5mL) was added and the reaction mixture cooled to -78 °C. Boron tribromide (1.0 M in CH_2Cl_2, 0.19mL, 0.190 mmol) was added drop-wise and the reaction mixture stirred at -78 °C for 3hr. The reaction mixture was quench with sat. aq, $NaHCO_3$ (1 mL) and stirred rapidly whilst warming to RT. The crude mixture was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL) and the biphasic solution passed through a hydrophobic frit. The organic phase was concentrated *in vacuo* to give a crude gum. This was purified by flash chromatography (12g SiO_2, linear gradient 0-50% EtOAc in hexanes) to give 4-(4,4-dimethyl-5-oxo-3-(4-(2,2,3,3-tetrafluoro-4-hydroxybutoxy)phenyl)-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile **71** (81mg, 0.147 mmol, 86% yield) as a foam. MS (ESI): *m/z* $[M-H]^-$ calcd $[C23H17F7N3O3S]^-$ 548.1, found 548. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.08 - 7.94 (m, 2H), 7.90 - 7.81 (m, 1H), 7.32 - 7.24 (m, 2H), 7.18 - 7.06 (m, 2H), 4.60 - 4.45 (m, 2H), 4.20 - 4.06 (m, 2H), 2.28 (br. s., 1H), 1.65 - 1.56 (m, 6H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.96 (s, 3F), -121.59 (m, 2F), -123.79 (m, 2F).

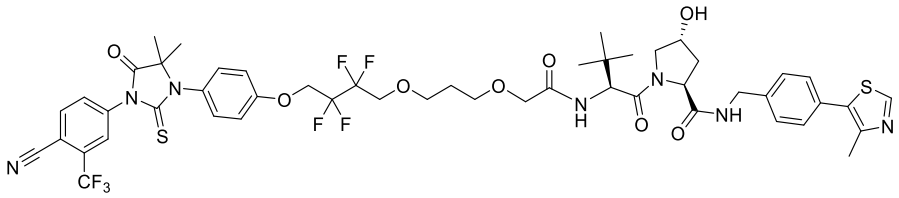
2-(3-(4-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)-2,2,3,3-tetrafluorobutoxy)propoxy)acetic acid 73



An oven-dried 25 mL flask with stirrer was charged with 4-[4,4-dimethyl-5-oxo-3-[4-(2,2,3,3-tetrafluoro-4-hydroxy-butoxy)phenyl]-2-thioxo-imidazolidin-1-yl]-2-(trifluoromethyl)benzonitrile **71** (81 mg, 0.150 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous DMF (1.5 mL) was added and the reaction mixture cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 5.9 mg, 0.150 mmol) was added in a single portion and the reaction mixture stirred for 15 min. A solution of *tert*-butyl 2-(3-(tosyloxy)propoxy)acetate (102 mg, 0.290 mmol) in anhydrous DMF (0.5 mL) was added and the reaction mixture allowed to warm to RT overnight. The reaction mixture was quenched with sat. ammonium chloride (1 mL) and partitioned between EtOAc (5 mL) and H_2O (5 mL). The aqueous phase was extracted with EtOAc (2 x 5 mL) and the combined organics washed with 10% aq. lithium chloride soln. (10 mL) and brine (10 mL), then dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo* to give a crude residue. This was purified by flash chromatography (12g SiO_2, linear gradient 5-50% EtOAc in hexanes) to give *tert*-butyl 2-(3-(4-

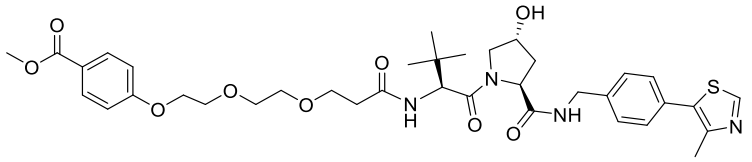
(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)-2,2,3,3-tetrafluorobutoxy)propoxy)acetate **72** (59 mg). An oven-dried 10 mL flask with stirrer was charged with *tert*-butyl 2-[3-[4-[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenoxy]-2,2,3,3-tetrafluoro-butoxy]propoxy]acetate **72** (59 mg). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous CH_2Cl_2 (1 mL) and trifluoroacetic acid (1 mL) were added and the reaction mixture stirred at 25 °C for 5 h. The reaction mixture was concentrated *in vacuo* to give 2-(3-(4-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)-2,2,3,3-tetrafluorobutoxy)propoxy)acetic acid **73** which was used without further purification.

(2*S*,4*R*)-1-((*S*)-2-(2-(3-(4-(4-(3-(4-Cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)-2,2,3,3-tetrafluorobutoxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide 20g



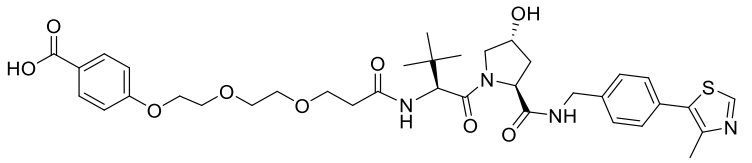
An oven-dried 25 mL flask with stirrer was charged with 2-[3-[4-[4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-imidazolidin-1-yl]phenoxy]-2,2,3,3-tetrafluoro-butoxy]propoxy]acetic acid **73** (54 mg, 0.081 mmol) and(2*S*,4*R*)-1-[(2*S*)-2-amino-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride **9** (38 mg, 0.080 mmol) and HATU (34 mg, 0.089 mmol). The flask was sealed with a septum, evacuated and back-filled with nitrogen (x3). Anhydrous DMF (1 mL) and *N*-ethyl-*N*-isopropyl-propan-2-amine (42 uL, 0.240 mmol) was added and the reaction mixture stirred at 25 °C overnight. The reaction mixture was then quenched with sat. aq. ammonium chloride (1 mL) and partitioned between EtOAc (10 mL) and H_2O (10 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL) and the combined organics washed with 10% aq. lithium chloride soln. (10 mL) and brine (10 mL), then dried (Na_2SO_4), filtered and the filtrate concentrated *in vacuo* to give a crude oil. This was purified by HPLC (5 to 95% MeCN in H_2O with 0.1% NH_3) to give (2*S*,4*R*)-1-((*S*)-2-(2-(3-(4-(4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)phenoxy)-2,2,3,3-tetrafluorobutoxy)propoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **20g** (17 mg, 0.020 mmol, 19%) as an amorphous solid. MS (ESI): *m/z* $[M+H]^+$ calcd $[C50H55F7N7O8S2]^+$ 1078.3, found 1078.5. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.05 - 7.94 (m, 2H), 7.87 (d, *J* = 1.83 Hz, 1H), 7.43 - 7.33 (m, 4H), 7.30 - 7.24 (m, 3H), 7.16 (d, *J* = 8.62 Hz, 1H), 7.14 - 7.06 (m, 2H), 4.74 (t, *J* = 8.0 Hz, 1H), 4.64 - 4.43 (m, 5H), 4.36 (dd, *J* = 5.23, 14.95 Hz, 1H), 4.11 (d, *J* = 11.55 Hz, 1H), 4.05 - 3.87 (m, 4H), 3.78 - 3.69 (m, 2H), 3.68 - 3.57 (m, 3H), 2.86 (br. s., 1H), 2.66 - 2.56 (m, 1H), 2.54 (s, 3H), 2.19 - 2.06 (m, 1H), 1.93 (t, *J* = 6.14 Hz, 2H), 1.60 (s, 6H), 0.96 (s, 9H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.87 (s, 3F), -121.14 (t, *J* = 13.52 Hz, 2F), -121.65 (t, *J* = 13.52 Hz, 2F). UPLC analysis (method D), 6.66 min, 97%.

Methyl 4-(2-(2-(3-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)ethoxy)ethoxy)benzoate 74h



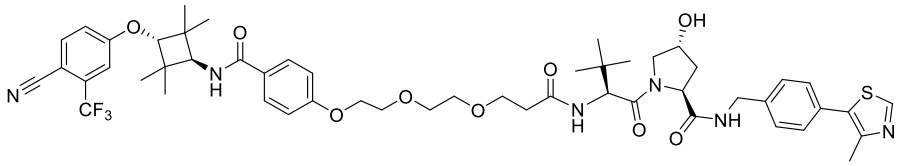
To an oven dried 25 mL flask was added 3-[2-[2-(4-methoxycarbonylphenoxy)ethoxy]ethoxy]propanoic acid **67h** (137 mg, 0.440 mmol) and (2*S*,4*R*)-1-[(2*S*)-2-amino-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride **9** (246 mg, 0.530 mmol). The flask was sealed under N2, then anhydrous DMF (4.4 mL) and diisopropylethylamine (0.2 mL, 1.1 mmol) were added and the reaction mixture cooled to 0 °C and stirred for 5 mins. Then O-(7-Aza-1H-benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (124 mg, 0.530 mmol) was added, the reaction allowed to warm to rt and stirred for 20 hrs. Upon completion the reaction was quenched with H_2O (5 mL) then partitioned between EtOAc (25 mL) and H_2O (25 mL). The aqueous phase was extracted with EtOAc (2 × 25mL), then the organic phases were combined, washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (gradient elution 1 to 10% MeOH in CH_2Cl_2) yielded methyl 4-[2-[2-[3-[[(1*S*)-1-[(2*S*,4*R*)-4-hydroxy-2-[[4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]amino]-3-oxo-propoxy]ethoxy]ethoxy]benzoate **74h** (121 mg, 0.167 mmol, 38% yield) as a colourless oil. MS (ESI): *m/z* $[M+H]^+$ calcd $[C37H49N4O9S]^+$ 725.3, found 725. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.05 – 7.94 (m, 2H), 7.44 – 7.31 (m, 5H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.97 – 6.89 (m, 2H), 4.77 (t, *J* = 8.0 Hz, 1H), 4.64 – 4.49 (m, 2H), 4.42 (d, *J* = 7.9 Hz, 1H), 4.34 (dd, *J* = 14.9, 5.2 Hz, 1H), 4.23 – 4.16 (m, 3H), 3.92 – 3.85 (m, 4H), 3.80 – 3.65 (m, 6H), 3.61 – 3.54 (m, 1H), 2.94 (d, *J* = 4.5 Hz, 1H), 2.62 (ddd, *J* = 12.8, 7.7, 4.6 Hz, 1H), 2.56 – 2.43 (m, 5H), 2.19 – 2.09 (m, 1H), 0.94 (s, 9H).

4-[2-[2-[3-[[(1S)-1-[(2S,4R)-4-hydroxy-2-[[4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]amino]-3-oxo-propoxy]ethoxy]ethoxy]benzoic acid 75h



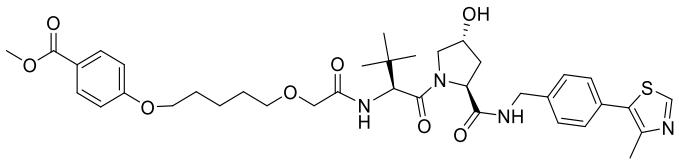
To a solution of methyl 4-[2-[2-[3-[[(1S)-1-[(2S,4R)-4-hydroxy-2-[[4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]amino]-3-oxo-propoxy]ethoxy]ethoxy]benzoate **74h** (120 mg, 0.170 mmol) in THF (1.7 mL) was added a solution of lithium hydroxide monohydrate (35 mg, 0.83 mmol) in H_2O (1.7 mL) and the reaction mixture was stirred at 35 °C for 18 hrs. After this time the reaction mixture was diluted with H_2O (20 mL), acidified to pH 2 with 1M HCl and extracted with CH_2Cl_2 (2 × 25 mL). The combined organics were washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo* to give 4-[2-[2-[3-[[(1*S*)-1-[(2*S*,4*R*)-4-hydroxy-2-[[4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]amino]-3-oxo-propoxy]ethoxy]ethoxy]benzoic acid **75h** (107 mg, 0.151 mmol, 91% yield) as a colourless oil. MS (ESI): *m/z* $[M-H]^-$ calcd $[C36H45N4O9S]^-$ 709.3, found 709.4. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 8.04 – 7.94 (m, 2H), 7.44 – 7.31 (m, 5H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 4.77 (t, *J* = 8.0 Hz, 1H), 4.66 – 4.49 (m, 3H), 4.34 (dd, *J* = 14.9, 5.1 Hz, 1H), 4.22 – 4.15 (m, 3H), 3.89 – 3.82 (m, 2H), 3.78 – 3.58 (m, 7H), 2.63 – 2.44 (m, 6H), 2.22 – 2.12 (m, 1H), 0.96 (s, 9H).

(2*S*,4*R*)-1-[(2*S*)-2-[3-[2-[2-[4-[[3-[4-Cyano-3-(trifluoromethyl)phenoxy]-2,2,4,4-tetramethyl-cyclobutyl]carbamoyl]phenoxy]ethoxy]ethoxy]propanoylamino]-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide 20h



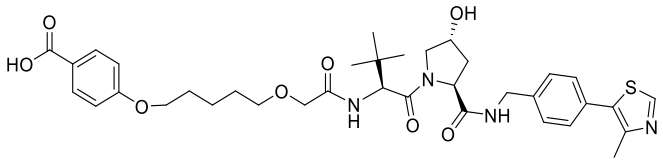
A 50 mL flask was charged with 4-[2-[2-[3-[[(1*S*)-1-[(2*S*,4*R*)-4-hydroxy-2-[[4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]amino]-3-oxo-propoxy]ethoxy]ethoxy]benzoic acid **75h** (100 mg, 0.140 mmol) and 4-(*trans*-3-amino-2,2,4,4-tetramethyl-cyclobutoxy)-2-(trifluoromethyl)benzonitrile hydrochloride (54 mg, 0.15 mmol). The flask was sealed under N_2, then anhydrous DMF (1.4 mL) and diisopropylethylamine (45 mg, 0.35 mmol) were added and the reaction stirred for 5 mins. HATU (64 mg, 0.17 mmol) was added and the reaction mixture stirred for 24 hrs. Upon completion the reaction was quenched with H_2O (25 mL) then partitioned between EtOAc (25 mL) and H_2O (25 mL). The aqueous phase was extracted with EtOAc (2 × 25 mL), then the organic phases were combined, washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (25g SiO_2, gradient elution 0 to 10% MeOH in CH_2Cl_2) yielded (2*S*,4*R*)-1-[(2*S*)-2-[3-[2-[2-[4-[[3-[4-cyano-3-(trifluoromethyl)phenoxy]-2,2,4,4-tetramethyl-cyclobutyl]carbamoyl]phenoxy]ethoxy]ethoxy]propanoylamino]-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide **20h** (99 mg, 0.098 mmol, 70% yield) as a white solid after lyophilisation. MS (ESI): *m/z* $[M+H]^+$ calcd $[C52H64N6O9F3S]^+$ 1005.4, found 1005.6. HRMS *m/z* (ES+) calcd. for $[C52H64N6O9F3S]^+$ 1005.4408 $[M+H]^+$, found 1005.4456. ^1H NMR (300 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.59 (t, *J* = 6.1 Hz, 1H), 8.15 – 8.05 (m, 1H), 7.96 (d, *J* = 9.4 Hz, 1H), 7.89 – 7.80 (m, 2H), 7.72 (d, *J* = 9.2 Hz, 1H), 7.48 – 7.34 (m, 5H), 7.30 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.07 – 6.97 (m, 2H), 5.16 (d, *J* = 3.5 Hz, 1H), 4.56 (d, *J* = 9.4 Hz, 1H), 4.50 – 4.32 (m, 4H), 4.27 – 4.04 (m, 4H), 3.80 – 3.72 (m, 2H), 3.71 – 3.47 (m, 8H), 2.61 – 2.52 (m, 1H), 2.44 (s, 3H), 2.43 – 2.30 (m, 1H), 2.11 – 1.82 (m, 2H), 1.24 (s, 6H), 1.14 (s, 6H), 0.94 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.40 (CO), 170.41 (CO), 169.99 (CO), 167.11 (CO), 162.28 (C_q), 161.32 (C_q), 151.93 (CH), 148.17 (C_q), 139.97 (C_q), 138.17 (CH), 133.22 (d, *J* = 31.9 Hz, C_q), 131.63 (C_q), 130.10 (C_q), 129.93 (CH), 129.10 (CH), 127.88 (CH), 127.27 (C_q), 119.14 (CH), 116.26 (CN), 114.94 (CH), 114.33 (CH), 100.07 (C_q), 84.54 (CH), 70.34 (CH_2), 69.96 (CH_2), 69.33 (CH), 69.30 (CH_2), 67.81 (CH_2), 67.42 (CH_2), 59.18 (CH), 58.60 (CH), 56.85 (CH_2), 56.76 (CH), 42.10 (CH_2), 40.77 (C_q), 38.42 (CH_2), 36.10 (CH_2), 35.84 (C_q), 26.79 (CH_3), 24.45 (CH_3), 23.57 (CH_3), 16.41 (CH_3). Signal for *C*F3 (expected quartet at 123 ppm) not distinguishable. ^{19}F NMR (282 MHz, Chloroform-*d*) δ -62.30. UPLC analysis (method C), 6.15 min, 93%.

Methyl 4-[5-[2-[[(1*S*)-1-[(2*S*,4*R*)-4-hydroxy-2-[[4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]amino]-2-oxo-ethoxy]pentoxy]benzoate 74i



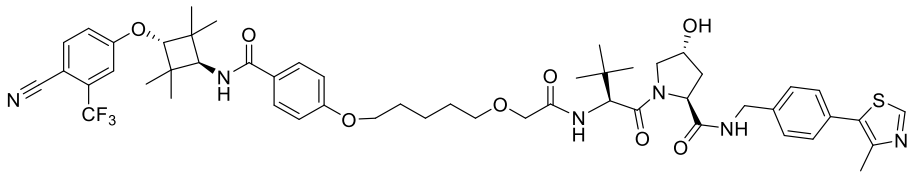
To an oven dried 25 mL flask was added 2-[5-(4-methoxycarbonylphenoxy)pentoxy]acetic acid **67i** (150 mg, 0.510 mmol) and (2*S*,4*R*)-1-[(2*S*)-2-amino-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride **9** (284 mg, 0.610 mmol). The flask was sealed under N_2, then anhydrous DMF (3.4 mL) and diisopropylethylamine (0.22 mL, 1.3 mmol) were added and the reaction mixture cooled to 0 °C and stirred for 5 mins. Then HATU (231 mg, 0.610 mmol) was added, the reaction allowed to warm to rt, and stirred for 23 hrs. Upon completion the reaction was quenched with H_2O (5 mL) then partitioned between EtOAc (25 mL) and H_2O (25 mL). The aqueous phase was extracted with EtOAc (2 × 25 mL), then the organic phased were combined, washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (25g SiO_2, gradient elution 0 to 5% MeOH in CH_2Cl_2) yielded methyl 4-[5-[2-[[(1S)-1-[(2S,4R)-4-hydroxy-2-[[4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]amino]-2-oxo-ethoxy]pentoxy]benzoate **74i** (328 mg, 0.463 mmol, 91% yield) as a colourless oil. MS (ESI): *m/z* $[M+H]^+$ calcd $[C37H49N4O8S]^+$ 709.3, found 709.4. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.04 – 7.95 (m, 2H), 7.44 – 7.30 (m, 5H), 7.19 (d, *J* = 8.6 Hz, 1H), 6.95 – 6.87 (m, 2H), 4.76 (t, *J* = 7.9 Hz, 1H), 4.65 – 4.46 (m, 3H), 4.35 (dd, *J* = 14.9, 5.3 Hz, 1H), 4.14 (d, *J* = 11.5 Hz, 1H), 4.03 (t, *J* = 6.3 Hz, 2H), 3.95 (d, *J* = 5.1 Hz, 2H), 3.90 (s, 3H), 3.63 (dd, *J* = 11.5, 3.7 Hz, 1H), 3.61 – 3.50 (m, 2H), 2.95 (s, 1H), 2.61 (ddd, *J* = 13.5, 7.7, 4.6 Hz, 1H), 2.53 (s, 3H), 2.20 – 2.07 (m, 1H), 1.92 – 1.51 (m, 6H), 0.96 (s, 9H).

4-[5-[2-[[(1*S*)-1-[(2*S*,4*R*)-4-Hydroxy-2-[[4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]amino]-2-oxo-ethoxy]pentoxy]benzoic acid 75i



To a solution of methyl 4-[5-[2-[[(1S)-1-[(2S,4R)-4-hydroxy-2-[[4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]amino]-2-oxo-ethoxy]pentoxy]benzoate **74i** (318 mg, 0.450 mmol) in THF (4.5 mL) was added a solution of lithium hydroxide monohydrate (92 mg, 2.2 mmol) in H_2O (4.5 mL) and the reaction mixture was stirred at 35 °C for 21 hrs. After this time the reaction mixture was diluted with H_2O (20 mL), acidified to pH 2 with 1M HCl and extracted with CH_2Cl_2 (2 × 25 mL). The combined organics were washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo* to give 4-[5-[2-[[(1*S*)-1-[(2*S*,4*R*)-4-hydroxy-2-[[4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]amino]-2-oxo-ethoxy]pentoxy]benzoic acid **75i** (318 mg, 0.458 mmol, quant. yield) as a beige coloured oil. MS (ESI): *m/z* $[M+H]^+$ calcd $[C36H47N4O8S]^+$ 695.3, found 695.5. ^1H NMR (300 MHz, Chloroform-*d*) δ 8.71 (s, 1H), 8.05 – 7.94 (m, 2H), 7.53 – 7.43 (m, 1H), 7.35 (s, 4H), 7.26 (s, 1H), 6.93 – 6.82 (m, 2H), 5.32 (s, 1H), 4.78 (t, *J* = 7.9 Hz, 1H), 4.66 – 4.52 (m, 3H), 4.34 (dd, *J* = 15.0, 5.2 Hz, 1H), 4.13 (d, *J* = 11.5 Hz, 1H), 4.03 – 3.85 (m, 4H), 3.68 (dd, *J* = 11.3, 3.6 Hz, 1H), 3.52 (t, *J* = 6.4 Hz, 2H), 2.62 – 2.47 (m, 1H), 2.51 (s, 3H), 2.24 – 2.11 (m, 1H), 1.90 – 1.76 (m, 2H), 1.76 – 1.64 (m, 2H), 1.61 – 1.45 (m, 2H), 0.98 (s, 9H).

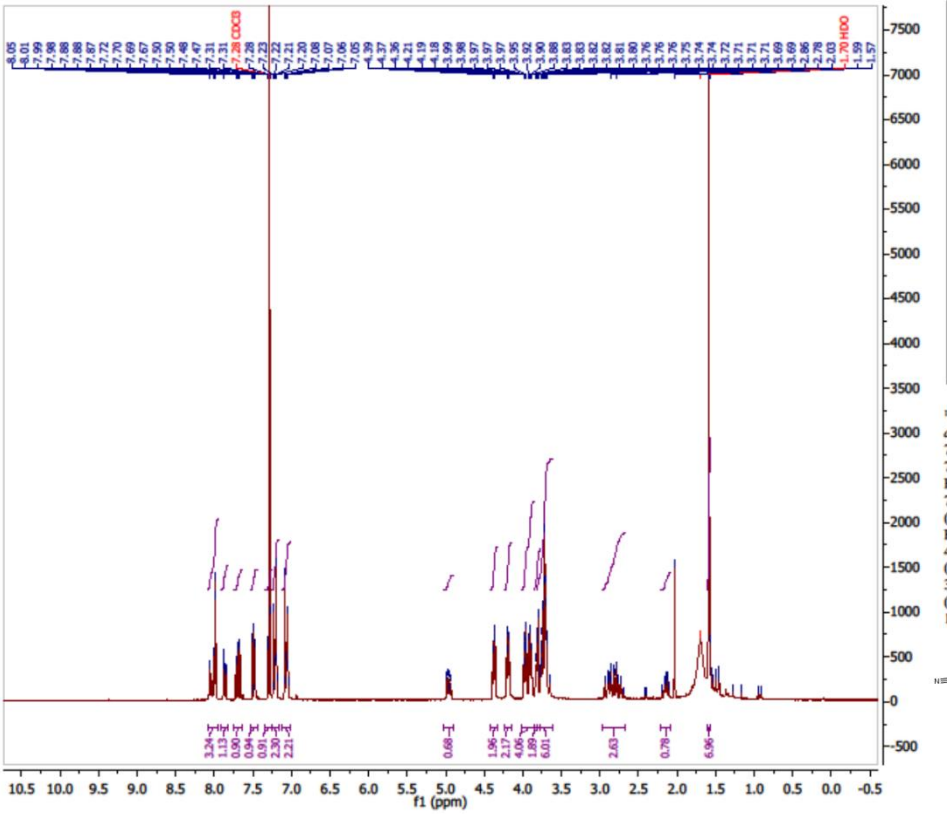
(2*S*,4*R*)-1-[(2*S*)-2-[[2-[5-[4-[[3-[4-Cyano-3-(trifluoromethyl)phenoxy]-2,2,4,4-tetramethyl-cyclobutyl]carbamoyl]phenoxy]pentoxy]acetyl]amino]-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide 20i



A 50 mL flask was charged with 4-[5-[2-[[(1*S*)-1-[(2*S*,4*R*)-4-hydroxy-2-[[4-(4-methylthiazol-5-yl)phenyl]methylcarbamoyl]pyrrolidine-1-carbonyl]-2,2-dimethyl-propyl]amino]-2-oxo-ethoxy]pentoxy]benzoic acid **75i** (98 mg, 0.14 mmol) and 4-(trans-3-amino-2,2,4,4-tetramethyl-cyclobutoxy)-2-(trifluoromethyl)benzonitrile hydrochloride (54 mg, 0.16 mmol). The flask was sealed under N_2, then anhydrous DMF (1.4 mL) and diisopropylethylamine (46 mg, 0.35 mmol) were added and the reaction stirred for 5 mins. Then HATU (64 mg, 0.17 mmol) was added and the reaction mixture stirred for 18 hrs. Upon completion the reaction was quenched with H_2O (25 mL) then partitioned between EtOAc (25 mL) and H_2O (25 mL). The aqueous phase was extracted with EtOAc (2 × 25 mL), then the organic phases were combined, washed with brine (25 mL), dried (hydrophobic frit) and concentrated *in vacuo*. Purification via silica gel chromatography (gradient elution 0 to 10% MeOH in CH_2Cl_2), followed by preparatory HPLC (5 to 95% MeCN in H_2O with 0.1% NH_3) yielded (2*S*,4*R*)-1-[(2*S*)-2-[[2-[5-[4-[[3-[4-cyano-3-(trifluoromethyl)phenoxy]-2,2,4,4-tetramethyl-cyclobutyl]carbamoyl]phenoxy]pentoxy]acetyl]amino]-3,3-dimethyl-butanoyl]-4-hydroxy-*N*-[[4-(4-methylthiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide **20i** (77 mg, 0.078 mmol, 55% yield) as a white solid after lyophilisation. MS (ESI): *m/z* $[M+H]^+$ calcd $[C52H64F3N6O8S]^+$ 989.4, found 989.7. ^1H NMR (300 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.63 (t, *J* = 6.0 Hz, 1H), 8.11 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.88 – 7.77 (m, 2H), 7.69 (d, *J* = 9.2 Hz, 1H), 7.50 – 7.34 (m, 6H), 7.29 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.05 – 6.93 (m, 2H), 5.18 (d, *J* = 3.4 Hz, 1H), 4.57 (d, *J* = 9.6 Hz, 1H), 4.50 – 4.21 (m, 5H), 4.13 – 3.98 (m, 3H), 3.94 (s, 2H), 3.73 – 3.57 (m, 2H), 3.51 (t, *J* = 6.3 Hz, 2H), 2.44 (s, 3H), 2.14 – 2.01 (m, 1H), 1.90 (ddd, *J* = 13.0, 9.0, 4.4 Hz, 1H), 1.77 (quin, *J* = 6.7 Hz, 2H), 1.69 – 1.57 (m, 2H), 1.56 – 1.43 (m, 2H), 1.24 (s, 6H), 1.14 (s, 6H), 0.95 (s, 9H). ^{19}F NMR (282 MHz, DMSO-d_6) δ -61.17. UPLC analysis (method C), 6.72 min, >98%.

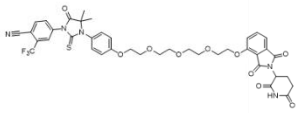
NMR spectra:

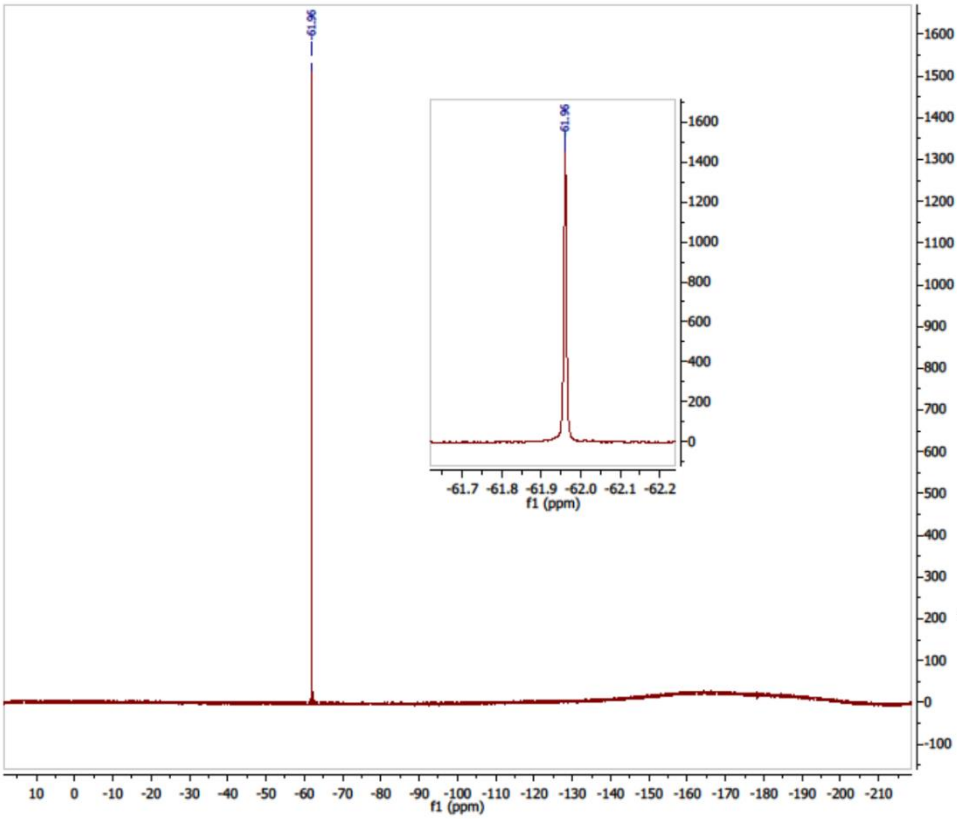
Compound **14**:



Parameter	Value
Title	tpcr2-083-3.10.fid
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	CDCl3
Temperature	295.8
Pulse Sequence	zg30
Experiment	1D
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	128
Receiver Gain	191.9
Relaxation Delay	1.0000
Pulse Width	14.0000
Acquisition Time	5.4526
Acquisition Date	2017-06-13T12:36:00
Spectrometer Frequency	300.13
Spectral Width	6009.6
Lowest Frequency	-1151.4
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

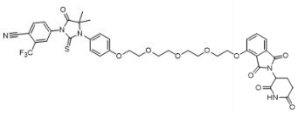
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.08 – 7.95 (m, 3H), 7.91 – 7.82 (m, 1H), 7.69 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.49 (dd, *J* = 7.3, 0.7 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.26 – 7.16 (m, 2H), 7.12 – 7.01 (m, 2H), 4.96 (dd, *J* = 12.1, 5.4 Hz, 1H), 4.42 – 4.33 (m, 2H), 4.24 – 4.15 (m, 2H), 4.02 – 3.86 (m, 4H), 3.86 – 3.77 (m, 2H), 3.81 – 3.62 (m, 6H), 2.97 – 2.67 (m, 3H), 2.22 – 2.08 (m, 1H), 1.59 (s, 6H).



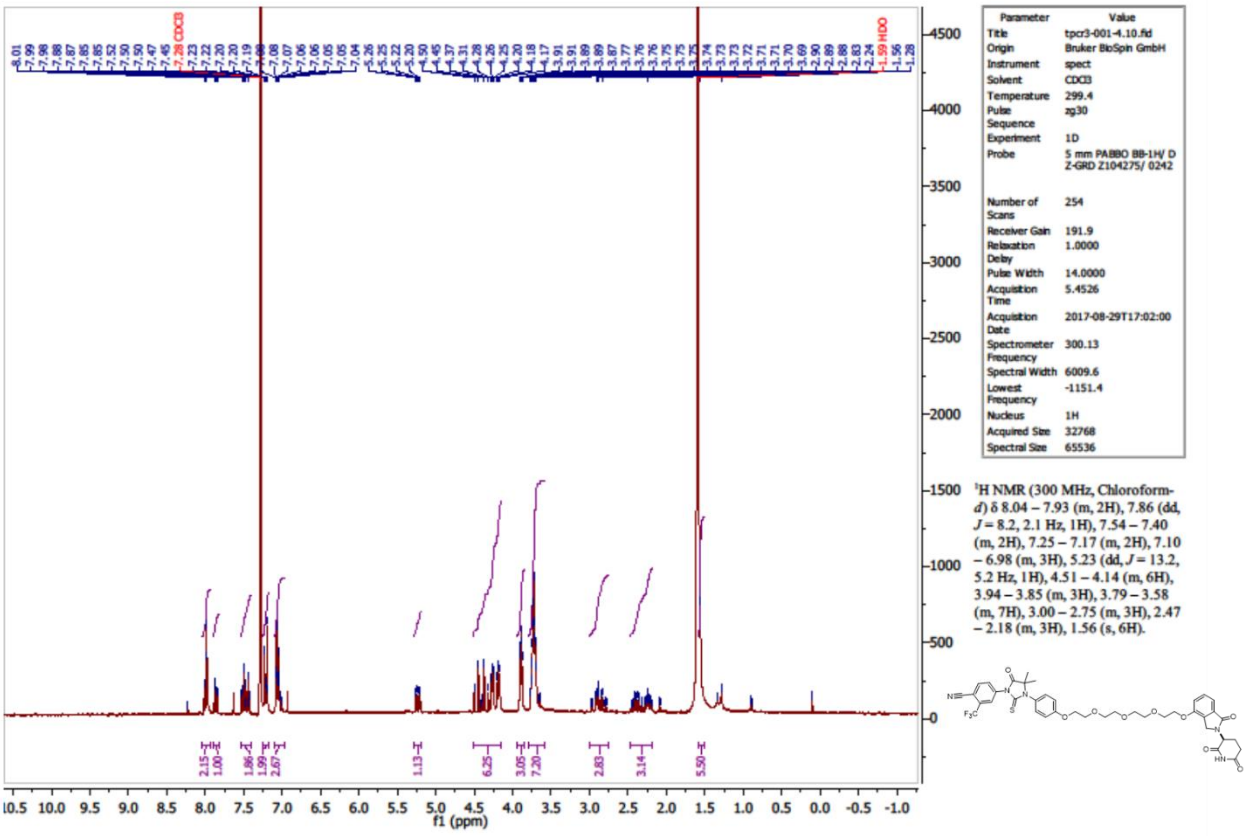


Parameter	Value
Title	tpcr2-083-3.11.fid
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	CDCl3
Temperature	295.8
Pulse Sequence	zgflqn
Experiment	1D
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	32
Receiver Gain	191.9
Relaxation Delay	1.0000
Pulse Width	15.0000
Acquisition Time	0.9787
Acquisition Date	2017-06-13T12:39:00
Spectrometer Frequency	282.38
Spectral Width	66964.3
Lowest Frequency	-61722.4
Nucleus	19F
Acquired Size	65536
Spectral Size	131072

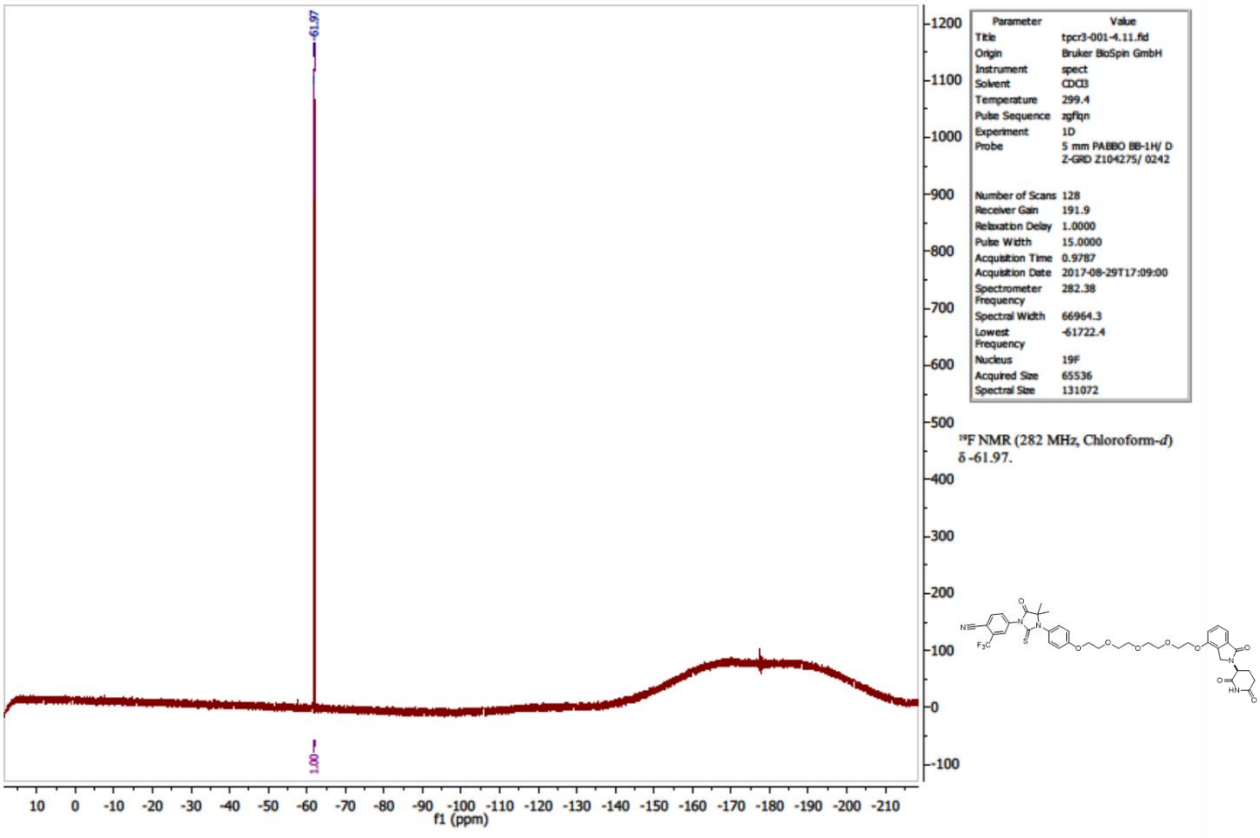
^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.96.



Compound **15**:

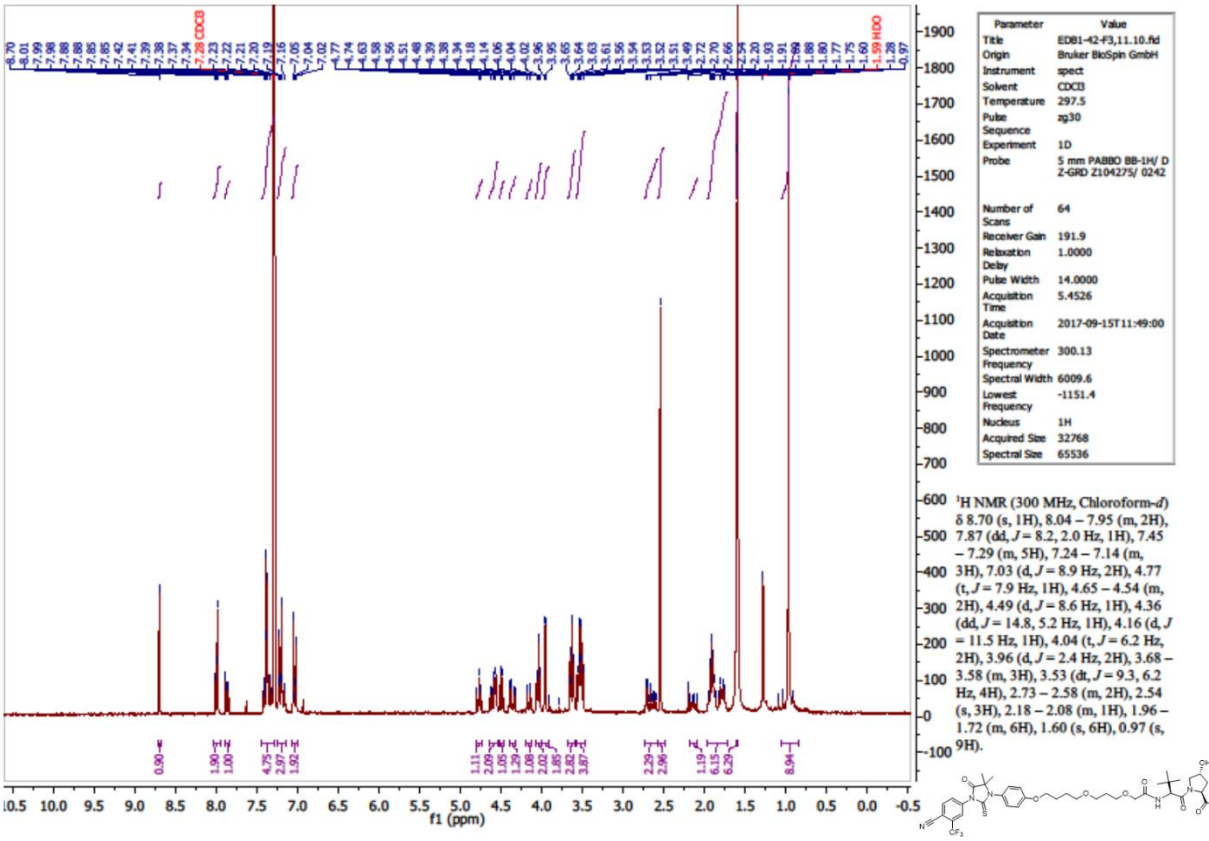


^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.04 – 7.93 (m, 2H), 7.86 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.25 – 7.17 (m, 2H), 7.10 – 6.98 (m, 3H), 5.23 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.51 – 4.14 (m, 6H), 3.94 – 3.85 (m, 3H), 3.79 – 3.58 (m, 7H), 3.00 – 2.75 (m, 3H), 2.47 – 2.18 (m, 3H), 1.56 (s, 6H).



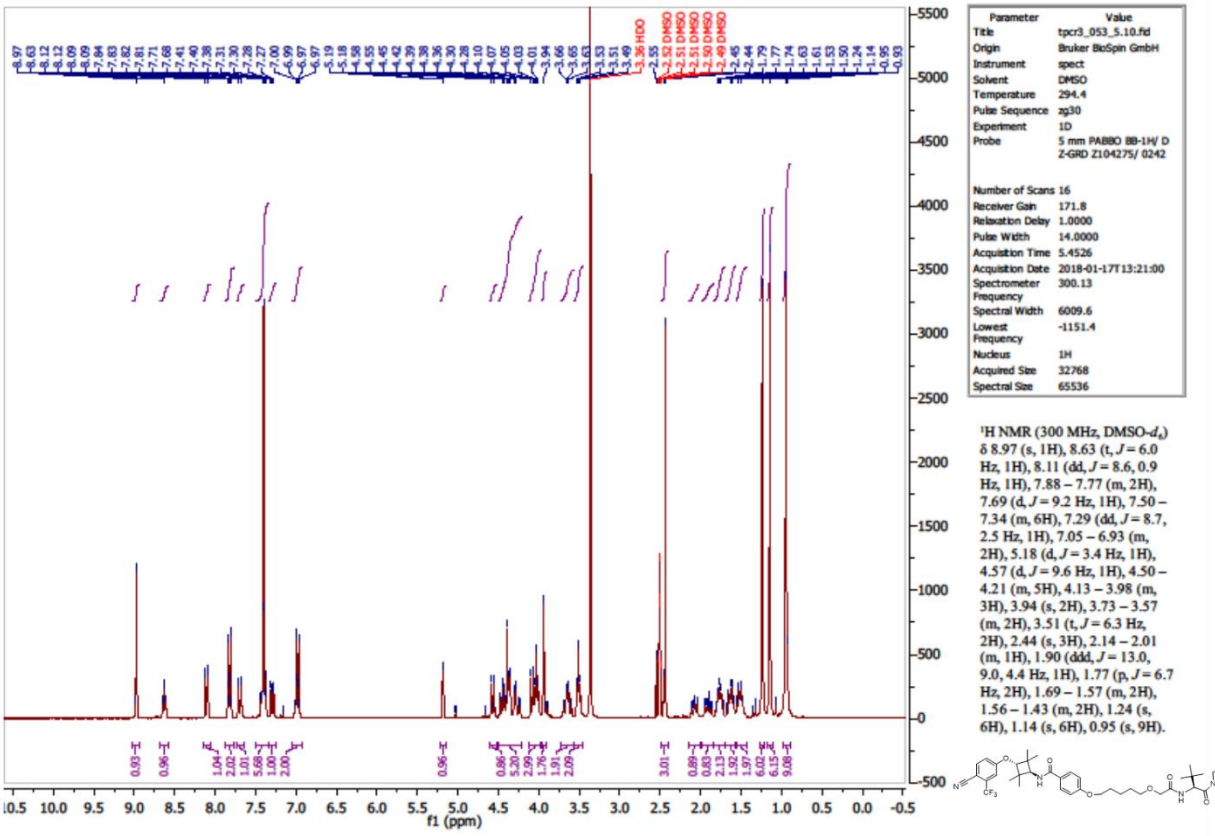
^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.97.

Compound **20a**:



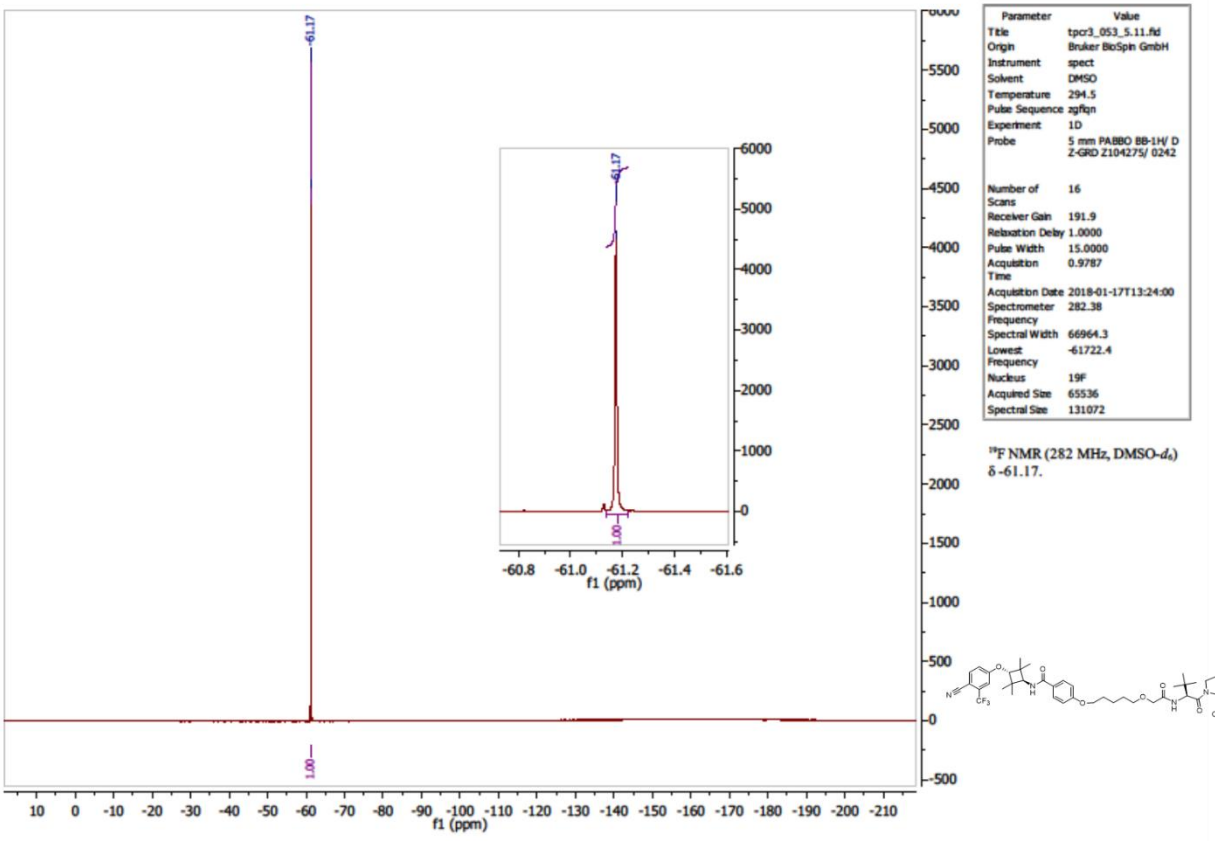
^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.04 – 7.95 (m, 2H), 7.87 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.45 – 7.29 (m, 5H), 7.24 – 7.14 (m, 3H), 7.03 (d, *J* = 8.9 Hz, 2H), 4.77 (t, *J* = 7.9 Hz, 1H), 4.65 – 4.54 (m, 2H), 4.49 (d, *J* = 8.6 Hz, 1H), 4.36 (dd, *J* = 14.8, 5.2 Hz, 1H), 4.16 (d, *J* = 11.5 Hz, 1H), 4.04 (t, *J* = 6.2 Hz, 2H), 3.96 (d, *J* = 2.4 Hz, 2H), 3.68 – 3.58 (m, 3H), 3.53 (dt, *J* = 9.3, 6.2 Hz, 4H), 2.73 – 2.58 (m, 2H), 2.54 (s, 3H), 2.18 – 2.08 (m, 1H), 1.96 – 1.72 (m, 6H), 1.60 (s, 6H), 0.97 (s, 9H).

Compound **20i**:



Parameter	Value
Title	tpcr3_053_5.10.fid
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	DMSO
Temperature	294.4
Pulse Sequence	zg30
Experiment	1D
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	16
Receiver Gain	171.8
Relaxation Delay	1.0000
Pulse Width	14.0000
Acquisition Time	5.4526
Acquisition Date	2018-01-17T13:21:00
Spectrometer Frequency	300.13
Spectral Width	6009.6
Lowest Frequency	-1151.4
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

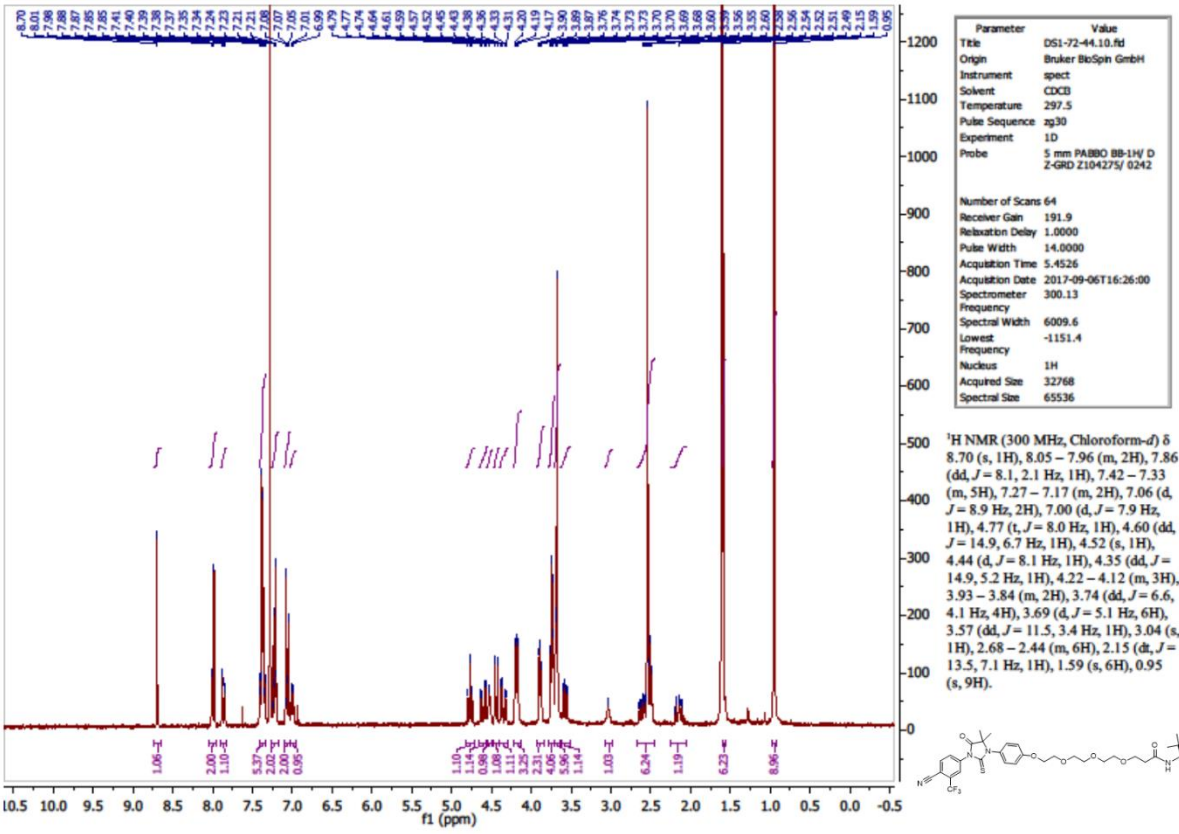
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.63 (t, J = 6.0 Hz, 1H), 8.11 (dd, J = 8.6, 0.9 Hz, 1H), 7.88 – 7.77 (m, 2H), 7.69 (d, J = 9.2 Hz, 1H), 7.50 – 7.34 (m, 6H), 7.29 (dd, J = 8.7, 2.5 Hz, 1H), 7.05 – 6.93 (m, 2H), 5.18 (d, J = 3.4 Hz, 1H), 4.57 (d, J = 9.6 Hz, 1H), 4.50 – 4.21 (m, 5H), 4.13 – 3.98 (m, 3H), 3.94 (s, 2H), 3.73 – 3.57 (m, 2H), 3.51 (t, J = 6.3 Hz, 2H), 2.44 (s, 3H), 2.14 – 2.01 (m, 1H), 1.90 (ddd, J = 13.0, 9.0, 4.4 Hz, 1H), 1.77 (p, J = 6.7 Hz, 2H), 1.69 – 1.57 (m, 2H), 1.56 – 1.43 (m, 2H), 1.24 (s, 6H), 1.14 (s, 6H), 0.95 (s, 9H).



Parameter	Value
Title	tpcr3_053_5.11.fid
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	DMSO
Temperature	294.5
Pulse Sequence	zgfqn
Experiment	1D
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	16
Receiver Gain	191.9
Relaxation Delay	1.0000
Pulse Width	15.0000
Acquisition Time	0.9787
Acquisition Date	2018-01-17T13:24:00
Spectrometer Frequency	282.38
Spectral Width	66964.3
Lowest Frequency	-61722.4
Nucleus	19F
Acquired Size	65536
Spectral Size	131072

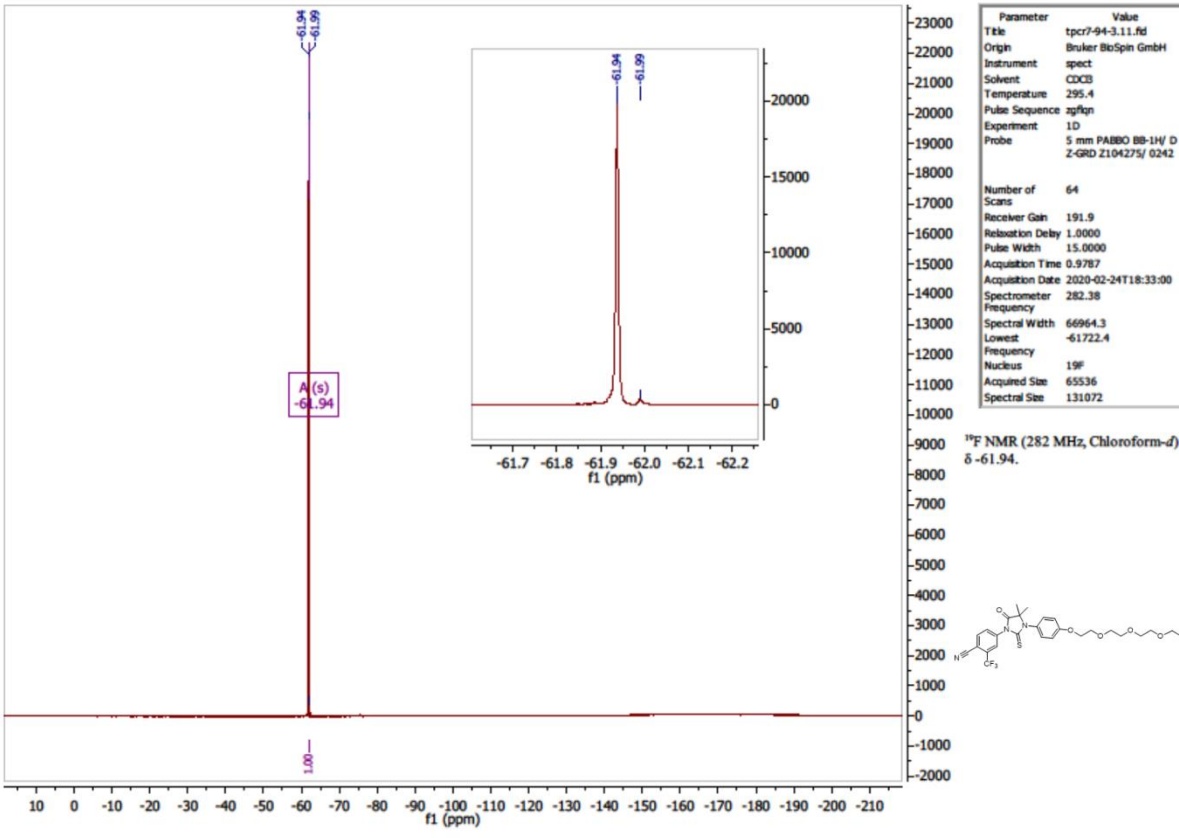
^{19}F NMR (282 MHz, DMSO-d_6) δ -61.17.

Compound **20d**:



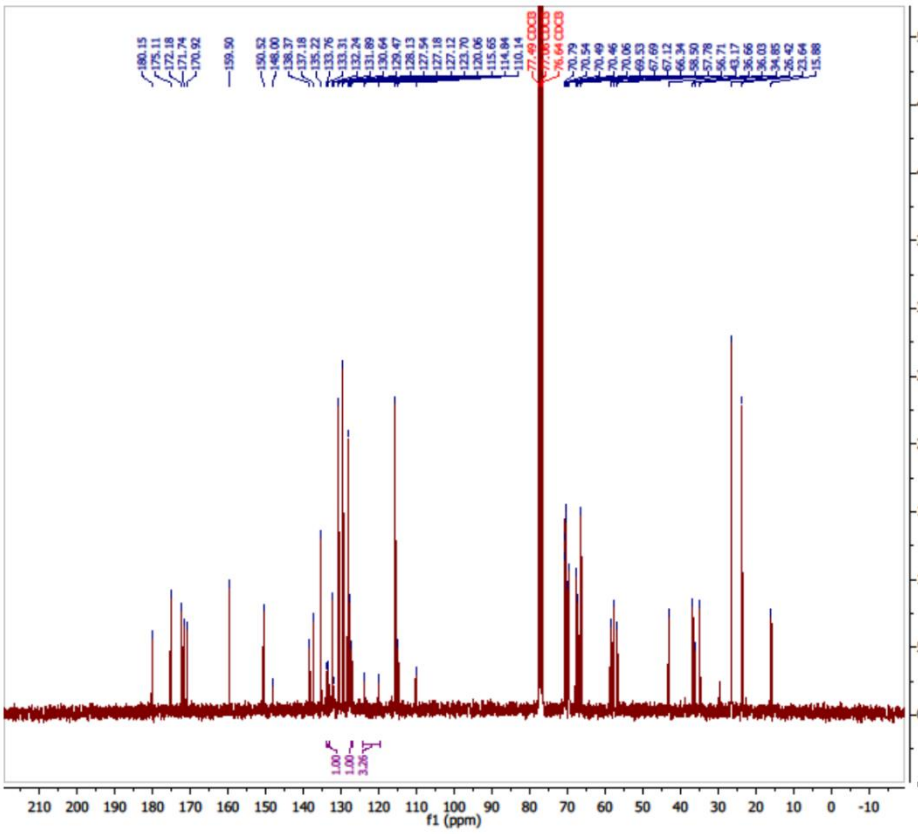
Parameter	Value
Title	DS1-72-44.10.fid
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	CDCl3
Temperature	297.5
Pulse Sequence	zg30
Experiment	1D
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	64
Receiver Gain	191.9
Relaxation Delay	1.0000
Pulse Width	14.0000
Acquisition Time	5.4526
Acquisition Date	2017-09-06T16:26:00
Spectrometer Frequency	300.13
Spectral Width	6009.6
Lowest Frequency	-1151.4
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.05 – 7.96 (m, 2H), 7.86 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.42 – 7.33 (m, 5H), 7.27 – 7.17 (m, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 7.00 (d, *J* = 7.9 Hz, 1H), 4.77 (t, *J* = 8.0 Hz, 1H), 4.60 (dd, *J* = 14.9, 6.7 Hz, 1H), 4.52 (s, 1H), 4.44 (d, *J* = 8.1 Hz, 1H), 4.35 (dd, *J* = 14.9, 5.2 Hz, 1H), 4.22 – 4.12 (m, 3H), 3.93 – 3.84 (m, 2H), 3.74 (dd, *J* = 6.6, 4.1 Hz, 4H), 3.69 (d, *J* = 5.1 Hz, 6H), 3.57 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.04 (s, 1H), 2.68 – 2.44 (m, 6H), 2.15 (dt, *J* = 13.5, 7.1 Hz, 1H), 1.59 (s, 6H), 0.95 (s, 9H).



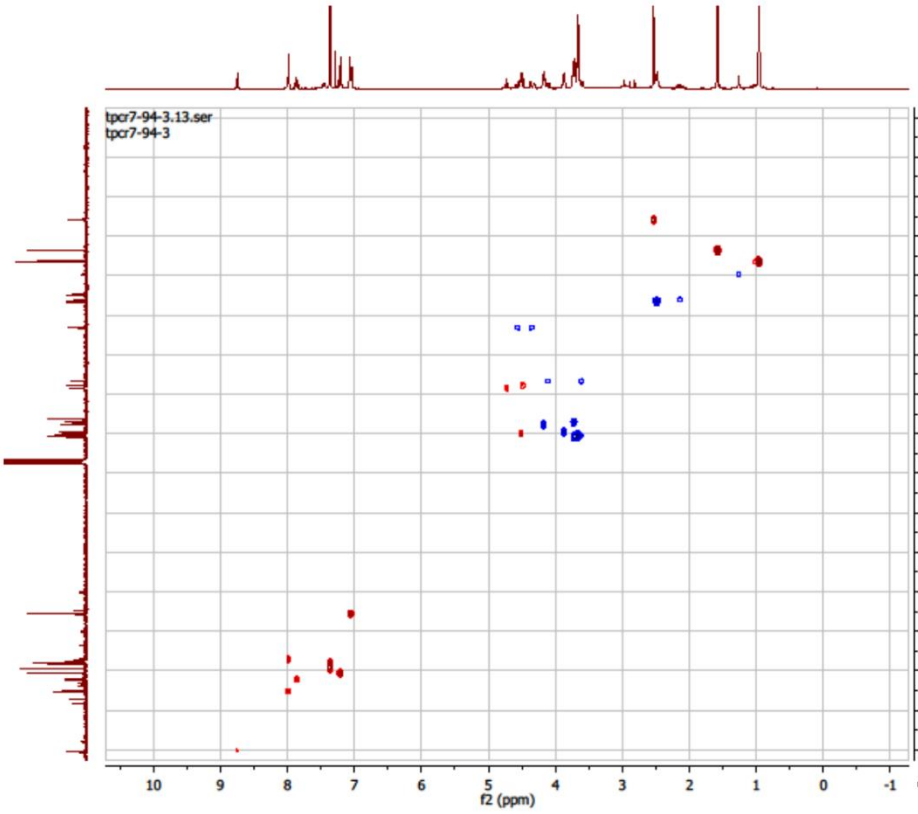
Parameter	Value
Title	tpcr7-94-3.11.fid
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	CDCl3
Temperature	295.4
Pulse Sequence	zgflqn
Experiment	1D
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	64
Receiver Gain	191.9
Relaxation Delay	1.0000
Pulse Width	15.0000
Acquisition Time	0.9787
Acquisition Date	2020-02-24T18:33:00
Spectrometer Frequency	282.38
Spectral Width	66964.3
Lowest Frequency	-61722.4
Nucleus	19F
Acquired Size	65536
Spectral Size	131072

^{19}F NMR (282 MHz, Chloroform-*d*) δ -61.94.

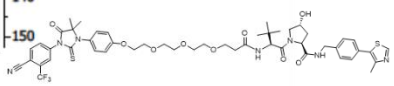


Parameter	Value
Title	tpcr7-94-3.12.fid
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	CDCl3
Temperature	295.6
Pulse Sequence	zgpg30
Experiment	1D
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	4096
Receiver Gain	191.9
Relaxation Delay	2.0000
Pulse Width	10.3000
Acquisition Time	1.8175
Acquisition Date	2020-02-24T23:01:00
Spectrometer Frequency	75.48
Spectral Width	18028.8
Lowest Frequency	-1468.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

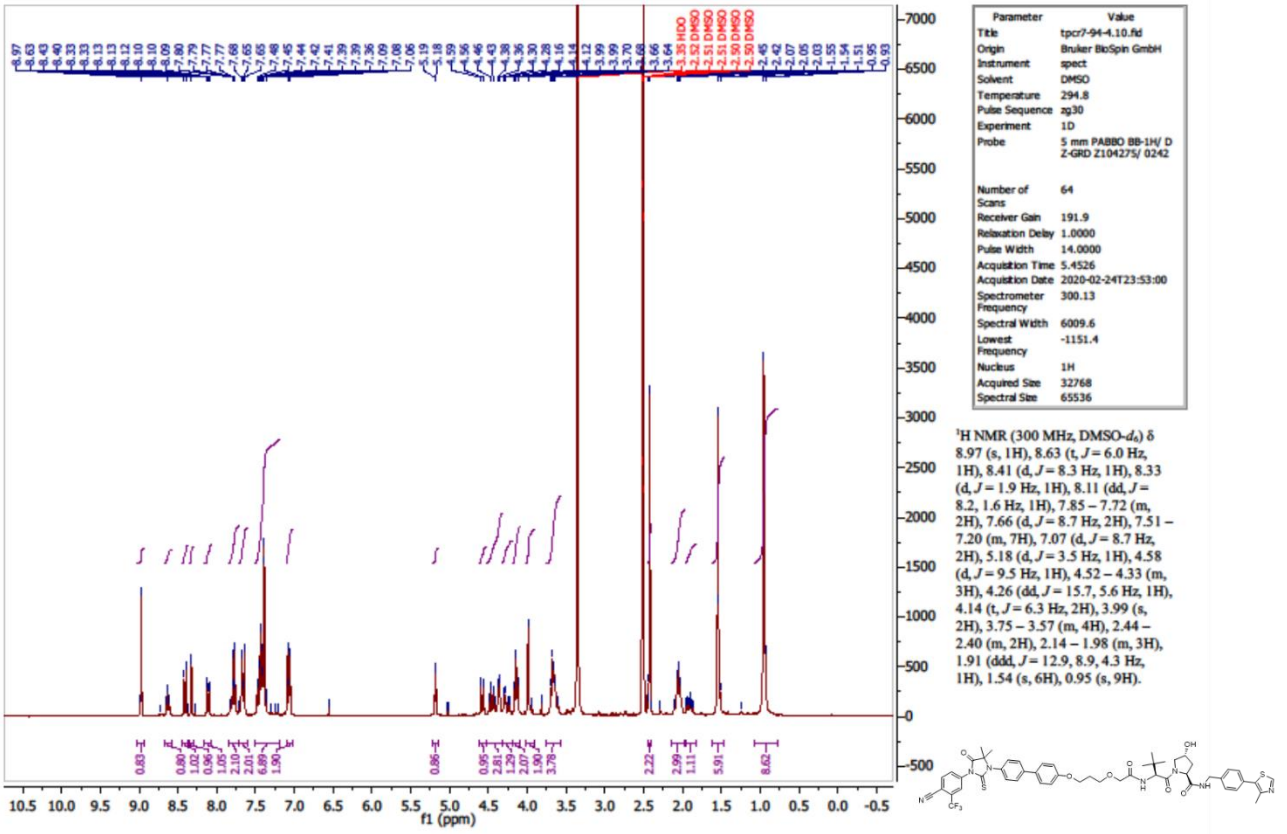
^{13}C NMR (75 MHz, $CDCl_3$) δ 180.15, 175.11, 172.18, 171.74, 170.92, 159.50, 150.52, 148.00, 138.37, 137.18, 135.22, 133.76, 133.31, 132.24, 131.89, 130.64, 129.47, 128.13, 127.54, 127.18, 127.12, 123.70, 120.06, 115.65, 114.84, 110.14, 70.79, 70.54, 70.49, 70.46, 70.06, 69.53, 67.69, 67.12, 66.34, 58.50, 57.78, 56.71, 43.17, 36.66, 36.03, 34.85, 26.42, 23.64, 15.88.



Parameter	Value
Title	tpcr7-94-3.13.ser
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	CDCl3
Temperature	295.3
Pulse Sequence	hsqcedetgpsp.3
Experiment	HSQC-EDITED
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	8
Receiver Gain	191.9
Relaxation Delay	1.0000
Pulse Width	14.0000
Presaturation Frequency	
Acquisition Time	0.1420
Acquisition Date	2020-02-24T23:04:00
Spectrometer Frequency	(300.13, 75.47)
Spectral Width	(3605.8, 12500.0)
Lowest Frequency	(-391.4, -968.1)
Nucleus	(1H, 13C)
Acquired Size	(512, 256)
Spectral Size	(512, 512)

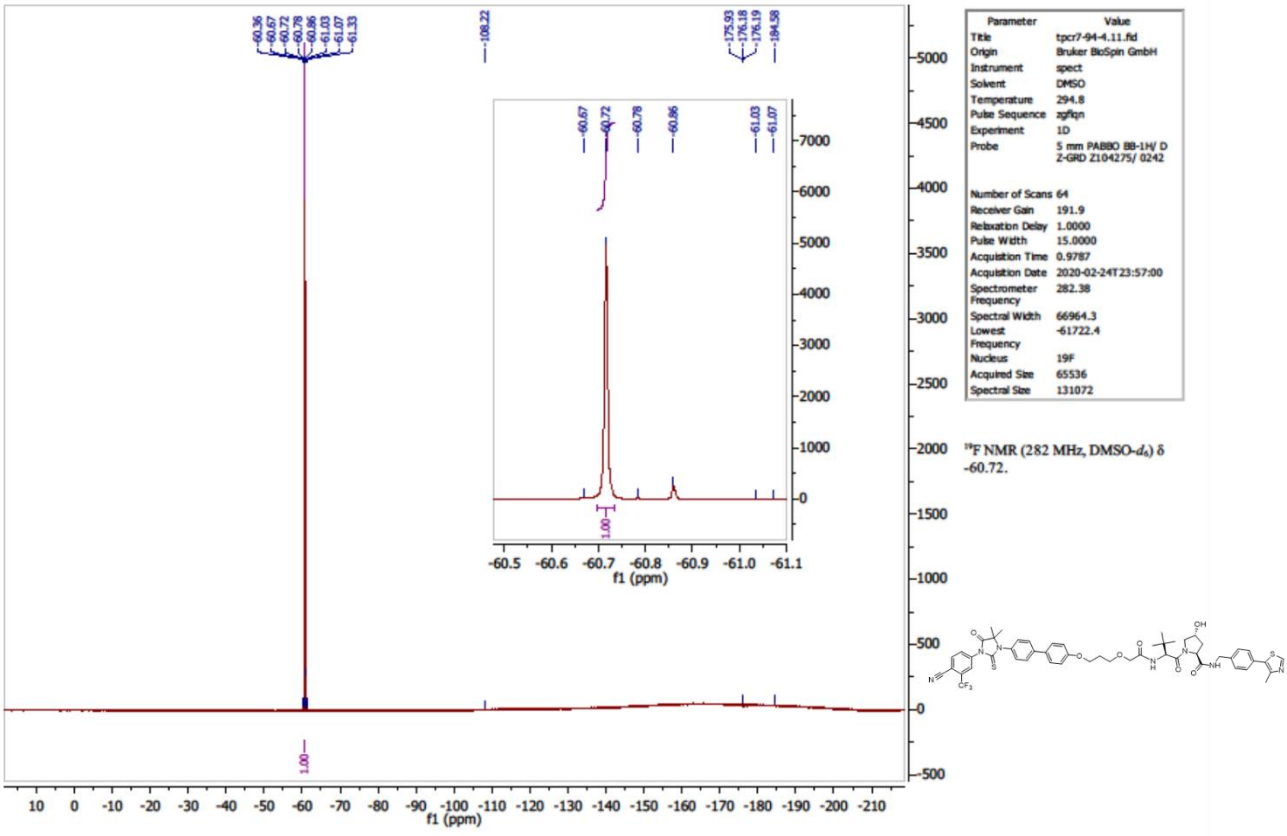


Compound **20e**:



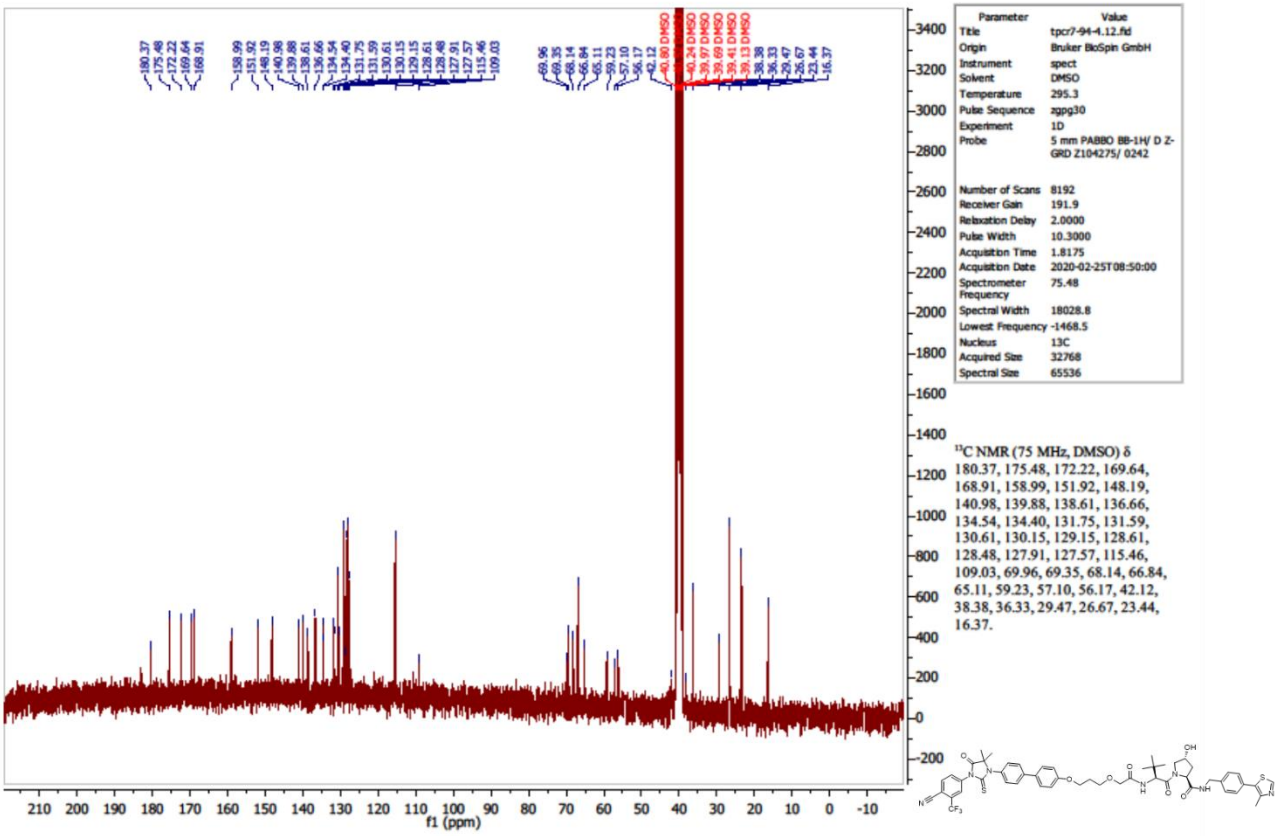
Parameter	Value
Title	tpcr7-94-4.10.fid
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	DMSO
Temperature	294.8
Pulse Sequence	zg30
Experiment	1D
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	64
Receiver Gain	191.9
Relaxation Delay	1.0000
Pulse Width	14.0000
Acquisition Time	5.4526
Acquisition Date	2020-02-24T23:53:00
Spectrometer Frequency	300.13
Spectral Width	6009.6
Lowest Frequency	-1151.4
Nucleus	1H
Acquired Size	32768
Spectral Size	65536

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.63 (t, J = 6.0 Hz, 1H), 8.41 (d, J = 8.3 Hz, 1H), 8.33 (d, J = 1.9 Hz, 1H), 8.11 (dd, J = 8.2, 1.6 Hz, 1H), 7.85 – 7.72 (m, 2H), 7.66 (d, J = 8.7 Hz, 2H), 7.51 – 7.20 (m, 7H), 7.07 (d, J = 8.7 Hz, 2H), 5.18 (d, J = 3.5 Hz, 1H), 4.58 (d, J = 9.5 Hz, 1H), 4.52 – 4.33 (m, 3H), 4.26 (dd, J = 15.7, 5.6 Hz, 1H), 4.14 (t, J = 6.3 Hz, 2H), 3.99 (s, 2H), 3.75 – 3.57 (m, 4H), 2.44 – 2.40 (m, 2H), 2.14 – 1.98 (m, 3H), 1.91 (ddd, J = 12.9, 8.9, 4.3 Hz, 1H), 1.54 (s, 6H), 0.95 (s, 9H).



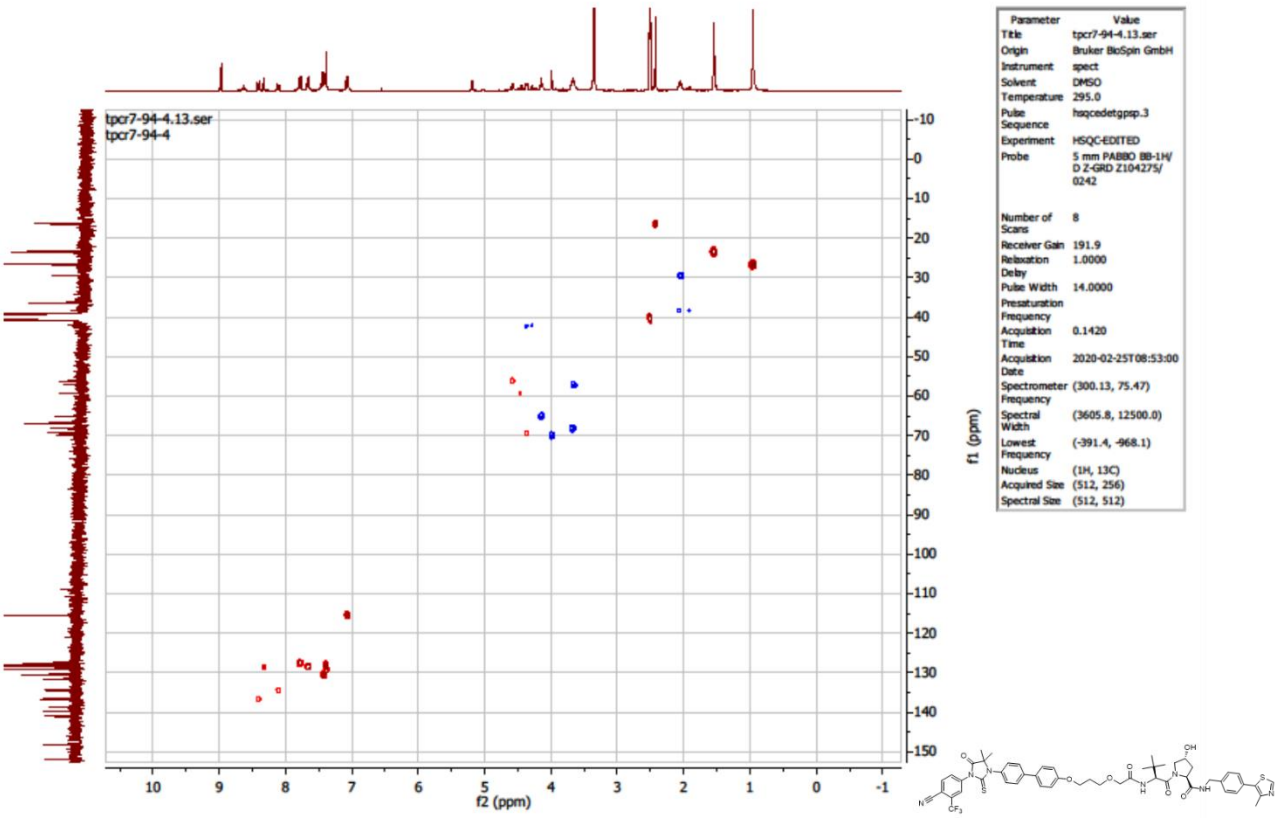
Parameter	Value
Title	tpcr7-94-4.11.fid
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	DMSO
Temperature	294.8
Pulse Sequence	zgflqn
Experiment	1D
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	64
Receiver Gain	191.9
Relaxation Delay	1.0000
Pulse Width	15.0000
Acquisition Time	0.9787
Acquisition Date	2020-02-24T23:57:00
Spectrometer Frequency	282.38
Spectral Width	66964.3
Lowest Frequency	-61722.4
Nucleus	19F
Acquired Size	65536
Spectral Size	131072

^{19}F NMR (282 MHz, DMSO-d_6) δ -60.72.



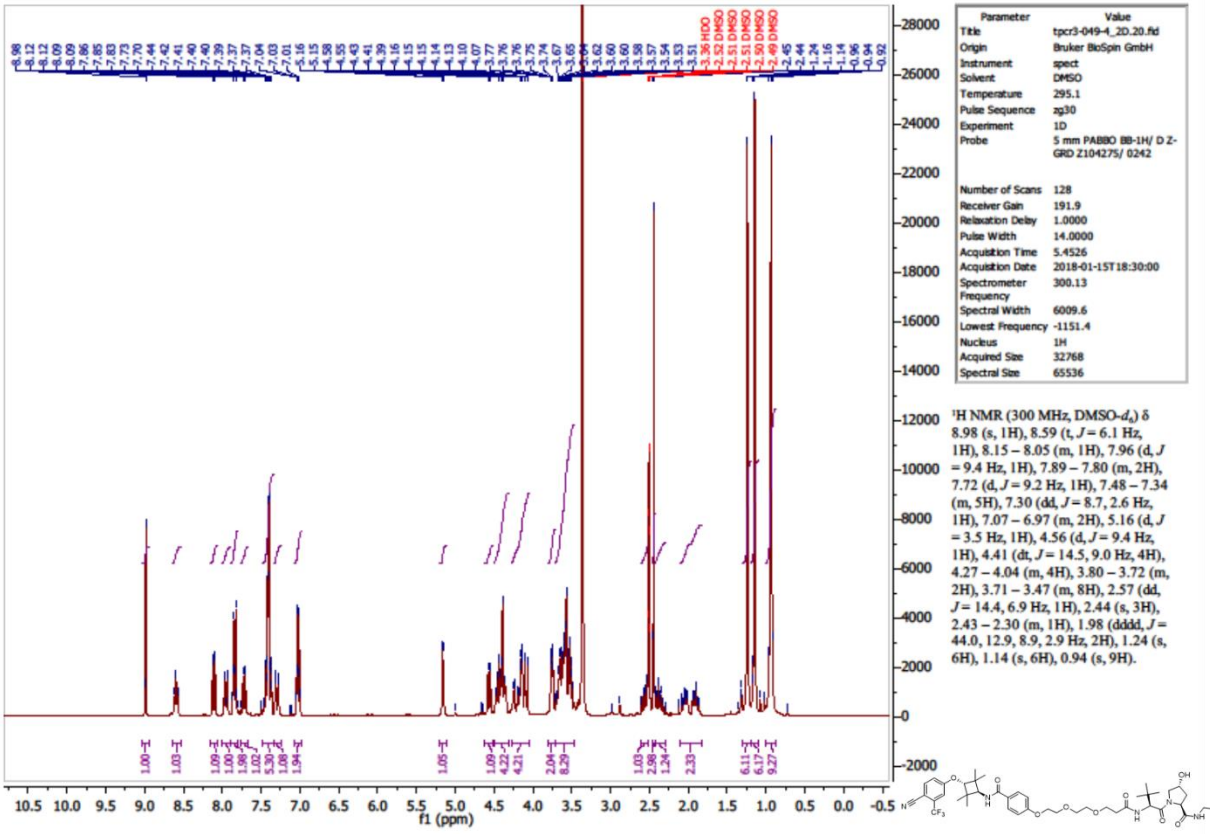
Parameter	Value
Title	tpcr7-94-4.12.fid
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	DMSO
Temperature	295.3
Pulse Sequence	zgpg30
Experiment	1D
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	8192
Receiver Gain	191.9
Relaxation Delay	2.0000
Pulse Width	10.3000
Acquisition Time	1.8175
Acquisition Date	2020-02-25T08:50:00
Spectrometer Frequency	75.48
Spectral Width	18028.8
Lowest Frequency	-1468.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

^{13}C NMR (75 MHz, DMSO) δ 180.37, 175.48, 172.22, 169.64, 168.91, 158.99, 151.92, 148.19, 140.98, 139.88, 138.61, 136.66, 134.54, 134.40, 131.75, 131.59, 130.61, 130.15, 129.15, 128.61, 128.48, 127.91, 127.57, 115.46, 109.03, 69.96, 69.35, 68.14, 66.84, 65.11, 59.23, 57.10, 56.17, 42.12, 38.38, 36.33, 29.47, 26.67, 23.44, 16.37.

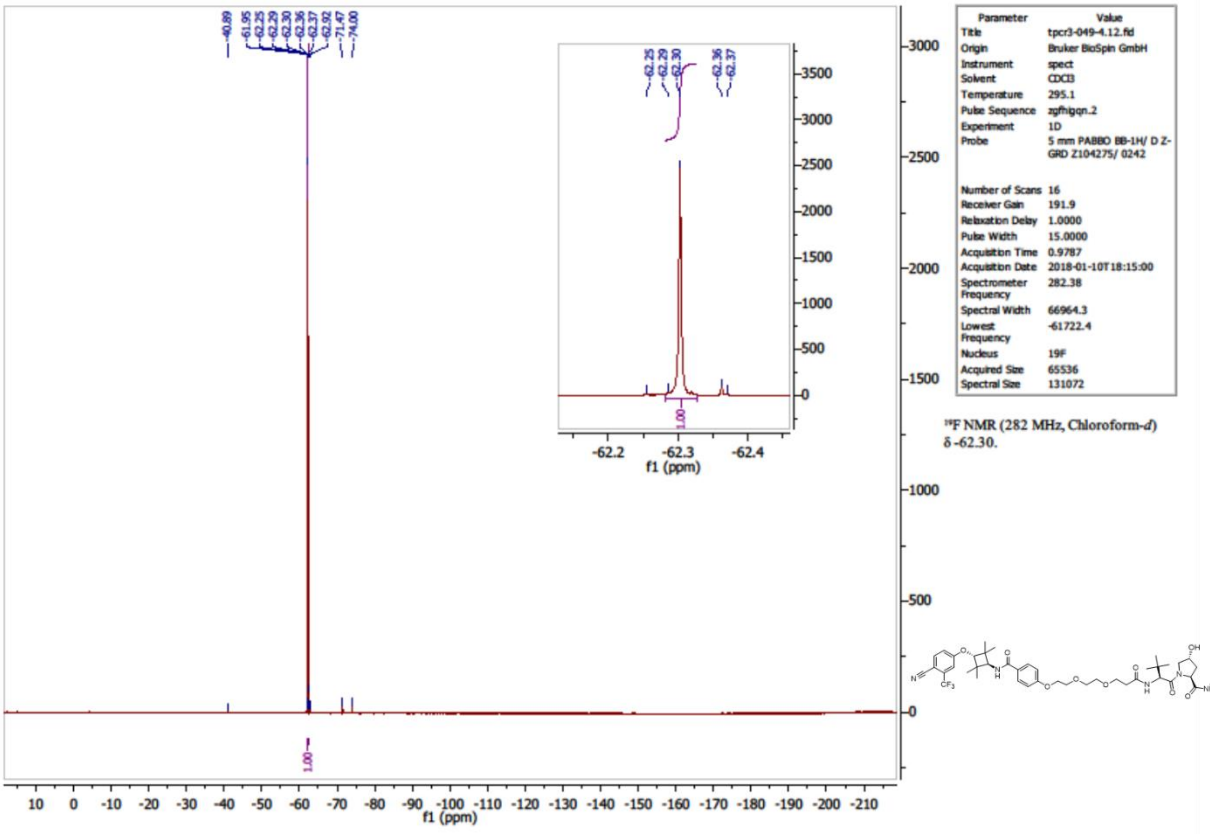


Parameter	Value
Title	tpcr7-94-4.13.ser
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	DMSO
Temperature	295.0
Pulse Sequence	hsqcedetgpsp.3
Experiment	HSQC-EDITED
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	8
Receiver Gain	191.9
Relaxation Delay	1.0000
Pulse Width	14.0000
Presaturation Frequency	
Acquisition Time	0.1420
Acquisition Date	2020-02-25T08:53:00
Spectrometer Frequency	(300.13, 75.47)
Spectral Width	(3605.8, 12500.0)
Lowest Frequency	(-391.4, -968.1)
Nucleus	(1H, 13C)
Acquired Size	(512, 256)
Spectral Size	(512, 512)

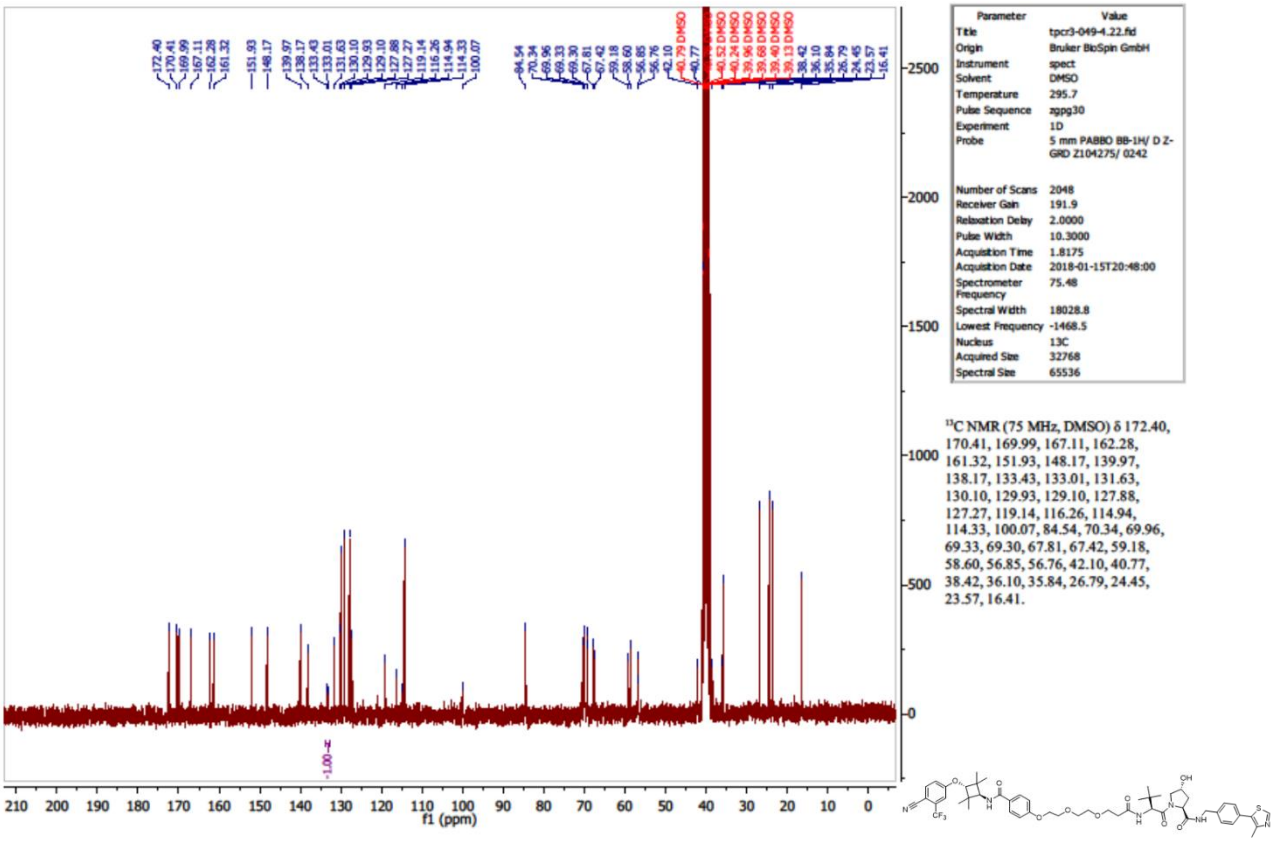
Compound **20h**:



^{1}H NMR (300 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.59 (t, J = 6.1 Hz, 1H), 8.15 – 8.05 (m, 1H), 7.96 (d, J = 9.4 Hz, 1H), 7.89 – 7.80 (m, 2H), 7.72 (d, J = 9.2 Hz, 1H), 7.48 – 7.34 (m, 5H), 7.30 (dd, J = 8.7, 2.6 Hz, 1H), 7.07 – 6.97 (m, 2H), 5.16 (d, J = 3.5 Hz, 1H), 4.56 (d, J = 9.4 Hz, 1H), 4.41 (dt, J = 14.5, 9.0 Hz, 4H), 4.27 – 4.04 (m, 4H), 3.80 – 3.72 (m, 2H), 3.71 – 3.47 (m, 8H), 2.57 (dd, J = 14.4, 6.9 Hz, 1H), 2.44 (s, 3H), 2.43 – 2.30 (m, 1H), 1.98 (dddd, J = 44.0, 12.9, 8.9, 2.9 Hz, 2H), 1.24 (s, 6H), 1.14 (s, 6H), 0.94 (s, 9H).

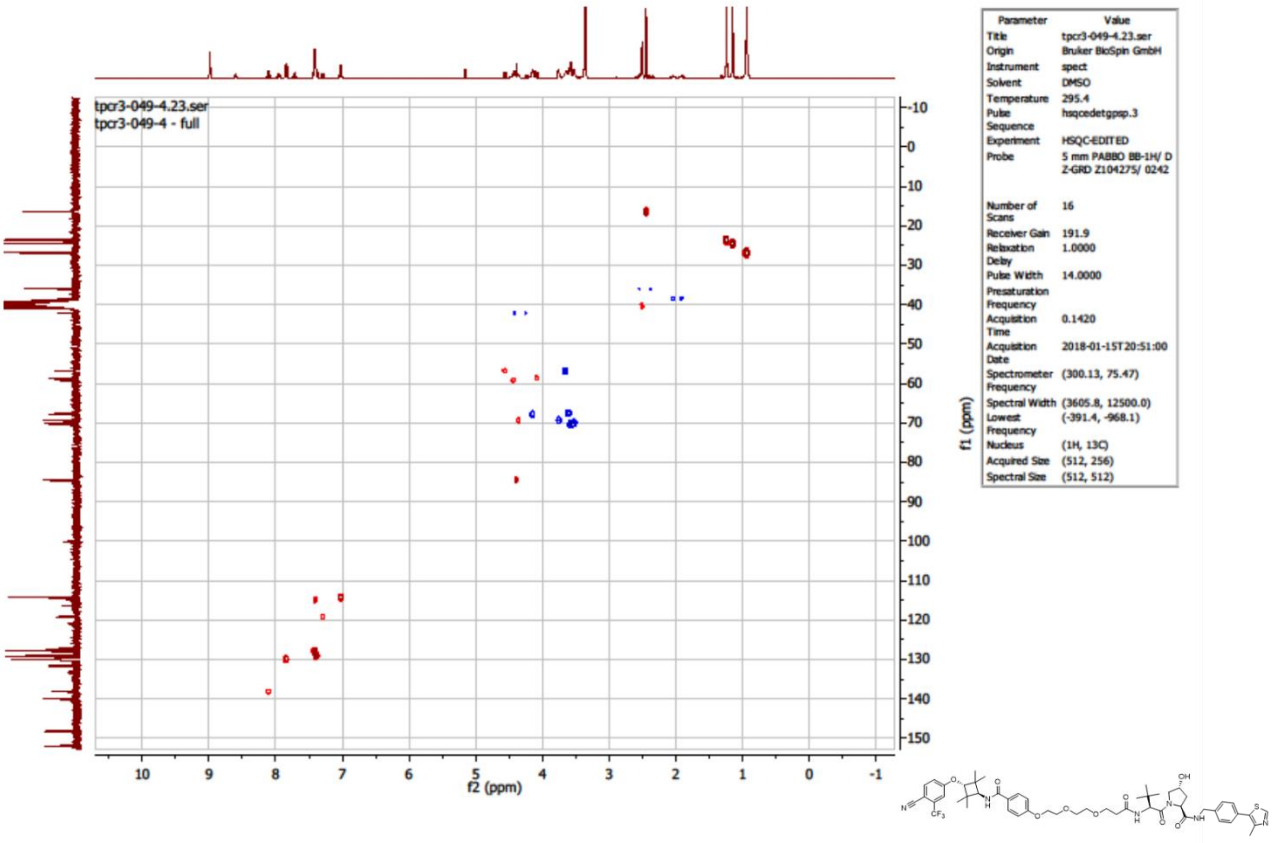


^{19}F NMR (282 MHz, Chloroform-d) δ -62.30.



Parameter	Value
Title	tpcr3-049-4.22.fid
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	DMSO
Temperature	295.7
Pulse Sequence	zgpg30
Experiment	1D
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	2048
Receiver Gain	191.9
Relaxation Delay	2.0000
Pulse Width	10.3000
Acquisition Time	1.8175
Acquisition Date	2018-01-15T20:48:00
Spectrometer Frequency	75.48
Spectral Width	18028.8
Lowest Frequency	-1468.5
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

^{13}C NMR (75 MHz, DMSO) δ 172.40, 170.41, 169.99, 167.11, 162.28, 161.32, 151.93, 148.17, 139.97, 138.17, 133.43, 133.01, 131.63, 130.10, 129.93, 129.10, 127.88, 127.27, 119.14, 116.26, 114.94, 114.33, 100.07, 84.54, 70.34, 69.96, 69.33, 69.30, 67.81, 67.42, 59.18, 58.60, 56.85, 56.76, 42.10, 40.77, 38.42, 36.10, 35.84, 26.79, 24.45, 23.57, 16.41.



Parameter	Value
Title	tpcr3-049-4.23.ser
Origin	Bruker BioSpin GmbH
Instrument	spect
Solvent	DMSO
Temperature	295.4
Pulse Sequence	hsqcedetgpsp.3
Experiment	HSQC-EDITED
Probe	5 mm PABBO BB-1H/ D Z-GRD Z104275/ 0242
Number of Scans	16
Receiver Gain	191.9
Relaxation Delay	1.0000
Pulse Width	14.0000
Presaturation Frequency	
Acquisition Time	0.1420
Acquisition Date	2018-01-15T20:51:00
Spectrometer Frequency	(300.13, 75.47)
Spectral Width	(3605.8, 12500.0)
Lowest Frequency	(-391.4, -968.1)
Nucleus	(1H, 13C)
Acquired Size	(512, 256)
Spectral Size	(512, 512)

References:

1. Gustafson, J. L.; Neklesa, T. K.; Cox, C. S.; Roth, A. G.; Buckley, D. L.; Tae, H. S.; Sundberg, T. B.; Stagg, D. B.; Hines, J.; McDonnell, D. P.; Norris, J. D.; Crews, C. M., Small-Molecule-Mediated Degradation of the Androgen Receptor through Hydrophobic Tagging. *Angew Chem Int Ed Engl* **2015,** *54* (33), 9659-62.
2. Molecular Operating Environment (MOE), 2018. 01; Chemical Computing Group Inc.: Montreal,

Canada, 2018.
3. Small-Molecule Drug Discovery Suite 2019-1; Schrödinger, LLC: New York, 2019.

4. Young, R. J.; Green, D. V.; Luscombe, C. N.; Hill, A. P., Getting physical in drug discovery II: the impact of chromatographic hydrophobicity measurements and aromaticity. *Drug Discov Today* **2011,** *16* (17-18), 822-30.
5. Valko, K.; Bevan, C.; Reynolds, D., Chromatographic Hydrophobicity Index by Fast-Gradient RP-HPLC: A High-Throughput Alternative to log P/log D. *Anal Chem* **1997,** *69* (11), 2022-9.
6. Valko, K.; Nunhuck, S.; Bevan, C.; Abraham, M. H.; Reynolds, D. P., Fast gradient HPLC method to determine compounds binding to human serum albumin. Relationships with octanol/water and immobilized artificial membrane lipophilicity. *J Pharm Sci* **2003,** *92* (11), 2236-48.
7. Nique, F.; Hebbe, S.; Peixoto, C.; Annoot, D.; Lefrancois, J. M.; Duval, E.; Michoux, L.; Triballeau, N.; Lemoullec, J. M.; Mollat, P.; Thauvin, M.; Prange, T.; Minet, D.; Clement-Lacroix, P.; Robin-Jagerschmidt, C.; Fleury, D.; Guedin, D.; Deprez, P., Discovery of diarylhydantoins as new selective androgen receptor modulators. *J Med Chem* **2012,** *55* (19), 8225-35.
8. Galdeano, C.; Gadd, M. S.; Soares, P.; Scaffidi, S.; Van Molle, I.; Birced, I.; Hewitt, S.; Dias, D. M.; Ciulli, A., Structure-guided design and optimization of small molecules targeting the protein-protein interaction between the von Hippel-Lindau (VHL) E3 ubiquitin ligase and the hypoxia inducible factor (HIF) alpha subunit with in vitro nanomolar affinities. *J Med Chem* **2014,** *57* (20), 8657-63.
9. Guo, C.; Linton, A.; Kephart, S.; Ornelas, M.; Pairish, M.; Gonzalez, J.; Greasley, S.; Nagata, A.; Burke, B. J.; Edwards, M.; Hosea, N.; Kang, P.; Hu, W.; Engebretsen, J.; Briere, D.; Shi, M.; Gukasyan, H.; Richardson, P.; Dack, K.; Underwood, T.; Johnson, P.; Morell, A.; Felstead, R.; Kuruma, H.; Matsimoto, H.; Zoubeidi, A.; Gleave, M.; Los, G.; Fanjul, A. N., Discovery of aryloxy tetramethylcyclobutanes as novel androgen receptor antagonists. *J Med Chem* **2011,** *54* (21), 7693-704.
10. Jung, M. E.; Ouk, S.; Yoo, D.; Sawyers, C. L.; Chen, C.; Tran, C.; Wongvipat, J., Structure-activity relationship for thiohydantoin androgen receptor antagonists for castration-resistant prostate cancer (CRPC). *J Med Chem* **2010,** *53* (7), 2779-96.