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Efficient synthesis of new perfluorinated or hybrid amphiphilic surfactants

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Abstract

A very simple pathway for the preparation of amphiphilic analogues of natural bioactive peptidoamines such as carnosine (β-alanylhistidine) or carcinine (β-alanylhistamine), is presented. The strategy makes it possible to synthesise original bialkylchain or trialkylchain perfluorinated surfactants with or without perhydrogenated chains.

Keywords: Perfluorinated surfactants; Hybrid surfactants; β-Alanine; Peptidoamine; Carcinine; Carnosine

1. Introduction

Fluorinated surfactants have particular properties such as thermal and chemical stability, high surface activity and low critical micelle concentration [1–8]. In this field, our research directed to the synthesis of amphiphilic perfluorinated molecules having specific properties leads us to structures containing peptidoamines [9]. Amongst them, the compounds comprising an imidazole group stemming from histidine or histamine are of special interest. It is the case of carnosine (β-alanylhistidine) or carcinine (β-alanylhistamine). Carnosine and the related dipeptide such as anserine are naturally occurring compounds, which contain histidine [10]. Numerous studies have showed that these types of peptides and peptidoamines possess strong antioxidant and complexing properties [11,12]. In particular, they form antioxidant complexes with copper ions [13]. Hybrid surfactants, which have a fluorocarbon and a hydrocarbon chains in the same molecule, have received attention [14]. This type of surfactant is expected to have interesting properties as a result of both hydrocarbon and fluorocarbon alkyl group in the molecule as hydrophobic groups [15–18].

Recently, we have published the synthesis of the perfluorinated monoalkylchain derivatives of peptidoamines and their surfactant and complexing properties [19–22]. This present paper reports the synthesis of bialkylchain perfluorinated analogues of peptidoamines with (hybrid compounds; **structure I**) or without perhydrogenated chain (perfluorinated bicatenar surfactants; **structure II**) (Scheme 1).

2. Results and discussion

Our strategy allows the possibility of the introduction of a first chain, which is perfluorinated and a second, which can be perfluorinated or perhydrogenated. We have prepared three categories of compounds (Scheme 2):

(1) the perfluorinated dialkylchain analogues of β-alanine (FnFn′Ala) or peptidoamine (derivatives of carnosine: FnFn′HisMe; derivatives of carcinine: FnFn′Ha);
(2) the hybrid analogues of β-alanine (FnHmAla) or peptidoamine (derivatives of carnosine: FnHmHisMe; derivatives of carcinine: FnHmHa);
(3) the perfluorinated trialkylchain analogues of β-alanine (FnHmHm′Ala) or peptidoamine (derivatives of carnosine: FnHmHm′HisMe; derivatives of carcinine: FnHmHm′Ha).

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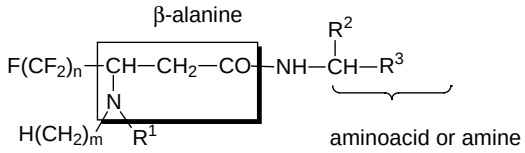
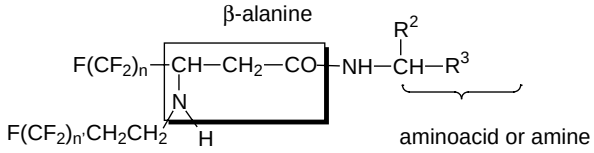
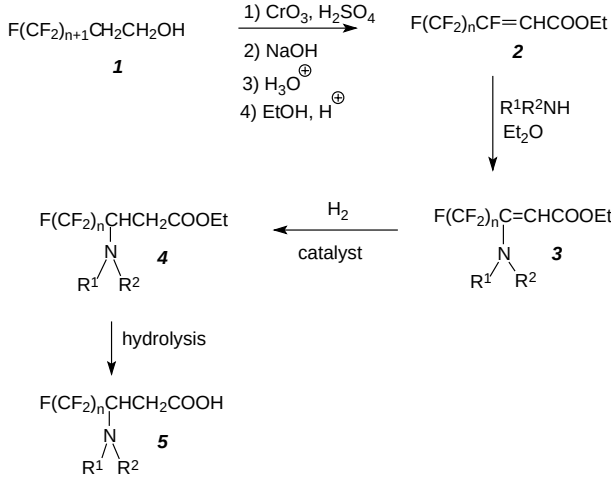


Structure I : hybrid surfactants



Structure II : perfluorinated surfactants

Scheme 1.



Scheme 3.

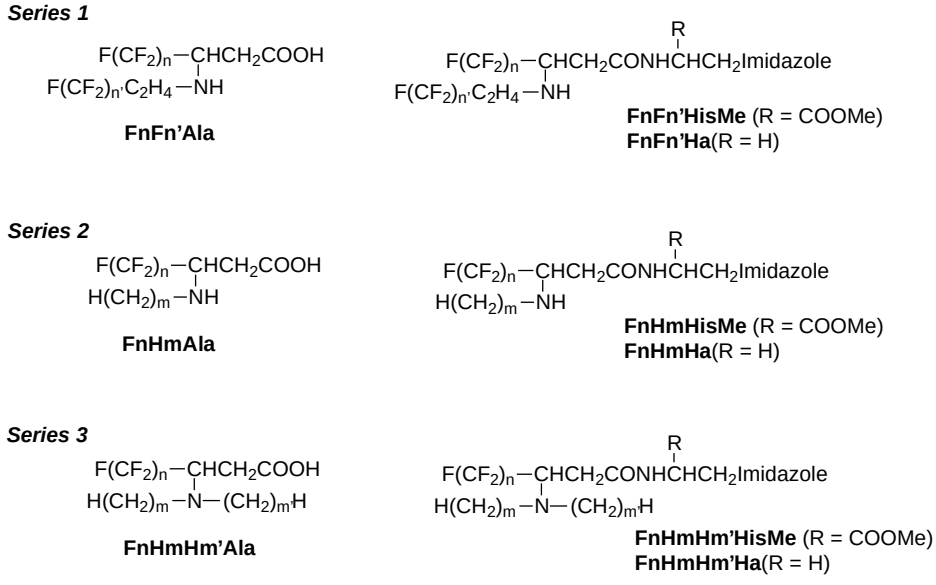
The synthesis starts with the preparation of analogues of β-alanine. (Scheme 3). The starting material corresponds to the 3-perfluoroalkyl-3-fluoroprop-2-enoate **2**, which was obtained from compound **1** by a well-known method [23,24]. The perfluorinated alcohol **1** is oxidised under Jones conditions. The elimination of HF can be carried out under simple conditions, using aqueous sodium hydroxide on account of the great acidity of the hydrogen between the carboxylic acid and the perfluorinated chain. An esterification leads to the unsaturated ester **2**. The overall yield of the three steps is practically quantitative and the conditions are very simple. The condensation of an amine to the unsaturated compound leads to the enamine **3**.

This reaction is very easy and efficient. The yields are very good and the reaction allows the preparation of many compounds (Table 1). Condensation is effective whatever the structure of the amine. Secondary amines react as well as primary amines.

The mechanism probably involves two steps: a Michael addition on the double bond and then fluoride elimination. The perfluoroalkylethyl amines used in this reaction are prepared from the iodo derivatives as described in previous work [25].

The hydrogenation of compounds **3** and an alkaline hydrolysis enable the analogue of β-alanine to be obtained. The conditions of hydrogenation are extreme for the compounds resulting from the primary amines, certainly, because of catalyst poisoning.

The following step consists of grafting an aminoacid on the analogues of β-alanine. We chose a classical method

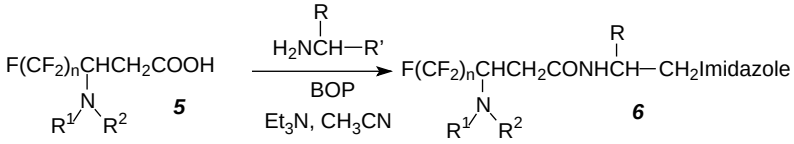


Scheme 2.

Table 1
Synthesis of the analogues of β-alanine **5** and precursors

Series	*n*	R^1	R^2	**3**[a]	**4**[a]	**5**[a]	**5** (Code)
Type: FnHmAla							
a	5	H	$H(CH_2)_{10}-$	84	89	95	(F5H10Ala)
b	7	H	$H(CH_2)_{10}-$	96	80	90	(F7H10Ala)
c	9	H	$H(CH_2)_{10}-$	99	93	94	(F9H10Ala)
d	5	H	$H(CH_2)_8-$	86	80	82	(F5H8Ala)
e	7	H	$H(CH_2)_8-$	73	94	76	(F7H8Ala)
Type: FnFn′Ala							
f	5	H	$F(CF_2)_8C_2H_4-$	80	87	95	(F5F8Ala)
g	7	H	$CF_3(CF_2)_7C_2H_4-$	80	85	93	(F7F8Ala)
h	9	H	$F(CF_2)_8C_2H_4-$	88	90	90	(F9F8Ala)
i	5	H	$F(CF_2)_6C_2H_4-$	67	93	98	(F5F6Ala)
j	7	H	$F(CF_2)_6C_2H_4-$	79	4	93	(F7F6Ala)
k	9	H	$F(CF_2)_6C_2H_4-$	80	80	94	(F9F6Ala)
Type: FnHmHm′Ala							
l	5	$H(CH_2)_6-$	$H(CH_2)_6-$	50	80	85	(F5H6H6Ala)
m	7	$H(CH_2)_6-$	$H(CH_2)_6-$	55	80	98	(F7H6H6Ala)
n	9	$H(CH_2)_6-$	$H(CH_2)_6-$	70	83	70	(F9H6H6Ala)
o	5	$H(CH_2)-$	$H(CH_2)_{12}-$	55	61	98	(F5H1H12Ala)
p	7	$H(CH_2)-$	$H(CH_2)_{12}-$	55	91	92	(F7H1H12Ala)
q	9	$H(CH_2)-$	$H(CH_2)_{12}-$	65	94	90	(F9H1H12Ala)

Code signification (cf. Scheme 2); for FnHmAla: *n* indicates the length of the initiale perfluorinated chain; H correspond to a perhydrogenated chain on the nitrogen and *m* indicates the number of carbons; for FnFn′Ala, the chain on nitrogen is perfluorinated and for FnHmHm′Ala the nitrogen is linked with two perhydrogenated chains with *m* and *m*′ carbons.
[a] Yield (%).

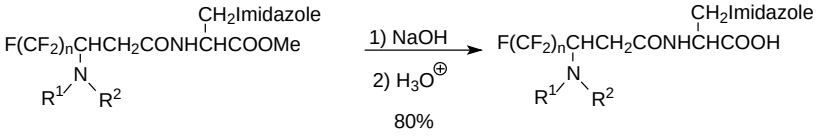


Scheme 4.

Table 2
Perfluoroalkyl analogues analogues of carnosine and carcinine

Series	Code	*n*	R^1	R^2	R	**6**[a]
a	F7H8HisMe	7	H	$H(CH_2)_8-$	$-CO_2Me$	72[b]
b	F7H10HisMe	7	H	$H(CH_2)_{10}-$	$-CO_2Me$	77, 5[b]
c	F9H10HisMe	9	H	$H(CH_2)_{10}-$	$-CO_2Me$	74, 5[b]
d	F5F6HisMe	5	H	$F(CF_2)_6C_2H_4-$	$-CO_2Me$	87[c]
e	F7F6HisMe	7	H	$F(CF_2)_6C_2H_4-$	$-CO_2Me$	73[c]
f	F9F6HisMe	9	H	$F(CF_2)_6C_2H_4-$	$-CO_2Me$	80[c]
g	F7H1H12HisMe	7	$H(CH_2)-$	$H(CH_2)_{12}-$	$-CO_2Me$	73[d]
h	F9H1H12HisMe	9	$H(CH_2)-$	$H(CH_2)_{12}-$	$-CO_2Me$	85[d]
i	F7H10Ha	7	H	$H(CH_2)_{10}-$	H	67[e]
j	F7H10Ha	5	H	$H(CH_2)_{10}$v	H	72[e]
k	F5F6Ha	5	H	$F(CF_2)_6C_2H_4-$	H	66, 5[f]

Code signification: cf. Scheme 2.
[a] Yield (%).
[b] FnHmHisMe.
[c] FnFn′HisMe.
[d] FnHmHm′HisMe.
[e] FnHmHa.
[f] FnFn′Ha.



Scheme 5.

using benzo-triazolyl-oxy-*tris*(dimethylamino)-phosphonium hexafluorophosphate (BOP) as peptide coupling reagent (Scheme 4). In all cases, the amine function of the analogues of β-alanine does not react and we obtain the pseudopeptide in good yield (Table 2).

Hydrolysis under usual basic conditions for an ester group of the derivatives of carnosine yields the surfactants **7**. (Scheme 5).

3. Conclusion

A simple and efficient method for the synthesis of perfluorinated or hybrid bicatenar and tricatenar lipopeptidoamines is reported. The syntheses have satisfactory yields; the method is suitable for numerous structures and should allow easy scale up.

4. Experimental section

4.1. General experimental procedures

All solvents were reagent grade and used without further purification. The progress of reaction and purity were determined using silica gel thin layer chromatographic (TLC) plates (Merck, Kieselgel 60 F254). NMR spectra were recorded on a Bruker AM 400 or AC 250 instrument. Chemical shifts are reported in parts per million (ppm) relative to TMS as internal standard for the ^{1}H spectra and to $CFCl_3$ for the ^{19}F spectra. Coupling constants (J) are in Hertz. IR spectra were recorded as thin film between sodium chloride plates on a Perkin Elmer 1600 spectrophotometer. Elemental analysis were performed by C.N.R.S-Vernaison.

Starting material **2** was prepared from the corresponding alcohol according to the published method [23].

4.2. General procedure for the preparation of perfluoroalkyl enamino esters **3**

To a solution of compound **2** (30 mmol) in diethyl ether (30 ml) were added 1.5 eq. of amine and 2 eq. of triethylamine in 30 ml of diethyl ether. The reaction mixture was stirred for 48 h at reflux. The mixture was diluted with ethyl acetate (100 ml) and washed with HCl 2 M (2 ml × 50 ml). The organic layer was dried over magnesium sulfate and evaporated under vacuum. The product was purified by chromatography on silica gel (light petroleum/ethyl acetate: 80/20).

4.2.1. Enaminoesters ***3a–f*** $R^1 = H$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$: (3-perfluoroalkyl-3-alkylamino-prop-2-enoic acid ethyl ester)

IR ν(C=O): 1670; ν(C=C): 1625. NMR ^{1}H ($CDCl_3$) δ: 0.9 (t, 3H, $^3J = 10$ Hz); 1.2–1.5 (m, $(2x + 3)$H); 1.65 (m, 2H); 3.3 (m, 2H); 4.2 (q, 2H, $^3J = 10$ Hz); 5.0 (s, 1H); 8.4 (t, 1H, $^3J = 5$ Hz) NMR ^{19}F ($CDCl_3$) δ: −81.5 (3F); −111.5 (2F); −123 to −121 ($(2n - 4)$F); −127 (2F). NMR ^{13}C ($CDCl_3$) δ: 14.5; 23; 27–32; 45.5; 60; 68.5; 87.5; 106.5–122; 149.5; 170. Calcd for $C_{20}H_{28}F_{11}NO_2$ (**3a**—F5H10): C, 47.1; H, 5.4; N, 2.7; F, 40.0. Found: C, 47.5; H, 5.2; N, 2.6; F, 40.8. Calcd for $C_{22}H_{28}F_{15}NO_2$ (**3b**—F7H10): C, 42.4; H, 4.5; N, 2.2. Found: C, 43.3; H, 4.5; N, 2.1. Calcd for $C_{24}H_{28}F_{19}NO_2$ (**3c**—F9H10): C, 39.8; H, 3.9; N, 1.9; F, 49.9. Found: C, 39.9; H, 3.8; N, 2.0; F, 50.4.

4.2.2. Enaminoesters ***3f–k*** $R^1 = H$; $R^2 = CF_3(CF_2)_xCF_2CH_2CH_2-$: (3-perfluoroalkyl-3-(2-perfluoroalkylethyl amino)-prop-2-enoic acid ethyl ester)

IR ν(C=O): 1670; ν(C=C): 1630. NMR ^{1}H ($CDCl_3$) δ: 1.3 (t, 3H, $^3J = 7$ Hz); 2.5 (m, 2H); 3.5 (dt, 2H, $^3J = 7$ and 7 Hz); 4.2 (q, 2H, $^3J = 7$ Hz); 5.15 (s, 2H); 8.5 (t, 1H, $^3J = 7$ Hz). NMR ^{19}F ($CDCl_3$) δ: −81.5 (6F); −111.5 (2F); −114.5 (2F); −122 to −124 ($(2n - 8)$F); −124 (4F). Calcd for $C_{20}H_{11}F_{28}NO_2$ (**3f**—F5F8): C, 29.0; H, 1.3; N, 1.7; F, 64.1. Found: C, 30.1; H, 1.2; N, 1.8; F, 62.2. Calcd for $C_{22}H_{11}F_{32}NO_2$ (**3g**—F7F8): C, 28.4; H, 1.2; N, 1.5; F, 65.4. Found: C, 29.1; H, 0.8; N, 1.3; F, 63.5. Calcd for $C_{18}H_{11}F_{24}NO_2$ (**3I**—F5F6): C, 29.6; H, 1,5; N, 1.9. Found: C, 29.8; H, 1.4; N, 2.1. Calcd for $C_{20}H_{11}F_{28}NO_2$ (**3j**—F7F6): C, 29.0; H, 1.3; N, 1.7; F, 64.1. Found: C, 29.4; H, 1.7; N, 2.0; F, 68.6.

4.2.3. Enaminoesters ***3o–q*** $R^1 = CH_3(CH_2)_xCH_2CH_2-$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$: (3-perfluoroalkyl-3-dialkylamino-prop-2-enoic acid ethyl ester)

IR ν(C=O): 1710; ν(C=C): 1600. NMR ^{1}H ($CDCl_3$) δ: 0.9 (t, 6H, $^3J = 7$ Hz); 1.3 (m, $(4x + 3)$H); 1.55 (m, 4H); 3.2 (t, 4H, $^3J = 8$ Hz); 4.20 (q, 2H, $^3J = 7$ Hz); 5.15 (s, 1H). NMR ^{19}F ($CDCl_3$) δ: −81 (3F); −107 (2F); −121 (2F); −121.5 to −124 (2n−4F); −126.5 (2F). NMR ^{13}C ($CDCl_3$) δ: 13.5; 22–32; 53; 59.5; 104.5; 107–121.5; 147.5; 164.5. Calcd for $C_{22}H_{32}F_{11}NO_2$ (**3l**—F5H6H6): C, 47.9; H, 5.8; N, 2.5; F, 37.9. Found: C, 48.9; H, 6.1; N, 2.4; F, 37.4. Calcd for $C_{24}H_{32}F_{15}NO_2$ (**3m**—F7H6H6): C, 44.2; H, 4.9; N, 2.1; F,

43.7. Found: C, 44.6; H, 4.3; N, 2.1, F, 43.4. Calcd for $C_{26}H_{32}F_{19}NO_2$ (**3n**—F9H6H6): C, 41.5; H, 4.3; N, 1.9; F, 48.0. Found: C, 41.7; H, 4.4; N, 1.8; F, 48.1.

*4.2.4. Enaminoesters **3l–n** $R^1 = CH_3$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$: (3-perfluoroalkyl-3-(alkymethyllamino)prop-2-enoic acid ethyl ester)*

IR ν(C=O): 1712; ν(C=C): 1605. NMR ^{1}H ($CDCl_3$) δ: 0.85 (t, 3H, $^3J = 7$ Hz); 1.3 (m, $(2x + 3)$H); 2.9 (s, 3H); 3.15 (t, 2H, $^3J = 7.5$ Hz); 4.20 (q, 2H, $^3J = 7$ Hz); 5.45 (s, 1H). NMR ^{19}F ($CDCl_3$) δ: −81.5 (3F); −108.5 (2F); −121.5 (2F); −122.5 to −124 ($(2n - 4)$F); −126.5 (2F). NMR ^{13}C ($CDCl_3$) δ: 14; 23–32.5; 43; 55; 60; 103; 105–122; 148; 165. Calcd for $C_{23}H_{34}F_{11}NO_2$ (**3o**—F5H1H12): C, 48.8; H, 6.1; N, 2.5, F, 36.9. Found: C, 49.3; H, 6.2; N, 2.3; F, 36.5. Calcd for $C_{25}H_{34}F_{15}NO_2$ (**3p**—F7H1H12): C, 45.1; H, 5.1; N, 2.1; F, 42.8. Found: C, 44.8; H, 4.7; N, 2.0; F, 42.7. Calcd for $C_{27}H_{34}F_{19}NO_2$ (**3q**—F9H1H12): C, 42.3; H, 4.5; N, 1.8, F, 47.1. Found: C, 42.1; H, 4.4; N, 1.7; F, 46.5.

*4.3. General procedure for the preparation of β-alanine esters analogues **4***

A solution of compound **3** (compounds **3a–l**) (30 mmol) in methanol (50 ml) was added to a suspension of Raney nickel in water (6 ml) or a solution of compound **3** (compounds **3m–r**) in ethylacetate (50 ml) was added to a suspension of palladium on charcoal (10%) in methanol. The mixture was stirred for 36 h under dihydrogen (80 bar) at 80 °C. The reaction mixture was cooled to room temperature and filtered through a short pad of celite. The filtrate was dried over magnesium sulfate for compounds **4a–l**. The solvent was evaporated under reduced pressure and the crude residue purified by chromatography. (ethylacetate/hexane. 1:1).

*4.3.1. β-Alanine esters analogues **4a–e** $R^1 = H$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$: (3-perfluoroalkyl-3-alkylamino-propanoic acid ethyl ester)*

IR ν(C=O): 1740; ν(CF): 1000–1300. NMR ^{1}H ($CDCl_3$) δ: 0.9 (t, 3H, $^3J = 7$ Hz); 1.2–1.4 (m, $(2x + 3)$H); 1.4 (m, 2H); 2.6 (t, 2H, $^3J = 7.5$ Hz); 2.65 (dd, 1H, $^3J = 15$ and 10 Hz); 2.73 (dd, 1H, $^3J = 15$ and 7 Hz); 3.9 (m, 1H) 4.2 (q, 2H, $^3J = 10$ Hz); NMR ^{19}F ($CDCl_3$) δ: −81.5 (3F); −111.5 (2F); −123 to −121 ($(2n - 4)$F); −127 (2F). NMR ^{13}C ($CDCl_3$) δ: 14.5; 22–31; 59; 61; 103–126; 171. Calcd for $C_{18}H_{26}F_{11}NO_2$ (**4d**—F5H8): C; 43.5, H; 5.3; N, 2.8, F, 42.0. Found: C, 43.9; H, 4.9; N, 2.5; F, 41.4.

*4.3.2. β-Alanine esters analogues **4f–k** $R^1 = H$; $R^2 = CF_3(CF_2)_xCF_2CH_2CH_2-$: (3-perfluoroalkyl-3-(perfluoroalkylethylamino)-propanoic acid ethyl ester)*

IR ν(C=O): 1740; ν(CF): 1000–1300. NMR ^{1}H ($CDCl_3$) δ: 1.3 (t, 3H, $^3J = 7.5$ Hz); 1.5 (m, 1H); 2.3 (m, 2H); 2.54 (dd, 1H, $^3J = 15.5$ and 9.5 Hz); 2.75 (dd, 1H, $^3J = 15.5$ and 4 Hz); 3.10 (t, 2H, $^3J = 7$); 3.8 (m, 1H); 4.2 (q, 2H, $^3J = 7.5$ Hz). NMR ^{19}F ($CDCl_3$) δ: −81 (6F); −114 (2F); −116 to −121 (2F); −122 to −124 ($2(n + m') - 8$)F); −127 (4F). NMR ^{13}C ($CDCl_3$) δ: 14; 32.5; 34.5; 40.5; 57; 61.5; 104–122.5; 170.5. Calcd for $C_{20}H_{13}F_{28}NO_2$ (**4f**—F5F8AlaOEt): C, 28.9; H, 1.5; N, 1.7; F, 63.9. Found: C, 28.6; H, 1.7; N, 1.9; F, 63.0.

*4.3.3. β-Alanine esters analogues **4o–q** $R^1 = CH_3(CH_2)_xCH_2CH_2-$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$: (3-perfluoroalkyl-3-dialkylamino-propanoic acid ethyl ester)*

IR ν(C=O): 1740; ν(CF): 1000–1300. NMR ^{1}H ($CDCl_3$) δ: 0.9 (t, 6H, $^3J = 7$ Hz); 1.2–1.35 (m, $(4x + 3)$H); 1.40 (m, 4H); 2.6 (m, 6H); 4.0 (m, 1H); 4.2 (q, 2H, $^3J = 7$ Hz). NMR ^{19}F ($CDCl_3$) δ: −81 (3F); −112 to −119 (2F); −121 to −124 ($(2n - 4)$F); −127 (2F). NMR ^{13}C ($CDCl_3$) δ: 14; 23–32; 59; 60; 64; 103–126; 171. Calcd for $C_{22}H_{34}F_{11}NO_2$ (**4l**—F5H6H6AlaOEt): C, 47.7; H, 6.2; N, 2.5; F, 37.8. Found: C, 47.5; H, 5.5; N, 2.3; F, 36.9.

*4.3.4. β-Alanine esters analogues **4l–n** $R^1 = CH_3$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$: (3-perfluoroalkyl-3-(methylalkylamino)-propanoic acid ethyl ester)*

IR ν(C=O): 1742. NMR ^{1}H ($CDCl_3$) δ: 0.85 (t, 3H, $^3J = 7$ Hz); 1.3 (m, $(2x + 3)$H); 1.45 (m, 2H); 2.35 (s, 3H); 2.60 (m, 2H); 2.62 (dd, 1H, $^3J = 15$ and 5.5 Hz);); 2.73 (dd, 1H, $^3J = 15$ and 10 Hz); 3.9 (m, 1H); 4.20 (q, 2H, $^3J = 7$ Hz). NMR ^{19}F ($CDCl_3$) δ: −81.5 (3F); −111 to −121 (2F); −122 to −124 ($(2n - 4)$F); −126 to −127 (2F). NMR ^{13}C ($CDCl_3$) δ: 14.5; 23–32.5; 43; 59; 60; 105–122; 171. Calcd for $C_{25}H_{36}F_{15}NO_2$ (**4p**—F7H1H12AlaOEt): C, 43.2; H, 5.0; N, 2.2; F, 44.6. Found: C, 43.3; H, 5.0; N, 2.1; F, 45.0. Calcd for $C_{27}H_{36}F_{19}NO_2$ (**4q**—F9H1H12AlaOEt): C, 40.7; H, 4.1; N, 1.9; F, 48.9. Found: C, 41.5; H, 4.4; N, 1.7; F, 49.5.

*4.4. General procedure for the preparation of perfluoroalkyl β-alanine analogues **5***

To a solution of 8 mmol of ester **4** in methanol (10 ml) were added 5 eq. of a 2N sodium hydroxide solution in methanol/water (90/10). The mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (100 ml) and added to 100 ml of 2N HCl. The aqueous layer was extracted with ethyl acetate (2 ml × 100 ml). The combined organic layers were dried over magnesium sulfate and the solvent was evaporated under reduce pressure.

*4.4.1. Perfluoroalkyl β-alanine analogues **5a–e** $R^1 = H$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$ (type FnHmAla) (3-perfluoroalkyl-3-alkylamino-propanoic acid)*

IR ν(C=O): 1715. NMR ^{1}H (CD_3OD) δ: 0.85 (t, 3H, $^3J = 7$ Hz); 1.35 (m, 2*x*H); 1.6 (m, 2H); 2.70 (dd, 1H, $^3J = 7.5$ and 16.5 Hz); 2.90 (m, 3H); 4.1 (m, 1H). NMR ^{19}F (CD_3OD) δ: −78.5 (3F); −112 to −117 (2F); −118 to

−120 ((2*n* − 4)F); −123 (2F). NMR ^{13}C (CD_3OD) δ: 13; 22–32; 25–35; 56; 172. Calcd for $C_{20}H_{26}F_{15}NO_2$ (**5b**—F7H10Ala): C, 40.2; H, 4.4; N, 2.3; F, 47.7. Found: C, 39.4; H, 4.4; N, 2.1; F, 45.6. Calcd for $C_{22}H_{26}F_{19}NO_2$ (**5c**—F9H10Ala): C, 38.8; H, 4.1; N, 2.0. Found: C, 39.3; H, 4.5; N, 2.5. Calcd for $C_{16}H_{22}F_{11}NO_2$ (**5d**—F5H8Ala): C, 40.9; H, 4.7; N, 3.0; F, 44.5. Found: C, 40.1; H, 4.6; N, 2.7; F, 43.9. Calcd for $C_{18}H_{22}F_{15}NO_2$ (**5e**—F7H8Ala): C, 36.5; H, 3.7; N, 2.3; F, 48.1. Found: C, 36.0; H, 3.7; N, 2.1; F, 48.5.

4.4.2. Perfluoroalkyl β-alanine analogues **5f–k** $R^1 = H$; $R^2 = CF_3(CF_2)_xCF_2CH_2CH_2-$ (type FnFn′Ala): (3-perfluoroalkyl-3-(perfluoroalkylethylamino)-propanoic acid)

IR ν(C=O): 1715. NMR ^{1}H (CD_3OD) δ: 2.3 (m, 2H); 2.6 (dd, 1H, ^3J = 4.5 and 16.5 Hz); 2.85 (dd, 1H, ^3J = 4 and 16.5 Hz); 3 (m, 1H); 3.1 (m, 1H); 3.85 (m, 1H). NMR ^{19}F (CD_3OD) δ: −81 (6F); −111 (2F); −112 to −117 (2F); −119 to −122 ((2*n* − 8)F); −124 (4F). NMR ^{13}C (CD_3OD) δ: 31.5; 34; 40; 56.5; 108–121.5; 173. Calcd for $C_{20}F_{32}H_9NO_2$ (**5g**—F7F8Ala): C, 26.6; H, 1.0; N, 1.5; F, 67.3. Found: C, 26.8; H, 1.1; N, 1.5; F, 63.1. Calcd for $C_{16}H_9F_{24}NO_2$ (**5I**—F5F6Ala): C, 27.3; H, 1.2; N, 1.9F, 64.8. Found: C, 26.2; H, 1.4; N, 1.7; F, 63.9. Calcd for $C_{18}H_9F_{28}NO_2$ (**5j**—F7F6Ala): C, 26.9; H, 1.1; N, 1.7; F, 66.2. Found: C, 28.30; H, 1.4; N, 1.6; F, 63.7. Calcd for $C_{20}H_9F_{32}NO_2$ (**5k**—F9F6Ala): C, 26.6; H, 1.0; N, 1.5; F, 67.3. Found: C, 26.6; H, 1.14; N, 1.5; F, 64.6.

4.4.3. Perfluoroalkyl β-alanine analogues **5l–n** $R^1 = CH_3(CH_2)_xCH_2CH_2-$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$ (type FnHmHm′Ala): (3-perfluoroalkyl-3-dialkylamino-propanoic acid)

IR ν(C=O): 1715. NMR ^{1}H (CD_3COCD_3) δ: 0.9 (t, 6H, ^3J = 6.5 Hz); 1.25 (m, 4*x*H); 1.45 (m, 4H); 2.7 (m, 6H); 4 (m, 1H); 10.5 (m, 1H). NMR ^{19}F ($CDCl_3$) δ: −82 (3F); −113 to −118 (4F); −122 to −124 ((2*n* − 6)F); −127 (2F). NMR ^{13}C ($CDCl_3$) δ: 4; 21–32; 48; 58; 66; 105–124; 176. Calcd for $C_{22}H_{30}F_{15}NO_2$ (**5m**—F7H6H6Ala): C, 42.2; H, 5.0; N, 2.2; F, 45.5. Found: C, 45.2; H, 5.3; N, 2.3; F, 46.3. Calcd for $C_{24}H_{30}F_{19}NO_2$ (**5n**—F9H6H6Ala): C, 39.7; H, 4.4; N, 1.9; F, 49.8. Found: C, 39.1; H, 4.4; N, 2.4; F, 50.5.

4.4.4. Perfluoroalkyl β-alanine analogues **5o–q** $R^1 = CH_3$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$ (type FnHmHm′Ala): (3-perfluoroalkyl-3-(methylalkylamino)-propanoic acid)

IR ν(C=O): 1715. NMR ^{1}H (CD_3OD) δ: 0.85 (t, 3H, ^3J = 7 Hz); 1.3 (m, 2*x*H); 1.45 (m, 2H); 2.1 (s, 3H); 2.6–2.85 (m, 4H); 4 (m; 1H). NMR ^{19}F (CD_3OD) δ: −81.5 (3F); −113 to −119 (4F); −121 to −124 ((2*n* − 8)F); −125 (2F); −127 (2F). NMR ^{13}C (CD_3OD) δ: 14; 22–32; 42.5; 56; 61.5; 107.5–123.5; 175. Calcd for $C_{21}H_{32}F_{11}NO_2$ (**5o**—F5H1H12Ala): C, 46.7; H, 6.0; N, 2.6; F, 38.7. Found: C, 46.6; H, 5.8; N, 2.7; F, 37.9. Calcd for $C_{23}H_{32}F_{15}NO_2$ (**5p**—F7H1H12Ala): C, 43.2; H, 5.0; N, 2.2; F, 44.6. Found: C, 43.1; H, 5.1; N, 2.2; F, 45.2. Calcd for $C_{25}H_{32}F_{19}NO_2$ (**5q**—F9H1H12Ala): C, 40.6; H, 4.3; N, 1.9; F, 48.8. Found: C, 40.7; H, 4.3; N, 1.9; F, 49.3.

4.5. General procedure for the preparation of perfluoroalkyl peptides analogues **6**

To a solution of 10 mmol of the analogues of β-alanine **5** in acetonitrile (20 ml) were added 3 eq. of triethylamine in 10 ml of acetonitrile, 1 eq. of BOP in 10 ml of acetonitrile, and 1 eq. of appropriate aminoacid ester in 10 ml of acetonitrile. The mixture was stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure and the crude residue was dissolved in ethyl acetate (100 ml) and the organic phases was washed with 20 ml of 2N aqueous HCl, 20 ml of brine, 20 ml of a saturated aqueous solution of $NaHCO_3$, and 50 ml of brine. The combined organic layers were dried over magnesium sulfate. The solvent was evaporated under reduced pressure and the crude residue was purified by chromatography on silica gel. (MeOH/ethyl acetate, 20/80).

4.5.1. Perfluoroalkyl peptides analogues **6a–c** $R^1 = H$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$ (type FnHmHisMe): 3-(1H-Imidazol-4-yl)-2-(3-perfluoroalkyl-3-alkylamino-propanoylamino)propionic acid methyl ester (bis hydrochloride)

IR ν(C=O ester): 1735. ν(C=O amide): 1655. NMR ^{1}H (CD_3OD) δ: 0.9 (t, 3H, ^3J = 7 Hz); 1.30 (m, 2*x*H); 1.4 (m, 2H); 2.6 (m, 4H); 3.05 (dd, 1H, ^3J = 8.5 and 15 Hz); 3.10 (dd, 1H, ^3J = 5.5 and 15 Hz); 3.75 (s, 3H); 3.8 (m, 1H); 4.7 (m, 1H); 6.9 (s, 1H); 7.6 (s, 1H). NMR ^{19}F (CD_3COCD_3) δ: −76.5 (3F); −109 to −111 (2F); −116 to −115 (2F); −116 to −118 ((2*n* − 6)F) −122 (2F). NMR ^{13}C (CD_3OD) δ: 14; 22–32; 48; 52; 53,5; 57; 116.5; 132.5; 134.5; 169.5; 171.5. Calcd for $C_{27}H_{37}Cl_2F_{15}N_4O_3$ (**6b**—F7H10HisMe): C, 39.5; H, 4.5; N, 6.8; F, 34.7. Found: C, 40.2; H, 4.8; N, 7.5; F, 36.0.

4.5.2. Perfluoroalkyl peptides analogues **6d–f** $R^1 = H$; $R^2 = CF_3(CF_2)_xCF_2CH_2CH_2-$ (type FnFn′HisMe): (3-(1H-Imidazol-4-yl)-2-{3-perfluoroalkyl-3-(perfluoroalkylethylamino)-propanoylamino}propionic acid methyl ester (bis hydrochloride))

IR ν(C=O ester): 1735. ν(C=O amide) = 1665. NMR ^{1}H (CD_3COCD_3) δ: 2.4 (m, 2H); 2.7 (m, 2H); 2.9 (m, 2H); 3.9 (m, 2H); 4.9 (m, 1H); 7.4 (m, 1H); 7.6 (s, 1H); 8.25 (t, 1H, ^3J = 7 Hz); 9 (s, 1H); 9,1 (m, 1H). Calcd for $C_{25}H_{20}Cl_2F_{28}N_4O_3$ (**6e**—F7H6HisMe): C, 29.2; H, 2.0; N, 5.4; F, 51.8. Found: C, 30.5; H, 1.5; N, 5.5; F, 52.5.

4.5.3. Perfluoroalkyl peptides analogues **6g–h** $R^1 = CH_3$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$ (type FnHmHm′HisMe): (3-(1H-Imidazol-4-yl)-2-[3-perfluoroalkyl-3-(methylalkylamino)-propanoylamino]propionic acid methyl ester (bis hydrochloride))

IR ν(C=O): 1740; ν(C=O amide) = 1665. NMR ^{1}H (CD_3OD) δ: 0.9 (t, 3H, ^3J = 7 Hz); 1.3 (m, 2*x*H); 1.5 (m,

2H); 2.4 (s, 3H); 2.6 (m, 2H); 2.80 (m, 4H); 3.75 (s, 3H); 4.0 (m, 1H); 4.8 (m, 1H); 7.3 (s, 1H); 7.8 (s, 1H). Calcd for $C_{28}H_{39}Cl_2F_{15}N_4O_3$ (**6g**—F07H1H12HisMe): C, 40.0; H, 4.7; N, 6.7; F, 34.1. Found: C, 40.8; H, 4.2; N, 6.0; F, 34.5.

*4.5.4. Perfluoroalkyl peptides analogues **6i–j** $R^1 = CH_3(CH_2)_xCH_2CH_2-$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$ (type FnHmHa): (3-(1H-Imidazol-4-yl)-2-{3-perfluoroalkyl-3-dialkylamino-propanoylamino}propionic acid methyl ester (bis hydrochloride))*

IR ν(C=O): 1740; ν(C=O amide) = 1665. NMR ^{1}H (CD_3OD) δ: 0.9 (t, 3H, $^3J = 7$ Hz); 1.35 (m, 2xH); 1.5 (m, 2H); 2.45 (dd, 1H, $^3J = 8.5$ and 15 Hz); 2.60 (dd, 1H, $^3J = 5$ and 15 Hz); 2.65 (m, 2H); 2.85 (t, 2H, $^3J = 11.5$ Hz); 3.8 (m, 1H); 7 (s, 1H); 7.8 (s, 1H). Calcd for $C_{25}H_{35}Cl_2F_{15}N_4O$ (**6j**—F7H10Ha): C, 39.3; H, 4.6; N, 7.3; F, 37.3. Found: C, 38.8; H, 4.2; N, 7.5; F, 37.5.

*4.5.5. Perfluoroalkyl peptides analogues **6k** $R^1 = H$; $R^2 = CF_3(CF_2)_xCF_2CH_2CH_2-$ (type FnFn′Ha): 3-perfluoroalkyl-3-(perfluoroalkylethylamino)-propanoic acid [2-(1H-imidazol-4-yl)-ethyl]-amide. (bis hydrochloride)*

IR ν(C=O): 1740; ν(C=O amide) = 1665. NMR ^{1}H (CD_3COCD_3) δ: 3.20 (dd, 1H, $^3J = 8$ and 15 Hz); 3.30 (m, 3H); 3.85 (m, 2H); 5.75 (m, 1H); 7,.4 (s, 1H); 8.0 (t, 1H, $^3J = 6$ Hz); 8.5 (s, 1H); 8.6 (m, 1H). Calcd for $C_{21}H_{18}Cl_2F_{24}N_4O$ (**6k**—F5F6Ha): C, 29.0; H, 2.1; N, 6.4; F, 52.4. Found: C, 30.5; H, 1.9; N, 6.5; F, 52.8.

*4.6. General procedure for the preparation of compounds **7***

The procedure of hydrolysis was similar to the preparation of compounds **5**.

*4.6.1. Perfluoroalkyl peptides analogues **7** $R^1 = H$; $R^2 = CH_3(CH_2)_xCH_2CH_2-$ (type FnHmHis): (3-(1H-Imidazol-4-yl)-2-(3-perfluoroalkyl-3-alkylamino-propanoylamino)propionic acid (bis hydrochloride))*

IR ν(C=O acid): 1720. ν(C=O amide): 1655. NMR ^{1}H (CD_3OD) δ: 0.8 (t, 3H, $^3J = 7$ Hz); 1.30 (m, 2xH); 1.4 (m, 2H); 2.8 (m, 4H); 3.05 (dd, 1H, $^3J = 8.5$ and 15 Hz); 3.10 (dd, 1H, $^3J = 5.5$ and 15 Hz); 4.3 (m, 1H); 4.8 (m, 1H); 7.3 (s, 1H); 8.8 (s, 1H). NMR ^{19}F (CD_3OD) δ: −76.8 (3F); −109 to −111 (2F); −116 to −115 (2F); −116 to −119 ((2n − 6)F) −122 (2F). Calcd for $C_{26}H_{35}Cl_2F_{15}N_4O_3$ (**7**—F7H10His): C, 38.7; H, 4.4; N, 6.9; F, 35.3. Found: C, 40.5; H, 4.5; N, 6.5; F, 35.9.

*4.6.2. Perfluoroalkyl peptides analogues **7** $R^1 = H$; $R^2 = CF_3(CF_2)_xCF_2CH_2CH_2-$ (type FnFn′His): (3-(1H-Imidazol-4-yl)-2-(3-perfluoroalkyl-3-perfluoroalkylethylamino-propanoylamino)propionic acid (bis hydrochloride))*

IR ν(C=O acid): 1720. ν(C=O amide) = 1665. NMR ^{1}H (CD_3COCD_3) δ: 2.6 (m, 2H); 2.7 (m, 2H); 3.2–3.7 (m, 4H); 4.9 (m, 1H); 7.4 (m, 1H); 7.6 (s, 1H); 8.25 (t, 1H, $^3J = 7$ Hz); 9 (s, 1H); 9,1 (m, 1H). Calcd for $C_{24}H_{18}Cl_2F_{28}N_4O_3$ (**7**—F7F6His): C, 28.4; H, 1.8; N, 5.5; F, 52.5. Found: C, 29.2; H, 2.1; N, 5.5; F, 52.9.

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