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Potent multitarget FAAH-COX inhibitors: Design and structure-activity relationship studies

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) exert their pharmacological effects by inhibiting cyclooxygenase (COX)-1 and COX-2. Though widely prescribed for pain and inflammation, these agents have limited utility in chronic diseases due to serious mechanism-based adverse events such as gastrointestinal damage. Concomitant blockade of fatty acid amide hydrolase (FAAH) enhances the therapeutic effects of the NSAIDs while attenuating their propensity to cause gastrointestinal injury. This favorable interaction is attributed to the accumulation of protective FAAH substrates, such as the endocannabinoid anandamide, and suggests that agents simultaneously targeting COX and FAAH might provide an innovative strategy to combat pain and inflammation with reduced side effects. Here, we describe the rational design and structure-active relationship (SAR) properties of the first class of potent multitarget FAAH-COX inhibitors. A focused SAR exploration around the prototype **10r** (ARN2508) led to the identification of achiral (**18b**) as well as racemic (**29a-c** and **29e**) analogs. Absolute configurational assignment and pharmacological evaluation of single enantiomers of **10r** are also presented. (S)-(+)-**10r** is the first highly potent and selective chiral inhibitor of FAAH-COX with marked *in vivo* activity, and represents a promising lead to discover novel analgesics and anti-inflammatory drugs.

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1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely utilized to treat pain and inflammation [1], but their chronic use is hindered by a variety of potentially serious adverse events that include gastrointestinal (GI) mucosal lesions, bleeding and perforations [2–5]. Conventional NSAIDs inhibit the two isoforms of cyclooxygenase (COX), COX-1 and COX-2, which catalyze the first committed steps in the biosynthetic pathway that converts arachidonic acid (AA) into inflammatory prostanoids such as prostaglandin E_2 (PGE_2) and thromboxane A_2 (TXA_2) [6]. The dual role of COX-1-derived PGE_2 as inflammation promoter and mucosal tissue protectant explains, at least in part, why NSAIDs cause damage to the GI tract [7–10]. Efforts to overcome this problem have led to the development of selective COX-2 inhibitors, which combine a high level of anti-inflammatory efficacy with a reduced propensity to cause injury to the GI mucosa [6]. Nevertheless, the use of COX-2 inhibitors has been linked to a distinctive set of adverse cardiovascular effects [11,12]. Thus, the need for safe and effective drugs that can be used in the treatment of chronic inflammatory disorders remains urgent.

A promising approach to meet this need is offered by targeting with a single agent more than one component of the inflammatory cascade [13–15]. Agents designed to achieve this objective include nitric oxide (NO) donors-NSAIDs [16,17], COX-2 inhibitors−NO−donors [18,19], hydrogen sulfide (H_2S) donors-NSAIDs [20–22], as well as compounds that block distinct enzymes of the AA pathway, such as COX/lipoxygenase [23,24] and COX-2/soluble epoxy hydrolase (sEH) [25]. Another potential multitarget strategy to treat inflammation is the concomitant inhibition of COX and fatty acid amide hydrolase (FAAH) [26] [27−33], a serine hydrolase

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that deactivates a family of analgesic and anti-inflammatory lipid amides that are produced by host-defense cells and other cells in the body [34,35]. These lipid mediators include the endocannabinoid anandamide (arachidonoylethanolamide) − which engages cannabinoid-1 (CB$_1$) and CB$_2$ receptors to suppress neutrophil migration [36] and prevent immune-cell recruitment [37,38] − as well as the endogenous peroxisome proliferator-activate receptor-α (PPAR-α) agonists, palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) [39—41]. In addition to opposing pain and inflammation, these FAAH substrates are also protective of the GI mucosa [42,43]. Indeed, studies in animal pain models have shown that co-administration of FAAH and COX inhibitors results in a synergistic potentiation of analgesia along with reduced gastric damage [44—46].

In several chronic inflammatory conditions, including inflammatory bowel disease (IBD), FAAH [47—49] and COX-2 [50] are expressed at abnormally high levels. This simultaneous up-regulation may help establish a pathological state that exacerbates inflammation by amplifying inflammatory COX-dependent signals at the expense of defensive FAAH-regulated mediators. This hypothesis predicts that drugs targeting both COX and FAAH should have substantial anti-inflammatory efficacy combined with reduced GI toxicity. In a recent study, we provided support to this hypothesis using a multitarget modulator based on the hybrid scaffold 1 (Fig. 1) [51]. This scaffold merges key pharmacophores of two known classes of FAAH and COX inhibitors − O-aryl carbamates [52—58] such as [3-(3-carbamoylphenyl)phenyl] N-cyclohexylcarbamate (URB597, 2) [54,57], and 2-aryl propionic acids [6] such as flurbiprofen, 3a [59—61] − which share a biphenyl core as a common structural motif (A and B rings, Fig. 1). Moreover, structure-activity relationship (SAR) studies of these scaffolds supported the hypothesis of additional elements of structural overlapping, such as the oxygenated substituents at the 3′-position of the A phenyl ring, corresponding to the carbamate functionality of 2 [53,54,56] and the ether moieties of 3b or 3c [61], respectively (Fig. 1).

This SAR work led to the identification of compound 10r ((±)-2-[3-fluoro-4-[3-(hexylcarbamoyloxy)phenyl]phenyl]propanoic acid, ARN2508) [51] as a potent in vivo active inhibitor of intracellular FAAH and COX activities, which exerts profound anti-inflammatory effects in mouse models of IBD without causing COX-dependent gastric toxicity [51]. In the present study, (a) we outline the in-depth SAR investigations that led to the discovery of compound 10r [51]; (b) we report an expansion of this SAR work, which culminated in the identification of several new and potent multi-target inhibitors (18b, 29a-c and 29e); and, finally (c) we describe the absolute configurational assignment and pharmacological properties of single enantiomers of 10r, identifying (S)-(+)-10r as the first chiral inhibitor of FAAH-COX with marked in vivo activity.

2. Results and discussion

2.1. Chemistry

Compounds 10a-t were synthesized from the corresponding phenol 8 through a carbamoylation reaction, using commercially available isocyanates, followed by the hydrolysis of the methyl esters 9a-t, under acidic conditions (Scheme 1).

The intermediate 8 was prepared in four steps, starting from the acid 4, obtained as previously described [62]. Compound 4 was converted to the corresponding methyl ester 5, under standard acidic conditions, to afford, after catalytic hydrogenation with ammonium formate in the presence of Pd/C, the resulting aniline 6. Compound 6 was then transformed into the corresponding diazonium salt, that was reacted in situ with NaI to obtain the phenyl iodide 7 in good yield, which was converted, under ligand less Suzuki cross coupling conditions [63], to the biphenyl derivatives 8 and 13a-c in excellent yield (Schemes 1—3).

3-Hydroxypropyl derivative 12 was synthesized by reduction of the methyl ester 8 to the alcohol 11 (Scheme 1). Although lithium aluminum hydride succeeded in reducing the ester 8, a significant des-fluorinated side product was observed and separation of the two compounds was troublesome. Therefore, a milder reducing agent, such as zirconium borohydride generated in situ, was used to afford a clean conversion of 8 to 11 [64], which was then converted to 12 under standard carbamoylation reaction conditions (Scheme 1).

Carbamates 15a-b and urea 15c were prepared from the corresponding phenols 13a-b and aniline 13c, respectively, through a carbamoylation reaction using n-hexyl-isocyanate, followed by acidic hydrolysis of the methyl esters 14a-c (Schemes 2 and 3). The reverse carbamate 15d was prepared upon activation of the aniline 13c with triphosgene, and, then, reaction with n-hexanol, followed by acidic hydrolysis of the methyl ester 14d (Scheme 3).

Compounds 18a and 21a-b were synthesized by reacting the phenyl iodides 16b and 19a-b, with (3-hydroxyphenyl)boronic acid under Suzuki cross coupling conditions, followed by carbamoylation reaction of phenols 17 and 20a-b under standard conditions (Schemes 4 and 5).

Compounds 18a and 21b were then transformed into the corresponding acids 18b and 21c under standard acidic hydrolysis (Schemes 4 and 5).

Compounds 29a-g were synthesized following the synthetic sequence described in Scheme 6 p-Nitrofluorobenzenes 22a-d were reacted with diethyl methylmalonate followed by decarboxylation to the corresponding acids 23a-d. 23a-d and the commercially available 23e were converted into methyl esters 24a-e in acidic MeOH. In addition, the phenolic intermediate 24d was directly converted into the corresponding O-Bn protected 24f,
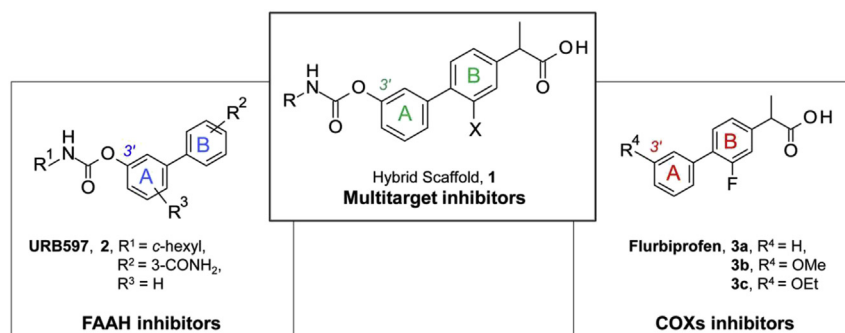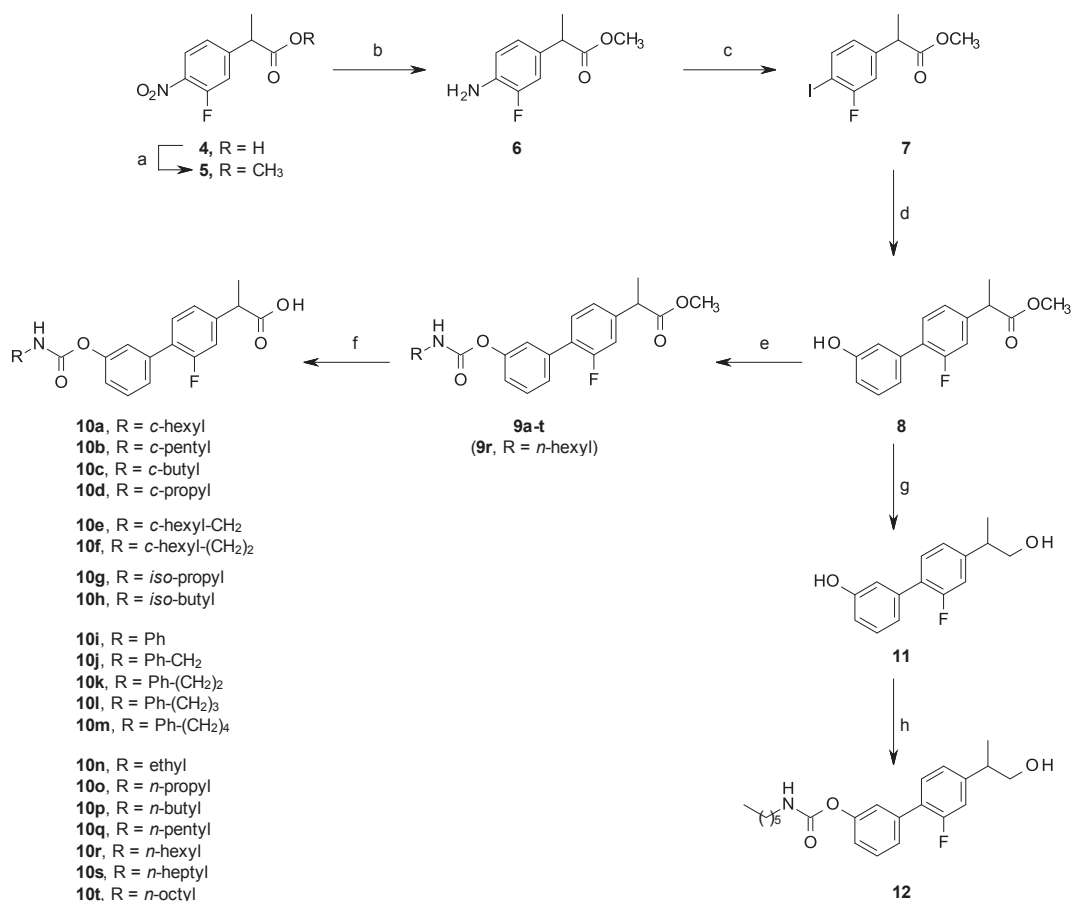

Fig. 1. Rational design of a 'hybrid scaffold' for FAAH and COX inhibition.

Scheme 1. Synthesis of compounds **10a-t** and **12**. Reagents and conditions: (a) MeOH, conc. H$_2$SO$_4$, rt, 15 h, 93%; (b) HCO$_2$NH$_4$, 10% Pd/C, MeOH, rt, 3 h, 94%; (c) NaNO$_2$, 3 M HCl, 0 °C, 30 min, then NaI, 60 °C, 2 h, 55%; (d) (3-hydroxyphenyl)boronic acid, Pd(OAc)$_2$, K$_2$CO$_3$, EGME/H$_2$O, rt, 15 h, 84%; (e) RNCO, DMAP, MeCN, rt, 15 h, 38–99%; (f) 6 M HCl, THF, rt, 2 d, 26–73%; (g) ZrCl$_4$, NaBH$_4$, THF, rt, 2 h, 96%; (h) n-hexyl-NCO, DMAP, MeCN, rt, 15 h, 73%.

under standard reaction conditions.

Reduction of the nitro group was carried out using iron in presence of HCl for compounds **24a** and **24f**, and ammonium formate in the presence of Pd/C for compounds **24b-c** and **24e**. Compound **25f** was obtained from **25e** by standard nitration reaction. Diazotation/Sandmayer reaction of the anilines **25a-f** gave the iodides **26a-f**, which were converted to carbamates **28a-f** via Suzuki and carbamoylation reactions. Compounds **28a-f** were then transformed into the corresponding acids **29a-f** under standard acidic hydrolysis. Finally, the aniline **29g** was obtained from the nitrophenyl **29f**, under standard hydrogenation conditions.

2.2. SAR exploration of the first class of potent multitarget FAAH-COX inhibitors

2.2.1. Rational drug design: merging strategy and identification of hit 10a

We started our SAR exploration with compound **10a** [51], which was designed by merging essential pharmacophores of the FAAH inhibitor, URB597, **2**, and those of the NSAID, flurbiprofen, **3a** (Fig. 1). The inhibitory potencies of **2**, **3a** and **10a** against rat brain FAAH, ovine testis COX-1 and human recombinant COX-2 are reported in Table 1.

Compound **10a** inhibited FAAH and COX activities with relatively weak potencies (IC$_{50}$ values, in μM: FAAH = 8.2; COX-1 = 7.9; COX-2 > 100). Nevertheless, these initial results encouraged us because **10a** was one of the most potent FAAH/COX-1 inhibitors

previously reported [27,28,30,32,33,65].

We started, therefore, an SAR exploration around **10a** with the objective of identifying chemical and structural determinants that might improve potency on the three targets in a balanced manner.

2.2.2. Study of the effect of the nature of R group: cycloalkanes, small-branched alkanes and phenyls

We prepared a series of analogs bearing cycloalkyl groups with different ring size at the N-terminal of the carbamate functionality (Table 1).

We observed that, while the potency against FAAH was retained with the c-pentyl analog **10b** (IC$_{50}$ = 4.8 μM), a 10-fold loss in potency occurred with the c-butyl derivative **10c** (IC$_{50}$ = 48.7 μM) and complete loss of activity (IC$_{50}$ > 100 μM) with the c-propyl derivative **10d**. With regard to COX activity, while the c-pentyl analog **10b** showed a comparable potency against COX-1 (IC$_{50}$ = 4.4 μM), the c-butyl analog **10c** was 10-fold more potent than compound **10a** (IC$_{50}$ = 0.72 μM). Conversely, the c-propyl analog **10d** displayed an IC$_{50}$ value similar to compounds **10a** and **10b** against COX-1 (=5.4 μM) and was indeed the only compound in this series that showed modest activity against COX-2 (IC$_{50}$ = 74.3 μM).

The N-terminal region of the carbamate functionality in **10a** may engage in beneficial interactions with the acyl chain-binding domain of FAAH [26] [56,57], as well as the hydrophobic channels present in COX-1 and COX-2 [6]. [61] To capture such interactions, we prepared a series of analogs bearing lipophilic aliphatic and aromatic N-terminal substituents with diverse steric properties
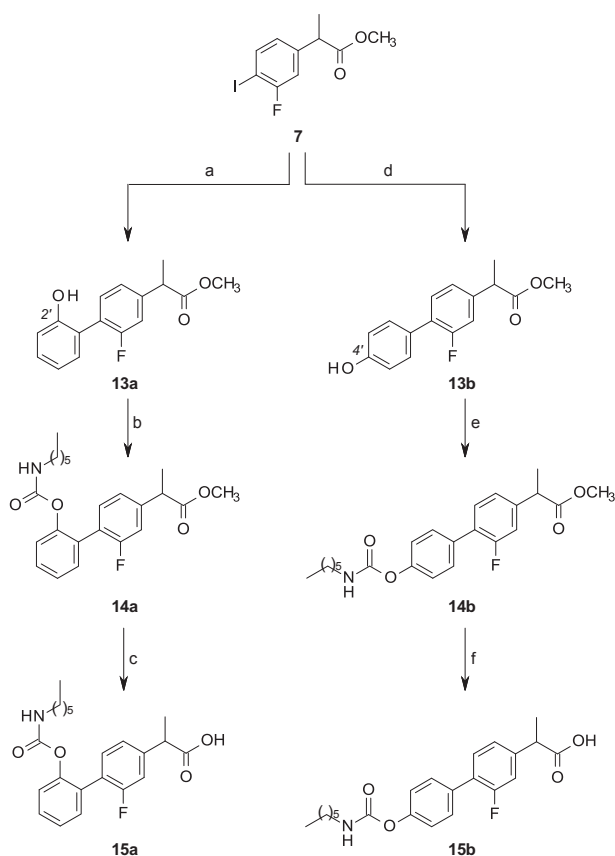
Scheme 2. Synthesis of compounds **15a-b**. Reagents and conditions: (a) (2-hydroxyphenyl)boronic acid, Pd(OAc)$_2$, K$_2$CO$_3$, EGME/H$_2$O, rt, 15 h, 84%; (b) *n*-hexyl-NCO, DMAP, MeCN, rt, 15 h, 88%; (c) 6 M HCl, THF, rt, 2 d, 90%; (d) (4-hydroxyphenyl) boronic acid, Pd(OAc)$_2$, K$_2$CO$_3$, EGME/H$_2$O, rt, 15 h, 59%; (e) *n*-hexyl-NCO, DMAP, MeCN, rt, 15 h, 72%; (f) 6 M HCl, THF, rt, 2 d, 46%.

(Table 1).

The insertion of a methylene group adjacent to the *c*-hexyl ring of **10a** - compound **10e**-led to a significant increase of potency toward FAAH (23-fold) and COX-1 (10-fold), but no COX-2 inhibition (IC$_{50}$ > 100 μM). A further homologation, compound **10f**, showed a 400-fold increase in potency toward FAAH and a 50-fold increase in potency toward COX-1, compared to **10a**. Interestingly, **10f** also inhibited COX-2 with an IC$_{50}$ of 10.8 μM.

Next, we investigated the effects of small and branched alkyl groups, the *iso*-propyl **10g** and the *iso*-butyl **10h** - as truncated analogs of **10a** and **10e**, respectively. These modifications were detrimental for FAAH and COX inhibitory activities compared to **10a** and **10e**, respectively.

While the replacement of the *c*-hexyl ring with a phenyl group (**10i**) was not tolerated by FAAH, in analogy to previous reports on the class of *O*-aryl carbamates [56,57], this modification led to a gain in inhibitory activity toward COX-1 and COX-2. The insertion of a methylene group adjacent to the phenyl ring of **10i** - compound **10j**-caused a 10-fold increase in potency toward FAAH, compared to **10i**, but had almost no impact on COX-1 activity and dramatic loss on COX-2. Homologation (**10k-m**) resulted in a progressive enhancement of the inhibitory potency toward FAAH, but this trend was more erratic for COX-1 and COX-2: compound **10l** was most active analog with IC$_{50}$ = 0.58 μM and 6.2 μM against COX-1 and COX-2, respectively.

These findings might reflect differences in the depth of

lipophilic pockets of FAAH and COX enzymes [6,26].

2.2.3. Study of the effect of the nature of the R group: linear alkanes. Identification of **10r** (ARN2508)

Since the (CH$_2$)$_n$ homologation at the N-terminal site appeared to be critical for the modulation of the biological activities at both targets, we prepared a series of carbamates bearing linear alkyl groups (alkyl = (CH$_3$(CH$_2$)$_n$) with *n* = 1 to 7) at N-terminal region (Table 2).

In analogy to the reported SAR results on the class of *O*-aryl carbamates [56], potency toward FAAH increased with increased length of the (CH$_2$)$_n$ chain (*n* = 1−7). A different trend was observed for COX-1 and COX-2, where insertion of short (CH$_2$)$_n$ chains (*n* = 1−2) led to compounds (**10n-o**) that were weak COX-1 inhibitors and had no activity against COX-2. On the other hand, insertion of *n* = 3−5 (CH$_2$)$_n$ chains (**10p-r**) increased the inhibitory potencies for COX-1 and COX-2 from sub-micromolar to nanomolar IC$_{50}$, whereas insertion of *n* = 6−7 (CH$_2$)$_n$ chains (**10s-t**) was detrimental.

These results are in agreement with those above reported in the homologation of the Ph(CH$_2$)$_n$ chain series (*n* = 1−4, compounds **10i-m**, Table 1).

From this SAR exploration, we identified **10r** (ARN2508) [51], which bears a *n*-hexyl chain at the N-terminal site, as a potent multitarget inhibitor of FAAH, COX-1 and COX-2 (IC$_{50}$: FAAH = 31 nM; COX-1 = 12 nM; COX-2 = 430 nM) (Table 2). In addition to its high balanced potency, the highest reported thus far [27,28,30,32,33,65], we found that **10r** displays no off−target activities on a panel of >90 biologically relevant targets, and effectively engages its intended targets after oral administration in mice [51].

These results encouraged us to initiate a more focused SAR exploration to define the effect of additional chemical and structural modifications in various regions of **10r** scaffold.

2.2.4. Focused SAR exploration around **10r** (ARN2508) and identification of **18b**, **29a-c**, **e** and (S)-(+)-**10r**

In particular, we focused our interest on the role and position of carbamate group in the *A* phenyl ring (Table 3 and Table 4), as well as the role of the propionic acid functionality and the fluorine atom in the *B* phenyl ring (Table 5 and Table 6).

2.2.4.1. Role and position of carbamate group in the A phenyl ring.
We first investigated the effect of the position of the carbamate group in the *A* phenyl ring, which indeed appeared to play an important role in the inhibition of both FAAH and COX (Table 3). In agreement with the rational design of our hybrid scaffold **1** (Fig. 1), the C(2′)-derivative **15a** (*ortho* derivative) showed a 70-fold decrease in potency toward FAAH, a 60-fold decrease in potency toward COX-1, and a complete loss of activity toward COX-2, when compared to the C(3′)-isomer **10r** (*meta* derivative) (Table 3).

On the other hand, the C(4′)-derivative **15b** (*para* derivative) exhibited a slight loss of potency toward FAAH compared to **10r**, but both COX inhibitions were completely suppressed (Table 3). These results support the hypothesis that the bent shape of the *O*-biphenyl moieties, which is known to better fit the FAAH enzyme surface [53], is also important in the recognition by COX-1 and COX-2, possibly through a better superimposition to the conformations adopted by the fatty acyl chain of the natural substrate/product (the first two *cis*-double bonds of AA) when bound to COX-1 [66] and COX-2 [67].

Next, we replaced the carbamate moiety with alternative functional groups, such as urea (**15c**) [51] and reversed carbamate (**15d**) [51] (Table 4).
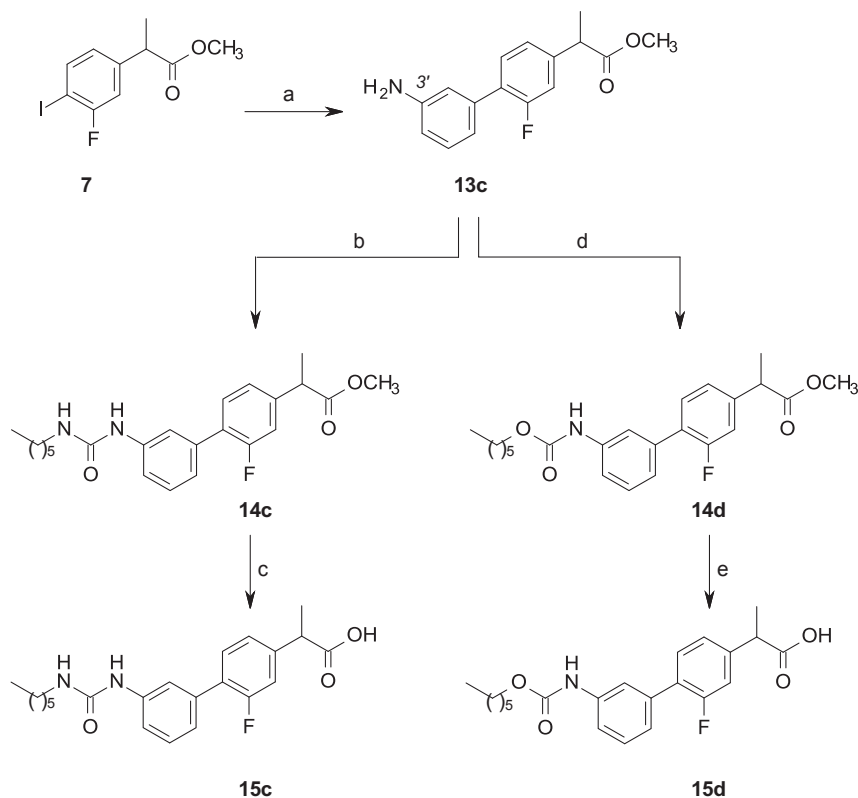
Scheme 3. Synthesis of compounds **15c-d**. Reagents and conditions: (a) (3-aminophenyl)boronic acid, Pd(OAc)$_2$, K$_2$CO$_3$, EGME/H$_2$O, rt, 15 h, 91%; (b) *n*-hexyl-NCO, DMAP, MeCN, rt, 15 h, 65%; (c) 6 M HCl, THF, rt, 2 d, 38%; (d) triphosgene, toluene, reflux, 15 h, then *n*-hexanol, rt, 15 h, 82%; (e) 6 M HCl, THF, rt, 2 d, 59%.
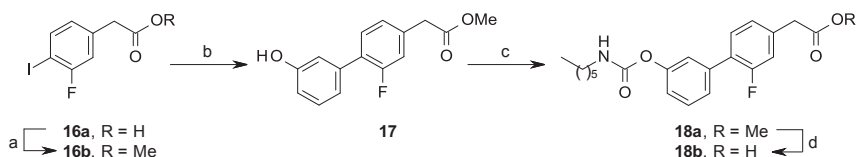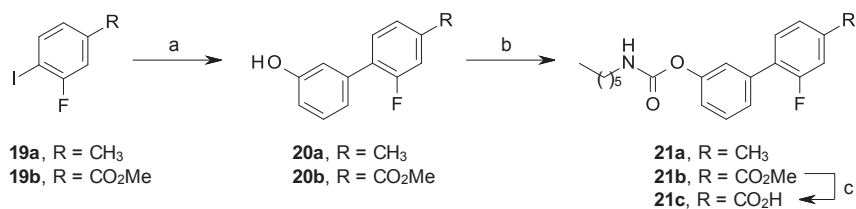

Scheme 4. Synthesis of compound **18b**. Reagents and conditions: (a) MeOH, conc. H$_2$SO$_4$, rt, 15 h, quant.; (b) (3-hydroxyphenyl)boronic acid, Pd(OAc)$_2$, K$_2$CO$_3$, EGME/H$_2$O, rt, 15 h, 71%; (c) *n*-hexyl-NCO, DMAP, MeCN, rt, 15 h, 64%; (d) 6 M HCl, THF, rt, 2 d, 62%.

Scheme 5. Synthesis of compound **21a** and **21c**. Reagents and conditions: (a) (3-hydroxyphenyl)boronic acid, Pd(OAc)$_2$, K$_2$CO$_3$, EGME/H$_2$O, rt, 15 h, 86—92%; (c) *n*-hexyl-NCO, DMAP, MeCN, rt, 15 h, 86%-quant.; (d) 6 M HCl, THF, rt, 2 d, 34%.

As expected from the rational design of our class of multitarget inhibitors, **15c** and **15d** showed a significant decrease in potency toward FAAH, whilst retaining COX-1 and COX-2 inhibitory activities compared to **10r**.

These results support the hypothesis that the mechanism of action of this class of compounds is similar to the one reported for the *O*-aryl carbamates (acylation of FAAH Ser 241) [57] and that COX inhibition does not rely on any irreversible binding mode at the expense of the carbamate group of **10r**. Reported dialysis experiments on **10r** are in agreement with this mechanistic speculation [51].

2.2.4.2. Role of the propionic acid functionality in the B phenyl ring. We then turned our attention to the role of the propionic acid in the B phenyl ring (Table 5).

Replacing the propionic acid group of **10r** with several substituents had only a minor impact on the potency toward FAAH, compared to the effect observed on COX activities. In fact, methyl ester **9r** retained FAAH inhibitory activity, compared to **10r**, but completely lost activity toward both COX-1 and COX-2. Replacement of the carboxylic acid of **10r** with the corresponding primary alcohol **12** resulted in a 10-fold improvement in potency toward FAAH (IC$_{50}$ = 3 nM), a 100-fold loss in potency
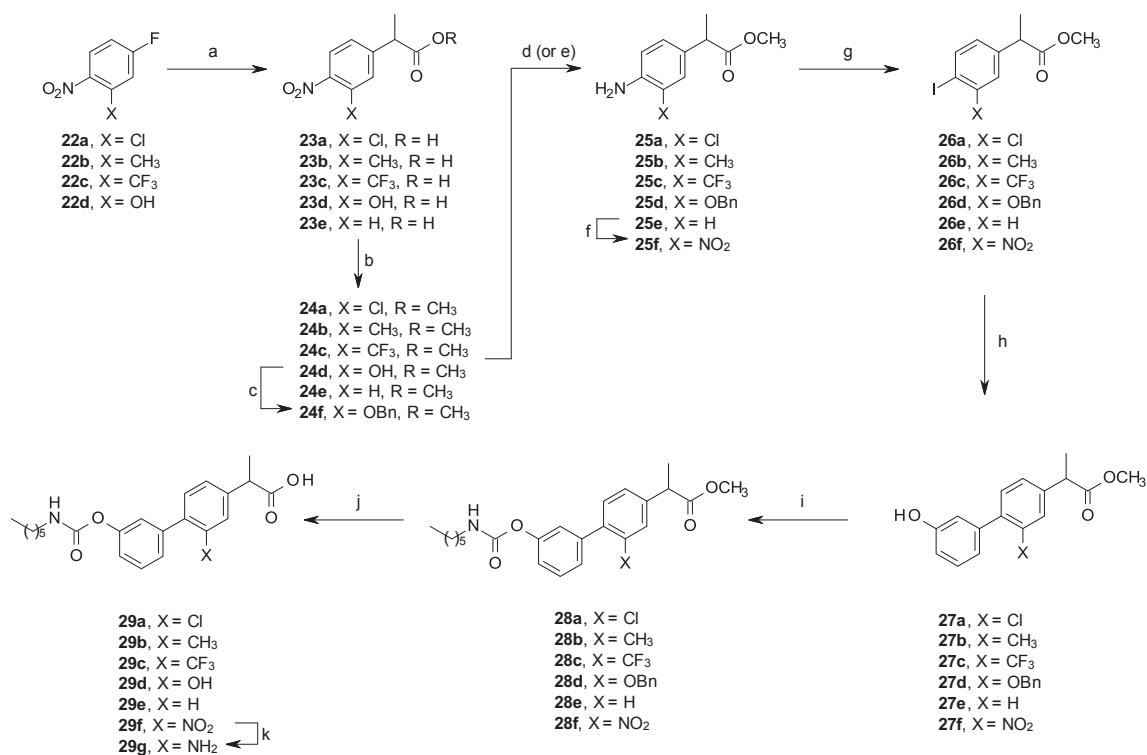
Scheme 6. Synthesis of compounds **29a-g**. Reagents and conditions: (a) diethyl methylmalonate, NaOH, DMF, rt, 15 h, then AcOH, H_2SO_4, H_2O 110 °C, 24 h, 48–87%; (b) MeOH, conc. H_2SO_4, rt, overnight, 81–98%; (c) BnBr, K_2CO_3, acetone, 60 °C, 15 h, 63%; (d) Fe, HCl, MeOH, 65 °C, 2 h, 64–94%, for **24a** and **24f**; (e) HCO_2NH_4, 10% Pd/C, MeOH, rt, 3 h, quant., for **24b-c**, and **24e**; (f) Ac_2O, HNO_3 0 °C, 2 h, then H_2SO_4, MeOH, 65 °C, 2 h, 98%; (g) $NaNO_2$, 3 M HCl, 0 °C, 30 min, then NaI, 60 °C, 2 h, 55–72%; (h) (3-hydroxyphenyl)boronic acid, Pd(OAc)₂, K_2CO_3, EGME/H_2O, rt, 15 h, 59–84%; (i) n-hexyl-NCO, DMAP, MeCN, rt, 15 h, 89%-quant.; (j) 2 M HCl, dioxane, 80 °C, 15 h, 73–95%; (k) cyclohexene, 10% Pd/C 80 °C, 2 h, then 2 M HCl, 55%.

Table 1
SAR exploration on the nature of R group: cycloalkanes, small-branched alkanes and phenyls.
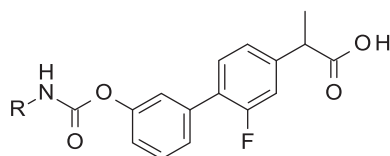
Compound	R	FAAH[a,b] $IC_{50}(\mu M)\pm SD$	COX-1[a,b] $IC_{50} (\mu M)\pm SD$	COX-2[a,b] $IC_{50} (\mu M)\pm SD$
2, URB597	−	0.0017 ± 0.001	>100	>100
3a, flurbiprofen	−	>100	0.15 ± 0.018	1.06 ± 0.53
10a	c-hexyl	8.2 ± 2.4	7.9 ± 2.1	>100
10b	c-pentyl	4.8 ± 3.2	4.4 ± 2.0	>100
10c	c-butyl	48.7 ± 9.0	0.72 ± 0.02	>100
10d	c-propyl	>100	5.4 ± 2.9	74.3 ± 6.1
10e	c-hexyl-CH_2	0.36 ± 0.06	0.60 ± 0.04	>100
10f	c-hexyl-$(CH_2)_2$	0.018 ± 0.007	0.15 ± 0.03	10.8 ± 2.2
10g	iso-propyl	>100	3.9 ± 2.1	>100
10h	iso-butyl	4.1 ± 2.1	8.2 ± 2.1	>100
10i	Ph	41.2 ± 3.4	0.27 ± 0.07	2.7 ± 0.3
10j	Ph-CH_2	4.18 ± 2.8	1.3 ± 0.6	>100
10k	Ph-$(CH_2)_2$	0.17 ± 0.07	6.3 ± 2.2	>100
10l	Ph-$(CH_2)_3$	0.09 ± 0.01	0.58 ± 0.09	6.2 ± 0.3
10m	Ph-$(CH_2)_4$	0.027 ± 0.010	3.7 ± 2.8	>100

[a] Values are reported as mean values of ≥3 experiments performed.
[b] IC_{50} values were not determined for compounds showing less than 50% inhibition at concentrations of 100 μM for FAAH and COXs.

toward COX-1 ($IC_{50} = 1.1$ μM) and in a complete loss of activity toward COX-2.

On the other hand, the removal of the α-methyl group, as in the achiral des-methylated derivative **18b**, caused a 2-fold decrease of the potency toward FAAH, compared to **10r** ($IC_{50} = 63$ nM and 31 nM, respectively), and a 180-fold reduction of potency toward

Table 2
SAR exploration on the nature of the R group: linear alkanes.
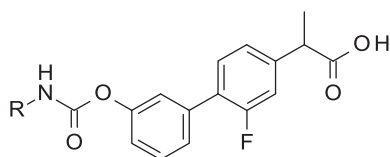
Compound	R	FAAH[a,b] IC$_{50}$(μM)$\pm$SD	COX-1[a,b] IC$_{50}$ (μM)$\pm$SD	COX-2[a,b] IC$_{50}$ (μM)$\pm$SD
10n	ethyl	>100	2.1 $\pm$ 0.9	>100
10o	*n*-propyl	>100	1.65 $\pm$ 0.06	>100
10p	*n*-butyl	7.0 $\pm$ 1.8	0.26 $\pm$ 0.07	>100
10q	*n*-pentyl	0.57 $\pm$ 0.15	0.020 $\pm$ 0.009	0.16 $\pm$ 0.02
10r, ARN2508	*n*-hexyl	0.031 $\pm$ 0.002	0.012 $\pm$ 0.002	0.43 $\pm$ 0.02
10s	*n*-heptyl	0.011 $\pm$ 0.003	0.37 $\pm$ 0.10	0.32 $\pm$ 0.005
10t	*n*-octyl	0.003 $\pm$ 0.002	0.99 $\pm$ 0.07	28.8 $\pm$ 8.4

[a] Values are reported as mean values of $\geq$3 experiments performed.
[b] IC$_{50}$ values were not determined for compounds showing less than 50% inhibition at concentrations of 100 μM for FAAH and COXs.

Table 3
Effect of the position of the carbamate functionality on the *A* phenyl ring.

Compound	Position	FAAH[a,b] IC$_{50}$ (μM) $\pm$SD	COX-1[a,b] IC$_{50}$ (μM) $\pm$SD	COX-2[a,b] IC$_{50}$ (μM) $\pm$SD
15a	C(2$'$)	2.2 $\pm$ 0.6	0.72 $\pm$ 0.04	>100
15b	C(4$'$)	0.068 $\pm$ 0.012	>100	>100

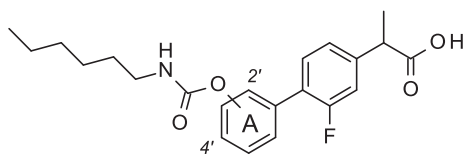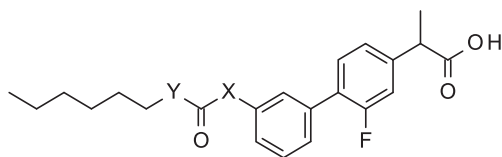[a] Values are reported as mean values of $\geq$3 experiments performed.
[b] IC$_{50}$ values were not determined for compounds showing less than 50% inhibition at concentrations of 100 μM for FAAH and COXs.

Table 4
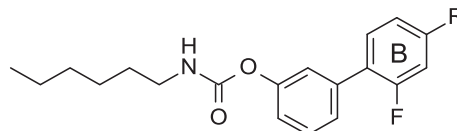Carbamate replacement: urea and reversed carbamate derivatives.

Compound	Y	X	FAAH[a] IC$_{50}$ (μM) $\pm$SD	COX-1[a] IC$_{50}$ (μM) $\pm$SD	COX-2[a] IC$_{50}$ (μM) $\pm$SD
15c	NH	NH	88.4 $\pm$ 2.3	0.014 $\pm$ 0.003	0.56 $\pm$ 0.12
15d	O	NH	14.9 $\pm$ 1.6	0.03 $\pm$ 0.01	0.17 $\pm$ 0.01

[a] Values are reported as mean values of $\geq$3 experiments performed.

Table 5
SAR exploration on the R group: role of the propionic acid functionality on the *B* phenyl ring.

Compound	R	FAAH[a,b] IC$_{50}$ (μM) $\pm$SD	COX-1[a,b] IC$_{50}$ (μM) $\pm$SD	COX-2[a,b] IC$_{50}$ (μM) $\pm$SD
9r	CH(CH$_3$)CO$_2$CH$_3$	0.052 $\pm$ 0.010	>100	>100
12	CH(CH$_3$)CH$_2$OH	0.003 $\pm$ 0.002	1.1 $\pm$ 0.3	>100
18b	CH$_2$CO$_2$H	0.063 $\pm$ 0.010	2.1 $\pm$ 0.1	0.24 $\pm$ 0.04
21a	CH$_3$	0.026 $\pm$ 0.09	>100	>100
21c	CO$_2$H	0.085 $\pm$ 0.006	>100	>100

[a] Values are reported as mean values of $\geq$3 experiments performed.
[b] IC$_{50}$ values were not determined for compounds showing less than 50% inhibition at concentrations of 100 μM for FAAH and COXs.

Table 6
SAR exploration on the role of the X substituent on the *B* phenyl ring.
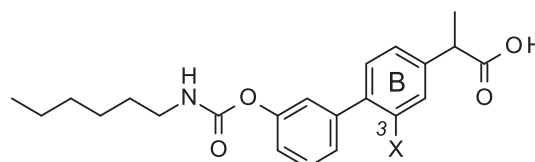
Compound	X	FAAH[a] IC$_{50}$(μM)$\pm$SD	COX-1[a] IC$_{50}$(μM)$\pm$SD	COX-2[a] IC$_{50}$(μM)$\pm$SD
29a	Cl	0.023 $\pm$ 0.008	0.009 $\pm$ 0.001	0.73 $\pm$ 0.21
29b	CH$_3$	0.010 $\pm$ 0.001	0.011 $\pm$ 0.001	1.40 $\pm$ 0.31
29c	CF$_3$	0.005 $\pm$ 0.001	0.01 $\pm$ 0.003	0.2 $\pm$ 0.08
29d	OH	0.035 $\pm$ 0.010	0.65 $\pm$ 0.07	13.0 $\pm$ 2.1
29e	H	0.003 $\pm$ 0.001	0.054 $\pm$ 0.011	0.69 $\pm$ 0.02
29f	NO$_2$	0.009 $\pm$ 0.002	0.13 $\pm$ 0.03	0.930 $\pm$ 0.15
29g	NH$_2$	0.049 $\pm$ 0.023	0.22 $\pm$ 0.09	12.1 $\pm$ 0.6

[a] Values are reported as mean values of $\geq$3 experiments performed.

We conclude that FAAH tolerates substituents with different steric and electronic properties at the *4*-position of the B phenyl ring, while COX-1 and COX-2 display a stringent requirement for a propionic or acetic acid groups in the same position.

2.2.4.3. Role of the fluorine atom in the B phenyl ring. To complete the SAR exploration of the B phenyl ring, we evaluated the effect of substituents with different electronic and steric properties, alternative to the fluorine atom (Table 6).

Substituting the fluorine with chlorine was tolerated: indeed, **29a** was virtually equipotent against FAAH and COX-1, and marginally less potent on COX-2, compared to **10r**. The same trend was observed with the methyl derivative **29b**, which was slightly more potent than **10r** against FAAH and equally potent on COX-1, but less active against COX-2. The CF$_3$ derivative **29c** showed a 6-fold and 2-fold increase in potency toward FAAH and COX-2, respectively, and was as potent as **10r** on COX-1.

Removal of the fluorine atom (**29e**) resulted in a 10-fold increase in potency toward FAAH, compared to **10r**, and a slight decrease in activity for COX-1 and COX-2.

Compounds **29d** and **29g**, which bear –OH or –NH$_2$ groups, respectively, inhibited FAAH with potencies similar to that of **10r**, whereas a clear loss in potency for both COX-1 and COX-2 was observed. On the other hand, the NO$_2$ derivative **29f** had higher

COX-1 (IC$_{50}$ = 2.1 μM and 12 nM, respectively). The activity against COX-2 was slightly improved (IC$_{50}$ = 0.24 μM and 0.43 μM respectively). The methyl analog **21a** [51] was active against FAAH in the same potency range of **10r** (IC$_{50}$ = 26 nM and 31 nM, respectively), while a completely loss of activity against COX enzymes was observed. A similar result was obtained with the carboxylic analog **21c**, which also showed a 3-fold reduction in potency toward FAAH, compared to **10r** (IC$_{50}$ = 85 nM and 31 nM, respectively).

potency toward FAAH but loss lower potency toward both COX-1 and COX-2. We interpret these results to suggest that the electronic and steric properties of the substituents in the 3-position of the B phenyl ring affect FAAH recognition only slightly, whereas these same substituents influence COX-1 and COX-2 more markedly, with lipophilic groups being better tolerated than polar or H-bond donator groups.

*2.2.4.4. Stereochemical and pharmacological studies of **10r** enantiomers.* Finally, we subjected the best studied member of this class of inhibitors, the racemic compound **10r** [51], to chiral HPLC separation and tested each of its enantiomers – (−)-**10r** (first eluted) and (+)-**10r** (second eluted) – for the ability to inhibit FAAH, COX-1 and COX-2 (Table 7). FAAH showed no preference for either enantiomer, with each being more active than the racemate **10r**. By contrast, in analogy to prior studies on different classes of FAAH/COX inhibitors [30,33], substantial differences were observed on COX-1 and COX-2. Compound (+)-**10r** was highly potent on both COX-1 (IC_{50} = 0.29 nM) and COX-2 (IC_{50} = 50 nM), whereas (−)-**10r** was weakly active on either target.

We completed our exploration on the two enantiomers of **10r** by assigning their absolute stereo-configurations. As reported in Supporting Information (Scheme S1), a stereochemical correlation study allowed us unambiguously to assign the absolute stereochemistry of (−)-**10r** and (+)-**10r** to the (R)- and (S)- configurations, respectively. These results are in agreement with earlier reports showing that the (S)-enantiomer is responsible for the COX-inhibiting activity of aryl-propionic acid derivatives such as flurbiprofen [29,31,33,59].

*2.2.4.5. In vivo experiments on (S)-(+)-**10r**.* Finally, pharmacological experiments indicate that compound (S)-(+)-**10r** strongly engages its intended molecular targets in live mice. Intravenous administration of (S)-(+)-**10r** (1 mg/kg) lowered the concentrations of two COX products in circulation, prostacyclin and TXA_2, as assessed surveying the stable metabolites, 6-keto-$PGF_{1\alpha}$ and TXB_2 (Fig. 2A and B). Moreover, (S)-(+)-**10r** increased plasma levels of the FAAH substrate, OEA (Fig. 2C). In addition, (S)-(+)-**10r** demonstrated no off−target activities on a panel of >90 biologically relevant receptors, enzymes [including *N*-acylethanolamine amide hydrolase (NAAA), which is the primary enzyme involved in the deactivation of PEA and OEA in innate immune cells] and ion channels (Table S1). Further pharmacological studies on the (R)- and (S)- series of this class of inhibitors will be reported in due course.

3. Conclusions

The present study outlines key SAR properties of a novel class of dual inhibitors of intracellular FAAH and COX activities, which are based on the hybrid scaffold **1**. Several chemical variations of this scaffold were considered, which involved the carbamate moiety at the 3′-position of the *A* phenyl ring, the R groups, and the propionic

Table 7
Evaluation of the enantiomers of **10r**.

Compound	FAAH[a] IC_{50}(μM) ±SD	COX-1[a] IC_{50} (μM) ±SD	COX-2[a] IC_{50} (μM) ±SD
(±)-**10r**	0.031 ± 0.002	0.012 ± 0.002	0.43 ± 0.02
(−)-**10r**[b]	0.0099 ± 0.002	4.0 ± 1.3	22.8 ± 8.7
(+)-**10r**[c]	0.0094 ± 0.0003	0.00029 ± 0.00004	0.050 ± 0.012

[a] Values are reported as mean values of ≥3 experiments performed.
[b] (R)-configured enantiomer of **10r** (see Supporting Information for details).
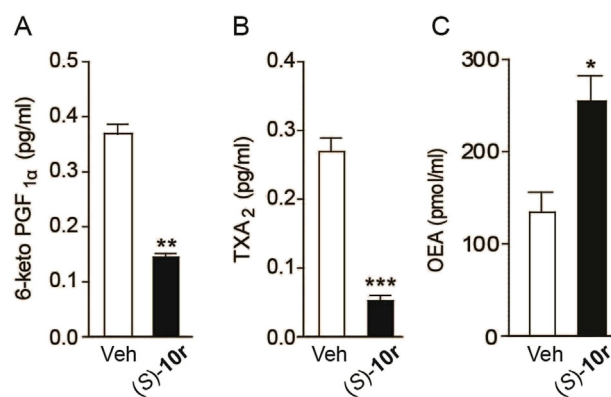[c] (S)-configured enantiomer of **10r** (see Supporting Information for details).

Fig. 2. Plasma levels of COX metabolites and FAAH substrate after intravenous administration of (S)-(+)-**10r** (1 mg/kg): 6-keto-$PGF_{1\alpha}$ (A) TXA_2 (B) and OEA (C). Results are expressed as mean ± s.e.m. of 6 independent determinations. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ compared to vehicle mice, two-tailed Student's t test.

acid moiety and fluorine atom in the *B* phenyl ring. Introduction of different alkyl and aromatic groups in the N-terminal region of the carbamate functionality improved inhibitory potency toward both FAAH and COX. A more focused exploration around the potent, selective and orally available racemic inhibitor **10r** [51] led to the identification of novel potent analogs, **29a-c**, and **e**. Because of the problems associated with the development of racemic compounds, we extended our studies and identified two additional molecules, the achiral compound **18b** and the enantiomer (S)-(+)-**10r**, which also display high inhibitory potency for FAAH/COX-1/COX-2.

The *in vivo* activity of (S)-(+)-**10r** suggests that this agent may be used to probe the therapeutic utility of simultaneous FAAH-COX inhibition, especially in pathologies in which these enzymes are abnormally expressed.

4. Experimental part

4.1. Synthesis

Solvents and reagents were obtained from commercial suppliers and were used without further purification. URB597 was prepared following a reported procedure [54]. Flurbiprofen was purchased from Sigma−Aldrich (Milan, Italy). Melting points were determined on a Büchi M−560 capillary melting point apparatus and are uncorrected. Automated column chromatography purifications were done using a Teledyne ISCO apparatus (CombiFlash® Rf) with pre-packed silica gel columns of different sizes (from 4 g until 120 g). Mixtures of increasing polarity of Cy and EtOAc or DCM and MeOH were used as eluents. Preparative TLC analyses were performed using Macherey−Nagel pre-coated 0.05 mm TLC plates (SIL G-50 UV_{254}). ^1H and ^{13}C NMR experiments were run on a Bruker Avance III 400 system (400.13 MHz for ^1H, and 100.62 MHz for ^{13}C), equipped with a BBI probe and Z-gradient coil. ^{19}F NMR experiments were run on a Bruker Avance III 600 system (546.6 MHz for ^{19}F), equipped with a 5 mm CryoProbe QCI $^1H/^{19}F−^{13}C/^{15}N−D$ quadruple resonance and a Z-gradient coil. Spectra were acquired at 300 K, using deuterated dimethylsulfoxide (DMSO-d_6) or deuterated chloroform (CDCl3) as solvents. Chemical shifts for ^1H and ^{13}C spectra were recorded in parts per million using the residual non-deuterated solvent as the internal standard (for DMSO-d_6: 2.50 ppm, ^1H; 39.52 ppm, ^{13}C; for CDCl3: 7.26 ppm, ^1H and 77.16 ppm, ^{13}C). Data are reported as follows: chemical shift (ppm), multiplicity (indicated as: bs, broad signal; s, singlet; d, doublet; t, triplet; q, quartet; p, quintet; sx, sextet; m, multiplet and combinations thereof), coupling constants (*J*) in Hertz (Hz) and integrated

intensity. UPLC/MS analyses were run on a Waters ACQUITY UPLC/MS system consisting of a SQD (Single Quadropole Detector) Mass Spectrometer equipped with an Electrospray Ionization interface and a Photodiode Array Detector. PDA range was 210−400 nm. Analyses were performed on an ACQUITY UPLC BEH C18 column (50 × 2.1 mmID, particle size 1.7 μm) with a VanGuard BEH C18 pre-column (5 × 2.1 mmID, particle size 1.7 μm). Mobile phase was either 10 mM NH$_4$OAc in H$_2$O at pH 5 adjusted with AcOH (A) and 10 mM NH$_4$OAc in MeCN−H$_2$O (95:5) at pH 5 (B). Electrospray ionization in positive and negative mode was applied. Analyses were performed with method A or B. *Method A* for compounds **10a-t**, **15a-d**, **18b**, **21c** and **29b-g**: Gradient: 5−95% B over 3 min. Flow rate 0.5 mL/min. Temperature 40 °C. *Method B* for compounds **9r**, **12**, **21a** and **29a**: Gradient: 50−100% B over 3 min. Flow rate 0.5 mL/min. Temperature 40 °C. Purifications by preparative HPLC/MS were run on a Waters Autopurification system consisting of a 3100 Single Quadropole Mass Spectrometer equipped with an Electrospray Ionization interface and a 2998 Photodiode Array Detector. HPLC system included a 2747 Sample Manager, 2545 Binary Gradient Module, System Fluidic Organizer and 515 HPLC Pump. PDA range was 210−400 nm. Purifications were performed on a XBridge™ Prep C18 OBD column (100 × 19 mmID, particle size 5 μm) with a XBridge™ Prep C18 (10 × 19 mmID, particle size 5 μm) Guard Cartridge. Mobile phase was 10 mM NH$_4$OAc in H$_2$O at pH 5 adjusted with AcOH (A) and 10 mM NH$_4$OAc in MeCN−H$_2$O (95:5) at pH 5 (B). Electrospray ionization in positive and negative mode was used. Analyses by chiral HPLC were run on a Waters Alliance HPLC instrument consisting of an e2695 Separation Module and a 2998 Photodiode Array Detector. PDA range was 210−400 nm. Analyses were performed isocratic on a Daicel ChiralPak AD column (250 × 4.6 mmID, particle size 10 μm). Mobile phase was 0.1% TFA Heptane/2-Propanol (75:25). Separations of **10r** by preparative chiral HPLC were run on a Waters Alliance HPLC instrument consisting of a 1525 Binary HPLC Pump, Waters Fraction Collector III and a 2998 Photodiode Array Detector. UV detection was at 240 nm. Purifications were performed isocratic on a Daicel ChiralPak AD column (250 × 10mmID, particle size 10 μm). Mobile phase was 0.1% TFA Heptane/2-Propanol (75: 25). Optical rotations were measured on a Rudolf Research Analytical Autopol II Automatic polarimeter using a sodium lamp (589 nm) as the light source; concentrations expressed in g/100 mL using CHCl$_3$ as a solvent and a 1 dm cell. Accurate mass measurement was performed on a Synapt G2 Quadrupole-ToF Instrument (Waters, USA), equipped with an ESI ion source; compounds were diluted to 50 μM in H$_2$O/MeCN and analyzed. Leucine Enkephalin (2 ng/mL) was used as lock mass reference compound for spectra calibration. All final compounds displayed ≥95% purity as determined by NMR and UPLC/MS analysis.

All the analytical data of intermediate compounds are reported in Supporting Material.

4.1.1. (±)-2-(3-fluoro-4-nitro-phenyl)propanoic acid (4)

Compound **4** was obtained as brown clear oil (4.50 g, 81%), according to the procedure reported in the literature starting from 2,4-difluoronitrobenzene (4.77 g, 30 mmol) [62].

4.1.2. (±)-Methyl 2-(4-nitro-3-fluoro-phenyl)propanoate (5)

To a solution of **4** (4.50 g, 21.11 mmol) in MeOH (40 mL), concentrated H$_2$SO$_4$ (0.1 mL) was added and the resulting solution was stirred at rt overnight. After solvent evaporation, the crude oil was diluted with Et$_2$O (15 mL) and filtered through a pad of SiO$_2$ to afford **5** as orange-brown oil (4.45 g, 93%).

4.1.3. (±)-Methyl 2-(4-amino-3-fluoro-phenyl)propanoate (6)

To a solution of **5** (12.60 g, 55.46 mmol) in MeOH (222 mL) was added 10% Pd/C (2.35 g, 2.22 mmol) followed by addition of HCO$_2$NH$_4$ (20.98 g, 332.8 mmol). The solution was stirred at rt for 3 h, then, filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc and filtered through a pad of SiO$_2$ to afford **6** as an orange oil (10.33 g, 94%).

4.1.4. (±)-Methyl 2-(3-fluoro-4-iodo-phenyl)propanoate (7)

A solution of NaNO$_2$ (0.70 g, 10.21 mmol) in H$_2$O (1.5 mL) was added slowly to a solution of **6** (1.75 g, 9.76 mmol) in a 3N HCl solution (29 mL) at 0 °C. After 30 min, NaI (1.54 g, 10.25 mmol) was added at 0 °C under stirring. The resulting mixture was slowly warmed to rt in 5 min, and then heated at 60 °C for 3 h. After cooling down to rt, the mixture was extracted with Et$_2$O and the organic phase was then washed with a 1 M solution of Na$_2$SO$_3$ (15 mL) and dried over Na$_2$SO$_4$. The residue was dissolved in EtOAc (50 mL), treated with activated carbon and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the yellow oil was purified by column chromatography (Cy: EtOAc, 95:5) to give **7** as a pale yellow oil (1.70 g, 55%).

4.1.5. General procedure for Suzuki cross coupling reaction (procedure A, 8, 13a-c, 17, 20a, b, 27a-f)

To a solution of the corresponding boronic acid (1.2 mmol) in EGME/H$_2$O (3:1, 0.25 M) were added Pd(OAc)$_2$ (0.05 mmol) and K$_2$CO$_3$ (1.2 mmol), followed by the addition of the corresponding phenyl iodide (1.0 mmol). The dark reaction mixture was stirred at rt for 15 h, then diluted with EtOAc (40 mL) and filtered through a pad of Celite. The resulting filtrate was washed with H$_2$O (20 mL) and a 1 M solution of Na$_2$SO$_3$ (20 mL). After separation, the organic phase was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residues were purified by column chromatography (Cy/EtOAc).

4.1.5.1. (±)-Methyl 2-[3-fluoro-4-(3-hydroxyphenyl)phenyl]propanoate (8).
Compound **8** was prepared according to general procedure A using **7** (3.27 g, 10.61 mmol) and 3-hydroxyphenylboronic acid (1.76 g, 12.74 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **8** as a colorless oil (2.46 g, 84%).

4.1.5.2. (±)-Methyl 2-[3-fluoro-4-(2-hydroxyphenyl)phenyl]propanoate (13a).
Compound **13a** was prepared according to general method A using **7** (0.31 g, 1 mmol) and 2-hydroxyphenylboronic acid (0.17 g, 1.2 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **13a** as a white oil (230 mg, 84%).

4.1.5.3. (±)-Methyl 2-[3-fluoro-4-(4-hydroxyphenyl)phenyl]propanoate (13b).
Compound **13b** was prepared according to general procedure A using **7** (0.31 g, 1 mmol) and 4-hydroxyphenylboronic acid (0.17 g, 1.2 mmol). The crude was purified by column chromatography (Cy/EtOAc, 95: 5) to afford **13b** as a white solid (173 mg, 59%).

4.1.5.4. (±)-Methyl 2-[4-(3-aminophenyl)-3-fluoro-phenyl]propanoate (13c).
Compound **13c** was prepared according to general procedure A using **7** (0.92 g, 3 mmol) and (3-aminophenyl)boronic acid monohydrate (0.56 g, 3.6 mmol). The crude was purified by column chromatography (Cy/EtOAc, 8: 2) to afford **13c** as a yellow oil (750 mg, 91%).

4.1.5.5. Methyl 2-[3-fluoro-4-(3-hydroxyphenyl)phenyl]acetate (17).
Compound **17** was prepared according to general procedure A using **16b** (1.00 g, 3.50 mmol) and 3-hydroxyphenylboronic acid (0.58 g,

4.20 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **19a** as white solid (0.65 g, 71%).

*4.1.5.6. 3-(2-Fluoro-4-methyl-phenyl)phenol (**20a**).* Compound **20a** was prepared according to general procedure A using aryl iodide **19a** (236 g, 1 mmol) and 3-hydroxyphenylboronic acid (0.17 g, 1.2 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **20a** as a colorless oil (187 mg, 92%).

*4.1.5.7. Methyl 3-fluoro-4-(3-hydroxyphenyl)benzoate (**20b**).* Compound **20b** was prepared according to general procedure A using aryl iodide **19b** (1 g, 3.57 mmol) and 3-hydroxyphenylboronic acid (0.59 g, 4.29 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **20b** as a white solid (0.84 g, 86%).

*4.1.5.8. (±)-Methyl 2-[3-chloro-4-(3-hydroxyphenyl)phenyl]propanoate (**27a**).* Compound **27a** was prepared according to general procedure A using **26a** (2.74 g, 8.44 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to give **27a** as a white solid (1.57 g, 64%).

*4.1.5.9. (±)-Methyl 2-[4-(3-hydroxyphenyl)-3-methyl-phenyl]propanoate (**27b**).* Compound **27b** was prepared according to general procedure A using **26b** (1.14 g, 3.75 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to give **27b** as a colorless oil (0.72 g, 71%).

*4.1.5.10. (±)-Methyl 2-[4-(3-hydroxyphenyl)-3-(trifluoromethyl) phenyl]propanoate (**27c**).* Compound **27c** was prepared according to general procedure A using **26c** (1.07 g, 3 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to give **27c** as a white solid (0.78 g, 80%).

*4.1.5.11. (±)-Methyl 2-[3-benzyloxy-4-(3-hydroxyphenyl)phenyl] propanoate (**27d**).* Compound **27d** was prepared according to general procedure A using **26d** (1.00 g, 2.52 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to give **27d** as a clear oil (0.58 g, 63%).

*4.1.5.12. (±)-Methyl 2-[4-(3-hydroxyphenyl)phenyl]propanoate (**27e**).* Compound **27e** was prepared according to general procedure A using **26e** (1.45 g, 5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 8: 2) to afford **27e** as a white oil (760 mg, 59%).

*4.1.5.13. (±)-Methyl 2-[4-(3-hydroxyphenyl)-3-nitro-phenyl]propanoate (**27f**).* Compound **27f** was prepared according to general procedure A using **26f** (1.76 g, 5.25 mmol). The crude was purified by column chromatography (Cy/EtOAc, 8: 2) to give **27f** as a yellow solid (1.1 g, 74%).

*4.1.6. General procedure for carbamoylation reaction (procedure B, **9a-t**, **12**, **14a-c**, **18a**, **28a-f**)*
To a solution of the corresponding phenol or aniline (1 mmol) in MeCN (0.5 M) was added DMAP (0.1 mmol) and the corresponding isocyanate (3.0 mmol). The resulting solution was stirred at rt for 15 h, then the solvent was concentrated under reduced pressure. The residues were purified by column chromatography (Cy/EtOAc or DCM/MeOH).

*4.1.6.1. (±)-Methyl 2-[4-[3-(cyclohexylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoate (**9a**).* Compound **9a** was prepared according to general procedure B using **8** (274 mg, 1 mmol) and *c*-hexyl isocyanate (376 mg, 3 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9a** as a white solid (261 mg, 65%).

*4.1.6.2. (±)-Methyl 2-[4-[3-(cyclopentylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoate (**9b**).* Compound **9b** was prepared according to general procedure B using **8** (274 mg, 1 mmol) and *c*-pentyl isocianate (333 mg, 3 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9b** as a white solid (235 mg, 61%).

*4.1.6.3. (±)-Methyl 2-[4-[3-(cyclobutylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoate (**9c**).* Compound **9c** was prepared according to general procedure B using **8** (274 mg, 1 mmol) and *c*-butyl isocyanate (291 mg, 3 mmol). The crude colorless oil of **9c** was used in the next step without further purification.

*4.1.6.4. (±)-Methyl 2-[4-[3-(cyclopropylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoate (**9d**).* Compound **9d** prepared according to general procedure B using **8** (274 mg, 1 mmol) and *c*-propyl isocyanate (250 mg, 3 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9d** as a white solid (59 mg, 38%).

*4.1.6.5. (±)-Methyl 2-[4-[3-(cyclohexylmethylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoate (**9e**).* Compound **9e** was prepared according to general procedure B using **8** (137 mg, 0.50 mmol) and *c*-hexyl methyl isocyanate (209 mg, 1.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9e** as a white solid (165 mg, 80%).

*4.1.6.6. (±)-Methyl 2-[4-[3-(2-cyclohexylethylcarbamoyloxy) phenyl]-3-fluoro-phenyl]propanoate (**9f**).* Compound **9f** was prepared according to general procedure B using **8** (137 mg, 0.50 mmol) and *c*-hexyl ethyl isocyanate (230 mg, 1.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9f** as a white solid (179 mg, 84%).

*4.1.6.7. (±)-Methyl 2-[3-fluoro-4-[3-(isopropylcarbamoyloxy)phenyl] phenyl]propanoate (**9g**).* Compound **9g** was prepared according to general procedure B using **8** (157 mg, 0.57 mmol) and isopropyl isocyanate (145 mg, 1.71 mmol). The crude was purified by column chromatography (Cy/EtOAc, 8: 2) to afford **9g** as a white solid (159 mg, 77%).

*4.1.6.8. (±)-Methyl 2-[3-fluoro-4-[3-(isobutylcarbamoyloxy)phenyl] phenyl]propanoate (**9h**).* Compound **9h** was prepared according to general procedure B using **8** (129 mg, 0.47 mmol) and isobutyl isocyanate (140 mg, 1.41 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9h** as a white solid (138 mg, 78%).

*4.1.6.9. (±)-Methyl 2-[3-fluoro-4-[3-(phenylcarbamoyloxy)phenyl] phenyl]propanoate (**9i**).* Compound **9i** was prepared according to general procedure B using **8** (137 mg, 0.5 mmol) and phenyl isocyanate (179 mg, 3 mmol) to afford **9i** as a colorless oil (161 mg, 82%).

*4.1.6.10. (±)-Methyl 2-[4-[3-(benzylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoate (**9j**).* Compound **9j** was prepared according to general procedure B using **8** (137 mg, 0.5 mmol) and benzylisocyanate (199 mg, 1.5 mmol) to afford **9j** as a colorless oil which was used in the next step without further purification.

*4.1.6.11. (±)-Methyl 2-[3-fluoro-4-[3-(phenethylcarbamoyloxy) phenyl]phenyl]propanoate (**9k**).* Compound **9k** was prepared

according to general procedure B using **8** (137 mg, 0.5 mmol) and phenylethyl isocyanate (221 mg, 1.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9k** as a white solid (165 mg, 71%).

4.1.6.12. (±)-Methyl 2-[3-fluoro-4-[3-(3-phenylpropylcarbamoyloxy) phenyl]phenyl]propanoate (9l). Compound **9l** was prepared according to general procedure B using **8** (137 mg, 0.5 mmol) and phenylpropyl isocyanate (241 mg, 1.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9l** as a white solid (174 mg, 79%).

4.1.6.13. (±)-Methyl 2-[3-fluoro-4-[3-(4-phenylbutylcarbamoyloxy) phenyl]phenyl]propanoate (9m). Compound **9m** was prepared according to general procedure B using **8** (121 mg, 0.44 mmol) and phenylbutyl isocyanate (231 mg, 1.32 mmol). The crude was purified by column chromatography (Cy/EtOAc, 8: 2) to afford **9m** as a white solid (171 mg, 86%).

4.1.6.14. (±)-Methyl 2-[4-[3-(ethylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoate (9n). Compound **9n** was prepared according to general procedure B using **8** (185 mg, 0.68 mmol) and ethyl isocyanate (145 mg, 2.04 mmol). The crude was purified by column chromatography (Cy/EtOAc, 8: 2) to afford **9n** as a white solid (176 mg, 75%).

4.1.6.15. (±)-Methyl 2-[3-fluoro-4-[3-(propylcarbamoyloxy)phenyl] phenyl]propanoate (9o). Compound **9o** was prepared according to general procedure B using **8** (137 mg, 0.50 mmol) and *n*-propyl isocyanate (128 mg, 1.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9o** as a white solid (87 mg, 48%).

4.1.6.16. (±)-Methyl 2-[4-[3-(butylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoate (9p). Compound **9p** was prepared according to general procedure B using **8** (137 mg, 0.50 mmol) and *n*-butyl isocyanate (149 mg, 1.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9p** as a white solid (135 mg, 72%).

4.1.6.17. (±)-Methyl 2-[3-fluoro-4-[3-(pentylcarbamoyloxy)phenyl] phenyl]propanoate (9q). Compound **9q** was prepared according to general procedure B using **8** (128 mg, 0.47 mmol) and *n*-pentyl isocyanate (159 mg, 1.41 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1), the title compound to afford **9q** as a white solid (158 mg, 87%).

4.1.6.18. (±)-Methyl 2-[3-fluoro-4-[3-(hexylcarbamoyloxy)phenyl] phenyl]propanoate (9r). Compound **9r** was prepared according to general procedure B using **8** (137 mg, 0.5 mmol) and *n* hexyl isocyanate (191 mg, 1.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9r** as a white solid (170 mg, 85%). Mp: 89–91 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (t, J = 5.6 Hz, 1H, NH), 7.50 (t, J = 8.2 Hz, 1H, H-5), 7.47 (t, J = 7.9 Hz, 1H, h-11), 7.37 (d, J = 7.2 Hz, 1H, H-10), 7.24 (m, 3H, H-2 H-6 H-8), 7.13 (dd, J = 8.0, 1.4 Hz, 1H, H-12), 3.91 (q, J = 7.1 Hz, 1H, CH), 3.62 (s, 3H, OCH$_3$), 3.06 (q, J = 6.7 Hz, 2H, R-H-1′), 1.48 (p, J = 6.22 Hz, 2H, R-H-2′), 1.43 (d, J = 7.2 Hz, 3H, CH$_3$), 1.28 (m, 6H, R-H-3′ R-H-4′R-H-5′), 0.87 (t, J = 6.9 Hz, 3H, R-H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.74 (COOH), 158.82 (d, J = 246.7 Hz, C-3), 154.17 (C-9), 151.21 (HNCOO), 142.75 (d, J = 7.8 Hz, C-7), 135.82 (C-1), 130.76 (d, J = 3.5 Hz, C-5), 129.42 (C-11), 125.98 (d, J = 13.0 Hz, C-4), 125.20 (C-10), 124.02 (C-6), 121.86 (C-8), 121.20 (C-12), 115.20 (d, J = 23.4 Hz, C-2), 51.95 (OCH$_3$), 43.77 (CH), 40.45 (R-C-1′), 30.91 (R-C-4′), 29.12 (R-C-2′), 25.88 (R-C-3′), 22.02 (R-C-5′), 18.28 (CH$_3$), 13.87 (R-C-6′).

^{19}F NMR (564 MHz, DMSO-d_6): δ 117.0. UPLC/MS analysis: Rt 2.00 min. MS (ES) C$_{23}$H$_{28}$FNO$_4$ requires: 401, found 402 [M+H]$^+$. HRMS C$_{23}$H$_{29}$NO$_4$F [M+H]$^+$: calculated 402.2081 measured 402.2087 Δppm 1.5.

4.1.6.19. (±)-Methyl 2-[3-fluoro-4-[3-(heptylcarbamoyloxy)phenyl] phenyl]propanoate (9s). Compound **9s** was prepared according to general procedure B using **8** (137 mg, 0.50 mmol) and *n*-heptyl isocyanate (212 mg, 1.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9s** as a white solid (171 mg, 82%).

4.1.6.20. (±)-Methyl 2-[3-fluoro-4-[3-(octylcarbamoyloxy)phenyl] phenyl]propanoate (9t). Compound **9t** was prepared according to general procedure B using **8** (109 mg, 0.40 mmol) and *n*-octyl isocyanate (186 mg, 1.2 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **9t** as a white solid (171 mg, 99%).

4.1.6.21. (±)-[3-[2-fluoro-4-(2-hydroxy-1-methyl-ethyl)phenyl] phenyl] N-hexylcarbamate (12). Compound **12** was prepared according to general procedure B using **11** (123 mg, 0.50 mmol) and *n*-hexyl isocyanate (127 mg, 1 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **12** as a colorless oil (137 mg, 73%). Mp: 59–60 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (t, J = 5.7 Hz, 1H, NH), 7.46 (t, J = 7.7 Hz, 1H, H-5), 7.44 (t, J = 8.5 Hz, 1H, H-11), 7.36 (m, 1H, H-10), 7.23 (m, 1H, H-8), 7.17 (m, 2H, H-2 H-6), 7.12 (ddd, J = 8.1, 2.3, 1.1 Hz, 1H, H-12), 4.69 (t, J = 5.2 Hz, 1H, OH), 3.51 (m, 2H, CH$_2$), 3.06 (q, J = 6.8 Hz, 2H, R-H-1′), 2.87 (h, J = 6.8 Hz, 1H, CH), 1.46 (h, J = 7.1 Hz, 2H, R-H-2′), 1.29 (m, 6H, R-H-3′R-H-4′R-H-5′), 1.21 (d, J = 7.0 Hz, 3H, CH$_3$), 0.87 (t, J = 6.7 Hz, 3H, R-H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.8 (d, J = 246.0 Hz, C-3), 154.1 (C-9), 151.1 (HNCOO), 147.7 (d, J = 7.3 Hz, C-7), 136.2 (C-1), 130.1 (d, J = 2.4 Hz, C-5), 129.3 (C-11), 125.1 (C-10), 124.8 (d, J = 12.7 Hz, C-4), 124.0 (C-6), 121.7 (C-8), 120.9 (C-12), 114.9 (d, J = 22.4 Hz, C-2), 66.5 (CH$_2$), 41.4 (CH), 40.4 (R-C-1′), 30.9 (R-C-4′), 29.1 (R-C-2′), 25.8 (R-C-3′), 22.0 (R-C-5′), 17.7 (CH$_3$), 13.8 (R-C-6′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 118.0. UPLC/MS analysis: Rt 2.60 min. MS (ES) C$_{22}$H$_{28}$FNO$_3$ requires 373, found 374 [M+H]$^+$. HRMS C$_{22}$H$_{29}$NO$_3$F [M+H]$^+$: calculated 374.2131 measured 374.2149 Δppm 4.8.

4.1.6.22. (±)-Methyl 2-[3-fluoro-4-[2-(hexylcarbamoyloxy)phenyl] phenyl]propanoate (14a). Compound **14a** was prepared according to general procedure B using **13a** (137 mg, 0.5 mmol) and *n*-hexyl isocyanate (191 mg, 1.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **14a** as a white oil (178 mg, 88%).

4.1.6.23. (±)-Methyl 2-[3-fluoro-4-[4-(hexylcarbamoyloxy)phenyl] phenyl]propanoate (14b). Compound **14b** was prepared according to general procedure B using **13b** (137 mg, 0.5 mmol) and *n*-hexyl isocyanate (191 mg, 1.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **14b** as a white solid (146 mg, 72%).

4.1.6.24. (±)-Methyl 2-[3-fluoro-4-[3-(hexylcarbamoylamino) phenyl]phenyl]propanoate (14c). Compound **14c** was prepared according to general procedure B using **13c** (153 mg, 0.56 mmol) and *n*-hexyl isocyanate (214 mg, 1.7 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **14c** as a white solid (146 mg, 65%).

4.1.6.25. Methyl 2-[3-fluoro-4-[3-(hexylcarbamoyloxy)phenyl] phenyl]acetate (18a). Compound **18a** was prepared according to

general procedure B using **17** (130 mg, 0.50 mmol) and *n*-hexyl isocyanate (191 mg, 1.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **18a** as a white solid (123 mg, 64%).

4.1.6.26. [3-(2-fluoro-4-methyl-phenyl)phenyl]   N-hexylcarbamate (21a). Compound **21a** was prepared according to general procedure B using **20a** (101 mg, 0.50 mmol) and *n*-hexyl isocyanate (191 mg, 1.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **20a** as a white solid (142 mg, 86%). Mp: 56–57 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (t, $J = 5.7$ Hz, 1H, NH), 7.45 (t, $J = 7.9$ Hz, 1H, H-5), 7.41 (t, $J = 8.0$, 1H, H-11), 7.35 (d, J = 6.8 Hz, 1H, H-10), 7.22 (m, 1H, H-8), 7.12 (m, 3H, H-2 H-6 H-11), 3.06 (q, $J = 6.8$ Hz, 2H, R-H-1′), 2.36 (s, 3H, CH$_3$), 1.47 (p, $J = 6.9$ Hz, 2H, R-H-2′), 1.28 (m, 6H, H-3′ H-4″ H-5′), 0.87 (t, $J = 6.8$ Hz, 3H, H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.8 (d, $J = 247.0$ Hz, C-3), 154.2 (C-9), 151.1 (HNCOO), 140.0 (d, $J = 8.3$ Hz, C-7), 136.2 (C-1), 130.2 (d, $J = 3.6$ Hz, C-5), 129.3 (C-11), 125.5 (C-10), 125.1 (C-6), 124.3 (d, $J = 12.9$ Hz, C-4), 121.7 (C-8), 120.9 (C-12), 116.4 (d, $J = 22.3$ Hz, C-2), 40.4 (R-C-1′), 30.9 (R-C-4′), 29.1 (R-C-2′), 25.8 (R-C-3′), 22.0 (R-C-5′), 20.4 (CH$_3$), 13.8 (R-C-6′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 118.0. UPLC/MS analysis: Rt 2.17 min. MS (ES) $C_{20}H_{24}FNO_2$ requires 329, found 330 [M+H]$^+$. HRMS $C_{20}H_{25}NO_2F$ [M+H]$^+$: calculated 330.1869 measured 330.189 Δppm 6.4.

4.1.6.27. Methyl 3-fluoro-4-[3-(hexylcarbamoyloxy)phenyl]benzoate (21b). Compound **21b** was prepared according to general procedure B using **20b** (0.84 g, 3.41 mmol) and *n*-hexyl isocyanate (1.30 g, 10.23 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **21b** as a white solid (1.27 g, quant.).

4.1.6.28. (±)-Methyl 2-[3-chloro-4-[3-(hexylcarbamoyloxy)phenyl] phenyl]propanoate (28a). Compound **28a** was prepared according to general procedure B using **27a** (1.57 g, 5.40 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to give **28a** as a colorless oil (2.12 g, 94%).

4.1.6.29. (±)-Methyl 2-[4-[3-(hexylcarbamoyloxy)phenyl]-3-methyl-phenyl]propanoate (28b). Compound **28b** was prepared according to general procedure B using **27b** (0.72 g, 2.66 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to give **28b** a white solid (0.94 g, 89%).

4.1.6.30. (±)-Methyl 2-[4-[3-(hexylcarbamoyloxy)phenyl]-3-(tri-fluoromethyl)phenyl]propanoate (28c). Compound **28c** was prepared according to general procedure B using **27c** (0.78 g, 2.41 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to give **28c** as a white solid (1.02 g, 94%).

4.1.6.31. (±)-Methyl 2-[3-benzyloxy-4-[3-(hexylcarbamoyloxy) phenyl]phenyl]propanoate (28d). Compound **28d** was prepared according to general procedure B using **27d** (1.00 g, 2.52 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to obtain **28d** as a clear oil (0.72 g,quant.).

4.1.6.32. (±)-Methyl 2-[4-[3-(hexylcarbamoyloxy)phenyl]phenyl] propanoate (28e). Compound **28e** was prepared according to general procedure B using **27e** (128 mg, 0.5 mmol). The crude was purified by column chromatography (Cy/EtOAc, 9: 1) to afford **28e** as a white solid (123 mg, 64%).

4.1.6.33. (±)-Methyl 2-[4-[3-(hexylcarbamoyloxy)phenyl]-3-nitro-phenyl]propanoate (28f). Compound **28f** was prepared according to general procedure B using **27f** (0.85 g, 2.82 mmol). The crude was purified by column chromatography (Cy/EtOAc 9: 1) to give **28f** as a

yellow oil (1.17 g, 97%).

4.1.7. General procedure for methyl ester hydrolysis (procedure C, 10a-t, 15a-d, 18b, 21c, 29a-f)

To a solution of the corresponding methyl ester (1.0 mmol) in THF (0.1 M) was added 6 M HCl (5 mL) and the mixture was stirred at rt until the disappearance of the starting material was noted by UPLC-MS analysis. H$_2$O (10 mL) was added and the suspension was extracted with EtOAc (20 mL). After evaporation, the organic phase was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residues were purified by crystallization (Et$_2$O/Cy, Et$_2$O/pentane, TBME), preparative TLC (Cy/EtOAc) or preparative HPLC.

4.1.7.1. (±)-2-[4-[3-(cyclohexylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoic acid (10a). Compound **10a** was prepared according to general procedure C using **9a** (261 mg, 0.65 mmol). The crude was purified by preparative HPLC to afford **10a** as a white solid (65 mg, 26%). Mp: 152–153 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H, COOH), 7.73 (d, $J = 7.8$, 1H, NH), 7.50 (t, $J = 8.3$, 1H, H-5), 7.47 (t, $J = 7.9$, 1H, H-11), 7.37 (d, $J = 7.7$, 1H, H-10), 7.24 (m, 3H, H-2 H-6 H-8), 7.14 (d, $J = 8.0$, 1H, H-12), 3.78 (q, $J = 7.1$, 1H, CH), 3.33 (m, 1H, R-H-1′), 1.84 (m, 2H, R-H-2′), 1.71 (m, 2H, R-H-3′), 1.56 (m, 1H, R-H-4′), 1.41 (d,$J = 7.1$, 3H, CH$_3$), 1.23 (m, 5H, R-H-2′ R-H-3′, R-H-4′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7 (COOH), 158.7 (d, $J = 246.1$ Hz, C-3), 153.3 (C-9), 151.2 (HNCOO), 143.4 (d,$J = 8.0$ Hz, C-7), 135.9 (C-1), 130.6 (C-5), 129.4 (C-11), 125.7 (d, $J = 13.0$ Hz, C-4), 125.1 (C-10), 124.0 (C-6), 121.8 (C-8), 121.1 (C-12), 115.1 (d, $J = 23.2$ Hz, C-2), 49.7 (R-C-1′), 44.0 (CH), 32.4 (R-C-2′), 25.1 (R-C-4′), 24.5 (R-C-3′), 18.2 (CH$_3$). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.41 min. MS (ES) $C_{22}H_{24}FNO_4$ requires 385, found 386 [M+H]$^+$. HRMS $C_{22}H_{25}NO_4F$ [M+H]$^+$: calculated 386.1768 measured 386.1781 Δppm 3.4.

4.1.7.2. (±)-2-[4-[3-(cyclopentylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoic acid (10b). Compound **10b** was prepared according to general procedure C using **9b** (235 mg, 0.61 mmol). The crude was purified by crystallization from TBME to afford **10b** as a white solid (95 mg, 42%). Mp: 151–152 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H, COOH), 7.81 (d, $J = 7.2$, 1H, NH), 7.50 (t, $J = 8.3$, 1H, H-5), 7.47 (t, $J = 7.9$, 1H, H-11), 7.37 (d,$J = 7.5$, 1H, H-10), 7.23 (m, 3H, H-2 H-6 H-8), 7.14 (dd, $J = 7.9, 2.3$, 1H, H-12), 3.85 (h, $J = 6.6$, 1H, R-H-1′), 3.78 (q,$J = 7.1$, 1H, CH), 1.83 (m, 2H, R-H-2′), 1.67 (m, 2H, R-H-3′), 1.50 (m, 4H, R-H-2′ R-H-3′), 1.41 (d,$J = 7.1$, 3H, CH$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7 (COOH), 158.7 (d,$J = 247.4$ Hz, C-3), 153.6 (C-9), 151.1 (HNCOO), 143.4 (d,$J = 7.8$ Hz, C-7), 135.9 (C-1), 130.6 (C-5), 129.4 (C-11), 125.7 (d, $J = 13.0$ Hz, C-4), 125.1 (C-10), 124.0 (C-6), 121.8 (C-8), 121.2 (C-12), 115.1 (d, $J = 23.2$ Hz, C-2), 52.3(R-C-1′), 44.0 (CH), 32.1 (R-C-2′), 23.2 (R-C-3′), 18.2 (CH$_3$). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.41 min. MS (ES) $C_{21}H_{22}FNO_4$ requires 371, found 372 [M+H]$^+$. HRMS $C_{21}H_{23}NO_4F$ [M+H]$^+$: calculated 372.1611 measured 372.1603 Δppm −2.1.

4.1.7.3. (±)-2-[4-[3-(cyclobutylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoic acid (10c). Compound **10c** was prepared according to general procedure C using **9c**. The crude was purified by preparative HPLC to afford **10c** as a white solid (66 mg, 37% over 2 steps). Mp: 140–141 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H, COOH), 8.10 (d,$J = 7.9$, 1H, NH), 7.49 (t,$J = 8.3$, 1H, H-5), 7.46 (t, $J = 7.9$, 1H, H-11), 7.38 (d,$J = 7.0$, 1H, H-10), 7.23 (m, 3H, H-2 H-6 H-8), 7.13 (m, 1H, H-12), 4.02 (h,$J = 8.2$, 1H, R-H-1′), 3.78 (q,$J = 7.1$, 1H, CH), 2.18 (m, 2H, R-H-2′), 1.98 (m, 2H, R-H-2′), 1.61 (m, 2H, R-H-3′), 1.41 (d,$J = 7.1$, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7 (COOH), 158.7 (d, $J = 246.2$ Hz, C-3), 152.9 (C-9), 151.0 (HNCOO), 143.43 (d, $J = 7.7$ Hz, C-7), 135.9 (C-1), 130.6 (d, $J = 2.9$ Hz, C-5), 129.4 (C-11),

125.7 (d, $J = 12.7$ Hz, C-4), 125.2 (C-10), 124.0 (C-6), 121.9 (C-8), 121.2 (C-12), 115.1 (d, $J = 23.3$ Hz, C-2), 45.7 (R-C-1′), 44.0 (CH), 30.1 (R-C-2′), 18.2 (CH$_3$), 14.3 (R-C-3′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.17 min. MS (ES) C$_{20}$H$_{20}$FNO$_4$ requires 357, found 358 [M+H]$^+$. HRMS C$_{20}$H$_{21}$NO$_4$F [M+H]$^+$: calculated 358.1455 measured 358.1452 Δppm −0.8.

4.1.7.4. (±)-2-[4-[3-(cyclopropylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoic acid (10d). Compound **10d** was prepared according to general procedure C using **9d** (59 mg, 0.17 mmol). The crude was purified by preparative HPLC to afford **10d** as a white solid (35 mg, 60%). Mp: 117−188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H, COOH), 7.97 (d, $J = 2.3$, 1H, NH), 7.50 (t, $J = 8.4$, 1H, H-5), 7.47 (t, $J = 7.9$, 1H, H-11), 7.38 (d, $J = 7.5$, 1H, H-10), 7.23 (m, 3H, H-2 H-6 H-8), 7.14 (d, $J = 7.9$, 1H, H-12), 3.78 (q, $J = 7.1$, 1H, CH), 2.57 (m, 1H, R-H-1′), 1.41 (d, $J = 7.1$, 3H, CH$_3$), 0.64 (m, 2H, R-H-2′), 0.50 (m, 2H, R-H-2′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7 (COOH), 158.7 (d, $J = 246.5$ Hz, C-3), 154.8 (C-9), 151.0 (HNCOO), 143.4 (d, $J = 7.9$ Hz, C-7), 135.9 (C-1), 130.6 (d, $J = 2.2$ Hz, C-5), 129.4 (C-11), 125.7 (d, $J = 13.1$ Hz, C-4), 125.2 (C-10), 124.0 (C-6), 121.8 (C-8), 121.2 (C-12), 115.1 (d, $J = 23.0$ Hz, C-2), 44.0 (CH), 23.0 (R-C-1′), 18.2 (CH$_3$), 5.7 (R-C-2′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 1.96 min. MS (ES) C$_{19}$H$_{18}$FNO$_4$ requires 343, found 344 [M+H]$^+$. HRMS C$_{19}$H$_{19}$NO$_4$F [M+H]$^+$: calculated 344.1298 measured 344.1298 Δppm 0.

4.1.7.5. (±)-2-[4-[3-(cyclohexylmethylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoic acid (10e). Compound **10e** was prepared according to general procedure C using **9e** (157 mg, 0.38 mmol). The crude was purified by crystallization from pentane/Et$_2$O to afford **10e** as a white solid (93 mg, 61%). Mp: 142−143 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H, COOH), 7.79 (t, $J = 5.9$ Hz, 1H, NH), 7.50 (t, $J = 8.1$, 1H, H-5), 7.47 (t, $J = 7.9$, 1H, H-11), 7.37 (d, $J = 7.6$ Hz, 1H, H-10), 7.24 (m, 3H, H-2 H-6 H.8), 7.13 (dd, $J = 7.6$, 1.8 Hz, 1H, H-12), 3.78 (q, $J = 7.1$ Hz, 1H, CH), 2.92 (t, $J = 6.3$ Hz, 2H, R-H-1′), 1.67 (m, 5H, R-H-3′ R-H-4′R-H-5′), 1.46 (m, 1H, R-H-2′), 1.41 (d, $J = 7.1$ Hz, 3H, CH$_3$), 1.18 (m, 3H, R-H-4′ R-H-5′), 0.90 (m, 2H, R-H-3′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.2 (COOH), 159.2 (d, $J = 246.4$ Hz, C-3), 154.8 (C-9), 151.7 (HNCOO), 143.9 (d, $J = 7.6$ Hz, C-7), 136.4 (C-1), 131.1 (d, $J = 3.7$ Hz, C-5), 129.9 (C-11), 126.2 (d, $J = 13.0$ Hz, C-4), 125.6 (C-10), 124.5 (d, $J = 2.9$ Hz, C-6), 122.3 (d, $J = 3.0$ Hz, C-8), 121.6 (C-12), 115.6 (d, $J = 23.3$ Hz, C-2), 47.2 (R-C-1′), 44.5 (CH), 38.1 (R-C-2′), 30.7 (R-C-3′), 26.5 (R-C-5′), 25.8 (R-C-4′), 18.7 (CH$_3$). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.57 min. MS (ES) C$_{23}$H$_{26}$FNO$_4$ requires 399, found 400 [M+H]$^+$. HRMS C$_{23}$H$_{27}$NO$_4$F [M+H]$^+$: calculated 400.1924 measured 400.193 Δppm 1.5.

4.1.7.6. (±)-2-[4-[3-(2-cyclohexylethylcarbamoyloxy)phenyl]-3-fluoro-phenyl]propanoic acid (10f). Compound **10f** was prepared according to general procedure C using **9f** (149 mg, 0.35 mmol). The crude was purified by crystallization from pentane/Et$_2$O to afford **10f** as a white solid (98 mg, 68%). Mp: 118−119 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H, COOH), 7.74 (t, $J = 5.6$ Hz, 1H, NH), 7.48 (m, 2H, H-5), 7.37 (d, $J = 7.0$ Hz, 1H, H-11), 7.23 (m, 3H, H-2 H-6 H-8), 7.13 (dd, $J = 7.7$, 1.8 Hz, 1H, H-12), 3.78 (q, $J = 7.1$ Hz, 1H, CH), 3.09 (q, $J = 6.7$ Hz, 2H, R-H-1′), 1.66 (m, 5H, R-H-5′ R-H-4′ R-H-6′), 1.41 (d, $J = 7.1$ Hz, 3H, CH$_3$), 1.34 (m, 3H, R-H-2′ R-H-3′), 1.19 (m, 3H, R-H-5′ R-H-6′), 0.88 (m, 2H, R-H-4′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7 (COOH), 158.7 (d, $J = 246.5$ Hz, C-3), 154.1 (C-9), 151.2 (HNCOO), 143.4 (d, $J = 7.8$ Hz, C-7)), 135.9 (C-1), 130.6 (d, $J = 3.5$ Hz, C-5), 129.4 (C-11), 125.7 (d, $J = 13.1$ Hz, C-4), 125.1 (C-10), 124.0 (d, $J = 3.1$ Hz, C-6), 121.8 (C-8), 121.1 (C-12), 115.1 (d, $J = 23.1$ Hz, C-2), 44.0 (CH), 38.2 (R-C-1′), 36.6 (R-C-2′), 34.4 (R-C-4′), 26.0 (R-C-6′), 25.7 (R-C-5′), 18.2 (CH$_3$). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3.

UPLC/MS analysis: Rt 2.69 min. MS (ES) C$_{24}$H$_{28}$FNO$_4$ requires 413, found 414 [M+H]$^+$. HRMS C$_{24}$H$_{29}$NO$_4$F [M+H]$^+$: calculated 414.2081 measured 414.2096 Δppm 3.6.

4.1.7.7. (±)-2-[3-fluoro-4-[3-(isopropylcarbamoyloxy)phenyl]phenyl]propanoic acid (10g). Compound **10g** was prepared according to general procedure C using **9g** (159 mg, 0.44 mmol). The crude was purified by crystallization from pentane/Et$_2$O to afford **10g** as a white solid (65 mg, 43%). Mp: 131−132 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.43 (s, 1H, COOH), 7.73 (d, $J = 7.6$ Hz, 1H, NH), 7.51 (t, $J = 8.1$ Hz, 1H, H-5), 7.48 (t, $J = 7.9$ Hz, 1H, H-11), 7.39 (d, $J = 7.5$ Hz, 1H, H-10), 7.25 (m, 3H, H-2 H-6 H-8), 7.15 (d, $J = 7.9$ Hz, 1H, H-12), 3.79 (q, $J = 7.1$ Hz, 1H, CH), 3.67 (m, $J = 6.9$ Hz, 1H, R-H-1′), 1.42 (d, $J = 7.1$ Hz, 3H, CH$_3$), 1.15 (d, $J = 6.5$ Hz, 6H, R-H-2′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.3 (COOH), 159.2 (d, $J = 246.5$ Hz, C-3), 153.7 (C-9), 151.6 (HNCOO), 143.9 (d, $J = 8.0$ Hz, C-7), 136.4 (C-1), 131.1 (d, $J = 3.7$ Hz, C-5), 129.8 (C-11), 126.2 (d, $J = 13.1$ Hz, C-4), 125.6 (C-10), 124.5 (d, $J = 3.2$ Hz, C-6), 122.3 (C-8), 121.7 (C-12), 115.6 (d, $J = 23.1$ Hz, C-2), 44.5 (CH), 43.1 (R-C-1′), 22.8 (R-C-2′), 18.7 (CH$_3$). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.09 min. MS (ES) C$_{19}$H$_{20}$FNO$_4$ requires 345, found 346 [M+H]$^+$. HRMS C$_{19}$H$_{21}$NO$_4$F [M+H]$^+$: calculated 346.1455 measured 346.1458 Δppm 0.9.

4.1.7.8. (±)-2-[3-fluoro-4-[3-(isobutylcarbamoyloxy)phenyl]phenyl]propanoic acid (10h). Compound **10h** was prepared according to general procedure C using **9h** (138 mg, 0.38 mmol). The crude was purified by crystallization from pentane/Et$_2$O to afford **10h** as a white solid (57 mg, 42%). Mp: 128−130 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H, COOH), 7.84 (t, $J = 5.9$ Hz, 1H, NH), 7.51 (t, $J = 8.1$ Hz, 1H, H-5), 7.48 (t, $J = 7.9$ Hz, 1H, H-11), 7.39 (d, $J = 7.7$ Hz, 1H, H-10), 7.25 (m, 3H, H-2 H-6 H-8), 7.15 (dd, $J = 8.0$, 1.5 Hz, 1H, H-12), 3.79 (q, $J = 7.1$ Hz, 1H, CH), 2.91 (t, $J = 6.4$ Hz, 2H, R-H-1′), 1.76 (hept, $J = 6.7$ Hz, 1H, R-H-2′), 1.42 (d, $J = 7.1$ Hz, 3H, CH$_3$), 0.90 (d, $J = 6.7$ Hz, 6H, R-H-3′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.2 (COOH), 159.2 (d, $J = 246.3$ Hz, C-3), 154.9 (C-9), 151.7 (HNCOO), 143.9 (d, $J = 7.7$ Hz, C-7), 136.4 (C-1), 131.1 (d, $J = 3.5$ Hz, C-5), 129.9 (C-11), 126.2 (d, $J = 13.1$ Hz, C-4), 125.6 (C-10), 124.5 (d, $J = 3.1$ Hz, C-6), 122.3 (d, $J = 2.9$ Hz, C-8), 121.6 (C-12), 115.6 (d, $J = 23.1$ Hz, C-2), 48.5 (R-C-1′), 44.5 (CH), 28.7 (R-C-2′), 20.4 (R-C-3′), 18.7 (CH$_3$). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.24 min. MS (ES) C$_{20}$H$_{22}$FNO$_4$ requires 359, found 360 [M+H]$^+$. HRMS C$_{20}$H$_{23}$NO$_4$F [M+H]$^+$: calculated 360.1611 measured 360.1631 Δppm 5.6.

4.1.7.9. (±)-2-[3-fluoro-4-[3-(phenylcarbamoyloxy)phenyl]phenyl]propanoic acid (10i). Compound **10i** was prepared according to general procedure C using **9i** (87 mg). The crude was purified by preparative HPLC to afford **10i** as a white solid (31 mg, 37%). Mp: 145−146 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H, COOH), 10.26 (s, 1H, NH), 7.53 (m, 4H, H-5 H-11 R- Ph-3′), 7.45 (d, $J = 6.8$ Hz, 1H, H-12), 7.40 (s, 1H, H-8), 7.33 (t, $J = 7.9$ Hz, 2H, R- Ph-2′), 7.26 (m, 3H, H-2 H-6 H-10), 7.05 (t, $J = 7.4$ Hz, 1H, R- Ph-4′), 3.78 (q, $J = 7.1$ Hz, 1H, CH), 1.41 (d, $J = 7.1$ Hz, 3H, CH$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7 (COOH), 158.8 (d, $J = 246.5$ Hz, C-3), 151.5 (C-9), 150.5 (HNCOO), 143.5 (d, $J = 8.0$ Hz, C-7), 138.5 (R-Ph-1′), 136.1 (C-1), 130.6 (d, $J = 2.9$ Hz, C-5), 129.6 (C-11), 128.8 (R- Ph-3′), 125.7 (C-10), 125.6 (d, $J = 13.1$ Hz, C-4), 124.0 (C-6), 122.9 (R- Ph-4′), 122.0 (C-8), 121.3 (C-12), 118.4 (R-Ph-2′), 115.2 (d, $J = 23.3$ Hz, C-2), 44.1, 18.2. ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.05 min. MS (ES) C$_{22}$H$_{18}$FNO$_4$ requires 379, found 380 [M+H]$^+$. HRMS C$_{22}$H$_{19}$NO$_4$F [M+H]$^+$: calculated 380.1298 measured 380.1296 Δppm −0.5.

4.1.7.10. (±)-2-[4-[3-(benzylcarbamoyloxy)phenyl]-3-fluoro-phenyl] propanoic acid (10j). Compound **10j** was prepared according to general procedure C using **9j**. The crude was purified by preparative HPLC to afford **10j** as a white solid (69 mg, 35% over 2 steps). Mp: 120–122 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H, COOH), 8.36 (t, J = 6.1, 1H, NH), 7.49 (m, 2H H-5 H-11), 7.36 (m, 5H, H-10 R-Ph-2′ R-Ph-3′), 7.27 (m, 2H, H-8 R-Ph-4′), 7.23 (m, 2H, H-2 H-6), 7.17 (dd, J = 7.8, 1.7, 1H, H-12), 4.29 (d, J = 6.1, 2H, R-H-1′), 3.78 (q, J = 7.1, 1H, CH), 1.41 (d, J = 7.1, 3H, CH$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7 (COOH), 158.7 (d, J = 246.3 Hz, C-3), 154.5 (C-9), 151.1 (HNCOO), 143.4 (d, J = 7.6 Hz, C-7), 139.1 (R-Ph-1), 135.9 (C-1), 130.6 (d, J = 2.8 Hz, C-5), 129.4 (C-11), 128.3 (R-Ph-3), 127.1 (R-Ph-2), 126.9 (R-Ph-4), 125.7 (d, J = 12.9 Hz, C-4), 125.3 (C-10), 124.0 (C-6), 121.8 (C-8), 121.2 (C-12), 115.1 (d, J = 23.2 Hz, C-2), 44.1 (CH), 44.0 (R-C-1′), 18.2 (CH$_3$). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.27 min. MS (ES) C$_{23}$H$_{20}$FNO$_4$ requires 393, found 394 [M+H]$^+$. HRMS C$_{23}$H$_{21}$NO$_4$F [M+H]$^+$: calculated 394.1455 measured 394.1462 Δppm 1.8.

4.1.7.11. (±)-2-[3-fluoro-4-[3-(phenethylcarbamoyloxy)phenyl] phenyl]propanoic acid (10k). Compound **10k** was prepared according to general procedure C using **9k**. The crude was purified by crystallization from Et$_2$O/pentane to afford **10k** as a white solid (58 mg, 41%). Mp: 104 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.45 (s, 1H, COOH), 7.88 (t, J = 5.6 Hz, 1H, NH), 7.51 (t, J = 8.0 Hz, 1H, H-5), 7.48 (t, J = 7.9 1H, H-11), 7.37 (m, 1H, R-Ph-4), 7.31 (m, 2H, R-Ph-3), 7.23 (m, 6H, H-10 H-2 H-6 H-8 R-Ph-2), 7.11 (dd, J = 7.7, 1.7 Hz, 1H, H-12), 3.78 (q, J = 7.1 Hz, 1H, CH), 3.31 (q, J = 7.7 Hz, 2H, R-H-1′), 2.80 (t, J = 7.4 Hz, 2H, R-H-2′), 1.41 (d, J = 7.1 Hz, 3H, CH$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.2 (COOH), 159.2 (d, J = 245.8 Hz, C-3), 154.6 (C-9), 151.1 (HNCOO), 143.9 (d, J = 7.7 Hz, C-7), 139.5 (R-Ph-1), 136.4 (C-1), 131.1 (d, J = 3.4 Hz, C-5), 129.9 (C-11), 129.1 (R-Ph-2), 128.8 (R-Ph-3), 126.6 (R-Ph-4), 126.2 (d, J = 13.0 Hz, C-4), 125.7 (C-10), 124.5 (d, J = 2.8 Hz, C-6), 122.3 (d, J = 2.6 Hz, C-8), 121.6 (C-12), 115.6 (d, J = 23.1 Hz, C-2), 44.5 (CH), 42.5 (R-C-1′), 35.6 (R-C-2′), 18.7 (CH$_3$). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.37 min. MS (ES) C$_{24}$H$_{22}$FNO$_4$ requires 407, found 408 [M+H]$^+$. HRMS C$_{24}$H$_{23}$NO$_4$F [M+H]$^+$: calculated 408.1611 measured 408.1626 Δppm 3.7.

4.1.7.12. (±)-2-[3-fluoro-4-[3-(3-phenylpropylcarbamoyloxy)phenyl] phenyl]propanoic acid (10l). Compound **10l** was prepared according to general procedure C using **9l** (174 mg, 0.40 mmol). The crude was purified by preparative TLC (Cy/EtOAc, 5: 5) to afford **10l** as a white solid (44 mg, 26%). Mp: 82–83 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H, COOH), 7.87 (t, J = 5.53 Hz, 1H, NH), 7.51 (t, J = 8.04 Hz, 1H, H-5), 7.48 (t, J = 8.20 Hz, 1H, H-11), 7.38 (d, J = 7.2 Hz, 1H, R-Ph-4), 7.22 (m, 9H, H-2 H-6 H-8 H-10 H-12 R-Ph-2 R-Ph-3), 3.78 (q, J = 6.5 Hz, 1H, CH), 3.09 (q, J = 6.3 Hz, 2H, R-H-1′), 2.63 (t, J = 7.3 Hz, 2H, R-H-2′), 1.78 (p, J = 6.7 Hz, 2H, R-H-3′), 1.41 (d, J = 6.9 Hz, 3H, CH$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.2 (COOH), 159.2 (d, J = 246.1 Hz, C-3), 154.7 (C-9), 151.6 (HNCOO), 143.9 (d, J = 8.1 Hz, C-7), 142.0 (R-Ph-1), 136.4 (C-1), 131.1 (d, J = 3.3 Hz, C-5), 129.9 (C-11), 128.8 (R-Ph-3), 128.7 (R-Ph-2), 126.2 (R-Ph-4), 125.7 (d, J = 3.5 Hz, C-4), 124.6 (C-10) 124.5 (C-6), 122.3 (C-8), 121.70 (C-12), 115.6 (d, J = 23.5 Hz, C-2), 44.5 (CH), 40.5 (R-C-1′), 32.8 (R-C-3′), 31.4 (R-C-2′), 18.7 (CH$_3$). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.46 min. MS (ES) C$_{25}$H$_{24}$FNO$_4$ requires 421, found 422 [M+H]$^+$. HRMS C$_{25}$H$_{25}$NO$_4$F [M+H]$^+$: calculated 422.1768 measured 422.1776 Δppm 1.9.

4.1.7.13. (±)-2-[3-fluoro-4-[3-(4-phenylbutylcarbamoyloxy)phenyl] phenyl]propanoic acid (10m). Compound **10m** was prepared according to general procedure C using **9m** (171 mg, 0.38 mmol). The crude was purified by preparative TLC (Cy/EtOAc, 5: 5) to afford **10m** as a white solid (70 mg, 43%). Mp: 101–102 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H, COOH), 7.80 (t, J = 5.7 Hz, 1H, NH), 7.47 (m, 2H, H-5 H-8), 7.37 (d, J = 7.3 Hz, 1H, R- Ph-4), 7.19 (m, 9H, H-2 H-6 H-8 H-10 H-12 R- Ph-2 R- Ph-3), 3.78 (q, J = 7.1 Hz, 1H, CH), 3.10 (q, J = 6.6 Hz, 2H, R-H-1′), 2.60 (t, J = 7.5 Hz, 2H, R-H-4′), 1.60 (q, J = 7.9 Hz, 2H, R-H-3′), 1.50 (q, J = 7.2 Hz, 2H, R-H-2′), 1.41 (d, J = 7.1 Hz, 3H, CH$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.2 (COOH), 159.2 (d, J = 246.3 Hz, C-3), 154.7 (C-9), 151.6 (HNCOO), 143.9 (d, J = 7.5 Hz, C-7), 142.5 (R-Ph-1), 136.4 (C-1), 131.0 (d, J = 3.6 Hz, C-5), 129.9 (C-11), 128.7 (R-Ph-3), 128.6 (R-Ph-2), 126.1 (R-Ph-4), 125.7 (d, J = 2.4 Hz, C-4), 124.6 (C-10) 124.5 (C-6), 122.3 (d, J = 3.1 Hz, C-8), 121.6 (C-12), 115.6 (d, J = 23.2 Hz, C-2), 44.5 (CH), 40.7 (R-C-1′), 35.2 (R-C-4′), 29.3 (R-C-2′), 28.7 (R-C-3′), 18.7 (CH$_3$). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.59 min. MS (ES) C$_{26}$H$_{26}$FNO$_4$ requires 435, found 436 [M+H]$^+$. HRMS C$_{26}$H$_{27}$NO$_4$F [M+H]$^+$: calculated 436.1924 measured 436.1936 Δppm 2.8.

4.1.7.14. (±)-2-[4-[3-(ethylcarbamoyloxy)phenyl]-3-fluoro-phenyl] propanoic acid (10n). Compound **10n** was prepared according to general procedure C using **8** (104 mg, 0.30 mmol). The crude was purified by crystallization from Et$_2$O/pentane to afford **10n** as a white solid (37 mg, 37%). Mp: 93–94 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H, COOH), 7.79 (t, J = 5.5 Hz, 1H, NH), 7.51 (t, J = 8.3 Hz, 1H, H-5), 7.48 (t, J = 7.9 Hz, 1H, H-11), 7.39 (d, J = 7.5 Hz, 1H, H-10), 7.25 (m, 3H, H-2 H-6 H-8), 7.15 (d, J = 7.9 Hz, 1H, H-12), 3.79 (q, J = 7.1 Hz, 1H, CH), 3.12 (p, J = 7.1 Hz, 2H, R-H-1′), 1.42 (d, J = 7.1 Hz, 3H, CH$_3$), 1.10 (t, J = 7.2 Hz, 3H, R-H-2′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.3 (COOH), 159.2 (d, J = 245.9 Hz, C-3), 154.5 (C-9), 151.6 (HNCOO), 143.9 (d, J = 7.6 Hz, C-7), 136.4 (C-1), 131.1 (d, J = 3.6 Hz, C-5), 129.9 (C-11), 126.2 (d, J = 13.0 Hz, C-4), 125.7 (C-10), 124.5 (d, J = 3.0 Hz, C-6), 122.3 (d, J = 3.1 Hz, C-8), 121.7 (C–C-12), 115.6 (d, J = 23.4 Hz, C-2), 44.5 (CH), 35.7 (R-C-1′), 18.7 (CH$_3$), 15.3 (R-C-2′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 1.95 min. MS (ES) C$_{18}$H$_{18}$FNO$_4$ requires 331, found 332 [M+H]$^+$. HRMS C$_{18}$H$_{19}$NO$_4$F [M+H]$^+$: calculated 332.1298 measured 332.1304 Δppm 1.8.

4.1.7.15. (±)-2-[3-fluoro-4-[3-(propylcarbamoyloxy)phenyl]phenyl] propanoic acid (10o). Compound **10o** was prepared according to general procedure C using **8** (87 mg, 0.24 mmol). The crude was purified by preparative TLC (Cy/EtOAc, 5: 5) to afford **10o** as a white solid (57 mg, 68%). Mp: 113–114 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H), 7.79 (t, J = 5.7 Hz, 1H), 7.50 (t, J = 8.3 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.37 (d, J = 6.9 Hz, 1H), 7.24 (ddt, J = 9.9, 3.9, 1.7 Hz, 3H), 7.14 (ddd, J = 8.2, 2.4, 1.1 Hz, 1H), 3.78 (q, J = 7.1 Hz, 1H), 3.03 (td, J = 7.1, 5.9 Hz, 2H), 1.49 (h, J = 7.3 Hz, 2H), 1.41 (d, J = 7.2 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7 (COOH), 158.7 (d, J = 246.5 Hz, C-3), 154.2 (C-9), 151.2 (HNCOO), 143.4 (d, J = 7.8 Hz, C-7), 135.9 (C-1), 130.6 (C-5), 129.4 (C-11), 125.7 (d, J = 12.9 Hz, C-4), 125.1 (C-10), 124.0 (C-6), 121.8 (C-8), 121.1 (C-12), 115.1 (d, J = 23.2 Hz, C-2), 44.0 (CH), 42.2 (R-C-1′), 22.4 (R-C-2′), 18.2 (CH$_3$), 11.2 (R-C-3′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.10 min. MS (ES) C$_{19}$H$_{20}$FNO$_4$ requires 345, found 346 [M+H]$^+$. HRMS C$_{19}$H$_{21}$NO$_4$F [M+H]$^+$: calculated 346.1455 measured 346.1459 Δppm 1.2.

4.1.7.16. (±)-2-[4-[3-(butylcarbamoyloxy)phenyl]-3-fluoro-phenyl] propanoic acid (10p). Compound **10p** was prepared according to general procedure C using **9p** (135 mg, 0.36 mmol). The crude was purified by crystallization from Cy/Et$_2$O to afford **10p** as a white solid (75 mg, 58%). Mp: 110–111 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H, COOH), 7.79 (t, J = 5.7 Hz, 1H, NH), 7.50 (t, J = 8.3 Hz, 1H, H-5), 7.47 (t, J = 7.9 Hz, 1H, H-11), 7.37 (d, J = 7.0 Hz, 1H, H-10), 7.23 (m, 3H, H-2 H-6 H-8), 7.13 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H, H-12),

3.78 (q, J = 7.1 Hz, 1H, CH), 3.06 (q, J = 6.8 Hz, 2H, R-H-1′), 1.46 (p, J = 6.9 Hz, 2H, R-H-2′), 1.40 (d, J = 7.2 Hz, 3H, CH$_3$), 1.32 (h, J = 7.1 Hz, 2H, R-H-3′), 0.89 (t, J = 7.3 Hz, 3H, R-H-4′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.8 (COOH), 158.8 (d, J = 246.0 Hz, C-3), 154.2 (C-9), 151.2 (HNCOO), 143.4 (d, J = 8.0 Hz, C-7), 135.9 (C-1), 130.6 (d, J = 2.9 Hz, C-5), 129.4 (C-11), 125.7 (d, J = 12.8 Hz, C-4), 125.2 (C-10), 124.0 (C-6), 121.8 (C-8), 121.2 (C-12), 115.2 (d, J = 23.3 Hz, C-2), 44.1 (CH), 40.1 (R-C-1′), 31.3 (R-C-2′), 19.4 (R-C-3′), 18.2 (CH$_3$), 13.6 (R-C-4′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.25 min. MS (ES) C$_{20}$H$_{22}$FNO$_4$ requires 359, found 360 [M+H]$^+$. HRMS C$_{20}$H$_{23}$NO$_4$F [M+H]$^+$: calculated 360.1611 measured 360.1615 Δppm 1.1.

4.1.7.17. (±)-2-[3-fluoro-4-[3-(pentylcarbamoyloxy)phenyl]phenyl] propanoic acid (10q). Compound **10q** was prepared according to general procedure C using **9q** (149 mg, 0.39 mmol). The crude was purified by crystallization from pentane/Et$_2$O to afford **10q** as a white solid (85 mg, 59%). Mp: 105–106 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H, COOH), 7.77 (t, J = 5.7 Hz, 1H, NH), 7.51 (t, J = 7.9 Hz, 1H, H-5), 7.48 (t, J = 7.7 Hz, 1H, H-11), 7.37 (d, J = 8.6 Hz, 1H, H-10), 7.23 (m, 3H, H-2 H-6 H-8), 7.14 (dd, J = 8.1, 2.2 Hz, 1H, H-12), 3.78 (q, J = 7.1 Hz, 1H, CH), 3.06 (q, J = 6.8 Hz, 2H, R-H-1′), 1.48 (p, J = 7.2 Hz, 2H, R-H-2′), 1.41 (d, J = 7.2 Hz, 3H, CH$_3$), 1.29 (m, 4H, R-H-3″ R-H-4″), 0.88 (t, J = 6.9 Hz, 3H, R-H-5′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.2 (COOH), 159.2 (d, J = 246.4 Hz, C-3), 154.6 (C-9), 151.7 (HNCOO), 143.9 (d, J = 7.6 Hz, C-7), 136.4 (C-1), 131.1 (d, J = 3.6 Hz, C-5), 129.9 (C-11), 126.2 (d, J = 13.2 Hz, C-4), 125.6 (C-10), 124.5 (d, J = 3.3 Hz, C-6), 122.3 (C-8), 121.6 (C-12), 115.6 (d, J = 23.4 Hz, C-2), 44.5 (CH), 40.9 (R-C-1′), 29.3 (R-C-2′), 28.9 (R-C-4′), 22.2 (R-C-3′), 18.7 (CH$_3$), 14.38 (R-C-5′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.42 min. MS (ES) C$_{21}$H$_{24}$FNO$_4$ requires 373, found 374 [M+H]$^+$. HRMS C$_{21}$H$_{25}$NO$_4$F [M+H]$^+$: calculated 374.1768 measured 374.1778 Δppm 2.7.

4.1.7.18. (±)-2-[3-fluoro-4-[3-(hexylcarbamoyloxy)phenyl]phenyl] propanoic acid (10r). Compound **10r** was prepared according to general procedure C using **9r** (142 mg, 0.35 mmol). The crude was purified by crystallization from Et$_2$O/pentane to afford **10r** as a white solid (41 mg, 30%). Mp: 102–103 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H, COOH), 7.79 (t, J = 5.7 Hz, 1H, NH), 7.51 (t, J = 8.1 Hz, 1H, H-5), 7.48 (t, J = 7.9 Hz, 1H, H-11), 7.39 (d, J = 7.7 Hz, 1H, H-10), 7.25 (m, 3H, H-2 H-6 H-8), 7.15 (dd, J = 8.7, 1.5 Hz, 1H, H-12), 3.79 (q, J = 7.1 Hz, 1H, CH), 3.07 (q, J = 6.8 Hz, 2H, R-H-1′), 1.47 (p, J = 6.3 Hz, 2H, R-H-2′), 1.42 (d, J = 7.1 Hz, 3H, CH$_3$), 1.30 (m, 6H, R-H-3′ R-H-4′ R-H-5′), 0.88 (t, J = 7.0 Hz, 3H, R-H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.2 (COOH), 159.2 (d, J = 246.4 Hz, C-3), 154.6 (C-9), 151.7 (HNCOO), 143.9 (d, J = 8.0 Hz, C-7), 136.4 (C-1), 131.0 (d, J = 3.5 Hz, C-5), 129.9 (C-11), 126.2 (d, J = 13.1 Hz, C-4), 125.6 (C-10), 124.5 (d, J = 3.0 Hz, C-6), 122.3 (d, J = 2.6 Hz, C-8), 121.6 (C-12), 115.6 (d, J = 23.2 Hz, C-2), 44.5 (CH), 40.9 (R-C-1′), 31.4 (R-C-4′), 29.6 (R-C-2′), 26.3 (R-C-3′), 22.5 (R-C-5′), 18.7 (CH$_3$), 14.3 (R-C-6′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.60 min. MS (ES) C$_{22}$H$_{26}$FNO$_4$ requires 387, found 388 [M+H]$^+$. HRMS C$_{22}$H$_{27}$NO$_4$F [M+H]$^+$: calculated 388.1924 measured 388.1927 Δppm 0.8.

4.1.7.19. (±)-2-[3-fluoro-4-[3-(heptylcarbamoyloxy)phenyl]phenyl] propanoic acid (10s). Compound **10s** was prepared according to general procedure C using **9s** (160 mg, 0.38 mmol). The crude was purified by crystallization from pentane/Et$_2$O to afford **10s** as a white solid (85 mg, 55%). Mp: 104–105 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H, COOH), 7.77 (t, J = 5.7 Hz, 1H, NH), 7.50 (t, J = 8.0 Hz, H-5), 7.47 (t, J = 7.7 Hz, H-11), 7.37 (d, J = 7.7 Hz, 1H, H-10), 7.24 (m, 3H, H-2 H-6 H-8), 7.13 (dd, J = 8.0, 2.2 Hz, 1H, H-12), 3.78 (q, J = 7.1 Hz, 1H, CH), 3.06 (q, J = 6.8 Hz, 2H, R-H-1′), 1.47 (p,

J = 7.0 Hz, 2H, R-H-2′), 1.41 (d, J = 7.1 Hz, 3H, CH$_3$), 1.27 (m, 8H, R-H-3′ R-H-4′ R-H-5′ R-H-6′), 0.86 (t, J = 6.8 Hz, 3H, R-H-7′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.7 (COOH), 158.7 (d, J = 246.5 Hz, C-3), 154.1 (C-9), 151.2 (HNCOO), 143.4 (d, J = 7.6 Hz, C-7), 135.9 (C-1), 130.6 (d, J = 3.6 Hz, C-5), 129.4 (C-11), 125.7 (d, J = 13.1 Hz, C-4), 125.2 (C-10), 124.0 (d, J = 3.2 Hz, C-6), 121.8 (C-8), 121.1 (C-12), 115.1 (d, J = 23.3 Hz, C-2), 44.0 (CH), 40.4 (R-C-1′), 31.2 (R-C-4′), 29.1 (R-C-2′), 28.3 (R-C-5′), 26.1 (R-C-3′), 22.0 (R-C-6′), 18.2 (CH$_3$), 13.9 (R-C-7′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.70 min. MS (ES) C$_{23}$H$_{28}$FNO$_4$ requires 401, found 402 [M+H]$^+$. HRMS C$_{23}$H$_{29}$NO$_4$F [M+H]$^+$: calculated 402.2081 measured 402.2096 Δppm 3.7.

4.1.7.20. (±)-2-[3-fluoro-4-[3-(octylcarbamoyloxy)phenyl]phenyl] propanoic acid (10t). Compound **10t** was prepared according to general procedure C using **9t** (141 mg, 0.33 mmol). The crude was purified by crystallization from pentane/Et$_2$O to afford **10t** as a white solid (41 mg, 30%). Mp: 103–104 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.49 (s, 1H, COOH), 7.78 (t, J = 5.6 Hz, 1H, NH), 7.50 (t, J = 8.1 Hz, 1H, H-5), 7. 48 (t, J = 7.8 Hz, 1H, H-11), 7.39 (d, J = 7.3 Hz, 1H, H-10), 7.25 (m, 3H, H-2 H-6 H-8), 7.15 (d, J = 7.9 Hz, 1H, H-12), 3.79 (q, J = 7.1 Hz, 1H, Ch), 3.07 (q, J = 6.7 Hz, 2H, R-H-1′), 1.48 (p, J = 6.6 Hz, 2H, R-H-2′), 1.42 (d, J = 7.1 Hz, 3H, CH$_3$), 1.28 (d, J = 6.2 Hz, 10H, R-H-3′ R-H-4′ R-H-5′ R-H-6′ R-H-7′), 0.87 (t, J = 6.6 Hz, 3H, R-H-8′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.2 (COOH), 159.2 (d, J = 246.4 Hz, C-3), 154.6 (C-9), 151.7 (HNCOO), 143.9 (d, J = 8.0 Hz, C-7), 136.4 (C-1), 131.0 (d, J = 3.6 Hz, C-5), 129.9 (C-11), 126.23 (d, J = 13.1 Hz, C-4), 125.6 (C-10), 124.5 (d, J = 3.1 Hz, C-6), 122.3 (C-8), 121.6 (C-12), 115.6 (d, J = 23.3 Hz, C-2), 44.5 (CH), 40.9 (R-C-1′), 31.7 (R-C-6′), 29.6 (R-C-2′), 29.1 (R-C-4′), 29.1 (R-C-5′), 26.7 (R-C-3′), 22.5 (R-C-7′), 18.7 (CH$_3$), 14.4 (R-C-8′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.86 min. MS (ES) C$_{24}$H$_{30}$FNO$_4$ requires 415, found 416 [M+H]$^+$. HRMS C$_{24}$H$_{31}$NO$_4$F [M+H]$^+$: calculated 416.2237 measured 416.2249 Δppm 2.9.

4.1.7.21. (±)-2-[3-fluoro-4-[2-(hexylcarbamoyloxy)phenyl]phenyl] propanoic acid (15a). Compound **15a** was prepared according to general procedure C using **14a** (200 mg, 0.5 mmol). The crude was purified by preparative TLC (Cy/EtOAc, 5: 5) to afford **15a** as a white oil (175 mg, 90%). Mp: 61–63 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.47 (s, 1H, COOH), 7.55 (t, J = 5.7 Hz, 1H, NH), 7.42 (td, J = 7.6, 1.9 Hz, 1H, H-10), 7.36 (dd, J = 7.7, 1.9 Hz, 1H, H-12), 7.28 (m, 2H, H-5 H-11), 7.17 (m, 3H, H-2 H-6 H-9), 3.76 (q, J = 7.1 Hz, 1H, CH), 2.92 (q, J = 6.6 Hz, 2H, R-H-1′), 1.40 (d, J = 7.1 Hz, 3H, CH$_3$), 1.32 (p, J = 6.6 Hz, 2H, R-H-2′), 1.25 (m, 6H, R-H-3′ R-H-4′ R-H-5′), 0.86 (t, J = 6.8 Hz, 3H, R-H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.8 (COOH), 158.9 (d, J = 246.2 Hz, C-3), 154.0 (C-8), 148.5 (HNCOO), 143.2 (d, J = 7.5 Hz, C-7), 131.3 (C-5), 131.0 (C-12), 128.9 (C-10), 128.1 (C-1), 125.0 (C-11), 123.4 (C-9), 123.3 (C-6), 123.1 (C-4), 114.5 (d, J = 22.9 Hz, C-2), 44.1 (CH), 40.2 (R-C-1′), 30.8 (R-C-4′), 28.9 (R-C-2′), 25.6 (R-C-3′), 22.0 (R-C-5′), 18.3 (CH$_3$), 13.8 (R-C-6′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.47 min. MS (ES) C$_{22}$H$_{26}$FNO$_4$ requires 387, found 388 [M+H]$^+$. HRMS C$_{22}$H$_{27}$NO$_4$F [M+H]$^+$: calculated 388.1924 measured 388.1945 Δppm 5.4.

4.1.7.22. (±)-2-[3-fluoro-4-[4-(hexylcarbamoyloxy)phenyl]phenyl] propanoic acid (15b). Compound **15b** was prepared according to general procedure C using **14b** (146 mg, 036 mmol). The crude was purified by crystallization from Et$_2$O/Cy to afford **15b** as a white solid (65 mg, 46%). Mp: 136–137 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (s, 1H, COOH), 7.78 (t, J = 5.6 Hz, 1H, NH), 7.53 (d, J = 7.5, 2H, H-8 H-12), 7.48 (t, J = 8.3 Hz, 1H, H-5), 7.23 (m, 2H, H-2 H-6), 7.19 (d, J = 8.6 Hz, 2H, H-9 H-11), 3.77 (q, J = 7.1, 1H, CH), 3.06 (q, J = 6.7, 2H, R-H-1′), 1.47 (p, J = 6.7, 2H, R-H-2′), 1.41 (d, J = 7.4, 3H, CH$_3$), 1.29 (m,

6H, R-H-3′ R-H-4′ R-H-5′), 0.88 (t, $J = 6.7$, 3H, R-H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.8 (COOH), 158.8 (d, $J = 245.9$ Hz, C-3), 154.1 (C-10), 150.7 (HNCOO), 143.0 (d, $J = 8.0$ Hz, C-7), 131.4 (C-1), 130.5 (C-5), 129.5 (C-8 C-12), 125.9 (d, $J = 13.2$ Hz, C-4), 124.0 (C-6), 121.8 (C-9 C-11), 115.1 (d, $J = 23.3$ Hz, C-2), 44.0 (CH), 40.4 (R-C-1′), 30.9 (R-C-4′), 29.1 (R-C-2′), 25.8 (R-C-3′), 22.0 (R-C-5′), 18.2 (CH$_3$), 13.8 (R-C-6′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.59 min. MS (ES) $C_{22}H_{26}FNO_4$ requires 387, found 388 [M+H]$^+$. HRMS $C_{22}H_{27}NO_4F$ [M+H]$^+$: calculated 388.1924 measured 388.194 Δppm 4.1.

4.1.7.23. (±)-2-[3-fluoro-4-[3-(hexylcarbamoylamino)phenyl]phenyl]propanoic acid (15c).

Compound **15c** was prepared according to general procedure C using **14c** (117 mg, 0.29 mmol). The crude was purified by preparative TLC (DCM/MeOH, 9: 5) to afford **15c** as a white solid (43 mg, 38%). Mp: 84–85 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H, COOH), 8.49 (s, 1H, NH′), 7.59 (m, 1H, H-8), 7.43 (t, $J = 8.1$ Hz, 1H, H-5), 7.39 (d, $J = 8.8$ Hz, 1H, H-10), 7.30 (t, $J = 7.9$ Hz, 1H, H-11), 7.22 (d, $J = 2.5$ Hz, 1H, H-6), 7.20 (m, 1H, H-2), 7.04 (d, $J = 7.1$ Hz, 1H, H-12), 6.14 (t, $J = 5.6$ Hz, 1H, NH), 3.76 (q, $J = 7.1$ Hz, 1H, CH), 3.07 (q, $J = 6.6$ Hz, 2H, R-H-1′), 1.45 (m, 2H, R-H-2′), 1.40 (d, $J = 7.1$ Hz, 3H, CH$_3$), 1.29 (m, 6H, R-H-3′ R-H-4′ R-H-5), 0.87 (t, $J = 6.7$ Hz, 3H, R-H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.3 (COOH), 159.2 (d, $J = 245.8$ Hz, C-3), 155.6 (HNCONH′), 143.47 (d, $J = 8.0$ Hz, C-7), 141.3 (C-9), 135.7 (C-1), 130.9 (d, $J = 3.8$ Hz, C-5), 129.3 (C-11), 127.3 (d, $J = 13.2$ Hz, C-4), 124.3 (C-10), 121.7 (C-12), 118.2 (C-6), 117.4 (C-8), 115.5 (d, $J = 23.1$ Hz), 44.5 (CH), 39.5 (R-C-1′), 31.4 (R-C-4′), 30.1 (R-C-2′), 26.5 (R-C-2′), 22.5 (R-C-3′), 18.7 (CH$_3$), 14.4 (R-C-6′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.2. UPLC/MS analysis: Rt 2.32 min. MS (ES) $C_{22}H_{27}FN_2O_3$ requires 386, found 387 [M+H]$^+$. HRMS $C_{22}H_{28}N_2O_3F$ [M+H]$^+$: calculated 387.2084 measured 387.2091 Δppm 1.8.

4.1.7.24. (±)-2-[3-fluoro-4-[3-(hexoxycarbonylamino)phenyl]phenyl]propanoic acid (15d).

Compound **15d** was prepared according to general procedure C using **14d** (143 mg, 0.36 mmol). The crude was purified by preparative TLC (Cy/EtOAc, 5: 5) to afford **15d** as a white solid (82 mg, 59%). Mp: 63–64 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 1H, COOH), 9.70 (s, 1H, NH), 7.66 (s, 1H, H-8), 7.49 (d, $J = 8.3$ Hz, 1H, H-10), 7.42 (t, $J = 8.3$ Hz, 1H, H-5), 7.36 (t, $J = 7.9$ Hz, 1H, H-11), 7.23 (m, 1H, H-6), 7.21 (m, 1H, H-2), 7.14 (d, $J = 6.8$ Hz, 1H, H-12), 4.08 (t, $J = 6.6$ Hz, 2H, R-H-1′), 3.77 (q, $J = 7.1$ Hz, 1H, CH), 1.62 (p, $J = 6.7$ Hz, 2H, R-H-2′), 1.40 (d, $J = 7.1$ Hz, 3H, CH$_3$), 1.30 (m, 6H, R-H-3′ R-H-4′ R-H-5′), 0.87 (t, $J = 6.9$ Hz, 3H, R-H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.3 (COOH), 159.2 (d, $J = 246.1$ Hz, C-3), 154.1 (OCONH), 143.6 (d, $J = 8.0$ Hz, C-7), 139.9 (C-9), 135.8 (C-1), 130.9 (d, $J = 3.7$ Hz, C-5), 129.44 (C-11), 127.0 (d, $J = 13.2$ Hz, C-4), 124.4 (d, $J = 3.1$ Hz, C-6), 123.1 (C-12), 118.9 (C-8), 118.0 (C-10), 115.6 (d, $J = 23.4$ Hz, C-2), 64.7 (R-C-1′), 44.5 (CH), 31.3 (R-C-2′), 28.9 (R-C-4′), 25.5 (R-C-2′), 22.5 (R-C-3′), 18.7 (CH$_3$), 14.3 (R-C-6′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.2. UPLC/MS analysis: Rt 2.64 min. MS (ES) $C_{22}H_{26}FNO_4$ requires 387, found 388 [M+H]$^+$. HRMS $C_{22}H_{27}NO_4F$ [M+H]$^+$: calculated 388.1924 measured 388.1934 Δppm 2.6.

4.1.7.25. 2-[3-Fluoro-4-[3-(hexylcarbamoyloxy)phenyl]phenyl]acetic acid (18b).

Compound **18b** was prepared according to general procedure C using **18a** (123 mg, 0.32 mmol). The crude was purified by crystallization from pentane/Et$_2$O to afford **18b** as a white solid (73 mg, 62%). Mp: 90–92 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.44 (s, 1H, COOH), 7.77 (t, $J = 5.7$ Hz, 1H, NH), 7.48 (t, $J = 8.1$ Hz, 1H, H-5), 7.47 (t, $J = 8.0$ Hz, 1H, H-11), 7.37 (dq, $J = 7.8$, 1.5 Hz, 1H, H-10), 7.23 (m, 2H, H-2 H-8), 7.20 (dd, $J = 7.9$, 1.7 Hz, 1H, H-6), 7.13 (ddd, $J = 8.1$, 2.4, 1.0 Hz, 1H, H-12), 3.66 (s, 2H, CH$_2$), 3.06 (td, $J = 7.1$, 5.8 Hz, 2H, R-H-1′), 1.47 (p, $J = 7.1$ Hz, 2H, R-H-2′), 1.29 (m, 6H, R-H-3′ R-H-4′ R-H-

5′), 0.87 (t, $J = 7.0$ Hz, 3H, R-H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.1 (COOH), 158.6 (d, $J = 245.9$ Hz, C-3), 154.2 (C-9), 151.2 (HNCOO), 137.2 (d, $J = 8.4$ Hz, C-7), 136.0 (C-1), 130.3 (d, $J = 3.5$ Hz, C-5), 129.4 (C-11), 126.0 (d, $J = 3.1$ Hz, C-6), 125.5 (d, $J = 13.2$ Hz, C-4), 125.2 (C-10), 121.8 (C-8), 121.1 (C-12), 117.1 (d, $J = 23.2$ Hz, C-2), 40.4 (CH), 39.8 (R-C-1′), 30.9 (R-C-4′), 29.1 (R-C-2′), 25.9 (R-C-3′), 22.0 (R-C-5′), 13.8 (R-C-6′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 118.0. UPLC/MS analysis: Rt 2.43 min. MS (ES) $C_{20}H_{24}FNO_2$ requires 373, found 374 [M+H]$^+$. HRMS $C_{21}H_{25}NO_4F$ [M+H]$^+$: calculated 374.1768 measured 374.1763 Δppm −1.3.

4.1.7.26. 3-fluoro-4-[3-(hexylcarbamoyloxy)phenyl]benzoic acid (21c).

Compound **21c** was prepared according to general procedure C using **21b** (1.27 g, 3.40 mmol). Mp: 180–181 °C. The crude was purified by column chromatography (DCM/MeOH, 99: 1) to afford **21b** as a white solid (0.41 g, 34%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.32 (s, 1H, COOH), 7.85 (dd, $J = 8.0$, 1.4 Hz, 1H, H-6), 7.80 (t, $J = 5.7$ Hz, 1H, NH), 7.76 (dd, $J = 11.3$, 1.2 Hz, 1H, H-2), 7.68 (t, $J = 7.9$ Hz, 1H, H-5), 7.51 (t, $J = 7.9$ Hz, 1H, H-11), 7.44 (dq, $J = 7.7$, 1.5 Hz, 1H, H-12), 7.32 (q, $J = 1.7$ Hz, 1H, H-8), 7.19 (ddd, $J = 8.0$, 2.4, 1.1 Hz, 1H, H-10), 3.06 (td, $J = 7.1$, 6.0 Hz, 2H, R-H-1′), 1.46 (p, $J = 6.8$ Hz, 2H, R-H-2′), 1.28 (m, 6H, R-H-3′ R-H-4′ R-H-5′), 0.87 (t, $J = 6.6$ Hz, 3H, R-H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0 (COOH), 158.7 (d, $J = 247.8$ Hz, C-3), 154.2 (C-9), 151.3 (HNCOO), 135.2 (C-1), 132.3 (d, $J = 6.6$ Hz, C-7), 131.6 (d, $J = 13.4$ Hz, C-4), 131.1 (C-5), 129.6 (C-11), 125.7 (C-6), 125.4 (C-12), 122.1 (C-8), 122.0 (C-10), 116.7 (d, $J = 24.3$ Hz, C-2), 40.5 (R-C-1′), 30.9 (R-C-4′), 29.1 (R-C-2′), 25.9 (R-C-3′), 22.0 (R-C-5′), 13.9 (R-C-6′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 116.4. UPLC/MS analysis: Rt 2.28 min. MS (ES) $C_{20}H_{22}FNO_4$ requires 359, found 360 [M+H]$^+$. HRMS $C_{20}H_{23}NO_4F$ [M+H]$^+$: calculated 360.1611 measured 360.1617 Δppm 1.7.

4.1.7.27. (±)-2-[3-chloro-4-[3-(hexylcarbamoyloxy)phenyl]phenyl]propanoic acid (29a).

Compound **29a** was prepared according to general procedure C using **28a** (2.12 g, 5.07 mmol). The crude was purified by column chromatography (DCM/MeOH, 98: 2) to give **29a** as a white solid (1.95 g, 98%). Mp: 48–59 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.49 (s, 1H, COOH), 7.76 (t, $J = 5.6$ Hz, 1H, NH), 7.48 (d, $J = 1.4$ Hz, 1H, H-2), 7.45 (t, $J = 8.3$ Hz, 1H, H-11), 7.39 (d, $J = 7.9$ Hz, 1H, H-5), 7.34 (dd, $J = 8.0$ Hz 1.4 Hz, 1H, H-6), 7.26 (d, $J = 7.7$ Hz, 1H, H-10), 7.14 (m, 2H, H-8 H-12), 3.78 (q, $J = 7.1$ Hz, 1H, CH), 3.05 (q, $J = 6.7$ Hz, 2H, R-H-1′), 1.46 (p, $J = 7.3$ Hz, 2H, R-H-2′), 1.41 (d, $J = 7.1$ Hz, 3H, CH$_3$), 1.29 (m, 6H, R-H-3′ R-H-4′ R-H-5′), 0.87 (t, $J = 6.7$ Hz, 3H, R-H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.8 (COOH), 154.1 (C-9), 150.8 (NHCOO), 142.7 (C-7), 139.4 (C-1), 137.3 (C-3), 131.4 (C-5), 131.0 (C-4), 129.0 (C-11), 128.9 (C-2), 126.7 (C-6), 125.7 (C-10), 122.3 (C-12), 121.0 (C-8), 43.9 (CH), 40.4 (R-C-1′), 30.9 (R-C-4′), 29.1 (R-C-2′), 25.9 (R-C-3′), 22.0 (R-C-5′), 18.3 (CH$_3$), 13.9 (R-C-6′). UPLC/MS analysis: Rt 1.24 min. MS (ES) $C_{22}H_{26}ClNO_4$ requires 403, found 404, 406 [M+H]$^+$, 402, 404 [M−H]$^-$. HRMS $C_{22}H_{27}NO_4Cl$ [M+H]$^+$: calculated 404.1629; measured 404.1644 Δppm 3.7.

4.1.7.28. (±)-2-[4-[3-(hexylcarbamoyloxy)phenyl]-3-methyl-phenyl]propanoic acid (29b).

Compound **29b** was prepared according to general procedure C using **28b** (0.94 g, 2.36 mmol). The crude was purified by column chromatography (DCM/MeOH, 98: 2) to give **29b** as a white solid (0.76 g, 84%). Mp: 89–90 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H, COOH), 7.75 (t, $J = 5.7$ Hz, 1H, NH), 7.43 (t, $J = 7.9$ Hz, 1H, H-11), 7.22 (s, 1H, H-2), 7.17 (m, 3H, H-5 H-6 H-10), 7.09 (ddd, $J = 8.1$, 2.4, 1.0 Hz, 1H, H-12), 7.05 (m, 1H, H-8), 3.69 (q, $J = 7.1$ Hz, 1H, CH), 3.06 (q, $J = 6.8$ Hz, 2H, R-H-1′), 2.24 (s, 3H, Ph-CH$_3$), 1.47 (p, $J = 7.3$ Hz, 2H, R-H-2′), 1.40 (d, $J = 7.1$ Hz, 3H, CH$_3$), 1.29 (m, 6H, H-3′ H-4′ H-5′), 0.88 (t, $J = 6.8$ Hz, 3H, H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.2 (COOH), 154.2 (C-9), 150.9 (HNCOO),

142.0 (C-7), 140.4 (C-1), 138.9 (C-3), 134.7 (C-4), 129.5 (C-5), 129.4 (C-2), 129.0 (C-11), 125.4 (C-6), 125.0 (C-10), 122.1 (C-8), 120.1 (C-12), 44.3 (CH), 40.4 (R-C-1'), 30.9 (R-C-4'), 29.1 (R-C-2'), 25.9 (R-C-3'), 22.0 (R-C-5'), 20.1 (Ph-CH$_3$), 18.4 (CH$_3$), 13.9 (R-C-6'). UPLC/MS analysis: Rt 2.70 min. MS (ES) C$_{23}$H$_{29}$NO$_4$ requires 383, found 384 [M+H]$^+$, 382 [M−H]$^−$. HRMS C$_{23}$H$_{30}$NO$_4$ [M+H]$^+$: calculated 384.2175; measured 384.2177 Δppm 0.5.

4.1.7.29. (±)-2-[4-[3-(hexylcarbamoyloxy)phenyl]-3-(tri-fluoromethyl)phenyl]propanoic acid (29c). Compound **29c** was prepared according to general procedure C using **28c** (1.02 g, 2.26 mmol). The crude was purified by column chromatography (DCM/MeOH, 98: 2) to give **29c** as a white solid (0.8 g, 81%). Mp: 95−97 °C [dec]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (s, 1H, COOH), 7.75 (t, J = 5.7 Hz, 1H, NH), 7.73 (d, J = 1.7 Hz, 1H, H-2), 7.64 (dd, J = 8.0, 1.6 Hz, 1H, H-6), 7.43 (t, J = 7.9 Hz, 1H, H-11), 7.39 (d, J = 7.9 Hz, 1H, H-5), 7.15 (m, 2H, H-10 H-12), 7.02 (s, 1H, H-8), 3.91 (q, J = 7.1 Hz, 1H, CH), 3.05 (q, J = 6.9 Hz, 2H, R-H-1'), 1.47 (p, J = 6.9 Hz, 2H, R-H-2'), 1.44 (d, J = 7.3 Hz, 1H, CH$_3$), 1.27 (m, 6H, R-H-3' R-H-4' R-H-5'), 0.85 (t, J = 6.6 Hz, 3H, R-H-6'). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.8 (COOH), 154.0 (C-9), 150.5 (HNCOO), 141.4 (C-7), 140.0 (C-4), 138.2 (C-1), 132.3 (C-5), 131.3 (C-6), 128.8 (C-11), 126.7 (q, J = 29.1 Hz, C-3), 125.2 (C-10), 125.1 (C-2), 124.0 (q, J = 274.2 Hz, CF$_3$), 121.8 (C-8), 121.1 (C-12), 44.0 (CH), 40.4 (R-C-1'), 30.9 (R-C-4'), 29.1 (R-C-2'), 25.9 (R-C-3'), 22.0 (R-C-5'), 18.3 (CH$_3$), 13.8 (R-C-6'). ^{19}F NMR (564 MHz, DMSO-d_6): δ 54.3. UPLC/MS analysis: Rt 2.63 min. MS (ES) C$_{24}$H$_{28}$F$_3$NO$_3$ requires 437, found 438 [M+H]$^+$, 436 [M−H]$^−$. HRMS C$_{23}$H$_{27}$NO$_4$F$_3$ [M+H]$^+$: calculated 438.1892; measured 438.189 Δppm −0.5.

4.1.7.30. (±)-2-[4-[3-(hexylcarbamoyloxy)phenyl]phenyl]propanoic acid (29e). Compound **29e** was prepared according to general procedure C using **28e** (123 mg, 0.32 mmol). The crude was purified by crystallization from Et$_2$O/pentane to afford **29e** as a white solid (73 mg, 62%). Mp: 125−127 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H, COOH), 7.76 (t, J = 5.7 Hz, 1H, NH), 7.62 (d, J = 8.2 Hz, 2H, H-3 H-5), 7.42 (d, J = 8.2 Hz, 1H, H-12), 7.44 (t, J = 7.7 Hz, 1H, H-11), 7.38 (d, J = 8.2 Hz, 2H, H-2 H-6), 7.34 (s, 1H, H-8), 7.08 (d, J = 7.7 Hz, 1H, H-10), 3.73 (q, J = 7.1 Hz, 1H, CH), 3.06 (q, J = 6.8 Hz, 2H, R-H-1'), 1.47 (p, J = 6.9 Hz, 2H, R-H-2'), 1.39 (d, J = 7.1 Hz, 3H, CH$_3$), 1.29 (m, 6H, R-H-3' R-H-4' R-H-5'), 0.88 (t, J = 6.7 Hz, 3H, R-H-6'). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.7 (COOH), 154.7 (C-9), 152.1 (HNCOO), 141.6 (C-7), 141.2 (C-4), 138.3 (C-1), 130.1 (C-11), 128.5 (C-2 C-6), 127.2 (C-3 C-5), 123.5 (C-12), 121.1 (C-10), 120.2 (C-8), 44.7 (CH), 40.9 (R-C-1'), 31.4 (R-C-4'), 29.6 (R-C-2'), 26.3 (R-C-3'), 22.5 (R-C-5'), 18.9 (CH$_3$), 14.3 (R-C-6'). UPLC/MS analysis: Rt 2.30 min. MS (ES) C$_{22}$H$_{27}$NO$_4$ requires 369, found 370 [M+H]$^+$. HRMS C$_{22}$H$_{28}$NO$_4$ [M+H]$^+$: calculated 370.2018; measured 370.2027 Δppm 2.4.

4.1.7.31. (±)-2-[4-[3-(hexylcarbamoyloxy)phenyl]-3-nitro-phenyl] propanoic acid (29f). Compound **29f** was prepared according to general procedure C using **28f** (0.26 g, 0.51 mmol). The crude was purified by column chromatography (DCM/MeOH, 97: 3) to give **29f** as a cream colored solid (870 mg, 77%). Mp: 93−94 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.66 (s, 1H, COOH), 7.91 (d, J = 1.7 Hz, 1H, H-2), 7.79 (t, J = 5.7 Hz, 1H, NH), 7.69 (dd, J = 8.0, 1.7 Hz, 1H, H-6), 7.53 (d, J = 8.0 Hz, 1H, H-5), 7.44 (t, J = 7.9 Hz, 1H, H-11), 7.16 (m, 2H, H-10 H-12), 7.07 (t, J = 1.9 Hz, 1H, H-8), 3.92 (q, J = 7.1 Hz, 1H, CH), 3.05 (q, J = 6.8 Hz, 2H, R-H-1'), 1.46 (p, J = 7.1 Hz, 2H, R-H-2'), 1.45 (d, J = 7.2 Hz, 3H, CH$_3$), 1.28 (m, 6H, R-H-3' R-H-4' R-H-5'), 0.86 (t, J = 7.1 Hz, 3H, R-H-6'). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.6 (COOH), 154.0 (C-9), 151.2 (HNCOO), 148.6 (C-3), 142.6 (C-7), 137.8 (C-1), 132.7 (C-4), 132.1 (C-6), 131.9 (C-5), 129.6 (C-11), 124.3 (C-12), 123.2 (C-2), 121.6 (C-10), 120.9 (C-8), 43.9 (CH), 40.5 (R-C-1'), 30.9

(R-C-4'), 29.1 (R-C-2'), 25.9 (R-C-3'), 22.0 (R-5'), 18.2 (CH$_3$), 13.9 (R-C-6'). UPLC/MS analysis: Rt 2.44 min. MS (ES) C$_{22}$H$_{26}$N$_2$O$_6$ requires 414, found 415 [M+H]$^+$, 369 [M−H − CO$_2$]$^−$. HRMS C$_{22}$H$_{27}$N$_2$O$_6$ [M+H]$^+$: calculated 415.1869; measured 415.188 Δppm 2.6.

4.1.8. (±)-3-[2-fluoro-4-(2-hydroxy-1-methyl-ethyl)phenyl]phenol (11)
To a solution of ZrCl$_4$ (291 mg, 1.25 mmol) in THF (5 mL), NaBH$_4$ (189 mg, 5 mmol) was added at rt. Upon mixing the reagents, gas evolution is immediately observed and a cream colored suspension was obtained. A solution of **8** (274 mg, 1 mmol) in THF (1 mL) was added and the mixture was stirred at rt for 2 h. The reaction was carefully quenched by the addition of 2 M HCl (5 mL) and then extracted with EtOAc. The solvent was removed under reduced pressure and the residue was purified by column chromatography (Cy/EtOAc, 7: 3) to afford **11** as a white solid (235 mg, 96%).

4.1.9. (±)-Methyl 2-[3-fluoro-4-[3-(hexoxycarbonylamino)phenyl] phenyl]propanoate (14d)
To a suspension of **13c** (114 mg, 0.44 mmol) in toluene (10 mL), triphosgene was added (392 mg, 1.32 mmol) and the resulting mixture was refluxed for 15 h n-hexanol (224 mg, 2.20 mmol) was added and stirring was continued at rt for further 15 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (Cy/EtOAc, 9:1) to afford **14d** as a white solid (145 mg, 82%).

4.1.10. Methyl 2-(3-fluoro-4-iodo-phenyl)acetate (16b)
To a solution of **16a** (1 g, 3.57 mmol) in MeOH (54 mL), concentrated H$_2$SO$_4$ (0.1 mL) was added and the resulting solution was stirred at rt overnight. After solvent evaporation, the crude oil was diluted with Et$_2$O (15 mL) and filtered through a pad of SiO$_2$ to afford **16b** as a yellow liquid (1.03 g, quant.).

4.1.11. (±)-2-(3-chloro-4-nitro-phenyl)propanoic acid (23a)
Step 1: To a solution of **22a** (4.70 g, 27.0 mmol) and diethyl methylmalonate (4.13 mL, 25.0 mmol) in DMF (31 mL), NaOH (1.11 g, 28 mmol) was added. The mixture was stirred at rt for 15 h. The dark red solution was poured into ice, acidified with concentrated HCl (4 mL) and extracted with TBME. The organic solvent was washed with brine, dried over Na$_2$SO$_4$ and evaporated under reduced pressure to give orange oil (8.24 g) which was used for the next step without any further purification.
Step 2: H$_2$O (25 mL), AcOH (38 mL) and H$_2$SO$_4$ (13 mL) were added to the orange oil (8.24 g, 25 mmol) and the reaction mixture was refluxed for 24 h. AcOH was removed under reduced pressure, and the mixture was extracted with DCM. The organic layer was then extracted with a saturated aqueous Na$_2$CO$_3$ solution and the aqueous layer was acidified with 1N HCl, and extracted with DCM. The organic layer was dried over Na$_2$SO$_4$ and evaporated to give **23a** as an orange oil (5.00 g, 87%).

4.1.12. (±)-Methyl 2-(3-chloro-4-nitro-phenyl)propanoate (24a)
23a (5.00 g, 21.78 mmol) was dissolved in MeOH (27 mL), H$_2$SO$_4$ (58 mL, 1.09 mmol) was added and the mixture was stirred for 15 h. The solvent was removed under reduced pressure and the residue taken up in TBME, activated carbon was added and then the mixture passed through an allumina pad. The solvent was removed under reduced pressure to give **24a** as a yellow oil (4.57 g, 86%).

4.1.13. (±)-Methyl 2-(4-amino-3-chloro-phenyl)propanoate (25a)
Iron powder (4.19 g, 75 mmol) was added to a solution of **24a** (4.57 g, 18.76 mmol) in MeOH/HCl (7:1, 40 mL). The mixture was refluxed for 2 h, then filtered through a pad of Celite. The solvent

was removed under reduced pressure and taken up in H$_2$O, the thick slurry was basified with K$_2$CO$_3$, EtOAc was added, filtered through a pad of Celite and the two phases separated. The organic layer was dried over Na$_2$SO$_4$ and evaporated to give **25a** as an orange oil (2.57 g, 64%).

4.1.14. (±)-Methyl 2-(3-chloro-4-iodo-phenyl)propanoate (26a)

A solution of NaNO$_2$ (0.91 g, 13.2 mmol) in H$_2$O (2 mL) was added slowly to a solution of **25a** (2.57 g, 12.03 mmol) in a mixture of 2N HCl (54 mL) and dioxane (24 mL) at 0 °C. After stirring for 15 min at 0 °C, NaI (1.98 g, 13.23 mmol) was added, and then the mixture was stirred for 15 h, after which Na$_2$SO$_3$ was added. The solution was extracted with TBME, dried over Na$_2$SO$_4$, passed through an alumina pad and evaporated. The residue was purified by column chromatography (Cy: EtOAc, 95: 5) to obtain **26a** as a colorless oil (2.74 g, 70%).

4.1.15. (±)-2-(3-methyl-4-nitro-phenyl)propanoic acid (23b)

Step 1: To a solution of **22b** (3.26 mL, 26.75 mmol) and diethyl methylmalonate (4.59 mL, 25 mmol) in DMF (31 mL), NaOH (1.11 g, 27.75 mmol) was added. The mixture was stirred at rt for 15 h. The dark red solution was poured into ice, acidified with concentrated HCl (10 mL) and extracted with Et$_2$O. The organic solvent was washed with brine, dried over Na$_2$SO$_4$ and evaporated under reduced pressure to give yellow oil (7.73 g) which was used for the next step without any further purification.

Step 2: H$_2$O (25 mL), AcOH (41 mL) and H$_2$SO$_4$ (12 mL) were added to the oil (7.73 g, 25 mmol) and the mixture was refluxed for 24 h. AcOH was removed under reduced pressure and the product was extracted with DCM and washed with brine. The organic layer was treated with aqueous K$_2$CO$_3$, and the separated aqueous layer was acidified with concentrated HCl, extracted with DCM, washed with brine and dried over Na$_2$SO$_4$. After removal of the solvent **23b** was obtained as brown clear oil (2.50 g, 48%) which was used for the next step without any further purification.

4.1.16. (±)-Methyl 2-(3-methyl-4-nitro-phenyl)propanoate (24b)

To a solution of **23b** (2.5 g, 11.95 mmol) in MeOH (120 mL), H$_2$SO$_4$ (0.22 mL, 1.2 mmol) was added and the mixture was stirred at rt for 15 h. The solvent was removed under reduced pressure and the residue was dissolved in Et$_2$O and passed through a pad of alumina. The solvent was evaporated to obtain **24b** as a yellow oil (2.17 g, 81%).

4.1.17. (±)-Methyl 2-(4-amino-3-methyl-phenyl)propanoate (25b)

To a mixture of **24b** (2.17 g, 9.72 mmol) and Pd/C (0.52 g, 0.49 mmol), HCO$_2$NH$_4$ (3.68 g, 58.33 mmol) was added and stirred for 1 h. The catalyst was filtered through a pad of Celite and the solvent evaporated. The residue was taken up in EtOAc, passed through a pad os SiO$_2$ and evaporated to **25b** as a yellow oil (1.85 g, 98%).

4.1.18. (±)-Methyl 2-(4-iodo-3-methyl-phenyl)propanoate (26b)

A solution of NaNO$_2$ (0.71 g, 10.24 mmol) in H$_2$O (2 mL) was added slowly to a solution of **25b** (1.85 g, 9.57 mmol) in 2N HCl (43 mL) at 0 °C. After stirring for 30 min a solution of NaI (2.15 g, 14.36 mmol) was added dropwise and the mixture was allowed to reach rt and stirred for 2 h, then warmed to 60 °C for other 2 h Na$_2$SO$_3$ was added and the product was extracted with Et$_2$O, dried over Na$_2$SO$_4$ and evaporated. The residue was purified by column chromatography (Cy/EtOAc, 95: 5) to give **26b** as clear oil (1.14 g, 39%).

4.1.19. (±)-2-[4-nitro-3-(trifluoromethyl)phenyl]propanoic acid (23c)

Step 1: To a solution of **22c** (3.74 mL, 26.75 mmol) and diethyl methylmalonate (4.13 mL, 25 mmol) in DMF (30 mL), NaOH (1.11 g, 27.75 mmol) was added. The mixture was stirred at rt for 15 h. The mixture was stirred at rt for 15 h. The dark red solution was poured into ice, acidified with concentrated HCl (4 mL) and extracted with TBME. The organic solvent was washed with brine, dried over Na$_2$SO$_4$ and evaporated under reduced pressure to give orange oil (9.1 g) which was used for the next step without any further purification. *Step 2*: H$_2$O (25 mL), AcOH (37 mL) and H$_2$SO$_4$ (12 mL) were added to the orange oil and the mixture was refluxed for 24 h. AcOH was removed under reduced pressure, and the mixture was extracted with DCM. The organic layer was then extracted with a saturated aqueous Na$_2$CO$_3$ solution and the aqueous layer was acidified with 1N HCl, and extracted with DCM. The organic layer was dried over Na$_2$SO$_4$ and evaporated to give **23c** as an orange oil (5.59 g, 85%).

4.1.20. (±)-Methyl 2-[4-nitro-3-(trifluoromethyl)phenyl] propanoate (24c)

23c (5.59 g, 21.24 mmol) was dissolved in MeOH (28 mL), H$_2$SO$_4$ (58 mL, 1.06 mmol) was added and the mixture was stirred for 19 h. The solvent was removed under reduced pressure and the residue taken up in TBME, activated carbon was added and then the mixture passed through an allumina pad. The solvent was removed under reduced pressure to give **24c** as an orange oil (5.70 g, 97%).

4.1.21. (±)-Methyl 2-[4-amino-3-(trifluoromethyl)phenyl] propanoate (25c)

To a mixture of **24c** (5.59 g, 20.17 mmol) and Pd/C (1.07 g, 1.01 mmol) in MeOH (100 mL) HCO$_2$NH$_4$ (7.63 g, 121.00 mmol) was added and stirred at rt for 1 h. The catalyst was filtered through a pad of Celite and the solvent evaporated. The residue was taken up in EtOAc, passed through a pad os SiO$_2$ and evaporated to **25c** as a dark red oil (4.94 g, quant.).

4.1.22. (±)-Methyl 2-[4-iodo-3-(trifluoromethyl)phenyl]propanoate (26c)

A solution of NaNO$_2$ (1.48 g, 21.38 mmol) in H$_2$O (4 mL) was added slowly to a solution of **25c** (4.94 g, 19.98 mmol) in 2N HCl (90 mL) at 0 °C. After stirring for 30 min a solution of NaI (4.49 g, 29.97 mmol) was added dropwise and the mixture was allowed to reach rt and stirred for 2 h, then warmed to 60 °C for other 2 h Na$_2$SO$_3$ was added and the product was extracted with TBME, dried over Na$_2$SO$_4$ and evaporated. The residue was purified by column chromatography (Cy: EtOAc, 95: 5) to give **26c** as clear oil (5.51 g, 77%).

4.1.23. (±)-2-[4-[3-(hexylcarbamoyloxy)phenyl]-3-hydroxy-phenyl]propanoic acid (29d)

To a solution of **28d** (0.72 g, 1.49 mmol) in EtOH (29 mL), Pd/C (78 mg, 74 mmol) and cyclohexene (9 mL, 88 mmol) were added and the mixture was stirred at 80 °C for 2 h. The catalyst was filtered through a pad of Celite and the solvent was removed under reduced pressure. The residue oil was taken up in dioxane (15 mL), 2 M HCl (15 mL) was added and the solution was stirred at 80 °C for 15 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (DCM/MeOH, 98: 2) to obtain **29d** as a white solid (414 mg, 73%). Mp: 61–62 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 1H, COOH), 9.63 (s, 1H, OH), 7.74 (t, J = 5.7 Hz, 1H, NH), 7.38 (m, 2H, H-11 H-12), 7.25 (m, 1H, H-8), 7.22 (d, J = 7.9 Hz, 1H, H-5), 7.02 (m, 1H, H-10), 6.90 (d, J = 1.5 Hz, 1H, H-11), 6.81 (dd, J = 7.9, 1.5 Hz, 1H, H-2), 3.61 (q, J = 7.0 Hz, 1H, CH), 3.06 (q, J = 6.8 Hz, 2H, R-H-1′), 1.47 (p, J = 7.5 Hz, 2H, R-H-2′),

1.36 (d, J = 7.1 Hz, 3H, CH$_3$), 1.28 (m, 6H, R-H-3′ R-H-4′ R-H-5′), 0.88 (t, J = 6.8 Hz, 3H, R-H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.2 (COOH), 154.3 (C-9), 154.2 (C-3), 150.8 (HNCOO), 141.9 (C-7), 139.4 (C-1), 130.20 (C-5), 128.6 (C-11), 125.4 (C-12), 125.3 (C-4), 122.0 (C-8), 119.8 (C-10), 118.7 (C-6), 114.9 (C-2), 44.4 (CH), 40.4 (R-C-1′), 30.9 (R-C-4′), 29.2 (R-C-2′), 25.9 (R-C-3′), 22.0 (R-C-5′), 18.4 (CH$_3$), 13.9 (R-C-6′). UPLC/MS analysis: Rt 2.33 min. MS (ES) C$_{22}$H$_{27}$NO$_5$ requires 385, found 386 [M+H]$^+$, 384 [M−H]$^-$. HRMS C$_{22}$H$_{28}$NO$_5$ [M+H]$^+$: calculated 386.1967; measured 386.1975 Δppm 2.1.

4.1.24. (±)-Methyl 2-(4-nitrophenyl)propanoate (**24e**)

To a solution of **23e** (1.95 g, 10 mmol) in MeOH (20 mL), concentrated H$_2$SO$_4$ (0.1 mL) was added and the resulting solution was stirred overnight at rt. After solvent evaporation, the crude oil was diluted with Et$_2$O (15 mL) and filtered through a pad of SiO$_2$ to afford **24e** as yellow oil (2.10 g, quant.)

4.1.25. (±)-Methyl 2-(4-aminophenyl)propanoate (**25e**)

To a solution of **24e** (1.05 g, 5 mmol) in MeOH (20 mL) was added 10% Pd/C (0.37 g, 0.35 mmol) followed by the addition of HCO$_2$NH$_4$ (1.9 g, 30 mmol). The solution was stirred at rt for 1 h. The solution was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc and filtered through a pad of SiO$_2$ to afford **25e** as an off-white solid (0.89 g, quant.).

4.1.26. (±)-Methyl 2-(4-iodophenyl)propanoate (**26e**)

A solution of NaNO$_2$ (0.69 g, 10 mmol) in H$_2$O (1.5 mL) was added slowly to a solution of **25e** (1.75 g, 9.76 mmol) in 28 mL of 3N HCl at 0 °C. After stirring for 1 h at 0 °C, NaI (1.50 g, 10 mmol) was added. The resultant mixture was slowly warmed to rt for 5 min, and heated at 60 °C for 2 h. After cooling down to rt, the mixture was extracted with Et$_2$O and the organic phase was then washed with a 1 M solution of Na$_2$SO$_3$ (20 mL), dried over Na$_2$SO$_4$. After evaporation, the residue was dissolved in EtOAc (40 mL) and treated with activated carbon and filtered through a pad of Celite. The solvent was removed under reduced pressure and the orange oil was purified by column chromatography (Cy/EtOAc, 95:5) to give **26e** as a clear oil (2.05 g, 72%).

4.1.27. (±)-Methyl 2-(4-amino-3-nitro-phenyl)propanoate (**25f**)

Step 1: A solution of **25e** (3.58 g, 20 mmol) in Ac$_2$O (100 mL) was heated at 130 °C for 1 h. The solution was poured into H$_2$O, stirred for 3 h, then evaporated. The residual solid was taken up in H$_2$O and filtered under vaccum to obtain a yellow solid. This solid was dissolved in MeOH (100 mL) and 37% HCl (5 mL) was added. The solution was stirred for 2 h and the organic solvent was removed under reduced pressure. H$_2$O was added and the precipitate was filtered under vacuum and washed with H$_2$O to obtain methyl 2-(4-acetamidophenyl)propanoate as a cream colored solid (2.21 g, 50%).

Step 2: (±)-Methyl 2-(4-acetamidophenyl)propanoate (2.21 g, 10 mmol) in Ac$_2$O (10 mL) was cooled to 0 °C. HNO$_3$ (1 mL, 14 mmol) was added and the mixture was stirred for 2 h. The yellow solution was poured in ice while stirring was continued. The aqueous layer was extracted with DCM, the organic layer was evaporated and the residue was taken up in DCM and washed with saturated aqueous NaHCO$_3$ solution, dried over Na$_2$SO$_4$ and evaporated to give (±)-methyl 2-(4-acetamido-3-nitro-phenyl)propanoate as a dark orange oil (2.60 g, 98%). *Step 3*: To a solution of (±)-methyl 2-(4-acetamido-3-nitro-phenyl)propanoate (2.60 g, 9.77 mmol) in MeOH (98 mL) H$_2$SO$_4$ (10 mL, 183 mmol) was added and the mixture was stirred at reflux for 2 h. MeOH was evaporated under reduced pressure and the solution was carefully poured into a aqueous solution of Na$_2$CO$_3$ (2 M, 120 mL), then extracted with EtOAc, dried over Na$_2$SO$_4$ and evaporated to give **25f** as a dark orange oil (2.20 g, quant.) which was used in the next step without further purification.

4.1.28. (±)-Methyl 2-(4-iodo-3-nitro-phenyl)propanoate (**26f**)

A solution of NaNO$_2$ (0.74 g, 10.79 mmol) in H$_2$O (2 mL) was added slowly to a solution of **25f** (2.20 g, 9.81 mmol) in a mixture of 2N HCl (44 mL) and dioxane (20 mL) at 0 °C. After stirring for 5 min at 0 °C, NaI (1.47 g, 9.81 mmol) was added and the reaction mixture was stirred for 30 min, after which Na$_2$SO$_3$ was added. The solution was extracted with TBME, dried over Na$_2$SO$_4$ and evaporated. The residue which was purified by column chromatography (Cy: EtOAc, 95: 5) to obtain **26f** as a yellow oil (1.00 g, 30%).

4.1.29. (±)-2-[3-amino-4-[3-(hexylcarbamoyloxy)phenyl]phenyl] propanoic acid hydrochloride (**29g**)

To a solution of **29g** (0.87 g, 2.10 mmol) in MeOH (21 mL), Pd/C (223 mg, 0.21 mmol), cyclohexene (5.32 mL, 52.48 mmol) were added and the solution was stirred at 80 °C for 2 h. The mixture was filtered through a pad of Celite and the solvent removed under reduced pressure to give a residue which was purified by column chromatography (DCM/MeOH, 96: 4) to obtain a glassy oil, which was dissolved in dioxane (10 mL) and concentrated HCl (1 mL) was added. The solvent was removed under reduced pressure and the residue oil was suspended in DCM and Et$_2$O. The solid was filtered under vacuum to obtain **29g** as an off-white solid (488 mg, 55%). Mp: 180 °C [dec]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.51 (s, 1H, COOH), 7.79 (t, J = 5.7 Hz, 1H, NH), 7.48 (t, J = 7.9 Hz, 1H, H-11), 7.35 (d, J = 7.8 Hz, 1H, H-12), 7.29 (d, J = 7.6 Hz, 2H, H-2 H-5), 7.22 (m, 2H, H-6 H-8), 7.16 (dd, J = 8.0, 1.9 Hz, 1H, H-10), 3.73 (q, J = 7.0 Hz, 1H, CH), 3.05 (q, J = 6.8 Hz, 2H, R-H-1′), 1.45 (p, J = 7.3 Hz, 2H, R-H-2′), 1.39 (d, J = 7.1 Hz, 3H, CH$_3$), 1.29 (m, 6H, R-H-3′ R-H-4′ R-H-5′), 0.87 (t, J = 6.7 Hz, 3H, R-H-6′), NH$_3^+$ not visible. ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.9 (COOH), 154.2 (C-9), 151.4 (HNCOO), 145.1 (C-3), 142.1 (C-7), 138.1 (C-1), 131.3 (C-2), 129.7 (C-11), 125.5 (C-12), 124.9 (C-6), 122.1 (C-8), 121.2 (C-10), 120.8 (C-5), 44.2 (CH), 40.5 (R-C-1′), 31.0 (R-C-4′), 29.2 (R-C-2′), 25.9 (R-C-3′), 22.1 (R-C-5′), 18.3 (CH$_3$), 13.9 (R-C-6′). UPLC/MS analysis: Rt 2.46 min. MS (ES) C$_{22}$H$_{28}$N$_2$O$_4$ requires 384, found 385 [M+H]$^+$, 383 [M−H]$^-$. HRMS C$_{22}$H$_{29}$N$_2$O$_4$ [M+H]$^+$: calculated 385.2127; measured 385.2161 Δppm 8.8.

4.1.30. Chiral HPLC separation of **10r**

10r (500 mg, 1.29 mmol) was subjected to chiral HPLC separation to afford the two enantiomers.

4.1.30.1. (−)-2-[3-fluoro-4-[3-(hexylcarbamoyloxy)phenyl]phenyl] propanoic acid ((−)-**10r**).

First eluted enantiomer (15.2 min), 112 mg (45%). Mp: 99–100 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H, COOH), 7.79 (t, J = 5.7 Hz, 1H, NH), 7.51 (t, J = 8.1 Hz, 1H, H-5), 7.48 (t, J = 7.9 Hz, 1H, H-11), 7.39 (d, J = 7.7 Hz, 1H, H-10), 7.25 (m, 3H, H-2 H-6 H-8), 7.15 (dd, J = 8.7, 1.5 Hz, 1H, H-12), 3.79 (q, J = 7.1 Hz, 1H, CH), 3.07 (q, J = 6.8 Hz, 2H, R-H-1′), 1.47 (p, J = 6.3 Hz, 2H, R-H-2′), 1.42 (d, J = 7.1 Hz, 3H, CH$_3$), 1.30 (m, 6H, R-H-3′ R-H-4′ R-H-5′), 0.88 (t, J = 7.0 Hz, 3H, R-H-6′). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.2 (COOH), 159.2 (d, J = 246.4 Hz, C-3), 154.6 (C-9), 151.7 (HNCOO), 143.9 (d, J = 8.0 Hz, C-7), 136.4 (C-1), 131.0 (d, J = 3.5 Hz, C-5), 129.9 (C-11), 126.2 (d, J = 13.1 Hz, C-4), 125.6 (C-10), 124.5 (d, J = 3.0 Hz, C-6), 122.3 (d, J = 2.6 Hz, C-8), 121.6 (C-12), 115.6 (d, J = 23.2 Hz, C-2), 44.5 (CH), 40.9 (R-C-1′, 31.4 (R-C-4′), 29.6 (R-C-2′), 26.3 (R-C-3′), 22.5 (R-C-5′), 18.7 (CH$_3$), 14.3 (R-C-6′). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.58 min. MS (ES) C$_{22}$H$_{26}$FNO$_4$ requires 387, found 388 [M+H]$^+$. [α]$_D^{20}$ −29° (c 1.0, CHCl$_3$). >99.5% ee. HRMS C$_{22}$H$_{27}$NO$_4$F [M+H]$^+$: calculated 388.1924; measured 388.1919 Δppm −1.3.

*4.1.30.2. (+)-2-[3-fluoro-4-[3-(hexylcarbamoyloxy)phenyl]phenyl] propanoic acid ((+)-**10r**). Second eluted* enantiomer (25.7 min), 172 mg (45%). Mp: 101–102 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H, COOH), 7.79 (t, J = 5.7 Hz, 1H, NH), 7.51 (t, J = 8.1 Hz, 1H, H-5), 7.48 (t, J = 7.9 Hz, 1H, H-11), 7.39 (d, J = 7.7 Hz, 1H, H-10), 7.25 (m, 3H, H-2 H-6 H-8), 7.15 (dd, J = 8.7, 1.5 Hz, 1H, H-12), 3.79 (q, J = 7.1 Hz, 1H, CH), 3.07 (q, J = 6.8 Hz, 2H, R-H-1'), 1.47 (p, J = 6.3 Hz, 2H, R-H-2'), 1.42 (d, J = 7.1 Hz, 3H, CH$_3$), 1.30 (m, 6H, R-H-3' R-H-4'R-H-5'), 0.88 (t, J = 7.0 Hz, 3H, R-H-6'). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.2 (COOH), 159.2 (d, J = 246.4 Hz, C-3), 154.6 (C-9), 151.7 (HNCOO), 143.9 (d, J = 8.0 Hz, C-7), 136.4 (C-1), 131.0 (d, J = 3.5 Hz, C-5), 129.9 (C-11), 126.2 (d, J = 13.1 Hz, C-4), 125.6 (C-10), 124.5 (d, J = 3.0 Hz, C-6), 122.3 (d, J = 2.6 Hz, C-8), 121.6 (C-12), 115.6 (d, J = 23.2 Hz, C-2), 44.5 (CH), 40.9 (R-C-1'), 31.4 (R-C-4'), 29.6 (R-C-2'), 26.3 (R-C-3'), 22.5 (R-C-5'), 18.7 (CH$_3$), 14.3 (R-C-6'). ^{19}F NMR (564 MHz, DMSO-d_6): δ 117.3. UPLC/MS analysis: Rt 2.59 min. MS (ES) $C_{22}H_{26}FNO_4$ requires 387, found 388 [M+H]$^+$. $[\alpha]_D^{20}$ +29° (*c* 1.0, CHCl$_3$). >99.5% ee. HRMS $C_{22}H_{27}NO_4F$ [M+H]$^+$: calculated 388.1924; measured 388.1927 Δppm 0.8.

4.2. Enzyme assays

Quantitative ^{1}H NMR analyses of DMSO-d_6 stock solutions of tested compounds are performed using PULCON method (PULse Length based CONcentration determination, Bruker software, topspin 3.0) [68,69].

4.2.1. In vitro rat FAAH radiometric assay

Rat FAAH was prepared from male Sprague Dawley rat brains, homogenized in a potter in 20 mM of Tris HCl pH 7.4, 0.32 M sucrose. The radiometric assay used to measure FAAH activity was performed in eppendorf tubes: 50 µg of total rat brain homogenate were pre-incubated in 445.5 µL of assay buffer (50 mM Tris–HCl pH 7.4, 0.05% Fatty acid-free bovine serum albumin (BSA)) with 4.5 µL of inhibitor (at appropriate concentration in DMSO) or DMSO alone (to measure FAAH total activity) for 10 min at 37 °C. The blank (no activity control) was prepared using 445.5 µL of assay buffer and 4.5 µL of DMSO without the 50 µg of total rat brain homogenate.

After 10 min of pre-incubation with test compounds, the reaction was started by adding of 50 µL of substrate and incubating for 30 min at 37 °C. The substrate was prepared in assay buffer in order to achieve the final concentration of 1 µM arachidonoyl ethanolamide (Cayman Chemical N. 90050) and 0.6 nM anandamide [ethanolamine-1-^{3}H] (American Radiolabeled Chemicals Inc., ART. 0626, conc. 1 mCi/mL, S.A. 60 Ci/mmol). The reaction was stopped by adding cold 1:1 CHCl$_3$/MeOH. After 10 min of centrifugation (845 × g at 4 °C) 600 µL of aqueous phase were transferred into scintillation vials previously filled with 3 mL of scintillation fluid (Ultima Gold™, Perkin Elmer Inc., Cat. 6013329). Radioactivity was measured by liquid scintillation counting (MicroBeta2 LumiJET Perkin Elmer Inc.).

4.2.2. In vitro COX assay

COX activity was measured using a commercial kit (COX Inhibitor Screening Assay Kit - Cayman Chemical N. 560131) which includes both ovine COX-1 and human recombinant COX-2 enzymes. Inhibitors were pre-incubated with either ovine COX-1 or human COX-2 in order to screen isozyme-specific inhibition. Differently than described in the kit protocol, the reaction was carried out in the presence of 5 µM arachidonic acid while for the blank sample (no activity) the two enzymes were inactivated for 40 min at 100 °C. It was then measured the amount of PGF2α produced by reduction with SnCl$_2$ of COX-derived PGH2, via enzyme immunoassay (EIA) using a PG-specific antibody and competing with a PG-acetylcholinesterase conjugate.

Absorbance was measured at 412 nm with a *Tecan Infinite M200 plate reader* and data were processed according to manufacturer's instructions.

The median inhibitory concentrations (IC$_{50}$) were determined by non-linear regression analysis of the Log [concentration]/response curves generated with mean replicate values using a four parameter Hill equation curve fitting with GraphPad Prism 5 (GraphPad Software Inc., CA–USA). IC$_{50}$ values are means of ≥3 experiments performed in duplicate.

4.2.3. Ex vivo lipid analyses

All procedures performed were in accordance with the Ethical Guidelines of the International Association for the Study of Pain, Italian regulations on the protection of animals used for experimental and other scientific purposes (D.M. 116192), and European Economic Community regulations (O.J. of E.C. L 358/1 12/18/1986). Great care was taken to minimize suffering of the animals and to reduce the number of animals used. Mice were housed in groups of 5 in ventilated cages containing autoclaved cellulose paper as nesting material with free access to food and water. They were maintained under a 12 h light/dark cycle (lights on at 08:00 a.m.), at controlled temperature (21 ± 1 °C) and relative humidity (55 ± 10%). The animals were randomly divided in groups of 6. Behavioral testing was performed between 9:00 a.m. and 5:00 p.m. Scientists running the experiments were not aware of the treatment protocol at the time of the test (blind procedure). Mice were decapitated under anesthesia 1 h after intravenous injection of (S)-(+)-**10r**) (1 mg/kg). Blood (0.3 mL) was collected through a left cardioventricular puncture with heparinized syringes and centrifuged at 2000 × g for 30 min to obtain plasma. OEA was extracted from plasma and measured by LC/MS as described. Briefly, 300 µL of plasma were centrifuged with cold acetone (1 mL) containing [^{2}H$_4$]-OEA (Cayman Chemical). Lipids were extracted with CHCl$_3$ (2 vol), the organic phases were washed with water (1 vol), collected, dried under nitrogen and reconstituted in MeOH (0.2 mL). LC/MS analyses were conducted on a Xevo TQ LC-MS/MS system (Waters) equipped with a BEH C18 column (Waters, Milford MA), using a linear gradient of MeCN in water. Quantification was performed monitoring the MRM transitions. Analyte peak areas were compared with a standard calibration curve (1 nM–10 µM). Tissue levels of TXA$_2$ and 6-keto-PGF$_{1\alpha}$ were determined using ELISA kits (ABcam, Cambridge, UK), following manufacturer's instructions.

Conflict of interest

Acknowledgment

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.12.036.

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