

Accepted Manuscript

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

Marco Migliore, Damien Habrant, Oscar Sasso, Clara Albani, Sine Mandrup Bertozzi, Andrea Armirotti, Daniele Piomelli, Rita Scarpelli



PII: S0223-5234(15)30422-0

DOI: [10.1016/j.ejmech.2015.12.036](https://doi.org/10.1016/j.ejmech.2015.12.036)

Reference: EJMECH 8276

To appear in: *European Journal of Medicinal Chemistry*

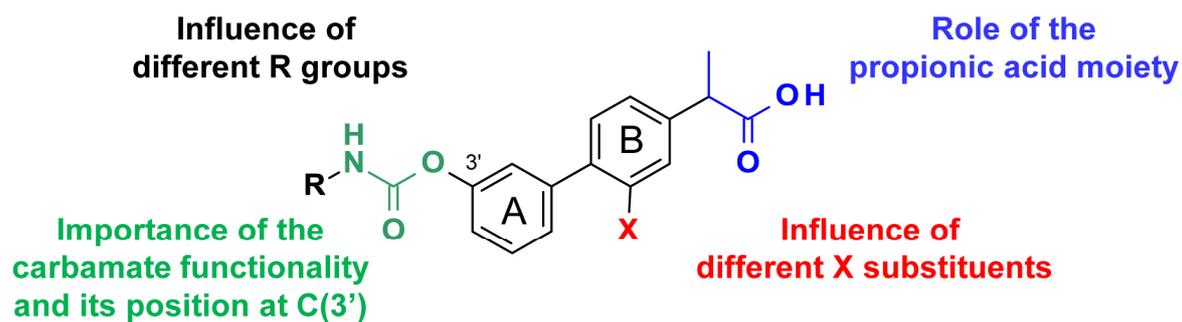
Received Date: 28 October 2015

Revised Date: 9 December 2015

Accepted Date: 19 December 2015

Please cite this article as: M. Migliore, D. Habrant, O. Sasso, C. Albani, S.M. Bertozzi, A. Armirotti, D. Piomelli, R. Scarpelli, Potent multi-target FAAH-COX inhibitors: Design and structure-activity relationship studies, *European Journal of Medicinal Chemistry* (2016), doi: 10.1016/j.ejmech.2015.12.036.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Hybrid Scaffold
Multitarget
FAAH/COX inhibitors

ACCEPTED MANUSCRIPT

Potent Multi-target FAAH-COX Inhibitors: Design and Structure-Activity Relationship Studies

*Marco Migliore,^a Damien Habrant,^{a,1} Oscar Sasso,^a Clara Albani,^{a,2} Sine Mandrup Bertozzi,^a
Andrea Armirotti,^a Daniele Piomelli^{a,b*} and Rita Scarpelli^{a*}*

^aDrug Discovery and Development, Fondazione Istituto Italiano di Tecnologia, Via Morego 30,
16163 Genova, Italy

^bDepartments of Anatomy and Neurobiology, Pharmacology and Biological Chemistry,
University of California, Irvine, USA, 92697-4621

Present addresses:

¹In-Cell-Art, 21 rue de la Noue Bras de Fer, 44200 Nantes, France.

²Covagen AG, Wagistrasse 25, 8952, Zürich Schlieren, Switzerland.

*Corresponding authors:

piomelli@uci.edu; phone: +1(949) 824-9179

rita.scarpelli@iit.it; phone: +39 010 71781233

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 multi-target 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.

KEYWORDS. FAAH, COX, hybrid scaffold, multitarget inhibitors, structure-activity relationship, inflammation.

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 E₂ (PGE₂) and thromboxane A₂ (TXA₂). [6] The dual role of COX-1-derived PGE₂ 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 (H₂S) 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 multi-target strategy to treat inflammation is the concomitant inhibition of COX and fatty acid amide hydrolase (FAAH) [26], [27-33] a serine hydrolase 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 (arachidonylethanolamide) – which engages cannabinoid-1 (CB₁) and CB₂ 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 multi-target modulator based on the hybrid scaffold **1** (**Figure 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, **Figure 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 (**Figure 1**).

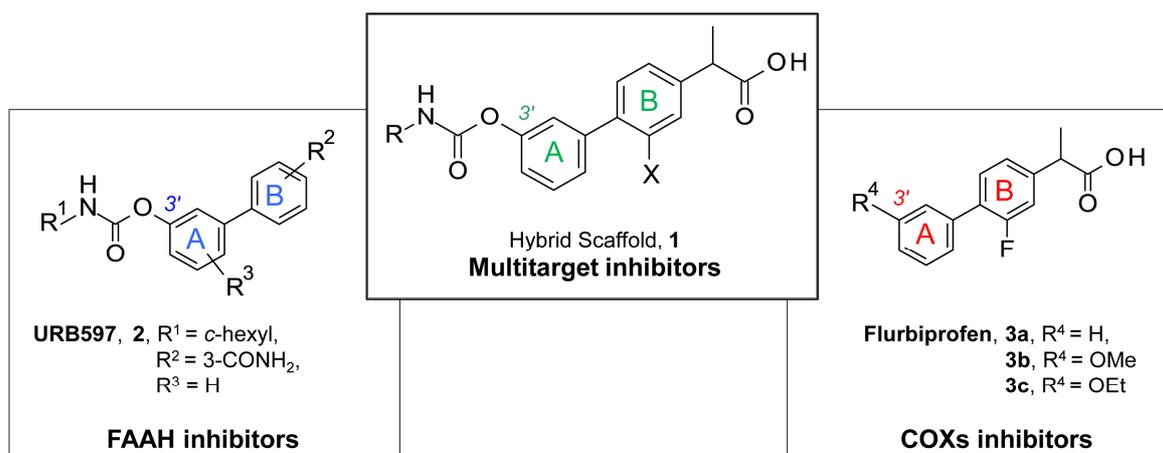


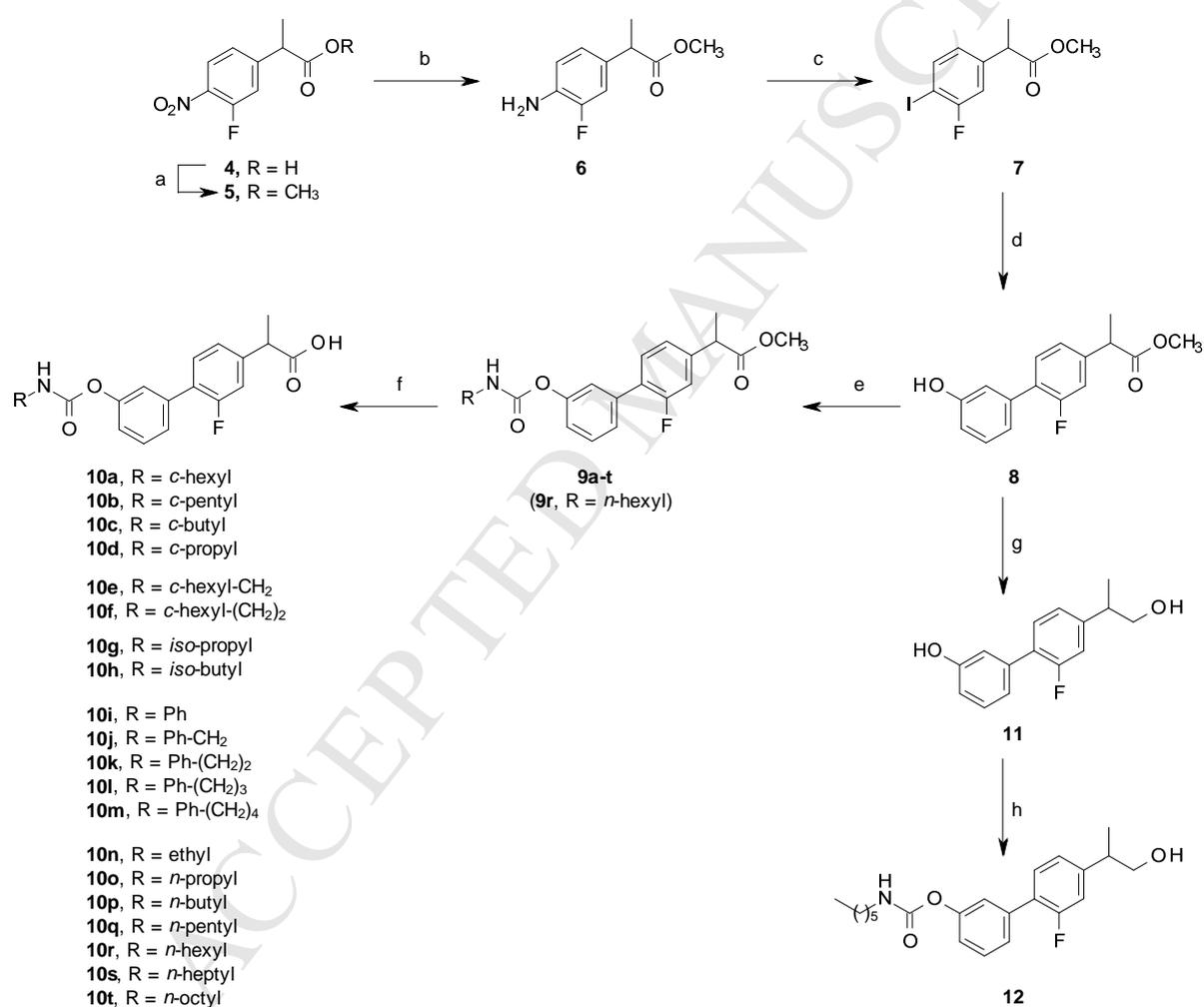
Figure 1. Rational design of a 'hybrid scaffold' for FAAH and COX inhibition.

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 multitarget 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**).

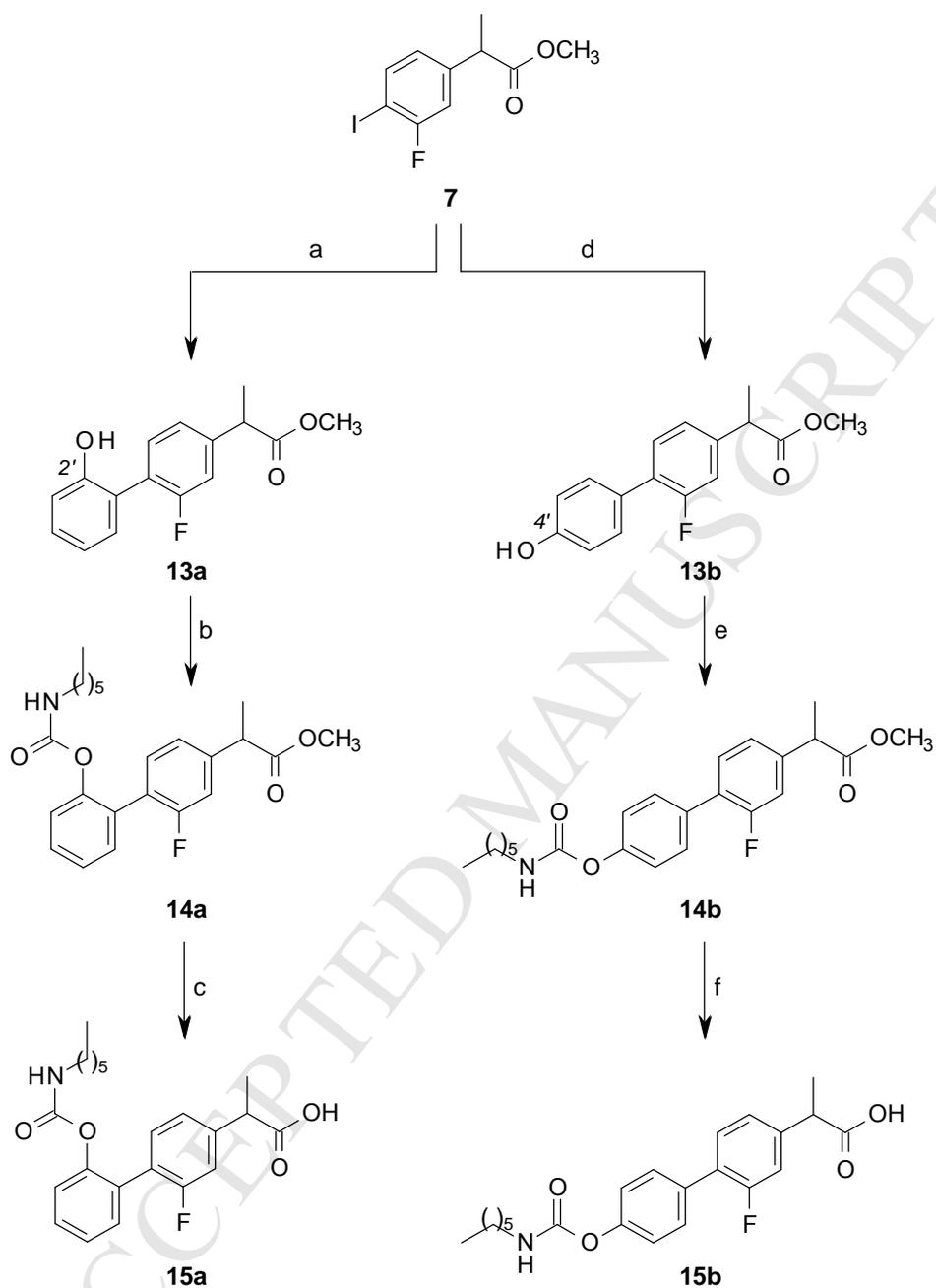


Scheme 1. Synthesis of compounds **10a-t** and **12**. Reagents and conditions: (a) MeOH, conc. H₂SO₄, rt, 15 h, 93%; (b) HCO₂NH₄, 10% Pd/C, MeOH, rt, 3 h, 94%; (c) NaNO₂, 3M HCl, 0 °C, 30 min, then NaI, 60 °C, 2 h, 55%; (d) (3-hydroxyphenyl)boronic acid, Pd(OAc)₂, K₂CO₃, EGME/H₂O, rt, 15 h, 84%; (e) RNCO, DMAP, MeCN, rt, 15 h, 38-99%; (f) 6M HCl, THF, rt, 2 d, 26-73%; (g) ZrCl₄, NaBH₄, THF, rt, 2 h, 96%; (h) *n*-hexyl-NCO, DMAP, MeCN, rt, 15 h, 73%.

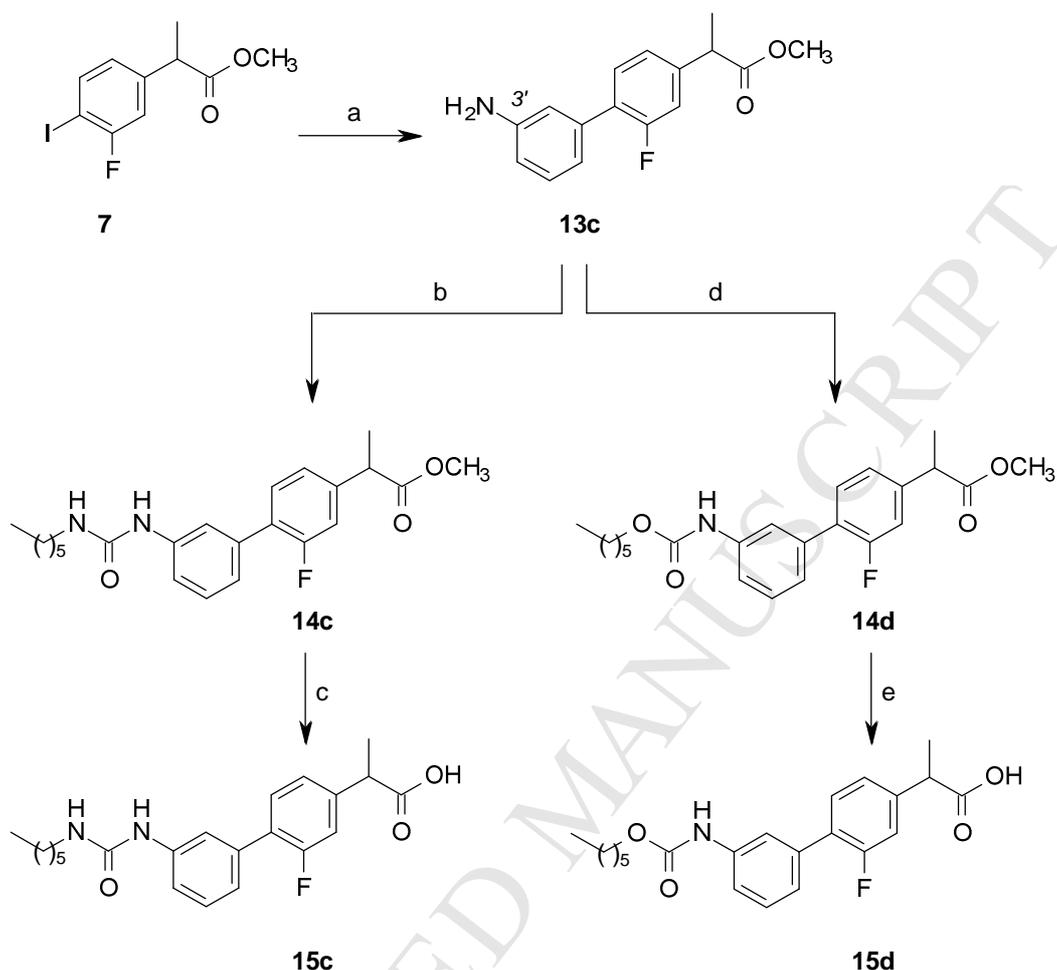
The intermediate **8** was prepared in four steps, starting from the acid **4**, obtained as previously described. [62] Compound **4** was converted to the corresponding methyl ester **5**, under standard acidic conditions, to afford, after catalytic hydrogenation with ammonium formate in the presence 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** (**Scheme 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**).



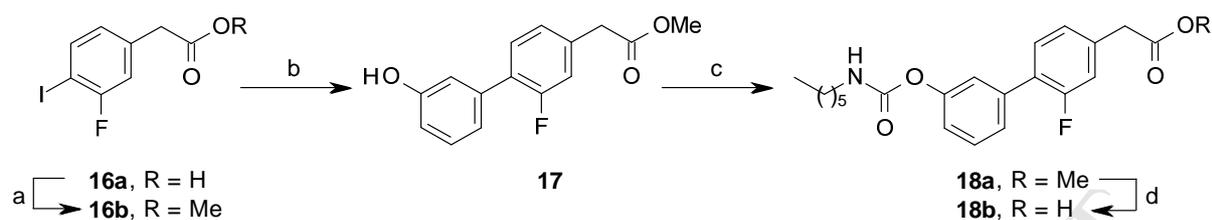
Scheme 2. Synthesis of compounds **15a-b**. Reagents and conditions: (a) (2-hydroxyphenyl)boronic acid, Pd(OAc)₂, K₂CO₃, EGME/H₂O, rt, 15 h, 84%; (b) *n*-hexyl-NCO, DMAP, MeCN, rt, 15 h, 88%; (c) 6M HCl, THF, rt, 2 d, 90%; (d) (4-hydroxyphenyl)boronic acid, Pd(OAc)₂, K₂CO₃, EGME/H₂O, rt, 15 h, 59%; (e) *n*-hexyl-NCO, DMAP, MeCN, rt, 15 h, 72%; (f) 6M HCl, THF, rt, 2 d, 46%.



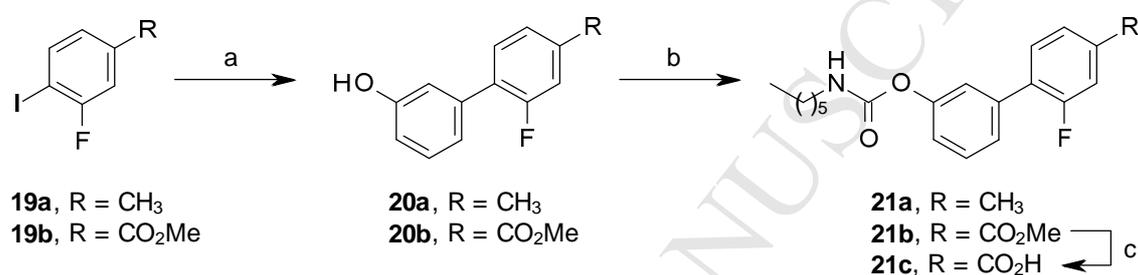
Scheme 3. Synthesis of compounds **15c-d**. Reagents and conditions: (a) (3-aminophenyl)boronic acid, Pd(OAc)₂, K₂CO₃, EGME/H₂O, rt, 15 h, 91%; (b) *n*-hexyl-NCO, DMAP, MeCN, rt, 15 h, 65%; (c) 6M HCl, THF, rt, 2 d, 38%; (d) triphosgene, toluene, reflux, 15 h, then *n*-hexanol, rt, 15 h, 82%; (e) 6M HCl, THF, rt, 2 d, 59%.

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 (**Scheme 4** and **5**).

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



Scheme 4. Synthesis of compound **18b**. Reagents and conditions: (a) MeOH, conc. H₂SO₄, rt, 15 h, quant.; (b) (3-hydroxyphenyl)boronic acid, Pd(OAc)₂, K₂CO₃, EGME/H₂O, rt, 15 h, 71%; (c) *n*-hexyl-NCO, DMAP, MeCN, rt, 15 h, 64%; (d) 6M HCl, THF, rt, 2 d, 62%.

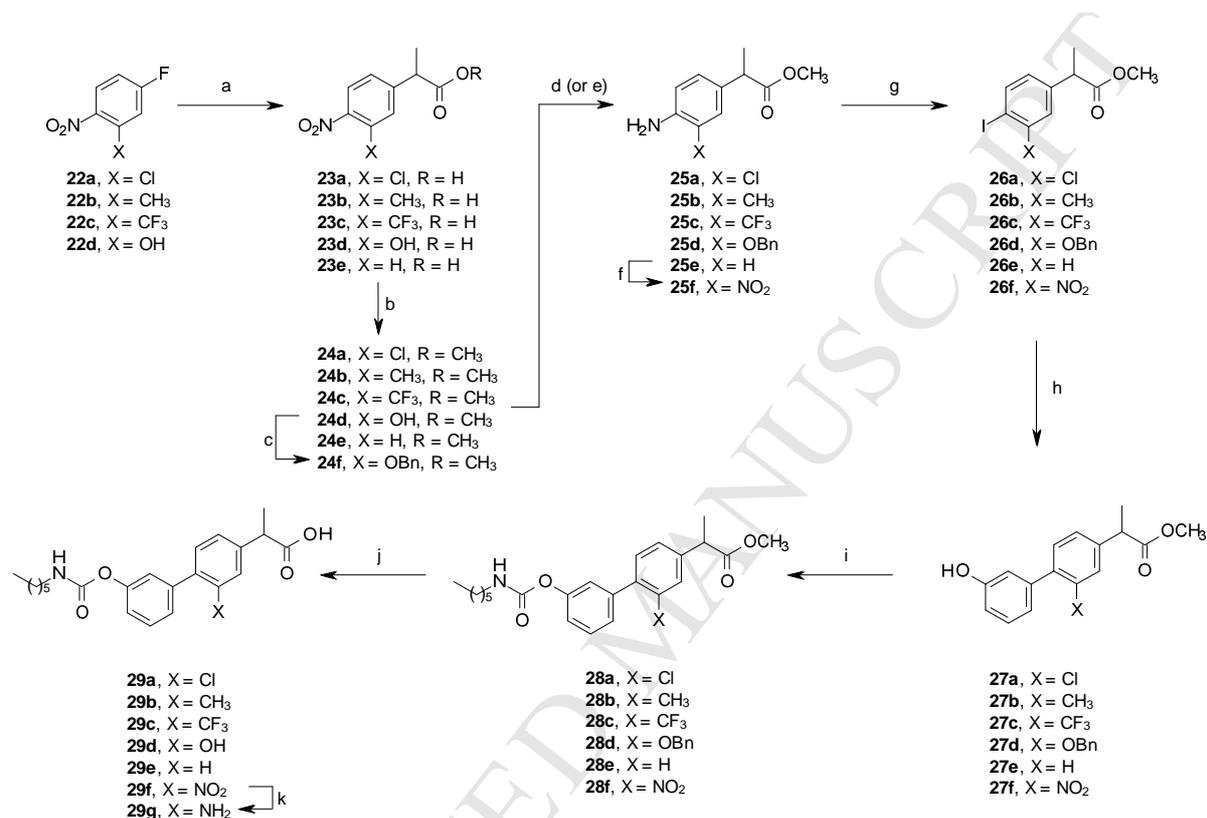


Scheme 5. Synthesis of compound **21a** and **21c**. Reagents and conditions: (a) (3-hydroxyphenyl)boronic acid, Pd(OAc)₂, K₂CO₃, EGME/H₂O, rt, 15 h, 86-92%; (b) *n*-hexyl-NCO, DMAP, MeCN, rt, 15 h, 86%-quant.; (c) 6M HCl, THF, rt, 2 d, 34%.

Compounds **29a-g** were synthesized following the synthetic sequence described in **Scheme 6**. *p*-Nitrofluorobenzenes **22a-d** were reacted with diethylmethylmalonate 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**, 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/Sandmeyer 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.



Scheme 6. Synthesis of compounds **29a-g**. Reagents and conditions: (a) diethyl methylmalonate, NaOH, DMF, rt, 15 h; then AcOH, H₂SO₄, H₂O 110 °C, 24 h, 48-87%; (b) MeOH, conc. H₂SO₄, rt, overnight, 81-98%; (c) BnBr, K₂CO₃, acetone, 60 °C, 15 h, 63%; (d) Fe, HCl, MeOH, 65 °C, 2 h, 64-94%, for **24a** and **24f**; (e) HCO₂NH₄, 10% Pd/C, MeOH, rt, 3 h, quant., for **24b-c**, and **24e**; (f) Ac₂O, HNO₃ 0 °C, 2 h then H₂SO₄, MeOH, 65 °C, 2 h, 98%; (g) NaNO₂, 3M HCl, 0 °C, 30 min, then NaI, 60 °C, 2 h, 55-72%; (h) (3-hydroxyphenyl)boronic acid, Pd(OAc)₂, K₂CO₃, EGME/H₂O, rt, 15 h, 59-84%; (i) *n*-hexyl-NCO, DMAP, MeCN, rt, 15 h, 89%-quant.; (j) 2M HCl, dioxane, 80 °C, 15 h, 73-95%; (k) cyclohexene, 10% Pd/C 80 °C, 2 h then 2M HCl, 55%.

2.2. SAR exploration of the first class of potent multi-target 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** (**Figure 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**.

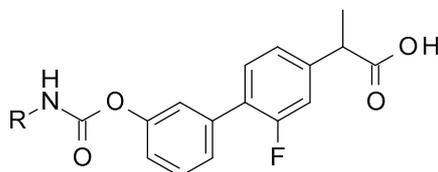
Compound **10a** inhibited FAAH and COX activities with relatively weak potencies (IC_{50} values, in μM : FAAH = 8.2; COX-1 = 7.9; COX-2 > 100). Nevertheless, these initial results encouraged us because **10a** was one of the most potent FAAH/COX-1 inhibitors previously reported. [27, 28, 30, 32, 33, 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**).

Table 1. SAR exploration on the nature of R group: cycloalkanes, small-branched alkanes and phenyls.



Compound	R	FAAH ^{a,b}	COX-1 ^{a,b}	COX-2 ^{a,b}
		IC ₅₀ (μ M) \pm SD	IC ₅₀ (μ M) \pm SD	IC ₅₀ (μ M) \pm SD
2 , URB597	-	0.0017 \pm 0.001	>100	>100
3a , flurbiprofen	-	>100	0.15 \pm 0.018	1.06 \pm 0.53
10a	<i>c</i> -hexyl	8.2 \pm 2.4	7.9 \pm 2.1	>100
10b	<i>c</i> -pentyl	4.8 \pm 3.2	4.4 \pm 2.0	> 100
10c	<i>c</i> -butyl	48.7 \pm 9.0	0.72 \pm 0.02	>100
10d	<i>c</i> -propyl	>100	5.4 \pm 2.9	74.3 \pm 6.1
10e	<i>c</i> -hexyl-CH ₂	0.36 \pm 0.06	0.60 \pm 0.04	>100
10f	<i>c</i> -hexyl-(CH ₂) ₂	0.018 \pm 0.007	0.15 \pm 0.03	10.8 \pm 2.2
10g	<i>iso</i> -propyl	>100	3.9 \pm 2.1	>100
10h	<i>iso</i> -butyl	4.1 \pm 2.1	8.2 \pm 2.1	>100
10i	Ph	41.2 \pm 3.4	0.27 \pm 0.07	2.7 \pm 0.3
10j	Ph-CH ₂	4.18 \pm 2.8	1.3 \pm 0.6	>100
10k	Ph-(CH ₂) ₂	0.17 \pm 0.07	6.3 \pm 2.2	>100
10l	Ph-(CH ₂) ₃	0.09 \pm 0.01	0.58 \pm 0.09	6.2 \pm 0.3
10m	Ph-(CH ₂) ₄	0.027 \pm 0.010	3.7 \pm 2.8	>100

^a Values are reported as mean values of ≥ 3 experiments performed; ^bIC₅₀ values were not determined for compounds showing less than 50% inhibition at concentrations of 100 μ M for FAAH and COXs.

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

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 (**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 ($IC_{50}>100 \mu M$). 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 $10.8 \mu M$.

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 $IC_{50} = 0.58 \mu\text{M}$ and $6.2 \mu\text{M}$ 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]

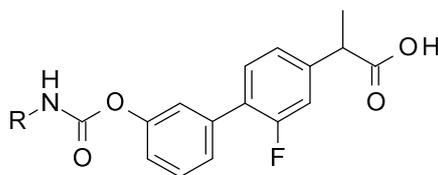
2.2.3. Study of the effect of the nature of the R group: linear alkanes. Identification of **10r** (ARN2508).

Since the $(\text{CH}_2)_n$ 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 = $(\text{CH}_3(\text{CH}_2)_n)$ 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 $(\text{CH}_2)_n$ chain ($n = 1-7$). A different trend was observed for COX-1 and COX-2, where insertion of short $(\text{CH}_2)_n$ 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 $n = 3-5$ $(\text{CH}_2)_n$ chains (**10p-r**) increased the inhibitory potencies for COX-1 and COX-2 from sub-micromolar to nano-molar IC_{50} , whereas insertion of $n = 6-7$ $(\text{CH}_2)_n$ chains (**10s-t**) was detrimental.

These results are in agreement with those above reported in the homologation of the Ph(CH₂)_n chain series ($n = 1-4$, compounds **10i-m**, **Table 1**).

Table 2. SAR exploration on the nature of the R group: linear alkanes



Compound	R	FAAH ^{a,b}	COX-1 ^{a,b}	COX-2 ^{a,b}
		IC ₅₀ (μM)±SD	IC ₅₀ (μM)±SD	IC ₅₀ (μM)±SD
10n	ethyl	>100	2.1±0.9	>100
10o	<i>n</i> -propyl	>100	1.65±0.06	>100
10p	<i>n</i> -butyl	7.0±1.8	0.26±0.07	>100
10q	<i>n</i> -pentyl	0.57±0.15	0.020±0.009	0.16±0.02
10r , ARN2508	<i>n</i> -hexyl	0.031±0.002	0.012±0.002	0.43±0.02
10s	<i>n</i> -heptyl	0.011±0.003	0.37±0.10	0.32±0.005
10t	<i>n</i> -octyl	0.003±0.002	0.99±0.07	28.8±8.4

^aValues are reported as mean values of ≥ 3 experiments performed; ^bIC₅₀ values were not determined for compounds showing less than 50% inhibition at concentrations of 100 μM for FAAH and COXs.

From this SAR exploration, we identified **10r** (ARN2508), [51] which bears a *n*-hexyl chain at the *N*-terminal site, as a potent multi-target inhibitor of FAAH, COX-1 and COX-2 (IC₅₀: 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]

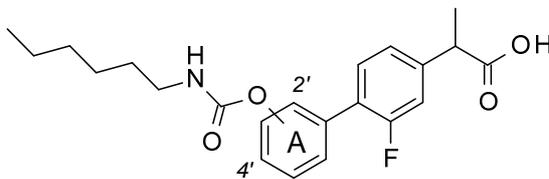
These results encouraged us to initiate a more focused SAR exploration to define the effect of additional chemical and structural modifications in various regions of **10r** scaffold.

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** (**Figure 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**).

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

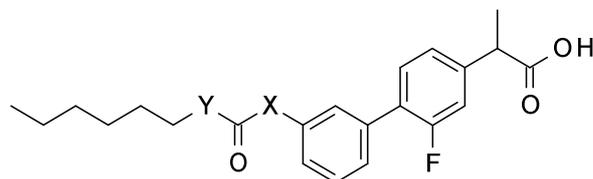
Compound	position	FAAH ^{a,b}	COX-1 ^{a,b}	COX-2 ^{a,b}
		IC ₅₀ (μM) ±SD	IC ₅₀ (μM) ±SD	IC ₅₀ (μM) ±SD
15a	C(2')	2.2±0.6	0.72±0.04	>100
15b	C(4')	0.068±0.012	>100	>100

^aValues are reported as mean values of ≥ 3 experiments performed; ^bIC₅₀ values were not determined for compounds showing less than 50% inhibition at concentrations of 100 μM for FAAH and COXs.

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**).

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**.

Table 4. Carbamate replacement: urea and reversed carbamate derivatives

Compound	Y	X	FAAH ^a	COX-1 ^a	COX-2 ^a
			IC ₅₀ (μM) ±SD	IC ₅₀ (μM) ±SD	IC ₅₀ (μM) ±SD
15c	NH	NH	88.4±2.3	0.014±0.003	0.56±0.12
15d	O	NH	14.9±1.6	0.03±0.01	0.17±0.01

^aValues are reported as mean values of ≥ 3 experiments performed.

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]

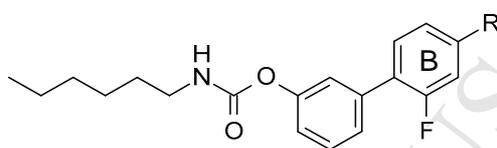
2.2.4.2. Role of the propionic acid functionality in the B phenyl ring.

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

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



Compound	R	FAAH ^{a,b}	COX-1 ^{a,b}	COX-2 ^{a,b}
		IC_{50} (μ M) \pm SD	IC_{50} (μ M) \pm SD	IC_{50} (μ M) \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

^aValues 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 μ M for FAAH and COXs.

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 COX-1 (IC_{50} = 2.1 μ M and 12 nM, respectively). The activity against COX-2 was slightly improved (IC_{50} = 0.24 μ M and 0.43 μ M 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).

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**).

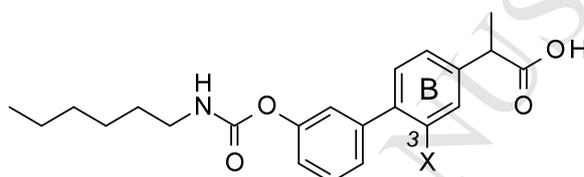
Substituting the fluorine with chlorine was tolerated: indeed, **29a** was virtually equipotent against FAAH and COX-1, and marginally less potent on COX-2, compared to **10r**. The same trend was observed with the methyl derivative **29b**, which was slightly more potent than **10r** against FAAH and 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 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 donor groups.

Table 6. SAR exploration on the role of the X substituent on the B phenyl ring



Compound	X	FAAH ^a	COX-1 ^a	COX-2 ^a
		IC ₅₀ (μ M) \pm SD	IC ₅₀ (μ M) \pm SD	IC ₅₀ (μ M) \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

^aValues are reported as mean values of ≥ 3 experiments performed.

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.

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

Compound	<i>r</i> -FAAH ^a	COX-1 ^a	COX-2 ^a
	$IC_{50}(\mu M) \pm SD$	$IC_{50}(\mu M) \pm SD$	$IC_{50}(\mu M) \pm SD$
(±)- 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

^aValues 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).

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 TXA₂, as assessed surveying the stable metabolites, 6-keto-PGF_{1 α} and TXB₂ (**Figure 2A** and **2B**). Moreover, (*S*)-(+)-**10r** increased plasma levels of the FAAH substrate, OEA (**Figure 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.

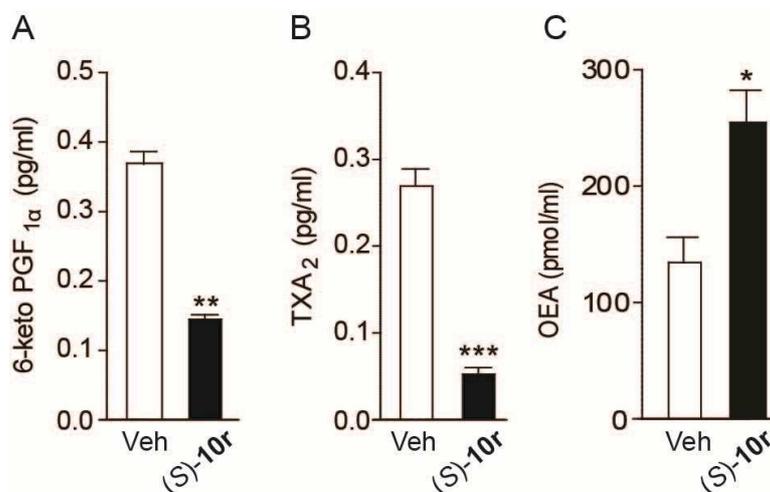


Figure 2. Plasma levels of COX metabolites and FAAH substrate after intravenous administration of (S)-(+)-**10r** (1 mg/kg): 6-keto-PGF_{1α} (A) TXA₂ (B) and OEA (C). Results are expressed as mean ± s.e.m. of 6 independent determinations. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ compared to vehicle mice, two-tailed Student's t test.

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 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 UV₂₅₄). ¹H and ¹³C-NMR experiments were run on a Bruker Avance III 400 system (400.13 MHz for ¹H, and 100.62 MHz for ¹³C), equipped with a BBI probe and Z-gradient coil. ¹⁹F-NMR experiments were run on a Bruker Avance III 600 system (546.6 MHz for ¹⁹F), equipped with a 5 mm CryoProbe QCI ¹H/¹⁹F-¹³C/¹⁵N-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 ¹³C 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, ¹³C; for

CDCl₃: 7.26 ppm, ¹H and 77.16 ppm, ¹³C). 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 Quadrupole 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 (50x2.1 mmID, particle size 1.7 μm) with a VanGuard BEH C18 pre-column (5x2.1 mmID, particle size 1.7 μm). Mobile phase was either 10 mM NH₄OAc in H₂O at pH 5 adjusted with AcOH (A) and 10 mM NH₄OAc in MeCN-H₂O (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 to 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 to 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 Quadrupole 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 XBridgeTM Prep C18 OBD column (100x 19 mmID, particle size 5 μm) with a XBridgeTM Prep C18 (10x 19 mmID, particle size 5 μm) Guard Cartridge. Mobile phase was 10 mM NH₄OAc in H₂O at pH 5 adjusted with AcOH (A) and 10 mM NH₄OAc in MeCN-H₂O (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 (250x4.6 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 x 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 $\text{H}_2\text{O}/\text{MeCN}$ and analyzed. Leucine Enkephalin (2 ng/mL) was used as lock mass reference compound for spectra calibration. All final compounds displayed $\geq 95\%$ purity as determined by NMR and UPLC/MS analysis.

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

4.1.1. (\pm)-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. (\pm)-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_2SO_4 (0.1 mL) was added and the resulting solution

was stirred at rt overnight. After solvent evaporation, the crude oil was diluted with Et₂O (15 mL) and filtered through a pad of SiO₂ 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 HCO₂NH₄ (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 SiO₂ 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 NaNO₂ (0.70 g, 10.21 mmol) in H₂O (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 Et₂O and the organic phase was then washed with a 1M solution of Na₂SO₃ (15 mL) and dried over Na₂SO₄. 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/H₂O (3:1, 0.25 M) were added Pd(OAc)₂ (0.05 mmol) and K₂CO₃ (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 H₂O (20 mL) and a 1M solution of Na₂SO₃ (20 mL). After separation, the organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The residues were purified by column chromatography (Cy/EtOAc).

4.1.5.1. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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 (\pm)-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 (\pm)-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 carbamylation 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 isocyanate (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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. (\pm)-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. ¹H 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, OCH₃), 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, CH₃), 1.28 (m, 6H, R-H-3' R-H-4' R-H-5'), 0.87 (t, *J* = 6.9 Hz, 3H, R-H-6'). ¹³C 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 (OCH₃), 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 (CH₃), 13.87 (R-C-6'). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.0. UPLC/MS analysis: Rt 2.00 min. MS (ES) C₂₃H₂₈FNO₄ requires: 401, found 402 [M+H]⁺. HRMS C₂₃H₂₉NO₄F [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. (\pm)-[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. ¹H 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, CH₂), 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, CH₃), 0.87 (t, *J* = 6.7 Hz, 3H, R-H-6'). ¹³C 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 (CH₂), 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 (CH₃), 13.8 (R-C-6'). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 118.0. UPLC/MS analysis: Rt 2.60 min. MS (ES) C₂₂H₂₈FNO₃ requires 373, found 374 [M+H]⁺. HRMS C₂₂H₂₉NO₃F [M+H]⁺: calculated 374.2131 measured 374.2149 Δ ppm 4.8.

4.1.6.22. (\pm)-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. (\pm)-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. (\pm)-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. ^1H 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, CH₃), 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 (CH₃), 13.8 (R-C-6'). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 118.0. UPLC/MS analysis: Rt 2.17 min. MS (ES) C₂₀H₂₄FNO₂ requires 329, found 330 [M+H]⁺. HRMS C₂₀H₂₅NO₂F [M+H]⁺: calculated 330.1869 measured 330.189 Δ ppm 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 (\pm)-Methyl 2-[4-[3-(hexylcarbamoyloxy)phenyl]-3-(trifluoromethyl)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 (\pm)-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 (\pm)-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 (\pm)-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 6M HCl (5 mL) and the mixture was stirred at rt until the disappearance of the starting material was

noted by UPLC-MS analysis. H₂O (10 mL) was added and the suspension was extracted with EtOAc (20 mL). After evaporation, the organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The residues were purified by crystallization (Et₂O/Cy, Et₂O/ pentane, TBME), preparative TLC (Cy/EtOAc) or preparative HPLC.

4.1.7.1. (\pm)-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. ¹H 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, CH₃), 1.23 (m, 5H, R-H-2' R-H-3', R-H-4'). ¹³C 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 (CH₃). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.3. UPLC/MS analysis: Rt 2.41 min. MS (ES) C₂₂H₂₄FNO₄ requires 385, found 386 [M+H]⁺. HRMS C₂₂H₂₅NO₄F [M+H]⁺: calculated 386.1768 measured 386.1781 Δ ppm 3.4.

4.1.7.2. (\pm)-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. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) 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, $\text{DMSO-}d_6$) 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, $\text{DMSO-}d_6$): δ 117.3. UPLC/MS analysis: Rt 2.41 min. MS (ES) $\text{C}_{21}\text{H}_{22}\text{FNO}_4$ requires 371, found 372 $[\text{M}+\text{H}]^+$. HRMS $\text{C}_{21}\text{H}_{23}\text{NO}_4\text{F}$ $[\text{M}+\text{H}]^+$: calculated 372.1611 measured 372.1603 Δppm -2.1.

4.1.7.3. (\pm)-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. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) 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, $\text{DMSO-}d_6$) 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, $\text{DMSO-}d_6$): 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 $C_{20}H_{21}NO_4F$ $[M+H]^+$: calculated 358.1455 measured 358.1452 Δ ppm -0.8.

4.1.7.4. (\pm)-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. 1H 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, CH₃), 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 (CH₃), 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 $C_{19}H_{19}NO_4F$ $[M+H]^+$: calculated 344.1298 measured 344.1298 Δ ppm 0.

4.1.7.5. (\pm)-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/Et₂O to afford **10e** as a white solid (93 mg, 61%). Mp: 142-143 °C. 1H 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, CH₃), 1.18 (m, 3H, R-H-4' R-H-5'), 0.90 (m, 2H, R-H-3'). ¹³C 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 (CH₃). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.3. UPLC/MS analysis: Rt 2.57 min. MS (ES) C₂₃H₂₆FNO₄ requires 399, found 400 [M+H]⁺. HRMS C₂₃H₂₇NO₄F [M+H]⁺: calculated 400.1924 measured 400.193 Δ ppm 1.5.

4.1.7.6. (\pm)-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/Et₂O to afford **10f** as a white solid (98 mg, 68%). Mp: 118-119 °C. ¹H 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, CH₃), 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'). ¹³C 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 (CH₃). ¹⁹F 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 $C_{24}H_{29}NO_4F$ $[M+H]^+$: calculated 414.2081 measured 414.2096 Δ ppm 3.6.

4.1.7.7. (\pm)-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/Et₂O to afford **10g** as a white solid (65 mg, 43%). Mp: 131-132 °C. ¹H 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, CH₃), 1.15 (d, J = 6.5 Hz, 6H, R-H-2'). ¹³C 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 (CH₃). ¹⁹F 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 $C_{19}H_{21}NO_4F$ $[M+H]^+$: calculated 346.1455 measured 346.1458 Δ ppm 0.9.

4.1.7.8. (\pm)-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/Et₂O to afford **10h** as a white solid (57 mg, 42%). Mp: 128-130 °C. ¹H 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, CH₃), 0.90 (d, $J = 6.7$ Hz, 6H, R-H-3'). ¹³C 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 (CH₃). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.3. UPLC/MS analysis: Rt 2.24 min. MS (ES) C₂₀H₂₂FNO₄ requires 359, found 360 [M+H]⁺. HRMS C₂₀H₂₃NO₄F [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. ¹H 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, CH₃). ¹³C 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. ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.3. UPLC/MS analysis: Rt 2.05 min. MS (ES) C₂₂H₁₈FNO₄ requires 379, found 380 [M+H]⁺. HRMS C₂₂H₁₉NO₄F [M+H]⁺: calculated 380.1298 measured 380.1296 Δppm -0.5.

4.1.7.10. (\pm)-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. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) 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, $\text{DMSO-}d_6$) 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, $\text{DMSO-}d_6$): δ 117.3. UPLC/MS analysis: Rt 2.27 min. MS (ES) $\text{C}_{23}\text{H}_{20}\text{FNO}_4$ requires 393, found 394 $[\text{M}+\text{H}]^+$. HRMS $\text{C}_{23}\text{H}_{21}\text{NO}_4\text{F}$ $[\text{M}+\text{H}]^+$: calculated 394.1455 measured 394.1462 Δppm 1.8.

4.1.7.11. (\pm)-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_2O / pentane to afford **10k** as a white solid (58 mg, 41%). Mp: 104°C. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) 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, $\text{DMSO-}d_6$) 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 (CH₃). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.3. UPLC/MS analysis: Rt 2.37 min. MS (ES) C₂₄H₂₂FNO₄ requires 407, found 408 [M+H]⁺. HRMS C₂₄H₂₃NO₄F [M+H]⁺: calculated 408.1611 measured 408.1626 Δ ppm 3.7.

4.1.7.12. (\pm)-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. ¹H 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, CH₃). ¹³C 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 (CH₃). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.3. UPLC/MS analysis: Rt 2.46 min. MS (ES) C₂₅H₂₄FNO₄ requires 421, found 422 [M+H]⁺. HRMS C₂₅H₂₅NO₄F [M+H]⁺: calculated 422.1768 measured 422.1776 Δ ppm 1.9.

4.1.7.13. (\pm)-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. ^1H 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, CH₃). ^{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 (CH₃). ^{19}F NMR (564 MHz, DMSO- d_6): δ 117.3. UPLC/MS analysis: Rt 2.59 min. MS (ES) C₂₆H₂₆FNO₄ requires 435, found 436 [M+H]⁺. HRMS C₂₆H₂₇NO₄F [M+H]⁺: calculated 436.1924 measured 436.1936 Δ ppm 2.8.

4.1.7.14. (\pm)-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 Et₂O/ pentane to afford **10n** as a white solid (37 mg, 37%). Mp: 93-94 °C. ^1H 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, CH₃), 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 (CH₃), 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) C₁₈H₁₈FNO₄ requires 331, found 332 [M+H]⁺. HRMS C₁₈H₁₉NO₄F [M+H]⁺: calculated 332.1298 measured 332.1304 Δ ppm 1.8.

4.1.7.15. (\pm)-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. ^1H 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 (CH₃), 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) C₁₉H₂₀FNO₄ requires 345, found 346 [M+H]⁺. HRMS C₁₉H₂₁NO₄F [M+H]⁺: calculated 346.1455 measured 346.1459 Δ ppm 1.2.

4.1.7.16. (\pm)-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/Et₂O to afford **10p** as a white solid (75 mg, 58%). Mp: 110-111 °C. ¹H 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, CH₃), 1.32 (h, *J* = 7.1 Hz, 2H, R-H-3'), 0.89 (t, *J* = 7.3 Hz, 3H, R-H-4'). ¹³C 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 (CH₃), 13.6 (R-C-4'). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.3. UPLC/MS analysis: Rt 2.25 min. MS (ES) C₂₀H₂₂FNO₄ requires 359, found 360 [M+H]⁺. HRMS C₂₀H₂₃NO₄F [M+H]⁺: calculated 360.1611 measured 360.1615 Δ ppm 1.1.

4.1.7.17. (\pm)-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/Et₂O to afford **10q** as a white solid (85 mg, 59%). Mp: 105-106 °C. ¹H 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, CH₃), 1.29 (m, 4H, R-H-3' R-H-4'), 0.88 (t, $J = 6.9$ Hz, 3H, R-H-5'). ¹³C 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 (CH₃), 14.38 (R-C-5'). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.3. UPLC/MS analysis: Rt 2.42 min. MS (ES) C₂₁H₂₄FNO₄ requires 373, found 374 [M+H]⁺. HRMS C₂₁H₂₅NO₄F [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 Et₂O/ pentane to afford **10r** as a white solid (41 mg, 30%). Mp: 102-103 °C. ¹H 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, CH₃), 1.30 (m, 6H, R-H-3' R-H-4' R-H-5'), 0.88 (t, $J = 7.0$ Hz, 3H, R-H-6'). ¹³C 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 (CH₃), 14.3 (R-C-6'). ¹⁹F 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 $C_{22}H_{27}NO_4F$ $[M+H]^+$: calculated 388.1924 measured 388.1927 Δ ppm 0.8.

4.1.7.19. (\pm)-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/Et₂O to afford **10s** as a white solid (85 mg, 55%). Mp: 104-105 °C. ¹H 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, CH₃), 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'). ¹³C 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 (CH₃), 13.9 (R-C-7'). ¹⁹F 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 $C_{23}H_{29}NO_4F$ $[M+H]^+$: calculated 402.2081 measured 402.2096 Δ ppm 3.7.

4.1.7.20. (\pm)-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/Et₂O to afford **10t** as a white solid (41 mg, 30%). Mp: 103-104 °C. ¹H 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, $J = 6.6$, 2H, R-H-2'), 1.42 (d, $J = 7.1$ Hz, 3H, CH₃), 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'). ¹³C 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 (CH₃), 14.4 (R-C-8'). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.3. UPLC/MS analysis: Rt 2.86 min. MS (ES) C₂₄H₃₀FNO₄ requires 415, found 416 [M+H]⁺. HRMS C₂₄H₃₁NO₄F [M+H]⁺: calculated 416.2237 measured 416.2249 Δ ppm 2.9.

4.1.7.21. (\pm)-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. ¹H 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, CH₃), 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'). ¹³C 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 (CH₃), 13.8 (R-C-6'). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.3. UPLC/MS analysis: Rt 2.47 min. MS (ES) C₂₂H₂₆FNO₄ requires 387, found 388 [M+H]⁺. HRMS C₂₂H₂₇NO₄F [M+H]⁺: calculated 388.1924 measured 388.1945 Δ ppm 5.4.

4.1.7.22. (\pm)-2-[3-fluoro-4-[4-(hexylcarbamoyloxy)phenyl]phenyl]propanoic acid (**15b**).

Compound **15b** was prepared according to general procedure C using **14b** (146 mg, 0.36 mmol). The crude was purified by crystallization from Et₂O/Cy to afford **15b** as a white solid (65 mg, 46%). Mp: 136-137 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.48 (s, 1H, COOH), 7.78 (t, $J = 5.6$, 1H, NH), 7.53 (d, $J = 7.5$, 2H, H-8 H-12), 7.48 (t, $J = 8.3$, 1H, H-5), 7.23 (m, 2H, H-2 H-6), 7.19 (d, $J = 8.6$, 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, CH₃), 1.29 (m, 6H, R-H-3' R-H-4' R-H-5'), 0.88 (t, $J = 6.7$, 3H, R-H-6'). ¹³C 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 (CH₃), 13.8 (R-C-6'). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.3. UPLC/MS analysis: Rt 2.59 min. MS (ES) C₂₂H₂₆FNO₄ requires 387, found 388 [M+H]⁺. HRMS C₂₂H₂₇NO₄F [M+H]⁺: calculated 388.1924 measured 388.194 Δ ppm 4.1.

4.1.7.23. (\pm)-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. ^1H 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, CH₃), 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 (CH₃), 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) C₂₂H₂₇N₂O₃ requires 386, found 387 [M+H]⁺. HRMS C₂₂H₂₈N₂O₃F [M+H]⁺: calculated 387.2084 measured 387.2091 Δ ppm 1.8.

4.1.7.24. (\pm)-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. ^1H 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, CH₃), 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 (CH₃), 14.3 (R-C-6'). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 117.2. UPLC/MS analysis: Rt 2.64 min. MS (ES) C₂₂H₂₆FNO₄ requires 387, found 388 [M+H]⁺. HRMS C₂₂H₂₇NO₄F [M+H]⁺: calculated 388.1924 measured 388.1934 Δ ppm 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/Et₂O to afford **18b** as a white solid (73 mg, 62%). Mp: 90-92 °C. ¹H 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, CH₂), 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'). ¹³C 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'). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 118.0. UPLC/MS analysis: Rt 2.43 min. MS (ES) C₂₀H₂₄FNO₂ requires 373, found 374 [M+H]⁺. HRMS C₂₁H₂₅NO₄F [M+H]⁺: calculated 374.1768 measured 374.1763 Δ ppm -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%). ¹H 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'). ¹³C 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'). ¹⁹F NMR (564 MHz, DMSO-*d*₆): δ 116.4. UPLC/MS analysis: Rt 2.28 min. MS (ES) C₂₀H₂₂FNO₄ requires 359, found 360 [M+H]⁺. HRMS C₂₀H₂₃NO₄F [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. ¹H 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, CH₃), 1.29 (m, 6H, R-H-3' R-H-4' R-H-5'), 0.87 (t, $J = 6.7$ Hz, 3H, R-H-6'). ¹³C 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 (CH₃), 13.9 (R-C-6'). UPLC/MS analysis: Rt 1.24 min. MS (ES) C₂₂H₂₆ClNO₄ requires 403, found 404, 406 [M+H]⁺, 402, 404 [M-H]⁻. HRMS C₂₂H₂₇NO₄Cl [M+H]⁺: calculated 404.1629; measured 404.1644 Δ ppm 3.7.

4.1.7.28. (\pm)-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. ¹H 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-CH₃), 1.47 (p, $J = 7.3$ Hz, 2H, R-H-2'), 1.40 (d, $J = 7.1$ Hz, 3H, CH₃), 1.29 (m, 6H, H-3' H-4' H-5'), 0.88 (t, $J = 6.8$ Hz, 3H, H-6'). ¹³C 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-CH₃), 18.4 (CH₃), 13.9 (R-C-6'). UPLC/MS analysis: Rt 2.70 min. MS (ES) C₂₃H₂₉NO₄ requires 383, found 384 [M+H]⁺, 382 [M-H]⁻. HRMS C₂₃H₃₀NO₄ [M+H]⁺: calculated 384.2175; measured 384.2177 Δ ppm 0.5.

4.1.7.29. (\pm)-2-[4-[3-(hexylcarbamoyloxy)phenyl]-3-(trifluoromethyl)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]. ^1H 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, CH₃), 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, CF₃), 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 (CH₃), 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) C₂₄H₂₈F₃NO₃ requires 437, found 438 [M+H]⁺, 436 [M-H]⁻. HRMS C₂₃H₂₇NO₄F₃ [M+H]⁺: calculated 438.1892; measured 438.189 Δ ppm -0.5.

4.1.7.30. (\pm)-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 Et₂O/ pentane to afford **29e** as a white solid (73 mg, 62%). Mp: 125-127 °C. ^1H 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, CH₃), 1.29 (m, 6H, R-H-3' R-H-4' R-H-5'), 0.88 (t, $J = 6.7$ Hz, 3H, R-H-6').
¹³C 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 (CH₃), 14.3 (R-C-6'). UPLC/MS analysis: Rt 2.30 min. MS (ES) C₂₂H₂₇NO₄
 requires 369, found 370 [M+H]⁺. HRMS C₂₂H₂₈NO₄ [M+H]⁺: calculated 370.2018; measured
 370.2027 Δ ppm 2.4.

4.1.7.31. (\pm)-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. ¹H 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, CH₃), 1.28 (m, 6H, R-H-3' R-H-4' R-
 H-5'), 0.86 (t, $J = 7.1$ Hz, 3H, R-H-6'). ¹³C 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 (CH₃), 13.9 (R-C-6').
 UPLC/MS analysis: Rt 2.44 min. MS (ES) C₂₂H₂₆N₂O₆ requires 414, found 415 [M+H]⁺, 369
 [M-H - CO₂]⁻. HRMS C₂₂H₂₇N₂O₆ [M+H]⁺: calculated 415.1869; measured 415.188 Δ ppm 2.6.

4.1.8. (\pm)-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 2M 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. (\pm)-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** (1g, 3.57 mmol) in MeOH (54 mL), concentrated H_2SO_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_2O (15 mL) and filtered through a pad of SiO_2 to afford **16b** as a yellow liquid (1.03 g, quant.).

4.1.11. (\pm)-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 Na₂SO₄ 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:* H₂O (25 mL), AcOH (38 mL) and H₂SO₄ (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 Na₂CO₃ solution and the aqueous layer was acidified with 1N HCl, and extracted with DCM. The organic layer was dried over Na₂SO₄ 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), H₂SO₄ (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 alumina 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 H₂O, the thick slurry was basified with K₂CO₃, EtOAc was added, filtered through a pad of Celite and the two phases separated. The organic layer was dried over Na₂SO₄ and evaporated to give **25a** as an orange oil (2.57 g, 64%).

4.1.14 (\pm)-Methyl 2-(3-chloro-4-iodo-phenyl)propanoate (**26a**). A solution of NaNO₂ (0.91 g, 13.2 mmol) in H₂O (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 Na₂SO₃ was added. The solution was extracted with TBME, dried over Na₂SO₄, 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. (\pm)-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 Et₂O. The organic solvent was washed with brine, dried over Na₂SO₄ 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:* H₂O (25 mL), AcOH (41 mL) and H₂SO₄ (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 K₂CO₃, and the separated aqueous layer was acidified with concentrated HCl, extracted with DCM, washed with brine and dried over Na₂SO₄. 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. (\pm)-Methyl 2-(3-methyl-4-nitro-phenyl)propanoate (**24b**). To a solution of **23b** (2.5 g, 11.95 mmol) in MeOH (120 mL), H₂SO₄ (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 Et₂O 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. (\pm)-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), HCO₂NH₄ (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 of SiO₂ and evaporated to **25b** as a yellow oil (1.85 g, 98%).

4.1.18. (\pm)-Methyl 2-(4-iodo-3-methyl-phenyl)propanoate (**26b**). A solution of NaNO₂ (0.71 g, 10.24 mmol) in H₂O (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. Na₂SO₃ was added and the product was extracted with Et₂O, dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (Cy/EtOAc, 95: 5) to give **26b** as clear oil (1.14 g, 39%).

4.1.18. (\pm)-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_2SO_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_2O (25 mL), AcOH (37 mL) and H_2SO_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_2CO_3 solution and the aqueous layer was acidified with 1N HCl, and extracted with DCM. The organic layer was dried over Na_2SO_4 and evaporated to give **23c** as an orange oil (5.59 g, 85%).

4.1.19. (\pm)-Methyl 2-[4-nitro-3-(trifluoromethyl)phenyl]propanoate (**24c**). **23c** (5.59 g, 21.24 mmol) was dissolved in MeOH (28 mL), H_2SO_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 alumina pad. The solvent was removed under reduced pressure to give **24c** as an orange oil (5.70 g, 97%).

4.1.20. (\pm)-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_2NH_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 of SiO_2 and evaporated to **25c** as a dark red oil (4.94 g, quant.).

4.1.21. (\pm)-Methyl 2-[4-iodo-3-(trifluoromethyl)phenyl]propanoate (**26c**). A solution of NaNO_2 (1.48 g, 21.38 mmol) in H_2O (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. Na₂SO₃ was added and the product was extracted with TBME, dried over Na₂SO₄ and evaporated. The residue was purified by column chromatography (Cy: EtOAc, 95: 5) to give **26c** as clear oil (5.51 g, 77%).

4.1.22. (\pm)-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), 2M 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. ¹H 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, CH₃), 1.28 (m, 6H, R-H-3' R-H-4' R-H-5'), 0.88 (t, J = 6.8 Hz, 3H, R-H-6'). ¹³C 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 (CH₃), 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 Δ ppm 2.1.

4.1.23. (\pm)-Methyl 2-(4-nitrophenyl)propanoate (**24e**). To a solution of **23e** (1.95 g, 10 mmol) in MeOH (20 mL), concentrated H_2SO_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_2O (15 mL) and filtered through a pad of SiO_2 to afford **24e** as yellow oil (2.10 g, quant.)

4.1.24. (\pm)-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_2NH_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.).

4.1.25. (\pm)-Methyl 2-(4-iodophenyl)propanoate (**26e**). A solution of $NaNO_2$ (0.69g, 10 mmol) in H_2O (1.5 mL) was added slowly to a solution of **25e** (1.75g, 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_2O and the organic phase was then washed with a 1M solution of Na_2SO_3 (20 mL), dried over Na_2SO_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%).

4.1.26. (\pm)-Methyl 2-(4-amino-3-nitro-phenyl)propanoate (**25f**). *Step 1*: A solution of **25e** (3.58 g, 20 mmol) in Ac₂O (100 mL) was heated at 130 °C for 1 h. The solution was poured into H₂O, stirred for 3 h then evaporated. The residual solid was taken up in H₂O and filtered under vacuum 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. H₂O was added and the precipitate was filtered under vacuum and washed with H₂O to obtain methyl 2-(4-acetamidophenyl)propanoate as a cream colored solid (2.21 g, 50%). *Step 2*: (\pm)-Methyl 2-(4-acetamidophenyl)propanoate (2.21 g, 10 mmol) in Ac₂O (10 mL) was cooled to 0 °C. HNO₃ (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 NaHCO₃ solution, dried over Na₂SO₄ and evaporated to give (\pm)-methyl 2-(4-acetamido-3-nitro-phenyl)propanoate as a dark orange oil (2.60 g, 98%). *Step 3*: To a solution of (\pm)-methyl 2-(4-acetamido-3-nitro-phenyl)propanoate (2.60 g, 9.77 mmol) in MeOH (98 mL) H₂SO₄ (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 Na₂CO₃ (2M, 120 mL), then extracted with EtOAc, dried over Na₂SO₄ and evaporated to give **25f** as a dark orange oil (2.20 g, quant.) which was used in the next step without further purification.

4.1.27. (\pm)-Methyl 2-(4-iodo-3-nitro-phenyl)propanoate (**26f**). A solution of NaNO₂ (0.74 g, 10.79 mmol) in H₂O (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 Na₂SO₃ was added. The solution was extracted with TBME, dried over Na₂SO₄ 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%).

4.1.28. (\pm)-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 Et₂O. The solid was filtered under vacuum to obtain **29g** as an off-white solid (488 mg, 55 %). Mp: 180 °C [dec]. ¹H 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, CH₃), 1.29 (m, 6H, R-H-3' R-H-4' R-H-5'), 0.87 (t, *J* = 6.7 Hz, 3H, R-H-6'), NH₃⁺ not visible. ¹³C 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 (CH₃), 13.9 (R-C-6'). UPLC/MS analysis: Rt 2.46 min. MS (ES)

$C_{22}H_{28}N_2O_4$ requires 384, found 385 $[M+H]^+$, 383 $[M-H]^-$. HRMS $C_{22}H_{29}N_2O_4$ $[M+H]^+$: calculated 385.2127; measured 385.2161 Δ ppm 8.8.

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

4.1.29.1. (-)-2-[3-fluoro-4-[3-(hexylcarbamoyloxy)phenyl]phenyl]propanoic acid ((-)-**10r**). First eluted enantiomer (15.2 min), 112 mg (45%). Mp: 99-100 °C. 1H 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, CH₃), 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 (CH₃), 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 $[M+H]^+$. $[\alpha]_D^{20}$ -29° (c 1.0, CHCl₃). >99.5% ee. HRMS $C_{22}H_{27}NO_4F$ $[M+H]^+$: calculated 388.1924; measured 388.1919 Δ ppm -1.3.

4.1.29.2. (+)-2-[3-fluoro-4-[3-(hexylcarbamoyloxy)phenyl]phenyl]propanoic acid ((+)-**10r**). Second eluted enantiomer (25.7 min), 172 mg (45%). Mp: 101-102 °C. 1H 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, CH₃), 1.30 (m, 6H, R-H-3' R-H-4' R-H-5'), 0.88 (t, $J = 7.0$ Hz, 3H, R-H-6'). ¹³C 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 (CH₃), 14.3 (R-C-6'). ¹⁹F NMR (564 MHz, DMSO- d_6): δ 117.3. UPLC/MS analysis: Rt 2.59 min. MS (ES) C₂₂H₂₆FNO₄ requires 387, found 388 [M+H]⁺. $[\alpha]_D^{20} +29^\circ$ (c 1.0, CHCl₃). >99.5% ee. HRMS C₂₂H₂₇NO₄F [M+H]⁺: calculated 388.1924; measured 388.1927 Δ ppm 0.8.

4.2. Enzyme assays.

Quantitative ¹H 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 μ g of total rat brain homogenate were pre-incubated in 445.5 μ L of assay buffer (50mM 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- ^3H] (American Radiolabeled Chemicals Inc., ART. 0626, conc. 1 mCi/mL, S.A. 60 Ci/mmol). The reaction was stopped by adding cold 1:1 $\text{CHCl}_3/\text{MeOH}$. After 10 min of centrifugation (845xg at 4 °C) 600 μL of aqueous phase were transferred into scintillation vials previously filled with 3 mL of scintillation fluid (Ultima GoldTM, Perkin Elmer Inc., Cat. 6013329). Radioactivity was measured by liquid scintillation counting (MicroBeta2 LumiJET Perkin Elmer Inc.).

4.2.3. *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 PGF2 α 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.

4.2.4. 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 ($55 \pm 10\%$). 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 1h 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 $2000 \times g$ for 30 min to obtain plasma. OEA was extracted from plasma and measured by LC/MS as described. Briefly, 300 μ L of plasma were centrifuged with cold acetone (1 mL) containing [2H_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 to 10 μ M). Tissue levels of TXA₂ and 6-keto-PGF_{1 α} were determined using ELISA kits (ABcam, Cambridge, UK), following manufacturer's instructions.

Conflict of interest: The authors declare the following competing financial interest: Daniele Piomelli, Rita Scarpelli, Marco Migliore, Damien Habrant are inventors on the patent application WO2014023643, filed by the University of California and Fondazione Istituto Italiano di Tecnologia, which protects novel compounds disclosed in this paper.

Acknowledgement: The authors thank Dr Angelo Reggiani for helpful discussions, Ms Silvia Venzano and Mr Luca Goldoni for technical support and the National Institute on Drug Abuse (grant DA012413 to D.P.) for financial support.

Appendix A. Supplementary material: Supplementary data related to this article including ¹H, ¹³C NMR data and UPLC/MS analysis of all the intermediates for the preparation of tested compounds **9r**, **10a-t**, **12**, **15a-d**, **18b**, **21a**, **c**, **29a-g**; experimental details for the absolute configurational assignment of compounds (-)-**10r** and (+)-**10r** (**Scheme S1**); *in vitro* pharmacology data of (S)-(+)-**10r** on a panel of >90 biologically relevant targets (**Table S1**); copies of ¹H, ¹³C ¹⁹F NMR data and UPLC/MS analysis of the tested compounds **9r**, **10a-t**, **12**, **15a-d**, **18b**, **21a**, **c**, **29a-g** can be found at [http:// XXXX](http://XXXX).

REFERENCES

- [1] J. Steinmeyer, Pharmacological basis for the therapy of pain and inflammation with nonsteroidal anti-inflammatory drugs, *Arthritis Res*, 2 (2000) 379-385.
- [2] J.F. Fries, NSAID gastropathy: the second most deadly rheumatic disease? Epidemiology and risk appraisal, *J Rheumatol Suppl*, 28 (1991) 6-10.
- [3] R. Tamblyn, L. Berkson, W.D. Dauphinee, D. Gayton, R. Grad, A. Huang, L. Isaac, P. McLeod, L. Snell, Unnecessary prescribing of NSAIDs and the management of NSAID-related gastropathy in medical practice, *Ann Intern Med*, 127 (1997) 429-438.
- [4] B.K. Reuter, N.M. Davies, J.L. Wallace, Nonsteroidal anti-inflammatory drug enteropathy in rats: role of permeability, bacteria, and enterohepatic circulation, *Gastroenterology*, 112 (1997) 109-117.
- [5] N.M. Davies, J.L. Wallace, Nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: new insights into an old problem, *J Gastroenterol*, 32 (1997) 127-133.
- [6] A.L. Blobaum, L.J. Marnett, Structural and functional basis of cyclooxygenase inhibition, *J Med Chem*, 50 (2007) 1425-1441.
- [7] J.L. Wallace, NSAID gastroenteropathy: past, present and future, *Can J Gastroenterol*, 10 (1996) 451-459.
- [8] J.L. Wallace, Prostaglandins, NSAIDs, and gastric mucosal protection: why doesn't the stomach digest itself?, *Physiol Rev*, 88 (2008) 1547-1565.
- [9] J.L. Wallace, L. Vong, NSAID-induced gastrointestinal damage and the design of GI-sparing NSAIDs, *Curr Opin Investig Drugs*, 9 (2008) 1151-1156.
- [10] E. Ricciotti, G.A. FitzGerald, Prostaglandins and inflammation, *Arterioscler Thromb Vasc Biol*, 31 (2011) 986-1000.
- [11] J.A. Mitchell, T.D. Warner, COX isoforms in the cardiovascular system: understanding the activities of non-steroidal anti-inflammatory drugs, *Nat Rev Drug Discov*, 5 (2006) 75-86.
- [12] J. Zhang, E.L. Ding, Y. Song, Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials, *JAMA*, 296 (2006) 1619-1632.
- [13] C.A. Rouzer, L.J. Marnett, Endocannabinoid oxygenation by cyclooxygenases, lipoxygenases, and cytochromes P450: cross-talk between the eicosanoid and endocannabinoid signaling pathways, *Chem Rev*, 111 (2011) 5899-5921.
- [14] F. Piscitelli, V. Di Marzo, "Redundancy" of endocannabinoid inactivation: new challenges and opportunities for pain control, *ACS Chem Neurosci*, 3 (2012) 356-363.
- [15] S. Maione, B. Costa, V. Di Marzo, Endocannabinoids: a unique opportunity to develop multitarget analgesics, *Pain*, 154 Suppl 1 (2013) S87-93.
- [16] J.L. Wallace, L.J. Ignarro, S. Fiorucci, Potential cardioprotective actions of no-releasing aspirin, *Nat Rev Drug Discov*, 1 (2002) 375-382.
- [17] L. Lazzarato, M. Donnola, B. Rolando, E. Marini, C. Cena, G. Coruzzi, E. Guaita, G. Morini, R. Fruttero, A. Gasco, S. Biondi, E. Ongini, Searching for new NO-donor aspirin-like molecules: a new class of nitrooxy-acyl derivatives of salicylic acid, *J Med Chem*, 51 (2008) 1894-1903.
- [18] R.R. Ranatunge, M. Augustyniak, U.K. Bandarage, R.A. Earl, J.L. Ellis, D.S. Garvey, D.R. Janero, L.G. Letts, A.M. Martino, M.G. Murty, S.K. Richardson, J.D. Schroeder, M.J. Shumway, S.W. Tam, A.M. Trocha, D.V. Young, Synthesis and selective cyclooxygenase-2 inhibitory activity of a series of novel, nitric oxide donor-containing pyrazoles, *J Med Chem*, 47 (2004) 2180-2193.

- [19] K. Chegaev, L. Lazzarato, P. Tosco, C. Cena, E. Marini, B. Rolando, P.A. Carrupt, R. Fruttero, A. Gasco, NO-donor COX-2 inhibitors. New nitrooxy-substituted 1,5-diarylimidazoles endowed with COX-2 inhibitory and vasodilator properties, *J Med Chem*, 50 (2007) 1449-1457.
- [20] J.L. Wallace, Hydrogen sulfide-releasing anti-inflammatory drugs, *Trends Pharmacol Sci*, 28 (2007) 501-505.
- [21] J.L. Wallace, G. Caliendo, V. Santagada, G. Cirino, S. Fiorucci, Gastrointestinal safety and anti-inflammatory effects of a hydrogen sulfide-releasing diclofenac derivative in the rat, *Gastroenterology*, 132 (2007) 261-271.
- [22] J.L. Wallace, G. Caliendo, V. Santagada, G. Cirino, Markedly reduced toxicity of a hydrogen sulphide-releasing derivative of naproxen (ATB-346), *Br J Pharmacol*, 159 (2010) 1236-1246.
- [23] C. Charlier, C. Michaux, Dual inhibition of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) as a new strategy to provide safer non-steroidal anti-inflammatory drugs, *Eur J Med Chem*, 38 (2003) 645-659.
- [24] P.N. Rao, Q.H. Chen, E.E. Knaus, Synthesis and structure-activity relationship studies of 1,3-diarylprop-2-yn-1-ones: dual inhibitors of cyclooxygenases and lipoxygenases, *J Med Chem*, 49 (2006) 1668-1683.
- [25] S.H. Hwang, K.M. Wagner, C. Morisseau, J.Y. Liu, H. Dong, A.T. Weckslar, B.D. Hammock, Synthesis and structure-activity relationship studies of urea-containing pyrazoles as dual inhibitors of cyclooxygenase-2 and soluble epoxide hydrolase, *J Med Chem*, 54 (2011) 3037-3050.
- [26] M. Seierstad, J.G. Breitenbucher, Discovery and development of fatty acid amide hydrolase (FAAH) inhibitors, *J Med Chem*, 51 (2008) 7327-7343.
- [27] M.T. Cocco, C. Congiu, V. Onnis, M. Morelli, O. Cauli, Synthesis of ibuprofen heterocyclic amides and investigation of their analgesic and toxicological properties, *Eur J Med Chem*, 38 (2003) 513-518.
- [28] S. Holt, B. Paylor, L. Boldrup, K. Alajakku, S. Vandevoorde, A. Sundstrom, M.T. Cocco, V. Onnis, C.J. Fowler, Inhibition of fatty acid amide hydrolase, a key endocannabinoid metabolizing enzyme, by analogues of ibuprofen and indomethacin, *Eur J Pharmacol*, 565 (2007) 26-36.
- [29] K.C. Duggan, D.J. Hermanson, J. Musee, J.J. Prusakiewicz, J.L. Scheib, B.D. Carter, S. Banerjee, J.A. Oates, L.J. Marnett, (R)-Profens are substrate-selective inhibitors of endocannabinoid oxygenation by COX-2, *Nat Chem Biol*, 7 (2011) 803-809.
- [30] A.D. Favia, D. Habrant, R. Scarpelli, M. Migliore, C. Albani, S.M. Bertozzi, M. Dionisi, G. Tarozzo, D. Piomelli, A. Cavalli, M. De Vivo, Identification and Characterization of Carprofen as a Multitarget Fatty Acid Amide Hydrolase/Cyclooxygenase Inhibitor, *Journal of Medicinal Chemistry*, 55 (2012) 8807-8826.
- [31] M.A. Windsor, D.J. Hermanson, P.J. Kingsley, S. Xu, B.C. Crews, W. Ho, C.M. Keenan, S. Banerjee, K.A. Sharkey, L.J. Marnett, Substrate-Selective Inhibition of Cyclooxygenase-2: Development and Evaluation of Achiral Profen Probes, *ACS Med Chem Lett*, 3 (2012) 759-763.
- [32] C.J. Fowler, E. Bjorklund, A.H. Lichtman, P.S. Naidu, C. Congiu, V. Onnis, Inhibitory properties of ibuprofen and its amide analogues towards the hydrolysis and cyclooxygenation of the endocannabinoid anandamide, *J Enzyme Inhib Med Chem*, 28 (2013) 172-182.
- [33] M. Cipriano, E. Bjorklund, A.A. Wilson, C. Congiu, V. Onnis, C.J. Fowler, Inhibition of fatty acid amide hydrolase and cyclooxygenase by the N-(3-methylpyridin-2-yl)amide derivatives of flurbiprofen and naproxen, *Eur J Pharmacol*, 720 (2013) 383-390.

- [34] C.N. Serhan, N. Chiang, T.E. Van Dyke, Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators, *Nat Rev Immunol*, 8 (2008) 349-361.
- [35] C. Morisseau, B.D. Hammock, Impact of soluble epoxide hydrolase and epoxyeicosanoids on human health, *Annu Rev Pharmacol Toxicol*, 53 (2013) 37-58.
- [36] F. Massa, G. Marsicano, H. Hermann, A. Cannich, K. Monory, B.F. Cravatt, G.L. Ferri, A. Sibae, M. Storr, B. Lutz, The endogenous cannabinoid system protects against colonic inflammation, *J Clin Invest*, 113 (2004) 1202-1209.
- [37] M.T. Cencioni, V. Chiurchiu, G. Catanzaro, G. Borsellino, G. Bernardi, L. Battistini, M. Maccarrone, Anandamide suppresses proliferation and cytokine release from primary human T-lymphocytes mainly via CB2 receptors, *PLoS One*, 5 (2010) e8688.
- [38] V. Chiurchiu, M.T. Cencioni, E. Bisicchia, M. De Bardi, C. Gasperini, G. Borsellino, D. Centonze, L. Battistini, M. Maccarrone, Distinct modulation of human myeloid and plasmacytoid dendritic cells by anandamide in multiple sclerosis, *Ann Neurol*, 73 (2013) 626-636.
- [39] J. Fu, S. Gaetani, F. Oveisi, J. Lo Verme, A. Serrano, F. Rodriguez De Fonseca, A. Rosengarth, H. Luecke, B. Di Giacomo, G. Tarzia, D. Piomelli, Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-alpha, *Nature*, 425 (2003) 90-93.
- [40] J. LoVerme, R. Russo, G. La Rana, J. Fu, J. Farthing, G. Mattace-Raso, R. Meli, A. Hohmann, A. Calignano, D. Piomelli, Rapid broad-spectrum analgesia through activation of peroxisome proliferator-activated receptor-alpha, *J Pharmacol Exp Ther*, 319 (2006) 1051-1061.
- [41] M. Suardiaz, G. Estivill-Torres, C. Goicoechea, A. Bilbao, F. Rodriguez de Fonseca, Analgesic properties of oleylethanolamide (OEA) in visceral and inflammatory pain, *Pain*, 133 (2007) 99-110.
- [42] D.E. Wilson, Role of prostaglandins in gastroduodenal mucosal protection, *J Clin Gastroenterol*, 13 Suppl 1 (1991) S65-71.
- [43] K. Wright, N. Rooney, M. Feeney, J. Tate, D. Robertson, M. Welham, S. Ward, Differential expression of cannabinoid receptors in the human colon: cannabinoids promote epithelial wound healing, *Gastroenterology*, 129 (2005) 437-453.
- [44] P.S. Naidu, L. Booker, B.F. Cravatt, A.H. Lichtman, Synergy between enzyme inhibitors of fatty acid amide hydrolase and cyclooxygenase in visceral nociception, *J Pharmacol Exp Ther*, 329 (2009) 48-56.
- [45] O. Sasso, R. Bertorelli, T. Bandiera, R. Scarpelli, G. Colombano, A. Armirotti, G. Moreno-Sanz, A. Reggiani, D. Piomelli, Peripheral FAAH inhibition causes profound antinociception and protects against indomethacin-induced gastric lesions, *Pharmacol Res*, 65 (2012) 553-563.
- [46] T.W. Grim, S. Ghosh, K.L. Hsu, B.F. Cravatt, S.G. Kinsey, A.H. Lichtman, Combined inhibition of FAAH and COX produces enhanced anti-allodynic effects in mouse neuropathic and inflammatory pain models, *Pharmacol Biochem Behav*, 124 (2014) 405-411.
- [47] D. Richardson, R.G. Pearson, N. Kurian, M.L. Latif, M.J. Garle, D.A. Barrett, D.A. Kendall, B.E. Scammell, A.J. Reeve, V. Chapman, Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis, *Arthritis Res Ther*, 10 (2008) R43.
- [48] A. Di Sabatino, N. Battista, P. Biancheri, C. Rapino, L. Rovedatti, G. Astarita, A. Vanoli, E. Dainese, M. Guerci, D. Piomelli, S.L. Pender, T.T. MacDonald, M. Maccarrone, G.R. Corazza, The endogenous cannabinoid system in the gut of patients with inflammatory bowel disease, *Mucosal Immunol*, 4 (2011) 574-583.

- [49] J. Suarez, Y. Romero-Zerbo, L. Marquez, P. Rivera, M. Iglesias, F.J. Bermudez-Silva, M. Andreu, F. Rodriguez de Fonseca, Ulcerative colitis impairs the acylethanolamide-based anti-inflammatory system reversal by 5-aminosalicylic acid and glucocorticoids, *PLoS One*, 7 (2012) e37729.
- [50] Singer, II, D.W. Kawka, S. Schloemann, T. Tessner, T. Riehl, W.F. Stenson, Cyclooxygenase 2 is induced in colonic epithelial cells in inflammatory bowel disease, *Gastroenterology*, 115 (1998) 297-306.
- [51] O. Sasso, M. Migliore, D. Habrant, A. Armirotti, C. Albani, M. Summa, G. Moreno-Sanz, R. Scarpelli, D. Piomelli, Multitarget fatty acid amide hydrolase/cyclooxygenase blockade suppresses intestinal inflammation and protects against nonsteroidal anti-inflammatory drug-dependent gastrointestinal damage, *FASEB J*, 29 (2015) 2616-2627.
- [52] S. Kathuria, S. Gaetani, D. Fegley, F. Valino, A. Duranti, A. Tontini, M. Mor, G. Tarzia, G. La Rana, A. Calignano, A. Giustino, M. Tattoli, M. Palmery, V. Cuomo, D. Piomelli, Modulation of anxiety through blockade of anandamide hydrolysis, *Nat Med*, 9 (2003) 76-81.
- [53] G. Tarzia, A. Duranti, A. Tontini, G. Piersanti, M. Mor, S. Rivara, P.V. Plazzi, C. Park, S. Kathuria, D. Piomelli, Design, synthesis, and structure-activity relationships of alkylcarbamic acid aryl esters, a new class of fatty acid amide hydrolase inhibitors, *J Med Chem*, 46 (2003) 2352-2360.
- [54] M. Mor, S. Rivara, A. Lodola, P.V. Plazzi, G. Tarzia, A. Duranti, A. Tontini, G. Piersanti, S. Kathuria, D. Piomelli, Cyclohexylcarbamic acid 3'- or 4'-substituted biphenyl-3-yl esters as fatty acid amide hydrolase inhibitors: synthesis, quantitative structure-activity relationships, and molecular modeling studies, *J Med Chem*, 47 (2004) 4998-5008.
- [55] G. Tarzia, A. Duranti, G. Gatti, G. Piersanti, A. Tontini, S. Rivara, A. Lodola, P.V. Plazzi, M. Mor, S. Kathuria, D. Piomelli, Synthesis and structure-activity relationships of FAAH inhibitors: cyclohexylcarbamic acid biphenyl esters with chemical modulation at the proximal phenyl ring, *ChemMedChem*, 1 (2006) 130-139.
- [56] M. Mor, A. Lodola, S. Rivara, F. Vacondio, A. Duranti, A. Tontini, S. Sanchini, G. Piersanti, J.R. Clapper, A.R. King, G. Tarzia, D. Piomelli, Synthesis and quantitative structure-activity relationship of fatty acid amide hydrolase inhibitors: modulation at the N-portion of biphenyl-3-yl alkylcarbamates, *J Med Chem*, 51 (2008) 3487-3498.
- [57] M. Mileni, S. Kamtekar, D.C. Wood, T.E. Benson, B.F. Cravatt, R.C. Stevens, Crystal structure of fatty acid amide hydrolase bound to the carbamate inhibitor URB597: discovery of a deacylating water molecule and insight into enzyme inactivation, *J Mol Biol*, 400 (2010) 743-754.
- [58] J.R. Clapper, G. Moreno-Sanz, R. Russo, A. Guijarro, F. Vacondio, A. Duranti, A. Tontini, S. Sanchini, N.R. Sciolino, J.M. Spradley, A.G. Hohmann, A. Calignano, M. Mor, G. Tarzia, D. Piomelli, Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism, *Nat Neurosci*, 13 (2010) 1265-1270.
- [59] R.G. Kurumbail, A.M. Stevens, J.K. Gierse, J.J. McDonald, R.A. Stegeman, J.Y. Pak, D. Gildehaus, J.M. Miyashiro, T.D. Penning, K. Seibert, P.C. Isakson, W.C. Stallings, Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents, *Nature*, 384 (1996) 644-648.
- [60] B.S. Selinsky, K. Gupta, C.T. Sharkey, P.J. Loll, Structural analysis of NSAID binding by prostaglandin H2 synthase: time-dependent and time-independent inhibitors elicit identical enzyme conformations, *Biochemistry*, 40 (2001) 5172-5180.

- [61] C.I. Bayly, W.C. Black, S. Leger, N. Ouimet, M. Ouellet, M.D. Percival, Structure-based design of COX-2 selectivity into flurbiprofen, *Bioorg Med Chem Lett*, 9 (1999) 307-312.
- [62] G. Lu, R. Franzén, X.J. Yu, Y.J. Xu, Synthesis of Flurbiprofen via Suzuki Reaction Catalyzed by Palladium Charcoal in Water, *Chinese Chemical Letters*, 17 (2006) 461-464.
- [63] A. Del Zotto, F. Amoroso, W. Baratta, P. Rigo, Very Fast Suzuki-Miyaura Reaction Catalyzed by Pd(OAc)₂ under Aerobic Conditions at Room Temperature in EGME/H₂O, *European Journal of Organic Chemistry*, 2009 (2009) 110-116.
- [64] S. Narasimhan, R. Balakumar, Zirconium Borohydride - a Versatile Reducing Agent for the Reduction of Electrophilic and Nucleophilic Substrates, *Synthetic Communications*, 30 (2000) 4387-4395.
- [65] W.C. Bartolini, Brian M.; Chen, Barbara; Chien, Yueh-Tyng; Currie, Mark G.; Milne, Todd G.; Pearson, J.J.Z. James Philip; Talley, Craig, Cyclooxygenase 2 (COX-2) and fatty acid amide hydrolase (FAAH) inhibitors for therapeutic use, WO2005002525.
- [66] M.G. Malkowski, S.L. Ginell, W.L. Smith, R.M. Garavito, The productive conformation of arachidonic acid bound to prostaglandin synthase, *Science*, 289 (2000) 1933-1937.
- [67] J.R. Kiefer, J.L. Pawlitz, K.T. Moreland, R.A. Stegeman, W.F. Hood, J.K. Gierse, A.M. Stevens, D.C. Goodwin, S.W. Rowlinson, L.J. Marnett, W.C. Stallings, R.G. Kurumbail, Structural insights into the stereochemistry of the cyclooxygenase reaction, *Nature*, 405 (2000) 97-101.
- [68] G. Wider, L. Dreier, Measuring protein concentrations by NMR spectroscopy, *J Am Chem Soc*, 128 (2006) 2571-2576.
- [69] I.W. Burton, M.A. Quilliam, J.A. Walter, Quantitative ¹H NMR with external standards: use in preparation of calibration solutions for algal toxins and other natural products, *Anal Chem*, 77 (2005) 3123-3131.

Highlights

Potent Multi-target FAAH-COX Inhibitors: Design and Structure-Activity Relationship Studies

Marco Migliore,^a Damien Habrant,^{a,1} Oscar Sasso,^a Clara Albani,^{a,2} Sine Mandrup Bertozzi,^a
Andrea Armirotti,^a Daniele Piomelli^{a,b*} and Rita Scarpelli^{a*}

- Rational design - SAR exploration of the first class of potent multitarget inhibitors of FAAH and COX enzymes;
- Focused SAR studies around **10r** (ARN2508) identified novel leads **18b** and **29a-c, e**;
- Stereochemical and pharmacological studies of **10r** enantiomers are reported;
- Animal studies indicate that (*S*)-(+)-**10r** strongly inhibits FAAH and COX activities *in vivo*.