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Nucleophilic ring-opening of activated aziridines: A one-step method for labeling biomolecules with fluorine-18

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ABSTRACT

The direct labeling of biomolecules with fluorine-18 is highly desirable. An option is the ring-opening of an activated aziridine moiety in a biomolecule using ^{18}F-fluoride. Therefore, a series of aziridine-based model compounds and three aziridine-based biomolecules four aziridine-based model compounds were synthesized and evaluated as potential precursors for a direct one-step radiolabeling with fluorine-18. High to moderate yields of ^{18}F-incorporation were achieved under mild labeling conditions. The influence of different activating groups, reaction temperature, solvent and base was investigated. The applicability of this method for the direct ^{18}F-radiolabeling of biomolecules for positron emission tomography (PET) studies is illustrated with examples.

1. Introduction

Molecular imaging has the potential to detect disease progression or therapeutic effectiveness earlier than most conventional methods in the fields of oncology, neurology, and cardiology. Of the several promising molecular imaging technologies, PET is of particular interest for diagnosis and drug development because of its high sensitivity and ability to provide quantitative and kinetic data [1–7]. Positron emitting isotopes such as carbon-11, nitrogen-13, and oxygen-15 can replace their non-radioactive counterparts in target compounds to produce tracers for PET imaging that are chemically identical to the original molecules and have the same pharmacological properties. Of all the PET isotopes, fluorine-18 is the most convenient labeling isotope due to its relatively long physical half-life (110 min). The physical half-life of 110 min allows for more complex multi-step radiosynthesis and distribution to PET centers that lack radiochemistry facilities. In addition, its low ß$^+$ energy of 635 keV results in high resolution and a low radiation dose to patients [8].

The direct labeling of peptides and other biomolecules is difficult to accomplish due in part to the harsh reaction conditions employed during nucleophilic substitution reactions. Thus, the fluorine-18 labeling of peptides such as bombesin [9,10], somatostatin [11–13], neurotensin [14], and RGD [15,16] have been accomplished using indirect methods. The indirect methods involve the coupling of ^{18}F-labeled prosthetic groups to biomolecules *via* appropriate functionalities [17]. This requires a multi-step procedure which is time consuming. A direct labeling method is therefore highly desirable.

Schirrmacher et al. [18] described the direct labeling of ^{18}F-Tyr3-Octreotate via ^{18}F–^{19}F isotope exchange on a silicon atom under mild conditions, but reported low specific activity due to high levels of non-radioactive fluorinated compound. This problem was solved only by utilizing an indirect method, employing an efficient two-step labeling procedure and using very small amounts of precursor in the isotope exchange reaction [19]. Recently, Mu et al. [20] developed a silicon-based direct and facile ^{18}F-labeling of peptides using hydroxyl or hydrogen as a leaving group.

Very few publications are known which describe the nucleophilic ring-opening of aziridines using ^{18}F-fluoride [21,22]. The preparation of ^{18}F-labeled 2-fluoroethylamines, -amides and

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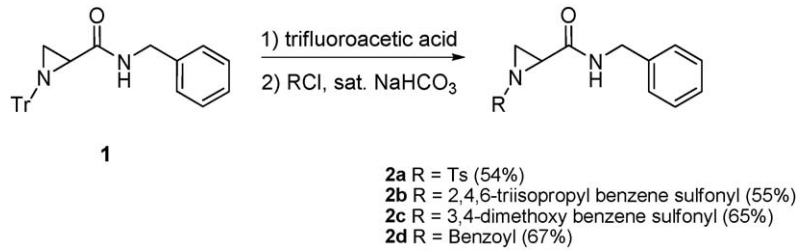


Scheme 1. Preparation of aziridine-based model compounds **2a**–**d**.

-sulfonamides is performed by at least a two-step procedure applying ^{18}F-2-fluoroethylamine [23,24] or ^{18}F-2-bromofluoroethane [25,26]. The ring-opening of appropriate aziridine may deliver such structural motifs by a single-step synthesis. Very recently, Vasdev et al. [27] developed a highly regioselective method which involves the ring-opening of *N*-benzyloxycarbonyl-protected 2-methylaziridine with [^{18}F] fluoride. This method allows the generation of new ^{18}F-labeled amines for incorporation into radiopharmaceuticals.

Nucleophilic ring-opening of aziridines with halides is well known [28,29], however, relatively few reports are found for the ring-opening of aziridines with fluoride as the nucleophile. The most often used fluorination reagents are $BF_3{\cdot}OEt_2$ [29–31], HF*Pyridine (Olah's Reagent) [32,33], diethylaminosulfur trifluoride (DAST) and $LiBF_4$ [34], TBAF [35,36], KHF_2 [37] or KF [38]. Unfortunately, for nucleophilic fluorine-18 radiolabeling, ^{18}F-fluorination reagents are limited. Among the above mentioned non-radioactive fluorination reagents, only [^{18}F]-TBAF and [^{18}F]-KF are mostly used for direct nucleophilic ^{18}F-fluorination reactions. Here, we present the nucleophilic ring-opening of appropriately activated aziridines as an option for direct labeling of biomolecules such as peptides and nucleosides under mild conditions.

2. Results and discussion

2.1. Synthesis of aziridine-based model compounds

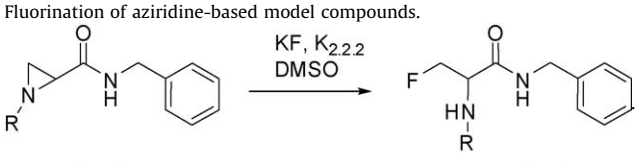
First, several 2-carboxylic acid benzyl amide substituted aziridines as model compounds were prepared and fluorinated under non-radioactive conditions in order to evaluate the potential of the envisaged approach (Scheme 1, Table 1). In this study, no questions on stereochemistry were pursued and as such racemic compounds were used as starting materials except for the thymidine derivatives. Preliminary investigations were performed in order to get an idea about the reactivity of the prepared aziridines, regioselectivity of the reaction as well as the by-product profile.

N-benzyl-1-tritylaziridine-2-carboxamide **1** was prepared according to published procedures [39–42]. Detritylation of compound **1** with trifluoroacetic acid and subsequent treatment of the resulting intermediate with different phenyl substituted sulfonyl chlorides and benzoyl chloride afforded activated aziridines **2a**–**d** (Scheme 1). Protection of the nitrogen in the aziridine ring with a trityl group as a first step was necessary as the aziridine quickly decomposed if an electron withdrawing group was placed on the nitrogen in the presence of a carboxylate moiety. The aziridine ring is much more stable if the side chain contains amide functionality.

The non-radioactive fluorinated compounds were synthesized as reference compounds for the identification of the ^{18}F-labeled compounds. Model compounds **2a**–**d** were treated with KF and Kryptofix in DMSO under varying temperatures and reaction times (Table 1).

The tosyl-activated aziridine **2a** (Table 1, entry 1) gave 17% of product **3a** after 1 h at room temperature (RT). By increasing the reaction temperature to 50 °C, a higher conversion of **2a** to **3a** was observed after 1 h (Table 1, entry 2). Isolation and structure elucidation revealed compound **3a** as the main product. The corresponding regioisomer was not observed but only small amounts of hydrolysed or rearranged side products were generated. Introducing the less electron deficient 2,4,6-triisopropylphenylsulfonyl group (**2b**) resulted in a reduced reactivity at RT but gave a much cleaner conversion at 50 °C yielding high amounts of **3b** (Table 1, entry 4). Here again, only one regioisomer was obtained. With the dimethoxyphenylsulfonyl aziridine derivative

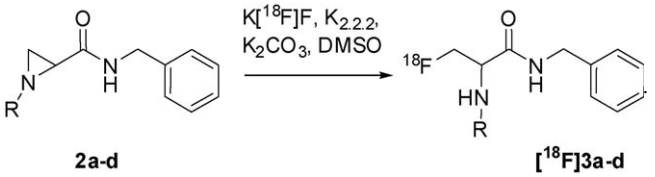
Table 1
Fluorination of aziridine-based model compounds.



Entry	Nr	R	Temp. (°C)	Reaction time (h)	HPLC yield (%)	Isolated yield (%)
1	**2a**	4-Me$C_6H_4SO_2$	25	1	17	n.i.
2	**2a**	4-Me$C_6H_4SO_2$	50	1[a]	64	47
3	**2b**	2,4,6-(iPr)$_3C_6H_2SO_2$	25	1	l.c.	n.i.
4	**2b**	2,4,6-(iPr)$_3C_6H_2SO_2$	50	1[a]	79	60
5	**2c**	3,4-(MeO)$_2C_6H_2SO_2$	50	1	l.c.	n.i.
6	**2c**	3,4-(MeO)$_2C_6H_2SO_2$	80	1[a]	40	23
7	**2d**	Benzoyl	50	1	l.c.	n.i.
8	**2d**	Benzoyl	80	1	0	0

l.c.: very low conversion by TLC, not analyzed by HPLC, n.i.: not isolated. Precursor: $K_{2.2.2}$: KF = 1:1.1:1.1.
[a] Complete consumption of starting material.

Table 2
^{18}F-Radiolabeling of aziridine-based model compounds.



Entry	Nr	Precursor	Temp. (°C)	Reaction time (min)	HPLC Conversion (%)
1	**2a**	4-Me$C_6H_4SO_2$	50	15	74
2	**2a**	4-Me$C_6H_4SO_2$	60	15	81
3	**2a**	4-Me$C_6H_4SO_2$	70	15	95
4	**2b**	2,4,6-(iPr)$_3C_6H_2SO_2$	50	15	54
5	**2b**	2,4,6-(iPr)$_3C_6H_2SO_2$	60	15	97
6	**2b**	2,4,6-(iPr)$_3C_6H_2SO_2$	70	15	89
7	**2c**	3,4-(MeO)$_2C_6H_2SO_2$	50	15	66
8	**2c**	3,4-(MeO)$_2C_6H_2SO_2$	60	15	80
9	**2c**	3,4-(MeO)$_2C_6H_2SO_2$	70	15	97
10	**2d**	Benzoyl	50	15	0
11	**2d**	Benzoyl	60	15	0
12	**2d**	Benzoyl	70	15	0

All experiments were carried out with 2 mg of precursor dissolved in 200 μl DMSO. Conversion was determined from radio-HPLC chromatogram, representing the percentage of radioactivity area of product related to the total radioactivity. The final product was confirmed by co-injection with cold reference.

2c, no conversion was observed at 50 °C, however, heating the reaction mixture to 80 °C afforded the desired compound **3c** in 22% isolated yield (Table 1, entries 5 and 6). The *N*-benzoylaziridine **2d** did not yield the expected product **3d** under the above mentioned reaction conditions (Table 1, entries 7 and 8).

2.2. ^{18}F-Radiolabeling of aziridine-based model compounds

The reaction of ^{18}F-fluoride with the aziridine-based model compounds was investigated using standard fluorination conditions and DMSO as solvent. Table 2 shows the radiolabeling conditions and the results obtained. Nearly quantitative ^{18}F-incorporation was achieved (Table 2, entries 3, 5 and 9) under mild labeling conditions for most model compounds.

Moreover, no significant differences in the radiolabeling yield were observed with the different substituents on the phenylsulfonyl ring. The most activating moiety gave the best radiolabeling yield of 74% at the mildest applied temperature of 50 °C (Table 2, entry 1), while the other two activating groups, 2,4,6-tri*iso*propylphenylsulfonyl and 3,4-dimethoxyphenylsulfonyl (Table 2, entries 4 and 7) afforded ^{18}F-incorporation in 54% and 66%, respectively. At a higher temperature of 70 °C, higher ^{18}F-incorporations were observed for all *N*-sulfonated aziridines **2a–c** (Table 2, entries 3, 6 and 9). Aziridine model compound **2b** (entry 5) gave a decay corrected radiochemical yield of 55% after semi-preparative HPLC purification. The specific activity achieved was greater than 58 GBq/μmol. In contrast to *N*-sulfonated aziridines **2a–c**, no ^{18}F-incorporation was observed for *N*-benzoyl aziridine **2d** under the tested conditions (Table 2, entries 10–12). These results are in line with the data obtained from the "cold" fluorination experiments (Table 1, entries 7 and 8).

In order to check the stability of these model compounds under physiological conditions, time dependent hydrolysis in water and human plasma was assessed. The ^{18}F-labeled model compound was incubated either in water or in human plasma at 37 °C and stability was then monitored by reversed-phase HPLC. For instance, after 2 h 85% of compound [^{18}F] **3b** was still present in water solution and around 80% was recovered in human plasma.

2.3. Synthesis of aziridine-based biomolecules

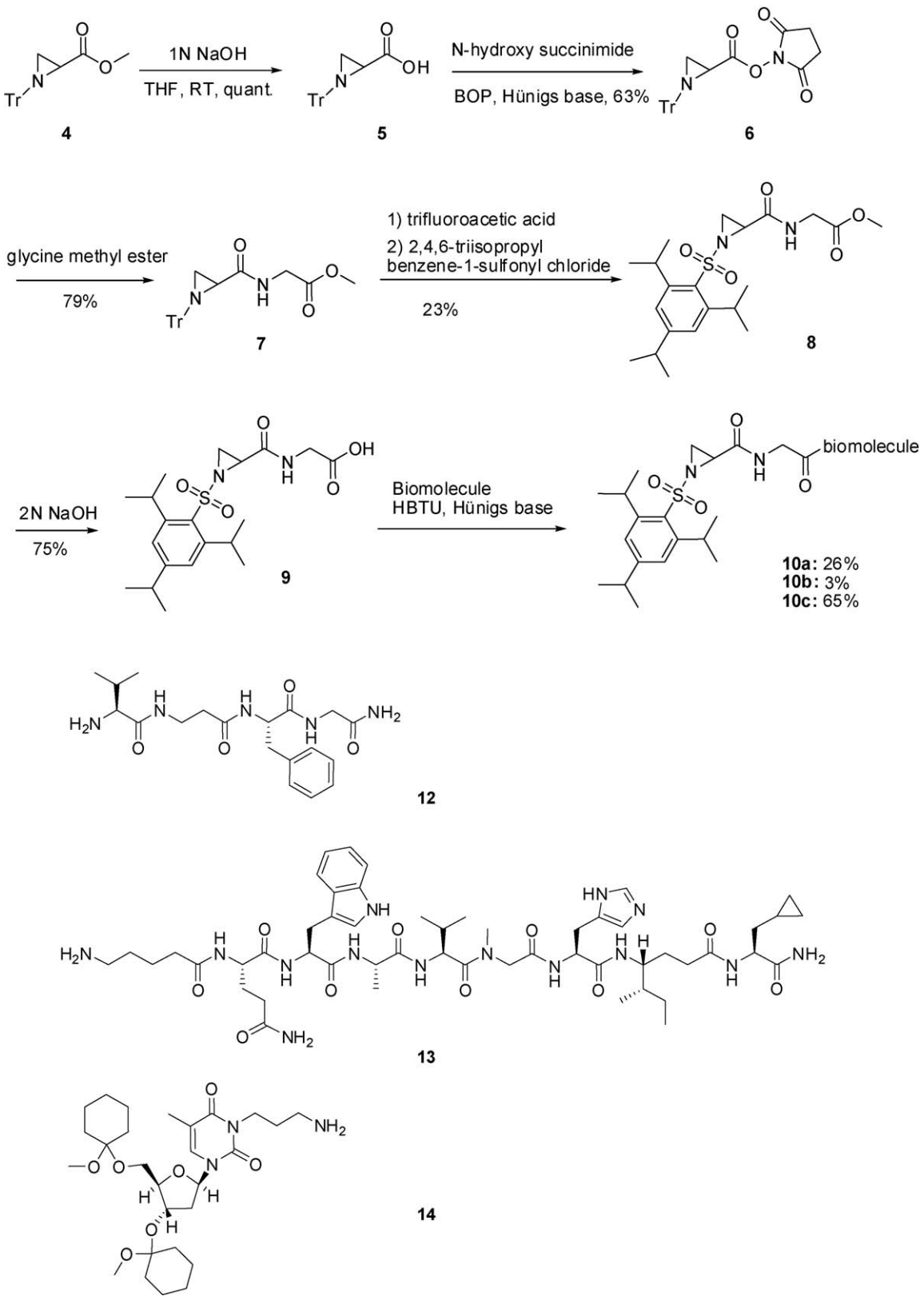
Based on the ^{18}F-labeling efficiency and stability of the model compounds, the corresponding acid derivative of 2,4,6-tri*iso*propylphenylsulfonyl activated aziridine was selected as the best building block for coupling to target molecules. Active ester **6** was prepared from compound **4** in a two-step procedure [41,42]. Unfortunately, the *N*-sulfonated aziridine derivatives **5** and **6** are extremely labile therefore active ester **6** was transformed to amide **7** by reaction with glycine methyl ester (Scheme 2). After cleavage of the trityl protecting group, the triisopropylphenylsulfonyl group was introduced to activate the aziridine towards fluorination. Saponification led to carboxylic acid **9** as the key intermediate. Precursor compounds **10a–c** were obtained by coupling building block **9** to peptides **12**, **13** and thymidine derivative **14**. Peptides **12** and **13** were prepared by using standard Fmoc-solid-phase peptide synthesis protocols [43].

The synthetic pathway to thymidine derivative **14** is depicted in Scheme 3. The hydroxyl groups of commercially available thymidine were protected with methoxy cyclohexane (MCH) in the presence of a catalytic amount of *para*-toluene sulfonic acid. *N*-alkylation with *N*-(3-bromopropyl)phthalimide afforded compound **16** in 91% yield. No *O*-alkylation side product was observed. Treatment of compound **16** with hydrazine hydrate at RT led to the desired free amine **14** in 74% yield.

To investigate the utility of this new labeling approach, two different peptides (**10a** and **10b**) and a protected thymidine derivative (**10c**) were submitted to radiofluorination (Table 3). The reference compounds **11a** and **11b** were obtained by coupling [(2*R*,*S*)-3-fluoro-2-(2,4,6-triisopropylphenylsulfonylamido)propanamide]-acetic acid to the corresponding peptides **a** and **b**[24]. Reference compound **11c** was prepared by ^{19}F-fluorination of **10c**.

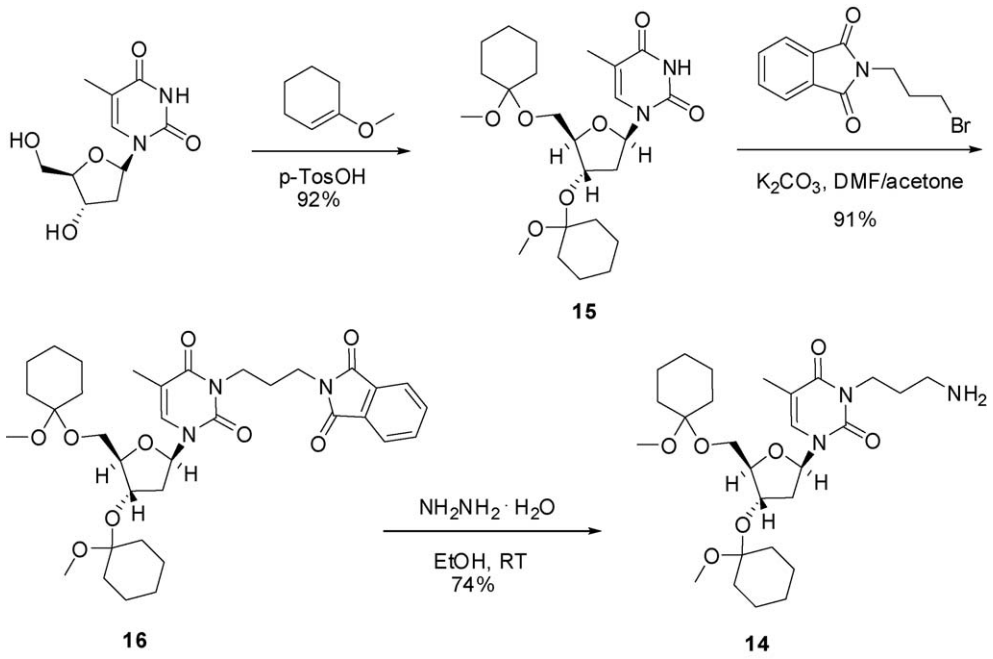
2.4. ^{18}F-radiolabeling of the aziridine-based biomolecules

^{18}F-labeling of the biomolecules was carried out under the same reaction conditions as previously described for the model compounds. As a very low conversion was initially obtained with the aziridine-based peptides (Table 3, entries 1–4, 7), reaction parameters such as solvent, temperature and base were



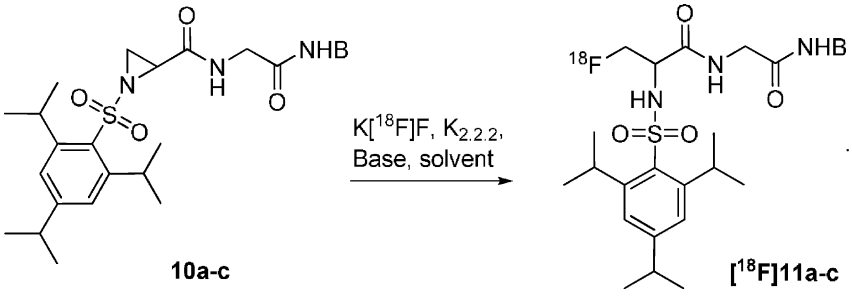
Scheme 2. Preparation of aziridine-based precursor biomolecules.

investigated. By increasing the temperature up to 90 °C and changing the base, i.e. potassium carbonate to caesium carbonate, a slight increase in the radiolabeling yield (up to 16%) was observed with the tetrapeptide **10a** (Table 3, entry 6). Only 7% conversion was achieved with the octapeptide **10b** (Table 3, entry 8), whereas under similar conditions thymidine derivative **10c** (Table 3, entries 10 and 11) gave a 10-fold higher conversion. By increasing the temperature to 90 °C and changing the base from K_2CO_3 to Cs_2CO_3, the radiolabeling yield of **10c** could be improved from 67% to 87%.



Scheme 3. Synthesis of compound **14**.

Table 3
Radiolabeling of aziridine-based biomolecules.



Entry	Nr	Temp. (°C)	Base	Solvent	HPLC Conversion (%)
1	**10a**	50	K_2CO_3	DMSO	n.c.
2	**10a**	60	K_2CO_3	DMSO	3
3	**10a**	60	K_2CO_3	DMF	2
4	**10a**	70	K_2CO_3	DMSO	0.3
5	**10a**	70	Cs_2CO_3	DMSO	12
6	**10a**	90	Cs_2CO_3	DMSO	16
7	**10b**	60	K_2CO_3	DMSO	n.c.
8	**10b**	70	Cs_2CO_3	DMSO	7
9	**10b**	90	Cs_2CO_3	DMSO	2.5
10	**10c**	60	K_2CO_3	DMSO	67
11	**10c**	90	Cs_2CO_3	DMSO	87

All experiments were carried out with 2 mg of precursor dissolved in 150 μl solvent. Conversion was determined from radio-HPLC chromatogram representing the percentage of radioactivity area of product related to the total radioactivity. The final product was confirmed by co-injection with cold reference. n.c.: no conversion observed.

3. Conclusion

Several aziridine-based model compounds with different activating groups were synthesized and labeled with fluorine-18 in moderate to high yields. The nucleophilic ring-opening of the aziridine derivatives was highly regioselective since only 3-fluoro-2-amino-amides were obtained as indicated by NMR. The application of the most promising building block for the labeling of biomolecules was demonstrated. Compared to the multi-step synthetic procedures, the aziridine approach is simple and straightforward although for the peptides modest radiochemical yields were obtained. Further investigations on the nucleophilic ring-opening of the aziridine-based biomolecules in the presence of different additives such as tetrabutylammonium bisulfate [38] or 1,8-diazabicyclo[5,4,0]-undec-7-ene (DBU) [39] with the aim to improve the radiolabeling efficiency are warranted. Finding a proper balance between the stability and the reactivity of the aziridines towards nucleophilic fluorination should also be taken into consideration. In conclusion, nucleophilic ring-opening of activated aziridines may be potentially useful for the one-step labeling of peptides or biomolecules with fluorine-18.

4. Experimental

4.1. General

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel, NH_2 or RP-18 (60 F_{254}) plates (0.25 mm) precoated with a fluorescent indicator. Preparative thin-layer chromatography (preparative TLC) was performed on silica gel (60F-254) plates (0.5 mm with concentrating zone) precoated with a fluorescent indicator. Preparative HPLC purifications of peptides were performed on a Luna C18 column (5 μm, 150 mm × 15 mm) with H_2O (+0.1% TFA)/CH_3CN (+0.1% TFA) and a gradient depending on polarity of 5–30 or 5–40% CH_3CN over 20 min; flow rate: 15 ml/min. Nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 (frequencies: 1H: 300 MHz, 13C: 75 MHz) or Bruker Avance 400 (frequencies: 1H: 400 MHz, 13C: 100 MHz) spectrometers with the corresponding solvent signals as an internal standard. ^{1}H NMR, ^{13}C NMR spectra were recorded as δ values relative to the solvent signal. Coupling constants are reported in Hertz. The multiplicity is defined by s (singlet), d (doublet), t (triplet), sept (septet), br (broad), m (multiplet). High resolution mass spectra (HRMS) were performed on an Autospec Q, Fisons (VG Analytical), 70 eV for EI-HR and a Q-Tof Premier, with UPLC for ESI-HR. All amino acid residues were, if not further specified, L-amino acid residues. Ava is 5-aminopentanoic acid, FA01010 is (4*R*,5*S*)-4-amino-5-methylheptanoic acid and Cpa is 2-amino-3-cyclopropylpropanamide.

4.2. Preparation and characterization of compounds **2a–c**

4.2.1. N-Benzyl-1-tosylaziridine-2-carboxamide (**2a**)

300 mg (0.72 mmol) **1** was dissolved in chloroform (13 ml), cooled down to 0 °C and titrated with trifluoroacetic acid (0.23 ml, 2.92 mmol) until complete conversion. Saturated sodium bicarbonate solution (ca. 2.8 ml) was added until pH 6–7 was reached and the solution was concentrated. The residue was taken up in ethyl acetate (13 ml), treated with saturated sodium bicarbonate solution (13 ml) followed by p-toluene sulfonic acid chloride (271 mg, 1.43 mmol). The reaction mixture was stirred overnight at room temperature. The organic phase was separated, dried over sodium sulfate and concentrated. The residue was purified by flash chromatography on silica gel with hexane/ethyl acetate (2:1) to give 128 mg (54%) of **2a**.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.81 (d, ^3J = 8.3 Hz, 2H, aryl), 7.36 (d, ^3J = 8.3 Hz, 2H, aryl), 7.29–7.26 (m, 3H, aryl), 7.10 (dd, ^3J = 6.8 Hz, ^4J = 2.0 Hz, 2H, aryl), 6.41 (bt, 1H, NH), 4.36 (m, 2H, CH_2NHBn), 3.30 (dd, ^3J = 7.6, 4.1 Hz, 1H, CHN_{Az}), 2.83 (d, ^3J = 7.6 Hz, 1H, CH_2N_{Az}), 2.47 (s, 3H, CH_3), 2.41 (d, ^3J = 4.1 Hz, 1H, CH_2N_{Az}) ppm.

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 165.6 (C=O), 145.5 (Ar–C), 137.3 (Ar–C), 133.4 (Ar–C), 130.1 (Ar–CH), 128.8 (Ar–CH), 128.2 (Ar–CH), 127.6 (Ar–CH), 127.5 (Ar–CH), 43.0 (CH_2–N), 38.2 (CH–N_{Az}), 33.4 (CH_2–N_{Az}), 21.7 (CH_3) ppm.

IR (KBr) = 3223, 3083, 1651, 1332, 1165, 915.

MS (ESI+): *m*/*z* (%) = 331 (M, 100), 243 (2).

HRMS: calcd for $C_{17}H_{19}O_3N_2S$: 331.1116, found: 331.1112.

4.2.2. N-Benzyl-1-(2,4,6-triisopropylphenylsulfonyl)aziridine-2-carboxamide (**2b**)

This compound was prepared in an analogous way to **2a** to give 177 mg (55%) of **2b**.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 4H, aryl), 7.17 (s, 2H, aryl), 7.15 (m, 1H, aryl), 6.32 (br t, 1H, NH), 4.36 (m, 2H, CH_2NHBn), 4.20 (sept, ^3J = 6.7 Hz, 2H, $CH(CH_3)_2$), 3.42 (dd, ^3J = 7.6, 4.1 Hz, 1H, CHN_{Az}), 2.91 (sept, ^3J = 6.7 Hz, 1H, $CH(CH_3)_2$), 2.87 (d, ^3J = 7.6 Hz, 1H, CH_2N_{Az},1H), 2.38 (d, ^3J = 4.1 Hz, 1H, CH_2N_{Az}), 1.26 (d, ^3J = 6.7 Hz, 6H, CH_3), 1.20 (d, ^3J = 6.7 Hz, 6H, CH_3), 1.17 (d, ^3J = 6.7 Hz, 6H, CH_3) ppm.

^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 165.0 (C=O), 153.8 (Ar–C), 150.7 (Ar–C), 138.7 (Ar–C), 131.0 (Ar–C), 128.4 (Ar–CH), 127.3 (Ar–CH), 127.1 (Ar–CH), 124.0 (Ar–CH), 42.1 (CH_2–N), 36.9 (CH–N_{Az}), 33.6 ($CH(CH_3)_2$), 31.6 (CH_2–N_{Az}), 29.4 ($CH(CH_3)_2$), 24.8 (CH_3), 24.7 (CH_3), 23.5 (CH_3) ppm.

IR (KBr) = 3278, 2959, 1658, 1164.

MS (ESI+): *m*/*z* (%) = 443 (M, 100).

HRMS: calcd for $C_{25}H_{35}O_3N_2S$: 443.2368, found: 443.2374.

4.2.3. N-Benzyl-1-(3,4-dimethoxyphenylsulfonyl)aziridine-2-carboxamide (**2c**)

This compound was prepared in an analogous way to **2a** to give 170 mg (65%) of **2c**.

^{1}H NMR (400.1, $CDCl_3$): δ = 7.51 (dd, ^3J = 8.5 Hz, ^4J = 2.1 Hz, 1H, aryl), 7.34–7.26 (m, 4H, aryl), 7.11–7.08 (m, 2H, aryl), 6.96 (d, ^3J = 8.6 Hz, 1H, aryl), 6.41 (bt, 1H, NH), 4.39 (dd, ^2J = 14.7 Hz, ^3J = 6.0 Hz, 1H, CH_2NHBn), 4.33 (dd, ^2J = 14.7 Hz, ^3J = 5.7 Hz, 1H, CH_2NHBn), 3.97 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3.29 (dd, ^3J = 7.5, 4.2 Hz, 1H, CHN_{Az}), 2.83 (d, ^3J = 7.5 Hz, 1H, CH_2N_{Az}), 2.42 (d, ^3J = 4.2 Hz, 1H, CH_2N_{Az}) ppm.

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 165.6 (C=O), 154.0 (Ar–C), 149.4 (Ar–C), 137.2 (Ar–C), 128.8 (Ar–CH), 127.7 (Ar–CH), 127.7 (Ar–C), 127.4 (Ar–CH), 122.5 (Ar–CH), 110.7 (Ar–CH), 110.2 (Ar–CH), 56.3 (CH_3), 43.0 (CH_2–N), 38.4 (CH–N_{Az}), 33.4 (CH_2–N_{Az}) ppm.

IR (KBr) = 3261, 1652, 1508, 1324, 1262, 1162.

MS (EI): *m*/*z* (%) = 377 (M, 100).

HRMS: calcd for $C_{18}H_{21}O_5N_2S$: 377.1171, found: 377.1181.

4.2.4. 1-Benzoyl-N-benzylaziridine-2-carboxamide (**2d**)

This compound was prepared in an analogous way to **2a** with 100 mg (0.24 mmol) **1** to give 45 mg (67%) of **2d**.

^{1}H NMR (600.13, $CDCl_3$): δ = 7.91 (d, ^3J = 7.3 Hz, 2H, aryl), 7.51 (t, ^3J = 7.3 Hz, 1H, aryl), 7.36 (t, ^3J = 7.7 Hz, 2H, aryl), 7.29 (t, ^3J = 7.3 Hz, 2H, aryl), 7.25–7.19 (m, 3H, aryl), 6.61 (bt, 1H, NH), 4.47 (dd, ^2J = 14.7 Hz, ^3J = 6.2 Hz, 1H, CH_2NHBn), 4.40 (dd, ^2J = 14.7 Hz, ^3J = 5.8 Hz, 1H, CH_2NHBn), 3.14 (dd, ^3J = 6.6, 3.3 Hz, 1H, CHN_{Az}), 2.68 (d, ^3J = 6.6 Hz, 1H, CH_2N_{Az}), 2.42 (d, ^3J = 3.3 Hz, 1H, CH_2N_{Az}) ppm.

^{13}C NMR (150.92 MHz, $CDCl_3$): δ = 177.24 (C=O), 167.33 (C=O), 137.70 (Ar–C), 133.50 (Ar–CH), 131.76 (Ar–C), 129.07 (Ar–CH), 128.85 (Ar–CH), 128.68 (Ar–CH), 127.78 (Ar–CH), 43.28 (CH_2–N), 37.40 (CH–N_{Az}), 32.28 (CH_2–N_{Az}) ppm.

IR (KBr) = 3330, 1673, 1659, 1348.

MS (EI): *m*/*z* (%) = 280 (M-1, 2%), 175 (15), 147 (15), 105 (100), 77 (50), 91 (25).

HRMS: calcd for $C_{17}H_{17}O_2N_2$: 281.1290, found: 281.1289.

4.3. General procedure for fluorination of aziridine-based model compound **3a–c**

4.3.1. N-Benzyl-3-fluoro-2-(4-methylphenyl sulfonamido)-propanamide (**3a**)

30 mg (0.091 mmol) of **2a** was dissolved in DMSO (2 ml) followed by the addition of 37.6 mg (0.1 mmol) Kryptofix ($K_{2.2.2}$) and 5.8 mg (0.1 mmol) KF. The reaction mixture was stirred at 50 °C for 1 h, taken up in ethyl acetate and extracted with saturated ammonium chloride solution. The combined aqueous phases were extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel with hexane/ethyl acetate (2:1) to give (47%) of **3a**.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 7.76 (d, ^3J = 8.4 Hz, 2H, aryl), 7.38–7.26 (m, 3H, aryl), 7.32 (d, ^3J = 8.4 Hz, 2H, aryl), 7.19 (d, ^3J = 8.1 Hz, 2H), 6.72 (bt, 1H, $NHCH_2$Bn), 5.41 (d, ^3J = 7.4 Hz, 1H,

$NHSO_2$), 4.84 (ddd, $^2J_{H,F}$ = 45.7 Hz, $^2J_{H,H}$ = 9.4 Hz, ^3J = 3.8 Hz, 1H, CH_2F), 4.45 (dd, ^2J = 14.9 Hz, ^3J = 6.1 Hz, 1H, CH_2Bn), 4.40 (dd, ^2J = 14.9 Hz, ^3J = 5.8 Hz, 1H, CH_2Bn), 4.20 (ddd, $^2J_{H,F}$ = 47.5 Hz, $^2J_{H,H}$ = 9.4 Hz, ^3J = 5.5 Hz, 1H, CH_2F), 3.95 (m, 1H, $CHCH_2F$), 2.44 (s, 3H, CH_3) ppm.

^{13}C NMR (150.92 MHz, d_6-DMSO): δ = 167.33 (C=O), 142.86 (Ar–C), 138.77 (Ar–C), 138.26 (Ar–C), 129.59 (Ar–CH), 128.40 (Ar–CH), 127.20 (Ar–CH), 126.95 (Ar–CH), 126.74 (Ar–CH), 83.63; 82.48 ($J_{C,F}$ = 174.3 Hz, CH_2F), 56.46; 56.33 ($^2J_{C,F}$ = 21.6 Hz, CH_2FCH–N), 42.39 (CH_2–N), 21.20 (CH_3) ppm.

IR (KBr) = 3336, 3259, 1653, 1330, 1163.

MS (EI): *m*/*z* (%) = 351 (M, 100%).

HRMS: calcd for $C_{17}H_{20}O_3N_2SF$: 351.1179, found: 351.1178.

4.3.2. N-Benzyl-3-fluoro-2-(2,4,6-triisopropylphenylsulfonamido)-propanamide (3b)

This compound was prepared in an analogous way to **3a** to give 14 mg (60%) of **3b**.

^1H NMR (400.1 MHz, $CDCl_3$): δ = 7.35–7.16 (m, 5H, aryl), 7.19 (s, 2H, aryl), 6.84 (bt, 1H, $NHCH_2Bn$), 5.40 (d, ^3J = 7.3 Hz, 1H, $NHSO_2$), 4.90 (ddd, $^2J_{H,F}$ = 45.7 Hz, $^2J_{H,H}$ = 9.1 Hz, ^3J = 3.3 Hz, 1H, CH_2F), 4.51 (dd, ^2J = 14.9 Hz, ^3J = 6.3 Hz, 1H, CH_2Bn), 4.40 (dd, ^2J = 14.9 Hz, ^3J = 5.5 Hz, 1H, CH_2Bn), 4.25 (ddd, $^2J_{H,F}$ = 47.7 Hz, $^2J_{H,H}$ = 9.3 Hz, ^3J = 5.1 Hz, 1H, CH_2F), 4.06 (m, 1H, $CHCH_2F$), 4.02 (sept, ^3J = 6.8 Hz, 2H, $CH(CH_3)_2$), 2.91 (sept, ^3J = 6.8 Hz, 1H, $CH(CH_3)_2$), 1.19 (m, 18H, CH_3) ppm.

^{13}C NMR (100.5 MHz, d_6-DMSO): δ = 167.5 (C=O), 152.2 (Ar–C), 149.7 (Ar–C), 138.7 (Ar–C), 133.8 (Ar–C), 128.4 (Ar–CH), 127.2 (Ar–CH), 127.0 (Ar–CH), 123.6 (Ar–CH), 84.0; 82.3 ($J_{C,F}$ = 174.1, CH_2F), 56.0; 55.8 ($^2J_{C,F}$ = 21.5 Hz, CH_2FCH–N), 42.5 (CH_2–N), 33.5 ($CH(CH_3)_2$), 29.2 ($CH(CH_3)_2$), 24.8 (CH_3), 23.6 (CH_3) ppm.

IR (KBr) = 3379, 2961, 1672.

MS (EI): *m*/*z* (%) = 463 (M, 100), 259 (23).

HRMS: calcd for $C_{25}H_{36}O_3N_2SF$: 463.2431, found: 463.2440.

4.3.3. N-Benzyl-2-(3,4-dimethoxyphenylsulfonylamino)-3-fluoropropanamide (3c)

This compound was prepared in an analogous way to **3a** at 80 °C to give 7.2 mg (23%) of **3c**.

^1H NMR (400.1, $CDCl_3$): δ = 7.48 (dd, ^3J = 8.3 Hz, ^4J = 2 Hz, 1H, aryl), 7.34–7.26 (m, 5H, aryl), 7.18 (d, ^3J = 8.2 Hz, 1H, aryl), 6.92 (d, ^3J = 8.4 Hz, 1H, aryl), 6.71 (bt, 1H, $NHCH_2Bn$), 5.43 (d, ^3J = 7.3, 1H, $NHSO_2$), 4.84 ($^2J_{H,F}$ = 45.7 Hz, $^2J_{H,H}$ = 9.4 Hz, ^3J = 3.8 Hz, 1H, CH_2F), 4.45 (dd, ^2J = 14.9 Hz, ^3J = 6.1 Hz, 1H, CH_2Bn), 4.41 (dd, ^2J = 14.9 Hz, ^3J = 5.6 Hz, 1H, CH_2Bn), 4.26 ($^2J_{H,F}$ = 47.5 Hz, $^2J_{H,H}$ = 9.4 Hz, ^3J = 5.5 Hz, 1H, CH_2F), 3.95 (s, 3H, CH_3), 3.93 (m, 1H, $CHCH_2F$), 3.90 (s, 3H, CH_3) ppm.

IR (KBr) = 3334, 2956, 1642, 1512.

MS (EI): *m*/*z* (%) = 397 (M, 100), 247 (15), 122 (40), 111 (36).

HRMS: calcd for $C_{18}H_{22}O_5N_2SF$: 397.1233, found: 397.1241.

4.4. Synthesis and characterization of aziridine-based biomolecules (10a–c) and their corresponding standard references (11a–c)

4.4.1. 2,5-Dioxopyrrolidin-1-yl 1-tritylaziridine-2-carboxylate (6)

910 mg (2.76 mmol) **5** was dissolved in dichloromethane, benzotriazole-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) (1.34 g, 3.04 mmol) and N-hydroxysuccinimide (318 mg, 2.76 mmol) were added and the solution was cooled down to 0 °C. Then diisopropylethylamine (0.76 ml, 4.42 mmol) was added slowly and the reaction was stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane, washed with 10% citric acid and brine, dried over sodium sulfate and concentrated. The residue was purified by flash chromatography on silica gel with toluene/ethyl acetate (1:1) to give 760 mg (63%) of compound **6**.

^1H NMR (300.1 MHz, MeOD): δ = 7.45 (m, 6H, aryl), 7.30–7.17 (m, 9H, aryl), 2.84 (s, 4H, CH_2CH_2), 2.44 (m, 1H, CHN_{Az}), 2.09 (m, 1H, CH_2N_{Az}), 1.60 (d, ^2J = 6.0 Hz, 1H, CH_2N_{Az}) ppm.

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 168.8 (C=O), 167.0 (C=O), 143.0 (Ar–C), 129.3 (Ar–CH), 127.9 (Ar–CH), 127.2 (Ar–CH), 74.7 (C–Ar_3), 30.1 (CH–N_{Az}), 29.7 (CH_2–N_{Az}), 25.6 (CH_2CH_2) ppm.

IR (KBr) = 3058, 1812, 1783, 1739, 1203.

MS (EI): *m*/*z* (%) = 449 (M+Na, 15), 367 (35), 243 (100).

HRMS: calcd for $C_{26}H_{22}O_4N_2Na$: 449.1477, found: 449.1478.

4.4.2. Methyl 2-(1-tritylaziridine-2-carboxamido)acetate (7)

218 mg (1.74 mmol) glycine methylester hydrochloride was dissolved in DMF (10 ml) and treated with triethylamine (0.36 ml, 2.6 mmol). After 30 min at room temperature 740 mg (1.74 mmol) **6** was added. The reaction mixture was stirred for 2 h at 50 °C and then concentrated. The residue was purified by flash chromatography on silica gel with toluene/ethyl acetate (1:1) to give 550 mg (79%) of **7**.

^1H NMR (400.1 MHz, $CDCl_3$): δ = 7.45–7.43 (m, 6H, aryl), 7.32–7.17 (m, 9H, aryl), 4.22 (dd, ^2J = 18.1 Hz, ^3J = 6.0 Hz, 1H, CH_2N), 4.10 (dd, ^2J = 18.1 Hz, ^3J = 5.3 Hz, 1H, CH_2N), 3.81 (s, 3H, CH_3O), 2.05 (m, 2H, CHN_{Az}, CH_2N_{Az}), 1.50 (d, ^3J = 5.8 Hz, 1H, CH_2N_{Az}) ppm.

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 171.3 (C=O), 170.31 (C=O), 143.2 (Ar–C), 129.3 (Ar–CH), 127.8 (Ar–CH), 127.2 (Ar–CH), 74.6 (C–Ar_3), 52.4 (CH_3–O), 40.6 (CH_2–N), 34.0 (CH–N_{Az}), 29.9 (CH_2–N_{Az}).

IR (KBr) = 3379, 1753, 1669, 1521, 1210, 707.

MS (EI): *m*/*z* (%) = 401 (M, 4), 243 (100), 165 (4).

HRMS: calcd for $C_{25}H_{25}O_3N_2$: 401.1865, found: 401.1868.

4.4.3. Methyl-2-(1-(2,4,6-triisopropylphenylsulfonyl)aziridine-2-carboxamido]acetate (8)

1.05 g (2.62 mmol) **7** was dissolved in chloroform (45 ml), cooled down to 0 °C and titrated with trifluoroacetic acid (0.81 ml, 10.49 mmol) until complete conversion. The mixture was neutralized with saturated sodium bicarbonate solution (ca. 8 ml) and concentrated. The residue was suspended in ethyl acetate (16 ml) and saturated sodium bicarbonate solution (16 ml) followed by triisopropyl benzyl sulfonic acid chloride (1.99 g, 6.55 mmol). The reaction mixture was stirred overnight at room temperature. The phases were separated, the aqueous phase was extracted with ethyl acetate and the combined organic phases were dried over sodium sulfate and concentrated. The residue was purified by flash chromatography on silica gel with hexane/ethyl acetate (2:1) to give 258 mg (23%) of **8**.

^1H NMR (300.1 MHz, MeOD): δ = 7.33 (s, 2H, aryl), 4.33 (sept, ^3J = 6.8 Hz, 2H, $CH(CH_3)_2$), 3.98 (m, 2H, CH_2–N), 3.73 (s, 3H, CH_3O), 3.43 (dd, ^3J = 7.4, 4.2 Hz, 1H, CHN_{Az}), 2.98 (sept, ^3J = 7.0 Hz, 2H, $CH(CH_3)_2$), 2.87 (d, ^3J = 7.4 Hz, 1H, CH_2N_{Az}), 2.60 (d, ^3J = 4.2 Hz, 1H, CH_2N_{Az}), 1.32–1.28 (m, 18H, CH_3) ppm.

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 169.4 (C=O), 166.4 (C=O), 154.3 (Ar–C), 151.4 (Ar–C), 130.0 (Ar–C), 124.1 (Ar–CH), 52.5 (CH_3–O), 40.8 (CH_2–N), 37.3 (CH–N_{Az}), 34.3 ($CH(CH_3)_2$), 33.5 (CH_2–N_{Az}), 29.9 ($CH(CH_3)_2$), 24.9 (CH_3), 24.8 (CH_3), 23.5 (CH_3).

IR (KBr) = 3404, 2961, 1753, 1696, 1152.

MS (EI): *m*/*z* (%) = 425 (M, 100).

HRMS: calcd for $C_{21}H_{33}O_5N_2S$: 425.2110, found: 425.2102.

4.4.4. 2-(1-(2,4,6-Triisopropylphenylsulfonyl)aziridine-2-carboxamido) acetic acid (9)

410 mg (0.97) **8** was dissolved in tetrahydrofuran (12 ml), cooled down to 0 °C and treated with 0.58 ml (1.16 mmol) 2N sodium hydroxide solution. The reaction mixture was stirred at room temperature for 2 h and concentrated. The residue was taken up in water, carefully neutralized with citric acid and extracted with ethyl acetate. The combined organic phases were washed

with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel with hexane/ethyl acetate (2:1) to yield 299 mg (75%) of **9**.

^{1}H NMR (300.1 MHz, MeOD): δ = 7.27 (s, 2H, aryl), 4.27 (sept, ^3J = 6.8 Hz, 2H, $CH(CH_3)_2$), 3.90 (m, 2H, CH_2–N), 3.39 (dd, ^3J = 7.3, 4.1 Hz, 1H, CHN_{Az}), 2.93 (sept, ^3J = 7.0 Hz, 2H, $CH(CH_3)_2$), 2.78 (d, ^3J = 7.3 Hz, 1H, CH_2N_{Az}), 2.55 (d, ^3J = 4.1 Hz, 1H, CH_2N_{Az}), 1.30–1.23 (m, 18H, CH_3) ppm.

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 172.7 (C=O), 166.8 (C=O), 154.4 (Ar–C), 151.4 (Ar–C), 129.9 (Ar–C), 124.2 (Ar–CH), 40.7 (CH_2–N), 37.1 (CH–N_{Az}), 34.3 ($CH(CH_3)_2$), 33.5 (CH_2–N_{Az}), 30.0 ($CH(CH_3)_2$), 24.9 (CH_3), 24.8 (CH_3), 23.5 (CH_3).

IR (KBr) = 3363, 2960, 1743, 1650, 1328.

MS (EI): *m*/*z* (%) = 411 (M, 100).

HRMS: calcd for $C_{20}H_{31}O_5N_2S$: 411.1954, found: 411.1967.

4.4.5. 2-(1-(2,4,6-Triisopropylphenylsulfonyl)aziridine-2-carboxamido)-N-methylcarbonyl-Val-βAla-Phe-Gly-NH_2 (10a)

0.1 mmol resin bound tetrapeptide **12**, swollen in DMF (3 ml), was added to a solution of **9** (123 mg, 0.3 mmol), *o*-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HBTU) (113.7 mg, 0.3 mmol) and diisopropylethylamine (104.5 μl, 0.6 mmol) in 1.5 ml DMF. The mixture was shaken for 4 h, filtered and the remaining resin was washed with DMF and dichloromethane and dried under vacuum. Then the resin was treated with 1.5 ml of a mixture containing 85% TFA, 5% water, 5% phenol and 5% triisopropyl silane for 2 h, filtered followed by precipitation of the product in 20 ml MTBE. The precipitate was purified by HPLC to give 20 mg (25.5%) of **10a**.

HPLC-MS (ES+): *m*/*z* $[M+H]^+$ calcd: 784.4, found: 784.6.

4.4.6. 2-(1-(2,4,6-Triisopropylphenylsulfonyl)aziridine-2-carboxamido)-N-methylcarbonyl-Ava-Gln-Trp-Ala-Val-Gly-His-FA01010-Cpa-NH_2 (10b)

0.15 mmol resin bound octapeptide **13**, swollen in DMF (3 ml), was added to a solution of **9** (92.3 mg, 0.22 mmol), HBTU (85.3 mg, 0.22 mmol) and (26.13 μl, 0.15 mmol) diisopropylethylamine in 1.0 ml DMF. The mixture was shaken for 14 h, filtered and the remaining resin was washed with DMF and dichloromethane and dried under vacuum. Then the resin was treated with 1.5 ml of a mixture containing 85% TFA, 5% water, 5% phenol and 5% triisopropyl silane for 3 h, filtered followed by precipitation of the product in 40 ml MTBE. The precipitate was purified by HPLC to give 7.3 mg (3.3%) **10b**.

HPLC-MS (ES+): *m*/*z* $[(M+2H)/2]^+$ calcd: 727.4, found: 727.6.

Compound **10c** was synthesized via the following synthetic procedures.

4.4.7. 1-((2R,4S,5R)-4-(1-Methoxycyclohexyloxy)-5-(1-methoxycyclohexyloxymethyl) tetrahydrofuran-2-yl]-5-methylpyrimidine-2,4(1H, 3H)-dione (15)

Thymidine (2 g, 8.26 mmol) was dissolved in dichloromethane (150 ml) followed by the addition of methoxy cyclohexene (8.42 g, 24.77 mmol) and *p*-toluene sulfonic acid (50 mg, 0.26 mmol). The reaction mixture was stirred over night at RT, diluted with dichloromethane and washed with saturated bicarbonate solution and brine. The organic phase was dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel with hexane/ethyl acetate (1:4) to give 3.55 g (92%) of the title compound.

^{1}H NMR (300.1 MHz, DMSO-d_6): δ = 11.30 (s, 1H, NH), 7.46 (d, ^4J = 1.1 Hz, =CH), 6.11 (dd, ^3J = 7.5, 6.4 Hz, 1H, 1CH), 4.39 (m, 1H, CH–O), 3.96 (m, 1H, CH–O), 3.46 (dd, ^2J = 10.6 Hz, ^3J = 4.0 Hz, 1H, CH_2–O), 3.44 (dd, ^2J = 10.6 Hz, ^3J = 4.6 Hz, 1H, CH_2–O), 3.06 (s, 3H, CH_3–O), 3.05 (s, 3H, CH_3–O), 2.14 (m, 1H, 2′CH_2), 1.75 (s, 3H, CH_3–C=C), 1.75–1.25 (m, 20H, cyclohexyl) ppm.

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 163.6 (C=O), 150.2 (C=O), 135.5 (=CH), 110.7 (=CCH_3), 101.3 (OCO), 100.4 (OCO), 85.1 (CHO), 84.9 (CHO), 69.8 (NCO), 59.6 (CH_2O), 48.0 (CH_3O), 47.7 (CH_3O), 40.0, 34.1, 33.8, 33.3, 33.1, 25.5, 25.3, 22.9, 22.9, 22.8 (cyclohexyl), 12.5 (CH_3–C=).

IR (KBr) = 3199, 3068, 2939, 1692, 1094.

MS (ESI−): *m*/*z* (%) = 465 (M-1, 20), 399 (100), 227 (47).

HRMS: calcd for $C_{24}H_{37}O_7N_2$: 465.2601, found: 465.2608. $[\alpha]_D^{25}$ 19.3 (c 1.02 g/100 ml MeOH).

4.4.8. 2-(3-(3-[(2R,4S,5R)-4-(1-Methoxycyclohexyloxy)-5-((1-methoxycyclohexyloxyl)tetrahydrofuran-2-yl]-5-methyl-2,6-dioxo-2,3-dihydro-pyrimidin-1(6H)-yl)propyl-isoindole-1,3-dione (16)

15 (5 g, 10.72 mmol) and potassium carbonate (4 g, 28.93 mmol) were dissolved in DMF/acetone (50 ml, 1/1) followed by the addition of *N*-(3-bromopropyl) phthalimide (3.74 g, 13.93 mmol) in DMF/acetone (10 ml, 1/1). The reaction mixture was stirred at 50 °C for 6 h and 4 d at RT. The precipitate formed was filtered off, washed with acetone and the combined organic phases were concentrated. The residue was taken up in water and dichloromethane, phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel with hexane/ethyl acetate (1:4) to yield 6.4 g (91%) of the compound.

^{1}H NMR (300.1 MHz, DMSO-d_6): δ = 7.83–7.78 (m, 4H, aryl), 7.50 (d, ^4J = 1.1 Hz, =CH), 6.10 (dd, ^3J = 7.2, 6.6 Hz, 1H, 1CH), 4.38 (m, 1H, CH–O), 3.96 (m, 1H, CH–O), 3.79 (t, ^3J = 8.3 Hz, 2H, CH_2–N), 3.55 (t, ^3J = 7.0 Hz, 2H, CH_2–N), 3.47 (dd, ^2J = 10.4 Hz, ^3J = 3.6 Hz, 1H, CH_2–O), 3.43 (dd, ^2J = 10.4 Hz, ^3J = 4.3 Hz, 1H, CH_2–O), 3.06 (s, 3H, CH_3–O), 3.04 (s, 3H, CH_3–O), 2.14 (m, 1H, 2CH_2), 1.85 (hept, ^3J = 7.0 Hz, CH_2), 1.75 (s, 3H, CH_3–C=C), 1.75–1.25 (m, 20H, cyclohexyl) ppm.

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 168.3 (C=O), 163.3 (C=O), 150.8 (C=O), 133.8 (Ar–CH), 133.6 (=CH), 132.2 (Ar–C), 123.2 (Ar–CH), 109.9 (=CCH_3), 101.3 (OCO), 100.4 (OCO), 85.6 (CHO), 85.1 (CHO), 69.8 (NCO), 59.6 (CH_2O), 48.0 (CH_3O), 47.7 (CH_3O), 40.1 (cyclohexyl), 39.1 (CH_2N), 36.0 (CH_2N), 34.2, 33.8, 33.3, 33.1, 26.9, 25.5, 25.4, 22.94, 22.9, 22.9, 22.8 (CH_2, cyclohexyl), 13.2 (CH_3–C=).

IR (KBr) = 2935, 1710, 1666, 1642, 1090, 1040.

MS (ESI+): *m*/*z* (%) = 676 (M+Na, 100), 654 (M+1, 12), 412 (29).

HRMS: calcd for $C_{35}H_{48}O_9N_3$: 654.3391, found: 654.3387.

$[\alpha]_D^{25}$ + 18.9 (c 1.08 g/100 ml MeOH).

4.4.9. 3-(3-Aminopropyl)-1-((2R,4S,5R)-4-(1-methoxycyclohexyloxy)-5-(1-methoxy cyclohexyloxymethyl) tetrahydrofuran-2-yl]-5-methylpyrimidine-2,4(1H, 3H)-dione (14)

16 (6.3 g, 9.64 mmol) was dissolved in ethanol (250 ml) and treated with hydrazine hydrate (1.27 ml, 26.09 mmol). The reaction mixture was stirred at RT for 4 d, the precipitate was filtered off and the solution was concentrated. The residue was purified by flash chromatography on silica gel with dichloromethane/methanol (4:1) to yield 3.77 g (74%) of compound **14**.

^{1}H NMR (300.1 MHz, DMSO-d_6): δ = 7.52 (d, ^4J = 1.1 Hz, 1H, =CH), 6.15 (dd, ^3J = 7.2, 6.6 Hz, 1H, 1′CH), 4.38 (m, 1H, CH–O), 3.97 (m, 1H, CH–O), 3.80 (t, ^3J = 7.4 Hz, 2H, CH_2–N), 3.47 (dd, ^2J = 10.5 Hz, ^3J = 3.8 Hz, 1H, CH_2–O), 3.43 (dd, ^2J = 10.5 Hz, ^3J = 4.4 Hz, 1H, CH_2–O), 3.06 (s, 3H, CH_3–O), 3.04 (s, 3H, CH_3–O), 2.18 (m, 1H, 2′CH_2), 1.80 (s, 3H, CH_3–C=C), 1.72 (m, 2H, CH_2), 1.57–1.24 (m, 20H, cyclohexyl) ppm.

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 163.4 (C=O), 150.7 (C=O), 133.3 (=CH), 109.7(=CCH_3), 101.1 (OCO), 100.2 (OCO), 85.4 (CHO), 84.9 (CHO), 69.6 (NCO), 59.4 (CH_2O), 47.7 (CH_3O), 47.5 (CH_3O), 39.9 (cyclohexyl), 39.0 (CH_2N), 38.4 (CH_2N), 34.0, 33.6, 33.1, 32.9, 31.3, 25.3, 25.2, 22.7, 22.6 (CH_2, cyclohexyl), 13.0 (CH_3–C=).

IR (KBr) = 2939, 1700, 1670, 1654, 1467, 1095.
MS (ESI+): *m*/*z* (%) = 524 (M+1, 15), 492 (100), 412 (10).
HRMS: calcd for $C_{27}H_{46}O_7N_3$: 524.3336, found: 524.3330.
$[\alpha]_D^{25}$ + 22.7 (c 1.07 g/100 ml MeOH).

*4.4.10. N-(2-(3-(3-((2R,4S,5R)-4-(1-Methoxycyclohexyloxy)-5-(1-methoxycyclohexyloxymethyl) tetrahydrofuran-2-yl]-5-methyl-2,6-dioxo-2,3-dihydropyrimidine-1-(6H)-yl)propylamino-2-oxoethyl-1-(2,4,6-triisopropylphenylsulfonyl)aziridine-2-carboxamido (**10c**)*

60 mg (0.15 mmol) **9** was dissolved in 4 ml dichloromethane, to this was added diisopropylcarbodiimide (DIC) (46 μl, 0.29 mmol) followed by the addition of compound **14** (76.5 mg, 0.15 mmol). The reaction mixture was stirred overnight at room temperature and concentrated. The residue was purified by flash chromatography on silica gel with dichloromethane/methanol (9:1) to give 87 mg (65%) of **10c**.

^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.56 (s, 1H, =CH), 7.21 (s, 2H, aryl), 7.01 (t, ^3J = 5.9 Hz, 1H, NH), 6.72 (br t, 1H, NH), 6.35 (m, 1H, 1′CH), 4.51 (m, 1H, CH–O), 4.28 (sept, ^3J = 6.6 Hz, 2H, $CH(CH_3)_2$), 4.16 (m, 1H, CH–O), 4.08 (dd, ^2J = 16.8 Hz, ^3J = 6.2 Hz, 1H, CH_2–N), 3.97 (m, 2H, $C(O)CH_2$–N), 3.76 (dd, ^2J = 16.8 Hz, ^3J = 4.4 Hz, 1H, CH_2–N), 3.67 (dd, ^2J = 10.6 Hz, ^3J = 2.6 Hz, 1H, CH_2–O), 3.57 (dd, ^2J = 10.6 Hz, ^3J = 2.6 Hz, 1H, CH_2–O), 3.44 (dd, ^2J = 7.4 Hz, ^3J = 4.0 Hz, 1H, CHN_{Az}), 3.21 (s, 3H, CH_3–O), 3.18 (s, 3H, CH_3–O), 3.16 (m, 2H, CH_2–N), 2.92 (sept, ^3J = 7.0 Hz, 1H, $CH(CH_3)_2$), 2.86 (d, ^3J = 7.4 Hz, 1H, CH_2N_{Az}), 2.66 (d, ^3J = 4.0 Hz, 1H, CH_2N_{Az}), 2.36 (m, 1H, 2′CH_2), 2.05 (m, 1H, $2CH_2$), 1.91 (s, 3H, CH_3–C=C), 1.82–1.76 (m, 6H, cyclohexyl, CH_2), 1.54–1.37 (m, 16H, cyclohexyl), 1.30–1.26 (m, 18H, CH_3) ppm.

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 167.5 (C=O), 166.7 (C=O), 164.1 (C=O), 154.2 (Ar–C), 151.4 (Ar–C), 151.1 (C=O), 134.1 (=CH), 130.1 (Ar–C), 124.1 (Ar–CH), 109.9 (=CCH_3), 101.4 (OCO), 100.4 (OCO), 85.7 (CHO), 85.2 (CHO), 69.7 (NCO), 59.5 (CH_2O), 48.0 (CH_3O), 47.7 (CH_3O), 42.7 (CH_2–N), 40.2 (cyclohexyl), 38.2 (CH_2–N), 37.5 (CH–N_{Az}), 35.5 (CH_2N), 34.3 ($CH(CH_3)_2$), 34.2, 33.8, 33.5, 33.3 (cyclohexyl), 33.3 (CH_2–N_{Az}), 29.9 ($CH(CH_3)_2$), 27.2, 25.5, 25.3 (CH_2, cyclohexyl), 24.9 (CH_3), 24.9 (CH_3), 23.5 (CH_3), 22.9, 22.9, 22.9, 22.8 (CH_2, cyclohexyl), 13.2 (CH_3–C=).

IR (KBr) = 3347, 2952, 1702, 1671, 1643.
MS (ESI+): *m*/*z* (%) = 938 (M+Na, 15), 692 (100).
HRMS: calcd for $C_{47}H_{73}O_{11}N_5SNa$: 938.4925, found: 938.4943.
$[\alpha]_D^{25}$ − 10.3 (c 1.01 g/100 ml MeOH).

*4.4.11. (RS)-3-Fluoro-2-(2,4,6-triisopropylphenylsulfonamido) propanamide-N-methylcarbonyl-Val-ßAla-Phe-Gly-NH_2 (**11a**)*

0.05 mmol resin bound tetrapeptide, swollen in DMF (1 ml) was filtered and added to a solution of [2(*RS*)-3-fluoro-2-(2,4,6-triisopropylphenylsulfonylamido)propanamide]-acetic acid (64.6 mg, 0.15 mmol), HBTU (56.9 mg, 0.15 mmol) and diisopropylethylamine (26 μl, 0.15 mmol) in 1.0 ml DMF. The mixture was shaken for 4 h, filtered and the remaining resin was washed with DMF and dichloromethane and dried under vacuum. Then the resin was treated with 1.5 ml of a mixture containing 85% TFA, 5% water, 5% phenol and 5% triisopropyl silane for 2 h, filtered followed by precipitation of the product in 20 ml MTBE. The precipitate was purified by HPLC to give 11.6 mg (29%) of **11a**.

HPLC-MS (ES+): *m*/*z* $[M+H]^+$ calcd: 804.4, found: 804.5.

*4.4.12. (RS)-3-Fluoro-2-(2,4,6-triisopropylphenylsulfonamido)propanamide-N-methylcarbonyl-Ava-Gln-Trp-Ala-Val-Gly-His-Fa01010-Cpa-NH_2 (**11b**)*

0.05 mmol resin bound tetrapeptide, swollen in DMF (1 ml) was filtered and added to a solution of ((2*RS*)-3-fluoro-2-(2,4,6-triisopropylphenylsulfonamido)propanamide)-acetic acid (43.0 mg, 0.1 mmol), HBTU (37.9 mg, 0.1 mmol) and diisopropylethylamine (35 μl, 0.2 mmol) in 1.0 ml DMF. The mixture was shaken for 4 h, filtered and the remaining resin was washed with DMF and dichloromethane and dried under vacuum. Then the resin was treated with 1.5 ml of a mixture containing 85% TFA, 5% water, 5% phenol and 5% triisopropyl silane for 2 h, filtered followed by precipitation of the product in methyl tert-butyl ether (MTBE) (20 ml). The precipitate was purified by HPLC to give 7.8 mg (10.5%) of **11b**.

HPLC-MS (ES+): *m*/*z* $[M+H]^+$ calcd: 1473.8, found: 1473.8.

*4.4.13. (RS)-3-Fluoro-N-(2-(3-(3-((2R,4S,5R)-4-(1-methoxycyclohexyloxy)-5-(1-methoxycyclohexyloxymethyl) tetrahydrofuran-2-yl]-5-methyl-2,6-dioxo-2,3-dihydropyrimidine-1-(6H)-yl)propylamino-2-oxoethyl-2-(2,4,6-triisopropylphenylsulfonamido)propanamide (**11c**)*

30 mg (0.033 mmol) **10c** was dissolved in DMSO (1.5 ml) followed by 13.6 mg (0.036 mmol) Kryptofix ($K_{2.2.2}$) and 2.1 mg (0.036 mmol) KF. The reaction mixture was stirred at 50 °C for 30 min until complete disappearance of the starting material. The mixture was then diluted with ethyl acetate, washed with saturated aqueous ammonium chloride solution, brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by preparative TLC on silica gel with dichloromethane/methanol (9.1) to give 5 mg (16%) of **11c**.

^{1}H NMR (600.1 MHz, $CDCl_3$): δ = 7.62 (s, 1H, =CH), 7.52 (dd, ^3J = 7.0, 5.1 Hz, 1H, NH), 7.30 (dd, ^3J = 6.6, 5.9 Hz, 1H, NH), 7.18 (s, 2H, aryl), 6.84 (d, ^3J = 9.2 Hz, 1H, NH), 6.34 (dd,^3J = 7.4, 6.1 Hz, 1H, 1′CH), 4.89 (ddd, $^2J_{H,F}$ = 55.8 Hz, $^2J_{H,H}$ = 9.1 Hz, ^3J = 3.6 Hz, 1H, CH_2F), 4.51 (m, 1H, CH–O), 4.42 (ddd, $^2J_{H,F}$ = 57.3 Hz, $^2J_{H,H}$ = 9.1 Hz, ^3J = 4.0 Hz, 1H, CH_2F), 4.32 (dd, ^2J = 16.8 Hz, ^3J = 7.3 Hz, 1H, $C(O)CH_2$–N), 4.21–4.15 (m, 2H, $C(O)CH_2$–N, CH–O), 4.11 (sept, ^3J = 7.0 Hz, 2H, $CH(CH_3)_2$), 4.01–3.97 (m, 2H, CH_2–N), 3.71–3.66 (m, 2H, CH–NSO_2aryl, CH_2–O), 3.57 (dd, ^2J = 10.6 Hz, ^3J = 2.9 Hz, 1H, CH_2–O), 3.30 (m, 1H, CH_2–N), 3.21 (s, 3H, CH_3), 3.18 (s, 3H, CH_3), 3.02 (m, 1H, CH_2–N), 2.91 (sept, ^3J = 7.0 Hz, 1H, $CH(CH_3)_2$), 2.40 (ddd, ^2J = 13.2 Hz, ^3J = 6.1, 3.0 Hz, 1H, 2′CH_2), 2.07–2.03 (m, 1H, 2′CH_2), 1.88 (s, 3H, CH_3–C=C), 1.86–1.83 (m, 2H, CH_2), 1.80–1.72 (m, 4H, cyclohexyl), 1.60–1.45 (m, 16H, cyclohexyl), 1.27–1.24 (div. d, 18H, CH_3) ppm.

^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 168.5 (C=O), 168.0 (C=O), 164.9 (C=O), 153.7 (Ar–C), 150.6 (Ar–C), 150.6 (C=O), 134.8 (=CH), 131.6 (Ar–C), 124.1 (Ar–CH), 109.5 (=CCH_3), 101.4 (OCO), 100.5 (OCO), 85.9 (CHO), 85.2 (CHO), 82.7; 81.6 ($J_{C,F}$ = 173.5 Hz, CH_2F), 69.6 (NCO), 59.5 (CH_2O), 55.9; 55.8 ($^2J_{C,F}$ = 21.0 Hz, CH_2FCH–N), 48.0 (CH_3O), 47.7 (CH_3O), 43.4 (CH_2–N), 40.3 (cyclohexyl), 38.3 (CH_2–N), 34.9 (CH_2N), 34.2 ($CH(CH_3)_2$), 34.1, 33.8, 33.3, 33.1 (cyclohexyl), 29.9 ($CH(CH_3)_2$), 26.8, 25.5, 25.3 (CH_2, cyclohexyl), 25.0 (CH_3), 24.8 (CH_3), 23.5 (CH_3), 22.9, 22.9, 22.9, 22.8 (CH_2, cyclohexyl), 13.1 (CH_3–C=).

IR (KBr) = 3371, 2950, 2937, 1695, 1666, 1463, 1093.
MS (ESI−): *m*/*z* (%) = 935 (M-1, 30), 822 (100), 710 (60).
HRMS: calcd for $C_{47}H_{74}O_{11}N_5SK$: 974.4727, found: 974.4741.

4.5. ^{18}F-Radiolabeling of synthesized compounds

*4.5.1. N-Benzyl-3-[^{18}F]fluoro-2-(4-methylphenyl sulfonamido)-propanamide ([^{18}F]**3a**)*

No-carrier added [^{18}F]fluoride was produced *via* the ^{18}O(p, n)^{18}F nuclear reaction by irradiation of enriched [^{18}O]H_2O. [^{18}F]Fluoride was trapped on an anion-exchange resin cartridge (Sep-Pak QMA light, Waters). The cartridge was eluted with a solution of Kryptofix (5 mg), potassium carbonate (1 mg) in water (500 μl) and MeCN (1 ml). The solvent was removed by heating at 110 °C under vacuum for 10 min with a stream of nitrogen. Anhydrous MeCN (1 ml) was added and evaporated. This step of adding acetonitrile (1 ml) was repeated again to give the dried K[^{18}F]F/$K_{2.2.2}$ complex. A solution of **5a** (2 mg, 30 mM) in

anhydrous DMSO (200 μl) was added. After heating at 70 °C for 15 min, the reaction was cooled to room temperature and diluted with MeCN (1 ml). The crude reaction mixture was analyzed using an analytical HPLC (Column Nucleosil C18, 250 mm × 4 mm, 5 μm, 1 ml/min, solvent A: H_2O, solvent B: MeCN, gradient 10–40% B in 15 min), the incorporation yield was 95%. The ^{18}F-labeled product was confirmed by co-injection with the ^{19}F cold standard on the same column.

4.5.2. N-Benzyl-3-[^{18}F]fluoro-2-(2,4,6-triisopropylphenylsulfonamido)-propanamide ([^{18}F]3b)

A solution of **2b** (2 mg, 22 mM) in anhydrous DMSO (200 μl) was added to the dried K[^{18}F]F/$K_{2.2.2}$ complex (1.2 GBq). After heating at 60 °C for 15 min, the reaction was cooled to room temperature and diluted with MeCN (1 ml). The crude reaction mixture was analyzed using an analytical HPLC (Column Nucleosil C18, 250 × 4 mm, 5 μm, 1 ml/min, solvent A: H_2O, solvent B: MeCN, gradient 40–95% B in 20 min), the incorporation yield was 97%. The ^{18}F labeled product was confirmed by co-injection with the ^{19}F cold standard on the same column.

4.5.3. N-Benzyl-2-(3,4-dimethoxyphenylsulfonylamino)-3-[^{18}F]fluoropropanamide ([^{18}F]3c)

A solution of **2c** (2 mg, 26 mM) in anhydrous DMSO (200 μl) was added to the dried K[^{18}F]F/$K_{2.2.2}$ complex (4.2 GBq). After heating at 70 °C for 15 min, the reaction was cooled to room temperature and dilute with MeCN (1 ml). The crude reaction mixture was analyzed using an analytical HPLC (Column Nucleosil C18, 250 mm × 4 mm, 5 μm, 1 ml/min, solvent A: H_2O, solvent B: MeCN, gradient 10–60% B in 15 min), the incorporation yield was 97%. The ^{18}F labeled product was confirmed by co-injection with the ^{19}F cold standard on the same column.

4.5.4. (RS)-3-[^{18}F]Fluoro-2-(2,4,6-triisopropylphenylsulfonamido)propanamide-N-methylcarbonyl-Val-ßAla-Phe-Gly-NH_2 ([^{18}F]11a)

A solution of **10a** (2 mg, 12.7 mM) in anhydrous DMSO (200 μl) was added to the dried K[^{18}F]F/$K_{2.2.2}$ complex (3.4 GBq). After heating at 60 °C for 15 min, the reaction was cooled to room temperature and diluted with MeCN (1 ml). The crude reaction mixture was analyzed using an analytical HPLC (Column Lichrosorb RP18, 250 mm × 4 mm, 5 μm, 1 ml/min, solvent A: H_2O, solvent B: MeCN, gradient 15–95% B in 20 min), the incorporation yield was 49%. The ^{18}F labeled product was confirmed by co-injection with the ^{19}F cold standard on the same column.

4.5.5. (RS)-3-[^{18}F]Fluoro-2-(2,4,6-triisopropylphenylsulfonamido)propanamide-N-methylcarbonyl-Ava-Gln-Trp-Ala-Val-Gly-His-FA01010-Cpa-NH_2 ([^{18}F]11b)

A solution of **10b** (2 mg, 6.8 mM) in anhydrous DMSO (200 μl) was added to the dried K[^{18}F]F/$K_{2.2.2}$ complex (3.5 GBq). After heating at 70 °C for 15 min, the reaction was cooled to room temperature and diluted with MeCN (1 ml). The crude reaction mixture was analyzed using an analytical HPLC (Column Lichrosphere100 RP18e, 5 μm, 1 ml/min, solvent A: 10 mM K_2HPO_4 in H_2O, solvent B: 10 mM K_2HPO_4 in MeCN/H_2O (7:3), gradient 5–95% in 20 min), the incorporation yield was 7.2%. The ^{18}F labeled product was confirmed by co-injection with the ^{19}F cold standard on the same column.

4.5.6. (RS)-3-[^{18}F]Fluoro-N-(2-(3-(3-((2R,4S,5R)-4-(1-methoxycyclohexyloxy)-5-(1-methoxycyclohexyloxymethyl) tetrahydrofuran-2-yl]-5-methyl-2,6-dioxo-2,3-dihydropyrimidine-1-(6H)-yl)propylamino-2-oxoethyl-2-(2,4,6-triisopropylphenylsulfonamido)propanamide ([^{18}F]11c)

A solution of **10c** (2 mg, 11 mM) in anhydrous DMSO (200 μl) was added to the dried K[^{18}F]F/$K_{2.2.2}$ complex (2.4 GBq). After heating at 90 °C for 20 min, the reaction was cooled to room temperature and diluted with MeCN (1 ml). The crude reaction mixture was analyzed using an analytical HPLC (Column Lichrosphere100 RP18e, 5 μm, 1 ml/min, solvent A: H_2O, solvent B: MeCN, gradient 5–95% in 10 min + iso95% 10 min), the incorporation yield was 87%.

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