

Article

Syntheses of Precursors and Reference Compounds of the Melanin-Concentrating Hormone Receptor 1 (MCHR1) Tracers [¹¹C]SNAP-7941 and [¹⁸F]FE@SNAP for Positron Emission Tomography

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Abstract: The MCH receptor has been revealed as a target of great interest in positron emission tomography imaging. The receptor's eponymous substrate melanin-concentrating hormone (MCH) is a cyclic peptide hormone, which is located predominantly in the hypothalamus with a major influence on energy and weight regulation as well as water balance and memory. Therefore, it is thought to play an important role in the pathophysiology of adiposity, which is nowadays a big issue worldwide. Based on the selective and high-affinity MCH receptor 1 antagonist SNAP-7941, a series of novel SNAP derivatives has been developed to provide different precursors and reference compounds for the radiosyntheses of the novel PET radiotracers [¹¹C]SNAP-7941 and [¹⁸F]FE@SNAP. Positron emission tomography promotes a better understanding of physiologic parameters on a molecular level, thus giving a deeper insight into MCHR1 related processes as adiposity.

Keywords: MCH receptor 1 (MCHR1); SNAP-7941; *rac*SNAP-7941; positron emission tomography; adiposity

1. Introduction

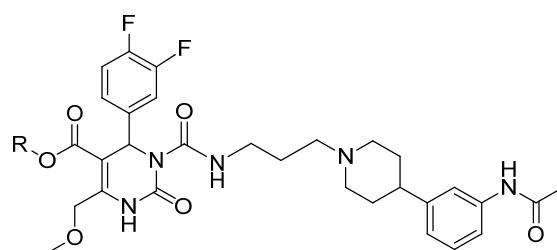
Reports have suggested that the melanin-concentrating hormone (MCH), a cyclic peptide located predominantly in the hypothalamus, plays a significant role in regulation of food intake and stress in rodents. This hormone, which consists of 19 amino acids, regulates physiological functions such as water balance, energy metabolism, general arousal, attention state and is also assumed to be involved in memory and psychiatric disorders, although its role therein still remains largely unknown [1–6].

MCH-producing neurons innervate vast parts of the brain [1–6], but the lateral hypothalamus where most of these neurons have been localized, is considered as the regulatory center for food intake, body temperature, blood pressure, rhythm of sleep, and the reward center which is closely connected with emotions [5]. Animal experiments with MCH overexpressing mice proved the correlation between adiposity and MCH expression: compared with genetic unmodified mice, MCH-OE mice were hyperphagic, hyperleptinaemic, and had higher blood concentrations of glucose. Additionally, these animals were significantly hyperinsulinaemic and showed insulin resistance after insulin injection [3,7,8].

As described by Kokkotou *et al* [8], the adipose-derived hormone leptin determines the regulation of the expression of MCH, other hypothalamic hormones, and the expression of the MCH receptor (MCHR). By gaining deeper insight in the function of the MCHR1 through positron emission tomography (PET), useful information about adiposity can be obtained for future research [3,9]. PET is an important tool both in medical diagnostics and clinical research of molecular processes due to its non-invasive nature as an imaging technique. Based on the already established selective, high-affinity MCHR1 antagonist SNAP-7941 (**1**), which has anorectic, antidepressant, and anxiolytic effects [10–14], the present study aimed at the synthesis and evaluation of precursors and reference standards of the novel MCH receptor 1 PET tracers [¹¹C]SNAP-7941 (**1a**) and [¹⁸F]FE@SNAP (**4a**) [15,16] (Figure 1).

Figure 1. Structure of SNAP-7941 and derivatives **1a–6**.

- 1:** R=CH₃
- 1a:** R=[¹¹C]CH₃
- 2:** R=H
- 3:** R=(CH₂)₂OTs
- 4:** R=(CH₂)₂F
- 4a:** R=(CH₂)₂[¹⁸F]F
- 5:** R=(CH₂)₃OTs
- 6:** R=(CH₂)₃F



In particular, this paper focuses on the synthesis of the novel MCHR1 PET tracers' **1a** and **4a**, non-radioactive reference compound FE@SNAP **4** as well as the precursors SNAP-acid **2** and TOE@SNAP **3**, which represents the preliminary non-radioactive work paving the way for the subsequent radiosyntheses [15,16].

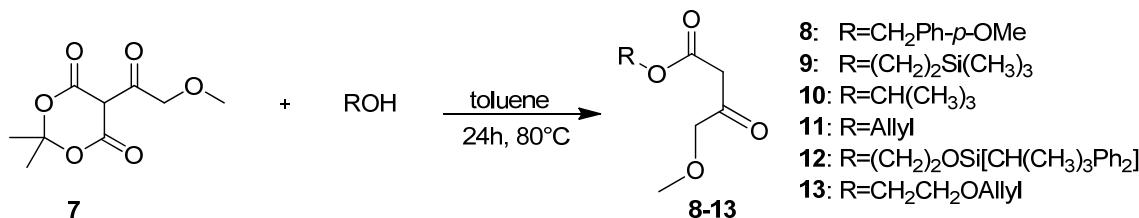
Compounds **2**, **3**, and **5** can either serve as precursors for radioactive labeling or regarding **3** for non-radioactive fluorination. The reference compounds **1**, **4**, and **6** serve as standards for the quality

control of the radiosyntheses. Regarding the tracer [¹¹C]SNAP-7941 (**1a**), *rac*SNAP-7941 **1** [10–14] can be used as a reference compound. *In-vivo* studies, biodistribution, and micro PET investigations of the radiotracers [¹¹C]SNAP-7941 **1a** and [¹⁸F]FE@SNAP **4a** are going to be future challenges directly based on this work.

2. Results and Discussion

All SNAP derivatives and intermediates were produced as racemates, deviating from Borowsky *et al* [1]. The complete reaction sequence is depicted in scheme 1–14. Instead of using methoxymethyl acetoacetate as a starting material for the subsequent Biginelli cyclization, a series of different beta-ketoesters **8–13** carrying different protecting groups for easier cleavage was synthesized (Scheme 1).

Scheme 1. Syntheses of β -ketoesters **8–13**.



Therefore, the first step of the reaction pathway was the preparation of 5-(methoxyacetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**7**) from Meldrum's acid, which was then reacted with altogether six different alcohols in toluene at 80 °C overnight to give β -ketoesters **8–13**. Depending on the alcohol, six different protecting groups were attached as esters: *p*-methoxybenzyl, 2-(trimethylsilyl)ethyl, *t*-butyl, 2-(allyloxy)ethyl and 2-(*tert*-butyldiphenyl-silyloxy)ethyl. The comparison of yields is given in Graph 1 of Figure 2.

As shown in Schemes 2, 4, 5, and 6, the synthesis of *rac*SNAP-7941 **1** was accomplished according to the literature without any modifications to the reaction conditions [17]. Derivatives **29–34** have been substituted with different protecting groups instead of the methyl ester moiety. The Biginelli cyclization reaction was conducted based on an alternative method of Murali Dhar *et al.* [18]. SNAP derivatives **29–32** were used for the synthesis of the precursor SNAP-acid **2**, compounds **33** and **34** served as starting material for the hydroxyethyl derivative **35**, as depicted in Scheme 10.

The syntheses leading to **2** and the allyl protected derivatives **11**, **18**, **25**, and **32** were performed as already described by Philippe *et al.* [15], as were those of compounds **3** and **4** [16]. The syntheses of the already known compounds **1**, **14**, **21** and **28** were carried out according to Schönberger [17]. For completeness of this paper, they are depicted in Schemes 2 and 4–6 as well.

In the next step, a Biginelli reaction was performed using urea, the respective beta ketoesters **8–13** or methoxymethyl acetoacetate, and difluorobenzaldehyde as starting materials, followed by addition of copper oxide, acetic acid, and boron trifluoride diethyl etherate in THF. The mixtures were refluxed for 8 hours to give the seven different pyrimidinones **14–20** (Scheme 2).

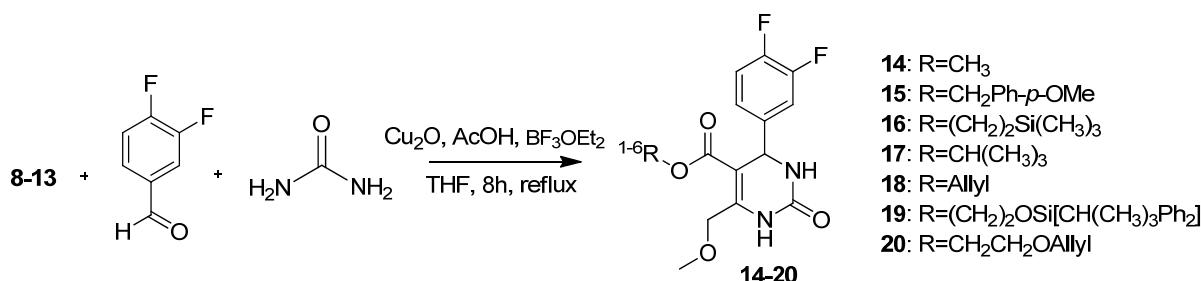
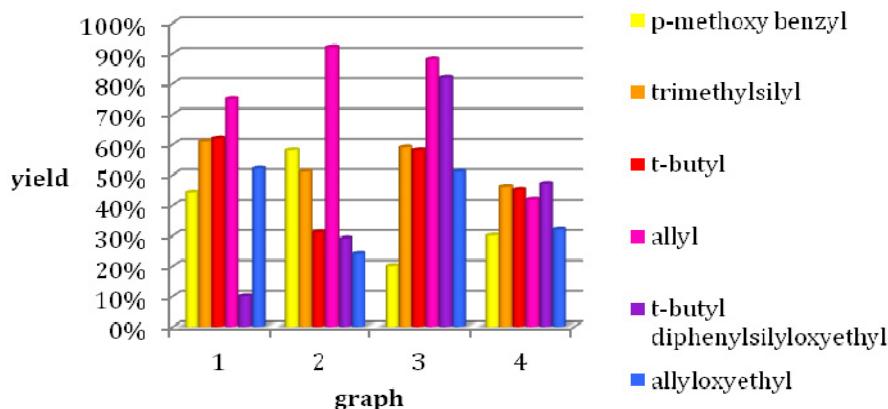
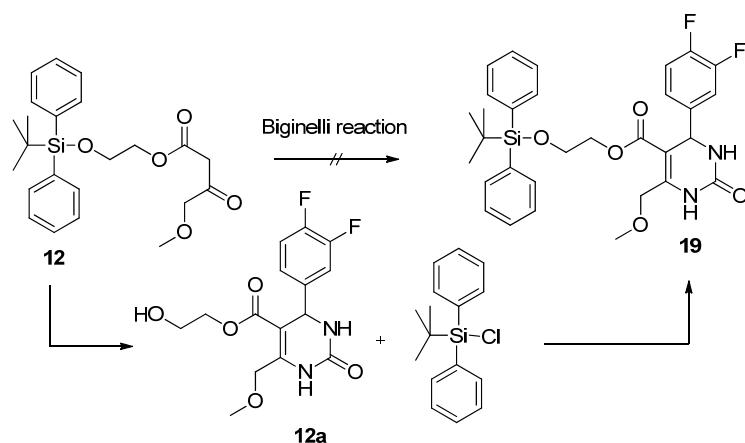
Scheme 2. Biginelli cyclizations.

Figure 2/Graph 2 shows a comparison of the different yields of pyrimidinones **15–20** related to the protecting groups. Cyclization using the *t*-butylester **10**, for example, gave only 30% of the corresponding pyrimidinone **17**, whereas the best yields were accomplished using the allyl protected ester **11**. Allyl pyrimidinone **18** was obtained in an excellent 90% yield.

Figure 2. Yields for different steps in the synthesis of the six SNAP derivatives. Graph 1: synthesis of β -ketoesters **8–13**; graph 2: Biginelli cyclization of **15–20**; graph 3: synthesis of **22–27** in a one-pot two-step reaction; graph 4: synthesis of the SNAP derivatives **29–34**.

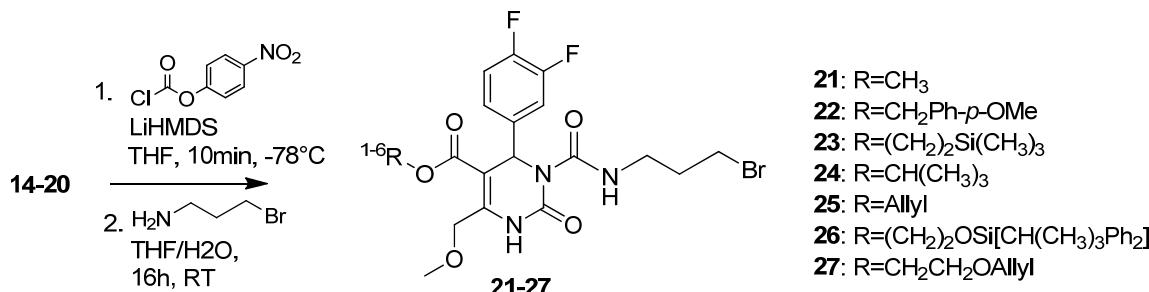


Unfortunately, while reacting the *t*-butyltrimethylsilyloxyethyl protected ester **12** the protecting group was cleaved during the cyclization step, affording hydroxyethyl pyrimidinone **12a** as shown in Scheme 3. Hence, the protecting group had to be reattached in an additional step.

Scheme 3. Biginelli cyclization with *t*-butyltrimethylsilyloxyethyl protected ester **12**.

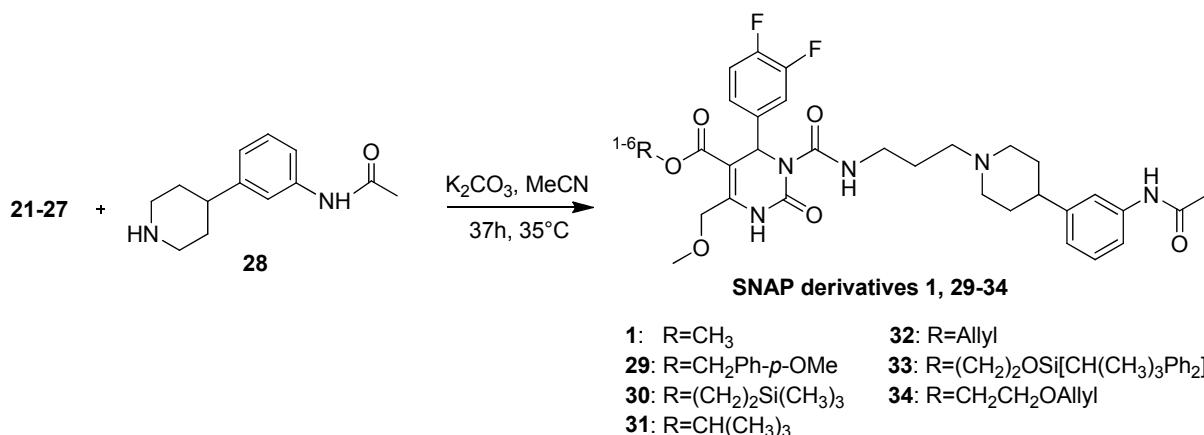
A 3-bromopropylcarbamoyl side chain was attached to the pyrimidinones **14–20** in a one-pot two-step reaction, yielding compounds **21–27** (Scheme 4). Again, the allyl protected compound **25** was obtained in excellent yields of 85% as shown in Figure 2/Graph 3.

Scheme 4. Attachment of the 3-bromopropylcarbamoyl side chain to pyrimidinones **14–20**.



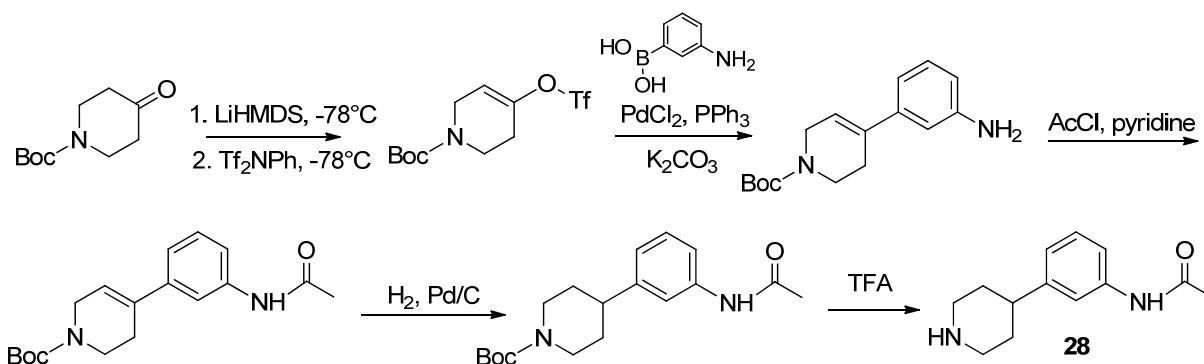
The side chain **28** was attached onto compounds **21–27** by addition of potassium carbonate, giving *rac*SNAP-7941 **1** or SNAP derivatives **29–34** (Scheme 5), respectively, exhibiting a similar pattern of yields as in the previous reactions in correlation to the corresponding protection group (Figure 2/Graph 4).

Scheme 5. Syntheses of the SNAP derivatives **1, 29–34**.



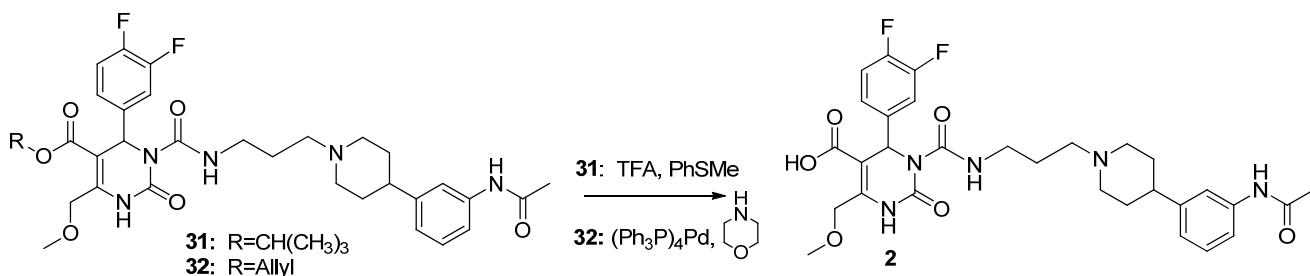
The *N*-(piperidinylphenyl)acetamide side chain **28** was obtained according to Schönberger [17] via Suzuki coupling, hydrogenation and acetylation followed by cleavage of the *t*-butyloxycarbonyl protecting group as shown in Scheme 6.

Scheme 6. Synthesis of *N*-(piperidinyl)acetamide compound **28**.



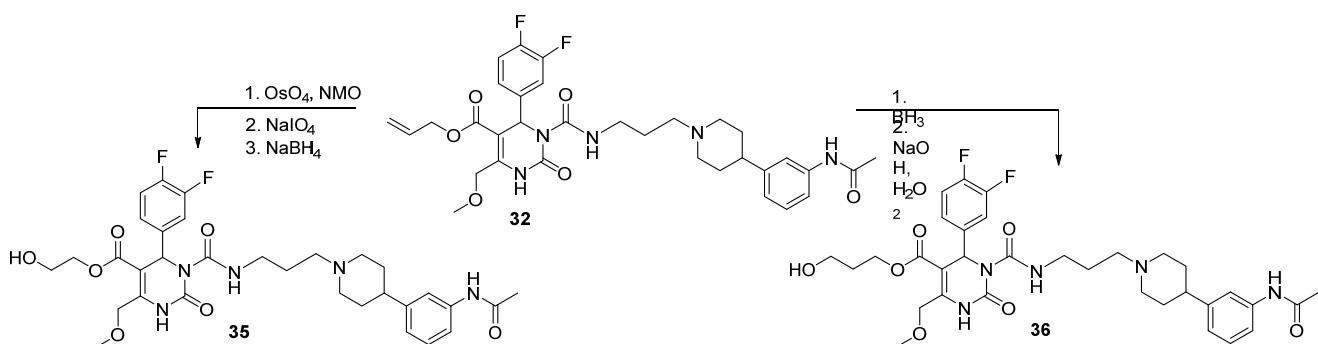
Compounds **29–32** were subjected to cleavage reactions in order to obtain SNAP-acid **2**. Unfortunately, only the *t*-butyl protected compound **31** and the allyl protected compound **32** could be converted into the free carboxylic acid **2** (Scheme 7).

Scheme 7. Cleavage of esters **31** and **32** to furnish SNAP-acid **2**.



In total, regarding the superior yields of **32** as shown in Figure 2, the synthesis of allyl ester **32** was established as the most effective route of preparing the PET precursor SNAP-acid **2**. Additionally, allyl ester **32** served as starting material for the hydroxyethyl ester HE@SNAP **35** as well as for the hydroxypropyl ester HP@SNAP **36**, which were subjected to tosylation for subsequent fluorination (Scheme 8). The tosylated compounds **3** and **5** were prepared as two alternative precursors of the desired target compounds **4** and **6**, in order to compare the feasibility of fluorination of the tosyl ethyl derivative **3** to the tosyl propyl derivative **5**.

Scheme 8. Synthesis of hydroxylethyl and hydroxypropyl esters **35** and **36**.



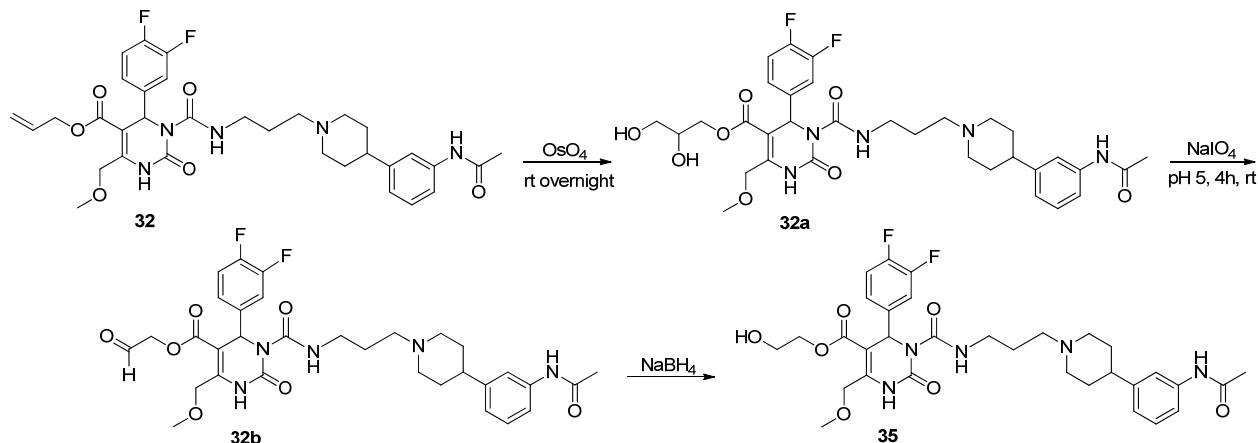
The synthesis of **35** required three reaction steps, starting with the oxidation of the allyl protecting group using osmium tetroxide performed by adapting and combining different methods [19–21]. This yielded 2,3-dihydroxypropyl ester **32a**, as depicted in Scheme 9.

Then, a glycol cleavage of the 2,3-dihydroxypropyl group was performed with sodium periodate adapting methods of Botti *et al.* [22] and Adam *et al.* [23] to yield aldehyde **32b**, which was subjected to reduction under standard conditions with sodium borohydride [24] to give 2-hydroxylethyl ester **35**.

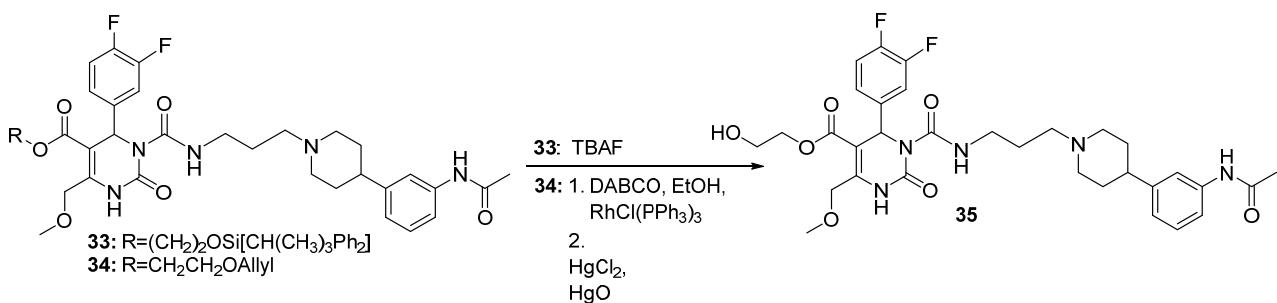
The hydroxypropyl analogue **36** was synthesized in a one-pot two-step reaction as shown above in Scheme 8 adapting the methods of Heidecke/Lindhorst and Park *et al.* [25,26]. The cleavage to hydroxypropyl ester **36** was accomplished in an anti-Markovnikov reaction using a borane-tetrahydrofuran complex and hydrogen peroxide. Although the unconsumed starting material could be partially recovered by column chromatography, the reaction afforded only a moderate 26% yield. A second and

third approach to HE@SNAP **35** was made accessible by the cleavage of the protecting groups of SNAP derivatives **33** and **34**, respectively (Scheme 10).

Scheme 9. Synthesis of hydroxyethyl ester **35** via glycol cleavage.

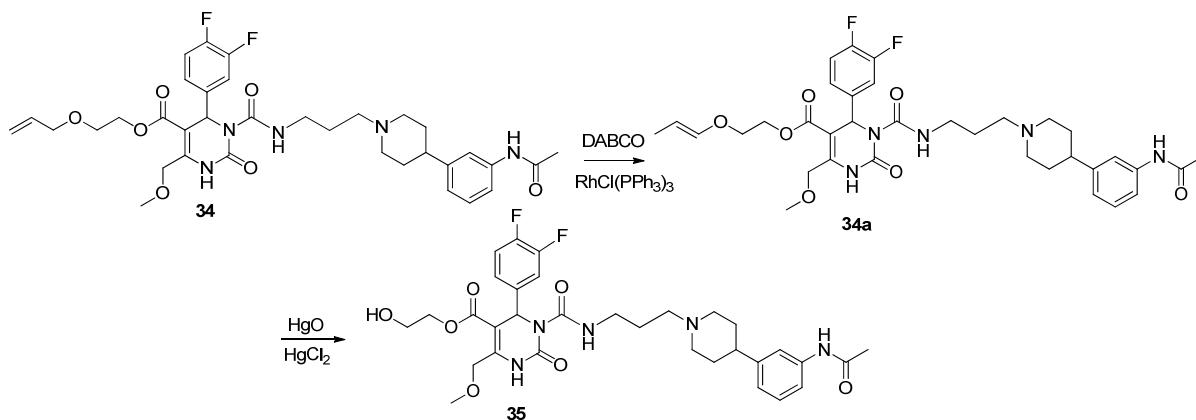


Scheme 10. Synthesis of hydroxyethyl ester **35** via SNAP derivatives **33** and **34**.



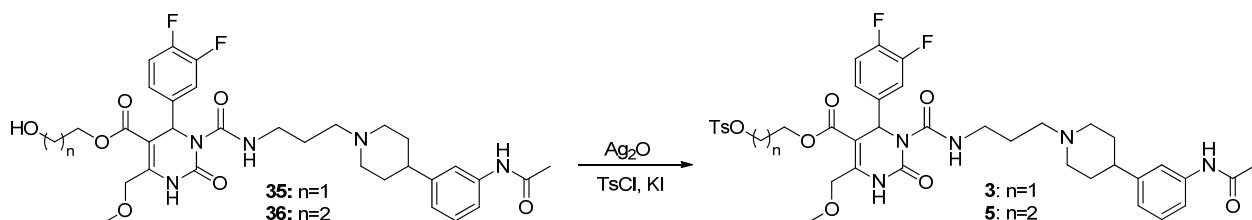
The protecting group of compound **33** was cleaved in a standard procedure [27] using tetrabutyl-ammonium fluoride, while the allyloxyethyl ester **34** had to be isomerized first with a Wilkinson catalyst as depicted in Scheme 11. Isomerization of the allyl group was conducted in the presence of diazabicyclooctane and the catalyst, adapting a method of Smith *et al.* [28]. Mercury-induced cleavage of the newly formed vinyl ether [29] give satisfying yields, regarding the feasibility of recycling the starting material.

Scheme 11. Reaction sequence to hydroxyethyl ester **35**.



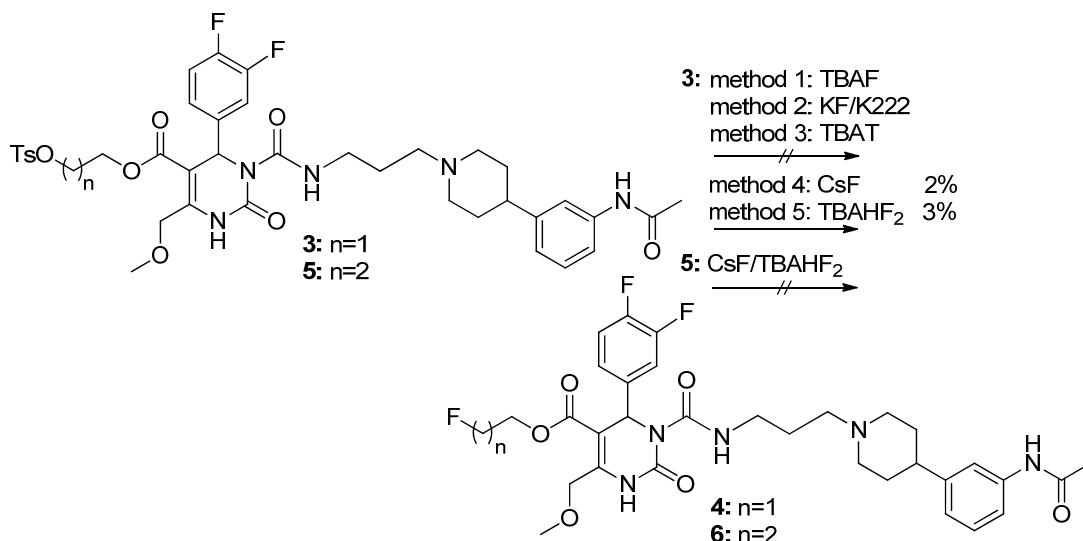
Compounds **35** and **36** were used for tosylation yielding 2-(tosyloxy)ethyl ester TOE@SNAP **3** and 3-(tosyloxy)propyl ester TOP@SNAP **5**, respectively. Since common tosylation methods [30–32] were not applicable, tosylation was achieved using silver oxide and tosyl chloride in the presence of potassium iodide adapting a method of Bouzide *et al.* [33]. Comparing the yields, TOE@SNAP **3** was obtained with 63%, whereas the tosylpropyl derivative **5** gave a poorer 31% yield (Scheme 12).

Scheme 12. Preparation of tosylated SNAP derivatives **3** and **5**.



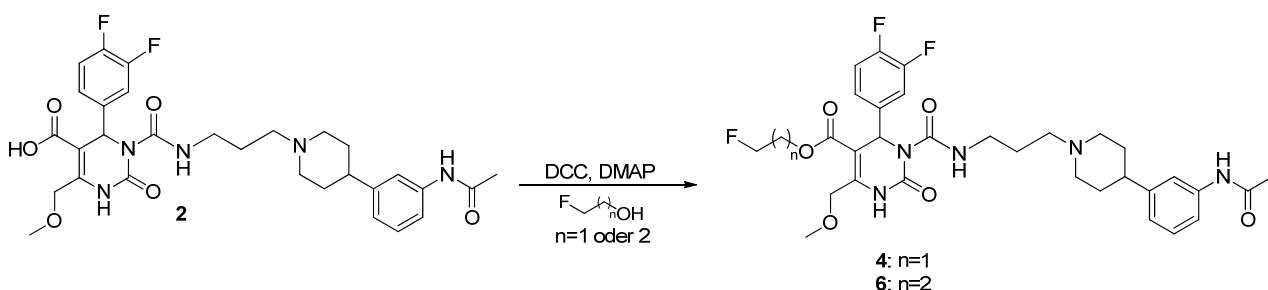
The tosylated derivatives **3** and **5** were intended to be used for the following fluorination to afford the final compounds **4** and **6** (Scheme 13).

Scheme 13. Conversion of tosylated SNAP precursors **3** and **5**.



Unfortunately, different fluorination methods such as reactions with tetrabutylammonium fluoride [30], crown ether Kryptofix® K2.2.2 and potassium fluoride [34], or tetrabutylammonium-(triethylsilyl) difluorosilicate [35] were unsuccessful. Minor yields of **4** (2%–3%) could be obtained by fluorination with cesium fluoride [36] and tetrabutylammoniumhydrogen difluoride [37]. Conversion of compound **5** to fluoropropyl ester **6** under similar reaction conditions was confirmed by high resolution mass spectrometry (HRMS) analysis but purification and isolation could not be accomplished due to the probable instability of this product. Attempting to react the hydroxyethyl derivative **35** with diaminosulfur trifluoride by adapting a method of Shanab [30] did not provide the fluoroethyl ester **4** either.

Hence, another approach to **4** and **6** had to be established leading to the Steglich esterification [16,38,39] of SNAP-acid **2** (Scheme 14) which is therefore employed as a precursor for the reference compound FE@SNAP **4**, for the PET tracer [¹¹C]SNAP-7941 **1a** via ¹¹C-methylation [15], and for the second tracer [¹⁸F]FE@SNAP **4a** [16].

Scheme 14. Conversion of SNAP-acid **2** to fluorinated derivatives **4** and **6**.

Acid **2** was reacted with dicyclohexylcarbodiimide, 4-dimethylaminopyridine, and fluoroethanol or fluoropropanol, respectively, giving the fluoroethylated reference compound **4** in trace yields of 4% but again did not afford **6** in acceptable quantity, although the conversion was confirmed via mass spectrometry. Fluoropropyl ester **6** could not be isolated by different chromatographic purification methods. Therefore, the synthesis of the propylated compounds **36**, **5**, and **6** was not further pursued due to the better yields and superior purification properties of the ethylated compounds **35**, **3**, and **4**.

3. Experimental

3.1. General

All commercial chemicals and solvents used in the synthetic steps were purchased from Aldrich (Vienna, Austria) or Fisher Scientific (Vienna, Austria) and used as received. Reactions were monitored by thin layer chromatography (TLC) using appropriate developing solvents and pre-coated silica gel plates (UV 254 nm) purchased from Merck and Co. (Vienna, Austria). $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were recorded on a Bruker Avance DPX-200 spectrometer, a Varian UnityPlus 500 spectrometer or a Bruker Avance 500 spectrometer. Chemical shifts are reported in δ (ppm) relative to tetramethylsilane (TMS) as internal standard and multiplicities are given as singlet (s), doublet (d), quartet (q), multiplet (m) and broad singlet (br s). IR-spectra were recorded on a Perkin Elmer FT-IR Spectrum 1000 spectrophotometer. High resolution mass spectral data were obtained on a Finnigan MAT 8230 or on a Finnigan MAT 900 S. Elemental analyses were performed at the Mass Spectrometry Centre of the Faculty of Chemistry (University of Vienna).

3.2. Syntheses

Synthesis of compounds **1**, **14**, **21** and **28** was conducted according to Schönberger [17]. Synthesis of compounds **2**, **7**, **11**, **18**, **25** and **32** was conducted according to Philippe *et al.* [15]. Synthesis of compounds **3** and **4** was conducted according to Philippe *et al.* [16].

3-(Tosyloxy)propyl-3-(3-(3-acetamidophenyl)piperidin-1-yl)propyl-carbamoyl)-4-(3,4-difluoro-phenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**5**). To a stirred solution of alcohol **36** (116 mg, 0.18 mmol) in CH_2Cl_2 (1.0 mL), freshly produced Ag_2O (83 mg, 0.36 mmol), tosyl chloride (69 mg, 0.36 mmol) and KI (60 mg, 0.36 mmol) were added. The mixture was stirred at 40 °C until completion of the reaction (TLC-monitoring). Thereafter, the reaction mixture was filtered and the solvent evaporated *in vacuo*. The residue was purified via column chromatography (silica gel,

eluent: $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9:1) to give 23 mg (26.1%) of product **5**. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 1.87–1.97 (m, 8H, 9b- CH_2 , 19- CH_2 , 22,22'-(CH_2)₂), 2.05–2.08 and 3.08–3.15 (m, 4H, 21,21'-(CH_2)₂), 2.15 (s, 3H, 32- CH_3), 2.42–2.51 (m, 6H, Tos- CH_3 , 20- CH_2 , 23- CH), 3.37–3.40 (m, 2H, 18- CH_2), 3.45 (s, 3H, 7-OCH₃), 3.94–4.04 (m, 2H, 9c-OCH₂), 4.10–4.18 (m, 2H, 9a-OCH₂), 4.65 (s, 2H, 6-OCH₂), 6.58 (s, 1H, 3- CH), 6.92 (d, 1H, J = 7.2 Hz, 29- CH), 7.04–7.26 (m, 5H, 11- CH , 14- CH , 15- CH , 27- CH , 28- CH), 7.30–7.34 (m, 2H, 3',3''-(CH_2)₂), 7.44 (s, 1H, 30-NH), 7.72–7.76 (m, 2H, 2',2''-(CH_2)₂), 7.99 (s, 1H, 1-NH), 8.96 (t, 1H, J = 5.2 Hz, 17-NH); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): δ (ppm) 21.6 (Tos- CH_3), 24.5 (32- CH_3), 26.0 (19- CH_2), 29.6 (9b- CH_2), 32.4 (22,22'-(CH_2)₂), 39.4 (18- CH_2), 42.2 (23- CH), 52.9 (3- CH), 54.1 (21,21'-(CH_2)₂), 56.4 (20- CH_2), 59.1 (7-OCH₃), 60.4 (9c- CH_2OH), 66.6 (9a-OCH₂), 68.0 (6-OCH₂), 101.2 (4-C), 116.0/116.3 (11- CH), 117.2/117.5 (14- CH), 117.7 (27- CH), 118.1 (25- CH), 122.7 (29- CH), 122.9/123.0/123.1/123.2 (15- CH), 127.8 (2',2''-(CH_2)₂), 128.9/129.0 (28- CH), 129.9 (3',3''-(CH_2)₂), 132.7 (1'-C), 137.5 (10-C), 138.3 (26-C), 144.9 (4'-C), 146.6 (5-C), 146.8 (24-C), 152.1 (2-CO), 153.2 (16-CO), 163.8 (8-COO), 168.6 (31-CON); MS: m/z (%): 812 (1), 371 (46), 286 (56), 231 (43), 71 (29), 70 (100), 65 (28), 57 (38), 56 (55); HRMS: Calcd. for $\text{C}_{40}\text{H}_{48}\text{F}_2\text{N}_5\text{O}_9\text{S} [\text{M} + \text{H}]^+$: 812.3141. Found: 812.3148.

4-Methoxybenzyl 4-methoxy-3-oxobutanotate (8). 5-(2-Methoxyacetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (7, 724 mg, 3.35 mmol) and (4-methoxyphenyl)methanol (925 mg, 6.69 mmol) in toluene (10.0 mL) were heated to 80 °C for 24 h. After cooling to room temperature the solvent was removed *in vacuo* and the residue was partly purified by column chromatography (silica gel, eluent: petroleum ether/EtOAc 3:1) to give 372 mg (44.0%) of **8** as a brown oil. The crude product was reacted without further purification in the next step.

2-(Trimethylsilyl)ethyl 4-methoxy-3-oxobutanoate (9). A mixture of 5-(2-methoxyacetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (7, 3.60 g, 16.65 mmol) and 2-(trimethylsilyl)ethanol (4.8 mL, 3.94 g, 33.32 mmol) in toluene (50.0 mL) was heated to 80 °C for 24 h. After cooling to room temperature the solvent was removed *in vacuo* and the residue was purified by column chromatography (silica gel, eluent: petroleum ether/EtOAc 9:1) to give 2.35 g (61.0%) of **9** as a light brown oil. $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) −0.01 (s, 9H, Si(CH_3)₃), 0.91–1.00 (m, 2H, SiCH₂), 3.36 (s, 3H, OCH₃), 3.43 (s, 2H, 2- CH_2), 4.03 (s, 2H, 4-OCH₂), 4.12–4.21 (m, 2H, OCH₂); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): δ (ppm) −1.7 (Si(CH_3)₃), 17.1 (SiCH₂), 45.8 (2- CH_2), 59.2 (OCH₃), 63.6 (OCH₂), 77.2 (4-OCH₂), 167.0 (1-COO), 201.5 (3-CO); MS m/z (%): 232 (1), 147 (8), 117 (8), 75 (64), 74 (12), 73 (100), 72 (9), 59 (9), 45 (12); HRMS: Calcd. for $\text{C}_8\text{H}_{16}\text{O}_4\text{Si} [\text{M} - \text{C}_2\text{H}_4]$: 204.0818. Found: 204.0813.

t-Butyl 4-methoxy-3-oxobutanoate (10). 5-(2-Methoxyacetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (7, 6.40 g, 19.60 mmol) and 2-methylpropan-2-ol (9.00 g, 121.42 mmol) were dissolved in toluene (90.0 mL) and the mixture was stirred for 24 h at 80 °C. After cooling to room temperature, the solvent and excess alcohol were removed *in vacuo* and the residue was purified by column chromatography (RP silica gel, eluent: ACN/H₂O 9:1) and Kugelrohr distillation (b.p. ca 260 °C) to give compound **10** as a brown oil (3.44 g, 62.0%). $^1\text{H-NMR}$ (200 MHz, CDCl_3): δ (ppm) 1.40 (s, 9H, *t*-but-(CH_3)₃), 3.34 (s, 2H, 2- CH_2), 3.36 (s, 3H, 5-OCH₃), 4.02 (s, 2H, 4-CH₂); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): δ (ppm) 27.8 (*t*-but-(CH_3)₃), 47.0 (2- CH_2), 59.1 (OCH₃), 77.1 (4-OCH₂), 81.9 (*t*-but-C), 166.0 (1-COO), 201.8

(3-CO); MS: *m/z* (%) 132 (5), 115 (6), 87 (4), 69 (5), 59 (33), 58 (8), 57 (100), 56 (13), 45 (51), 43 (16), 42 (11), 41 (26); HRMS: Calcd. for C₅H₈O₄ [M – C₄H₈]: 132.0423. Found: 132.0424.

2-(*t*-Butyldiphenylsilyloxy)ethyl 4-methoxy-3-oxobutanoate (12). First, 2-(*t*-butyldiphenylsilyloxy)-ethanol was freshly prepared. To a mixture of ethylene glycol (5.59 g, 90.00 mmol), imidazole (6.13 g, 90.00 mmol), and absolute CH₂Cl₂ (140 mL) *t*-butylchlorodiphenylsilane (23.03 mL, 24.74 g, 90.00 mmol) dissolved in absolute CH₂Cl₂ was added dropwise at 0 °C. After stirring for 24 h at room temperature, the reaction mixture was extracted with water to remove unreacted ethylene glycol. The solvent was removed under reduced pressure to give 21.81 g (81.1%) of 2-(*t*-butyldiphenylsilyloxy)ethanol as a colorless oil which crystallized upon cooling to afford colorless crystals. The crude product (21.69 g, 72.19 mmol) was used for the next step without further purification and heated to 80 °C for 24 h with 5.23 g (24.21 mmol) of 5-(2-methoxyacetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (7) in toluene (73.0 mL). After cooling to room temperature the solvent was removed *in vacuo* and the residue was purified by column chromatography (reversed-phase silica gel, eluent: acetonitrile/H₂O 4:1→1:0) to give 3.10 g (10.4%) of **12** as reddish brown oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.07 (s, 9H, *t*-but-(CH₃)₃), 3.40 (s, 3H, OCH₃), 3.49 (s, 2H, 2-CH₂), 3.85–3.90 (m, 2H, 9b-OCH₂), 4.08 (s, 2H, 4-OCH₂), 4.24–4.29 (m, 2H, 9a-OCH₂), 7.37–7.45 (m, 6H, 2'-(CH₂), 4'-(CH₂), 6'-(CH₂)), 7.66–7.70 (m, 4H, 3'-(CH₂), 5'-(CH₂)); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 19.1 (*t*-but-C), 26.7 (*t*-but-(CH₃)₃), 45.6 (2-CH₂), 59.3 (OCH₃), 61.7 (9b-OCH₂), 66.3 (9a-OCH₂), 77.2 (4-OCH₂), 127.7 (3'-(CH₂), 5'-(CH₂)), 129.7 (4'-(CH₂)), 133.2 (1'-(C)₂), 135.5 (2'-(CH₂), 6'-(CH₂)), 166.9 (1-COO), 201.3 (3-CO); MS: *m/z* (%) 383 (4), 349 (3), 243 (18), 199 (89), 185 (24), 184 (48), 165 (65), 154 (42), 139 (24), 111 (56), 94 (23), 69 (33), 45 (100); HRMS: *m/z* calcd. for C₂₃H₃₀O₅SiNa [M + Na]⁺: 437.1760. Found: 437.1760.

2-Hydroxyethyl 4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (12a). To a well-stirred solution of allyloxyethyl 4-methoxy-3-oxobutanoate (**12**, 3.00 g, 7.24 mmol), 3,4-difluorobenzaldehyde (1.20 g, 8.44 mmol) and urea (0.73 g, 12.15 mmol) in THF (7.0 mL), Cu₂O (117 mg, 0.82 mmol), glacial acetic acid (47 μL) and boron trifluoride diethyl etherate (1.29 mL, 1.46 g, 10.32 mmol) were added. The resulting reaction mixture was heated under reflux for 8 h. After cooling to room temperature the mixture was poured onto a mixture of ice (12 g) and NaHCO₃ (2 g). The resulting cloudy solution was filtered over Celite and washed with CH₂Cl₂ (10 mL). The biphasic solution was separated in a separatory funnel and the aqueous phase was washed with CH₂Cl₂ (3 × 7 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 9:1) to give 0.90 g (36.3%) of **12a** as yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 3.44 (s, 3H, 7-OCH₃), 3.71 (m, 2H, 9b-CH₂OH), 4.12–4.20 (m, 2H, 9a-OCH₂), 4.63 (s, 2H, 6-OCH₂), 5.37 (d, *J* = 2.4 Hz, 3-CH), 6.77 (s, 1H, 2a-CH), 7.02–7.18 (m, 3H, 11-CH, 14-CH, 15-CH), 7.75 (s, 1H, 1-NH); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 54.3 (3-CH), 59.1 (7-OCH₃), 60.9 (9b-CH₂OH), 65.9 (9a-OCH₂), 68.5 (6-OCH₂), 98.2 (4-C), 115.4/115.8 (11-CH), 117.3/117.7 (14-CH), 122.4/122.5 (15-CH), 140.5 (10-C), 148.2 (5-C), 152.3 (2-CO), 164.8 (8-COO); MS: *m/z* (%) 342 (22), 310 (14), 280 (33), 267 (74), 253 (27), 229 (100), 221 (24), 167 (50), 153 (38), 45 (40); HRMS: *m/z* calcd. for C₁₅H₁₆F₂N₂O₅Na [M + Na]⁺: 365.0925. Found: 365.0932.

Allyloxyethyl 4-methoxy-3-oxobutanoate (13). A mixture of 5-(2-methoxyacetyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (7, 38.74 g, 179.20 mmol) and allyl alcohol (57.4 mL, 537.60 mmol) in toluene (10.0 mL) was heated to 80 °C for 24 h. After cooling to room temperature the solvent was removed *in vacuo* and the residue was purified by bulb-to-bulb distillation to give 20.04 g (51.7%) of **13** as a yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 3.36 (s, 2H), 3.65 (m, 2H), 3.96–3.99 (m, 2H), 4.04 (s, 2H), 4.22–4.27 (m, 2H), 5.27 (d, *J* = 19.1, 2H), 5.88 (m, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 45.6, 59.2, 64.3, 67.5, 71.9, 77.1, 117.1, 134.4, 166.9, 201.3; MS: *m/z* (%): 73 (23), 69 (37), 60 (23), 57 (41), 55 (60), 43 (100), 42 (17), 41 (87); HRMS: *m/z* calcd. for C₁₀H₁₆O₅: 216.0998. Found: 216.1003.

4-Methoxybenzyl 4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (15). To a well-stirred solution of 4-methoxybenzyl 4-methoxy-3-oxobutanoate (**8**, 330 mg, 1.31 mmol), 3,4-difluorobenzaldehyde (192 mg, 1.35 mmol) and urea (118 mg, 1.96 mmol) in THF (1.2 mL), Cu₂O (19 mg, 0.13 mmol), glacial acetic acid (7.6 μL) and boron trifluoride diethyl etherate (0.2 mL, 240 mg, 1.69 mmol) were added. The resulting reaction mixture was heated under reflux for 8 h. After cooling to room temperature the mixture was poured onto ice (2 g) and NaHCO₃ (200 mg). The resulting cloudy solution was filtered over Celite and washed with CH₂Cl₂ (5 mL). The biphasic solution was separated in a separatory funnel and the aqueous phase was washed with CH₂Cl₂ (3 × 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated *in vacuo*. The product was partly purified by column chromatography (silica gel, eluent: EtOAc/MeOH 4:1) to give 315 mg (57.5%) of **15** as a yellow oil. The crude product was reacted without further purification in the next step.

2-(Trimethylsilyl)ethyl 4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (16). To a well-stirred solution of 2-(trimethylsilyl)ethyl 4-methoxy-3-oxobutanoate (**9**, 2.35 g, 10.11 mmol), 3,4-difluorobenzaldehyde (1.48 mg, 10.41 mmol) and urea (910 mg, 15.17 mmol) in THF (8.7 mL), Cu₂O (146 mg, 1.02 mmol), glacial acetic acid (59 μL) and boron trifluoride diethyl etherate (1.6 mL, 1.82 g, 12.80 mmol) were added. The resulting reaction mixture was heated under reflux for 8 h (TLC monitoring EtOAc/hexane 1:1). After cooling to room temperature the mixture was poured onto ice (15 g) and NaHCO₃ (3 g). The resulting cloudy solution was filtered over Celite and washed with CH₂Cl₂ (12 mL). The biphasic solution was separated in a separatory funnel and the aqueous phase was washed with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 9:1) to give 2.05 mg (51.0%) of **16** as yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) −0.01 (s, 9H, 9c-Si(CH₃)₃), 0.84–0.93 (m, 2H, 9b-SiCH₂), 3.42 (s, 3H, 7-OCH₃), 4.05–4.14 (m, 2H, 9a-OCH₂), 4.62 (s, 2H, 6-OCH₂), 5.31 (s, 2H, 2a-NH), 6.96 (s, 1H, 3-CH), 7.01–7.15 (m, 3H, 11-CH, 14-CH, 15-CH), 7.65 (s, 1H, 1-NH); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) −1.7 (9c-Si(CH₃)₃), 17.4 (9b-SiCH₂), 54.3 (3-CH), 59.0 (7-OCH₃), 62.3 (9a-OCH₂), 68.5 (6-OCH₂), 98.8 (4-C), 115.4/115.8 (11-CH), 117.1/117.6 (14-CH), 122.4/122.5 (15-CH), 140.5 (10-C), 147.1 (5-C), 152.5 (2-CO), 165.0 (8-COO); MS *m/z* (%): 398 (1), 370 (11), 355 (27), 323 (13), 293 (11), 281 (11), 257 (10), 253 (9), 225 (10), 185 (10), 167 (13), 84 (12), 75 (13), 73 (100), 45 (26); HRMS: Calcd. for C₁₈H₂₄F₂N₂O₄SiNa [M + Na]⁺: 421.1371. Found: 421.1365.

t-Butyl-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**17**). To a stirred mixture of *t*-butyl 4-methoxy-3-oxobutanoate **10** (3.00 g, 15.94 mmol), 3,4-difluorobenzaldehyde (1.8 mL, 2.33 g, 16.40 mmol) and urea (1.44 g, 23.98 mmol) in THF (14.0 mL), Cu₂O (230 mg, 1.61 mmol) and CH₃COOH were added at room temperature, followed by dropwise addition of boron trifluoride diethyl etherate (2.5 mL, 2.88 g, 20.20 mmol). The resulting mixture was stirred and refluxed for 8 h. After cooling to room temperature, the reaction mixture was poured into a mixture of ice (25 g) and NaHCO₃ (5 g). The resulting mixture was filtered over Celite and washed with CH₂Cl₂ (20 mL). The organic phase was separated from the filtrate and the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over Na₂SO₄ and the solvent was evaporated *in vacuo* to give 4.92 g of raw product (a brown oil) that was purified *via* column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 9:1) to give compound **17** as a yellow oil (1.74 g, 30.8%). ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.32 (s, 9H, *t*-but-(CH₃)₃), 3.41 (s, 3H, 7-OCH₃), 4.60 (s, 2H, 6-OCH₂), 5.24 (s, 1H, 3-CH), 7.00–7.08 (m, 3H, 11-CH, 14-CH, 15-CH), 7.60 (s, 1H, NH); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 28.0 (*t*-but-(CH₃)₃), 54.7 (3-CH), 58.9 (7-OCH₃), 68.5 (6-OCH₂), 81.1 (*t*-but-C), 99.9 (4-C), 115.4/115.7 (11-CH), 117.1/117.4 (14-CH), 122.37/122.45/122.5/122.6 (15-CH), 140.7 (10-C), 146.3 (5-C), 152.5 (2-C), 164.03 (8-COO); MS: *m/z* (%): 354 (1), 298 (11), 265 (6), 221 (6), 185 (39), 121 (11), 71 (23), 70 (12), 69 (22), 57 (100), 55 (20), 43 (19), 41 (17); HRMS: Calcd. for C₁₇H₂₀F₂N₂O₄Na [M + Na]⁺: 377.1289. Found: 377.1284.

*2-(t-Butyldiphenylsilyloxy)ethyl 4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**19**). To a mixture of 2-hydroxyethyl 4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**12a**, 0.78 g, 2.28 mmol), imidazole (155 mg, 2.28 mmol), and absolute CH₂Cl₂ (140 mL), *tert*-butylchlorodiphenylsilane (0.6 mL, 626 mg, 2.28 mmol) dissolved in absolute CH₂Cl₂ was added dropwise at 0 °C. After stirring for 24 h at room temperature, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 9:1) to give 1.20 g (90.7%) of **19** as a colorless oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.06 (s, 9H, *t*-but-(CH₃)₃), 3.42 (s, 3H, 7-OCH₃), 3.79–3.83 (m, 2H, 9b-OCH₂), 4.06–4.29 (m, 2H, 9a-OCH₂), 4.63 (s, 2H, 6-OCH₂), 5.27 (d, 1H, *J* = 2.9 Hz, 3-CH), 6.59 (s, 1H, 2a-NH), 6.96–7.15 (m, 3H, 11-CH, 14-CH, 15-CH), 7.36–7.46 (m, 6H, 2'-(CH)₂, 4'-(CH)₂, 6'-(CH)₂, 7.63–7.76 (m, 5H, 1-NH, 3'-(CH)₂, 5'-(CH)₂); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 19.1 (*t*-but-C), 26.7 (*t*-but-(CH₃)₃), 54.4 (3-CH), 59.0 (7-OCH₃), 62.0 (9b-OCH₂), 65.4 (9a-OCH₂), 68.5 (6-OCH₂), 98.4 (4-C), 115.3/115.7 (11-CH), 117.2/117.5 (14-CH), 122.4/122.5/122.6 (15-CH), 127.7 (3'-(CH)₂, 5'-(CH)₂), 129.8 (4'-(CH)₂), 133.1 (1'-(C)₂), 135.4 (2'-(CH)₂, 6'-(CH)₂), 140.4 (10-C), 147.5 (5-C), 152.3 (2-CO), 164.6 (8-COO); MS: *m/z* (%): 580 (1), 523 (18), 493 (4), 282 (15), 281 (100), 251 (51), 238 (12), 235 (12), 199 (18), 165 (18), 140 (30), 135 (12), 45 (10); HRMS: *m/z* calcd. for C₃₁H₃₄F₂N₂O₅SiNa [M + Na]⁺: 603.2103. Found: 603.2121.*

*Allyloxyethyl 4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**20**). To a well-stirred solution of allyloxyethyl 4-methoxy-3-oxobutanoate (**13**, 20.04 g, 98.68 mmol), 3,4-difluorobenzaldehyde (9.8 mL, 12.55 g, 88.34 mmol) and urea (7.95 g, 132.51 mmol) in THF (113 mL), Cu₂O (1.26 g, 8.83 mmol), glacial acetic acid (506 μL) and boron trifluoride diethyl etherate (114.8 mL, 130.17 g, 917.04 mmol) were added. The resulting reaction mixture was*

heated under reflux for 8 h. After cooling to room temperature the mixture was poured on a mixture of ice (125 g) and NaHCO₃ (25 g). The resulting cloudy solution was filtered over Celite and washed with CH₂Cl₂ (5 mL). The biphasic solution was separated in a separatory funnel and the aqueous phase was washed with CH₂Cl₂ (3 × 40 mL). The combined organic layers were dried over Na₂SO₄, filtered and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, eluent: EtOAc/petroleum ether 3:1) to give 9.00 g (24.4%) of **20** as yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 3.43 (s, 3H), 3.94–4.23 (m, 6H), 4.63 (s, 2H), 5.16–5.29 (m, 2H), 5.76–5.96 (m, 1H), 6.52 (s, 1H), 7.04–7.21 (m, 3H), 7.66 (s, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 54.5, 59.1, 63.3, 67.7, 68.5, 71.9, 98.4, 115.6/115.9, 117.2, 117.4/117.6, 134.2, 147.6, 152.2, 164.5; MS: *m/z* (%) 382 (14), 280 (51), 269 (28), 222 (31), 221 (39), 167 (51), 45 (35), 41 (100); HRMS: *m/z* calcd for C₁₈H₂₁O₅F₂N₂: 383.1419. Found: 383.1426; CHN: calcd for C₁₈H₂₁O₅F₂N₂·H₂O: C, 55.20; H, 5.16; N, 7.15. Found: C, 54.60; H, 5.10; N, 6.82.

4-Methoxybenzyl 3-((3-bromopropyl)carbamoyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (22). To a solution of 4-methoxybenzyl 4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**15**, 252 mg, 0.60 mmol) and 4-nitrophenylchloroformate (425 mg, 2.11 mmol) in THF (7.5 mL), LiHMDS (1.7 mL, 284 mg, 1.70 mmol, 1 M in THF) was added dropwise at -78 °C. After 10 min the reaction was quenched with water (190 μL) and the mixture was allowed to warm to 0 °C. After addition of K₂CO₃ (333 mg, 2.41 mmol) and 3-aminopropylbromide hydrobromide (396 mg, 1.69 mmol) the reaction mixture was stirred at room temperature overnight. The yellow suspension was washed with saturated aqueous NaHCO₃ and the biphasic solution was separated in a separatory funnel. The aqueous phase was extracted with Et₂O (2 × 20 mL). The combined organic layers were dried over Na₂SO₄ and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 9:1) to give 70 mg (19.9%) of **22** as yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.20–1.25 (m, 2H, 20-CH₂), 1.99–2.08 (m, 2H, 19-CH₂), 3.39–3.41 (m, 2H, 18-CH₂), 3.43 (s, 3H, 7-OCH₃), 3.91 (s, 3H, PMB-OCH₃), 4.63 (s, 2H, 6-OCH₂), 5.46 (s, 2H, PMB-OCH₂), 6.59 (s, 1H, 3-CH), 6.79–6.85 (m, 3H, 11-CH, 14-CH, 15-CH), 6.99–7.14 (m, 4H, PMB-2'-CH, 3'-CH, 5'-CH, 6'-CH), 7.72 (s, 1H, 1-NH), 8.86 (t, 1H, J = 4.4 Hz, 17-NH); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 30.4 (20-CH₂), 32.1 (19-CH₂), 39.1 (18-CH₂), 53.2 (3-CH), 55.2 (PMB-OCH₃), 59.2 (7-OCH₃), 66.7 (PMB-OCH₂), 68.0 (6-OCH₂), 106.9 (4-C), 113.9 (PMB-3'-CH, 5'-CH), 116.0/116.4 (11-CH), 117.1/117.4 (14-CH), 123.1 (15-CH), 130.3 (PMB-2'-CH, 6'-CH), 145.7 (2-CO), 153.3 (16-CO), 167.6/167.7 (8-COO), 5-C and 10-C not found; MS *m/z* (%): 325 (57), 294 (81), 279 (31), 265 (29), 222 (20), 137 (28), 121 (100), 45 (37); HRMS: Calcd. for C₂₅H₂₆F₂N₃O₆Br [M – H]⁻: 580.0903. Found: 580.0895.

2-(Trimethylsilyl)ethyl 3-((3-bromopropyl)carbamoyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (23). To a solution of 2-(trimethylsilyl)ethyl 4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**16**, 590 mg, 1.48 mmol) and 4-nitrophenylchloroformate (1.05 mg, 5.18 mmol) in THF (18.5 mL), LiHMDS (4.2 mL, 694 mg, 4.15 mmol, 1 M in THF) was added dropwise at -78 °C. After 10 min the reaction was quenched with water (460 μL) and the mixture was allowed to warm to 0 °C. After addition of K₂CO₃

(819 mg, 5.93 mmol) and 3-aminopropylbromide hydrobromide (973 mg, 4.44 mmol), the reaction mixture was stirred at room temperature overnight. The yellow suspension was washed with saturated aqueous NaHCO₃ and the biphasic solution was separated in a separatory funnel. The aqueous phase was extracted with Et₂O (2 × 20 mL). The combined organic layers were dried over Na₂SO₄ and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, eluent: EtOAc/petroleum ether 1:1 and CH₂Cl₂/MeOH 9.5:0.5) to give 490 mg (59.0%) of **23** as yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 0.14 (s, 9H, 9c-Si(CH₃)₃), 1.05–1.15 (m, 2H, 9b-SiCH₂), 1.34–1.41 (m, 2H, 20-CH₂), 2.18–2.28 (m, 19-CH₂), 3.49–3.56 (m, 18-CH₂), 3.59 (s, 3H, 7-OCH₃), 4.18–4.35 (m, 2H, 9a-OCH₂), 4.81 (s, 2H, 6-OCH₂), 6.78 (s, 1H, 3-CH), 7.12–7.39 (m, 3H, 11-CH, 14-CH, 15-CH), 7.87 (s, 1H, 1-NH), 9.02 (t, 1H, J = 5.6 Hz, 17-NH); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) –1.7 (9c-Si(CH₃)₃), 17.5 (9b-SiCH₂), 30.4 (20-CH₂), 32.2 (19-CH₂), 39.1 (18-CH₂), 53.0 (3-CH), 59.1 (7-OCH₃), 63.1 (9a-OCH₂), 68.1 (6-OCH₂), 101.9 (4-C), 116.0/116.4 (11-CH), 117.1/117.4 (14-CH), 123.0/123.1 (15-CH), 137.4/137.5 (10-C), 147.4/147.6 (5-C), 152.5 (2-CO), 153.3 (16-CO), 164.3 (8-COO); MS m/z (%): 536 (100), 508 (4), 436 (15), 421 (9), 378 (71), 350 (40), 328 (3), 306 (5), 278 (17), 234 (14); HRMS: Calcd. for C₂₂H₃₀O₅F₂N₃BrSiNa [M + Na]⁺: 584.1004. Found: 584.1008.

t-Butyl-3-(3-bromopropylcarbamoyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**24**). To a solution of pyrimidinone **17** (1.65 g, 4.66 mmol) and *p*-nitrophenylchloroformate (3.29 g, 16.32 mmol) in THF (60.0 mL), LiHMDS (13.0 mL, 2.18 g, 13.03 mmol, 1 M in THF) was slowly added at –78 °C. After 10 min, the reaction was completed by addition of H₂O (1.5 mL), warmed to 0 °C and neutralised with K₂CO₃ (2.57 g, 18.60 mmol). Thereafter, 3-aminopropylbromide hydrobromide (3.06 g, 13.98 mmol) was added and the reaction mixture was allowed to warm to room temperature overnight. The resulting yellow suspension was washed with NaHCO₃ twice, the layers were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were dried over Na₂SO₄. After purification of the raw product (5.23 g, brown oil) *via* column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 9.5:0.5), the bromide **24** could be obtained as a yellow oil (1.41 g, 58.2%). ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.23 (t, 2H, J = 7.1 Hz, 20-CH₂), 1.39 (s, 9H, *t*-but-(CH₃)₃), 2.04–2.21 (m, 2H, 19-CH₂), 3.35–3.42 (m, 2H, 18-CH₂), 3.45 (s, 3H, 7-OCH₃), 4.65 (s, 2H, 6-OCH₂), 6.54 (s, 1H, 3-CH), 7.02–7.23 (m, 3H, 11-CH, 14-CH, 15-CH), 7.73 (s, 1H, 1-NH), 8.91 (t, 1H, J = 5.6 Hz, 17-NH); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 28.1 (*t*-but-(CH₃)₃), 30.5 (20-CH₂Br), 32.1 (19-CH₂), 39.1 (18-CH₂), 53.6 (3-CH), 59.0 (7-OCH₃), 68.1 (6-OCH₂), 81.7 (*t*-but-C), 103.1 (4-C), 116.1/116.4 (11-CH), 117.0/117.3 (14-CH), 123.1 (15-CH), 137.8 (10-C), 147.5 (5-C), 152.5 (2-CO), 153.4 (16-CO), 163.3 (8-COO); MS: m/z (%) 518 (1), 353 (4), 322 (44), 297 (73), 279 (34), 266 (100), 265 (37), 221 (16), 185 (14), 167 (10), 57 (33), 41 (30); HRMS: Calcd. for C₂₁H₂₆F₂N₃O₅BrNa [M + Na]⁺: 540.0922. Found: 540.0904.

2-(*t*-Butyl diphenylsilyloxy)ethyl 3-((3-bromopropyl)carbamoyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**26**). To a solution of 2-(*t*-butyl diphenylsilyloxy)ethyl 4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**19**, 1.10 g, 1.89 mmol) and 4-nitrophenylchloroformate (1.34 g, 6.65 mmol) in THF (24.0 mL), LiHMDS (5.3 mL, 892 mg, 5.33 mmol, 1 M in THF) was added dropwise at –78 °C. After 10 min the reaction was quenched with water (9.0 mL) and the mixture was allowed to warm to 0 °C.

After addition of K_2CO_3 (1.05 g, 7.60 mmol) and 3-aminopropylbromide hydrobromide (1.25 g, 5.71 mmol) the reaction mixture was stirred at room temperature overnight. The yellow suspension was washed with saturated aqueous $NaHCO_3$ and the biphasic solution was separated in a separatory funnel. The aqueous phase was extracted with Et_2O . The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, eluent: $EtOAc/petroleum\ ether\ 1:1$) to give 1.16 g (82.2%) of **26** as a yellow oil. 1H -NMR (200 MHz, $CDCl_3$): δ (ppm) 0.96 (s, 9H, t-but-(CH_3)₃), 1.17–1.24 (m, 2H, 20- CH_2), 2.01–2.11 (m, 2H, 19- CH_2), 3.32–3.51 (m, 5H, 18- CH_2 , 7-O CH_3), 3.74–3.79 (m, 2H, 9b-O CH_2), 4.12–4.24 (m, 2H, 9a-O CH_2), 4.61 (s, 2H, 6-O CH_2), 6.64 (s, 1H, 3- CH), 6.78–7.20 (m, 3H, 11- CH , 14- CH , 15- CH), 7.28–7.37 (m, 6H, 2'-(CH)₂, 4'-(CH)₂, 6'-(CH)₂), 7.54–7.58 (m, 4H, 3'-(CH)₂, 5'-(CH)₂), 7.73 (s, 1H, 1-NH), 8.86 (t, $J = 5.7$ Hz, 17-NH); ^{13}C -NMR (50 MHz, $CDCl_3$): δ (ppm) 19.0 (t-but-C), 26.6 (t-but-(CH_3)₃), 30.4 (20- CH_2), 32.1 (19- CH_2), 39.1 (18- CH_2), 53.2 (3- CH), 59.1 (7-O CH_3), 61.8 (9b-O CH_2), 65.7 (9a-O CH_2), 68.1 (6-O CH_2), 101.6 (4-C), 115.5/115.8/116.2 (11- CH), 117.2/117.5 (14- CH), 123.0/123.1/ 123.2 (15- CH), 127.7 (3'-(CH)₂, 5'-(CH)₂), 129.8 (4'-(CH)₂), 133.1 (1'-(C)₂), 135.4 (2'-(CH)₂, 6'-(CH)₂), 137.4 (10-C), 145.9 (5-C), 152.5 (2-CO), 153.3 (16-CO), 164.6 (8-COO); MS: m/z (%) 768 (53), 686 (2), 603 (100), 560 (47), 540 (16), 460 (1), 238 (2); HRMS: m/z calcd for $C_{35}H_{40}F_2N_3O_6BrSiNa$ [M + Na]⁺: 766.1736. Found: 766.1728.

Allyloxyethyl 3-((3-bromopropyl)carbamoyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**27**). To a solution of allyloxyethyl 4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**20**, 9.00 g, 23.56 mmol) and 4-nitrophenylchloroformate (16.65 g, 82.60 mmol) in THF (300.0 mL), LiHMDS (66.08 mL, 11.06 g, 66.08 mmol, 1 M in THF) was added dropwise at –78 °C. After 10 min the reaction was quenched with water (9.0 mL) and the mixture was allowed to warm to 0 °C. After addition of K_2CO_3 (13.03 g, 94.40 mmol) and 3-aminopropylbromide hydrobromide (15.50 g, 70.80 mmol) the reaction mixture was stirred at room temperature overnight. The yellow suspension was washed with saturated aqueous $NaHCO_3$ and the biphasic solution was separated in a separatory funnel. The aqueous phase was extracted with Et_2O . The combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, eluent: $CH_2Cl_2/MeOH\ 10:1$) to give 6.60 g (51.3%) of **27** as a yellow oil. 1H -NMR (200 MHz, $CDCl_3$): δ (ppm) 2.02–2.08 (m, 2H), 3.36–3.47 (m, 5H), 3.60–3.62 (m, 2H), 3.94–4.29 (m, 6H), 4.65 (s, 1H), 5.15–5.28 (m, 2H), 5.75–5.94 (m, 1H), 6.64 (s, 1H), 7.02–7.25 (m, 3H), 7.77 (s, 1H), 8.89 (t, $J = 5.6$ Hz, 1H); ^{13}C -NMR (50 MHz, $CDCl_3$): δ (ppm) 30.4, 32.1, 39.1, 59.1, 63.7, 67.6, 68.1, 71.9, 101.5, 116.0/116.4, 117.1, 117.3/117.4, 122.9, 134.2, 137.8, 146.0, 152.5, 153.2, 163.9; MS: m/z (%) 546 (2), 381 (64), 350 (52), 311 (30), 280 (48), 279 (100), 249 (33), 222 (47), 220 (32), 167 (29), 41 (91); HRMS: m/z calcd. for $C_{22}H_{26}O_6BrF_2N_3H$: 548.1035. Found (M+1)⁺: 548.1044; CHN: Calcd. for $C_{22}H_{26}O_6BrF_2N_3H \cdot H_2O$: C, 47.58; H, 4.73; N, 7.57. Found: C, 47.47; H, 4.81; N, 7.28.

4-Methoxybenzyl 3-((3-(4-(3-acetamidophenyl)piperidin-1-yl)propyl)carbamoyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**29**). Under an argon atmosphere a mixture of N -(3-(piperidin-4-yl)phenyl)acetamide (**28**, 109 mg, 0.50 mmol), 4-methoxybenzyl 3-((3-bromopropyl)carbamoyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-

1,2,3,4-tetrahydropyrimidine-5-carboxylate (**22**, 190 mg, 0.33 mmol) and K₂CO₃ (480 mg, 3.40 mmol) in ACN (12.6 mL) was stirred at 35 °C for 37 h. The resulting yellow suspension was filtered and the filtration residue was washed with EtOAc. After removal of the solvent *in vacuo* the obtained oily residue was dissolved in EtOAc (10 mL) and the organic phase was washed with saturated aqueous NaHCO₃ (2 × 8 mL). The aqueous phase was washed with EtOAc (2 × 10 mL) and the combined organic layers were dried over Na₂SO₄, filtered and evaporated *in vacuo*. The obtained residue was purified by column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 10:1) to give 75 mg (30.3%) of **29** as yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.67–1.79 (m, 6H, 19-CH₂, 22,22'-(CH₂)₂), 2.00–2.13 and 3.08–3.13 (m, 7H, 21,21'-(CH₂)₂, 32-CH₃), 2.48–2.51 (m, 3H, 20-CH₂, 23-CH), 3.29–3.41 (m, 5H, 7-OCH₃, 18-CH₂), 3.78 (s, 3H, PMB-OCH₃), 4.65 (d, 2H, J = 2.6 Hz, 6-OCH₂), 6.62 (d, 1H, J = 6.2 Hz, 3-CH), 6.81–7.22 (m, 10H, 11-CH, 14-CH, 15-CH, 27-CH, 28-CH, 29-CH, 2'-CH, 3'-CH, 4'-CH, 5'-CH), 7.39 (25-CH), 7.97 (br s, 1H, 30-NH), 8.15 (s, 1H, 1-NH), 8.96–8.98 (m, 1H, 17-NH); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 24.3 (32-CH₃), 25.8 (19-CH₂), 32.2 (22,22'-(CH₂)₂), 39.2 (18-CH₂), 42.0 (23-CH), 53.2 (3-CH), 53.9 (21,21'-(CH₂)₂), 55.2 (PMB-OCH₃), 56.1 (20-CH₂), 59.0 (7-OCH₃), 66.3 (PMB-OCH₂), 68.0 (6-OCH₂), 101.9 (4-C), 113.9 (3'-CH, 5'-CH), 116.0/116.3 (11-CH), 117.0/117.4 (14-CH), 117.8 (27-CH), 118.0 (25-CH), 122.7 (29-CH), 123.0 (15-CH), 127.4 (1'-C), 128.8 (28-CH), 130.0 (2'-CH, 6'-CH), 137.8 (10-C), 138.4 (26-C), 145.9 (5-C), 146.5 (24-C), 152.3 (2-CO), 153.2 (16-CO), 164.1 (8-COO), 168.8 (31-CON), 4'-C not found; MS *m/z* (%): 301 (8), 231 (82), 213 (17), 167 (8), 153 (10), 121 (100), 95 (12), 70 (16), 57 (20); HRMS: Calcd. for C₃₈H₄₃F₂N₅O₇: 720.3209. Found: 720.3216.

2-(Trimethylsilyl)ethyl 3-((3-(4-(3-acetamidophenyl)piperidin-1-yl)propyl-carbamoyl)-4-(3,4-difluorophenyl)-6-methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (30). Under an argon atmosphere a mixture of *N*-(3-(piperidin-4-yl)phenyl)acetamide (**28**, 251 mg, 1.15 mmol), 2-(trimethylsilyl)ethyl 3-((3-bromopropyl)carbamoyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**23**, 420 mg, 0.75 mmol) and K₂CO₃ (1.09 g, 7.89 mmol) in ACN (28.0 mL) was stirred at 35 °C for 37 h. The resulting yellow suspension was filtered and the filtration residue was washed with EtOAc. After removal of the solvent *in vacuo* the obtained oily residue was dissolved in EtOAc (20 mL) and the organic phase was washed with saturated aqueous NaHCO₃ (2 × 15 mL). The aqueous phase was washed with EtOAc (2 × 20 mL) and the combined organic layers were dried over Na₂SO₄, filtered and evaporated *in vacuo*. The obtained residue was purified by column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 9:1 + 0.5% TEA) to give 240 mg (45.8%) of **30** as a yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) −0.02 (s, 9H, 9c-Si(CH₃)₃), 0.93–1.02 (m, 2H, 9b-SiCH₂), 1.76 (m, 6H, 19-CH₂, 22,22'-(CH₂)₂), 1.96–2.08 and 2.98–3.03 (m, 4H, 21,21'-(CH₂)₂), 2.15 (s, 3H, 32-CH₃), 2.43 (t, 3H, J = 6.8 Hz, 20-CH₂, 23-CH), 3.31–3.41 (m, 2H, 18-CH₂), 3.44 (s, 3H, 7-OCH₃), 4.15–4.24 (m, 2H, 9a-OCH₂), 4.68 (s, 2H, 6-OCH₂), 6.69 (s, 1H, 3-CH), 6.93 (d, 1H, J = 7.6 Hz, 29-CH), 7.03–7.35 (m, 5H, 11-CH, 14-CH, 15-CH, 27-CH, 28-CH), 7.49 (s, 1H, 25-CH), 8.05 (s, 1H, 30-NH), 8.25 (s, 1H, 1-NH), 9.02 (t, 1H, J = 5.1 Hz, 17-NH); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) −1.8 (9c-Si(CH₃)₃), 17.3 (9b-SiCH₂), 24.2 (32-CH₃), 26.2 (19-CH₂), 32.7 (22,22'-(CH₂)₂), 39.4 (18-CH₂), 42.4 (23-CH), 52.9 (3-CH), 54.1 (21,21'-(CH₂)₂), 56.5 (20-CH₂), 58.9 (7-OCH₃), 63.0 (9a-OCH₂), 67.9 (6-OCH₂), 102.0 (4-C), 115.9/116.2 (11-CH), 116.9/117.3 (14-CH), 117.6 (27-CH), 118.2 (25-CH), 122.5 (29-CH), 122.8/122.9 (15-CH), 128.6

(28-CH), 137.6 (10-C), 138.2 (26-C), 145.8 (5-C), 147.0 (24-C), 152.3 (2-CO), 153.1 (16-CO), 164.3 (8-COO), 168.7 (31-CON); MS *m/z* (%): 700 (26), 600 (2), 345 (8), 259 (4), 231 (4); HRMS: Calcd. for C₃₅H₄₈F₂N₅O₆Si [M + H]⁺: 700.3342. Found: 700.3343.

t-Butyl-3-(3-(4-(3-acetamidophenyl)piperidin-1-yl)propylcarbamoyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**31**). To a solution of N-(3-(piperidin-4-yl)phenyl)acetamide (**28**, 140 mg, 0.64 mmol) in ACN (16.0 mL), bromide **24** (215 mg, 0.41 mmol) and K₂CO₃ (605 mg, 4.38 mmol) were added under argon atmosphere and the mixture was stirred at 35 °C for 37 h. The yellow slurry was filtered, washed with EtOAc and the filtrate was evaporated to dryness. The oily residue was dissolved in EtOAc and washed twice with saturated NaHCO₃. Then the aqueous phase was extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and evaporated *in vacuo* prior to purification by column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 10:1). Product **31** was obtained as a yellow-brownish oil (133 mg, 49.4%). ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.41 (t-but-(CH₃)₃), 1.74–1.78 (m, 6H, 19-CH₂, 22,22'-(CH₂)₂), 1.94–2.07 and 2.98–3.03 (m, 4H, 21,21'-(CH₂)₂), 2.15 (s, 3H, 32-CH₃), 2.37–2.44 (m, 3H, 20-CH₂, 23-CH₂), 3.32–3.39 (m, 2H, 18-CH₂), 3.44 (s, 3H, 7-CH₃), 4.66 (s, 2H, 6-CH₂), 6.58 (s, 1H, 3-CH₂), 6.94 (d, 1H, J = 7.3 Hz, 29-CH₂), 7.03–7.34 (m, 6H, 11-CH₂, 14-CH₂, 15-CH₂, 25-CH₂, 27-CH₂, 28-CH₂), 7.45 (s, 1H, 30-NH), 7.82 (s, 1H, 1-NH), 9.00 (t, 1H, J = 5.2 Hz, 17-NH); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 24.4 (32-CH₃), 26.4 (19-CH₂), 28.1 (t-but-(CH₃)₃), 32.9 (22,22'-(CH₂)₂), 39.5 (18-CH₂), 42.5 (23-CH₂), 53.5 (3-CH₂), 54.3 (21,21'-(CH₂)₂), 56.5 (20-CH₂), 59.0 (7-OCH₃), 68.0 (6-OCH₂), 103.3 (4-C), 116.0/116.4 (11-CH₂), 116.9/117.3 (14-CH₂), 117.6 (27-CH₂), 118.3 (25-CH₂), 122.7 (29-CH₂), 123.0/123.09/123.14/123.2 (15-CH₂), 128.8 (28-CH₂), 138.0 (10-C), 138.1 (26-C), 144.8 (5-C), 147.2 (24-C), 152.3 (2-CO), 153.3 (16-CO), 163.5 (8-COO), 168.5 (31-CON); MS: *m/z* (%) 679 (100, [M + Na]⁺), 657 (20, [M + H]⁺), 621 (10), 601 (17), 324 (23), 302 (49); HRMS: Calcd. for C₃₄H₄₄F₂N₅O₆ [M + H]⁺: 656.3260. Found: 656.3277; IR: (v) (cm⁻¹) 3304, 2925, 1709, 1608, 1516, 1392, 1366, 1278, 1230, 1164, 1119, 1080, 772, 732, 701.

2-(*t*-Butyldiphenylsilyloxy)ethyl 3-((3-(4-(3-acetamidophenyl)piperidin-1-yl)propyl)carbamoyl-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**33**). Under an argon atmosphere a mixture of N-(3-(piperidin-4-yl)phenyl)acetamide (**28**) (239 mg, 1.09 mmol), 2-(*t*-butyldiphenylsilyloxy)ethyl 3-((3-bromopropyl)carbamoyl)-4-(3,4-difluorophenyl)-6(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**26**, 775 mg, 1.04 mmol) and K₂CO₃ (1.52 g, 11.00 mmol) in ACN (40 mL) was stirred at 35 °C for 37 h. The resulting yellow suspension was filtered and the filtration residue was washed with EtOAc. After removal of the solvent *in vacuo* the obtained oily residue was dissolved in EtOAc and the organic phase was washed with saturated aqueous NaHCO₃. The aqueous phase was washed with EtOAc and the combined organic layers were dried over Na₂SO₄, filtered and evaporated *in vacuo*. The obtained residue was purified by column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 9:1) to give 428mg (47.7%) of **33** as a yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.01 (s, 9H, t-but-(CH₃)₃), 1.25–1.32 (m, 2H, 20-CH₂), 1.74–1.94 (m, 6H, 19-CH₂, 22,22'-(CH₂)₂), 2.01–2.09 and 3.09–3.14 (m, 4H, 21,21'-(CH₂)₂), 2.14 (s, 3H, 32-CH₃), 2.48–2.60 (m, 3H, 20-CH₂, 23-CH₂), 3.30–3.41 (m, 5H, 18-CH₂, 7-OCH₃), 3.79–3.84 (m, 2H, 9b-OCH₂), 4.13–4.32 (m, 2H, 9a-OCH₂), 4.65 (s, 2H, 6-OCH₂), 6.69 (s, 1H, 3-CH₂), 6.90–7.26 (m, 7H, 11-CH₂, 14-CH₂, 15-CH₂,

25-CH₂, 27-CH₂, 28-CH₂, 29-CH₂), 7.33–7.42 (m, 6H, 2'-(CH₂)₂, 4'-(CH₂)₂, 6'-(CH₂)₂), 7.59–7.63 (m, 5H, 3'-(CH₂)₂, 5'-(CH₂)₂, 30-NH), 8.15 (s, 1H, 1-NH), 8.86 (t, J = 5.7 Hz, 17-NH); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 19.0 (t-but-C), 24.3 (32-CH₃), 25.8 (19-CH₂), 26.6 (t-but-(CH₃)₃), 32.1 (22,22'-(CH₂)₂), 39.2 (18-CH₂), 42.0 (23-CH), 53.1 (3-CH), 53.8 (21,21'-(CH₂)₂), 56.0 (20-CH₂), 59.0 (7-OCH₃), 61.8 (9b-OCH₂), 65.6 (9a-OCH₂), 68.0 (6-OCH₂), 101.7 (4-C), 115.8/116.2 (11-CH), 117.1/117.4 (14-CH), 117.8 (27-CH), 118.0 (25-CH), 122.9/ 122.8/123.0/123.1 (15-CH), 127.7 (3'-(CH₂)₂, 5'-(CH₂)₂), 128.8 (28-CH), 129.7 (4'-(CH₂)₂), 133.0 (1'-(C)₂), 135.4 (2'-(CH₂)₂, 6'-(CH₂)₂), 137.6 (10-C), 138.3 (26-C), 146.1 (5-C), 146.4 (24-C), 152.3 (2-CO), 153.1 (16-CO), 164.1 (8-COO), 168.7 (31-CON); MS: m/z (%) 883 (1), 523 (12), 281 (100), 231 (44), 199 (18), 168 (19), 140 (16), 70 (30), 57 (65), 56 (33), 45 (44), 43 (60), 41 (28); HRMS: m/z calcd. for C₄₈H₅₇F₂N₅O₇Si: 882.4074. Found: 882.4087.

Allyloxyethyl 3-((3-(4-(3-acetamidophenyl)piperidin-1-yl)propyl)carbamoyl-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (34). Under an argon atmosphere a mixture of N-(3-(piperidin-4-yl)phenyl)acetamide (**28**, 4.04 mg, 18.47 μmol), allyloxyethyl 3-((3-bromopropyl)carbamoyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**27**, 6.60 g, 12.08 mmol) and K₂CO₃ (17.58 g, 127.20 mmol) in ACN (12.6 mL) was stirred at 35 °C for 37 h. The resulting yellow suspension was filtered and the filtration residue was washed with EtOAc. After removal of the solvent *in vacuo* the obtained oily residue was dissolved in EtOAc and the organic phase was washed with saturated aqueous NaHCO₃. The aqueous phase was washed with EtOAc and the combined organic layers were dried over Na₂SO₄, filtered and evaporated *in vacuo*. The obtained residue was purified by column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 9:1) to give 2.66 g (32.2%) of **34** as a yellow oil. ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.72–1.81 (m, 6H), 1.99, 2.99 (m, 4H), 2.11 (s, 3H), 2.39 (m, 2H), 2.42 (m, 1H), 3.29, 3.39 (m, 2H), 3.37 (s, 3H), 3.55–3.60 (m, 2H), 3.92, 3.94 (d, J = 5.6 Hz, 2H), 4.17, 4.29 (m, 2H), 4.63 (m, 2H), 5.12–5.26 (m, 2H), 5.81 (m, 1H), 6.65 (s, 1H), 6.90 (d, J = 7.44, 1H), 6.98–7.19 (m, 5H), 7.25 (s, 1H), 7.44 (s, 1H), 7.95 (s, 1H), 8.98 (t, J = 5.3 Hz, 1H); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 24.4, 26.3, 32.8, 39.5, 42.5, 53.1, 54.2, 56.5, 58.9, 63.6, 67.6, 67.9, 71.9, 101.7, 115.9/116.3, 116.9, 117.2/117.3, 117.6, 118.2, 112.7, 122.8, 128.7, 134.2, 137.8, 138.2, 146.2, 147.16, 152.3, 153.0, 164.0, 168.6; MS: m/z (%) 280 (33), 231 (100), 221 (21), 167 (34), 70 (26), 45 (21), 44 (21), 43 (54), 42 (31), 41 (57); HRMS: m/z calcd. for C₃₅H₄₃O₇F₂N₅H: 684.3209. Found (M+1)⁺: 684.3195; CHN: calcd. for C₃₅H₄₃O₇F₂N₅H•H₂O: C, 59.90; H, 6.19; N, 9.98. Found: C, 59.09; H, 6.35; N, 9.69.

(E)-2-Prop-1-en-1-yloxyethyl 3-((3-(4-(3-acetamidophenyl)piperidin-1-yl)propyl)carbamoyl-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (34a). To a solution of allyloxyethyl 3-((3-(4-(3-acetamidophenyl)piperidin-1-yl)propyl)carbamoyl-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**34**, 1.45 g, 2.12 mmol) and DABCO (1.00 g, 8.90 mmol) in EtOH (20 mL, 90%), RhCl(PPh₃)₃ (0.51 g, 0.55 mmol) was added. The reaction mixture was stirred for 15 min, cooled to room temperature, and then quenched with water. The aqueous phase was extracted with Et₂O and dried with Na₂SO₄. After evaporation of the solvent, the crude product **34a** was used for the next step without further purification.

2-Hydroxyethyl 3-((3-(4-(3-acetamidophenyl)piperidine-1-yl)propyl)carbamoyl-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (35). Method 1 (from **32**): To a solution of OsO₄ (2.5% in *t*-butanol, 0.5 mL, 0.04 mmol), *N*-methyl morpholine *N*-oxide monohydrate (46 mg, 0.39 mmol), H₂O (0.8 mL), acetone (0.3 mL), and *t*-butanol (0.5 mL), allyl ester **32** (250 mg, 0.39 mmol) dissolved in dioxane (0.5 mL) was added dropwise. After stirring at room temperature overnight, the mixture was treated with celite (62 mg) and NaHSO₃ (5 mg) and filtered over celite. After evaporation of the solvent, the crude 2,3-dihydroxypropyl ester **32a** obtained was used for the next step.

To a solution of **32a** (267 mg) in CH₂Cl₂ (0.6 mL), a solution of NaIO₄ (93 mg, 0.44 mmol) in H₂O (0.6 mL) was added. The two-layered mixture was stirred for 3–4 h, followed by separation of the organic layer. After evaporation of the solvent and drying *in vacuo*, the crude residue **32b** was used in the next step without any further purification.

To a solution of **32b** (88 mg) in MeOH (3.0 mL), NaBH₄ (6.0 mg, 0.15 mmol) was added in portions under stirring, followed by stirring for another 45 min. The reaction was quenched with water, and the mixture extracted three times with Et₂O. The organic layer was washed with water. After evaporation of the solvent the crude product was purified *via* column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 10:1) to give 12 mg of **35** (13.3%) as a yellow oil.

Method 2 (from **33**): To a solution of 2-(*t*-butyldiphenylsilyloxy)ethyl 3-((3-(4-(3-acetamidophenyl)piperidin-1-yl) propyl)carbamoyl-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**33**) in THF (6.5 mL), TBAF (0.5 mL, 452 mg, 1.73, 1M in THF) was added dropwise. After stirring for 1.5 h at room temperature, the reaction was quenched with water (0.3 mL) and evaporated to dryness. The crude product was purified by column chromatography (reversed-phase silica gel, eluent: ACN/H₂O 5:1 and silica gel, eluent: EtOAc/MeOH 10:1) to give 126 mg (40.3%) of **35** as a yellow oil.

Method 3 (from **34a**): A solution of HgCl₂ (1.02 g, 3.76 mmol) in acetone/H₂O (10:1, 10 mL) was added dropwise over a period of 3 min under stirring to a solution of (*E*)-2-(prop-1-en-1-yloxy)ethyl 3-((3-(4-(3-acetamidophenyl)piperidin-1-yl)propyl)carbamoyl)-4-(3,4-difluorophenyl)-6-(methoxy-methyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **34a** and HgO (1.02 g, 4.71 mmol) in acetone/H₂O (10:1, 30 mL). After completion of the reaction (TLC-monitoring), HgO was removed by filtration over celite and the product was evaporated to dryness. The residue was purified by column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 10:1) where part of the educt **34a** could be recovered and used in another reaction again. The product was obtained in good yield (677 mg, 70.8%). ¹H-NMR (200 MHz, CDCl₃): δ (ppm) 1.74–1.85 (m, 6H, 19-CH₂, 22,22'-(CH₂)₂), 2.02–2.09 and 3.01–3.06 (m, 4H, 21,21'-(CH₂)₂), 2.09 (s, 3H, 32-CH₃), 2.42–2.45 (m, 3H, 20-CH₂, 23-CH), 3.27–3.31 (m, 2H, 18-CH₂), 3.39 (s, 3H, 7-OCH₃), 3.74 (t, 2H, J = 4.4 Hz, 9b-CH₂OH), 4.10–4.20 (m, 2H, 9a-OCH₂), 4.62 (s, 2H, 6-OCH₂), 6.62 (s, 1H, 3-CH), 6.86 (d, 1H, J = 7.5 Hz, 29-CH), 6.94–7.23 (m, 5H, 11-CH, 14-CH, 15-CH, 27-CH, 28-CH), 7.33–7.39 (m, 2H, 25-CH, 30-NH), 8.53 (s, 1H, 1-NH), 8.99 (t, 1H, J = 5.4 Hz, 17-NH); ¹³C-NMR (50 MHz, CDCl₃): δ (ppm) 24.1 (32-CH₃), 25.8 (19-CH₂), 32.2 (22,22'-(CH₂)₂), 39.2 (18-CH₂), 42.0 (23-CH), 53.0 (3-CH), 53.9 (21,21'-(CH₂)₂), 56.1 (20-CH₂), 58.9 (7-OCH₃), 60.3 (9b-CH₂OH), 66.2 (9a-OCH₂), 67.9 (6-OCH₂), 101.6 (4-C),

115.8/116.1 (11-CH), 117.1/117.4 (14-CH), 117.8 (27-CH), 118.0 (25-CH), 122.6 (29-CH), 122.7/122.8 (15-CH), 128.7 (28-CH), 137.6 (10-C), 138.3 (26-C), 146.4 (5-C), 147.4 (24-C), 152.2 (2-CO), 153.2 (16-CO), 164.1 (8-COO), 169.0 (31-CON); MS: *m/z* (%) 644 (32), 345 (16), 302 (100), 259 (17), 231 (20), 160 (4), 114 (5); HRMS: Calcd. for $C_{32}H_{40}F_2N_5O_7$ [M + H]⁺: 644.2896. Found: 644.2902.

3-Hydroxypropyl-3-(3-(4-(3-acetamidophenyl)piperidin-1-yl)propylcarbamoyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (36). A solution of BH₃-THF (1M, 0.31 mmol, 0.3 mL) was added dropwise to a solution of allyl ester **32** (131 mg, 0.21 mmol) in THF. The mixture was stirred at room temperature for 30 min prior to elimination of excess hydride ions via addition of water (0.4 mL). 3M NaOH solution (0.2 mL) and H₂O₂ solution (30%, 0.2 mL) were then added to the mixture. The stirred solution was heated to 60 °C for 2 h. Thereafter, the solution was cooled to room temperature and the solvent evaporated *in vacuo*. H₂O was added and the reaction mixture was washed several times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄ and evaporated *in vacuo*. The intermediate product (108 mg) gave after purification by column chromatography (silica gel, eluent: CH₂Cl₂/MeOH 10:1) 43 mg of educt **32** and 23 mg of product **36** (26.1%). ¹H-NMR (500 MHz, CDCl₃): δ (ppm) 1.81–1.95 (22,22'-(CH₂)₂), 1.82 (m, 9b-CH₂), 1.84 (m, 19-CH₂), 2.16 and 3.13 (21,21'-(CH₂)₂), 2.17 (s, 32-CH₃), 2.50 (m, 23-CH), 2.54 (m, 20-CH₂), 3.33 and 3.41 (m, 18-CH₂), 3.45 (s, 7-CH₃), 3.52–3.64 (m, 9c-CH₂), 4.22–4.31 (m, 9a-CH₂), 4.67 (s, 6-CH₂), 6.64 (s, 3-CH), 6.94 (d, 1H, J = 7.7 Hz, 29-CH), 7.08 (m, 14-CH), 7.09 (m, 15-CH), 7.18 (m, 11-CH), 7.21 (m, 28-CH), 7.39 (d, 1H, J = 7.9 Hz, 27-CH), 7.42 (s, 25-CH), 7.76 (s, 30-NH), 7.96 (s, 1-NH), 8.98 (t, 1H, J = 5.6 Hz, 17-NH); ¹³C-NMR (126 MHz, CDCl₃): δ (ppm) 24.6 (32-CH₃), 25.9 (19-CH₂), 31.6 (9b-CH₂), 32.2 (22,22'-(CH₂)₂), 39.3 (18-CH₂), 42.0 (23-CH), 53.0 (3-CH), 54.1 (21,21'-(CH₂)₂), 56.3 (20-CH₂), 59.1 (7-OCH₃), 58.7 (9c-CH₂OH), 61.5 (9a-OCH₂), 68.1 (6-OCH₂), 101.4 (4-C), 116.2 (d, J = 17.7, 11-CH), 117.4 (d, J = 17.3, 14-CH), 117.9 (27-CH), 118.1 (25-CH), 122.8 (29-CH), 123.1 (dd, J = 6.3, 3.6, 15-CH), 129.0 (28-CH), 137.6 (10-C), 138.3 (26-C), 146.5 (24-C), 146.6 (5-C), 150.0 (12- or 13-CF), 150.1 (12- or 13-CF), 152.2 (2-C), 153.3 (16-C), 164.5 (8-C), 168.6 (31-C); ¹⁹F-NMR (471 MHz, CDCl₃): δ (ppm) -136.7 (m, 12- or 13-CF), -138.1 (m, 12- or 13-CF); MS: *m/z* (%) 658 (48), 345 (5), 302 (100), 259 (13), 231 (14), 160 (5), 113 (5); HRMS: Calcd. for $C_{33}H_{47}F_2N_5O_7Na$ [M + Na]⁺: 680.3271. Found: 680.2858.

4. Conclusions

Based on the increasing need for antioesity drugs, two novel PET tracers for the MCHR1 have recently been developed, to investigate the role of the MCHR1 in terms of adiposity. The selective high-affinity MCHR1 antagonist SNAP-7941 **1** was used as a promising basis for the development of the PET tracers [¹¹C]SNAP-7941 **1a** and [¹⁸F]FE@SNAP **4a**] [1,15–17]. This paper focuses on the synthesis of the non-radioactive precursors and reference compounds of [¹¹C]SNAP-7941 **1a** and [¹⁸F]FE@SNAP **4a**].

While the racemic receptor antagonist **1** [10–14] itself served as a reference compound for the preparation of [¹¹C]SNAP-7941 **1a**, a new reference compound had to be synthesized for the novel fluoroethylated tracer [¹⁸F]FE@SNAP **4a** as already published by Philippe *et al.* [15,16]. The carboxylic

acid derivative SNAP-acid **2** served as precursor for the ^{11}C -methylation to afford the PET tracer [^{11}C]SNAP-7941, while [^{18}F]FE@SNAP was meant to be obtained in a first approach by ^{18}F -fluorination of the newly prepared tosylate **3**.

The synthesis of these polyfunctional SNAP derivatives comprised many commonly used syntheses, including numerous methods attempting to cleave the methyl ester of **1** to prepare SNAP-acid **2**, which unfortunately were unsuccessful. Therefore, new approaches to obtain the desired derivatives accessible had to be established. A rationale for the failure of these demethylation methods could lay: (1) in the electron density which is distributed from the adjacent nitrogen to the carbonyl carbon through the conjugated double bond and thus, hinders the attack of nucleophiles (like OH^-) and (2) in the circumstance that acidic conditions may affect the amide bonds. In summary, due to the failure of cleaving the methyl ester **1**, four different protecting groups (carboxyl esters) were chosen, leading to SNAP derivatives **29–32**. Finally, the precursor SNAP-acid **2** could be prepared through cleavage of the allyl protecting group of compound **32** [15,16]. Allyl-SNAP **32** was not only obtained in excellent yields compared with the other three protected derivatives, but was also used as starting material for two more SNAP derived compounds **35** and **36**.

As precursor for the tosylated compound **3**, HE@SNAP **35** was synthesized using three different methods, starting from either **32** or from the new derivatives **33** or **34**, respectively. Compound **35** was reacted to tosylate TOE@SNAP **3**, which could not be fluorinated in satisfying yields to furnish fluoroethyl ester FE@SNAP **4**. Additionally, in order to increase yields and feasibility of the fluorination step, a series of propylated compounds was prepared. Allyl ester **32** was reacted to the hydroxypropyl ester HP@SNAP **35**, followed by tosylation giving tosylpropyl ester TOP@SNAP **5**. Similarly to fluoroethyl ester FE@SNAP **4**, fluorination of **5** provided fluoropropyl ester FP@SNAP **6** only in low yields. The conversion was proved by mass spectrometry, but the isolation of **5** was hampered by decomposition during column chromatography.

Finally, fluoroethylation of the free SNAP-acid **2** (but not fluoropropylation) was achieved *via* Steglich esterification using DCC and DMAP. Thus, SNAP-acid **2** finally served as precursor for the radiosynthetically produced tracer [^{11}C]SNAP-7941 **1a** as well as for the non-radioactive reference compound FE@SNAP **4** instead of tosylate **3**, which is used as precursor for the tracer [^{18}F]FE@SNAP **4a** [15,16]. After radioactive labeling at the Medical University of Vienna [15,16], biodistribution and micro PET experiments will be the next step of this ongoing project, as recently shown by Philippe *et al.* [40].

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Conflicts of Interest

The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds **1–36** are available from the authors.

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