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Original article

P2′-truncated BACE-1 inhibitors with a novel hydroxethylene-like core

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ABSTRACT

Highly potent BACE-1 protease inhibitors derived from a novel hydroxyethylene-like core structure were recently developed by our group using X-ray crystal structure data and molecular modelling. In a continuation of this work guided by molecular modelling we have explored a truncated core motif where the P2′ amide group is replaced by an ether linkage resulting in a set of alkoxy, aryloxy and alkylaryl groups, with the overall aim to reduce molecular weight and the number of amide bonds to increase permeability and bestow the inhibitors with drug-like features. The most potent of these inhibitors displayed a BACE-1 IC_{50} value of 140 nM. The synthesis of these BACE-1 inhibitors utilizes readily available starting materials, furnishing the target compounds in good overall yields.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative, progressive and ultimately fatal disorder afflicting approximately 40 percent of the population over 80 years, with over 30 million people suffering from AD worldwide [1,2]. In addition to the disease burden of the individuals and social impact on families and society, the financial cost to society is staggering, estimated at over 100 billion USD per year in the US alone [3,4].

AD is characterized by the build-up of insoluble amyliod plaques and neurofibrillary tangles in the brain tissue [5]. Amyloid plaque is mainly constituted of aggregated Aβ(1-40) and Aβ(1-42) peptides with Aβ(1-42) being the major component [6,7]. These peptides are the cleavage products of amyloid precursor protein (APP), a trans-membrane protein, by the action of BACE-1 (β-site APP-cleaving enzyme) and γ-secretase. *In vitro*, the aggregation of Aβ peptides has shown to influence neurotoxicity [8,9]. In neuritic plaques found in the brain of AD patients amyloid-β42 (Aβ1-42) dominates [10].

Mice genetically deficient in BACE-1 show no Aβ build-up in the brain and are healthy and fertile [11–13]. These data together suggest that inhibition of BACE-1 would be a suitable therapeutic approach for AD. Intense research efforts are under way to identify safe and efficacious drugs based on selective BACE-1 inhibition in both the pharmaceutical industry and in academia [14–19].

As BACE-1 is a member of the aspartic protease family, most inhibitors in progress incorporate a non-cleavable transition-state isostere motif such as hydroxyethylamine (HEA), hydroxyethylene (HE), statine, or norstatine pseudopeptide backbone frameworks, where a hydroxy group is the key element [20]. Several research groups have reported on promising BACE-1 inhibitors containing substituted isophthalamides in the P2-P3 position and Vacca and co-workers have described 5-substituted isophthalamides coupled to hydroxyethylamine (HEA) cores that furnish potent and selective BACE-1 inhibitors [21].

Previously we have demonstrated that a statin motif incorporating a methyl-aryloxy or methyl-benzyloxy P1 substituent with a 5-substituted isophthalamide (**A**) [21] in the P2-P3 position furnishes highly potent BACE-1 inhibitors [22]. We have also recently disclosed a novel HE central core [23] having a methoxy P1′ substituent which renders BACE-1 inhibitors with higher potency and improved BACE-1/cathepsin D selectivity, *i.e.* inhibitor **1** (Fig. 1) displaying an IC_{50} value of 0.32 nM. In the same work we

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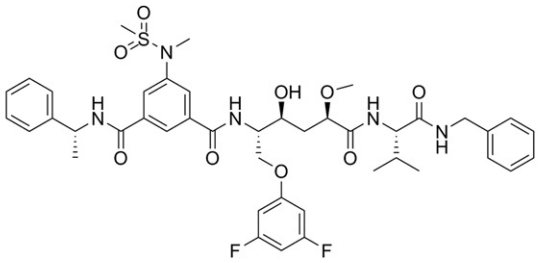
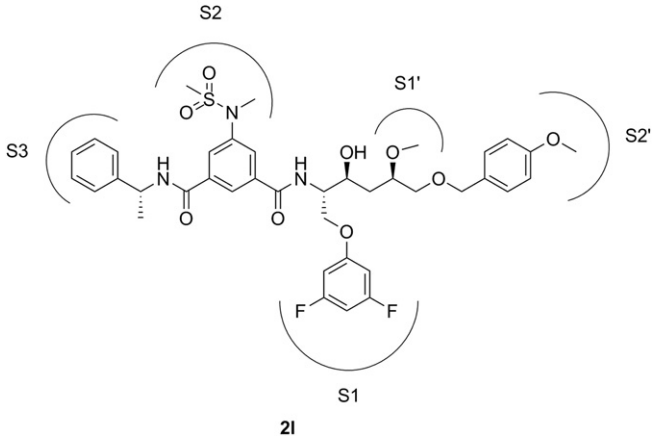


1
IC_{50} 0.32 nM



2l

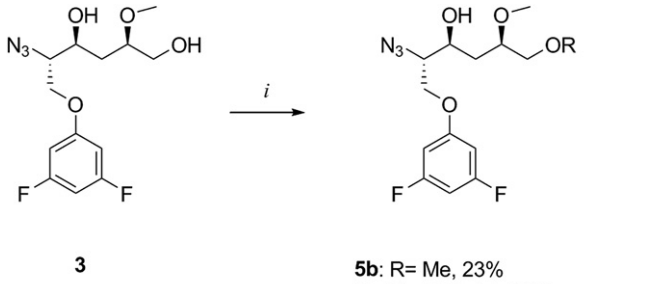
Fig. 1. Lead compound **1** and target compound **2l**.

have also shown that it is possible to truncate between the P2′ and P3′ position and still maintain activity, although these compounds are substantially less potent than lead compound **1**.

We now describe an approach to improve on the drug-like properties of this new template by both reducing molecular weight and decreasing the number of amide bonds (Fig. 1) rendering a template that could easily could be varied in the P2′ position, allowing for the introduction of different ethers as well as secondary amines.

The most potent of these inhibitors, the *p*-methoxy benzyl (PMB) ether **2l**, (Fig. 1) displayed a BACE-1 IC_{50} value of 140 nM.

In this study we report on the synthesis of BACE-1 inhibitors, which are developments of the previously described P1′-methoxy hydroxethylene-like scaffold, having more drug-like features although demonstrating somewhat lower potency. Further modelling and preparative work to explore this truncated template in BACE-1 inhibitor design is currently under way and will be reported elsewhere.



3

5b: R= Me, 23%
5c: R= *iso*-butyl, 14%
5d: R= methyl cyclopropyl, 43%
5e: R= $(CH_2)_2CF_3$, 36%
5f: R= allyl, 51%
5g: R= 4-fluorbenzyl, 29%
5h: R= 3-methoxybenzyl, 24%

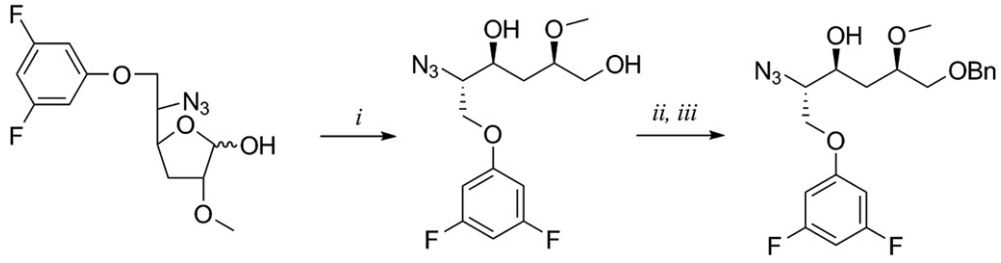
Scheme 2. Reagents and conditions: (i) NaH, RX, QI, DMF.

2. Chemistry

The lactol **4** (Scheme 1), synthesized from D-glucose in 8-steps according to the literature procedure [24–30], was reduced with $LiBH_4$, rendering diol **3** in 95% yield. Compound **3** was activated with dibutyl tinoxide, and regioselectively benzylated on the primary alcohol position using QI and benzyl bromide to generate **5a** (Scheme 1) in 38% yield. As selective methylation or allylation employing this tin activation procedure only provided low yields (10% or less) of the desired primary substituted hydroxyl group, a different strategy was employed.

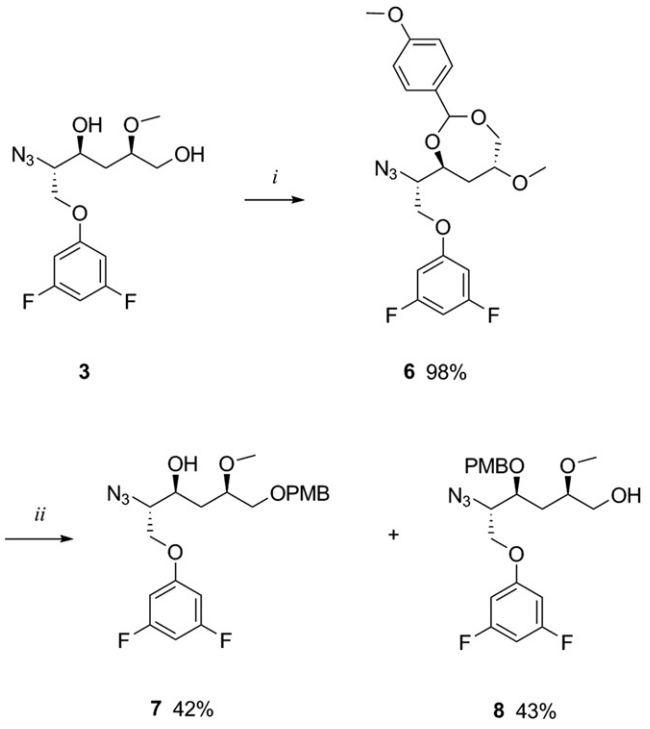
Treating diol **3** with sodium hydride and the appropriate organo halides yielded the ethers **5b**–**h** (Scheme 2), preferentially substituted at the primary hydroxyl group, in 14–51% yields. The undesired products, di-substituted and mono-substituted at the secondary hydroxyl group, were formed in low yields, 2–14%, and were readily separated by column chromatography.

For the conversion to the phenoxy ether, phenyl amines and benzyl amine a different synthesis strategy was employed. The secondary hydroxyl group was first protected as a *p*-methoxy benzyl (PMB) ether using a selective reductive opening of the *p*-methoxy-benzylidene acetal protected diol **6** [31]. The introduction of *p*-methoxy-benzylidene acetal (Scheme 3) was performed using anisaldehyde dimehtylacetal and *p*-TsOH in DMF under reduced pressure to furnish compound **6** in 98% yield. Using the described conditions for selective opening rendering the unsubstituted primary hydroxyl (*i.e.* $NaCNBH_3$, TMSCl, MeCN), products **7** and **8** were delivered in 43% and 42% yield, respectively [31]. The yield of compound **8** was not as high as expected, possibly due to differences between a seven membered ring acetal and a six membered ring acetal.[31] When using the alternative method described to generate the corresponding PMB-protected primary



4 **3** 95% **5a** 38%

Scheme 1. Reagents and conditions: (i): $LiBH_4$, THF, 0 °C; (ii) dibutyl tinoxide, toluene, reflux; (iii) QI, BnBr, 90 °C.



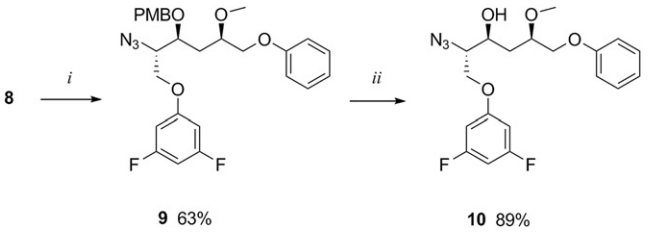
Scheme 3. Reagents and conditions: (i): Anisaldehyde dimehtylacetal, *p*-TsOH, DMF, reduced pressure, 50 °C; (ii) $NaCNBH_3$, TMSCl, MeCN, 0 °C.

hydroxyl group (*i.e.* $NaCNBH_3$, TFA, DMF) our results were in accordance with those reported and generated almost exclusively the product **7** [31].

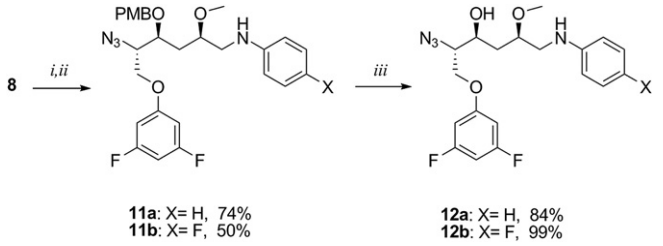
Compound **7** could readily be separated from the desired compound **8** and subsequently converted back to diol **3** in 90% yield by treatment with 10% TFA in DCM. Compound **8** was converted into its corresponding phenoxy ether **9** (Scheme 4) in 63% yield employing Mitsunobu conditions after which the PMB group was cleaved using DDQ to generate **10** in 89% yield.

Using Mitsunobu conditions (*i.e.* Ph_3P, DIAD and DCM) the nosylates [32] 2-nitro-*N*-phenyl-benzenesulfonamide and *N*-(4-fluoro-phenyl)-2-nitro-benzenesulfonamide, were reacted with compound **8** to deliver its corresponding nosylated phenyl amine and 4-fluoro phenyl amine, which were subjected to thiophenol and potassium carbonate cleavage of the nosyl activating group to obtain **11a** and **11b** (Scheme 5) in 74% and 50% yield (over two steps), respectively. The PMB-group was subsequently removed using 10% TFA in DCM to obtain **12a** and **12b** in 84% and 99% yield, respectively.

Compound **8** was converted into the nosylated benzyl amine **13** in 61% yield (Scheme 6) by Mitsunobu coupling with the nosylated benzyl amine (*N*-(benzyl)-2-nitro-benzenesulfonamide) [33]. This was followed by cleavage of the PMB-group using DDQ to generate **14** in 72% yield. To avoid undesired coupling of the benzyl amine



Scheme 4. Reagents and conditions: (i): Phenol, Ph_3P, DIAD, DCM; (ii) DDQ, DCM/H_2O 19:1.



Scheme 5. Reagents and conditions: (i): 2-Nitro-*N*-phenyl-benzenesulfonamide or *N*-(4-fluoro-phenyl)-2-nitro-benzenesulfonamide, DIAD, Ph_3P, DCM; (ii): PhSH, K_2CO_3, MeCN, 50 °C; (iii) TFA 10% in DCM, 30 min.

with carboxylic acid **A**, the nosyl protecting group was not removed until after coupling of the P2–P3 fragment. In order to confirm the stereochemical preference of the secondary hydroxyl group, which interacts with the catalytic Asp228 and Asp32 of BACE-1, the hydroxyl epimer was also prepared. The secondary hydroxyl group of **14** was thus inverted using Mitsunobu conditions, DIAD, triphenylphosphine and *p*-nitro benzoic acid, followed by benzoate saponification in 0.1 M NaOMe to deliver the hydroxyl epimer **15** in 51% yield over the two steps.

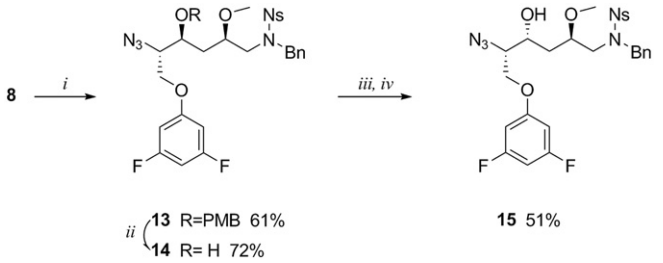
Reduction of the azide group in compounds **3**, **5b**–**e**, **8** and **12a** (Scheme 7) was achieved by hydrogenolysis providing the corresponding amines which were coupled directly without prior purification with carboxylic acid **A** using PyBOP [34] and DIPEA in DCM furnishing **2a**–**g** in yields ranging from 39 to 85% over the two steps. The azide group in **5a**, **5f**–**h**, **10** and **12b** was reduced into the corresponding amines employing Staudinger conditions [35] *i.e.* Ph_3P in methanol containing a few drops of water. The amines were used in the subsequent step without further purification and coupled to carboxylic acid **A**, using the same procedure *vide supra*, to give products **2h**–**m** in 39–92% yield.

Azides **14** and **15** (Scheme 8) were also reduced into its corresponding amines employing Staudinger conditions, coupled to carboxylic acid **A**, to obtain **16** and **17** in 90% and 92% yield, respectively. Compounds **16** and **17** were treated with thiophenol and potassium carbonate to deliver **2n** and **2o** in 50% and 52% yield, respectively.

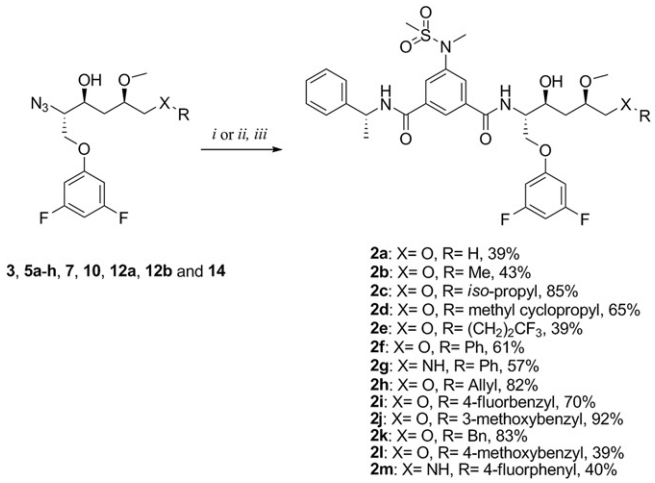
To evaluate two alternative P2-P3 groups, the azide moiety in compound **7** was selectively reduced by hydrogenolysis (Scheme 9) and coupled with carboxylic acids B [36] and C [37] to furnish the final products **18** and **19** in 66 and 76% yield, respectively.

3. Structure activity relationships

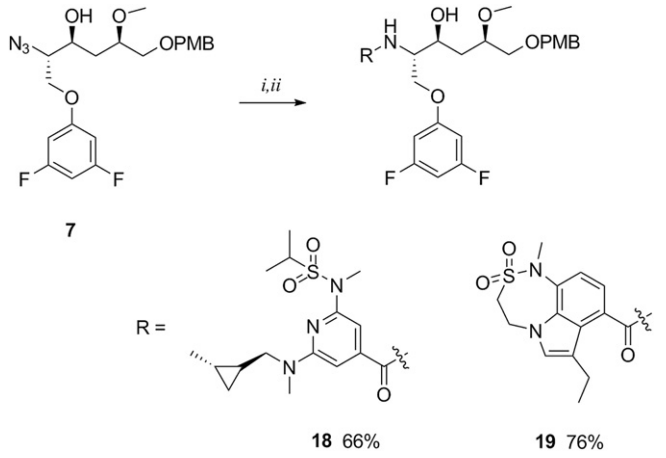
In a previous study we have demonstrated that an HE motif incorporating a methyl-aryloxy P1 substituent and a methoxy P1′ substituent coupled to isophathalamide **A** in the P2-P3 position furnish highly potent and cathepsin D selective BACE-1 inhibitors, *i.e.* inhibitor 1 [23] displaying an IC_{50} value of 0.32 nM. With the



Scheme 6. Reagents and conditions: (i): *N*-(benzyl)-2-nitro-benzenesulfonamide, DIAD, Ph_3P, DCM; (ii): DDQ, DCM/H_2O 19:1; (iii): *p*-nitro benzoic acid, DIAD, Ph_3P, THF; (iv): NaOMe 0.1 M, DOWEX H^+.



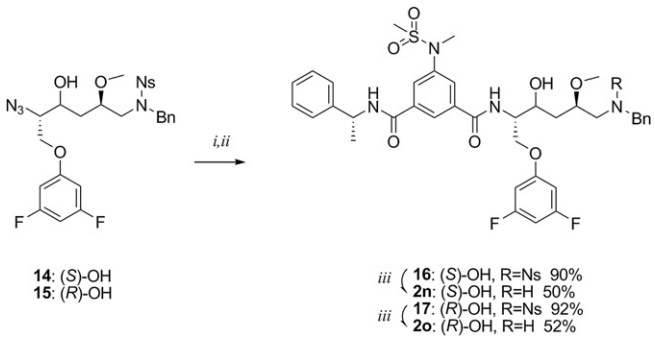
Scheme 7. Reagents and conditions: (i): H_2, Pd/C, MeOH; (ii): Ph_3P, H_2O, MeOH; (iii): PyBOP, DIPEA, **A**, DCM.



Scheme 9. Reagents and conditions: (i): H_2, Pd/C, MeOH; (ii): PyBOP, DIPEA, **B** or **C**, DCM.

aim to bestow this inhibitor class with more advantageous drug-like properties the two prime side amides having one side-chain and three backbone hydrogen bonds to the active site of BACE-1 were removed. All targets were screened against BACE-1 and the IC_{50} values are shown in Table 1. Modelling (Fig. 2) suggests that this truncation is likely to result in less active inhibitors unless an optimal P2′ group having efficient interactions in the S2′ pocket of BACE-1 can be introduced.

The shortening of the compounds will also position the capping P2′ group in the buried S2′ pocket rather than in the shallow S3′ pocket. Inhibitor **2c** with an IC_{50} of 484 nM (entry 3, Table 1) is exhibiting similar interactions as inhibitor **1** in the S2′ pocket, and with the loss of the amides and the P3′ interactions this compound is losing activity. Inhibitors **2k** and **2l** with IC_{50} values of 243 nM and 140 nM, respectively, (entry 11 and 12, Table 1) are having more extensive interactions in S2′, including aromatic stacking with Tyr71 and Arg128, increasing the activity compared to **2c**. According to the 3D structure the *p*-methoxy substituent in **2l** makes additional close contact interactions with Ser36, Asn37 and Ile126 in the bottom of the S2′ pocket, making it twice as active as **2k**. The *meta*-methoxybenzyl compound **2j** is loosing activity due to the restrictions in available space for a *m*-methoxy group in the S2′ pocket. Overall these inhibitors demonstrate a narrow SAR and relative modest potency indicating that additional interactions, *i.e.* a larger S1′ group or interacting with Tyr198 in proximity to the S2′ pocket, might be advantageous for delivering high potency inhibitors.



Scheme 8. Reagents and conditions: (i): Ph_3P, H_2O, MeOH; (ii): PyBOP, DIPEA, **A**, DCM; (iii): PhSH, K_2CO_3, MeCN, 50 °C.

In order to explore the impact on varying the P2-P3 substituents, the azide in compound **7** was reduced and coupled with acids **B** and **C** delivering compounds, **18** and **19** (entries 16 and 17, Table 1). Both showed an approximately tenfold decrease in potency compared to **2l** (entry 12, Table 1). Although all three carboxylic acids employed has shown similar impact on potency in previous studies, it indicates that the S2-S3-pockets are sensitive for the conformal changes that appear when the amide on the prime side is lost and the interactions with the S2′ pocket are changed. The phenyl amine **2g** is four times as potent as phenyl ether **2f**, this may be due to positive interaction between the nitrogen and the carbonyl of Gly34. Our results indicate that the interactions to the amides are of great importance, which suggests that, a major change in the P2′ position is required to regain activity and that likely new interactions are also required to make up for this loss. Work towards this end is currently under way.

4. Conclusions

Based on a novel hydroxyethylene-like core structure recently developed by our group, using X-ray crystal structure data and molecular modelling, a new series of drug-like truncated BACE-1 inhibitors were designed and synthesized where **2c**, **2k** and **2l** showed potency in the nanomolar range. These inhibitors are considerable less peptidic than those previously reported by our group but they also display less potency compared with the potent BACE-1 inhibitor **1**. We have showed that the interactions in the S2′ and S3′-pocket as well as the amide linkage is of key importance for potency and that loss or great change of these interactions must be compensated in other ways. We believe that truncated, less peptide like inhibitors is an area that need to be investigated further.

5. Experimental section

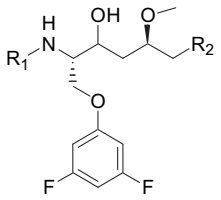
5.1. Protease enzyme assays

The BACE-1 assay was performed as previously described [22].

5.1.1. Modelling

Binding modes and enzyme interactions of inhibitors **2c**, **2k** and **2l** were investigated using GOLD docking [39] with visualisation using Sybyl [40]. The inhibitors were docked in Gold 200 times each using constraints for hydrogen bonding to the catalytic aspartic acids (Asp32 and Asp228) and to the backbone carbonyls of Gly34

Table 1
BACE-1 inhibitory activities.



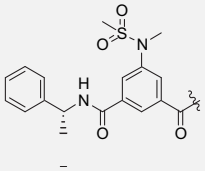
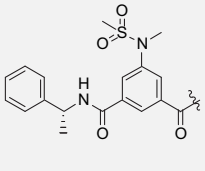
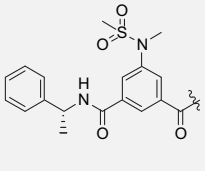
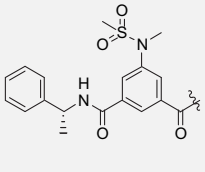
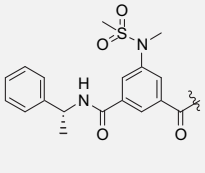
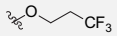
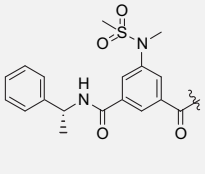
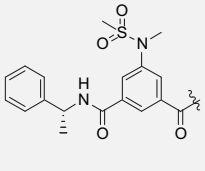
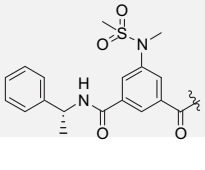
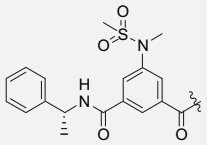
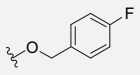
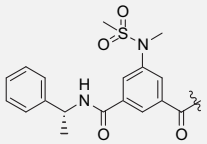
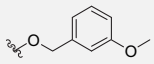
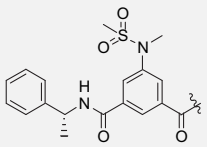
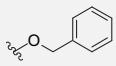
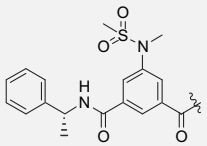
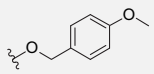
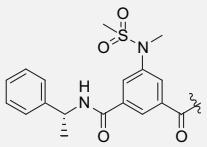
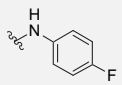
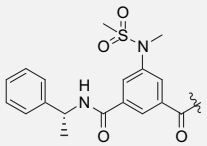
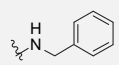
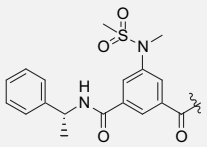
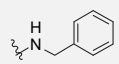
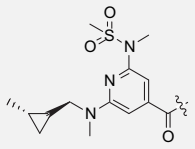
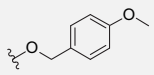
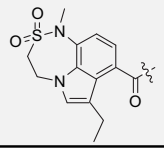
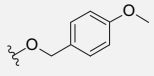
Entry	Cpd.	R_1	R_2	OH	IC_{50} (μM)
1	**2a**			(*S*)-OH	>10
2	**2b**			(*S*)-OH	>10
3	**2c**			(*S*)-OH	0.48
4	**2d**			(*S*)-OH	1.86
5	**2e**			(*S*)-OH	n.d.
6	**2f**			(*S*)-OH	6.50
7	**2g**			(*S*)-OH	1.50
8	**2h**			(*S*)-OH	2.03

Table 1 (*continued*)

Entry	Cpd.	R_1	R_2	OH	IC_{50} (μM)
9	**2i**			(*S*)-OH	>10
10	**2j**			(*S*)-OH	>10
11	**2k**			(*S*)-OH	0.24
12	**2l**			(*S*)-OH	0.14
13	**2m**			(*S*)-OH	1.50
14	**2n**			(*S*)-OH	>10
15	**2o**			(*R*)-OH	>10
16	**18**			(*S*)-OH	1.80
17	**19**			(*S*)-OH	1.50

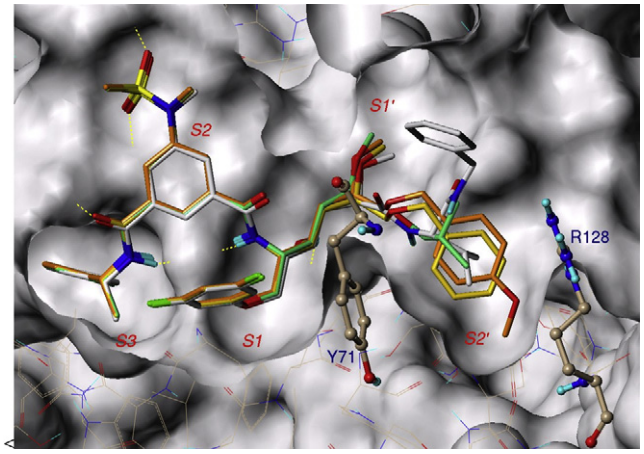


Fig. 2. Models of compounds **2c** (green), **2k** (yellow), and **2l** (orange) superimpositioned with an X-ray crystal structure of inhibitor **1** (white) co-crystallized with BACE-1 [38]. Tyr71 and Arg128 of the enzyme are included for clarity.

and Gly230. The binding conformations were evaluated using GoldScore. The X-ray crystal structure of inhibitor **1** [38] co-crystallized with BACE-1 was used as the starting point for the modelling and docking studies.

5.1.2. General methods

All glassware were dried over an open flame before use in connection with an inert atmosphere. Concentrations were performed under reduced pressure at <40 °C (bath temperature). Thin layer chromatography was performed using Merck silica gel 60 F-254 plates with detection by UV, charring with 8% sulphuric acid or ammonium molybdate (100 g): Ce(IV)sulphate (2 g): sulphuric acid (10%, 2L). Column chromatography was performed on silica (0.035–0.070 mm). NMR spectra were recorded at 25 °C on a Varian (400 MHz) or on a Bruker (400 MHz or 500 MHz) instrument using the solvent residual peak ($CDCl_3$ ^1H $\delta = 7.26$ and ^{13}C $\delta = 77.16$ or CD_3OD-d_4 ^1H $\delta = 3.31$ and $^{13}C = 49.0$) as standard. Unless stated otherwise, all materials were obtained from commercial suppliers and used without further purification. DCM was refluxed over CaH_2 and distilled onto 4 Å MS before use. Compound **2a**–**o**, **18** and **19** were further purified before the biological testing using preparative RP-HPLC, consisted of Waters 2767 auto-injector and fraction collector, Waters 996 photodiode array detector, and Micromass ZQ2000 mass detector (operated in +ESI). The preparative reversed phase column was an ACE C_8, 21 × 100 mm, 5 μm, 100 A from ACE (UK) and the mobile phases were based on water/acetonitrile containing 0.1%ammonium acetate. Optical rotations were measured at r t on a Perkin Elmer 341 polarimeter using a 10 cm, 1 mL cell. Mass spectra were recorded with a Bruker micrOTOF 125 spectrometer.

5.1.3. Synthetic experiments

*5.1.3.1. (2R,4S,5S)-5-azido-6-(3,5-difluoro-phenoxy)-2-methoxy-hexane-1,4-diol (**3**).* Under argon atmosphere $LiBH_4$ (200 mg, 9.22 mmol) was added to a stirred solution of **4** (1.45 g, 4.61 mmol) in dry THF (20 mL) at 0 °C. After 1 h the reaction mixture was quenched with water, extracted with ethyl acetate, dried over Na_2SO_4 and concentrated. After purification by silica gel chromatography (toluene–ethyl acetate, gradient 20:1–5:1) compound **3** in 95% yield (1.39 g, 4.38 mmol). $[\alpha]_D^{20}$ −5.8 (*c* 1.00, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 6.50–6.41 (m, 3H), 4.26 (dd, 1H, $J = 4.1$, 9.7 Hz), 4.15 (dd, 1H, $J = 8.0$, 9.8 Hz), 4.05 (m, 1H), 3.88 (m, 1H), 3.71 (m, 1H), 3.36–3.23 (m, 2H). 3.45 (s, 3H), 2.01–1.90 (m, 1H), 1.80 (m, 1H), 1.64 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, $^1J_{CF} = 246.6$ Hz), 163.7 (d, $^1J_{CF} = 246.6$ Hz), 160.2, (t, $^3J_{CF} = 13.9$ Hz), 98.6, (d, $^2J_{CF} = 29.1$ Hz, 2C), 97.1, (t, $^2J_{CF} = 25.7$ Hz), 80.4, 69.4, 64.6, 62.8, 57.1, 34.8; MS (ESI) *m*/*z* 340.1 $([M + Na]^+$ calcd for $C_{13}H_{17}F_2N_3NaO_4^+$ 340.1)

*5.1.3.2. (2S,3S,5R)-2-azido-6-benzyloxy-1-(3,5-difluoro-phenoxy)-5-methoxy-hexan-3-ol (**5a**).* Under argon atmosphere dibutyl tin-oxide (85 mg, 0.34 mmol) was added to a stirred solution of **3** (82 mg, 0.26 mmol) in dry toluene (3 mL). The reaction was refluxed for 2 h with a Dean–Stark trap. After 2 h benzyl bromide (61 μL, 0.52 mmol) and *tert*-butyl ammonium iodide (126 mg, 0.34 mmol) were added. The reaction mixture was refluxed 1 h before it was concentrated and purified by silica column chromatography (toluene–ethyl acetate, gradient 30:1–5:1) to give **5a** in 38% yield (40 mg, 98 μmol). $[\alpha]_D^{20}$ +1.8 (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 6.50–6.41 (m, 3H), 4.56 (d, 2H, $J = 2.8$ Hz), 4.24 (dd, 1H, $J = 4.1$, 9.8 Hz), 4.13 (dd, 1H, $J = 8.0$, 9.7 Hz), 4.04 (m, 1H), 3.72 (d, 1H, $J = 2.4$ Hz), 3.66 (m, 2H), 3.55 (d, 2H, $J = 4.5$ Hz), 3.45 (s, 3H), 1.94–1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, $^1J_{CF} = 246.5$ Hz), 163.7 (d, $^1J_{CF} = 246.5$ Hz), 160.3 (t, $^3J_{CF} = 13.6$ Hz), 137.8, 128.6, 128.0, 127.9, 98.6 (d, $^2J_{CF} = 28.2$ Hz, 2C), 97.1 (t, $^2J_{CF} = 25.7$ Hz), 80.1, 73.7, 71.1, 70.5, 68.6, 64.3, 57.6, 35.5; MS (ESI) *m*/*z* 430.2 $([M + Na]^+$ calcd for $C_{20}H_{23}F_2N_3NaO_4^+$ 430.2)

*5.1.3.3. 2(S,3S,5R)-2-azido-1-(3,5-difluoro-phenoxy)-5,6-dimethoxy-hexan-3-ol (**5b**).* NaH (60% in mineral oil) (15 mg, 0.37 mmol, 1.2 equiv) was added to a stirred solution of diol **3** (99 mg, 0.31 mmol, 1 equiv) in dry DMF (2 mL) at 0 °C. After 30 min methyl iodide (29 μL, 0.47 mmol, 1.5 equiv) and *tert*-butyl ammonium iodide (11 mg, 31 μmol, 0.1 equiv) were added. The reaction was allowed to reach r t and then left stirring for an additional 16 h. The reaction was quenched with MeOH, concentrated and purified by silica column chromatography (toluene–ethyl acetate, gradient 30:1–5:1) to give title compound **5b** in 23% yield (24 mg, 72 μmol). $[\alpha]_D^{20}$ −3.4 (*c* 0.5, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 6.50–6.41 (m, 3H), 4.26 (dd, 1H, $J = 4.1$, 9.8 Hz), 4.15 (dd, 1H, $J = 8.0$, 9.8 Hz), 4.05 (m, 1H), 3.76 (d, 1H, $J = 2.4$ Hz), 3.69 (m, 1H), 3.60 (m, 1H), 3.49 (m, 2H). 3.46 (s, 3H), 3.40 (s, 3 H), 1.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 163.9 (d, $^1J_{CF} = 246.5$ Hz), 163.7 (d, $^1J_{CF} = 246.5$ Hz), 160.3 (t, $^3J_{CF} = 13.9$ Hz), 98.6 (d, $^2J_{CF} = 28.4$ Hz, 2C), 97.1 (t, $^2J_{CF} = 25.9$ Hz), 79.8, 73.8, 70.2, 68.7, 64.5, 59.5, 57.5, 35.5; MS (ESI) *m*/*z* 354.1 $([M + Na]^+$ calcd for $C_{14}H_{19}F_2N_3NaO_4^+$ 354.1)

*5.1.3.4. (2S,3S,5R)-2-azido-1-(3,5-difluoro-phenoxy)-6-isobutoxy-5-methoxy-hexan-3-ol (**5c**).* Title compound **5c** was obtained from **3** as described for **5b**, in 14% yield (18 mg, 48 μmol). $[\alpha]_D^{20}$ −3.7 (*c* 1.00, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 6.50–6.41 (m, 3H), 4.26 (dd, 1H, $J = 4.2$, 9.8 Hz), 4.15 (dd, 1H, $J = 8.0$, 9.8 Hz), 4.06 (m, 1H), 3.85 (d, 1H, $J = 2.2$ Hz), 3.68 (m, 1H), 3.32 (m, 1H), 3.50 (m, 2H). 3.46 (s, 3H), 3.22 (m, 2H), 1.92–2.78 (m, 3H), 0.91 (d, 3H, $J = 1.3$ Hz), 0.89 (d, 3H, $J = 1.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 163.9 (d, $^1J_{CF} = 246.3$ Hz), 163.7 (d, $^1J_{CF} = 246.3$ Hz), 160.3 (t, $^3J_{CF} = 13.7$ Hz), 98.6 (d, $^2J_{CF} = 28.5$ Hz, 2C), 97.1 (t, $^2J_{CF} = 25.9$ Hz), 80.0, 78.8, 72.4, 70.3, 68.7, 64.4, 57.7, 35.6, 28.5, 19.5, 19.4; MS (ESI) *m*/*z* 374.2 $([M + H]^+$ calcd for $C_{17}H_{26}F_2N_3O_4^+$ 374.2)

*5.1.3.5. (2S,3S,5R)-2-azido-6-cyclopropylmethoxy-1-(3,5-difluoro-phenoxy)-5-methoxy-hexan-3-ol (**5d**).* Title compound **5d** was obtained from **3** as described for **5b**, in 43% yield (47 mg, 0.13 mmol). $[\alpha]_D^{20}$ −5.1 (*c* 1.0, MeOH); ^1H NMR (400 MHz, $CDCl_3$) δ 6.50–6.39 (m, 3H), 4.26 (dd, 1H, $J = 4.1$, 9.7 Hz), 4.16 (dd, 1H, $J = 8.0$, 9.8 Hz), 4.07 (m, 1H), 3.92 (d, 1H, $J = 2.3$ Hz), 3.68 (m, 1H), 3.62 (m, 1H), 3.55 (m, 2H). 3.45 (s, 3H), 3.38–3.26 (m, 2H), 1.86 (m, 2H), 1.05 (m, 1H), 0.55(m, 2H), 0.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$,) δ 163.9 (d, $^1J_{CF} = 246.8$ Hz), 163.7 (d, $^1J_{CF} = 246.8$ Hz), 160.3

(t, $^3J_{CF}$ = 13.6 Hz), 98.6 (d, $^2J_{CF}$ = 28.4 Hz, 2C), 97.1 (t, $^2J_{CF}$ = 25.9 Hz), 79.9, 76.5, 71.6, 70.0, 68.7, 64.5, 57.5, 35.8, 10.5, 31.2, 31.1; MS (ESI) *m/z* 394.2 ([M + Na]$^+$ calcd for $C_{17}H_{23}F_2N_3NaO_4^+$ 394.2)

*5.1.3.6. (2S,3S,5R)-2-azido-1-(3,5-difluoro-phenoxy)-5-methoxy-6-(4,4,4-trifluoro-butoxy)-hexan-3-ol (**5e**).* Title compound **5e** was obtained from **3** as described for **5b**, in 36% yield (48 mg, 011 mmol). $[\alpha]_D^{20}$ −4.1 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 6.63–6.51 (m, 3H), 4.27 (dd, 1H, *J* = 4.0, 10.0 Hz), 4.17 (dd, 1H, *J* = 7.8, 10.0 Hz), 3.93 (m, 1H), 3.76 (m, 1H), 3.61–3.49 (m, 5H). 3.41 (s, 3H), 2.30–2.17 (m, 2H), 1.81 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.3 (d, $^1J_{CF}$ = 244.9 Hz), 165.1 (d, $^1J_{CF}$ = 244.9 Hz), 162.1 (t, $^3J_{CF}$ = 13.9 Hz), 129.0 (d, $^1J_{CF}$ = 274.0 Hz), 99.5 (d, $^2J_{CF}$ = 29.0 Hz, 2C), 97.4 (t, $^2J_{CF}$ = 26.4 Hz), 79.0, 73.0, 70.6, 70.2, 69.2, 66.1, 57.5, 31.5 (dd, $^2J_{CF}$ = 28.8, 86.7 Hz), 31.0, 23.5 (dd, $^3J_{CF}$ = 2.9, 8.9 Hz); MS (ESI) *m/z* 450.1 ([M + Na]$^+$ calcd for $C_{17}H_{22}F_5N_3NaO_4^+$ 450.1)

*5.1.3.7. (2S,3S,5R)-6-allyloxy-2-azido-1-(3,5-difluoro-phenoxy)-5-methoxy-hexan-3-ol (**5f**).* Title compound **5f** was obtained from **3** as described for **5b**, in 51% yield (109 mg, 0.31 mmol). $[\alpha]_D^{20}$ −3.4 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 6.62–6.50 (m, 3H), 5.91 (m, 1H), 5.28 (m, 1H), 5.16 (m, 1H), 4.26 (dd, 1H, *J* = 4.0, 10.0 Hz), 4.16 (dd, 1H, *J* = 7.9, 10.0 Hz), 4.01 (m, 2H), 3.93 (m, 1H), 3.76 (m, 1H), 3.58 (m, 2H). 3.51 (m, 1H), 3.40 (s, 3H), 1.83 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.3 (d, $^1J_{CF}$ = 244.9 Hz), 164.0 (d, $^1J_{CF}$ = 244.9 Hz), 165.1 (t, $^1J_{CF}$ = 14.0 Hz), 136.0, 117.3, 99.5 (d, $^2J_{CF}$ = 29.2 Hz, 2C), 97.4 (t, $^2J_{CF}$ = 26.4 Hz), 79.0, 73.3, 72.3, 70.2, 69.2, 66.1, 57.5, 36.3; MS (ESI) *m/z* 380.1 ([M + Na]$^+$ calcd for $C_{16}H_{21}F_2N_3NaO_4^+$ 380.1)

*5.1.3.8. (2S,3S,5R)-2-azido-1-(3,5-difluoro-phenoxy)-6-(4-fluoro-benzyloxy)-5-methoxy-hexan-3-ol (**5g**).* Title compound **5g** was obtained from **3** as described for **5b**, in 29% yield (48 mg, 0.11 mmol). $[\alpha]_D^{20}$ +0.2 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.35 (m, 2 H), 7.04 (m, 2H), 6.60–6.50 (m, 3H), 4.51 (m, 2H), 4.23 (dd, 1H, *J* = 4.0, 10.1 Hz), 4.15 (dd, 1H, *J* = 7.8, 10.1 Hz), 3.90 (m, 1H), 3.74 (m, 1H), 3.61 (m, 2H), 3.54 (m, 1H), 3.40 (s, 3H), 1.85 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD,) δ 165.3 (d, $^1J_{CF}$ = 246.9 Hz), 165.1 (d, $^1J_{CF}$ = 246.9 Hz), 163.8 (d, $^1J_{CF}$ = 245.4 Hz), 162.0 (t, $^3J_{CF}$ = 13.6 Hz), 135.7 (d, $^4J_{CF}$ = 3.1 Hz), 130.8 (d, $^3J_{CF}$ = 8.2 Hz 2C), 116.0 (d, $^2J_{CF}$ = 21.8 Hz, 2C), 99.5 (d, $^2J_{CF}$ = 28.7 Hz 2C), 97.4 (t, $^3J_{CF}$ = 26.3 Hz), 79.0, 73.5, 72.2, 70.2, 69.2, 66.1, 57.5, 36.3; MS (ESI) *m/z* 448.1 ([M + Na]$^+$ calcd for $C_{20}H_{22}F_3N_3NaO_4^+$ 448.2)

*5.1.3.9. (2S,3S,5R)-2-azido-1-(3,5-difluoro-phenoxy)-5-methoxy-6-(3-methoxy-benzyloxy)-hexan-3-ol (**5h**).* Title compound **5h** was obtained from **3** as described for **5b**, in 24% yield (55 mg, 0.13 mmol). $[\alpha]_D^{20}$ −4.3 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (t, 1H, *J* = 7.8 Hz), 6.91 (m, 2H), 6.82 (m, 1H), 6.60–6.50 (m, 3H), 4.51 (dd, 2H, *J* = 4.1, 20.4 Hz), 4.22 (dd, 1H, *J* = 4.0, 10.1 Hz), 4.14 (dd, 1H, *J* = 7.8, 10.1 Hz), 3.87 (m, 1H), 3.77 (s, 3H), 3.73 (m, 1H), 3.60 (m, 2H), 3.54 (m, 1H), 3.40 (s, 3H), 1.85 (t, 2H, *J* = 3.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 165.2 (d, $^1J_{CF}$ = 245.4 Hz), 165.1 (d, $^1J_{CF}$ = 245.4 Hz), 162.0, (t, $^3J_{CF}$ = 13.7 Hz), 161.3, 141.2, 130.4, 121.0, 114.3, 114.2, 99.5 (d, $^2J_{CF}$ = 28.9 Hz 2C), 97.4 (t, $^2J_{CF}$ = 26.3 Hz), 79.0, 74.2, 72.0, 70.2, 69.2, 66.2, 57.4, 55.6, 36.3; MS (ESI) *m/z* 460.2 ([M + Na]$^+$ calcd for $C_{21}H_{25}F_2N_3NaO_5^+$ 460.2)

*5.1.3.10. (4S,6R)-4-[(1S)-1-azido-2-(3,5-difluoro-phenoxy)-ethyl]-6-methoxy-2-(4-methoxy-phenyl)-[1,3]dioxepane (**6**).* Anisaldehyde dimethylacetal (228 μL, 1.34 mmol) and *p*-TsOH (8 mg, 45 μmol) were added to a stirred solution of **3** (283 mg, 0.89 mmol) in freshly distilled DMF (10 mL). The reaction mixture was heated to 50 °C under reduced pressure. The reaction was followed by TLC, after approximately 1.5 h all starting material was consumed. A couple of drops of TEA were added and the reaction mixture was concentrated and purified by silica column chromatography (toluene–ethyl acetate, gradient 100:1–10:1) to give the product **6** in 98% yield (382 mg, 0.88 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2H), 6.89 (m, 2H), 6.38 (m, 1H), 6.07 (m, 2H), 5.77 (s, 1H), 4.33 (m, 1H), 4.23 (m, 1H), 3.86 (m, 1H), 3.78 (s, 3H) 3.55 (m, 3H), 3.48 (s, 3H), 3.06 (dd, 1H, *J* = 3.6, 9.2 Hz), 2.06 (m, 1H), 1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, $^1J_{CF}$ = 246.6 Hz), 163.7 (d, $^1J_{CF}$ = 246.6 Hz), 160.1 (t, $^3J_{CF}$ = 13.8 Hz), 159.9, 131.1, 128.0, 127.7, 113.7, 98.6 (d, $^2J_{CF}$ = 28.8 Hz, 2C), 97.3 (t, $^2J_{CF}$ = 25.7 Hz), 77.4, 76.5, 72.0, 67.9, 63.8, 62.8, 56.5, 55.5, 36.6; MS (ESI) *m/z* 458.2 ([M + Na]$^+$ calcd for $C_{21}H_{23}F_2N_3NaO_5^+$ 458.2)

*5.1.3.11. (2S,3S,5R)-2-azido-1-(3,5-difluoro-phenoxy)-5-methoxy-6-(4-methoxy-benzyloxy)-hexan-3-ol (**7**) and (2R,4S,5S)-5-azido-6-(3,5-difluoro-phenoxy)-4-(4-methoxy-benzyloxy)-hexan-1-ol (**8**).* A solution, kept at 0 °C, of Me_3SiCl (0.48 mL, 3.85 mmol) in MeCN (3 mL) was added drop wise to a stirred mixture of **6** (279 mg, 0.64 mmol), $NaCNBH_3$ (242 mg, 3.85 mmol) and 3 Å molecular sieves in MeCN (7.5 mL). The reaction mixture was stirred at 0 °C for 30 min and then allowed to reach r t before it was filtrated through Celite and evaporated. The residue was dissolved in DCM and washed with $NaHCO_3$(aq), the organic phase was dried over Na_2SO_4, evaporated and purified by silica column chromatography (toluene–ethyl acetate, gradient 60:1–3:1) to give the products **7** in 43% yield (121 mg, 0.27 mmol) and **8** in 42% yield (118 mg, 0.26 mmol,). (**7**) $[\alpha]_D^{20}$ −1.0 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.89 (m, 2H), 6.50–6.41 (m, 3H), 4.49 (m, 2H), 4.23 (dd, 1H, *J* = 4.1, 9.7 Hz), 4.13 (dd, 1H, *J* = 8.0, 9.6 Hz), 4.02 (m, 1H), 3.80 (s, 3H), 3.74 (d, 1H, *J* = 2.3 Hz), 3.67 (m, 1H), 3.62 (m, 1H), 3.52 (m, 1H), 3.43 (s, 3H), 1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, $^1J_{CF}$ = 246.7 Hz), 163.7 (d, $^1J_{CF}$ = 246.7 Hz), 160.3 (t, $^3J_{CF}$ = 13.6 Hz), 159.5, 129.8, 129.6, 114.0, 98.6 (d, $^2J_{CF}$ = 28.6 Hz, 2C), 97.1 (t, $^2J_{CF}$ = 25.8 Hz), 80.0, 73.4, 70.7, 70.4, 68.6, 64.4, 57.6, 55.4, 35.6; MS (ESI) *m/z* 460.2 ([M + Na]$^+$ calcd for $C_{21}H_{25}F_2N_3NaO_5^+$ 460.2). (**8**) $[\alpha]_D^{20}$ +1.7 (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.87 (m, 2H), 6.47–6.34 (m, 3H), 4.57 (d, 1H, *J* = 11.3 Hz), 4.46 (d, 1H, *J* = 11.3 Hz), 4.03 (m, 2H), 3.87 (m, 1H), 3.80 (s, 3H), 3.75 (m, 2H), 3.51 (m, 1H), 3.42 (m, 1H), 3.39 (s, 3H), 1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8 (d, $^1J_{CF}$ = 246.6 Hz), 163.6 (d, $^1J_{CF}$ = 246.6 Hz), 160.1 (t, $^3J_{CF}$ = 13.6 Hz), 159.7, 130.0, 129.6, 114.1, 98.6 (d, $^2J_{CF}$ = 28.5 Hz, 2C), 97.1 (t, $^2J_{CF}$ = 25.8 Hz), 78.2, 74.6, 71.9, 68.5, 63.3, 62.3, 57.2, 55.4, 31.6; MS (ESI) *m/z* 460.2 ([M + Na]$^+$ calcd for $C_{21}H_{25}F_2N_3NaO_5^+$ 460.2)

*5.1.3.12. (2S,3S,5R)-2-azido-1-(3,5-difluoro-phenoxy)-3-(4-methoxy-benzyloxy)-5-methoxy-6-phenoxy-hexane (**9**).* DIAD (28 μL, 0.14 mmol) was added drop wise at 0 °C to a stirred solution of **8** (44 mg, 0.10 mmol), phenol (14.3 mg, 0.15 mmol) and Ph_3P (37 mg, 0.14 mmol) in freshly distilled DCM (3 mL). The reaction mixture was allowed to reach r t. After 16 h the reaction mixture was evaporated and purified by column chromatography (toluene) to give the product **9** in 63% yield (33 mg, 63 μmol). $[\alpha]_D^{20}$ −3.6 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5H), 7.0–6.51 (m, 4H), 6.48–6.35 (m, 3H), 4.59 (d, 1H, *J* = 11.4 Hz), 4.45 (d, 1H, *J* = 11.4 Hz), 4.09–3.92 (m, 3H), 3.86 (m, 2H), 3.79 (s, 3H), 3.72 (m, 1H), 3.62 (m, 1H), 3.47 (s, 3H), 2.11 (m, 1H), 1.96 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 163.8 (d, $^1J_{CF}$ = 246.9 Hz), 163.7 (d, $^1J_{CF}$ = 246.9 Hz), 160.2, (t, $^3J_{CF}$ = 13.6 Hz), 159.6, 158.7, 130.8, 129.8, 129.7, 121.3, 114.7, 114.0, 98.6 (d, 2C, $^2J_{CF}$ = 28.6 Hz,), 97.1 (d, $^2J_{CF}$ = 25.8 Hz), 76.2, 74.4, 71.7, 69.2, 68.6, 62.5, 57.8, 55.4, 32.4; MS (ESI) *m/z* 536.2 ([M + Na]$^+$ calcd for $C_{27}H_{29}F_2N_3NaO_5$ 536.2)

*5.1.3.13. (2S,3S,5R)-2-azido-1-(3,5-difluoro-phenoxy)-5-methoxy-6-phenoxy-hexan-3-ol (**10**).* DDQ (12 mg, 0.05 mmol) was added at

0 °C to a stirred solution of **9** (20 mg, 39 μmol) in DCM:H_20 (19:1, 10 mL). The reaction was allowed to reach r t then stirred for an additional 3 h. The reaction mixture was washed with saturated $NaHCO_3$ (aq) and water, dried over Na_2SO_4, evaporated and purified by column chromatography (toluene–ethyl acetate, 50:1) to give the product **10** in 89% yield (14 mg, 35 μmol). $[\alpha]_D^{20}$ −3.6 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.26 (m, 2H), 6.92 (m, 2H), 6.56 (m, 3H), 4.27 (dd, 1H, *J* = 4.0, 10.1 Hz), 4.18 (m, 1H), 4.11 (m, 1H), 4.04 (m, 1H), 3.98 (m, 1H), 3.80 (m, 2H), 3.47 (s, 3H), 1.96 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.3 (d, $^1J_{CF}$ = 245.4 Hz), 165.1 (d, $^1J_{CF}$ = 245.4 Hz), 162.0 (t, $^3J_{CF}$ = 13.9 Hz), 160.2, 130.5, 122.0, 115.6, 99.5 (d, 2C $^2J_{CF}$ = 28.8 Hz), 97.4 (t, $^2J_{CF}$ = 26.3 Hz), 78.5, 70.2, 70.2, 69.1, 66.1, 57.7, 36.5; MS (ESI) *m*/*z* 416.1 ($[M + Na]^+$ calcd for $C_{19}H_{21}F_2N_3NaO_4^+$ 416.1)

5.1.3.14. N-(4-fluoro-phenyl)-2-nitro-benzenesulfonamide.. Nosylchloride (177 mg, 0.8 mmol) and pyridine (194 μL, 2.4 mmol) were added to a solution of 4-flouranilin (154 μL, 1.6 mmol) in freshly distilled DCM (2 mL). The reaction was stirred at r t for 2 h then quenched with 10% HCl (aq), the pH was set to ~1 before extracting with DCM (2×). The combined organic phases were washed with brine, dried over $MgSO_4$, concentrated and purified by silica column chromatography (toluene–ethyl acetate, 50:1) to give *N-(4-fluoro-phenyl)-2-nitro-benzenesulfonamide* in 70% yield (165 mg, 0.56 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, 1H, *J* = 1.3, 8.0 Hz), 7.76 (dd, 1H, *J* = 1.4, 7.8 Hz), 7.71 (dt, 1H, *J* = 1.4, 7.8 Hz), 7.58 (dt, 1H, *J* = 1.3, 7.7 Hz) 7.16 (m, 2H), 6.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (d, $^1J_{CF}$ = 246.8 Hz), 148.4, 134.2, 132.7, 132.0, 131.9, 131.4 (d, $^4J_{CF}$ = 3.4 Hz), 126.1 (d, $^3J_{CF}$ = 8.6 Hz 2C), 125.4, 116.5 (d, $^2J_{CF}$ = 22.9 Hz, 2C); MS (ESI) *m*/*z* 319.0 ($[M + Na]^+$ calcd for $C_{12}H_9FN_2NaO_4S^+$ 319.0). *2-Nitro-N-phenyl-benzenesulfonamide and N-(benzyl)-2-nitro-benzenesulfonamide* were prepared as described above and in accordance with previously published data [32,33].

*5.1.3.15. [(2R,4S,5S)-5-azido-6-(3,5-difluoro-phenoxy)-2-methoxy-4-(4-methoxy-benzyloxy)-hexyl]-(phenyl)-amine (**11a**).* DIAD (105 μL, 0.53 mmol, 1.4 equiv) was added drop wise at 0 °C to a stirred solution of **8** (167 mg, 0.38 mmol, 1 equiv), *2-nitro-N-phenyl-benzenesulfonamide* (144 mg, 0.52 mmol, 1.36 equiv) and Ph_3P (140 mg, 0.53 mmol, 1.4 equiv) in freshly distilled DCM (5 mL). The reaction mixture was allowed to reach r t, then left stirring over night. After evaporation the crude product was used without further purification. The crude product was dissolved in MeCN (5 mL) and thiophenol (118 μL, 1.15 mmol, 3 equiv) was added followed by potassium carbonate (158 mg, 1.15 mmol, 3 equiv). The reaction was heated to 50 °C and followed by TLC. After 3 h all starting material was consumed. The reaction mixture was evaporated, co-evaporated with toluene and then filtered through a short silica plug using ethyl acetate as eluent before concentration and purification by silica column chromatography (toluene–ethyl acetate, 50:1) to give **11a** in 74% yield (145 mg, 0.28 mmol). $[\alpha]_D^{20}$ +2.6 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27–7.16 (m, 4H), 6.89–6.85 (m, 2H), 6.77–6.71 (m, 1H), 6.64–6.59 (m, 2H), 6.48–6.35 (m, 3H), 4.56 (d, 1H, *J* = 11.4 Hz), 4.47 (d, 1H, *J* = 11.4 Hz), 4.06–4.01 (m, 2H), 3.92–3.84 (m, 2H), 3.80–3.75 (m, 1H), 3.79 (s, 3H), 3.63–3.56 (m, 1H), 3.39 (s, 3H), 3.30–3.22 (m, 1H), 3.16–3.07 (m, 1H), 1.98–1.92 (m, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$); δ 163.8 (d, $^1J_{CF}$ = 246.9 Hz), 163.7 (d, $^1J_{CF}$ = 246.9 Hz), 160.1 (t, $^3J_{CF}$ = 13.8 Hz), 159.7, 148.3, 130.1, 129.7, 129.5, 117.9, 114.1, 113.2, 98.6 (d, 2C, $^2J_{CF}$ = 28.6 Hz), 97.1 (t, $^2J_{CF}$ = 25.8 Hz), 76.3, 74.6, 71.9, 68.5, 62.4, 56.9, 55.4, 45.9, 32.8; MS (ESI) *m*/*z* 513.2 ($[M + H]^+$ calcd for $C_{27}H_{31}F_2N_4O_4^+$ 513.2)

*5.1.3.16. [(2R,4S,5S)-5-azido-6-(3,5-difluoro-phenoxy)-2-methoxy-4-(4-methoxy-benzyloxy)-hexyl]-(4-fluoro-phenyl)-amine (**11b**).* Title compound **11b** was obtained from **8** and *N-(4-fluoro-phenyl)-2-nitro-benzenesulfonamide*, as described for **11a**, in 50% yield (103 mg, 0.19 mmol). $[\alpha]_D^{20}$ −5.9 (*c* 1.00, $CHCl_3$); $[\alpha]_D^{20}$ −5.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 2H), 6.88 (m, 4H), 6.53 (m, 2H), 6.48–6.35 (m, 3H), 4.52 (m, 2H), 3.99 (m, 2H) 3.87 (m, 1H), 3.79 (s, 3H), 3.88 (m, 1H), 3.58 (m, 1H), 3.38 (s, 3H), 3.20 (d, 1H, *J* = 4.5, 12.5 Hz), 3.05 (d, 1H, *J* = 5.3, 12.5 Hz), 1.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, $^1J_{CF}$ = 245.6 Hz), 163.7 (d, $^1J_{CF}$ = 245.6 Hz), 160.1 (t, $^3J_{CF}$ = 13.7 Hz), 159.7, 156.1 (d, $^1J_{CF}$ = 234.8 Hz), 145.5 (d, $^4J_{CF}$ = 2.0 Hz), 130.0, 129.6, 115.8 (d, 2C $^2J_{CF}$ = 22.4 Hz), 114.0 (d, 2C $^3J_{CF}$ = 7.6 Hz), 98.6 (d, 2C $^2J_{CF}$ = 20.3 Hz), 97.1 (t, $^2J_{CF}$ = 26.0 Hz), 76.3, 75.6, 71.9, 68.5, 62.3, 56.9, 55.4, 46.7, 32.7, 29.8; MS (ESI) *m*/*z* 531.2 ($[M + H]^+$ calcd for $C_{27}H_{30}F_3N_4O_4^+$ 531.2)

*5.1.3.17. (2S,3S,5R)-2-azido-1-(3,5-difluoro-phenoxy)-,6-(phenylamino)-5-methoxy-hexan-3-ol (**12a**).* (128 mg, 0.25 mmol) of **11a** was stirred in a solution of TFA (10%) in freshly distilled DCM (1 mL) at r t for 40 min. The reaction was evaporated then co-evaporated 5 times with toluene before purification by silica column chromatography (toluene–ethyl acetate, 30:1–5:1) to afford **12a** in 84% yield (82 mg, 0.21 mmol). $[\alpha]_D^{20}$ +2.4 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.24 (m, 2H), 7.00–6.88 (m, 3H), 6.49–6.41 (m, 3H), 4.26 (dd, 1H, *J* = 3.9, 10.3 Hz), 4.15 (dd 1H. *J* = 8.2, 10.3 Hz), 4.06–4.01 (m, 1H), 3.84–3.77 (m, 1H), 3.72–3.67 (m, 1H), 3.50–3.38 (m, 1H), 3.41 (s, 3H), 3.32–3.24 (m, 1H), 2.07–1.95 (m, 1H), 1.87–1.77 (m, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 165.3 (d, $^1J_{CF}$ = 245.3 Hz), 165.1 (d, $^1J_{CF}$ = 245.3 Hz), 160.2 (t, $^3J_{CF}$ = 13.6 Hz), 144.1, 129.8, 116.5, 98.6 (d, 2C, $^2J_{CF}$ = 28.8 Hz), 97.2 (t, $^2J_{CF}$ = 25.8 Hz), 68.9, 68.8, 64.6, 57.0, 48.8, 35.6; MS (ESI) *m*/*z* 393.2 ($[M + H]^+$ calcd for $C_{19}H_{23}F_2N_4O_3^+$ 393.2)

*5.1.3.18. (2S,3S,5R)-2-azido-1-(3,5-difluoro-phenoxy)-,6-(4-fluoro-phenylamino)-5-methoxy-hexan-3-ol (**12b**).* Title compound **12b** was obtained from **11b**, as described for **12 a**, in 99% yield (38 mg, 93 μmol). $[\alpha]_D^{20}$ −12.1 (*c* 1.0, MeOH); $[\alpha]_D^{20}$ −12.1 (*c* 1.0, MeOH);^{1}H NMR (400 MHz, CD_3OD) δ 6.85 (m, 2H), 6.65 (m, 2H), 6.55 (m, 3H), 4.26 (dd, 1H, *J* = 3.9, 10.1 Hz), 4.15 (dd, 1H, *J* = 7.9, 10.1 Hz), 3.95 (m, 1H), 3.75 (m, 1H), 3.55 (m, 1H), 3.40 (s, 3H), 3.27 (d, 1H, *J* = 4.3, 13.2 Hz), 3.14 (d, 1H, *J* = 6.1, 13.2 Hz), 1.88 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.2 (d, $^1J_{CF}$ = 245.4 Hz), 165.1 (d, $^1J_{CF}$ = 245.4 Hz), 161.0 (t, $^3J_{CF}$ = 13.8 Hz), 157.2 (d, $^1J_{CF}$ = 233.4 Hz), 146.6 (d, $^4J_{CF}$ = 1.5 Hz), 129.6, 116.3 (d, 2C, $^2J_{CF}$ = 22.3 Hz), 115.1 (d, 2C, $^3J_{CF}$ = 7.4 Hz), 99.5 (d, 2C, $^2J_{CF}$ = 28.9 Hz), 97.4 (d, $^2J_{CF}$ = 26.7 Hz), 78.5, 70.2, 69.1, 66.3, 57.2, 48.0, 36.7; MS (ESI) *m*/*z* 411.2 ($[M + H]^+$ calcd for $C_{19}H_{22}F_3N_4O_3^+$ 411.2)

*5.1.3.19. N-[5S-azido-6-(3,5-difluoro-phenoxy)- 2R-methoxy-4S-(4-methoxy-benzyloxy)-hexyl]-N-benzyl-2-nitro-benzenesulfonamide (**13**).* DIAD (66 μL, 0.34 mmol) was added drop wise at 0 °C to a stirred solution of **8** (105 mg 0.24 mmol), *N-(benzyl)-2-nitro-benzenesulfonamide* (95 mg, 0.33 mmol) and Ph_3P (88 mg, 0.34 mmol) in freshly distilled DCM (5 mL). The reaction mixture was allowed to reach r t, then left stirring over night. After evaporation the crude product was purified by silica column chromatography (toluene–ethyl acetate, 50:1) to give **13** in 61% yield (104 mg, 0.146 mmol). $[\alpha]_D^{20}$ −1.8 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): δ 8.01 (m, 1H), 7.78 (m, 2H), 7.71 (m, 1H), 7.30–7.18 (m, 7H), 6.84 (m, 2H), 6.56–6.44 (m, 3H), 4.64 (m, 2H), 4.41 (m, 2H), 4.05 (m, 1H), 3.98 (m, 1H), 3.76 (s, 3H), 3.73 (m, 1H), 3.67 (m, 1H), 3.45–3.35 (m, 3H), 3.10 (s, 3H), 1.81–1.72 (m, 1H), 1.65–1.56 (m, 1H); ^{13}C NMR (100.5 MHz, CD_3OD): δ 163.9 (d, $^1J_{CF}$ = 247.0 Hz), 163.7 (d, $^1J_{CF}$ = 247.0 Hz), 161.8 (t, $^3J_{CF}$ = 13.6 Hz), 161.0, 149.4, 137.3, 135.2, 134.6, 133.0, 131.9, 131.3, 131.0, 129.7, 129.5, 129.0, 125.4, 114.8, 99.5 (d,2C, $^2J_{CF}$ = 28.8 Hz), 97.4 (t, $^2J_{CF}$ = 26.5 Hz), 78.0, 75.7, 72.9, 69.4, 63.8, 57.3, 55.7, 53.6, 51.6, 33.4; MS (ESI) *m*/*z* 734.2 ($[M + Na]^+$ calcd for $C_{34}H_{35}F_2N_5NaO_8S^+$ 734.2).

*5.1.3.20. N-[5S-azido-6-(3,5-difluoro-phenoxy)-4S-hydroxy-2R-methoxy-hexyl]-N-benzyl-2-nitro-benzenesulfonamide (**14**).* DDQ (56 mg, 0.25 mmol) was added at 0 °C to a stirred solution of **13** (136 mg, 0.19 mmol) in DCM:H_20 (19:1, 10 mL). The reaction was allowed to reach r t then stirred for an additional 3 h. The reaction mixture was washed with saturated $NaHCO_3$ (aq) and water and dried over Na_2SO_4 before it was concentrated and purified by silica column chromatography (toluene–ethyl acetate, gradient 60:1–10:1) to give **14** in 64% yield (72 mg, 0.12 mmol). $[\alpha]_D^{20}$ +9.6 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 1H), 7.69 (m, 3H), 7.27 (m, 5H), 6.47 (m, 3H), 4.64 (d, 2H, J = 7.9 Hz), 4.19 (dd, 1H, J = 4.2, 9.8 Hz), 4.07 (dd, 1H, J = 8.0, 9.7 Hz), 3.83 (m, 1H), 3.59 (m, 1H), 3.56–3.36 (m, 3H), 3.23 (s, 3H), 1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, $^1J_{CF}$ = 246.8 Hz), 163.7 (d, $^1J_{CF}$ = 246.8 Hz), 160.2 (t, $^3J_{CF}$ = 13.4 Hz), 148.8, 135.8, 133.8, 133.5, 131.8, 131.4, 128.9, 128.5, 128.3, 124,3, 98.6 (d, 2C, $^2J_{CF}$ = 28.6 Hz), 97.1 (t, $^2J_{CF}$ = 25.8 Hz), 79.7, 69.8, 68.8, 64.4, 57.5, 53.1, 49.8, 35.4; MS (ESI) *m*/*z* 614.2 ($[M + Na]^+$ calcd for $C_{26}H_{27}F_2N_5NaO_7S^+$ 614.2).

*5.1.3.21. N-[5S-azido-6-(3,5-difluoro-phenoxy)-4R-hydroxy-2R-methoxy-hexyl]-N-benzyl-2-nitro-benzenesulfonamide (**15**).* **14** (73 mg, 0.12 mmol), *p*-nitro benzaldehyde (37 mg, 0.22 mmol) and Ph_3P (55 mg, 0.21 mmol) was solved in THF (3 mL) and cooled to 0 °C before DIAD (42 μL, 0.21 mmol) was added drop wise. The reaction mixture was allowed to reach r t, then left stirring over night. After concentration and purification on a short silica plug the crude product was solved in 0.1 M NaOMe (10 mL), stirred in r t for 30 min, neutralized with Dowex H+, filtered, concentrated and purified by silica column chromatography (toluene–ethyl acetate 10:1) to yield the product **15** in 51% yield (37 mg, 62 μmol). $[\alpha]_D^{20}$ +2.6 (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (dd, 1H, J = 1.3, 7.9 Hz), 7.72–7.61 (m, 3H), 7.32–7.20 (m, 5H), 6.45 (m, 3H), 4.67 (d, 1H, J = 15.5 Hz), 4.56 (d, 1H, J = 15.5 Hz), 4.20 (dd, 1H, J = 3.3, 9.9 Hz), 3.99 (dd, 1H, J = 7.9, 9.9 Hz), 3.86 (m, 1H), 3.66 (m, 1H), 3.61 (m, 1H), 3.43 (d, 1H, J = 5.8 Hz), 3.21 (s, 3H), 2.87 (d, 1H, J = 4.7 Hz), 1.70 (m, 1H), 1.61 (m, 1H), 1.58 (s, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 163.8 (d, $^1J_{CF}$ = 247.2 Hz), 163.7 (d, $^1J_{CF}$ = 247.2 Hz), 160.2 (t, $^3J_{CF}$ = 13.8 Hz), 148.1, 135.4, 133.8, 131.9, 131.4, 129.0, 128.5, 128.3, 124.4, 98.7 (d, 2C, $^2J_{CF}$ = 28.7 Hz), 97.2 (t, $^2J_{CF}$ = 25.7 Hz), 78.0, 68.8, 68.3, 65.0, 58.1, 52.8, 49.7, 34.0; MS (ESI) *m*/*z* 614.2 ($[M + Na]^+$ calcd for $C_{26}H_{27}F_2N_5NaO_7S^+$ 614.2).

*5.1.3.22. N-[(1S,2S,4R)-1-(3,5-difluoro-phenoxymethyl)-2,5-dihydroxy-4-methoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2a**).* Palladium on charcoal (~5%) was added to a solution of **3** (19 mg, 59 μmol, 1 equiv) in MeOH (3 mL) under argon atmosphere. The flask was evacuated followed by addition of hydrogen gas (1 atm). The reaction mixture was stirred for 3 h before the Pd/C was filtered off and the filtrate was concentrated to yield the crude product that was used in the next step without further purification. Carboxylic acid **A** (22 mg, 59 μmol, 1 equiv) was dissolved in dry DCM (2 mL) and PyBOP (31 mg, 59 μmol, 1 equiv) was added followed by DIPEA (11 μL, 59 μmol, 1 equiv). After 30 min the crude amine (1 equiv dissolved in DCM) was added to the mixture, followed by DIPEA (11 μL, 59 μmol, 1 equiv). After 2 h, the reaction mixture was diluted with DCM, washed with Na_2CO_3 (sat.) and NH_4Cl (aq). The aqueous layers were extracted with DCM (3x), and the combined organic phases were washed with brine, dried ($MgSO_4$), concentrated and purified by silica column chromatography (toluene–ethyl acetate gradient 10:1–1:6) to yield compound **2a** in 39% yield (15 mg, 23 μmol). **2a** was further purified by LC-MS. $[\alpha]_D^{20}$ −23.4 (*c* 0.53, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (t, 1H, J = 1.6 Hz), 8.04 (m, 2H), 7.44–7.08 (m, 5H), 6.65–6.47 (m, 3H), 5.25 (m, 1H), 4.55 (m, 1H), 4.27 (dd, 1H, J = 6.5, 9.9 Hz), 4.17 (m, 2H), 3.69 (dd, 1H, J = 3.4, 11.4 Hz), 3.54–3.44 (m, 2H). 3.39 (s, 3H), 3.38 (s, 3H), 2.97 (s, 3H), 1.78 (m, 2H), 1.64 (d, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 169.1, 167.8, 165.3 (d, $^1J_{CF}$ = 245.0 Hz), 165.1 (d, $^1J_{CF}$ = 245.0 Hz), 162.3 (t, $^3J_{CF}$ = 13.9 Hz), 145.1, 143.8, 137.5, 137.1, 129.6, 129.4, 129.3, 129.2, 128.2, 127.3, 125.9, 98.6 (d, 2C, $^2J_{CF}$ = 29.1 Hz), 97.2 (t, $^2J_{CF}$ = 26.4 Hz), 80.8, 68.8, 68.2, 63.6, 57.4, 54.2, 51.0, 38.3, 36.3, 35.9, 22.1; HRMS (ESI) *m*/*z* 650.2340 ($[M + H]^+$ calcd for $C_{31}H_{38}F_2N_3O_8S^+$ 650.2342).

*5.1.3.23. N-[(1S,2S,4R)-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-4,5-dimethoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2b**).* Title compound **2b** was obtained from **5b** as described for **2a**, in 43% yield (19 mg, 29 μmol). **2b** was further purified by LC-MS. $[\alpha]_D^{20}$ −20.3 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (t, 1H, J = 1.6 Hz), 8.04 (m, 2H), 7.43–7.18 (m, 5H), 6.62 (m, 2H), 6.51(m, 1H), 5.25 (dd, 1H, J = 7.0, 14.0 Hz), 4.54 (m, 1H), 4.26 (dd, 1H, J = 6.5, 9.8 Hz), 4.16 (m, 2H), 3.60 (m 1H), 3.50 (dd, 1H, J = 3.6, 10.5 Hz), 3.43 (dd, 1H, J = 5.2, 10.5 Hz). 3.39 (s, 3H), 3.37 (s, 3H), 3.33 (s, 3H), 2.97 (s, 3H), 1.77 (m, 2H), 1.58 (d, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 169.0, 167.8, 165.3 (d, $^1J_{CF}$ = 245.0 Hz), 165.1 (d, $^1J_{CF}$ = 245.0 Hz), 162.3 (t, $^3J_{CF}$ = 13.6 Hz), 145.1, 143.8, 137.5, 137.1, 129.6, 129.3, 129.3, 129.2, 128.2, 127.3, 125.9, 99.6 (d, 2C, $^2J_{CF}$ = 28.7 Hz), 97.2 (t, $^2J_{CF}$ = 26.4 Hz), 79.1, 75.0, 68.8, 68.2, 59.4, 57.6, 54.2, 51.0, 38.3, 36.6, 35.9, 22.1; HRMS (ESI) *m*/*z* 686.2302 ($[M + Na]^+$ calcd for $C_{32}H_{39}F_2N_3NaO_8S^+$ 686.2318).

*5.1.3.24. N-[(1S,2S,4R)-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-5-isobutoxy-4-methoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2c**).* Title compound **2c** was obtained from **5c** as described for **2a**, in 85% yield (29 mg, 41 μmol). **2c** was further purified by LC-MS. $[\alpha]_D^{20}$ −15.7 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (t, 1H, J = 1.6 Hz), 8.05 (m, 2H), 7.40 (m, 2H), 7.33 (m, 2H), 7.23 (m, 1H), 6.62 (m, 2H), 6.51 (m, 1H), 5.25 (dd, 1H, J = 7.1, 14.1 Hz), 4.55 (m, 1H), 4.26 (dd, 1H, J = 6.6, 9.8 Hz), 4.17 (m, 2H), 3.60 (m, 1H), 3.49 (m, 2H). 3.40 (s, 3H), 3.37 (s, 3H), 3.19 (m, 2H), 2.97 (s, 3H), 1.79 (m, 3H), 1.58 (d, 3H, J = 7.1 Hz), 0.85 (d, 6H, J = 6.7 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 169.0, 167.8, 165.3 (d, $^1J_{CF}$ = 245.0 Hz), 165.1 (d, $^1J_{CF}$ = 245.0 Hz), 162.3 (t, $^3J_{CF}$ = 13.9 Hz), 145.0, 143.8, 137.4, 137.0. 129.6, 129.3, 128.2, 127.3, 125.9, 99.6 (d, 2C, $^2J_{CF}$ = 28.8 Hz), 97.2 (t, $^2J_{CF}$ = 26.3 Hz), 79.4, 79.2, 73.4, 68.7, 68.2, 57.7, 54.1, 51.0, 38.3, 36.9, 35.9, 29.6, 19.7, 19.7; HRMS (ESI) *m*/*z* 728.2790 ($[M + Na]^+$ calcd for $C_{35}H_{45}F_2N_3NaO_8S^+$ 728.2778).

*5.1.3.25. N-[(1S,2S,4R)-5-cyclopropylmethoxy-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-4-methoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2d**).* Title compound **2d** was obtained from **5d** as described for **2a**, in 65% yield (30 mg, 42 μmol). **2d** was further purified by LC-MS. $[\alpha]_D^{20}$ −17.7 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (t, 1H, J = 1.5 Hz), 8.04 (m, 2H), 7.44–7.08 (m, 5H), 6.62 (m, 2H), 6.51 (m, 1H), 5.25 (dd, 1H, J = 7.0, 14.0 Hz), 4.55 (m, 1H), 4.27 (dd, 1H, J = 6.5, 9.9 Hz), 4.17 (m, 2H), 3.58 (m, 2H), 3.50 (m, 1H). 3.40 (s, 3H), 3.37 (s, 3H), 3.28 (m, 2H), 2.97 (s, 3H), 1.79 (t, 2H, J = 6.5 Hz), 1.58 (d, 3H, J = 7.1 Hz), 0.97 (m, 1H), 0.46 (m, 2H), 0.16 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 169.0, 167.8, 165.3 (d, $^1J_{CF}$ = 245.0 Hz), 165.1 (d, $^1J_{CF}$ = 245.0 Hz), 162.3 (t, $^3J_{CF}$ = 14.0 Hz), 145.0, 143.8, 137.5, 137.0, 129.9, 129.6, 129.3, 129.3, 128.2, 127.3, 125.9, 99.6 (d, 2C, $^2J_{CF}$ = 29.0 Hz), 97.2 (t, $^2J_{CF}$ = 26.3 Hz), 79.2, 77.0, 72.7, 68.7, 68.2, 57.6, 54.2, 51.0, 38.3, 36.7, 35.9, 22.1, 11.4, 3.4, 3.4; HRMS (ESI) *m*/*z* 726.2647 ($[M + Na]^+$ calcd for $C_{35}H_{43}F_2N_3O_8SNa^+$ 726.2631).

*5.1.3.26. N-[(1S,2S,4R)-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-4-methoxy-5-(4,4,4-trifluoro-butoxy)-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2e**).* Title compound **2e** was obtained from **5e** as described for **2a**, in 39% yield (17 mg, 22 μmol). **2e** was further purified by LC-MS. $[\alpha]_D^{20}$

−18.4 (*c* 0.75, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (t, 1H, $J = 1.6$ Hz), 8.04 (m, 2H), 7.42–7.20 (m, 5H), 6.62 (m, 2H), 6.51 (m, 1H), 5.25 (dd, 1H, $J = 7.0, 14.0$), 4.55 (m, 1H), 4.26 (dd, 1H, $J = 6.5, 9.89$ Hz), 4.17 (m, 2H), 3.65–3.45 (m, 5H). 3.40 (s, 3H), 3.37 (s, 3H), 2.97 (s, 3H), 2.18 (m, 2H), 1.77 (m, 4H), 1.59 (d, 3H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 169.0, 167.8, 165.3 (d, $^1J_{CF} = 245.2$ Hz), 165.1 (d, $^1J_{CF} = 245.2$ Hz), 162.3 (t, $^3J_{CF} = 13.8$ Hz), 145.1, 143.8, 137.5, 137.0, 129.6, 129.4, 129.3, 128.2, 127.3, 125.9, 99.6 (d, 2C, $^2J_{CF} =$,28.9 Hz), 97.2 (t, $^2J_{CF} = 26.4$ Hz), 79.1, 73.2, 70.6, 68.8, 68.2, 57.7, 54.1, 51.0, 38.3, 36.7, 35.9, 31.4 (dd, $^2J_{CF} = 28.7, 86.5$ Hz), 23.5 (dd, $^3J_{CF} = 3.1, 9.1$ Hz), 22.1; HRMS (ESI) *m*/*z* 760.2677 ($[M + H]^+$ calcd for $C_{35}H_{43}F_5N_3O_8S^+$ 760.2686).

*5.1.3.27. N-[(1S,2S,4R)-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-4-methoxy-5-phenoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2f**).* Title compound **2f** was obtained from **10** as described for **2a**, in 61% yield (27 mg, 37 μmol). **2f** was further purified by LC-MS. $[\alpha]_D^{20}$ −18.7 (*c* 0.3, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (m, 1H), 7.98 (m, 2H), 7.37 (m, 4H), 7.28 (m, 2H), 6.95 (m, 2H), 6.87 (m, 2H), 6.60 (d, 1H, $J = 7.6$ Hz), 6.51 (m, 2H), 6.42 (m, 1H), 5.32 (m, 1H), 4.47 (m, 1H), 4.37 (m, 1H), 4.15 (m, 1H), 4.08 (dd, 1H, $J = 5.2, 9.3$ Hz), 4.03 (dd, 1H, $J = 4.6, 9.8$ Hz), 3.94 (m, 2H), 3.55 (s, 3H), 3.37 (s, 3H), 2.86 (s, 3H), 1.89 (m, 2H), 1.63 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 163.9 (d, $^1J_{CF} = 246.0$ Hz), 164.6, 163.8 (d, $^1J_{CF} = 246.0$ Hz), 160.4 (t, $^3J_{CF} = 13.5$ Hz), 158.4, 142.8, 142.5, 136.2, 135.5, 129.7, 129.0, 127.9, 127.8, 127.6, 126.4, 124.1, 121.4, 114.6. 98.7 (d, 2C, $^2J_{CF} = 28.8$ Hz), 96.9 (t, $^2J_{CF} = 25.9$ Hz), 80.3, 69.2, 69.1, 67.0, 58.1, 53.1, 50.0, 38.1, 36.3, 35.6, 21.8; HRMS (ESI) *m*/*z* 726.2627 ($[M + H]^+$ calcd for $C_{37}H_{42}F_2N_3O_8S^+$ 726.2655).

*5.1.3.28. N-[1S-(3,5-difluoro-phenoxymethyl)-2S-hydroxy-4R-methoxy-5-phenylamino-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2g**).* Title compound **2g** was obtained from **12a** as described for **2a**, in 57% yield (34 mg, 47 μmol). **2g** was further purified by LC-MS. $[\alpha]_D^{20}$ +17.4 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): δ 8.13 (m, 1H), 7.96 (m, 2H), 7.36 (m, 4H), 7.28 (m, 2H), 7.17 (m, 2H), 7.0 (d, 1H, $J = 8.7$ Hz), 6.74 (m, 2H), 6.64 (m, 2H), 6.49 (m, 2H), 6.41 (m, 1H), 5.30 (m, 1H), 4.44 (m, 1H), 4.31 (m, 1H), 4.13 (m, 1H), 4.07 (dd, 1H, $J = 5.5, 9.4$ Hz), 3.82 (m, 1H), 3.44 (s, 3H), 3.33 (s, 3H), 3.19 (dd, 1H, $J = 3.1, 12.8$ Hz) 2.83 (s, 3H), 1.97 (m, 1H), 1.77 (m, 1H), 1.60 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (100.5 MHz, CD_3OD): δ 169.0, 167.7, 163.8 (d, $^1J_{CF} = 246.2$ Hz), 163.7 (d, $^1J_{CF} = 246.2$ Hz), 162.2 (t, $J_{CF} = 13.9$ Hz), 150.0, 145.0, 143.7, 138.9, 137.4, 137.0, 130.1, 129.9, 129.6, 129.3, 129.2, 128.2, 127.3, 126.3, 126.0, 118.2, 114.1, 99.6 (d, 2C, $^2J_{CF} = 28.7$ Hz), 97.2 (t, $^2J_{CF} = 26.4$ Hz), 78.8, 68.8, 68.3, 57.4, 54.3, 50.9, 47.3, 38.3, 37.5, 35.9, 22.1; HRMS (ESI) *m*/*z* 725.2767 ($[M + H]^+$ calcd for $C_{37}H_{43}F_2N_4O_7S^+$ 725.2815).

*5.1.3.29. N-[(1S,2S,4R)-5-allyloxy-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-4-methoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2h**).* Ph_3P (21 mg, 80 μmol, 1.5 equiv) was added together with two drops of water to a solution of the **5f** (19 mg, 53 μmol, 1 equiv) in MeOH (3 mL). The reaction mixture was stirred for 16 h, concentrated to yield the crude compound which was used in the next step without further purification. Carboxylic acid **A** (20 mg, 53 μmol, 1 equiv) was dissolved in dry DCM (2 mL) and PyBOP (28 mg, 53 μmol, 1 equiv) was added followed by DIPEA (9 μL, 53 μmol, 1 equiv). After 30 min the crude amine (1 equiv, dissolved in DCM) was added to the mixture, followed by DIPEA (9 μL, 53 μmol, 1 equiv). After 2 h, the reaction mixture was diluted with DCM, washed with Na_2CO_3 (sat.) and NH_4Cl (aq). The aqueous layers were extracted with DCM (3x), and the combined organic phases were washed with brine, dried ($MgSO_4$), concentrated and purified by silica column chromatography (toluene–ethyl acetate gradient 10:1–1:6) to yield **2h** in 82% yield (30 mg, 43 μmol). **2h** was further purified by LC-MS. $[\alpha]_D^{20}$ −23.0 (*c* 0.80, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (t, 1H, $J = 1.6$ Hz), 8.04 (m, 2H), 7.43–7.21 (m, 5H), 6.65–6.48 (m, 3H), 5.86 (m, 1H), 5.24 (m, 2H), 5.11 (m, 1H), 4.55 (m, 1H), 4.26 (dd, 1H, $J = 6.5, 9.9$ Hz), 4.17 (m, 2H), 3.98 (m, 2H), 3.61 (m, 1H), 3.56 (dd, 1H, $J = 3.7, 10.5$ Hz), 3.48 (dd, 1H, $J = 5.1, 10.5$ Hz), 3.40 (s, 3H), 3.37 (s, 3H), 2.97 (s, 3H), 1.79 (t, 2H, $J = 6.6$ Hz), 1.58 (d, 3H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 169.0, 167.8, 165.3 (d, $^1J_{CF} = 244.6$ Hz), 165.1 (d, $^1J_{CF} = 244.6$ Hz), 162.3 (t, $^3J_{CF} = 13.8$ Hz), 145.0, 143.8, 137.5, 137.0, 136.0, 129.6, 129.3, 128.2, 127.2, 125.9, 117.2, 99.6 (d, 2C, $^2J_{CF} = 28.8$ Hz), 97.2 (t, $^2J_{CF} = 26.4$ Hz), 79.2, 73.2, 72.4, 68.8, 68.2, 57.7, 54.1, 51.0, 38.3, 36.7, 35.9, 22.1; HRMS (ESI) *m*/*z* 712.2496 ($[M + Na]^+$ calcd for $C_{34}H_{41}F_2N_3O_8SNa^+$ 712.2475).

*5.1.3.30. N-[(1S,2S,4R)-1-(3,5-difluoro-phenoxymethyl)-5-(4-fluoro-benzyloxy)-2-hydroxy-4-methoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2i**).* Title compound **2i** was obtained from **5g** as described for **2h**, in 70% yield (30 mg, 39 μmol). **2i** was further purified by LC-MS. $[\alpha]_D^{20}$ −1.9 (*c* 1.0, MeOH);^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (t, 1H, $J = 1.5$ Hz), 8.04 (m, 2H), 7.40 (m, 2H), 7.30 (m, 4H), 7.22 (m, 2H), 7.12 (m, 1H), 6.98 (m, 2H), 6.60 (m, 2H), 6.50 (m, 2H), 5.24 (dd, 1H, $J = 7.0, 14.1$), 4.54 (s, 1H), 4.47 (d, 2H, $J = 4.5$ Hz), 4.25 (dd, 1H, $J = 6.6, 10.0$ Hz), 4.17 (m, 2H), 3.64 (m, 1H), 3.58 (dd, 1H, $J = 3.7, 10.4$ Hz), 3.51 (dd, 1H, $J = 5.0, 10.4$ Hz), 3.38 (s, 3H), 3.35 (s, 3H), 2.94 (s, 3H), 1.81 (m, 2H), 1.58 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 169.0, 167.7, 165.2 (d, $^1J_{CF} = 245.1$ Hz), 165.1, (d, $^1J_{CF} = 245.1$ Hz), 163.7 (d, $^1J_{CF} = 244.4$ Hz), 162.3 (t, $^3J_{CF} = 13.8$ Hz), 145.0, 143.8, 137.4, 137.0, 135.6 (d, $^4J_{CF} = 3.3$ Hz), 130.7 (d, 2C, $^3J_{CF} = 8.2$ Hz), 129.9, 129.6, 129.4, 129.3, 129.2, 128.2, 127.3, 126.3, 125.9, 116.0 (d, 2C, $^2J_{CF} = 21.8$ Hz), 99.6 (d, 2C, $^2J_{CF} = 28.7$ Hz), 97.2 (t, $^2J_{CF} = 26.3$ Hz), 79.1, 73.4, 72.3, 68.8, 68.2, 57.7, 54.1, 60.0, 38.3, 36.7, 35.9, 22.1; HRMS (ESI) *m*/*z* 758.2683 ($[M + H]^+$ calcd for $C_{38}H_{43}F_3N_3O_8S^+$ 758.2717).

*5.1.3.31. N-[(1S,2S,4R)-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-4-methoxy-5-(3-methoxy-benzyloxy)-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2j**).* Title compound **2j** was obtained from **5h** as described for **2h**, in 92% yield (53 mg, 69 μmol). **2j** was further purified by LC-MS. $[\alpha]_D^{20}$ −12.4 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (t, 1H, $J = 1.5$ Hz), 8.04 (m, 21H), 7.40 (m, 2H), 7.32 (m, 2H), 7.26–7.09 (m, 2H), 6.85 (m, 2H), 6.78 (m, 1H), 6.60 (m, 2H), 6.50 (m, 1H), 5.24 (dd, 1H, $J = 7.0, 14.0$ Hz), 4.59 (bs, 1H), 4.55 (m, 1H), 4.48 (d, 2H, $J = 5.4$ Hz), 4.24 (dd, 1H, $J = 6.5, 9.9$ Hz), 4.15 (m, 2H), 3.73 (s, 3H), 3.67–3.56 (m, 2H), 3.51 (dd, 1H, $J = 4.8, 10.5$ Hz), 3.39 (s, 3H), 3.35 (s, 3H), 2.94 (s, 3H), 1.81 (m, 2H), 1.58 (d, 3H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 169.0, 167.7, 166.3, 165.2 (d, $^1J_{CF} = 245.4$ Hz), 165.1, (d, $^1J_{CF} = 245.4$ Hz), 162.3 (t, $^3J_{CF} = 13.9$ Hz), 161.2, 145.0, 143.8, 141.1, 137.4, 137.0, 130.4, 129.6, 129.3, 129.2, 128.2, 127.3, 125.9, 120,9, 114.1, 99.6 (d, 2C, $^2J_{CF} = 28.6$ Hz), 97.2 (t, $^2J_{CF} = 26.5$ Hz), 79.1, 74.1, 72.2, 68.8, 68.2, 57.7, 55.6, 54.2, 51.0, 38.3, 36.8, 35.9, 22.1; HRMS (ESI) *m*/*z* 792.2709 ($[M + Na]^+$ calcd for $C_{39}H_{45}F_2N_3O_9S^+$ 792.2737).

*5.1.3.32. N-[(1S,2S,4R)-5-benzyloxy-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-4-methoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2k**).* Title compound **2k** was obtained from **5a** as described for **2h**, in 83% yield (30 mg, 40 μmol). **2k** was further purified by LC-MS. $[\alpha]_D^{20}$ −11.8 (*c* 0.76, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (t, 1H, $J = 1.5$ Hz), 8.04 (m, 2H), 7.44–7.19 (m, 10H), 6.64–6.47 (m, 3H), 5.25 (dd, 1H, $J = 7.0, 14.1$), 4.54 (m, 3H), 4.25 (dd, 1H, $J = 6.4, 9.8$ Hz), 4.17 (m, 2H), 3.62 (m, 2H), 3.52 (dd, 1H, $J = 4.9, 10.4$ Hz), 3.39 (s, 3H), 3.36 (s, 3H), 2.95 (s, 3H), 1.81 (m, 2H), 1.58 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 169.0, 167.8, 165.3 (d, $^1J_{CF} = 245.1$ Hz), 165.2 (d, $^1J_{CF} = 245.1$ Hz), 162.3 (t, $^3J_{CF} = 13.9$ Hz),

145.1, 143.8, 139.6, 137.4, 137.0, 129.6, 129.4, 129.3, 128.8, 128.7, 128.2, 127.3, 125.9, 99.6 (d, 2C, $^2J_{CF}$ = 29.0 Hz), 97.2 (d, $^2J_{CF}$ = 26.5 Hz), 79.1, 74.3, 72.3, 68.8, 68.2, 57.7, 54.1, 50.9, 38.3, 36.8, 35.9, 22.1; HRMS (ESI) *m/z* 740.2837 ($[M+H]^+$ calcd for $C_{38}H_{44}F_2N_3O_8S^+$ 740.2812).

*5.1.3.33. N-[(1S,2S,4R)-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-4-methoxy-5-(4-methoxy-benzyloxy)-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2l**).* Title compound **2l** was obtained from **7** as described for **2h**, in 39% yield (18 mg, 23 μmol). **2l** was further purified by LC-MS. $[\alpha]_D^{20}$ −5.5 (*c* 0.76, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (t, 1H, *J* = 1.5 Hz), 8.21 (m, 1H), 8.08 (m, 1H), 7.39 (m, 2H), 7.32 (m, 2H), 7.23 (m, 3H), 6.83 (m, 2H), 6.62 (m, 2H), 6.54 (m, 1H), 5.21 (dd, 1H, *J* = 7.1, 14.2 Hz), 4.45 (d, 2H, *J* = 4.7 Hz), 4.28 (d, 2H, *J* = 6.0 Hz), 3.74 (s, 3H), 3.63–3.50 (m, 3H), 3.40 (s, 3H), 3.37 (s, 3H), 3.08 (dd, 1H, *J* = 6.0, 12.3 Hz), 2.93 (m, 4H), 2.02 (m, 1H), 1.91 (m, 1H), 1.49 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 179.6, 167.7, 165.2 (d, $^1J_{CF}$ = 245.8 Hz), 165.1 (d, $^1J_{CF}$ = 245.8 Hz), 162.1 (t, $^3J_{CF}$ = 13.8 Hz), 160.8, 145.1, 143.8, 137.6, 135.6, 131.5, 131.1, 130.6, 129.6, 129.6, 128.1, 127.7, 127.2, 114.8, 99.6 (d, 2C, $^2J_{CF}$ = 28.9 Hz), 97.4 (t, $^2J_{CF}$ = 26.5 Hz), 79.8, 74.0, 71.8, 68.6, 58.5, 55.7, 51.0, 41.8, 40.1, 38.2, 35.8, 31.5, 22.0;; HRMS (ESI) *m/z* 770.2916 ($[M+H]^+$ calcd for $C_{39}H_{46}F_2N_3O_9S^+$ 770.2917).

*5.1.3.34. N-[(1S,2S,4R)-1-(3,5-difluoro-phenoxymethyl)-5-(4-fluoro-phenylamino)-2-hydroxy-4-methoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2m**).* Title compound **2m** was obtained from **12b** as described for **2h**, in 40% yield (20 mg, 27 μmol). **2m** was further purified by LC-MS. $[\alpha]_D^{20}$ +14.2 (*c* 1.0, MeOH);^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, 1H, *J* = 5.5 Hz), 8.13 (t, 1H, *J* = 1.5 Hz), 7.95 (m, 2H), 7.40–7.22 (m, 5H), 7.17 (m, 1H), 6.90 (m, 2H), 6.62 (m, 2H) 6.55 (m 2H), 6.46 (m, 1H) 5.31 (m, 1H), 4.81 (m, 1H), 4.48 (dd, 1H, *J* = 3.8, 9.9 Hz), 4.41 (m, 1H), 4.18 (m, 1H), 3.95 (t, 1H, *J* = 9.5 Hz), 3.74 (d, 1H, *J* = 11.1 Hz), 3.54 (s, 3H), 3.33 (s, 3H), 3.29 (dd 1H, *J* = 4.8, 11.1 Hz), 2.84 (s, 3H), 2.43 (m, 2H), 1.70 (bs, 1H), 1.60 (d, 3H, *J* = 9.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 164.7, 163.9 (d, $^1J_{CF}$ = 246.7 Hz), 163.7 (d, $^1J_{CF}$ = 246.7 Hz), 160.3 (t, $^3J_{CF}$ = 15.5 Hz), 155.8 (d, $^1J_{CF}$ = 235.9 Hz), 143.5 (d, $^4J_{CF}$ = 2.2 Hz), 142.8, 142.3, 136.1, 135.9, 129.2, 128.9, 128.4, 127.8, 127.8, 127.8, 126.4, 125.4, 124.4, 116.0 (d, 2C, $^2J_{CF}$ = 22.1 Hz), 113.5 (d, 2C, $^3J_{CF}$ = 15.5 Hz), 98.7 (d, 2C, $^2J_{CF}$ = 28.5 Hz), 97.0 (t, $^2J_{CF}$ = 25.8 Hz), 80.1, 67.4, 58.0, 57.6, 55.5, 49.8, 49.3, 38.2, 35.5, 32,3, 21.8; HRMS (ESI) *m/z* 743.2697 ($[M+H]^+$ calcd for $C_{37}H_{42}F_3N_4O_7S^+$ 743.2721)

*5.1.3.35. N-[5-benzyl-(2-nitro-benzenesulfonyl)-amino-1S-(3,5-difluoro-phenoxymethyl)-2S-hydroxy-4R-methoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**16**).* Title compound **16** was obtained from **14** as described for **2h**, in 90% yield (80 mg, 86 μmol). $[\alpha]_D^{20}$ +12.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (m, 1H), 8.00 (m, 1H), 7.96 (m, 1H), 7.63 (m, 3H), 7.40–7.19 (m, 10H), 6.79 (m, 2H), 6.49 (m, 2H), 6.42 (m, 1H), 5.31 (m, 1H) 4.60 (dd, 2H, *J* = 15.7, 37.1 Hz), 4.22 (m, 1H),4.13–4.00 (m, 3H), 3.51 (m, 1H), 3.37 (m, 5H), 3.18 (s, 3H), 2.87 (s, 3H), 1.67 (m, 1H), 1.61 (d, 3H, *J* = 7.0 Hz), 1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 165.0 (d, $^1J_{CF}$ = 246.4 Hz), 164.8, 162.6 (d, $^1J_{CF}$ = 246.4 Hz), 160.3 (t, $^3J_{CF}$ = 13.7 Hz), 147.8142.9, 142.5, 136.3, 135.6, 135.3, 134.0, 133.4, 131.9, 131.4, 128.9, 128.9, 128.4, 128.3, 127.9, 127.8, 127.7, 126.4, 124.8, 123.9, 98.7 (d, 2C, $^2J_{CF}$ = 28.6 Hz), 96.9 (d, $^2J_{CF}$ = 25.8 Hz), 80.3, 77.4, 68.3, 66.9, 57.7, 52.8, 52.7, 50.8, 48.7, 38.1, 35.9, 35.7, 21.9; HRMS (ESI) *m/z* 924.2735 ($[M+H]^+$ calcd for $C_{44}H_{48}F_2N_5O_{11}S_2^+$ 924.2754)

*5.1.3.36. N-[5-benzyl-(2-nitro-benzenesulfonyl)-amino-1S-(3,5-difluoro-phenoxymethyl)-2R-hydroxy-4R-methoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**17**).* Title compound **17** was obtained from **15** as described for **2h**, in 92% yield (54 mg, 58 μmol). $[\alpha]_D^{20}$ +24.5 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (m, 1H), 7.98 (t, 1H, *J* = 1.9 Hz), 7.95 (m, 1H), 7.91 (dd, 1H, *J* = 1.3, 8.0 Hz), 7.73–7.57 (m, 3H), 7.38–7.28 (m, 4H), 7.25 (m, 4H), 7.16 (m, 2H), 6.93 (d, 1H, *J* = 8.4), 6.73 (d, 1H, *J* = 7.6 Hz), 6.50 (m, 2H) 6.38 (m, 1H), 5.29 (m, 1H), 4.68 (d, 1H, *J* = 15.4 Hz), 4.46 (d, 1H, *J* = 15.4 Hz), 4.33 (m, 2H), 4.13 (m, 2H), 3.57 (m, 2H), 3.33 (s, 3H), 3.30 (m, 1H), 3.17 (s, 3H), 2.84 (s, 3H), 1.75 (m, 2H), 1.65 (bs, 1H), 1.59 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 166.1, 164.9, 163.7 (d, $^1J_{CF}$ = 246.6 Hz), 163.5 (d, $^1J_{CF}$ = 246.6 Hz), 160.5 (t, $^3J_{CF}$ = 13.4 Hz), 148.0, 142.9, 142.5, 136.3, 135.7, 135.1, 134.0, 133.2, 132.0, 131.3, 129.0, 128.9, 128.5, 128.4, 128.2, 127.7, 126.4, 124.5, 124.0, 98.8 (d, 2C, $^2J_{CF}$ = 28.6 Hz), 97.0 (t, $^2J_{CF}$ = 25.9 Hz), 77.9, 67.8, 67.1, 58.0, 53.7, 52.8, 49.9, 48.9, 38.1, 35.8, 34.1, 21.8; HRMS (ESI) *m/z* 946.2591 ($[M+Na]^+$ calcd for $C_{44}H_{47}F_2N_5NaO_{11}S_2^+$ 946.2574)

*5.1.3.37. N-[5-benzylamino-1S-(3,5-difluoro-phenoxymethyl)-2S-hydroxy-4R-methoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2n**).* To a stirred solution of **16** (50 mg, 54 μmol, 1 equiv) in MeCN (3 mL) was added thiophenol (18 μL, 0.16 mmol, 3 equiv) and K_2CO_3 (22 mg, 0.16 mmol, 3 equiv). After 2 h of heating (50 °C) the reaction mixture was allowed to reach r t before it was concentrated and purified by silica column chromatography (toluene–ethyl acetate gradient 10:1–100% ethyl acetate) to yield the compound **2n** in 50% yield (20 mg, 27 μmol). **2n** was further purified by LC-MS.. $[\alpha]_D^{20}$ −14.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (m, 1H), 8.00 (m, 2H), 7.41–7.27 (m, 10H), 7.12 (d, 1H, *J* = 8.5 Hz), 6.75 (d, 1H, *J* = 7.8 Hz), 6.50 (m, 2H), 6.39 (m, 1H), 5.32 (m, 1H) 4.43 (m, 1H),4.16 (m, 2H), 4.07 (dd, 1H, *J* = 5.6, 9.2 Hz), 3.80 (dd, 2H, *J* = 13.0, 33.1 Hz), 3.61 (m, 1H), 3.37 (s, 3H), 3.30 (s, 3H), 3.07 (dd, 1H, *J* = 5.0, 12.1 Hz), 2.86 (s, 3H), 2.56 (m, 1H), 2.03 (m, 2H), 1.62 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 163.9 (d, $^1J_{CF}$ = 247.2 Hz), 164.7, 163.7 (d, $^1J_{CF}$ = 247.2 Hz), 160.7 (t, $^3J_{CF}$ = 13.9 Hz), 142.9, 142.4, 138.1, 136.1, 135.8, 129.0, 128.9, 128.6, 127.9, 127.9, 127.8, 126.4, 124.1, 98.7 (d, 2C, $^2J_{CF}$ = 28.6 Hz), 96.7 (d, $^2J_{CF}$ = 25.9 Hz), 77.4, 67.7, 63.0, 56.8, 54.0, 53.8, 50.6, 49.9, 38.3, 38.1, 35.6, 21.8 HRMS (ESI) *m/z* 739.2951 ($[M+H]^+$ calcd for $C_{38}H_{45}F_2N_4O_7S^+$ 739.2972)

*5.1.3.38. N-[5-benzylamino-1S-(3,5-difluoro-phenoxymethyl)-2R-hydroxy-4R-methoxy-pentyl]-5-(methanesulfonyl-methyl-amino)-N′-(1R-phenyl-ethyl)-isophthalamide (**2o**).* Title compound **2o** was obtained from **17** as described for **2n**, in 52% yield (21 mg, 28 μmol). **2o** vas further purified by LC-MS. $[\alpha]_D^{20}$ +41.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD): δ 8.22 (t, 1H, *J* = 1.6 Hz), 8.04 (m, 2H), 7.42–7.38 (m, 2H), 7.37–7.30 (m, 6H), 7.30–7.22 (m, 2H), 6.63.6.47 (m, 3H), 5.27–5.21 (m, 1H), 4.40–4.35 (m, 1H), 4.32 (d, 2H, *J* = 5.0 Hz), 4.04–3.99 (m, 1H), 3.90–3.82 (m, 2H), 3.68–3.62 (m, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 2.95 (s, 3H), 2.88 (dd, 1H, *J* = 4.8, 12.7 Hz), 2.77 (dd, 1H *J* = 6.0, 12.7 Hz), 2.00–1.93 (m, 1H), 1.63–1.56 (m, 1H), 1.59 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR (125.8 MHz, CD_3OD): δ 168.8, 167.9, 163.9 (d, $^1J_{CF}$ = 246.8 Hz), 163.7 (d, $^1J_{CF}$ = 246.8 Hz), 162.5 (t, $^3J_{CF}$ = 13.8 Hz), 145.1, 143.8, 137.5, 137.2, 129.9, 129.7, 129.6, 129.4, 129.1, 128.8, 128.2, 127.3, 126.0, 99.6 (d, 2C, $^2J_{CF}$ = 29.1 Hz), 97.1 (t, $^2J_{CF}$ = 26.3 Hz), 78.0, 68.8, 68.7, 57.7, 56.0, 54.1, 52.2, 51.0, 38.5, 38.3, 35.9; HRMS (ESI) *m/z* 739.2982 ($[M+H]^+$ calcd for $C_{38}H_{45}F_2N_4O_7S^+$ 739.2972)

*5.1.3.39. N-[1S-(3,5-difluoro-phenoxymethyl)-2S-hydroxy-4R-methoxy-5-(4-methoxy-benzyloxy)-pentyl]-2-[methyl-(2S-methyl-cyclopropyl-(S)-methyl)-amino]-6-[methyl-(propane-2-sulfonyl)-amino]-isonicotinamide (**18**).* Palladium on charcoal (∼5%) was added to a solution of **7** (68 mg, 0.16 mmol) in MeOH (3 mL) under argon atmosphere. The flask was evacuated followed by addition of hydrogen gas (1 atm). The reaction mixture was stirred over night. The Pd/C was

filtered off and the filtrate was concentrated to yield the crude product which was used in the next step without further purification. Carboxylic acid **B** (23 mg, 65 μmol) was dissolved in dry DCM (2 mL) and PyBOP (34 mg, 65 μmol) was added followed by DIPEA (12 μL, 65 μmol, 0.4 equiv). After 30 min the crude amine, dissolved in DCM, was added to the mixture, followed by DIPEA (12 μL, 65 μmol). After 2 h, the reaction mixture was diluted with DCM, washed with Na_2CO_3 (sat.) and NH_4Cl (aq). The aqueous layers were extracted with DCM (3x), and the combined organic phases were washed with brine, dried ($MgSO_4$), concentrated and purified by silica column chromatography (toluene–ethyl acetate gradient 10:1–1:6) to yield the crude compound **18**, in 66% yield (32 mg, 43 μmol). Compound **18** was further purified by LC-MS. $[\alpha]_D^{20}$ −3.4 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDOD_3$) δ 7.20 (m, 2H), 6.80 (m, 3H), 6.71 (m, 1H), 6.60 (m, 2H), 6.50 (m, 1H), 4.50 (m, 1H), 4.43 (m, 2H), 4.23 (dd, 1H, $J = 6.4$, 9.8 Hz), 4.16 (dd, 1H, $J = 7.1$, 9.8 Hz), 4.08 (m, 2H), 3.74 (s, 1H), 3.62 (m, 1H), 3.52 (m, 3H), 3.38 (m, 7H), 3.09 (s, 3H), 1.79 (m, 2H), 1.34 (d, 6H, $J = 6.9$ Hz), 1.01 (d, 3H, $J = 6.0$ Hz), 0.77 (m, 1H), 0.69 (m, 1H), 0.43 (m, 1H), 0.22 (m, 1H); ^{13}C NMR (100 MHz, $CDOD_3$) δ 169.7, 163.9 (d, $^1J_{CF} = 246.2$ Hz), 163.7 (d, $^1J_{CF} = 246.2$ Hz), 162.3 (t, $^3J_{CF} = 13.8$ Hz), 160.7, 159.1, 154.8, 146.6, 131.5, 130.5, 114.7, 100.6, 100.1, 99.6 (d, 2C, $^2J_{CF} = 28.8$ Hz), 97.2 (t, $^2J_{CF} = 26.3$ Hz), 79.0, 73.9, 71.7, 68.7, 68.2, 57.6, 56.0, 55.6, 54.7, 54.1, 36.8, 36.7, 36.5, 19.1, 18.8, 16.6, 16.6 12.6, 12.0; HRMS (ESI) *m/z* 749.3419 ($[M + H]^+$ calcd for $C_{37}H_{51}F_2N_4O_8S^+$ 749.3390).

*5.1.3.40. 2-Ethyl-6-methyl-7,7-dioxo-6,7,8,9-tetrahydro-7λ^6-thia-6,9a-diaza-benzo[cd]azulene-carboxylic acid [1S-(3,5-difluoro-phenoxymethyl)-2S-hydroxy-4R-methoxy-5-(4-methoxy-benzyloxy)-pentyl]-amide (**19**).* Palladium on charcoal (∼5%) was added to a solution of **7** (88 mg, 0.20 mmol) in MeOH (3 mL) under argon atmosphere. The flask was evacuated followed by addition of hydrogen gas (1 atm). The reaction mixture was stirred over night. The Pd/C was filtered off and the filtrate was concentrated to yield the crude product which was used in the next step without further purification. Carboxylic acid **C** (26 mg, 84 μmol) was dissolved in dry DCM (2 mL) and PyBOP (44 mg, 84 μmol) was added followed by DIPEA (15 μL, 84 μmol, 0.4 equiv). After 30 min the crude amine, dissolved in DCM was added to the mixture, followed by DIPEA (15 μL, 84 μmol). After 2 h, the reaction mixture was diluted with DCM, washed with Na_2CO_3 (sat.) and NH_4Cl (aq). The aqueous layers were extracted with DCM (3×), and the combined organic phases were washed with brine, dried ($MgSO_4$), concentrated and purified by silica column chromatography (toluene–ethyl acetate gradient 10:1–1:6) to yield the crude compound **19**, in 76% yield (45 mg, 64 μmol). Compound **19** was further purified by LC-MS. $[\alpha]_D^{20}$ −11.7 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDOD_3$) δ 8.08 (d, 1H, $J = 1.6$ Hz), 7.65 (d, 1H, $J = 1.5$ Hz), 7.14 (m, 2H), 7.07 (m, 1H), 6.72 (m, 2H), 6.61 (m, 2H), 6.49 (m, 1H), 4.57 (m, 1H), 4.49 (m, 2H) 4.39 (m, 2H), 4.25 (dd, 1H, $J = 6.8$, 9.9 Hz),4.16 (m, 2H), 3.89 (m, 2H), 3.68 (s, 3H), 3.62 (m, 1H), 3.54 (dd, 1H, $J = 3.8$, 10.6 Hz), 3.48 (dd, 1H, $J = 4.7$, 10.6 Hz), 3.46 (s, 3H), 3.37 (s, 3H), 2.75 (m, 2H), 1.81 (m, 2H), 1.31 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR (100 MHz, $CDOD_3$) δ 170.6, 165.2 (d, $^1J_{CF} = 244.9$ Hz), 165.1 (d, $^1J_{CF} = 244.9$ Hz), 162.3 (t, $^3J_{CF} = 13.8$ Hz), 160.7, 135.6, 131.9, 131.4, 130.4, 129.7, 129.2, 127.7, 127.4, 120.9, 119.1, 119.1, 114.6, 99.6 (d, 2C, $^2J_{CF} = 28.7$ Hz), 97.1 (t, $^2J_{CF} = 26.5$ Hz), 79.0, 73.8, 71.7, 68.7 68.3, 57.8, 57.6, 55.6, 53.9, 44.2, 40.2, 36.7, 18.9, 14.9; HRMS (ESI) *m/z* 724.2486 ($[M + Na]^+$ calcd for $C_{35}H_{41}F_2N_3O_8SNa^+$ 724.2475).

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