Discovery of potent BACE-1 inhibitors containing a new hydroxyethylene (HE) Scaffold: Exploration of P1′ alkoxy residues and an aminoethylene (AE) central core

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ABSTRACT

In a preceding study we have described the development of a new hydroxyethylene (HE) core motif displaying P1 aryloxymethyl and P1′ methoxy substituents delivering potent BACE-1 inhibitors. In a continuation of this work we have now explored the SAR of the S1′ pocket by introducing a set of P1′ alkoxy groups and evaluated them as BACE-1 inhibitors. Previously the P1 and P1′ positions of the classical HE template have been relatively little explored due to the complexity of the chemical routes involved in modifications at these positions. However, the chemistries developed for the current HE template renders substituents in both the P1 and P1′ positions readily available for SAR exploration. The BACE-1 inhibitors prepared displayed K_i values in the range of 1–20 nM, where the most potent compounds featured small P1′ groups. The cathepsin D selectivity which was high for the smallest P1′ substituents (P1′ = ethoxy, fold selectively >1500) dropped for larger groups (P1′ = benzyloxy, fold selectivity of 3). We have also confirmed the importance of both the hydroxyl group and its stereochemistry preference for this HE transition state isostere by preparing both the deoxygenated analogue and by inverting the configuration of the hydroxyl group to the R-configuration, which as expected resulted in large activity drops. Finally substituting the hydroxyl group by an amino group having the same configuration (S), which previously have been described to deliver potent BACE-1 inhibitors with advantageous properties, surprisingly resulted in a large drop in the inhibitory activity.

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1. Introduction

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by the progressive formation of insoluble amyloid plaques and neurofibrillary tangles in the brain.[1,2] The major component of the plaques, amyloid β peptides (Aβ) is generated from amyloid precursor protein (APP) by β-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE-1) and γ-secretase-mediated stepwise cleavages.[3] It is hypothesized that accumulation of these Aβ peptides and subsequent formation of plaques in the brain may be responsible for the onset and progression of the disease where the neurotoxicity of Aβ peptides cause neuronal cell death and brain inflammation ultimately leading to the dementia and AD.[4,5] As a result of the amyloid hypothesis, BACE-1 has been vigorously pursued as a prime molecular target for therapeutic intervention in AD.[6–10]

In a preceding study from our group we have disclosed the development of a novel HE transition state isostere, where a di-fluoro phenoxymethyl group was introduced in the P1 position and a methoxy group in the P1′ position furnishing highly potent inhibitors of BACE-1 (i.e., lead compound **1**),[11] which moreover exhibits very promising selectivity over cathepsin D. While BACE-1 HE isosteres generally employ a methyl group in the P1′ position we reasoned based on modeling and X-ray crystallography studies that both BACE-1 potency and cathepsin D selectivity might be enhanced by replacing this methyl group in the P1′ position by a more polar but still small methoxy group, which we were pleased to note was also the case. As deduced from 3D structural data[11,12] the oxygen of the methoxy group is involved in hydrogen bonding to a structural water molecule which in turn is hydrogen bonded to Thr72 of the BACE-1 enzyme. In contrast, cathepsin D has a lipophilic S1′ pocket and a polar methoxy group is subsequently less well accommodated than a methyl group, resulting in reduced cathepsin D potency and the desired enhanced selectivity over cathepsin D. The natural BACE-1 substrate has an Asp residue in

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the P1′ position[13] and it has previously been reported[14] that selectivity over cathepsin D can be enhanced by increasing the polarity of the side chain at the P1′ position although the BACE-1 inhibitors explored all displayed BACE-1 K_i values at best in the low μM.

Based on the encouraging results obtained in our previous study, cf. inhibitor **1**, we have now studied a range of P1′ alkoxy groups, to explore the selectivity differences between the S1′ pockets of BACE-1 and cathepsin D,[14] respectively. A number of P1′ groups, all featuring the alkoxy motif, have been synthesized and evaluated as BACE-1 inhibitors where the chemistry developed for this novel HE template has allowed the facile introduction of substituents in both the P1 and P1′ positions. Previously these positions have been relatively little explored due to the complexity of the chemical synthesis involved in modifications of the classical HE template.[15] Several groups have reported on BACE-1 inhibitors containing substituted isophthalamides as highly promising P2–P3 groups.[16] All our inhibitors in this series are equipped with the 5-substituted isophthalamide reported by Stachel et al. (Fig. 1).[17]

We herein report a series of new inhibitors, among those **2a–2f**, displayed BACE-1 K_i values in the range 1–20 nM, with the most potent compounds being those inhibitors having the smallest alkoxy P1′ groups and where the caphepsin D selectivity was high for the smallest P1′ substituents. Furthermore we confirmed the importance of a hydroxyl group with *S*-configuration and that a replacement of this hydroxyl group for an amine, unexpectedly was non-productive in this series.

2. Results and discussion

2.1. Chemistry

The target compounds **2a–j** were prepared as outlined in Schemes 1–4. The methyl glycoside **3** was synthesized from commercially available 1,2,5,6-diisopropylidene-α-D-glucose in seven steps according to literature procedures in an overall yield of 9%.[18–22] The conversion of the methyl glycoside **3** to the target compounds **2a–f** was achieved over several steps as shown in

Scheme 1. Glycoside **3** was treated with Ag₂O and reagent **12a** or **12b** from chemset **12** (Fig. 2) in DMF at room temperature to furnish compounds **4a** and **4b** in 47% and 34% yield, respectively.[23] Previous experience in our lab prompted us to use this method but due to low or zero yields in the following alkylation attempts, a switch to NaH was made with improved results. To prepare **4c–e**, glycoside **3** was treated with NaH in DMF at 0 °C and then reacted with the reagents **12c–e** from chemset **12** in DMF to deliver **4c–e** in 19%, 49% and 23% yield, respectively. Hydrolysis of the methyl glycosides **4a–e** in refluxing 1,4-dioxane in the presence of sulfuric acid for ~1 h followed by quenching with aqueous sodium carbonate afforded the desired products **5a–e** in 47%, 82%, 80%, 55% and 67% yield, respectively.[24] Subsequent oxidation of the anomeric hydroxyl group using pyridinium dichromate in dichloromethane (DCM) provided the corresponding lactones **6a–e** in 96%, 68%, 81%, 38% and 83% yield, respectively.[25] These lactones **6a–e** were ring opened with (*S*)-2-amino-*N*-benzyl-3-methyl-butyramide upon heating in diisopropylethylamine (DIPEA) using 2-hydroxy-pyridine as an activator of the lactone to give the ring opened amides **7a–e** in 70%, 84%, 87%, 77% and 97% yield, respectively.[26,27] The amine, (*S*)-2-amino-*N*-benzyl-3-methyl-butyramide was synthesised from Boc-Val-OH and benzylamine.[11] Reduction of the azide group in compounds **7a–e** was achieved using triphenylphosphine (Ph₃P) in methanol containing a few drops of water providing the corresponding amines which were coupled without prior purification with 5-(methanesulfonyl-methyl-amino)-*N*′-(1-phenyl-ethyl)-isophthalacid[17] using benzotriazole-1-yloxytris-(pyrrolidino)phosphonium hexafluorphosphate (Py-BOP) and DIPEA in DCM furnishing the target compounds **2a–d** and **2f** in 64%, 67%, 97%, 58%, and 43% yield, respectively.[21,28] Compound **7d** was reacted with hydrogen over a catalytically amount of palladium on activated carbon to reduce both the azide group and the double bond of the P1′ allyl group followed by coupling with the P2–P3 group using the same protocol, vide supra, to give product **2e** in 88% yield.

Target compound **2g** was prepared as shown in Scheme 2. Compound **8**,[11] was treated with 1,1′-thiocarbonyldiimidazole in
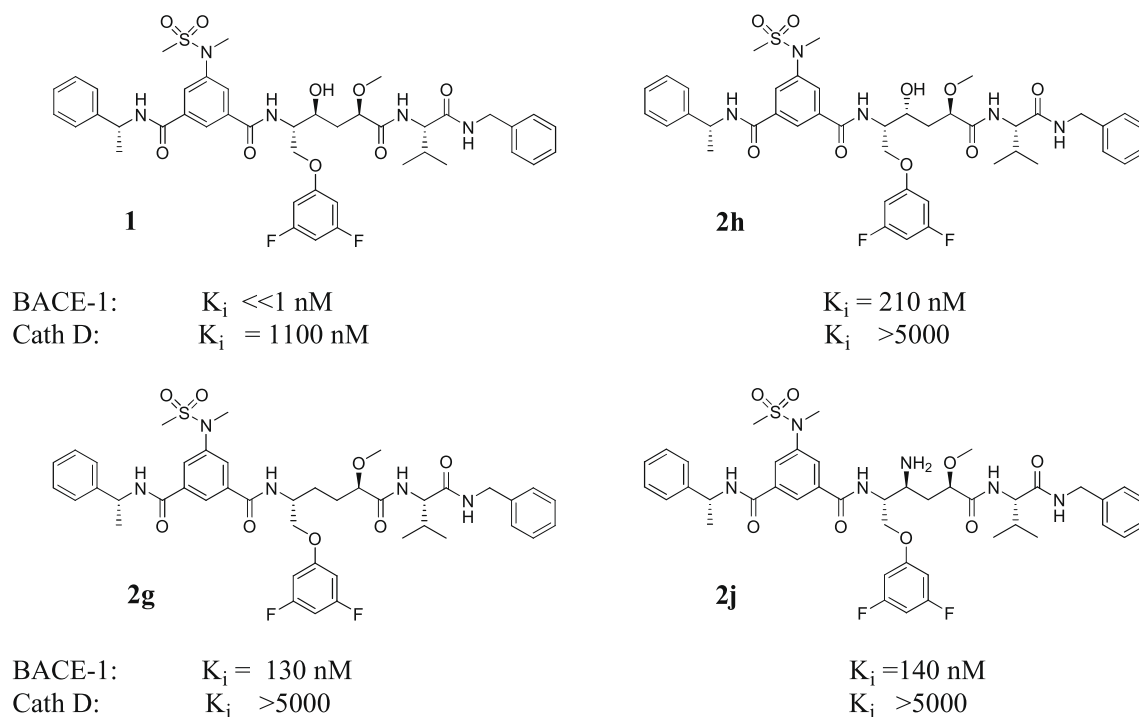

Figure 1. Stereochemistry effects comparison of AE (**2j**), HE (**1**, **2h** and compound **2g**) BACE-1 inhibitor K_i values and their caphepsin D selectivity.
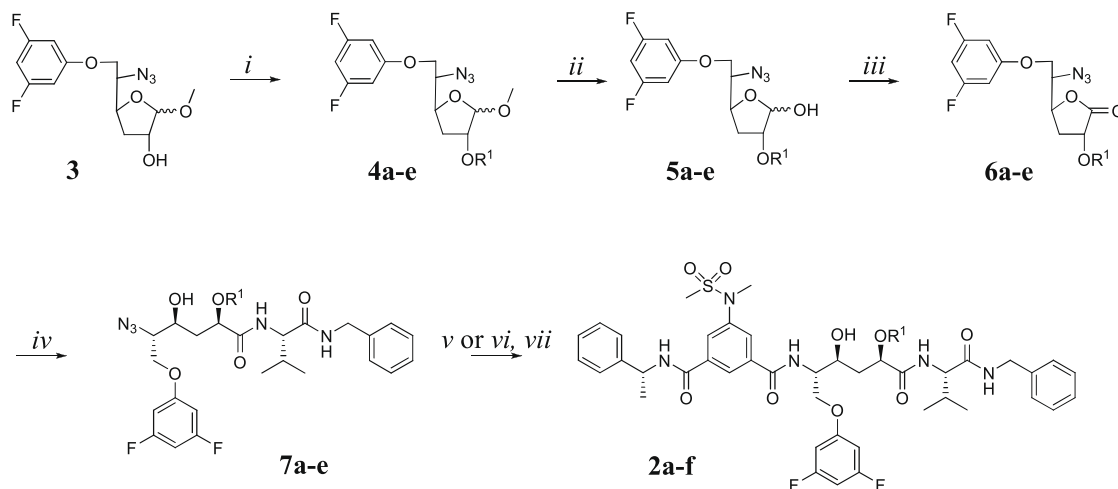
Scheme 1. Reagent and conditions: (i) R1X (**12**), NaH or Ag$_2$O, DMF, rt; (ii) H$_2$SO$_4$, 1,4-dioxane, reflux; (iii) PDC, DCM, rt; (iv) (S)-2-amino-*N*-benzyl-3-methyl-butyramide, 2-hydroxypyridine, DIPEA, 70 °C; (v) Ph$_3$P, H$_2$O, MeOH, rt; (vi) H$_2$, Pd/C, MeOH, rt; (vii) 5-(methanesulfonyl-methyl-amino)-*N'*-(1-phenyl-ethyl)-isophthalacid, Py-BOP, DIPEA, DCM, rt.
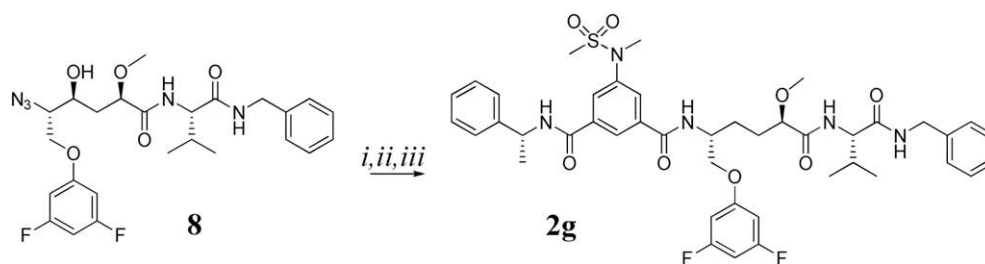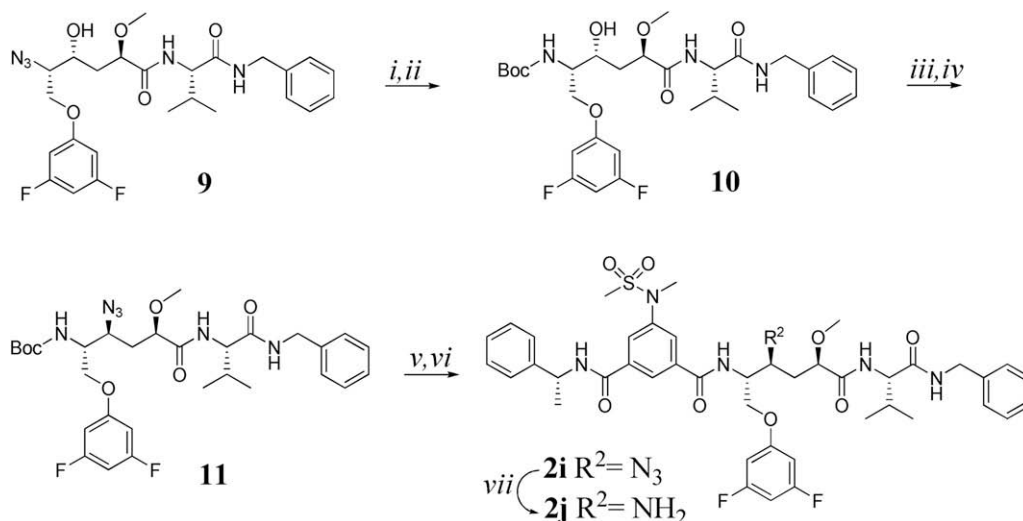

Scheme 2. Reagents and conditions: (i) TDI, DCE, reflux; (ii) Bu$_3$SnH, AIBN, toluene, reflux; (iii) 5-(methanesulfonyl-methyl-amino)-*N'*-(1-phenyl-ethyl)-isophthalacid, Py-BOP, DIPEA, DCM, rt.
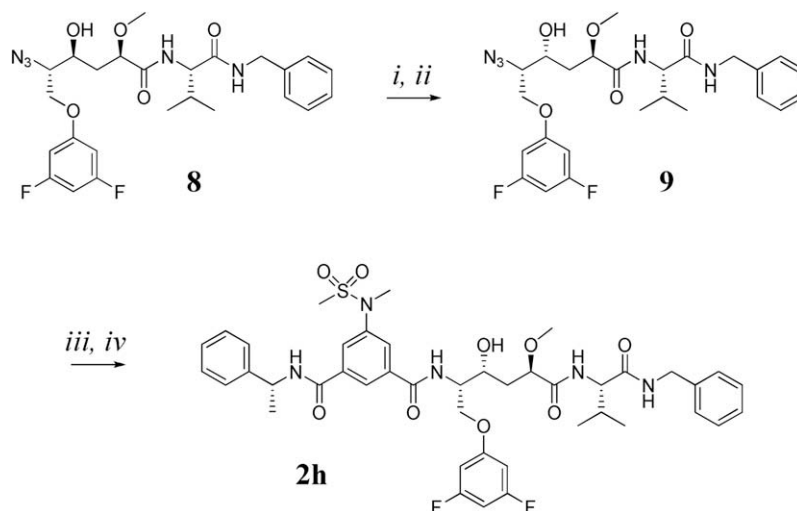

Scheme 3. Reagents and conditions: (i) Ph$_3$P, DIAD, *para*-nitrobenzoic acid, THF, rt; (ii) 0.1 M NaOMe in MeOH; (iii) Ph$_3$P, H$_2$O, MeOH; (iv) 5-(methanesulfonyl-methylamino)-*N'*-(1-phenyl-ethyl)-isophthalacid, Py-BOP, DIPEA, DCM, rt.

refluxing dichloroethane, without prior purification the formed thiocarbonyl ester was subsequently added to tributyltin hydride and a catalytically amount of AIBN in refluxing toluene, under these conditions also the azide is reduced as reported by Witczak and Whistler[29] The resulting amine was coupled without prior purification with 5-(methanesulfonyl-methyl-amino)-*N'*-(1-phenyl-ethyl)-isophthalacid using Py-BOP and DIPEA in DCM furnishing the target compound **2g** in 7% yield over three steps.[19,28]

The synthesis of target compound **2h** is outlined in Scheme 3. Compound **8** was reacted with Ph$_3$P, diisopropyl azocarboxylate (DIAD) and 4-nitrobenzoic acid in THF[30] furnishing the 4-nitro-benzoate ester which was hydrolyzed using 0.1 M sodium methox-ide in methanol delivering the inverted alcohol **9** in 23% yield. Reduction of the azide group in compound **9** was achieved using catalytic hydrogenation over palladium on activated carbon in methanol providing the corresponding amine which was coupled

Scheme 4. Reagents and conditions: (i) H$_2$, Pd/C, MeOH, rt; (ii) Boc$_2$O, 1 M NaOH, THF/H$_2$O 1:1; (iii) MsCl, pyridine, 0 °C; (iv) NaN$_3$, DMF, 60 °C; (v) TES, DCM/TFA 2:1, rt; (vi) 5-(methanesulfonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalacid, Py-BOP, DIPEA, DCM, rt; (vii) H$_2$, Pd/C, MeOH, rt.
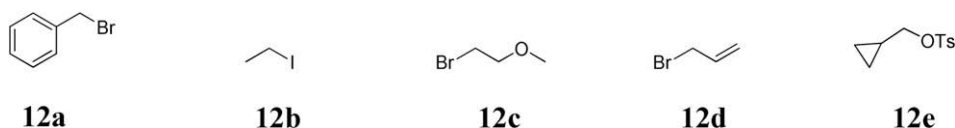
Figure 2. Diversity reagents **12**.

without further purification with 5-(methanesulfonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalacid using Py-BOP and DIPEA in DCM furnishing the target compound **2h** in 75% yield.

Catalytic hydrogenation of **9** over a catalytic amount palladium on active carbon in methanol followed by subsequent treatment with di-*tert*-butyl dicarbonate and sodium hydroxide in a mixture of THF and H$_2$O gave the Boc-protected compound **10** in 96% yield (Scheme 4). Compound **10** was converted to the corresponding azide **11** with inversion of configuration in 25% yield by treating the alcohol with methane sulfonyl chloride in the presence pyridine followed by displacement of the methane sulfonate group using sodium azide in DMF at 60 °C for 16 h. Targets compounds **2i** and **2j** were achieved by deprotecting the Boc group in compound **11** using trifluoroacetic acid and triethyl silane in DCM followed by coupling of the resulting amine with 5-(methanesulfonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalacid using Py-BOP and DIPEA in DCM furnishing the target compound **2i** in 85% yield. The corresponding amine **2j** was furnished in 85% yield by catalytic hydrogenation of **2i**.

2.2. Structure activity relationships

We have previously reported on the potent lead BACE-1 inhibitor **1**.[11] Based on the encouraging results from inhibitor **1**, we have in a continuation explored a set of P1' groups, all featuring the alkoxy motif, to expand on the SAR at this position. These modifications furnished highly active BACE-1 inhibitors, with K_i values ranging from 1 to 20 nM (inhibitors **2a–f**, Table 1) demonstrating that the S1'-pocket can accommodate larger substituents than previously anticipated. The S1' pocket in cathepsin D, as in most other aspartic proteases, comprise of hydrophobic residues, while it is primarily hydrophilic in BACE-1.[14] As expected there was a considerable drop in selectivity over cathepsin D with larger, hydrophobic substituents yielding an increase in potencies against cathepsin D. For the P1' benzyl substituent (inhibitor **2a**) the selec-

tivity was only a modest 1.6-fold. However, the small size P1' ethoxy group of inhibitor **2b** retained an excellent fold selectivity of >1500 over cathepsin D which is comparable with inhibitor **1**, having a P1' methoxy group. It shows that for this novel HE scaffold small and polar groups are advantageous for achieving both a high potency against BACE-1 as well as a high selectivity over cathepsin D. We have also confirmed the importance of the hydroxyl group which binds to the catalytic Asp32 and Asp228 for this HE transition state isostere (see Fig. 1) by preparing both the deoxygenated analogue **2g** and by inverting the configuration of the hydroxyl group to the R-configuration ((R) CH–OH, **2h**), where **2g** and **2h** displayed approximately 1000 and 2000-fold drop in activity, respectively, compared to lead inhibitor **1**. These results are consistent with the hydroxyl group of the HE central core making key hydrogen bond interactions to the catalytic Asp228 and Asp32, cf. earlier reported (R)-NH$_2$ aminoethylene.[31] We were also interested in evaluating the corresponding inhibitor structures where the hydroxyl group has been substituted with an amino group furnishing an aminoethylene (AE) isostere. Inhibitors containing primary amines have previously been used successfully in two classes of renin inhibitors[32,33] and in BACE-1 inhibitors containing either a aminoethylene (AE) isostere[31] or a truncated aminoethylene (AE) isostere.[34] It was found from X-ray crystallography that the primary amine of these BACE-1 inhibitors was engaging both catalytic aspartates Asp32 and Asp 228 with hydrogen bonding contacts. Notably, these AE isostere inhibitor structures delivered comparable BACE-1 inhibitory activities but importantly also bestows the inhibitors with advantageous physicochemical properties such as increased solubility and higher affinity for the acidic organelles wherein BACE-1 and sAPP are co-localized, rendering higher potencies in the cell-based assays. When the hydroxyl group in inhibitor **1** was exchanged for an amine, with retention of configuration, yielding the corresponding AE inhibitor structure **2j**, this resulted in a BACE-1 K_i value of 140 nM, providing an unexpected drop in potency in excess of 1000-fold.

Table 1
Target compounds and inhibition data
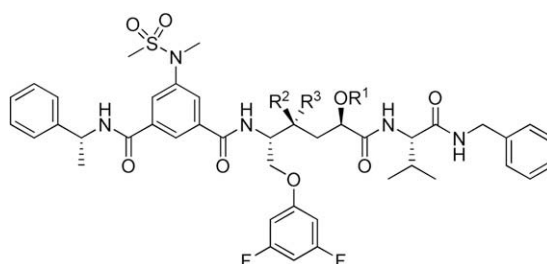
| Entry	Compound	R^1	R^2	R^3	K_i BACE-1[b] (nM)	K_i Cath D[b] (nM)
1	**2a**	Bn	OH	H	20	62
2	**2b**	Et	OH	H	2.1	3350
3	**2c**	(CH₂CH₂OCH₃)	OH	H	3.1	240
4	**2d**	Allyl	OH	H	3.3	130
5	**2e**	*n*-Prop	OH	H	3	61
6	**2f**	(cyclopropylmethyl)	OH	H	1.3	nd[a]
7	**2g**	Me	H	H	130	>5000
8	**2h**	Me	H	OH	210	>5000
9	**2i**	Me	N_3	H	70	>5000
10	**2j**	Me	NH_2	H	140	>5000

[a] nd = not determined.
[b] K_i values are the mean of at least two different experiments.

2.3. Modeling and X-ray crystallography analysis

Our earlier published crystal structure of inhibitor **1**[11] shows two structural water molecules buried in the S1'-pocket and a water mediated hydrogen bond network including the P1'-ether oxygen. The overall binding of compound **2c** is the same as for inhibitor **1** except that at least one of these two water molecules is displaced by the larger P1' substituents in compounds **2a–f**. The crystal structure of **2c** (Fig. 3) shows that the terminal methoxy oxygen of the P1'-tail overlays well with the position of one of the replaced water molecules. Similarly, as reported earlier for inhibitor **1**,[11] a structural water molecule forms hydrogen bond linkages between the inner-oxygen of the P1'-residue in **2c** and two amino acid residues in the active site (Fig. 4), namely Thr231 and Arg235.

Other residues in the S1'-pocket which are in close contact interactions with the larger P1' groups are Tyr198, Lys224, Ile226, Val332, and Thr329.

The variations in the position of the hydroxyl group in the HE isostere clearly show the importance of having a hydrogen bond network with both Asp32 and Asp228. The hydroxyl group of inhibitor **1** and **2a–f** is perfectly positioned in between the aspartic acid side chains, whereas modeling of the inverted alcohol **2h** shows interactions with only one of the aspartic acids (Asp32). The low activity of the amine **2j** cannot be readily explained from modeling and could be due to a shift in the degree of protonation of the amine in the active site, due to electronegative effects from the P1 aryloxy and P1' methoxy substituents, which would render less favorable binding to the catalytic Asp32 and Asp228. It could also
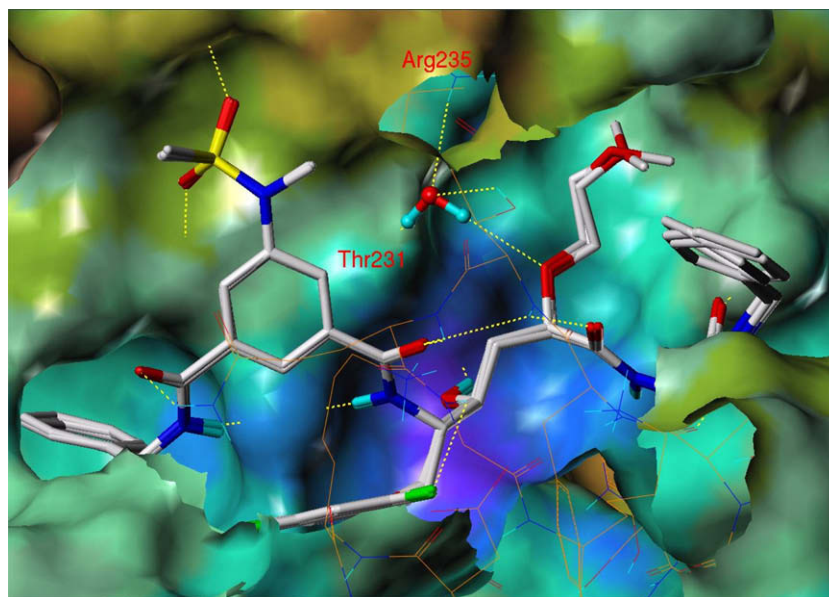
Figure 3. X-ray structure of inhibitor **2c** showing the flexibility of the P1'-tail and the hydrogen bond network with a structural water molecule including the inner-ether oxygen in the ligand and the residues Thr231 and Arg235.
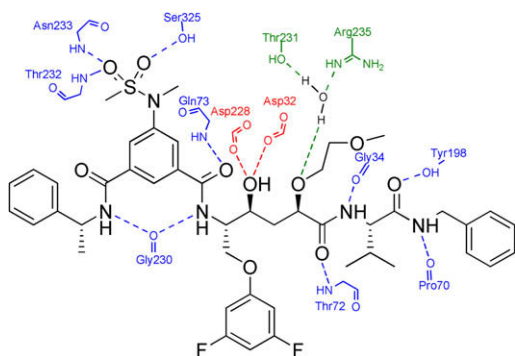
Figure 4. Overview of the hydrogen bonding network of inhibitor **2c**.

be attributed to a delicate balance between the over-all fit of these relatively large inhibitor structures and fine-tuned geometrical constraints in the active site making these inhibitors sensitive to small structural variations around the active site.

3. Conclusions

This study demonstrates that both potent and selective BACE-1 inhibitors can be achieved by exploiting the unique features of the S1′ pocket in BACE-1 with the newly developed HE template. Further investigation of this inhibitor series by reducing molecular weight and retaining the favorable structural elements is highly warranted and these efforts on inhibitor design and with cell-based activity data are forthcoming.

4. Experimental section

4.1. Protease enzyme assay

The BACE1 and cathepsin D assays were performed as previously described.[35]

4.2. Crystallography

The details of the crystallization and structure determination procedures have been published elsewhere.[35] Briefly, the complex of BACE-1 and **2c** was crystallized in the monoclinic space group P21 with cell dimensions of $a = 81.4$, $b = 102.5$, $c = 100.2$ and $\beta = 103.5°$. The structure was determined to 2.1 Å resolution with an R-value of 0.21 (R-free 0.24) and deposited in the RCSB PDB data base (3I25).

4.3. Modeling

All modeling experiments were performed using SYBYL 8.0 (Tripos Inc. 1699 South Hanley Road, St. Louis, Missouri, 63144, USA).

4.4. 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% sulfuric acid or ammonium molybdate (100 g): Ce(IV)sulfate (2 g): sulfuric acid (10%, 2 L). 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$_3$ ^{1}H δ 7.26 and ^{13}C δ 77.17 or CD$_3$OD-d_4 ^{1}H δ 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. Compounds **2a–j** 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, 100A from ACE (UK) and the mobile phases were based on water/acetonitrile containing 0.1%TFA.

Optical rotations were measured at room temperature on a Perkin–Elmer 341 polarimeter using a 10 cm, 1 mL cell.

4.5. LC–MS purity measurements

4.5.1. Chromatography system A

Column: ACE C$_8$, 50 × 3 mm, 3 µm particles; pump: Waters Alliance 2695; UV/vis-detector: Waters 996; MS detector: Waters ZQ; mobil phase A: 10 mM NH$_4$OAc in water; Mobil phase B: 10 mM NH$_4$OAc in 90% acetonitrile; gradient: 20–100% B in 5 min followed by 2 min at 100% B.

4.5.2. Chromatography system B

As chromatography system A except: mobil phase A: 0.2% HCOOH in water; mobil phase B: 0.18% HCOOH in 100% acetonitrile.

4.6. Synthetic procedures

4.6.1. Methyl 5-azido-3,5-dideoxy-6-O-(3,5-difluoryphenyl)-L-*lyxo*-hexofuranoside (3)

The methyl glycoside **3** was synthesized from commercially available 1,2,5,6-diisopropylidene-α-D-glucose in seven steps according to literature procedures in an overall yield of 9%.[18–22] ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.49–6.41 (m, 3H), 4.85 (s, 1H), 4.56–4.50 (m, 1H), 4.30 (t, J_{HH} = 4.5 Hz, 1H), 4.10–4.01 (m, 2H), 3.73–3.67 (m, 1H), 3.41 (s, 3H), 2.17–2.09 (m, 1H), 2.02–1.95 (m, 1H), 1.72 (d, J_{HH} = 4.6 Hz, 1H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 163.9 (d, $^1J_{CF}$ = 247.5 Hz), 163.7 (d, $^1J_{CF}$ = 247.5 Hz), 160.1 (t, $^3J_{CF}$ = 13.7 Hz), 109.6, 98.6 (d, $^2J_{CF}$ = 28.9 Hz, 2C), 97.2 (t, $^2J_{CF}$ = 25.9 Hz), 79.0, 75.8, 68.6, 64.7, 55.2, 35.0; MS (ESI) m/z 338.1 [(M+Na)$^+$ calcd for C$_{13}$H$_{15}$F$_2$N$_3$NaO$_4^+$ 338.1].

4.6.2. Methyl 5-azido-2-O-benzyl-3,5-dideoxy-6-O-(3,5-difluorophenyl)-L-*lyxo*-hexofuranoside (4a)

Compound **3** (226 mg, 0.717 mmol) was dissolved in DMF (5 mL), and benzyl bromide (0.68 mL, 5.76 mmol, 8 equiv) and Ag$_2$O (332 mg, 1.43 mmol, 2 equiv) were added. The reaction was stirred at room temperature over night. The reaction was quenched with CHCl$_3$ and the solids were filtered off. The filtrate was concentrated under vacuum and the residue was purified by column chromatography (isohexane→isohexane/ethyl acetate 10:1) to yield compound **4a** (136 mg, 0.337 mmol, 47%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40–7.27 (m, 5H), 6.50–6.41 (m, 3H), 4.98 (s, 1H), 4.53 (d, J_{HH} = 5.8 Hz, 2H), 4.55–4.48 (m, 1H), 4.10–4.01 (m, 3H), 3.73–3.67 (m, 1H), 3.41 (s, 3H), 2.11–2.06 (m, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 163.9 (d, $^1J_{CF}$ = 246.7 Hz), 163.7 (d, $^1J_{CF}$ = 246.7 Hz), 160.2 (t, $^3J_{CF}$ = 13.3 Hz), 137.7, 128.7, 128.0, 127.8, 107.3, 98.6 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.2 (t, $^2J_{CF}$ = 25.8 Hz), 82.8, 79.4, 71.6, 68.7, 64.4, 55.2, 32.8; MS (ESI) m/z 428.0 ([M+Na]$^+$ calcd for C$_{20}$H$_{21}$F$_2$N$_3$NaO$_4^+$ 428.1).

4.6.3. Methyl 5-azido-3,5-dideoxy-6-O-(3,5-difluorophenyl)-2-O-ethyl-L-*lyxo*-hexofuranoside (4b)

Compound **3** (248 mg, 0.787 mmol) was dissolved in DMF (5 mL), and ethyl iodide (0.50 mL, 6.29 mmol, 8 equiv) and Ag$_2$O (365 mg, 1.57 mmol, 2 equiv) were added. The reaction was stirred

at room temperature over night. The reaction mixture was quenched with $CHCl_3$ and the solids were filtered off. The filtrate was concentrated under vacuum and the residue was purified by column chromatography (isohexane→isohexane/ethyl acetate 20:1) to yield compound **4b** (92 mg, 0.267 mmol, 34%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.49–6.40 (m, 3H), 4.91 (s, 1H), 4.50–4.43 (m, 1H), 4.10–4.01 (m, 2H), 3.90 (t, J_{HH} = 2.8 Hz, 1H), 3.72–3.66 (m, 1H), 3.58–3.49 (m, 2H), 3.40 (s, 3H), 2.06–2.01 (m, 2H), 1.21 (t, J_{HH} = 7.0 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 163.9 (d, $^1J_{CF}$ = 246.7 Hz), 163.7 (d, $^1J_{CF}$ = 246.7 Hz), 160.2 (t, $^3J_{CF}$ = 13.3 Hz), 107.3, 98.4 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.2 (t, $^2J_{CF}$ = 25.8 Hz), 83.0, 79.3, 68.8, 65.1, 64.5, 55.3, 32.8, 15.5; MS (ESI) m/z 366.0 ([M+Na]$^+$ calcd for $C_{15}H_{19}F_2N_3NaO_4^+$ 366.1).

4.6.4. Methyl 5-azido-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-2-*O*-(2-methoxy-ethoxy)-L-*lyxo*-hexofuranoside (4c)

Compound **3** (161 mg, 0.511 mmol) dissolved in DMF (1 mL) was added to 60% sodium hydride (31 mg, 0.766 mmol, 1.5 equiv) dissolved in DMF (1 mL) at 0 °C. The reaction mixture was stirred for 30 min before 2-bromoethyl methyl ether (0.38 mL, 4.09 mmol, 8 equiv) was added at 0 °C. The reaction was then stirred in room temperature for 3 h and then quenched with methanol, concentrated and purified by column chromatography (isohexane→isohexane/ethyl acetate 20:1) to yield compound **4c** (37 mg, 0.099 mmol, 19%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.50–6.39 (m, 3H), 4.94 (s, 1H), 4.52–4.42 (m, 1H), 4.08–4.01 (m, 2H), 3.97–3.94 (m, 1H), 3.71–3.66 (m, 1H), 3.66–3.62 (m, 2H), 3.40 (s, 3H), 3.38 (s, 3H), 2.13–2.00 (m, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 163.8 (d, $^1J_{CF}$ = 246.7 Hz), 163.7 (d, $^1J_{CF}$ = 246.7 Hz), 160.2 (t, $^3J_{CF}$ = 13.3 Hz), 107.2, 98.6 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.2 (t, $^2J_{CF}$ = 25.8 Hz), 83.6, 79.3, 72.0, 69.0, 68.7, 64.4, 59.3, 55.3; MS (ESI) m/z 396.0 ([M+Na]$^+$ calcd for $C_{16}H_{21}F_2N_3NaO_5^+$ 396.1).

4.6.5. Methyl 2-*O*-allyl-5-azido-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-L-*lyxo*-hexofuranoside (4d)

Compound **3** (279 mg, 0.884 mmol) dissolved in DMF (2 mL) was added to 60% sodium hydride (31 mg, 0.766 mmol, 1.5 equiv) dissolved in DMF (4 mL) at 0 °C. The reaction mixture was stirred for 20 min before allyl bromide (0.61 mL, 7.07 mmol, 8 equiv) was added drop wise at 0 °C. The reaction was stirred in room temperature over night and then quenched with methanol, concentrated and purified by column chromatography (isohexane→isohexane/ethyl acetate 20:1) to yield compound **4d** (155 mg, 0.435 mmol, 49%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.49–6.40 (m, 3H), 5.95–5.82 (m, 1H), 5.33–5,24 (m, 1H), 5.23–5.17 (m, 1H), 4.93 (s, 1H), 4.51–4.43 (m, 1H), 4.08–4.04 (m, 2H), 4.04–4.01 (m, 2H), 3.96 (t, J_{HH} = 2.8 Hz, 1H), 3.72–3.66 (m, 1H), 3.40 (s, 3H), 2.05 (dd, J_{HH} = 7.8, 2.8 Hz, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 163.9 (d, $^1J_{CF}$ = 246.8 Hz), 163.7 (d, $^1J_{CF}$ = 246.8 Hz), 160.0 (t, $^3J_{CF}$ = 13.3 Hz), 134.1, 117.4, 107.2, 98.4 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.1 (t, $^2J_{CF}$ = 25.7 Hz), 82.5, 79.2, 70.4, 68.6, 64.3, 55.1, 32.6; MS (ESI) m/z 378.1 ([M+Na]$^+$ calcd for $C_{16}H_{19}F_2N_3NaO_4^+$ 378.1).

4.6.6. Methyl 5-azido-2-*O*-cyclopropylmethyl-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-L-*lyxo*-hexofuranoside (4e)

Hydroxymethyl-cyclopropane (5.92 mmol, 0.47 mL) was dissolved in pyridine (5 mL) and treated with tosylchloride (2.26 g, 11.84 mmol, 2 equiv) at 0 °C. After 30 min the reaction was quenched with methanol, diluted with DCM and washed with 10% NaCl (aq) (2× 20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. The tosylated alcohol was then used in the alkylating step without further purification. Compound **3** (622 mg, 1.97 mmol) dissolved in DMF (4 mL) was added to 60% sodium hydride (118 mg, 2.96 mmol, 1.5 equiv) dissolved in DMF (2 mL) at 0 °C. The reaction mixture was stirred for 30 min before the tosylated alcohol (5.92 mmol,

3 equiv) dissolved in DMF (4 mL) was added drop wise. The reaction was stirred in room temperature over night and then quenched with methanol, concentrated and purified by column chromatography (toluene/ethyl acetate 10:1) to yield compound **4e** (164 mg, 0.44 mmol, 23%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.48–6.40 (m, 3H), 4.92 (s, 1H), 4.52–4.40 (m, 1H), 4.10–4.00 (m, 2H), 3.74–3.65 (m, 1H), 3.40 (s, 3H), 3.37–3.35 (m, 2H), 3.34–3.30 (m, 1H), 2.07–2.01 (m, 2H), 0.57–0.51 (m, 2H), 0.23–0.17 (m, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 163.9 (d, $^1J_{CF}$ = 246.8 Hz), 163.7 (d, $^1J_{CF}$ = 246.8 Hz), 160.2 (t, $^3J_{CF}$ = 13.7 Hz), 106.8, 98.6 (d, $^2J_{CF}$ = 28.5 Hz, 2C), 97.2 (t, $^2J_{CF}$ = 25.9 Hz), 84.7, 79.2, 68.7, 64.4, 57.1, 55.2, 32.3, 10.8, 3.3, 3.2; MS (ESI) m/z 392.3 ([M+Na]$^+$ calcd for $C_{17}H_{21}F_2N_3NaO_4^+$ 392.1).

4.6.7. 5-Azido-2-*O*-benzyl-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-L-*lyxo*-hexofuranose (5a)

Compound **4a** (136 mg, 0.336 mmol) was dissolved in 1,4-dioxane:0.5 M H_2SO_4 1:1 (14 mL) and heated to reflux. After complete reaction (~1 h according to TLC), the reaction was cooled to room temperature and then neutralized with Na_2CO_3 (aq). The volatile solvents were concentrated under vacuum. The residue was dissolved in DCM and washed with H_2O (×2). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (isohexane→isohexane/ethyl acetate 10:1) to yield compound **5a** (61 mg, 0.157 mmol, 47%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39–7.27 (m, 5H), 6.50–6.41 (m, 3H), 5.39 (d, J_{HH} = 6. Hz, 1H), 4.58 (d, J_{HH} = 7.0 Hz, 2H), 4.55–4.49 (m, 1H), 4.20–4.16 (m, 2H), 4.04–4.01 (m, 1H), 3.83–3.78 (m, 1H), 3.03–3.00 (m, 1H), 2.25–2.09 (m, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 163.9 (d, $^1J_{CF}$ = 246.8 Hz), 163.7 (d, $^1J_{CF}$ = 246.8 Hz), 160.0 (t, $^3J_{CF}$ = 13.3 Hz), 137.7, 128.7, 128.1, 127.8, 100.9, 98.6 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.3 (t, $^2J_{CF}$ = 25.7 Hz), 83.6, 78.8, 71.6, 69.6, 63.4, 32.1; MS (ESI) m/z 414.0 ([M+Na]$^+$ calcd for $C_{19}H_{19}F_2N_3NaO_4^+$ 414.1).

4.6.8. 5-Azido-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-2-*O*-ethyl-L-*lyxo*-hexofuranose (5b)

Compound **5b** (72 mg, 0.219 mmol, 82%) was synthesized from **4b** (92 mg, 0.267 mmol) according to the method for the preparation of **5a**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.50–6.39 (m, 3H), 5.32 (d, J_{HH} = 4.4 Hz, 1H), 4.51–4.44 (m, 1H), 4.19–4.14 (m, 2H), 3.90 (d, J_{HH} = 4.7 Hz, 1H), 3.82–3.77 (m, 1H), 3.57–3.52 (m, 2H), 3.07 (d, J_{HH} = 5.4 Hz, 1H), 2.22–2.05 (m, 2H), 1.20 (t, J_{HH} = 7.0 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 164.0 (d, $^1J_{CF}$ = 246.8 Hz), 162.8 (d, $^1J_{CF}$ = 246.8 Hz), 160.0 (t, $^3J_{CF}$ = 13.3 Hz), 100.9, 98.6 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.3 (t, $^2J_{CF}$ = 25.7 Hz), 83.8, 78.7, 69.5, 65.1, 63.5, 32.1, 15.5; MS (ESI) m/z 352.0 ([M+Na]$^+$ calcd for $C_{14}H_{17}F_2N_3NaO_4^+$ 352.1).

4.6.9. 5-Azido-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-2-*O*-(2-methoxy-ethoxy)-L-*lyxo*-hexofuranose (5c)

Compound **5c** (49 mg, 0.136 mmol, 80%) was synthesized from **4c** (64 mg, 0.170 mmol) according to the method for the preparation of **5a**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.49–6.39 (m, 3H), 5.35 (d, J_{HH} = 5.8 Hz, 1H), 4.52–4.43 (m, 1H), 4.15 (d, J_{HH} = 6.0 Hz, 2H), 3.96–3.93 (m, 1H), 3.82–3.75 (m, 1H), 3.67–3.62 (m, 2H), 3.54–3.50 (m, 2H), 3.39 (s, 1H), 3.37 (s, 3H), 3.26 (d, J_{HH} = 5.8 Hz, 1H) 2.22–2.08 (m, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 163.9 (d, $^1J_{CF}$ = 246.8 Hz), 163.7 (d, $^1J_{CF}$ = 246.8 Hz), 160.0 (t, $^3J_{CF}$ = 13.3 Hz), 100.8, 98.6 (d, $^2J_{CF}$ = 28.6 Hz, 2C), 97.3 (t, $^2J_{CF}$ = 25.7 Hz), 84.5, 78.7, 72.0, 69.5, 69.0, 63.5, 59.2, 32.0; MS (ESI) m/z 382.0 ([M+Na]$^+$ calcd for $C_{15}H_{19}F_2N_3NaO_5^+$ 382.1).

4.6.10. 2-*O*-Allyl-5-azido-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-L-*lyxo*-hexofuranose (5d)

Compound **5d** (82 mg, 0.241 mmol, 55%) was synthesized from **4d** (155 mg, 0.435 mmol) according to the method for the prepara-

tion of **5a**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.51–6.39 (m, 3H), 5.97–5.81 (m, 1H), 5.36–5.32 (m, 1H), 5.32–5.25 (m, 1H), 5.22–5.17 (m, 1H), 4.53–4.45 (m, 1H), 4.17 (d, J_{HH} = 6.2 Hz, 2H), 4.06–4.02 (m, 2H), 3.96 (d, J_{HH} = 4.8 Hz, 1H), 3.15 (d, J_{HH} = 5.8 Hz, 1H), 2.24–2.04 (m, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 163.9 (d, $^1J_{CF}$ = 246.8 Hz), 163.7 (d, $^1J_{CF}$ = 246.8), 160.0 (t, $^3J_{CF}$ = 13.3 Hz), 134.2, 117.6, 100.9, 98.6 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.3 (t, $^2J_{CF}$ = 25.7 Hz), 83.4, 78.7, 70.5, 69.6, 63.5, 32.0; MS (ESI) m/z 364.1 ([M+Na]$^+$ calcd for C$_{15}$H$_{17}$F$_2$N$_3$NaO$_4^+$ 364.1).

4.6.11. 5-Azido-2-*O*-cyclopropylmethyl-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-L-*lyxo*-hexofuranose (5e)

Compound **5e** (47 mg, 0.132 mmol, 67%) was synthesized from **4e** (73 mg, 0.198 mmol) according to the method for the preparation of **5a**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.49–6.41 (m, 3H), 5.33 (br s, 1H), 4.53–4.47 (m, 1H), 4.19–4.16 (m, 2H), 3.95–3.92 (m, 1H), 3.82–3.77 (m, 1H), 3.38–3.31 (m, 2H), 2.24–2.05 (m, 2H), 1.30–1.22 (m, 1H), 1.14–0.98 (m, 1H), 0.63–0.51 (m, 2H), 0.26–0.18 (m, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 163.9 (d, $^1J_{CF}$ = 246.7 Hz), 163.7 (d, $^1J_{CF}$ = 246.7 Hz), 160.0 (t, $^3J_{CF}$ = 13.6 Hz), 101.0, 98.6 (d, $^2J_{CF}$ = 28.4 Hz, 2C), 97.3 (t, $^2J_{CF}$ = 25.8 Hz), 83.7, 78.7, 74.5, 69.6, 63.5, 32.1, 10.8, 3.4, 3.3; MS (ESI) m/z 378.1 ([M+Na]$^+$ calcd for C$_{16}$H$_{19}$F$_2$N$_3$NaO$_4^+$ 378.1).

4.6.12. 5-Azido-2-*O*-benzyl-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-L-*lyxo*-1,4-lactone (6a)

Compound **5a** (61 mg, 0.157 mmol) was dissolved in DCM (5 mL). At 0 °C pyridinium dichromate (88 mg, 0.235 mmol, 1.5 equiv) and 4 Å molecular sieves powder were added. The reaction was stirred over night in room temperature. The solids were filtered off and the filtrate was concentrated under vacuum, the residue was purified by column chromatography (isohexane→isohexane/ethyl acetate 15:1) to yield compound **6a** (59 mg, 0.150 mmol, 96%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41–7.30 (m, 5H), 6.52–6.40 (m, 3H), 4.96 (d, 1H, J_{HH} = 11.6 Hz), 4.82–4-76 (m, 1H), 4.70 (d, 1H, J_{HH} = 11.6 Hz), 4.36 (dd, J_{HH} = 5.7, 8.3 Hz), 4.22 (d, J_{HH} = 6.3 Hz, 2H), 3.92–3.87 (m, 1H), 2.53–2.35 (m, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 173.8, 163.9 (d, $^1J_{CF}$ = 247.3 Hz) 163.7 (d, $^1J_{CF}$ = 247.3 Hz), 159.5 (t, $^3J_{CF}$ = 13.3 Hz), 136.8, 128.7, 128.2, 98.5 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.5 (t, $^2J_{CF}$ = 25.7 Hz), 75.9, 72.6, 72.4, 68.5, 62.7, 32.7; MS (ESI) m/z 412.0 ([M+Na]$^+$ calcd for C$_{19}$H$_{17}$F$_2$N$_3$NaO$_4^+$ 412.1).

4.6.13. 5-Azido-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-2-*O*-ethyl-L-*lyxo*-1,4-lactone (6b)

Compound **6b** (49 mg, 0.150 mmol, 68%) was synthesized from **5b** (72 mg, 0.219 mmol) according to the method for the preparation of **6a**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.50–6.41 (m, 3H), 4.81–4.73 (m, 1H), 4.27 (dd, J_{HH} = 5.8, 8.2 Hz, 1H), 4.22 (d, J_{HH} = 6.4 Hz, 2H), 3.98–3.88 (m, 2H), 3.68–3.59 (m, 1H), 2.55–2.47 (m, 1H), 2.40–2.30 (m, 1H), 1.23 (t, J_{HH} = 7.0 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 174.0, 163.9 (d, $^1J_{CF}$ = 247.3 Hz), 163.7 (d, $^1J_{CF}$ = 247.3 Hz), 159.7 (t, $^3J_{CF}$ = 13.3 Hz), 98.6 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.6 (t, $^2J_{CF}$ = 25.7 Hz), 75.9, 73.3, 68.6, 66.6, 62.8, 32.7, 15.2; MS (ESI) m/z nd ([M+Na]$^+$ calcd for C$_{14}$H$_{15}$F$_2$N$_3$NaO$_4^+$ 350.1).

4.6.14. 5-Azido-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-2-*O*-(2-methoxy-ethoxy)-L-*lyxo*-1,4-lactone (6c)

Compound **6c** (40 mg, 0.111 mmol, 81%) was synthesized from **5c** (49 mg, 0.136 mmol) according to the method for the preparation of **6a**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.51–6.40 (m, 3H), 4.81–4.74 (m, 1H), 4.35 (dd, J_{HH} = 6.0, 8.5 Hz, 1H), 4.21 (d, J_{HH} = 6.4 Hz, 2H), 4.12–4.06 (m, 1H), 3.94–3.88 (m, 1H), 3.81–3.74 (m, 1H), 3.59–3.54 (m, 1H), 3.38 (s, 3H), 2.58–2.39 (m, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 173.9, 163.9 (d, $^1J_{CF}$ = 247.3 Hz), 163.7 (d, $^1J_{CF}$ = 247.3 Hz), 159.7 (t, $^3J_{CF}$ = 14.0 Hz), 98.6 (d, $^2J_{CF}$ = 29.5 Hz,

2C), 97.6 (t, $^2J_{CF}$ = 25.7 Hz), 75.8, 73.8, 71.8, 70.1, 68.6, 62.8, 59.2, 32.6; MS (ESI) m/z 358.0 ([M+H]$^+$ calcd for C$_{15}$H$_{18}$F$_2$N$_3$O$_5^+$ 358.1).

4.6.15. 2-*O*-Allyl-5-azido-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-L-*lyxo*-1,4-lactone (6d)

Compound **6d** (31 mg, 0.092 mmol, 38%) was synthesized from **5d** (82 mg, 0.241 mmol) according to the method for the preparation of **6a**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.52–6.41 (m, 3H), 5.97–5.85 (m, 1H), 5.38–5.24 (m, 2H), 4.82–4.77 (m, 1H), 4.44–4.37 (m, 1H), 4.34 (dd, J_{HH} = 5.8, 8.2 Hz 1H), 4.23 (d, J_{HH} = 6.3 Hz, 2H), 4.22–4.16 (m, 1H), 3.94–3.89 (m, 1H), 2.57–2.48 (m, 1H), 2.44–2.35 (m, 1H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 173.9, 163.9 (d, $^1J_{CF}$ = 247.1 Hz), 162.7 (d, $^1J_{CF}$ = 247.1 Hz), 159.7 (t, $^3J_{CF}$ = 13.7 Hz), 133.6, 118.6, 98.7 (d, $^2J_{CF}$ = 28.4 Hz, 2C), 97.7 (t, $^2J_{CF}$ = 25.8 Hz), 75.8, 72.4, 71.6, 68.6, 62.8, 32.7; MS (ESI) m/z 362.1 ([M+Na]$^+$ calcd for C$_{15}$H$_{15}$F$_2$N$_3$NaO$_4^+$ 362.1).

4.6.16. 5-Azido-2-*O*-cyclopropylmethyl-3,5-dideoxy-6-*O*-(3,5-difluorophenyl)-L-*lyxo*-1,4-lactone (6e)

Compound **6e** (39 mg, 0.110 mmol, 83%) was synthesized from **5e** (47 mg, 0.132 mmol) according to the method for the preparation of **6a**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.53–6.41 (m, 3H), 4.82–4.77 (m, 1H), 4.33 (dd, J_{HH} = 5.8, 8.2 Hz, 1H), 4.22 (d, J_{HH} = 6.3 Hz, 2H), 3.95–3.89 (m, 1H), 3.71 (dd, J_{HH} = 7.2, 10.0 Hz, 1H), 3.49 (dd, J_{HH} = 6.9, 10.2 Hz, 1H), 2.57–2.49 (m, 1H), 2.45–2.36 (m, 1H), 1.14–1.03 (m, 1H), 0.62–0.51 (m, 2H), 0.30–0.21 (m, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 174.0, 163.9 (d, $^1J_{CF}$ = 247.2 Hz), 163.7 (d, $^1J_{CF}$ = 247.2 Hz), 159.7 (t, $^3J_{CF}$ = 13.7 Hz), 98.6 (d, $^2J_{CF}$ = 28.8 Hz, 2C), 97.7 (t, $^2J_{CF}$ = 25.8 Hz), 75.9, 75.7, 73.0, 68.6, 62.8, 32.8, 10.6, 3.4, 3.1; MS (ESI) m/z 376.1 ([M+Na]$^+$ calcd for C$_{16}$H$_{17}$F$_2$N$_3$NaO$_4^+$ 376.1).

4.6.17. 5-Azido-2-benzyloxy-6-(3,5-difluoro-phenoxy)-4-hydroxy-hexanoid acid (1-benzylcarbamoyl-2-methyl-propyl)-amide (7a)

Compound **6a** (43 mg, 0.111 mmol) and (*S*)-2-amino-*N*-benzyl-3-methyl-butyramide (69 mg, 0.333 mmol, 3 equiv) were dissolved in diisopropyl ethyl amine (5 mL). 2-Hydroxy-pyridine (21 mg, 0.222, 2 equiv) was added and the mixture was heated to 70 °C over night, if needed a few drops of DMF was added for solubility. The reaction mixture was concentrated and the residue was purified by column chromatography (isohexane/ethyl acetate 10:1) to give compound **7a** (46 mg, 0.078 mmol, 70%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41–7.20 (m, 10H), 7.10 (d, J_{HH} = 8.8 Hz, 1H), 6.87 (t, J_{HH} = 5.6 Hz, 1H), 6.50–6.35 (m, 3H), 4.64 (d, J_{HH} = 11.6 Hz, 1H), 4.59 (d, J_{HH} = 11.6 Hz, 1H) 4.41 (d, J_{HH} = 5.6 Hz, 2H), 4.31 (dd, J_{HH} = 5.2, 8.8 Hz, 1H), 4.14–4.08 (m, 1H), 4.03–3.98 (dd, J_{HH} = 4.2, 9.8 Hz, 1H), 3.97–3.90 (m, 2H), 3.64–3.55 (m, 1H), 2.55 (d, J_{HH} = 7.6 Hz, 1H), 2.47–2.35 (m, 1H), 2.25–2.13 (m, 1H), 1.94–1.85 (m, 1H), 0.96 (d, J_{HH} = 6.9 Hz, 3H), 0.91 (d, J_{HH} = 6.9 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 172.6, 170.8, 163.9 (d, $^1J_{CF}$ = 246.8 Hz), 163.7 (d, $^1J_{CF}$ = 246.8 Hz), 160.1 (t, $^3J_{CF}$ = 13.6 Hz), 138.2, 136.6, 129.0, 128.9, 128.8, 128.1, 128.0, 127.7, 98.7 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.3 (t, $^2J_{CF}$ = 25.8 Hz), 77.0, 73.1, 68.9, 67.3, 64.7, 58.3, 43.8, 36.0, 29.9, 19.8, 17.6; MS (ESI) m/z 618.1 ([M+Na]$^+$ calcd for C$_{31}$H$_{35}$F$_2$N$_5$NaO$_5^+$ 618.3).

4.6.18. 5-Azido-6-(3,5-difluoro-phenoxy)-2-etoxy-4-hydroxy-hexanoid acid (1-benzylcarbamoyl-2-methyl-propyl)-amide (7b)

Compound **7b** (67 mg, 0.126 mmol, 84%) was synthesized from **6b** (49 mg, 0.150 mmol) according to the method for the preparation of **7a**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32–7.18 (m, 5H), 7.17–7.06 (m, 2H), 6.47–6.35 (m, 3H), 4.40 (t, J_{HH} = 5.1 Hz, 2H), 4.31 (dd, J_{HH} = 5.4, 9.1 Hz, 1H), 4.05 (dd, J_{HH} = 4.0, 9.6 Hz, 1H), 3.98–

3.90 (m, 3H), 3.66–3.52 (m, 3H), 3.04 (br s, 1H), 2.41–2.30 (m, 1H), 2.15–2.04 (m, 1H), 1.91–1.83 (m, 1H), 1.23 (t, J_{HH} = 7.0 Hz, 3H), 0.96 (d, J_{HH} = 6.8 Hz, 3H), 0.92 (d, J_{HH} = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 172.8, 171.0, 163.8 (d, $^1J_{CF}$ = 246.7 Hz), 163.7 (d, $^1J_{CF}$ = 246.7 Hz), 160.1 (t, $^3J_{CF}$ = 13.7 Hz), 138.3, 128.8, 127.9, 127.6, 98.6 (d, $^2J_{CF}$ = 29.1 Hz, 2C), 97.1 (t, $^2J_{CF}$ = 25.7 Hz), 77.9, 68.9, 67.6, 66.8, 64.7, 58.1, 43.6, 36.2, 30.1, 19.7, 17.6, 15.5; MS (ESI) m/z 556.1 ([M+Na]$^+$ calcd for C$_{26}$H$_{33}$F$_2$N$_5$NaO$_5$$^+$ 556.2).

4.6.19. 5-Azido-6-(3,5-difluoro-phenoxy)-4-hydroxy-2-(2-methoxy-etoxy)-hexanoid acid (1-benzylcarbamoyl-2-methyl-propyl)-amide (7c)

Compound **7c** (54 mg, 0.096 mmol, 87%) was synthesized from **6c** (40 mg, 0.110 mmol) according to the method for the preparation of **7a**.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 (d, J_{HH} = 8.8 Hz, 1H), 7.35–7.20 (m, 5H), 7.00 (t, J_{HH} = 5.6 Hz, 1H), 6.49–6.37 (m, 3H), 4.41 (dd, J_{HH} = 3.5, 5.8 Hz, 2H), 4.29 (dd, J_{HH} = 5.9, 8.6 Hz, 1H), 4.06 (dd, J_{HH} = 4.0, 9.7 Hz, 1H), 4.01–3.93 (m, 3H), 3.76–3.61 (m, 3H), 3.59–3.48 (m, 2H), 3.38 (s, 3H), 3.05 (d, J_{HH} = 6.8 Hz, 1H), 2.41–2.29 (m, 1H), 2.17–2.06 (m, 1H), 1.96–1.87 (m, 1H), 0.98 (d, J_{HH} = 6.8 Hz, 3H), 0.95 (d, J_{HH} = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 172.7, 171.0, 163.8 (d, $^1J_{CF}$ = 246.6 Hz), 163.7 (d, $^1J_{CF}$ = 246.6 Hz), 160.2, (t, $^3J_{CF}$ = 13.6 Hz), 138.4, 128.8, 127.9, 127.6, 98.6 (d, $^2J_{CF}$ = 29.1 Hz, 2C), 97.1 (t, $^2J_{CF}$ = 25.7 Hz), 78.6, 71.5, 70.7, 69.0, 68.0, 64.7, 59.1, 58.7, 43.6, 36.6, 30.0, 19.6, 17.6; MS (ESI) m/z 586.0 ([M+Na]$^+$ calcd for C$_{27}$H$_{35}$F$_2$N$_5$NaO$_6$$^+$ 586.2).

4.6.20. 2-Allyloxy-5-azido-6-(3,5-difluoro-phenoxy)-4-hydroxy-hexanoid acid (1-benzylcarbamoyl-2-methyl-propyl)-amide (7d)

Compound **7d** (39 mg, 0.071 mmol, 77%) was synthesized from **6d** (31 mg, 0.092 mmol) according to the method for the preparation of **7a**.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35–7.22 (m, 5H), 7.10 (d, J_{HH} = 8.8 Hz, 1H), 7.02 (t, J_{HH} = 5.4 Hz, 1H), 6.50–6.39 (m, 3H), 5.97–5.86 (m, 1H), 5.38–5.26 (m, 2H), 4.42 (d, J_{HH} = 5.5 Hz, 2H), 4.32 (dd, J_{HH} = 5.3 Hz, 1H), 4.13–4.02 (m, 4H), 3.97 (t, J_{HH} = 8.8 Hz, 2H), 3.70–3.63 (m, 1H), 2.82 (d, J_{HH} = 7.3 Hz, 1H), 2.45–2.37 (m, 1H), 2.22–2.14 (m, 1H), 1.96–1.88 (m, 1H), 0.98 (d, J_{HH} = 6.8 Hz, 3H), 0.94 (d, J_{HH} = 6.8 Hz, 3H); ^{13}C NMR (125.5 MHz, CDCl$_3$) δ 172.6, 170.9, 163.9 (d, $^1J_{CF}$ = 246.9 Hz), 163.8 (d, $^1J_{CF}$ = 246.9 Hz), 160.1 (t, $^3J_{CF}$ = 13.7 Hz), 138.3, 133.2, 128.8, 127.9, 127.6, 118.8, 98.7 (d, $^2J_{CF}$ = 28.9 Hz, 2C), 97.2 (t, $^2J_{CF}$ = 25.8 Hz), 77.1, 71.8, 69.0, 67.5, 64.8, 58.3, 43.7, 36.2, 30.0, 19.8, 17.6; MS (ESI) m/z 568.3 ([M+Na]$^+$ calcd for C$_{27}$H$_{33}$F$_2$N$_5$NaO$_5$$^+$ 568.2).

4.6.21. 5-Azido-2-cyclopropylmethoxy-6-(3,5-difluoro-phenoxy)-4-hydroxy-hexanoid acid (1-benzylcarbamoyl-2-methyl-propyl)-amide (7e)

Compound **7e** (60 mg, 0.107 mmol, 97%) was synthesized from **6e** (39 mg, 0.110 mmol) according to the method for the preparation of **7a**. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36–7.20 (m, 5H), 7.15 (d, J_{HH} = 8.8 Hz, 1H), 6.96 (t, J_{HH} = 5.5 Hz, 1H), 6.51–6.37 (m, 3H), 4.42 (d, J_{HH} = 5.7 Hz, 2H), 4.33–4.26 (m, 1H), 4.09–3.93 (m, 4H), 3.69–3.62 (m, 1H), 3.40 (d, J_{HH} = 6.9 Hz, 2H), 2.85 (d, J_{HH} = 6.9 Hz, 1H), 2.45–2.34 (m, 1H), 2.20–2.10 (m 1H), 1.95–1.87 (m, 1H), 1.13–1.04 (m, 1H), 0.98 (d, J_{HH} = 6.9 Hz, 3H), 0.94 (d, J_{HH} = 6.9 Hz, 3H), 0.64–0.57 (m, 2H), 0.27–0.21 (m, 2H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 172.8, 170.9, 163.9 (d, $^1J_{CF}$ = 246.8 Hz), 163.7 (d, $^1J_{CF}$ = 246.8 Hz), 160.1 (t, $^3J_{CF}$ = 13.7 Hz), 138.3, 128.8, 127.9, 127.6, 98.6 (d, $^2J_{CF}$ = 28.4 Hz, 2C), 97.2 (d, $^2J_{CF}$ = 25.7 Hz), 77.8, 75.4, 68.9, 67.9, 64.7, 58.3, 43.7, 36.2, 30.0, 19.7, 17.7, 10.8, 3.4, 3.3; MS (ESI) m/z 582.2 ([M+Na]$^+$ calcd for C$_{28}$H$_{35}$F$_2$N$_5$NaO$_5$$^+$ 582.3).

4.6.22. N-[(1S,2S,4R)-4-((S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-4-benzyl-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-butyl]-5-(methanesulfonyl-methyl-amino)-N′-((R)-1-phenyl-ethyl)-isophthalamide (2a)

Azide **7a** (46 mg, 0.078 mmol) and triphenyl phosphine (31 mg, 0.012 mmol, 1.5 equiv) were dissolved in MeOH (5 mL) and four drops of water were added. The reaction was stirred at room temperature over night and then concentrated under vacuum. Without further purification the formed amine was used in the next step. 5-(Methanesulfonyl-methyl-amino)-N′-(1-phenyl-ethyl)-isophthalacid (29 mg, 0.078 mmol, 1 equiv), Py-BOP (40 mg, 0.078 mmol, 1 equiv) and DIPEA (14 µL, 0.078 mmol, 1 equiv) were dissolved in DCM (2.5 mL). The mixture was stirred at room temperature for 30 min before the amine (~1 equiv) from the previous reaction dissolved in DCM (4 mL) and DIPEA (14 µL, 0.078 mmol, 1 equiv) were added. After complete reaction the mixture were washed with NaHCO$_3$ (1× 10 mL) and brine (1× 10 mL). The water phase was extracted with DCM (2× 10 mL). The organic layers were combined and dried over Na$_2$SO$_4$, concentrated under vacuum and purified by column chromatography (isohexane/ethyl acetate 1:1) to give compound **2a** (46 mg, 0.050 mmol, 64%). $[\alpha]_D^{20}$ − 19.7 (c 1.2, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.15 (t, J_{HH} = 1.4 Hz, 1H), 7.95–7.91 (m, 2H), 7.41–7.08 (m, 19H), 6.50–6.37 (m, 3H), 5.28–5.18 (m, 1H), 4.59 (d, J_{HH} = 2.4 Hz, 2H), 4.41–4.27 (m, 2H), 4.23 (dd, J_{HH} = 5.6, 8.8 Hz, 2H), 4.16 (dd, J_{HH} = 5.4, 14.6 Hz, 1H), 4.08–3.95 (m, 3H), 3.27 (s, 3H), 2.80 (s, 3H), 2.33–2.21 (m, 1H), 2.20–2.08 (m, 2H), 1.98–1.89 (m, 1H), 1.55 (d, J_{HH} = 6.9 Hz, 3H), 0.91 (d, J_{HH} = 6.8 Hz, 3H), 0.84 (d, J_{HH} = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 173.2, 171.0, 166.5, 165.0, 163.9 (d, $^1J_{CF}$ = 246.4 Hz), 163.7 (d, $^1J_{CF}$ = 246.4 Hz), 160.4 (t, $^3J_{CF}$ = 13.7 Hz), 143.1, 142.2, 138.2, 136.7, 136.0, 135.6, 129.0, 128.8, 128.7, 128.7, 128.1, 127.9, 127.6, 127.5, 126.4, 124.5, 98.7 (d, $^2J_{CF}$ = 28.8 Hz, 2C), 96.9 (t, $^2J_{CF}$ = 25.9 Hz), 77.0, 72.9, 67.3, 66.3, 58.3, 53.6, 50.0, 43.6, 36.0, 35.6, 30.2, 21.8, 19.7, 17.7; HRMS (ESI) m/z 950.3541 ([M+Na]$^+$ calcd for C$_{49}$H$_{55}$F$_2$N$_5$NaO$_9$S$^+$ 950.3581). LC–MS purity system A: t_R = 5.19 min, 99%; system B: t_R = 4.87 min, 100%.

4.6.23. N-[(1S,2S,4R)-4-((S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-(3,5-difluoro-phenoxymethyl)-4-ethyl-2-hydroxy-butyl]-5-(methanesulfonyl-methyl-amino)-N′-((R)-1-phenyl-ethyl)-isophthalamide (2b)

Compound **2b** (36 mg, 0.04 mmol, 67%) was synthesized from **7b** (67 mg, 0.13 mmol) that was reduced and then coupled to 5-(methanesulfonyl-methyl-amino)-N′-(1-phenyl-ethyl)-isophthalacid (24 mg, 0.06 mmol), according to the method for the preparation of **2a**. $[\alpha]_D^{20}$ − 19.8 (c 1.1, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.15 (t, J_{HH} = 1.5 Hz, 1H), 7.96–7.93 (m, 2H), 7.35–7.09 (m, 14H), 7.04 (d, J_{HH} = 7.7 Hz, 1H), 6.51–6.37 (m, 3H), 5.29–5.20 (m, 1H), 4.42–4.31 (m, 2H), 4.28–4.17 (m, 3H), 4.07–4.02 (m, 2H), 3.92 (t, J_{HH} = 5.1 Hz, 1H), 3.65–3.54 (m, 2H), 3.30 (s, 3H), 2.82 (s, 3H), 2.33–2.23 (m, 1H), 2.17–2.08 (m, 1H), 1.97–1.89 (m, 1H), 1.58 (d, J_{HH} = 7.0 Hz, 3H), 1.27 (t, J_{HH} = 7.0 Hz, 3H), 0.94 (d, J_{HH} = 6.8 Hz, 3H), 0.90 (d, J_{HH} = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 173.4, 171.0, 166.4, 164.9, 163.9 (d, $^1J_{CF}$ = 246.4 Hz), 163.7 (d, $^1J_{CF}$ = 246.4 Hz), 160.4 (t, $^3J_{CF}$ = 13.7 Hz), 143.0, 142.3, 138.2, 136.0, 135.6, 128.9, 128.7, 128.0, 127.9, 127.7, 127.6, 126.4, 124.5, 98.7 (d, $^2J_{CF}$ = 28.6 Hz, 2C), 96.9 (t, $^2J_{CF}$ = 25.9 Hz), 77.9, 67.2, 66.7, 66.5, 58.3, 53.6, 50.0, 43.6, 38.1, 36.1, 35.6, 30.3, 21.9, 19.7, 17.8, 15.6; HRMS (ESI) m/z 888.3396 ([M+Na]$^+$ calcd for C$_{44}$H$_{53}$F$_2$N$_5$NaO$_9$S$^+$ 888.3424). LC–MS purity system A: t_R = 4.89 min, 97%; system B: t_R = 4.59 min, 99%.

4.6.24. N-[(1S,2S,4R)-4-((S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-4-(2-methoxy-ethoxy)-butyl]-5-(methanesulfonyl-methyl-amino)-N′-((R)-1-phenyl-ethyl)-isophthalamide (2c)

Compound **2c** (42 mg, 0.05 mmol, 97%) was synthesized from **7c** (54 mg, 0.10 mmol) that was reduced and then coupled to

5-(methanesulfonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isoph-thalacid (18 mg, 0.05 mmol), according to the method for the prep-aration of **2a**. $[\alpha]_D^{20} - 14.7$ (c 1.3, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.16 (t, J_{HH} = 1.4 Hz, 1H), 7.96–7.93 (m, 2H), 7.53 (d, J_{HH} = 8.6 Hz, 1H), 7.37–7.09 (m, 14H), 6.50–6.37 (m, 3H), 5.31–5.21 (m, 1H), 4.43–4.32 (m, 2H), 4.29–4.17 (m, 3H), 4.07–4.02 (m, 2H), 3.95 (t, J_{HH} = 5.2 Hz, 1H), 3.76–3.70 (m, 1H), 3.68–3.49 (m, 3H), 3.37 (s, 3H), 3.30 (s, 3H), 2.82 (s, 3H), 2.30–2.19 (m, 1H), 2.16–2.05 (m, 1H), 1.98–1.89 (m, 1H), 1.58 (d, J_{HH} = 7.0 Hz, 3H), 0.94 (d, J_{HH} = 6.9 Hz, 3H), 0.92 (d, J_{HH} = 6.9 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 173.4, 171.1, 166.5, 165.0, 163.9 (d, $^1J_{CF}$ = 246.3 Hz), 163.7 (d, $^1J_{CF}$ = 246.3 Hz), 160.5 (t, $^3J_{CF}$ = 13.7 Hz), 143.1, 142.3, 138.2, 136.0, 135.7, 128.9, 128.7, 128.0, 128.0, 127.9, 127.6, 127.5, 126.4, 124.5, 98.7 (d, $^2J_{CF}$ = 28.6 Hz, 2C), 96.8 (t, $^2J_{CF}$ = 25.9 Hz), 78.4, 77.4, 71.5, 70.6, 67.3, 66.7, 59.1, 58.8, 53.6, 50.0, 43.6, 38.1, 36.6, 35.7, 30.2, 21.8, 19.5, 17.7; HRMS (ESI) m/z 918.3523 ([M+Na]$^+$ calcd for C$_{45}$H$_{55}$F$_2$N$_5$NaO$_9$S$^+$ 918.3530). LC–MS purity system A: t_R = 4.80 min, 95%; system B: t_R = 4.51 min, 96%.

4.6.25. N-[(1S,2S,4R)-4-((S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-4-allyloxy-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-butyl]-5-(methanesulfonyl-methyl-amino)-N'-((R)-1-phenyl-ethyl)-isophthalamide (2d)

Compound **2d** (18 mg, 0.02 mmol, 58%) was synthesized from **7d** (19 mg, 0.04 mmol) that was reduced and then coupled to 5-(methanesulfonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthal-acid (13 mg, 0.04 mmol), according to the method for the prepara-tion of **2a**. $[\alpha]_D^{20} + 5.4$ (c 1.3, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.16–8.15 (m, 1H), 7.94–7.92 (m, 2H), 7.66–7.59 (m, 1H), 7.58–7.51 (m, 1H), 7.48–7.41 (m, 1H), 7.34–7.05 (m, 12H), 6.48–6.37 (m, 3H), 5.95–5.84 (m, 1H), 5.34–5.19 (m, 3H), 4.39–4.30 (m, 2H), 4.30–4.16 (m, 3H), 4.10–3.97 (m, 5H), 3.27 (s, 3H), 2.81 (s, 3H), 2.33–2.21 (m, 1H), 2.20–2.06 (m, 1H), 1.97–1.90 (m, 1H), 1.56 (d, J_{HH} = 7.0 Hz, 3H), 0.94 (d, J_{HH} = 6.8 Hz, 3H), 0.89 (d, J_{HH} = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 173.3, 171.0, 166.5, 165.0, 163.9 (d, $^1J_{CF}$ = 246.5 Hz), 163.7 (d, $^1J_{CF}$ = 246.5 Hz), 160.4 (t, $^3J_{CF}$ = 13.7 Hz), 143.1, 142.3, 138.2, 136.0, 135.6, 133.3, 132.3, 132.2, 128.8, 128.8, 128.7, 128.6, 128.1, 128.1, 127.9, 127.6, 127.6, 126.4, 124.5, 118.7, 98.7 (d, $^2J_{CF}$ = 28.2 Hz, 2C), 96.9 (t, $^2J_{CF}$ = 25.9 Hz) 77.0, 71.7, 67.2, 66.2, 58.3, 53.6, 50.0, 43.6, 38.1, 36.0, 35.7, 30.2, 21.9, 19.7, 17.7; HRMS (ESI) m/z 878.3580 ([M+H]$^+$ calcd for C$_{45}$H$_{54}$F$_2$N$_5$O$_9$S$^+$ 878.3605). LC–MS purity system A: t_R = 5.00 min, 99%; system B: t_R = 4.69 min, 99%.

4.6.26. N-[(1S,2S,4R)-4-((S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-4-propyloxy-butyl]-5-(methanesulfonyl-methyl-amino)-N'-((R)-1-phenyl-ethyl)-isophthalamide (2e)

Azide **7d** (18 mg, 0.034 mmol) was dissolved in MeOH (4 mL) and a catalytical amount of Pd on carbon was added, the mixture was then treated with hydrogen gas (1 atm) for 2 h. Then the solids were filtered off and the filtrate was concentrated under vacuum. Without further purification the formed amine was used in the next step. 5-(Methanesulfonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthal-acid (13 mg, 0.034 mmol, 1 equiv), Py-BOP (18 mg, 0.034 mmol, 1 equiv) and DIPEA (6 μL, 0.034 mmol, 1 equiv) were dissolved in DCM (2 mL). The mixture was stirred at room temperature for 30 min before the amine (~1 equiv) from the previous reaction dis-solved in DCM (2 mL) and DIPEA (6 μL, 0.034 mmol, 1 equiv) were added. After complete reaction the mixture were washed with NaH-CO$_3$ (1× 10 mL) and brine (1× 10 mL). The water phase was ex-tracted with DCM (2× 10 mL). The organic layers were combined and dried over Na$_2$SO$_4$, concentrated under vacuum and purified by column chromatography (toluene/ethyl acetate 1:1) to give com-pound **2e** (26 mg, 0.030 mmol, 88%). $[\alpha]_D^{20} + 6.0$ (c 0.8, CHCl$_3$); ^{1}H

NMR (400 MHz, CDCl$_3$) δ 8.14–8.12 (m, 1H), 7.96–7.90 (m, 2H), 7.40–7.06 (m, 13H), 6.48–6.38 (m, 3H), 5.28–5.20 (m, 1H), 4.40–4.30 (m, 2H), 4.28–4.16 (m, 3H), 4.08–3.98 (m, 2H), 3.90 (t, J_{HH} = 5.0 Hz, 1H), 3.82–3.74 (m, 1H), 3.56–3.43 (m, 2H), 3.28 (s, 3H), 2.81 (s, 3H), 2.32–2.22 (m, 1H), 2.16–2.04 (m, 2H), 1.98–1.90 (m, 1H), 1.69–1.59 (m, 2H), 1.57 (d, J_{HH} = 6.9 Hz, 3H), 1.00–0.87 (m, 9H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 173.3, 171.0, 166.5, 165.1, 163.9 (d, $^1J_{CF}$ = 246.5 Hz), 163.7 (d, $^1J_{CF}$ = 246.5 Hz), 160.4 (t, $^3J_{CF}$ = 13.8 Hz), 143.1, 142.3, 138.2, 136.0, 135.6, 128.9, 128.7, 128.0, 127.9, 127.9, 127.6, 127.6, 126.5, 126.4, 124.4, 98.7 (d, $^2J_{CF}$ = 28.2 Hz, 2C), 96.9 (t, $^2J_{CF}$ = 25.9 Hz), 78.0, 72.8, 67.2, 66.5, 58.2, 53.6, 50.0, 43.6, 38.0, 36.0, 35.7, 30.4, 29.8, 23.2, 21.8, 19.7, 17.7, 10.8; HRMS (ESI) m/z 880.3749 ([M+H]$^+$ calcd for C$_{45}$H$_{56}$F$_2$N$_5$O$_9$S$^+$ 880.3761). LC–MS purity system A: t_R = 5.10 min, 99%; system B: t_R = 4.79 min, 99%.

4.6.27. N-[(1S,2S,4R)-4-((S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-4-cyclopropylmethoxy-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-butyl]-5-(methanesulfonyl-methyl-amino)-N'-((R)-1-phenyl-ethyl)-isophthalamide (2f)

Compound **2f** (27 mg, 0.03 mmol, 43%) was synthesized from **7e** (39 mg, 0.07 mmol) that was reduced and then coupled to 5-(methanesulfonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthal-acid (34 mg, 0.09 mmol), according to the method for the prepara-tion of **2a**. $[\alpha]_D^{20} - 13.6$ (c 1.0, MeOH); ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.93 (d, J_{HH} = 7.8 Hz, 1H), 8.60 (t, J_{HH} = 6.0 Hz, 1H), 8.36 (d, J_{HH} = 8.7 Hz, 1H), 8.30–8.28 (t, J_{HH} = 1.5 Hz, 1H), 8.10–8.07 (m, 1H), 8.05–8.03 (m, 1H), 7.71 (d, J_{HH} = 8.7 Hz, 1H), 7.43–7.13 (m, 10H), 6.66–6.47 (m, 3H), 5.30–5.20 (m, 3H), 4.64–4.54 (m, 1H), 4.37–4.32 (m, 2H), 4.31–4.11 (m, 5H), 3.43–3.30 (m, 1H), 3.36 (s, 3H), 2.95 (s, 3H), 2.13–2.01 (m, 1H), 2.01–1.91 (m, 3H), 1.58 (d, J_{HH} = 7.0 Hz, 3H), 1.16–0.98 (m, 1H), 0.91 (d, J_{HH} = 6.9 Hz, 3H), 0.87 (d, J_{HH} = 6.9 Hz, 3H) 0.58–0.47 (m, 2H), 0.28–0.18 (m, 2H); ^{13}C NMR (100.5 MHz, MeOD-d_4) δ 175.2, 173.2, 169.1, 167.7, 165.3 (d, $^1J_{CF}$ = 245.1 Hz), 165.1 (d, $^1J_{CF}$ = 245.1 Hz), 162.2 (t, $^3J_{CF}$ = 13.8 Hz), 145.1, 143.8, 139.7, 137.4, 136.9, 129.6, 129.5, 129.4, 128.6, 128.3, 128.2, 127.3, 126.0, 99.6 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.2 (t, $^2J_{CF}$ = 26.4 Hz), 78.3, 76.4, 68.6, 67.7, 59.8, 53.7, 51.0, 44.1, 38.4, 38.2, 35.9, 32.1, 22.2, 19.8, 18.6, 11.5, 3.8, 3.4; HRMS (ESI) m/z 892.3778 ([M+H]$^+$ calcd for C$_{46}$H$_{56}$F$_2$N$_5$O$_9$S$^+$ 892.3761). LC–MS purity system A: t_R = 5.23 min, 100%; system B: t_R = 4.82 min, 100%.

4.6.28. (2R,4S,5S)-5-Azido-6-(3,5-difluorophenoxy)-4-hydroxy-2-methoxy-hexanoic acid ((S)-1-benzylcarbamoyl-2-methyl-propyl)-amide (8)

Compound **8** was synthesized according to a protocol previ-ously reported by our group.[11]

4.6.29. N-[(1S,4R)-4-((S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-(3,5-difluoro-phenoxymethyl)-4-methoxy-butyl]-5-(methanesulfonyl-methyl-amino)-N'-((R)-1-phenyl-ethyl)-isophthalamide (2g)

A solution of **8** (54 mg, 0.104 mmol) in dry dichloroethane (5 mL) was refluxed. 1,1'-Thiocarbonyldiimidazole (32 mg, 0.177 mmol, 1.7 equiv) was added to the solution and the refluxing was continued for 2 h. The solvent was concentrated under vac-uum. Without further purification the formed thiocarbonyl ester was used in the next step. To a refluxing solution of Bu$_3$SnH (55 μL, 0.207 mmol, 2 equiv) and a catalytic amount of AIBN in tol-uene (10 mL), a solution of the previously prepared thiocarbonyl ester (0.104 mmol, 1 equiv) in toluene (3 mL) was added drop wise. The reaction mixture was refluxed for 2 h. The solvent was concen-trated under vacuum. Without further purification the formed amine was used in the next step. 5-(Methanesulfonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalacid (40 mg, 0.106 mmol,

1 equiv), Py-BOP (56 mg, 0.106 mmol, 1 equiv) and DIPEA (19 μL, 0.109 mmol, 1 equiv) were dissolved in DCM (2 mL). The mixture was stirred at room temperature for 30 min before the amine (~1 equiv) from the previous reaction dissolved in DCM (2 mL) and DIPEA (23 μL, 0.138 mmol, 1.3 equiv) were added. After complete reaction the mixture were washed with $NaHCO_3$ (1× 10 mL) and brine (1× 10 mL). The water phase was extracted with DCM (2× 10 mL). The organic layers were combined and dried over Na_2SO_4, concentrated under vacuum and purified by column chromatography (toluene/ethyl acetate 1:1) to give compound **2g** (6 mg, 0.007 mmol, 7%). $[\alpha]_D^{20}$ − 4.2 (c 0.4, MeOH); ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.92 (d, J_{HH} = 7.8 Hz, 1H), 8.60 (t, J_{HH} = 5.9 Hz, 1H), 8.53 (d, J_{HH} = 8.4 Hz, 1H), 8.22 (t, J_{HH} = 1.5 Hz, 1H), 8.02 (d, J_{HH} = 1.5 Hz, 2H), 7.80 (d, J_{HH} = 8.7 Hz, 1H), 7.43–7.39 (m, 2H), 7.35–7.29 (m, 2H), 7.28–7.13 (m, 6H), 6.64–6.47 (m, 3H), 5.29–5.20 (m, 1H), 4.50–4.40 (m, 1H), 4.38–4.27 (m, 2H), 4.23–4.17 (m, 1H), 4.12–4.03 (m, 2H), 3.41 (s, 3H), 3.35 (s, 3H), 2.94 (s, 3H), 2.11–2.01 (m, 1H), 1.95–1.68 (m, 4H), 1.58 (d, J_{HH} = 7.1 Hz, 3H), 0.93 (d, J_{HH} = 6.8 Hz, 3H), 0.93 (d, J_{HH} = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, MeOD-d_4) δ 174.9, 173.3, 168.8, 167.8, 165.3 (d, $^1J_{CF}$ = 244.8 Hz), 165.1 (d, $^1J_{CF}$ = 244.8 Hz), 162.4 (t, $^3J_{CF}$ = 13.6 Hz), 145.1, 143.8, 139.6, 137.4, 137.2, 129.6, 129.5, 129.3, 129.2, 128.6, 128.3, 128.2, 127.3, 125.9, 99.6 (d, $^2J_{CF}$ = 28.8 Hz, 2C), 97.2 (t, $^2J_{CF}$ = 26.6 Hz), 82.5, 71.3, 60.0, 58.6, 51.0, 50.5, 44.1, 38.3, 35.9, 32.1, 30.1, 27.3, 22.2, 19.8, 18.9; HRMS (ESI) m/z 836.3485 ([M+Na]$^+$ calcd for $C_{43}H_{52}F_2N_5O_8S^+$ 836.3499). LC–MS purity system A: t_R = 5.08 min, 99%; system B: t_R = 4.66 min, 100%.

4.6.30. (2R,4R,5S)-5-Azido-6-(3,5-difluoro-phenoxy)-4-hydroxy-2-methoxy-hexanoic acid ((S)-1-benzylcarbamoyl-2-methyl-propyl)-amide (9)

To a stirred solution of **8** (226 mg, 0.435 mmol) in THF, p-nitrobenzoic acid (131 mg, 0.783 mmol, 1.8 equiv) and triphenyl phosphine (194 mg, 0.74 mmol, 1.7 equiv) were added. The mixture was cooled to 0 °C (ice/water). Diisopropyl azodicarboxylate (146 μL, 0.74, 1.7 equiv) was added drop wise to the solution. The reaction was stirred in room temperature over night. The reaction mixture was concentrated and the residue was filtered through a short silica column, the filtrate was concentrated and the formed ester was dissolved in MeOH (10 mL), to this mixture 1 M NaOMe in MeOH (1 mL) was added. The reaction was stirred in room temperature for 1 h and then Dowex H$^+$ was added to neutralize the mixture. The solids were filtered off and the filtrate was concentrated under vacuum. The residue was purified by column chromatography (toluene/ethyl acetate 5:1) to give compound **9** (53 mg, 0.102 mmol, 23%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40–7.17 (m, 6H), 6.61 (t, J_{HH} = 5.7 Hz, 1H), 6.49–6.39 (m, 3H), 4.51–4.36 (m, 2H), 4.28–4.18 (m, 2H), 4.01–3.94 (m, 1H), 3.94–3.88 (m, 1H), 3.83–3.75 (m, 1H), 3.68–3.61 (m, 1H), 3.47 (s, 3H), 2.29–2.17 (m, 1H), 2.09–2.00 (m, 1H), 1.93–1.82 (m, 1H), 0.98 (d, J_{HH} = 6.8 Hz, 3H), 0.96 (d, J_{HH} = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 173.3, 170.7, 163.9 (d, $^1J_{CF}$ = 246.7 Hz), 163.7 (d, $^1J_{CF}$ = 246.7 Hz), 160.2 (t, $^3J_{CF}$ = 13.7 Hz), 137.9, 128.9, 127.9, 127.8, 98.7 (d, $^2J_{CF}$ = 28.5 Hz, 2C), 97.1 (t, $^2J_{CF}$ = 26.0 Hz), 80.3, 69.0, 68.5, 65.0, 58.9, 58.7, 43.7, 36.0, 30.8, 19.6, 18.3; MS (ESI) m/z 520.2 ([M+H]$^+$ calcd for $C_{25}H_{32}F_2N_5O_5^+$ 520.2).

4.6.31. N-[(1S,2R,4R)-4-((S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-4-methoxy-butyl]-5-(methanesulfonyl-methyl-amino)-N′-((R)-1-phenyl-ethyl)-isophthalamide (2h)

Azide **9** (22 mg, 0.042 mmol) was dissolved in MeOH (5 mL) and a catalytical amount of Pd on carbon was added, the mixture was then treated with hydrogen gas (1 atm) for 2 h. Then the solids were filtered off and the filtrate was concentrated under vacuum.

Without further purification the formed amine was used in the next step. 5-(Methanesulfonyl-methyl-amino)-N′-(1-phenyl-ethyl)-isophthalacid (16 mg, 0.042 mmol, 1 equiv), Py-BOP (22 mg, 0.042 mmol, 1 equiv) and DIPEA (7.5 μL, 0.042 mmol, 1 equiv) were dissolved in DCM (2 mL). The mixture was stirred at room temperature for 30 min before the amine (~1 equiv) from the previous reaction dissolved in DCM (2 mL) and DIPEA (7.5 μL, 0.042 mmol, 1 equiv) were added. After complete reaction the mixture were washed with $NaHCO_3$ (1× 10 mL) and brine (1× 10 mL). The water phase was extracted with DCM (2× 10 mL). The organic layers were combined and dried over Na_2SO_4, concentrated under vacuum and purified by column chromatography (toluene/ethyl acetate 1:1) to give compound **2h** (27 mg, 0.032 mmol, 75%). $[\alpha]_D^{20}$ + 5.1 (c 1.0, MeOH); ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.20 (t, J_{HH} = 1.6 Hz, 1H), 8.02–7.98 (m, 2H), 7.42–7.38 (m, 2H), 7.35–7.29 (m, 2H), 7.28–7.08 (m, 7H), 6.63–6.46 (m, 3H), 5.27–5.20 (m, 1H), 4.44–4.37 (m, 1H), 4.35–4.25 (m, 4H), 4.20 (d, J_{HH} = 7.6 Hz, 1H), 4.13–4.06 (m, 1H), 3.99 (dd, J_{HH} = 2.8, 10.2 Hz, 1H), 3.43 (s, 3H), 3.33 (s, 3H), 2.92 (s, 3H), 2.32 (s, 1H), 2.13–2.02 (m, 1H), 1.99–1.90 (m, 1H), 1.88–1.78 (m, 1H), 1.57 (d, J_{HH} = 7.1 Hz, 3H), 0.96–0.93 (m, 6H); ^{13}C NMR (100.5 MHz, MeOD-d_4) δ 175.4, 173.3, 168.8, 167.8, 165.2 (d, $^1J_{CF}$ = 244.8 Hz), 165.1 (d, $^1J_{CF}$ = 244.8 Hz), 162.5 (t, $^3J_{CF}$ = 13.9 Hz), 145.1, 143.7, 139.6, 137.4, 137.2, 129.9, 129.6, 129.5, 129.4, 129.2, 129.2, 128.6, 128.3, 128.2, 127.3, 126.3, 125.9, 99.6 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.1 (t, $^2J_{CF}$ = 26.3 Hz), 80.3, 68.7, 68.0, 60.0, 59.1, 55.7, 51.0, 44.0, 39.1, 38.3, 35.9, 32.1, 22.2, 19.8, 18.8; HRMS (ESI) m/z 852.3433 ([M+H]$^+$ calcd for $C_{43}H_{52}F_2N_5O_9S^+$ 852.3448). LC–MS purity system A: t_R = 4.45 min, 99%; system B: t_R = 4.12 min, 100%.

4.6.32. [(1S,2R,4R)-4-((S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-(3,5-difluoro-phenoxymethyl)-2-hydroxy-4-methoxy-butyl]-carbamic acid tert-butyl ester (10)

Azide **9** (53 mg, 0.102 mmol) was dissolved in MeOH (8 mL) and a catalytical amount of Pd on carbon was added, the mixture was then treated with hydrogen gas (1 atm) for 2 h. Then the solids were filtered off and the filtrate was concentrated under vacuum. To a mixture of the formed amine dissolved in THF/H$_2$O 1:1 (4 mL), 1 M NaOH in water (0.2 mL, 0.204 mmol, 2 equiv) and di-tert-butyl dicarbonate (44.5 mg, 0.204 mmol, 2 equiv) were added. The reaction was stirred in room temperature for 4 h. The volatile solvents were evaporated off and the residue was neutralized using 1 M HCl and then extracted with DCM (3× 7 mL). The organic layer was dried over Na_2SO_4, concentrated under vacuum and purified by column chromatography (toluene/ethyl acetate 2:1) to give compound **10** (58 mg, 0.098 mmol, 96%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33–7.17 (m, 6H), 6.80–6.70 (m, 1H), 6.46–6.34 (m, 3H), 5.08 (d, J_{HH} = 8.0 Hz, 1H), 4.48–4.30 (m, 2H), 4.28–4.20 (m, 1H), 4.17–4.00 (m, 2H), 4.00–3.78 (m, 4H), 3.43 (s, 3H), 2.26–2.15 (m, 1H), 2.05–1.81 (m, 2H), 1.42 (s, 9H), 0.96 (d, J_{HH} = 6.8 Hz, 3H), 0.93 (d, J_{HH} = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, CDCl$_3$) δ 173.3, 170.8, 163.8 (d, $^1J_{CF}$ = 246.1 Hz), 163.7 (d, $^1J_{CF}$ = 246.1 Hz), 160.6 (t, $^3J_{CF}$ = 13.7 Hz), 155.9, 146.9, 138.1, 128.8, 127.8, 127.6, 98.6 (d, $^2J_{CF}$ = 28.4 Hz, 2C), 96.8 (t, $^2J_{CF}$ = 25.8 Hz), 85.3, 80.5, 80.1, 68.9, 67.6, 58.8, 58.5, 54.3, 43.6, 36.6, 30.8, 28.5, 27.5, 19.6, 18.3; MS (ESI) m/z 616.3 ([M+Na]$^+$ calcd for $C_{30}H_{41}F_2N_3NaO_7^+$ 616.3).

4.6.33. [(1S,2S,4R)-2-Azido-4-((S)-1-benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-(3,5-difluoro-phenoxymethyl)-4-methoxy-butyl]-carbamic acid tert-butyl ester (11)

To a stirred solution of **10** (58 mg, 0.098 mmol) in pyridine (5 mL), methane sulfonyl chloride (15 μL, 0.195, 2 equiv) was added drop wise at 0 °C. The reaction was stirred in room temperature for 1 h. The reaction mixture was concentrated under vacuum, dissolved in toluene and concentrated again. The formed mesylate was dissolved in DMF (4 mL) and treated with sodium

azide (95.3 mg, 1.47 mmol, 15 equiv). The mixture was stirred at 60 °C over night. The reaction mixture was concentrated under vacuum. The residue was dissolved in diethyl ether (20 mL) and washed with H_2O (1× 10 mL), Brine (1× 10 mL) and H_2O (1× 10 mL) again. The organic layer was dried over Na_2SO_4, concentrated under vacuum and purified by column chromatography (toluene/ethyl acetate 9:1) to give compound **11** (15 mg, 0.024 mmol, 25%). ^{1}H NMR (400 MHz, MeOD-d_4) δ 7.33–7.26 (m, 4H), 7.25–7.18 (m, 2H), 7.17–7.09 (m, 1H), 6.89 (d, J_{HH} = 9.0 Hz, 1H), 6.65–6.47 (m, 3H), 4.43–4.32 (m, 2H), 4.22 (d, J_{HH} = 7.7 Hz, 1H), 4.12–4.00 (m, 3H), 3.96–3.88 (m, 2H), 3.41 (s, 3H), 2.14–1.93 (m, 3H), 1.46 (s, 9H), 0.95 (d, J_{HH} = 6.8 Hz, 3H), 0.95 (d, J_{HH} = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, MeOD-d_4) δ 174.1, 173.2, 165.2 (d, $^1J_{CF}$ = 244.9 Hz), 165.1 (d, $^1J_{CF}$ = 244.9 Hz), 162.0 (t, $^3J_{CF}$ = 13.8 Hz), 158.2, 139.7, 129.5, 128.7, 128.3, 99.7 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.4 (t, $^2J_{CF}$ = 26.3 Hz), 80.7, 80.3, 69.1, 60.5, 60.0, 58.7, 53.8, 44.1, 34.9, 32.2, 28.7, 19.8, 18.9; MS (ESI) m/z 641.3 ([M+Na]$^+$ calcd for $C_{30}H_{40}F_2N_6O_6^+$ 641.3).

4.6.34. N-[(1S,2S,4R)-2-Azido-4-((S)-1-benzylcarbamoyl-2-methyl-propylcarbamoyl)-1-(3,5-difluoro-phenoxymethyl)-4-methoxy-butyl]-5-(methanesulfonyl-methyl-amino)-N'-((R)-1-phenyl-ethyl)-isophthalamide (2i)

To a stirred solution of **11** (15 mg, 0.024 mmol), triethyl silane (10 μL, 0.06 mmol, 2.5 equiv) in DCM (2 mL) trifluoroacetic acid (1 mL) was added. After 15 min the mixture was concentrated under vacuum, dissolved in toluene and concentrated again. The residue was dissolved in DCM (10 mL), washed with NaHCO$_3$ (2× 5 mL), dried over Na_2SO_4 and concentrated under vacuum. Without further purification the formed amine was used in the next step.   5-(Methanesulfonyl-methyl-amino)-N'-(1-phenyl-ethyl)-isophthalacid (14 mg, 0.036 mmol, 1.5 equiv), Py-BOP (19 mg, 0.036 mmol, 1.5 equiv) and DIPEA (7 μL, 0.036 mmol, 1.5 equiv) were dissolved in DCM (1 mL). The mixture was stirred at room temperature for 30 min before the amine (∼1 equiv) from the previous reaction dissolved in DCM (2 mL) and DIPEA (5 μL, 0.024 mmol, 1 equiv) were added. After complete reaction the mixture were washed with NaHCO$_3$ (1× 10 mL) and brine (1× 10 mL). The water phase was extracted with DCM (2× 10 mL). The organic layers were combined and dried over Na_2SO_4, concentrated under vacuum and purified by column chromatography (toluene/ethyl acetate 1:1) to give compound **2i** (18 mg, 0.021 mmol, 85%). $[\alpha]_D^{20}$ − 4.9 (c 0.9, MeOH); ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.26 (t, J_{HH} = 1.5 Hz, 1H), 8.06–8.05 (m, 1H), 8.05–8.03 (m, 1H), 7.42–7.38 (m, 2H), 7.35–7.29 (m, 2H), 7.28–7.16 (m, 6H), 6.67–6.50 (m, 3H), 5.28–5.21 (m, 1H), 4.77–4.71 (m, 1H), 4.40–4.30 (m, 2H), 4.26–4.19 (m, 3H), 4.11–4.05 (m, 1H), 4.05–4.00 (m, 1H), 3.43 (s, 3H), 3.36 (s, 3H), 2.95 (s, 3H), 2.13–2.00 (m, 3H), 1.58 (d, J_{HH} = 7.0 Hz, 3H), 0.92 (d, J_{HH} = 6.8 Hz, 3H), 0.91 (d, J_{HH} = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, MeOD-d_4) δ 174.1, 173.2, 169.2, 167.8, 165.3 (d, $^1J_{CF}$ = 244.9 Hz), 165.1 (d, $^1J_{CF}$ = 244.9 Hz), 161.9 (t, $^3J_{CF}$ = 13.8 Hz), 145.1, 143.8, 139.7, 137.5, 136.8, 129.6, 129.5, 129.3, 128.6, 128.3, 128.2, 127.3, 126.1, 99.7 (d, $^2J_{CF}$ = 28.7 Hz, 2C), 97.5 (t, $^2J_{CF}$ = 26.3 Hz), 80.1, 68.7, 60.5, 60.1, 58.7, 53.0, 51.0, 44.1, 38.3, 35.9, 35.2, 32.2, 22.2, 19.8, 18.9; HRMS (ESI) m/z 899.3324 ([M+Na]$^+$ calcd for $C_{43}H_{50}F_2N_8O_8S^+$ 899.3333). LC–MS purity system A: t_R = 4.95 min, 99%; system B: t_R = 4.68 min, 100%.

4.6.35. N-[(1S,2S,4R)-4-((S)-1-Benzylcarbamoyl-2-methyl-propylcarbamoyl)-2-amino-1-(3,5-difluoro-phenoxymethyl)-4-methoxy-butyl]-5-(methanesulfonyl-methyl-amino)-N'-((R)-1-phenyl-ethyl)-isophthalamide (2j)

Azide **2i** (17 mg, 0.019 mmol) was dissolved in MeOH (4 mL) and a catalytic amount of Pd on carbon was added, the mixture was then treated with hydrogen gas (1 atm) for 2 h. Then the solids were filtered off and the filtrate was concentrated under vacuum.

The residue was purified by column chromatography (toluene/ethyl acetate 1:6→ethyl acetate/ammonia 1:0.01) to give compound **2j** (14 mg, 0.016 mmol, 85%). $[\alpha]_D^{20}$ − 1.9 (c 0.9, MeOH); ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.28 (t, J_{HH} = 1.6 Hz, 1H), 8.09–8.08 (m, 1H), 8.05–8.03 (m, 1H), 7.43–7.39 (m, 2H), 7.35–7.30 (m, 2H), 7.29–7.13 (m, 6H), 6.65–6.49 (m, 3H), 5.28–5.22 (m, 1H), 4.61–4.55 (m, 1H), 4.39–4-30 (m, 2H), 4.27–4.20 (m, 2H), 4.18 (d, J_{HH} = 7.4 Hz, 1H), 4.03–3.97 (m, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 2.96 (s, 3H), 2.12–2.03 (m, 1H), 1.99–1.95 (m, 1H), 1.86–1.77 (m, 1H), 1.58 (d, J_{HH} = 7.1 Hz, 3H), 0.91 (d, J_{HH} = 6.8 Hz, 3H), 0.90 (d, J_{HH} = 6.8 Hz, 3H); ^{13}C NMR (125.8 MHz, MeOD-d_4) δ 174.7, 173.3 169.1, 167.8, 165.2 (d, $^1J_{CF}$ = 244.6 Hz), 165.1 (d, $^1J_{CF}$ = 244.6 Hz), 162.1 (t, $^3J_{CF}$ = 13.9 Hz), 145.1, 143.8, 139.7, 137.5, 136.9, 129.6, 129.5, 129.5, 129.5, 129.4, 128.6, 128.3, 128.2, 127.3, 126.1, 99.7 (d, $^2J_{CF}$ = 29.1 Hz, 2C), 97.3 (t, $^2J_{CF}$ = 26.5 Hz), 81.1, 69.2, 60.0, 58.6, 53.7, 51.0, 50.3, 44.0, 38.4, 38.1, 36.0, 32.0, 22.1, 22.0, 19.8, 18.8; HRMS (ESI) m/z 851.3612 ([M+H]$^+$ calcd for $C_{43}H_{52}F_2N_6O_8S^+$ 851.3608). LC–MS Purity system A: t_R = 4.38 min, 97%; System B: t_R = 4.09 min, 97%.

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