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Development of LM98, a Small-Molecule TEAD Inhibitor Derived from Flufenamic Acid

Léa Mélin,[a] Shuay Abdullayev,[a] Ahmed Fnaiche,[a] Victoria Vu,[b] Narjara González Suárez,[a] Hong Zeng,[b] Magdalena M. Szewczyk,[b] Fengling Li,[b] Guillermo Senisterra,[b] Abdellah Allali-Hassani,[b] Irene Chau,[b] Aiping Dong,[b] Simon Woo,[c] Borhane Annabi,[a] Levon Halabelian,[b] Steven R. LaPlante,[c] Masoud Vedadi,[b, d] Dalia Barsyte-Lovejoy,[b, d] Vijayaratnam Santhakumar,[b] and Alexandre Gagnon*[a]

Dedicated to our dear friend and colleague Prof. Eric Marsault, who passed away on January 13th, 2021

The YAP-TEAD transcriptional complex is responsible for the expression of genes that regulate cancer cell growth and proliferation. Dysregulation of the Hippo pathway due to overexpression of TEAD has been reported in a wide range of cancers. Inhibition of TEAD represses the expression of associated genes, demonstrating the value of this transcription factor for the development of novel anti-cancer therapies. We report herein the design, synthesis and biological evaluation of LM98, a flufenamic acid analogue. LM98 shows strong affinity to TEAD, inhibits its autopalmitoylation and reduces the YAP-TEAD transcriptional activity. Binding of LM98 to TEAD was supported by ^{19}F-NMR studies while co-crystallization experiments confirmed that LM98 is anchored within the palmitic acid pocket of TEAD. LM98 reduces the expression of *CTGF* and *Cyr61*, inhibits MDA-MB-231 breast cancer cell migration and arrests cell cycling in the S phase during cell division.

Introduction

The Hippo signaling pathway plays a crucial role in organ size by controlling the balance between cell proliferation and apoptosis.[1] TEAD (transcriptional enhancer factor with TEA/ATTS domain), the downstream effector of the Hippo pathway, is composed of an N-terminal DNA binding domain and a C-terminal YAP-binding domain (YBD) that binds to co-regulator YAP (Yes-associated protein) or its paralog TAZ (transcriptional co-activator with PDZ-binding motif). Since TEAD does not possess an activation domain and because YAP and TAZ do not have a DNA binding domain, TEAD and coactivators YAP or TAZ must associate in the nucleus to form a transcriptionally active YAP/TAZ-TEAD complex. In the active Hippo pathway, external signals such as hormonal cues, cell junctions, extracellular matrix as well as proteins RASSF and NF2/Merlin trigger a cascade of kinases involving Mst1/2, Sav, Mob1 and Lats1/2 which ultimately results in the phosphorylation of YAP. Subsequent recruitment of phosphorylated YAP by protein 14-3-3 then leads to its retention and degradation in the cytoplasm, therefore precluding its interaction with TEAD and preventing the transcription of associated genes.[2,3] Conversely, in the inactive Hippo pathway, unphosphorylated YAP translocates to the nucleus where it binds to one of the four paralogs of TEAD[4,5] to initiate the transcription of target genes such as *Cyr61*, *CTGF* (Connective Tissue Growth Factor), *c-myc*, receptor tyrosine kinase *Axl* and *Survivin*.[6,7,8,9]

Numerous studies have shown that the dysregulation of the Hippo pathway can lead to various forms of cancer.[10,11] For instance, increased YAP expression and nuclear localization have been observed in liver, colon, ovarian, lung and prostate cancer[12,13] while upregulation of TEAD and poor patients survival were correlated with gastric, breast and prostate cancers.[14–17] Aberrant Hippo can lead to organ overgrowth and tumorigenesis, as demonstrated in mouse models where elevated nuclear YAP induced by a double Mst mutation resulted in an oversized liver with carcinoma.[18] The proto-oncogenic nature of YAP comes from its interaction with TEAD[19,20] which leads to the activation of genes that confer cancer-associated traits to cells such as the ability to induce chemoresistance and metastasis.[21–23] Silencing of the majority of YAP-inducible genes and attenuation of YAP-induced overgrowth in TEAD knockdowns suggest that TEAD is a highly valuable target for drug development.[19] Furthermore, TEAD

[a] L. Mélin, S. Abdullayev, A. Fnaiche, N. González Suárez, Prof. B. Annabi, Prof. A. Gagnon
Département de chimie, Université du Québec à Montréal
C.P. 8888, Succ. Centre-Ville, Montréal QC,
H3C 3P8 (Canada)
E-mail: gagnon.alexandre@uqam.ca
[b] Dr. V. Vu, H. Zeng, Dr. M. M. Szewczyk, Dr. F. Li, Dr. G. Senisterra, Dr. A. Allali-Hassani, I. Chau, Dr. A. Dong, Dr. L. Halabelian, Prof. M. Vedadi, Dr. D. Barsyte-Lovejoy, Dr. V. Santhakumar
Structural Genomics Consortium, University of Toronto
101 College St. MaRS South Tower, Toronto, ON, M5G 1 L7 (Canada)
[c] Dr. S. Woo, Prof. S. R. LaPlante
INRS-Centre Armand Frappier Santé Biotechnologie,
Université du Québec
531 Boulevard des Prairies, Laval, QC,
H7V 1B7 (Canada)
[d] Prof. M. Vedadi, Dr. D. Barsyte-Lovejoy
Department of Pharmacology and Toxicology
University of Toronto, Toronto, ON,
M5S 1 A8 (Canada)

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appears to be dispensable for tissue homeostasis in adults, therefore decreasing the risks of major adverse side effects.[24] Taken together, these results indicate that blocking the formation of the YAP-TEAD transcription complex can abolish the oncogenic function of YAP.[20]

The crystal structure of YAP2 with TEAD1 (PDB: 3KYS) shows that YAP wraps itself around the surface of TEAD via three distinct interaction surfaces that are composed of an antiparallel β-strand (interface 1), an α-helix (interface 2) and a twisted-coil region (interface 3) (Figure 1). Studies have demonstrated that out of these three interfaces, interface 3 is the most critical for heterodimer formation.[25] Disruption of the YAP-TEAD complex by cyclic or linear YAP-like peptides, cysteine-dense peptides or VGLL4-mimicking peptides has been reported.[26–30] However, the development of these compounds is compromised by poor pharmacokinetic profiles, low plasmatic stability and poor cell permeability that are commonly associated with peptides. Compounds that bind in a cavity formed by the C-terminal hTEAD1 region close to interface 3 were identified following a virtual screen of the ZINC database and their activity was confirmed by biophysical and *in cellulo* assays.[31] Similarly, CPD3.1, a tetracyclic molecule that blocks the interaction of YAP with TEAD1 and inhibits TEAD activity with an IC_{50} of 110 μM as well as TEAD targeted gene expression, cell proliferation and cell migration, was recently disclosed.[32] However, binding of small molecules to one of the interfaces between YAP and TEAD remains challenging due to the absence of well-defined druggable pockets.[33]

One way to circumvent that problem consists in indirectly disrupting the YAP-TEAD functional complex. Because they are highly disordered, YAP and TAZ are not suitable targets for medicinal chemistry endeavors. On the other hand, TEAD is much more attractive due to the presence of a well-defined hydrophobic pocket that is occupied by a palmitic acid (PA) molecule (shown in beige in Figure 1) and that is conserved within the TEAD family. Studies have shown that TEAD undergoes auto-palmitoylation through covalent bond formation between a conserved cysteine residue and palmitic acid. Some reports indicate that the absence of TEAD palmitoylation results in a drastic reduction of the affinity with YAP while other studies conclude that TEAD containing partial mutations retains its ability to interact with YAP, albeit with a lower affinity.[33–37] TEAD rigidification appears to be at the origin of these results.[38] The expression level and transcriptional activity of TEAD are also directly modulated by its palmitoylation status[39] and numerous studies agree on a loss of stability for non-palmitoylated TEAD.[38]

Small molecules inhibitors that bind to TEAD's palmitate pocket have been reported. For example, Pobbati and Poulsen reported that flufenamic acid (FA) **1** and niflumic acid (NA) **2**, two commercialized non-steroidal anti-inflammatory drugs (NSAID), inhibit TEAD's palmitoylation by binding inside the TEAD palmitate pocket (Figure 2).[40] Although this binding did not prevent the formation of the YAP-TEAD complex, it nevertheless resulted in a reduction in the expression of the Hippo-associated genes in MCF10 A breast cancer cells, suggesting that the YAP-TEAD complex was transcriptionally inactive. Compound MGH-CP1 **3**, reported by a team from Boston General Hospital, binds in the central pocket of TEAD2, reduces gene activation with an IC_{50} of 83 nM in a cell based Gal4-TEAD1 reporter assay, disrupts the YAP-TEAD complex and diminishes the expression of YAP-TEAD responsive genes *CTGF* and *Cyr61*.[38] Although many derivatives were disclosed, the

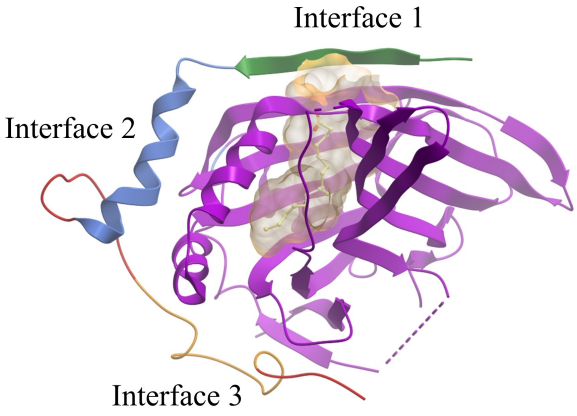


Figure 1. hYAP-hYBD of TEAD1 in the presence of palmitic acid (PA) (beige) (PDB: 3KYS and 5HGU). TEAD1's hYBD in purple, YAP in green (interface 1), blue (interface 2), red and orange (interface 3).

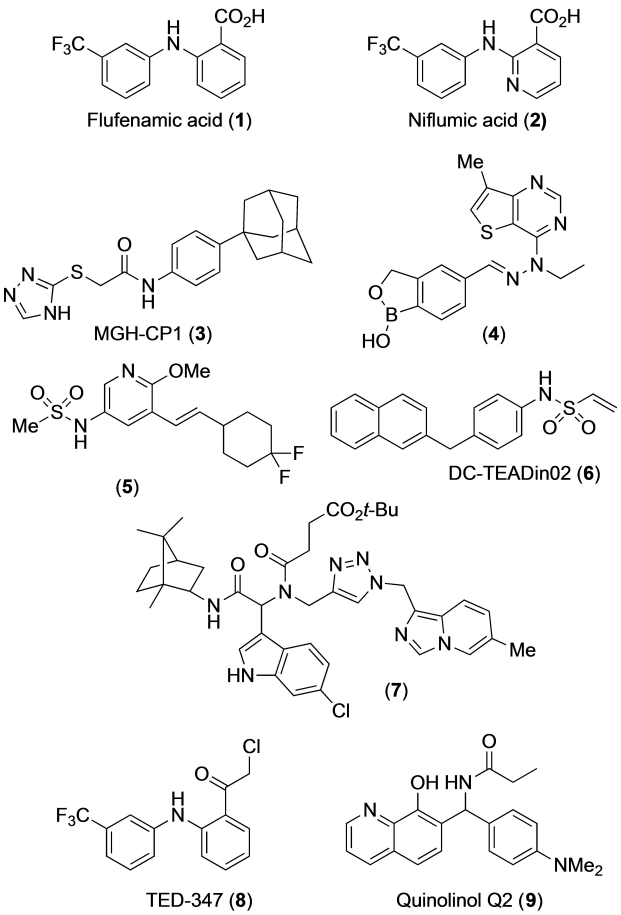


Figure 2. Examples of reported TEAD inhibitors and activators.

current development stage for **3** is not known. Similarly, compound **4**, recently reported by Inventiva, showed an IC_{50} of 260 nM in a cell-based TEAD-GAL4 transactivation reporter assay. Even though many analogues were reported, to the best of our knowledge, its development status has not been disclosed yet.[41] While preparing this manuscript, compound **5** and **7**, two reversible inhibitors targeting the TEAD palmitate binding pocket, have been published.[42,43]

Covalent TEAD inhibitors that react with the cysteine located at the entry of the palmitate pocket such as **6** and **8** have also been developed, further emphasizing the growing interest for compounds that bind in that pocket.[44,45] Although covalent inhibitor **6** inhibited TEAD autopalmitoylation with an IC_{50} value of 197 nM, it showed only minimal effect on YAP-TEAD interaction, contrary to inhibitor **8** which was found to disrupt the YAP-TEAD complex.[44,45] It should be noted that, similar to covalent inhibitor **6**, non-covalent inhibitors **2** and **5** also did not inhibit YAP-TEAD interaction, suggesting that the inhibition of TEAD activity is not due to the inability of TEAD to form a complex with YAP in cells.[40,42] Interestingly, binding of compounds inside TEAD's palmitate pocket can also, in some cases, result in increased TEAD activity, as demonstrated by quinolinol **9**.[46]

Although an increasing number of studies highlight the relevance of TEAD in the development of cancer, to our knowledge, there are currently no TEAD inhibitors on the market or in the clinic. Therefore, there is an urgent need for efficient small-molecule inhibitors targeting these oncogenic proteins. In light of the drug-like properties and modular structure of flufenamic acid **1**, its reversible mode of inhibition and its decent affinity to TEAD, we initiated a program aimed at thoroughly studying its SAR and improving its activity. While preliminary SAR studies have been reported for FA **1** and for the analogous covalent compound TED-347 (**8**), to the best of our knowledge, extensive and systematic SAR investigations around FA series **1** have not been reported. Herein, we would like to disclose our results on the design, synthesis and biological evaluation of new derivatives of flufenamic acid **1** that bind in the palmitate pocket of TEAD, inhibit TEAD's autopalmitoylation and reduce YAP-TEAD's transcriptional activity.

Results and Discussion

Synthesis of flufenamic acid derivatives and evaluation of their binding to TEAD. The aim of our initial medicinal chemistry efforts was to systematically study the structure-activity landscape of flufenamic acid (FA) **1** and to expand on the limited existing knowledge from the literature.[40,45] To do so, we divided FA **1** into four key sections: the left-hand side (LHS) aromatic ring, the central linker, the right-hand side (RHS) aromatic ring and the carboxylic acid (Figure 3a). To guide our SAR efforts, we superimposed the high-resolution co-crystal structures of palmitic acid (PA) (PDB: 5HGU, resolution: 2,05 Å; structure of PA shown in Figure 3b) with FA (PDB: 5DQ8, resolution: 2,3 Å) complexed to hTEAD2-YBD (Figure 3c). Preliminary observations suggested the presence of an internal H-bond interaction between the carboxylate and the NH functions of FA. As previously reported, the X-ray structures also revealed that FA and PA are anchored within the pocket via an H-bond interaction between their respective carboxylate functions and Cys380 as well as through an ionic interaction with the terminal amine of Lys357.[39] The overlay of the FA and PA co-crystal structures highlighted the presence of an empty hydrophobic space inside the pocket which appeared suitable for extensive diversification at the CF_3 position of FA, the most logical being the direct transposition of the palmitic acid alkyl chain onto the core of FA. Merouch *et al* showed the value of this approach by replacing the trifluoromethyl moiety with a methoxyethoxy group in the covalent TED series **8**.[45]

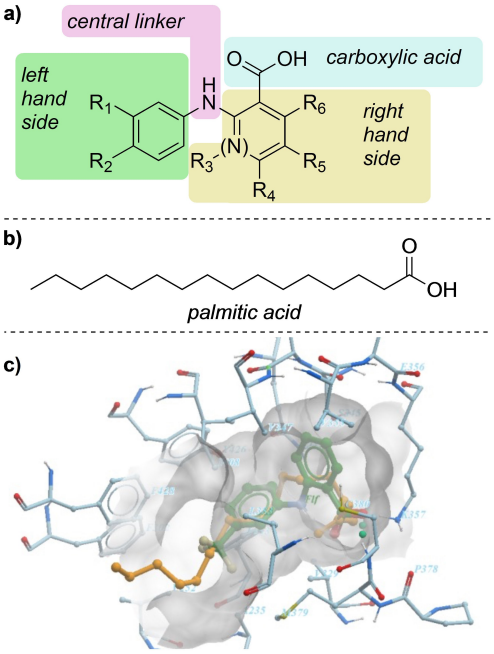
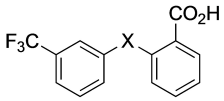


Figure 3. a) Subdivision of flufenamic acid (FA) in four key sections for SAR activities. **b)** Palmitic acid (PA). **c)** Superposition of PA (yellow; PBD 5HGU) and FA (green; PDB 5DQ8) in TEAD2's hYBD.

To explore the importance of the putative internal H-bond between the carboxylate and the NH of FA, we resynthesized FA (**1**) and prepared compounds where the central amino function of FA **1** is replaced by an ether (**10**), a thioether (**11**), a methylene (**12**) and an N-methylamine (**13**) (Table 1, see experimental section for the syntheses). Evaluation of the binding of compounds to TEAD4 by differential scanning fluorimetry (DSF), a fluorescence-based method that monitors the changes in melting temperature (T_m) upon ligand binding, was attempted.[48] However, some compounds interfered with the fluorescence read out, leading us to use differential static light scattering (DSLS) thermal shift assay instead.[47] In this assay, the increase in temperature of aggregation (ΔT_{agg}) of TEAD4 YBD upon compound binding, which is unaffected by fluorescence properties of the compounds, is monitored. We were pleased to see that resynthesized FA **1** showed weak but

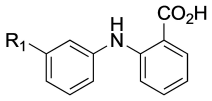
Table 1. Replacement of the central NH linker in flufenamic acid (FA) **1**.



Compounds	X	ΔT_{agg} [a]
1 (FA)	NH	1.3
10	O	0.7
11	S	0.4
12	CH_2	0.4
13	NMe	0.3

[a] ΔT_{agg} values are the average of three DSLS measurements at 25 μM of compound (n = 3).

Table 2. Structure-activity relationships of R_1 substituted FA derivatives.



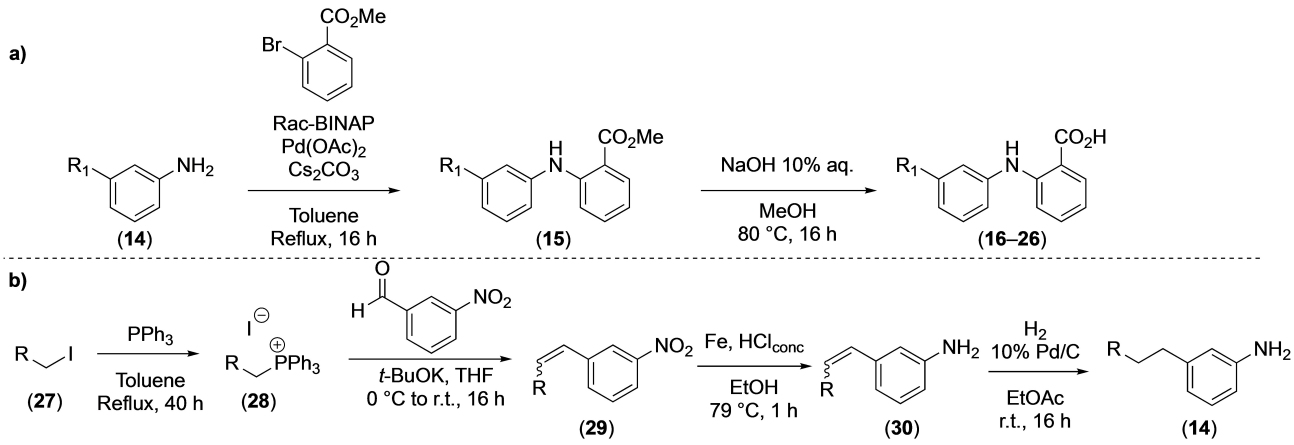
Compounds	R_1	ΔT_{agg} [a]
16	H	0.2
17	Me	0.1
18	Et	−0.1
19	*n*-Pr	2.9
20	*n*-Bu	3.4
21	*n*-Pent	4.4
22	*n*-Hex	5.2
23	*n*-Hept	6.0
24	*i*-Pr	2.6
25	*t*-Bu	1.5
26	Ph	2.1

[a] ΔT_{agg} values are the average of three DSLS measurements at 25 μM of compound (n = 3).

measurable stabilization of TEAD by DSLS ($\Delta T_{agg} = 1.3\,°C$), a value which is similar to the differential scanning fluorimetry (DSF) results previously published by Pobatti *et al.*[40] However, none of the NH replacements improved the affinity of compounds. NA **2** and MGH-CP1 **3** were also resynthesized in our laboratory as reference compounds. MGH-CP1 **3** was synthesized according to patent WO 2017/053706 A1.[38] Resynthesized NA **2** showed an almost negligible ΔT_{agg} value of 0.3 °C while resynthesized MGH-CP1 **3** afforded a higher shift of 3.0 °C.

Pobbati *et al* demonstrated that replacement of the trifluoromethyl group in FA **1** with a bromide or a hydrogen leads to drastic loss of affinity to TEAD while Meroueh *et al* showed that an ethoxymethoxy chain or a thiophene are valid CF_3 replacements.[40,45] To get a more complete picture, we designed a modular synthetic route that allows the rapid preparation of analogues of FA **1** with various groups at the CF_3 position (R_1 in Scheme 1a). Compounds **16**–**26** were prepared through a Buchwald-Hartwig N-arylation reaction between aniline **14** and 2-bromomethyl benzoate followed by saponification of the methyl ester. A similar palladium-catalyzed N-arylation reaction was used by Meroueh *et al* for the synthesis of covalent TED compounds **8**.[45] Anilines **14** were either obtained commercially or were prepared via Wittig olefination reaction between 3-nitrobenzaldehyde and phosphonium iodides **28** followed by reduction of the nitro group of **29** under Béchamp's conditions and reduction of the alkene in **30** under hydrogenation conditions (Scheme 1b). Phosphonium iodides **28** were prepared by reacting the corresponding alkyl iodides **27** with triphenylphosphine.

DSLS results indicate that the unsubstituted compound **16** lacking the CF_3 group, as previously shown by Pobbati *et al*, does not stabilize TEAD4 significantly (Table 2). Similarly, the methyl and ethyl derivatives **17** and **18** showed no protein stabilization. However, a gradual increase in ΔT_{agg} was observed with compounds **19** to **23** as the carbon chain increased from 3 to 7 carbons, demonstrating that the more an analogue resembles palmitic acid, the better its affinity to TEAD is. Furthermore, the pocket appeared to be large enough to accommodate an isopropyl or *tert*-butyl group on the upper West side as well as a phenyl ring, as shown by compounds **24**, **25** and **26**, respectively. To our knowledge, this is the first time that the tolerability of the TEAD's PA pocket towards bulky tertiary or secondary alkyl groups is demonstrated.

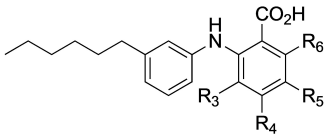


Scheme 1. a) General synthetic route for the synthesis of flufenamic acid derivatives **16**–**26. b)** Preparation of anilines **14**.

To assess the structure activity relationship (SAR) more accurately, we attempted to determine the affinities of our compounds for binding to TEAD4 by surface plasmon resonance (SPR). We used MGH-CP1 (compound **3**) as a control. However, we could not reliably detect binding of any of them including the control compound to TEAD4 by SPR (Supporting Information figure 1). We were also not successful in assessing the affinities of any of these compounds including compound **3** by isothermal titration calorimetry (ITC) due to poor solubility of compounds (Supporting Information figure 2). While DSLS is not an ideal quantitative assay for rank-ordering compounds for SAR studies, it has been shown that thermal shift data could meaningfully correlate with binding affinities of compounds measured by other methods.[49–52] Our DSLS data on compounds in this study also showed a wide range of stabilization effects with $\triangle T_{agg}$ values up to 10 °C. Therefore, we concluded that the DSLS data are valuable in rank-ordering our compounds, where other methods failed.

Using compound **22**, which showed one of the highest ΔT_{agg}, as a new lead compound, we next proceeded to explore the tolerance of the RHS towards the introduction of substituents. To our knowledge, the only derivative exploring modifications on the East side of the molecule is the C4-methoxy, reported by Meroueh *et al* in the covalent series **8**.[45] Because the co-crystal structure of FA with TEAD2 showed limited space in the pocket around the RHS, we began by walking a fluorine around the right-hand side aromatic ring, resulting in compounds **31** to **34** (Table 3). DSLS results show that this additional fluorine is well tolerated at every position and even leads, in some cases, to a non-negligible increase in affinity to TEAD. Substitution at C6 is of particular interest as it is pointing towards interface 1 between YAP and TEAD. We hypothesized that in addition to inhibiting TEAD's palmitoylation, directly disrupting one of the interaction surfaces could result in more potent inhibitors of the YAP-TEAD complex and thus stronger reduction of gene expression. Consequently, compound **35** with a C6-methyl group was prepared and was found to be well tolerated, thus providing an additional vector for future SAR investigations.

Table 3. Structure-activity relationships of compounds substituted on the right-hand side (RHS) aromatic group.



Compound	R_3	R_4	R_5	R_6	ΔT_{agg} [a]
22	H	H	H	H	5.2
31	F	H	H	H	5.2
32	H	F	H	H	6.4
33	H	H	F	H	6.2
34 (**LM98**)	H	H	H	F	6.4
35	H	H	H	Me	5.2

[a] ΔT_{agg} values are the average of three DSLS measurements at 25 μM of compound (n = 3).

As an orthogonal method to confirm binding, we used ^{19}F-NMR spectroscopy, where differences in the linewidth and/or intensity of the signal(s) of the compound in the free state (SF) and in the presence of protein (SP) may be used to monitor binding.[53,54] Before initiating the binding studies, an evaluation by ^{1}H-NMR of the compounds' free state behavior in aqueous buffer (10 mM HEPES-d_{18}, 150 mM NaCl, 0.5 mM TCEP-d_{15}, 10% D_2O, pH 7.4, 1% DMSO-d_6) was performed to minimize the chances of misleading results stemming from poor compound solubility. **LM98**, FA **1** and NA **2** showed measured concentrations by the ERETIC method[55] of 54, 53 and 47 μM, respectively, for a nominal concentration of 50 μM, demonstrating sufficient solubility for the ligand binding studies (Figure 4a–c). In the presence of TEAD (50 μM compound : 15 μM TEAD, a 3.33 : 1 compound : TEAD ratio), **LM98** showed clear evidence of binding based on the differential line broadening and signal intensity change of the ^{19}F-NMR signal of the SP sample compared to the SF sample (Figure 4d). Under the same conditions, FA **1** and NA **2** also showed evidence of binding based on the change in the ^{19}F-NMR signal intensity for the SP versus the SF sample (Figure 4e–f). In agreement with the results from the DSLS thermal shift assay, **LM98** appeared to be a much stronger binder to TEAD4 than the hit compounds FA and NA based on the greater change in the peak shape of the ^{19}F-NMR signal. With binding confirmed for all three compounds by ^{19}F-NMR spectroscopy, we moved to the next set of experiments to further characterize the binding of our compounds to TEAD.

To further elucidate the binding mode of our compounds and to identify additional opportunities for improvement in activity and physicochemical properties, we co-crystallized the

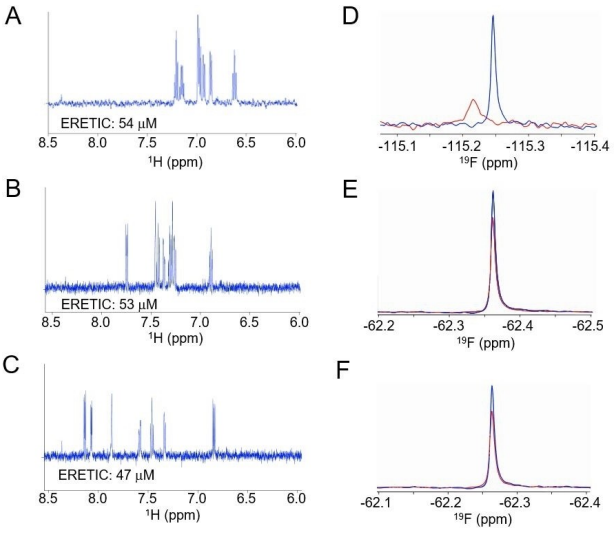


Figure 4. a) Aromatic region of free state ^{1}H-NMR spectrum of **LM98** (50 μM) in buffer. **b)** Aromatic region of free state ^{1}H-NMR spectrum of FA **1** (50 μM) in buffer. **c)** Aromatic region of free state ^{1}H-NMR spectrum of NA **2** (50 μM) in buffer. **d)** ^{19}F-NMR spectrum of **LM98** (50 μM): Free state in buffer (blue) and in presence of 15 μM TEAD4 (red). **e)** ^{19}F-NMR spectrum of FA **1** (50 μM): Free state in buffer (blue) and in presence of 15 μM TEAD4 (red). **f)** ^{19}F-NMR spectrum of NA **2** (50 μM): Free state in buffer (blue) and in presence of 15 μM TEAD4 (red).

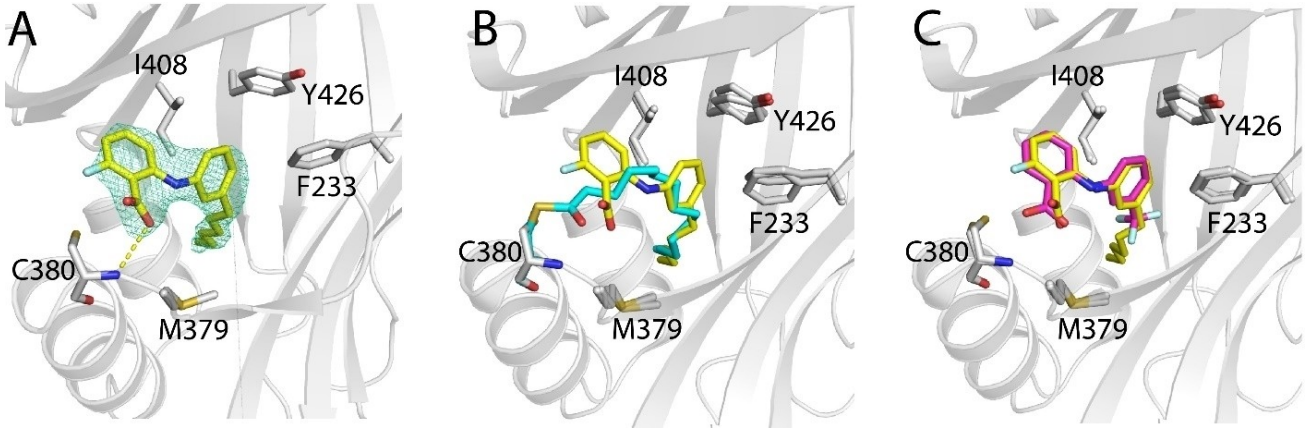
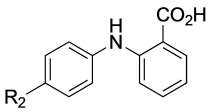


Figure 5. LM98 interaction with human TEAD2 YAP-binding domain. **a)** Co-crystal structure of *h*TEAD2 in complex with compound **LM98** (PDB ID: 6VAH). Compound **LM98** is shown in sticks and colored yellow. TEAD2 is shown in cartoon representation in grey with key hydrophobic pocket residues highlighted in sticks. The mFo-DFc electron density omit-map for compound **LM98** is displayed as green mesh contoured at 2.5σ. The polar interaction is displayed as a yellow dashed line. **b)** Overlay of TEAD2 bound to compound **LM98** (yellow) and palmitate (cyan) cross-linked to Cys380 (PDB: 5EMV). **c)** Overlay of TEAD2 bound to compound **LM98** (yellow) and FA (magenta) (PDB: 5DQ8).

human TEAD2 YAP-binding domain (residue range 221-451) in complex with **LM98**. As expected, the structure shows that **LM98** is anchored within the same palmitic acid binding pocket of TEAD2 as palmitate and flufenamic acid (Figure 5a–c). No significant structural changes were observed in the overall fold of TEAD2 upon binding to **LM98** compared to palmitate- and flufenamic acid-bound TEAD2 structures, with root-mean-square deviation (R.M.S.D.) of 0.56 Å over 194 Cα atoms between TEAD2-**LM98** (chain-A) and TEAD2-palmitate (chain-A) (PDB: 5EMV) and 0.66 Å over 192 Cα atoms between TEAD2-**LM98** (chain-A) and TEAD2-flufenamic (chain-A) (PDB: 5DQ8). The interaction between TEAD2 and **LM98** is mainly hydrophobic in nature with residues lining the palmitate-binding pocket. The hexyl chain moiety of **LM98** is docked into the same TEAD2 hydrophobic pocket as observed previously in palmitate-bound TEAD2 structure (PDB ID: 5EMV) (Figure 5b). **LM98** anchors itself into a hydrophobic pocket through H-bond interaction between the carboxylate group and main-chain amide nitrogen of Cys380 (Figure 5a), as well as via T-shaped pi-stacking interaction between the LHS phenyl ring of **LM98** and Phe233 of TEAD2, resembling the FA interaction with TEAD2 (PDB: 5DQ8) (Figure 5a–c).

Pobbati *et al* showed that substituents such as a methyl or difluoromethyl on the West side ring in *para* position relative to the NH are well tolerated.[40] In the covalent TED series **8**, Meroueh *et al* found that the introduction of a thiophene at that position is also tolerated.[45] With the objective of better understanding the impact of introducing groups at the *para* position (R_2), we prepared a small ensemble of compounds as shown in Table 4 and found that the *para* derivatives are not only well tolerated but that they even display higher thermal stabilization of TEAD4 than their *meta* counterparts. For instance, *para*-hexyl **36**, *para*-*tert*-butyl **37** and *para*-phenyl **38** gave ΔT_{agg} values of 6.6, 7.2 and 6.0 °C, respectively compared to 5.2, 1.5 and 2.1 °C for their *meta* analogues **22**, **25** and **26**. To the best of our knowledge, this unambiguous demonstration of an increase in affinity following the introduction of substituents on the West aryl ring of FA is unprecedented. Inspired by compound **3**, we prepared compound **39** that incorporates an adamantyl group in the R_2 position and observed a significant stabilization of the protein. Encouraged by this result, we then prepared the cyclohexyl derivative **40** which gave the highest ΔT_{agg} amongst all our FA derivatives.

Table 4. Structure-activity relationships of R_2 substituted derivatives on the left-hand side aryl group.



Compound	R_2	ΔT_{agg} [a]
36	*n*-Hex	6.6
37	*t*-Bu	7.2
38	Ph	6.0
39	Adamantyl	5.5
40	*c*-Hex	10

[a] Values shown are the average of three replicates by DSLS assay, with a compound concentration of 25 μM.

To explain these unexpected results, we performed docking studies on compound **36**, **39** and **40** in the hYBD of TEAD2 using the co-crystal structure of **LM98** (Figure 6). Our studies suggest that the central amine can rotate around the C–N–C bonds to accommodate the *para* substituent. Because the hexyl chain is flexible, it can easily adapt to the shape of the pocket, requiring small conformational changes to reach a conformation similar to the *meta*-substituted counterparts. However, for more voluminous groups such as the adamantyl and the cyclohexyl, the left-hand side aromatic ring needs to rotate. Our model suggests that this conformational change could allow the creation of new pi-stacking interactions, for example with Phe233, which could explain why these analogues show higher stabilization of TEAD.

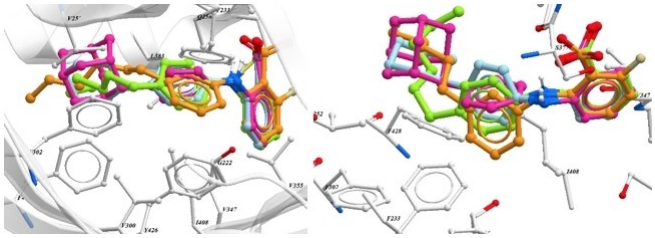
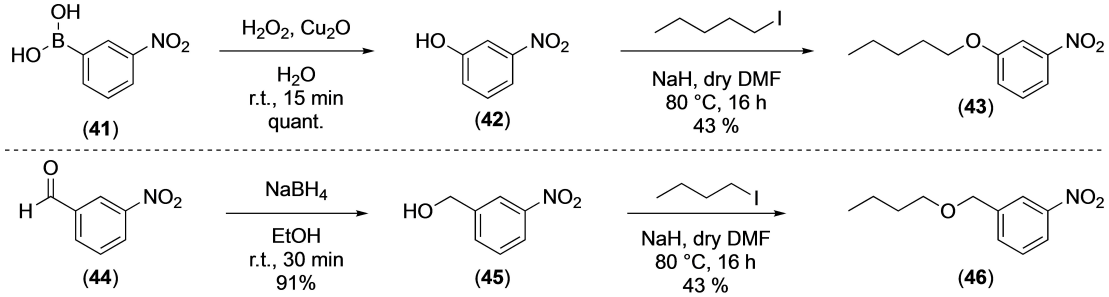


Figure 6. Docking studies of compound **36** (green), **39** (pink) and **40** (blue) in hYBD of TEAD2 overlaid with co-crystal structure of hDEAT2 in complex with **LM98** (orange) (PDB ID: 6VAH).

Being aware that these compounds are designed for optimal interactions with the hydrophobic palmitate pocket, we then proceeded with the incorporation of an oxygen atom in the R_1 and R_2 groups in order to improve their physicochemical properties. To do so, the general synthetic route was adapted, starting either with an *ipso*-hydroxylation on (3-nitrophenyl) boronic acid **41** or with a reduction of the carbonyl of 3-nitrobenzaldehyde **44** (Scheme 2). Phenol **42** and benzylic alcohol **45** thus obtained were then reacted via an S_N2 reaction with the corresponding iodoalkanes to yield key nitro-intermediates **43** and **46** which were converted into compounds **47**–**54** following the general synthetic route from Scheme 1. To further lower the lipophilicity of the compounds, we also prepared derivatives based on the NA scaffold where a nitrogen atom is present in the RHS ring *ortho* to the central NH linker.

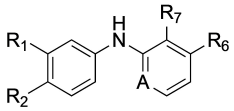
DSLS results indicate that the replacement of the first methylene unit by an oxygen atom is well tolerated, as indicated by compound **47** which gave a ΔT_{agg} of 7.0 °C compared to 5.2 °C for the corresponding carbon analogue **22** (Table 5). However, replacing the second methylene unit in **22** with an oxygen led to a drastic loss of affinity with TEAD, as indicated by compound **48**. The addition of a nitrogen atom on the RHS was well tolerated, as shown by compound **49** which is the NA analogue of **22**. Combining the beneficial features of **47** and **49** afforded compound **50** which unexpectedly showed a reduced ability to stabilize TEAD. Introduction of a nitrogen in the *para*-adamantyl compound **39** provided a substantial increase in the temperature of aggregation (8.4 °C for **51** vs 5.5 °C for **39**). A complete loss of affinity to TEAD was observed with compound **52**, an oxygenated version of **36**. However, some of the affinity could be re-established with the NA counterpart **53**. Finally, the impact of moving the carboxylic acid group to the *meta* position of the RHS relative to the NH connector was investigated with compound **54**. The fact that **54** retains its affinity to TEAD is interesting as well as unprecedented and supports our hypothesis that compounds can adapt inside the pocket by undergoing conformational changes.

Inhibition of palmitoylation. As co-crystals structure of **LM98** with TEAD2 confirmed our hypothesis that our compounds occupy central pocket of TEAD, we further wished to



Scheme 2. General routes for the synthesis of key intermediates incorporating an ether side chain on the LHS.

Table 5. Analogues with polar atoms in the LHS alkyl chains and the RHS ring.



Compound	R_1	R_2	A	R_6	R_7	ΔT_{agg} [a]
47	$CH_3(CH_2)_4O$	H	CH	H	CO_2H	7.0
48	$CH_3(CH_2)_3OCH_2$	H	CH	H	CO_2H	2.3
49	*n*-Hex	H	N	H	CO_2H	6.0
50	$CH_3(CH_2)_4O$	H	N	H	CO_2H	3.4
51	H	Adamantyl	N	H	CO_2H	8.4
52	H	$CH_3(CH_2)_4O$	CH	H	CO_2H	0.5
53	H	$CH_3(CH_2)_4O$	N	H	CO_2H	3.2
54	$CH_3(CH_2)_4O$	H	CH	CO_2H	H	4.5

[a] Values shown are the average of three replicates by DSLS assay, with a compound concentration of 25 μM.

demonstrate whether they can compete with palmityl CoA or not. Therefore, we treated TEAD4 with different concentrations of **LM98** (**34**) and six other representative compounds (**22**, **32**, **40**, **47**, **49** and **50**) as well as flufenamic acid (**1**) in the presence of palmityl CoA according to a protocol reported by Li and coworkers.[34] The formation of TEAD4-palmityl CoA covalent adduct was then monitored by mass spectrometry. Results indicate that all compounds dose-dependently reduce the covalent palmitoylation of TEAD4 (Supporting Information figure S3), confirming that our compounds can indeed compete with palmityl CoA. Compounds **40**, **49** and **50** showed less reduction of palmitoylation at the highest concentrations of the compounds probably due to their limited solubility at the highest concentrations.

Evaluation of YAP-TEAD interaction in cells. We established a cellular nano-BRET assay to evaluate whether our TEAD inhibitors would inhibit YAP-TEAD interaction.[56] In this assay, we measured the inhibition of interaction between C-terminally NanoLuc® (NL) tagged TEAD1 and C-terminally HaloTag® (HT) tagged YAP1 by our compounds by comparing the nano-BRET ratio in the presence and absence of compounds. None of the three compounds tested, **LM98** (**34**), **36** and **40**, reduced nano-BRET ratio indicating that our TEAD inhibitors do not inhibit YAP-TEAD interaction up to 30 μM compound concentration (Figure 7). This is not surprising; as discussed in the introduction section, while some TEAD inhibitors such as **3** and **8** inhibit YAP-TEAD interaction, others TEAD inhibitors, including niflumic acid **2** as well as compounds **5** and **6**, do not.

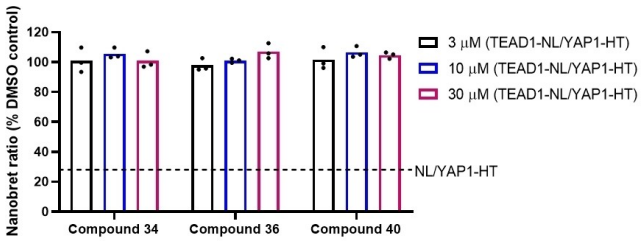


Figure 7. Compounds do not affect YAP1 and TEAD1 interaction in cells – NanoBRET assay. HEK293T were transfected with C-terminally NanoLuc® (NL) tagged TEAD1 or NL alone and C-terminally HaloTag® (HT) tagged YAP1. The following day cells were treated with compounds for 4 h. The interaction was measured using NanoBRET assay. The results are MEAN of 3 technical replicates. The line indicates the background NanoBRET signal from unspecific interaction between NL and YAP1-HT.

Inhibition of TEAD activation in cells. Having demonstrated that our compounds can compete with palmityl CoA *in vitro*, we next assessed whether they could inhibit TEAD mediated effects in cells. To examine the effects of our TEAD inhibitors, a dual-luciferase assay was used to measure TEAD activation through a YAP/TAZ-responsive synthetic promoter, the 8x-GTIIC TEAD reporter, which drives luciferase expression.[57] After 24 hours of treatment with increasing concentrations of NA (**2**) and **LM98** (**34**), HEK293 cells expressing the 8x-GTIIC TEAD reporter showed a significantly lower level of TEAD activation with **LM98** than with NA (Figure 8a). **LM98** also showed greater potency at inhibiting TEAD activation at lower concentrations, registering lower TEAD activation levels at 3 μM than NA (Figure 8a), without any increased toxicity in cells compared to NA (Figure 8b). Furthermore, compounds **23** and **33**, which showed comparable ΔT_{agg} to **LM98**, also showed similar reduction of TEAD activation. Compound **40**, which showed significantly better $\Delta T_{agg} = 10\,^{\circ}C$, showed almost a complete inhibition of TEAD activation at 30 μM while compound **35** which showed lower ΔT_{agg} of 5.2 °C showed no significant inhibition up to 30 μM (Supporting Information figure S4).

Inhibition of TEAD responsive genes and breast cancer cell migration. To determine the effect of our compounds on endogenous TEAD-mediated expression of Hippo-responsive genes, we then measured the levels of well-established TEAD responsive *CTGF* and *Cyr61* genes by RT-qPCR (Figure 9a). Compound **3** was selected as a reference compound since it was previously found to reduce the expression of *CTGF* and *Cyr61* and since we confirmed its binding in our DSLS assay.

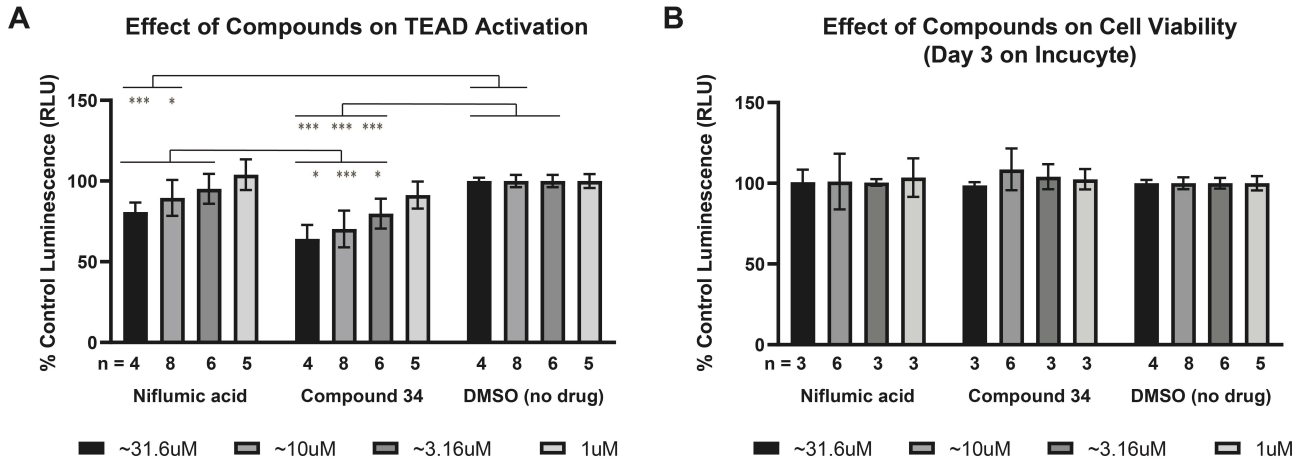


Figure 8. a) Effect of **LM98** (**34**) on TEAD activation in cells measured by dual-luciferase reporter assay. **b)** Effect of **LM98** (**34**) on cell viability. The toxicity of compounds on cell viability was measured using the Incucyte to measure cell confluence over a 3-day period. Results were generated by training the Incucyte analysis software to optimally detect cell confluence for HEK293 cells, averaging across technical replicates and normalizing to control "DMSO (no drug)" treatment.

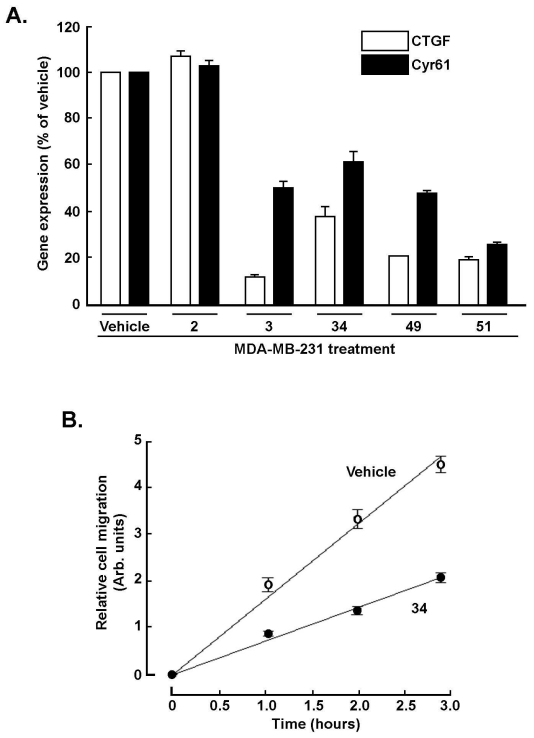


Figure 9. a) *CTGF* and *Cyr61* gene expression levels are altered by compounds **3**, **LM98** (**34**), **49** and **51**, but not by NA (**2**). Serum-starved MDA-MB-231 breast cancer cells were treated either with 10 μM of compounds or vehicle (DMSO) for 48 hours. Total RNA was isolated from cell monolayers. *CTGF* and *Cyr61* gene expression was then assessed by RT-qPCR as described in the Supporting Information. **b) LM98** (**34**) inhibits MDA-MB-231 breast cancer cell migration. Real-time cell migration was next performed using the xCELLigence system as described in the Supporting Information section. Serum-starved MDA-MB-231 breast cancer cells were treated either with 10 μM **LM98** (**34**) or vehicle (DMSO) for 48 hours. Data are representative of two independent experiments that were performed in triplicates (SEM is represented).

LM98 (**34**) was chosen because of its high affinity to TEAD in the DSLS assay, since its binding in the palmitic acid pocket was confirmed by X-ray crystallization, and because it reduced TEAD activation in the Luciferase assay. Compound **49** was selected as a niflumic acid version of **LM98** while compound **51** was chosen for the presence of the adamantyl group in the *para*-position of the left-hand side ring, and thus its structural resemblance to **3**. Niflumic acid **2**, which in our hands showed no binding in the DSLS assay and weak binding by ^{19}F-NMR, was selected as the negative control compound.

Treatment of human triple-negative MDA-MB-231 breast cancer cells with 10 μM **LM98** (**34**), **49** and **51**, significantly reduced *CTGF* and *Cyr61* transcript levels after 48 hours comparable to the levels of the published compound **3** at the same concentration while reference compound NA (**2**) did not show any significant effect at the same concentration. Since the Hippo-associated genes promote cell migration, we then studied the impact **LM98** (**34**) on MDA-MB-231 breast cancer cells migration using the real-time xCELLigence system and observed strong inhibition of cell migration compared to vehicle (Figure 9b).

Evaluation of the impact of LM98 on cell cycle division and wound healing. Given its capacity to alter cell migration, we also addressed whether **LM98** could impact cell cycle division by assessing G0/G1, S, and G2/M phases in MDA-MB-231 cells (Figure 10a). Cells were found trapped in the S phase upon treatment with 10 μM of **LM98** (Figure 10b). These results suggest that **LM98** can alter molecular events regulating cell division processes and cell proliferation.

The effect of **LM98** on the ability of cells to migrate in response to a wound was next assessed (Figure 10c). While vehicle-treated cells were able to partly rescue wounding, **LM98** treatment at 10 μM in MDA-MB-231 cells prevented migration of the wound region (Figure 10d). This property suggests that **LM98** can halt MDA-MB-231 cell migration.

Conclusion

We prepared flufenamic acid derivatives that target the central hydrophobic palmitate pocket of TEAD. A modular synthetic

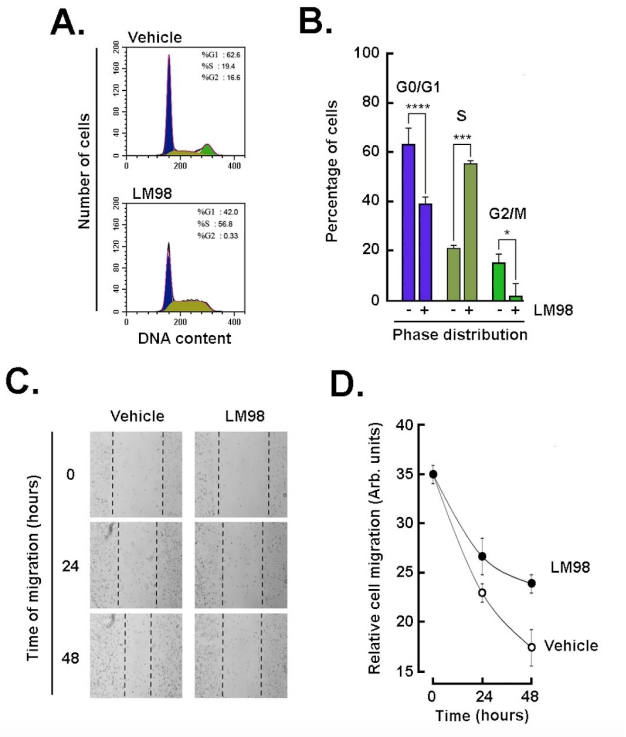


Figure 10. LM98 alters MDA-MB-231 breast cancer cell cycle division and wound healing. Human TNBC-derived MDA-MB-231 cells were cultured, followed by treatments with 10 μM **LM98** in serum-free media for 48 hours, fixation, and PI staining as described in the Supporting Information. **a)** Data acquisition was performed by flow cytometry in order to assess cell cycle phases. **b)** Data analysis was performed in order to assess the levels of cells in G0/G1, S, and G2/M phases. Significance: $p < 0.05$, $p < 0.01$, $p < 0.001$ versus the vehicle (0.1 % DMSO). **c)** Photomicrographs of cell migration, in the presence or absence of 10 μM **LM98**, to the scratched zone at different time points (magnification, ×20). **d)** Quantitative assessment of cells that migrated into the scratched zone. For each condition, representative fields within the scratch were photographed. Data are representative of two independent experiments. Data are representative of two independent experiments that were performed in triplicates (SEM is represented).

route was established that allow the expedient access to derivatives of flufenamic acid. Rational design combined with systematic SAR studies led to the discovery of **LM98** (**34**), a FA derivative that shows high affinity to TEAD in a DSLS biophysical assay. ^{19}F-NMR studies confirmed that **LM98** binds more strongly to TEAD than flufenamic or niflumic acid. Co-crystal structure showed that **LM98** binds in the palmitate pocket of TEAD while mass spectrometry measurements confirmed that this compound acts as a TEAD autopalmitoylation inhibitor. Although **LM98** did not disrupt the YAP-TEAD complex, it was found to interfere with the transcriptional activity of TEAD at concentrations that are not toxic to cells in a dual luciferase assay. Treatment of MDA-MB-231 cells with **LM98** resulted in a decrease in the expression of associated genes *CTGF* and *Cyr61* as shown by RT-qPCR. **LM98** displayed strong inhibition of MDA-MB-231 cancer cell migration and arrested cells in the S phase.

Experimental Section

General Chemistry Methods. Unless otherwise stated, reactions were performed in non-flame dried glassware and commercial reagents were used without further purification. Anhydrous solvents were obtained using an encapsulated solvent purification system and were further dried over 4 Å molecular sieves. The evolution of reactions was monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 precoated plates visualized by ultraviolet radiation (254 nm). Flash chromatography was performed employing 230–400 mesh silica using the indicated solvent system according to standard techniques. ^{1}H-NMR spectra were recorded on a Bruker Avance-III 300 MHz, 500 MHz or 600 MHz. ^{13}C-NMR spectra were recorded on a Bruker Avance-III 75 MHz, 126 MHz or 151 MHz spectrometer. ^{19}F-NMR were recorded on a Bruker Avance-III 282 MHz. Chemical shifts for ^{1}H-NMR spectra are recorded in parts per million from tetramethyl silane with the solvent resonance as the internal standard (chloroform-d, δ 7.26 ppm; methanol-d4, δ 3.34 ppm; dimethysulfoxide-d6, δ 2.54 ppm; acetone-d6, δ 2.09 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, s(br) = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of doublet of doublet), coupling constant *J* in Hz and integration. Chemical shifts for ^{13}C-NMR spectra are recorded in parts per million from tetramethyl silane using the solvent resonance as the internal standard (chloroform-d, δ 77.36 ppm; methanol-d4, δ 49.86 ppm; dimethysulfoxide-d6, δ 40.45 ppm; acetone-d6, δ 30.60 ppm). Purity was assessed on an Agilent 1260 infinity HPLC system equipped with an Agilent Eclipse Plus C18 (3.5 µM, 4.6×100 mm) column using a 20-minute gradient method (0 to 100% MeCN + 0.06% TFA in water + 0.06% TFA; the absorbance was measured at 254 nm). Purity is greater than 95% for all final compounds. HRMS were performed on a TOF LCMS analyzer using the electrospray (ESI) mode. MGH-CP1 **3** was synthesized according to WO 2017/053706 A1.[37]

Accession Codes. Coordinates and structure factors of *h*TEAD2-**34** complex are available in the Protein Data Bank (PDB) under accession code 6VAH. Coordinates for X-ray structure of **40** have been deposited in the Cambridge Crystallographic Date Centre (CCDC) under the number 2054155.

General Procedure A: nitro reduction. Metallic iron (4 equiv) was added to a solution of the appropriate nitro substrate (1.0 equiv) in 3:1 EtOH/$HCl_{conc.}$ (5 mL per mmol of substrate). After heating at 79 °C for 1 h, the reaction mixture was cooled down to room temperature and quenched with a slow addition of saturated aqueous solution of $NaHCO_3$ (50 mL). The aqueous phase was extracted with EtOAc (3×50 mL). Combined organic phases were washed with water (1×50 mL), brine (1×50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. If needed, the crude material was purified by flash column chromatography to provide the desired compound.

General Procedure B: Ullmann coupling. To a solution of the appropriate aniline substrate (1 equiv) in dry DMF (10 mL per mmol of substrate) were added K_2CO_3 (3 equiv), the appropriate benzoic acid derivative (1.1 equiv), Cu (0.2 equiv) and Cu_2O (0.1 equiv). The reaction mixture was stirred at 153 °C for 16 h, cooled down to room temperature, after which H_2O was added. The mixture was filtered over a plug a celite, rinsed with DCM and acidified with $HCl_{conc.}$ until pH < 3. If formation of a precipitate, filtration was performed. Otherwise, the aqueous phase was extracted with DCM (3×20 mL), combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield directly to the title compound.

General Procedure C: Buchwald-Hartwig coupling. To a solution of the appropriate amine substrate (1.0 equiv) in dry toluene (7 mL per mmol of substrate) was added the appropriate halogen benzoate (1.1 equiv), cesium carbonate (2.4 equiv) and a freshly prepared solution of $Pd(OAc)_2$/*Rac*-BINAP in dry toluene. This solution was obtained by stirring $Pd(OAc)_2$ (0.06 equiv) and *Rac*-BINAP (0.09 equiv) in dry toluene (3 mL per mmol of substrate) for 15 min with argon bubbling through the mixture. The main reaction mixture was heated at 120 °C for 16 h, cooled down to room temperature, filtered over a plug of celite and concentrated under reduced pressure. Purification by flash column chromatography provided the title compound.

General Procedure D: saponification. To a solution of the appropriate ester substrate (1.0 equiv) in MeOH (20 mL per mmol of substrate) was added an aqueous solution of NaOH at 10% (20 mL per mmol of substrate). The reaction mixture was stirred at 80 °C until completion as indicated by TLC, cooled down to room temperature after which the mixture was diluted with DCM and quenched with aqueous solution of HCl 1 M (20 mL). The aqueous phase was extracted with DCM (3×20 mL), combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. If not pure enough, the crude material was purified by flash column chromatography to provide the title compound.

General Procedure E: esterification. To a solution of the appropriate acid substrate (1.0 equiv) in MeOH (2 mL per mmol of substrate) was added H_2SO_4 (0.2 mL per mmol of substrate). The reaction mixture was stirred at 65 °C until completion as indicated by TLC, cooled down to room temperature after which the mixture was diluted with DCM and H_2O. The aqueous phase was extracted with DCM (3×20 mL). Combined organic phases were washed with saturated aqueous solution of $NaHCO_3$ (3×20 mL), brine (1×20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. If not pure enough, the crude material was purified by flash column chromatography to provide the title compound.

General Procedure F: Ullmann coupling. To a solution of the appropriate benzoic acid substrate (1.0 equiv) in *n*-butanol (0.5 mL per mmol of substrate) were added the appropriate aniline substrate (1.4 equiv), K_2CO_3 (1.4 equiv) and Cu (0.9 equiv). The reaction mixture was heated at 120 °C for 4 h and then allowed to cool down to room temperature. After removal of *n*-butanol under high vacuum, hot water (15 mL) was added to the residue. The

mixture was filtered through a pad of celite and washed with water. The filtrate was acidified with $HCl_{conc.}$ until pH < 3. The precipitate obtained was filtered on Büchner and then recrystallized in chloroform to yield the title compound.

2-((3-(Trifluoromethyl)phenyl)amino)benzoic acid (1) (Flufenamic acid; FA). 2-Bromobenzoic acid (605 mg, 3.00 mmol) was reacted with 3-aminobenzotrifluoride (678 mg, 4.20 mmol) according to general procedure F, affording flufenamic acid (FA) **1** (323 mg, 1.14 mmol, 38%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.07 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.51 (s, 1H), 7.46 (d, *J* = 7.0 Hz, 2H), 7.43–7.39 (m, 1H), 7.35 (d, *J* = 6.9 Hz, 1H), 7.27–7.25 (m, 1H), 6.85 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.52, 147.88, 141.34, 135.59, 132.96, 132.33, 131.90, 130.13, 125.51, 120.39, 119.06, 119.01, 118.52, 114.36; ^{19}F-NMR (282 MHz, $CDCl_3$) δ −62.80; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{10}F_3NO_2$: 282.0736, found 282.0740, HPLC purity: 98%.

2-(3-(Trifluoromethyl)phenoxy)benzoic acid (10). To a solution of 3-(trifluoromethyl)phenol (1.755 g, 10.82 mmol) in water (10 mL) were added K_2CO_3 (2.995 g, 21.66 mmol), 2-chloro-benzoic acid (3.389 g, 21.65 mmol), pyridine (882 μL, 10.9 mmol), Cu (104 mg, 1.63 mmol) and CuI (104 mg, 0.55 mmol). The reaction mixture was stirred at 100 °C for 16 h, then cooled down to room temperature. The reaction mixture was extracted with Et_2O, then the aqueous phases was acidified with $HCl_{conc.}$ until pH < 3. The precipitate formed was filtered on Büchner. Purification of 32 mg of crude by preparative reverse phase HPLC (H_2O + 0.01% TFA/MeCN + 0.01% TFA 100:0 to 0:100) provided **10** (13 mg, 0.071 mmol) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.56 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.31–7.26 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 1H), 6.96 (dd, *J* = 8.3, 0.8 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.45, 156.90, 156.29, 135.14, 133.47, 132.87, 130.72, 125.48, 124.65, 122.10, 121.41, 120.79, 120.25, 115.93.; ^{19}F-NMR (282 MHz, $CDCl_3$) δ −62.73; HRMS (ESI) calcd for $C_{14}H_9F_3O_3$: 282.0504, found 305.0403 $[M+Na]^+$; HPLC purity: 96%.

2-((3-(Trifluoromethyl)phenyl)thio)benzoic acid (11). To a solution of thiosalicylic acid (886 mg, 5.74 mmol) in DMF (10 mL) were added 3-bromobenzotrifluoride (1.44 g, 6.64 mmol), K_2CO_3 (1.21 g, 8.72 mmol) and CuCl (89 mg, 0.90 mmol). The reaction mixture was stirred at 153 °C for 7 h and cooled down to room temperature. The precipitate formed was filtered on Büchner and the solid was dissolved in water. The aqueous phase was acidified with $HCl_{conc.}$ until pH < 3, then extracted with EtOAc (3 × 15 mL). Purification by preparative reverse phase HPLC (H_2O + 0.01% TFA/MeCN + 0.01% TFA 100:0 to 0:100) provided **11** (16 mg, 0.053 mmol, 1%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.9 Hz, 1H), 7.83 (s, 1H), 7.71 (dd, *J* = 15.6, 7.7 Hz, 2H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 9.0 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.09, 143.00, 138.76, 134.28, 133.57, 132.41, 132.18, 132.11, 132.06, 130.36, 129.88, 127.81, 126.01, 125.19;^{19}F-NMR (282 MHz, $CDCl_3$) δ −62.75; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_9F_3O_2S$: 299.0348, found 299.0336; HPLC purity: 97%.

Ethyl 2-methylbenzoate (55). *o*-Toluic acid (2.050 g, 15.06 mmol) was dissolved in ethanol (20 mL) and $H_2SO_{4conc.}$ (1 mL) was added. The reaction was heated 78 °C for 16 h, cooled down to room temperature. After evaporation of the solvent, the residue was redissolved in Et_2O. The organic phase was washed with aqueous 1 N NaOH aqueous solution (1 × 20 mL), aqueous $NaHCO_3$ saturated solution (1 × 20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure to give ethyl 2-methylbenzoate **55** (2.290 g, 13,58 mmol, 90%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.40–7.33 (m, 1H), 7.22 (t, *J* = 6.9 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.61 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.59, 139.97, 131.77, 131.61, 130.47, 129.93, 125.63, 60.61, 21.67, 14.29.

Ethyl 2-(bromomethyl)benzoate (56). To a solution of ethyl 2-methylbenzoate **55** (1.45 g, 8.81 mmol) in CCl_4 (20 mL) were added *N*-bromosuccinimide (NBS) (1.57 g, 8.81 mmol) and benzoyl peroxide (58 mg, 0.24 mmol) under argon atmosphere. The reaction mixture was stirred at 80 °C for 4 h and then stirred at room temperature for 16 h. After filtration over a pad of celite, the filtrate was concentrated under vacuum. Purification by flash column chromatography (hexanes/EtOAc 90:10) provided ethyl 2-(bromomethyl)benzoate **56** (1.95 g, 8.03 mmol, 91%) as a colorless oil. Spectral data are consistent with literature values.[58] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90–7.85 (m, 1H), 7.42–7.33 (m, 2H), 7.30–7.23 (m, 1H), 4.86 (s, 2H), 4.36–4.26 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

Ethyl 2-(3-(trifluoromethyl)benzyl)benzoate (12). To a solution of ethyl 2-(bromomethyl)benzoate **56** (296 mg, 1.22 mmol) in toluene (3 mL) were added 3-trifluoromethylphenylboronic acid (342 mg, 1.80 mmol), $Pd(OAc)_2$ (14 mg, 0.062 mmol), PPh_3 (48 mg, 0.18 mmol) and K_3PO_4 (518 mg, 2.44 mmol). The reaction mixture was stirred at 80 °C for 16 h, cooled down to room temperature and concentrated under vacuum. The crude compound was used in the following step without any purification. Its saponification was performed according to general procedure D, providing **12** (126 mg, 0.450 mmol, 37%) without any need for purification as a white solid. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 1H), 4.50 (s, 2H); ^{13}C-NMR (151 MHz, $CDCl_3$) δ 172.69, 142.53, 141.83, 133.44, 132.44, 132.19, 132.00, 131.06, 130.84, 130.63, 130.42, 128.86, 127.01, 125.89, 125.87, 125.84, 125.82, 125.26, 123.46, 123.09, 123.06, 123.04, 123.01, 39.69; ^{19}F-NMR (282 MHz, $CDCl_3$) δ −62.54; HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{11}F_3O_2$: 281.0784, found 281.0795; HPLC purity: 99%.

Methyl 2-(methyl(3-(trifluoromethyl)phenyl)amino)benzoate (57). To a solution of **1** (48 mg, 0.17 mmol) in DMF (1 mL) was added NaH dry 90% (12 mg, 0.45 mmol). The reaction mixture was stirred for 40 min, after which a solution of MeI (85 mg, 0.60 mmol) in DMF (1 mL) was added. The reaction mixture was stirred at 80 °C for 16 h, then cooled down to room temperature. Purification by column chromatography (hexanes/EtOAc 95:5) provided methyl 2-(methyl(3-(trifluoromethyl)phenyl)amino)benzoate **57** (42 mg, 0.14 mmol, 80%) as a transparent oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.59 (td, *J* = 7.7, 1.7 Hz, 1H), 7.35 (td, *J* = 7.6, 1.2 Hz, 1H), 7.30 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.99–6.93 (m, 1H), 6.83 (t, *J* = 2.2 Hz, 1H), 6.69 (dd, *J* = 8.3, 2.4 Hz, 1H), 3.63 (s, 3H), 3.30 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.96, 149.47, 147.24, 133.82, 131.93, 129.89, 129.58, 129.36, 126.53, 116.71, 116.70, 114.06, 114.01, 113.96, 113.90, 109.59, 109.53, 109.48, 109.43, 52.24, 40.35; ^{19}F-NMR (282 MHz, $CDCl_3$) δ −62.76.

2-(Methyl(3-(trifluoromethyl)phenyl)amino)benzoic acid (13). Methyl 2-(methyl(3-(trifluoromethyl)phenyl)amino)benzoate **57** (39 mg, 0.13 mmol) was saponified according to general procedure D to afford **13** (29 mg, 0.098 mmol, 76%) as a yellow solid without the need for any purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.62 (td, *J* = 7.8, 1.7 Hz, 1H), 7.46 (td, *J* = 7.7, 1.2 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.16 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.07 (s, 1H), 6.90 (dd, *J* = 8.2, 2.2 Hz, 1H), 3.27 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.31, 149.34, 149.09, 135.23, 133.02, 132.43, 132.00, 131.58, 131.15, 129.87, 128.07, 128.00, 126.87, 122.25, 120.48, 118.02, 112.92, 41.61; ^{19}F-NMR (282 MHz, $CDCl_3$) δ −62.75; HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{12}F_3NO_2$: 296.0893, found 296.0887; HPLC purity: 99%.

2-(Phenylamino)benzoic acid (16). 2-Bromobenzoic acid (206 mg, 1.02 mmol) was reacted with aniline (138 mg, 1.48 mmol) according to general procedure F to afford **16** (92 mg, 0.43 mmol, 42%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.32 (s(br), 1H), 8.04 (dd, J= 8.1, 1.6 Hz, 1H), 7.41–7.32 (m, 3H), 7.28 (d, J=1.3 Hz, 1H), 7.23 (dd, J=8.6, 0.8 Hz, 1H), 7.17–7.10 (m, 1H), 6.76 (ddd, J=8.1, 7.0, 1.1 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.37, 149.07, 140.48, 135.35, 132.74, 129.58, 124.26, 123.30, 117.33, 114.19, 110.49; HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_{11}NO_2$: 214.0863, found 214.0865; HPLC purity: 99%.

2-(m-Tolylamino)benzoic acid (17). 2-Bromobenzoic acid (201 mg, 1.00 mmol) was reacted with *m*-toluidine (157 mg, 1.46 mmol) according to general procedure F to afford **17** (30 mg, 0.13 mmol, 13%) as a greenish solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.27 (s(br), 1H), 8.04 (dd, J=8.1, 1.5 Hz, 1H), 7.39–7.30 (m, 1H), 7.25–7.20 (m, 2H), 7.11–7.06 (m, 2H), 6.95 (d, J=7.5 Hz, 1H), 6.75 (t, J=7.5 Hz, 1H), 2.36 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 174.04, 149.20, 140.38, 139.54, 135.35, 132.75, 129.35, 125.08, 124.01, 120.27, 117.18, 114.31, 110.47, 21.57; HRMS (ESI) $[M+H]^+$ calcd for $C_{14}H_{13}NO_2$: 228.2710, found 228.1053; HPLC purity: 99%.

1-Nitro-3-vinylbenzene (58). Methyltriphenylphosphonium iodide (4.06 g, 10.0 mmol) and potassium *tert*-butoxide (1.12 g, 10.0 mmol) were stirred at 70 °C for 30 min in toluene (19 mL) under argon atmosphere. Then 3-nitrobenzaldehyde (756 mg, 5.00 mmol) was added. The reaction mixture was stirred at 110 °C for 3 h 30 under argon atmosphere, cooled down to room temperature and diluted with water. The aqueous phase was extracted with EtOAc (3× 20 mL). Combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc 95:5) to give 1-nitro-3-vinylbenzene **58** (541 mg, 3,62 mmol, 72%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09 (t, J=1.9 Hz, 1H), 7.97 (ddd, J=8.2, 2.1, 0.8 Hz, 1H), 7.60 (d, J=7.7 Hz, 1H), 7.39 (t, J= 7.9 Hz, 1H), 6.66 (dd, J=17.6, 10.9 Hz, 1H), 5.79 (d, J=17.6 Hz, 1H), 5.34 (d, J=10.9 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.36, 139.05, 134.54, 131.92, 129.31, 122.17, 120.57, 116.83..

3-Ethylaniline (59). To a solution of 1-nitro-3-vinylbenzene **58** (515 mg, 3.45 mmol) in EtOAc (10 mL) was added Pd/C 10% (1 mg). The reaction vessel was evacuated under vacuum and filled with hydrogen. The cycle was repeated twice and the suspension was stirred at room temperature for 16 h under H_2 atmosphere. The mixture was then filtered over a plug of celite, rinsed with DCM and concentrated under reduced pressure to afford 3-ethylaniline **59** (343 mg, 2.83 mmol, 82%) as a yellow oil which was used directly in the next step. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.22 (t, J=7.6 Hz, 1H), 6.77 (d, J=7.4 Hz, 1H), 6.65–6.58 (m, 2H), 3.69 (s(br), 2H), 2.71 (q, J= 7.6 Hz, 2H), 1.38 (t, J=7.6 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.43, 145.33, 129.07, 117.97, 114.59, 112.40, 28.74, 15.41.

2-((3-Ethylphenyl)amino)benzoic acid (18). 2-Bromobenzoic acid (291 mg, 1.45 mmol) was reacted with 3-ethylaniline **59** (240 mg, 1.98 mmol) according to general procedure F to afford **18** (132 mg, 0.547 mmol, 38%) as a brown solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.31 (s(br), 1H), 8.04 (dd, J=8.1, 1.6 Hz, 1H), 7.35 (ddd, J=8.6, 7.0, 1.7 Hz, 1H), 7.30 (d, J=8.4 Hz, 1H), 7.23 (d, J=7.8 Hz, 1H), 7.14–7.08 (m, 2H), 6.98 (d, J=7.6 Hz, 1H), 6.78–6.71 (m, 1H), 2.66 (q, J=7.6 Hz, 2H), 1.26 (t, J=7.6 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.59, 149.24, 145.97, 140.41, 135.33, 132.73, 129.42, 123.94, 122.91, 120.57, 117.15, 114.28, 110.38, 28.96, 15.68; HRMS (ESI) $[M+H]^+$ calcd for $C_{15}H_{15}NO_2$: 242.1176, found 242.1179; HPLC purity: >99%.

1-Nitro-3-(prop-1-en-1-yl)benzene (60). To a suspension of ethyltriphenylphosphonium bromide (140 mg, 0.377 mmol) and potassium carbonate (130 mg, 0.941 mmol) in toluene (3.1 mL) was added 3-nitrobenzaldehyde (47 mg, 0.31 mmol). The reaction mixture was heated at reflux for 48 h, then cooled down to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2. The organic phase was washed with H_2O (3×10 mL), brine (1×10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc 95:5) provided 1-nitro-3-(prop-1-en-1-yl)benzene **60** (32 mg, 0.20 mmol, 65%) as a colorless oil. A mixture of E/Z isomers in a 1:1 ratio was obtained. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15 (dt, J=6.5, 2.0 Hz, 1H), 8.04 (dddd, J=15.0, 8.2, 2.3, 1.1 Hz, 1H), 7.60 (ddt, J=7.5, 4.7, 1.4 Hz, 1H), 7.46 (dt, J= 17.3, 7.9 Hz, 1H), 6.50–6.37 (m, 1H), 5.95 (dq, J=11.6, 7.2 Hz, 1H), 1.94–1.89 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.78, 139.26, 134.88, 131.80, 129.86, 129.42, 129.14, 129.12, 127.86, 123.53, 121.46, 121.39, 120.49, 18.62, 14.68.

3-Propylaniline (61). To a solution of 1-nitro-3-(prop-1-en-1-yl) benzene **60** (570 mg, 3.49 mmol) in EtOAc (10 mL) was added Pd/C 10% (2.8 mg). The reaction vessel was evacuated under vacuum and filled back with hydrogen. The cycle was repeated twice and the suspension was stirred at room temperature for 16 h under H_2 atmosphere. The mixture was then filtered over a plug of celite, rinsed with DCM and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc 80:20) provided 3-propylaniline **61** (158 mg, 1.17 mmol, 33%) as a brown oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.18–7.10 (m, 1H), 6.67 (d, J= 7.6 Hz, 1H), 6.59–6.54 (m, 2H), 3.61 (s(br), 2H), 2.57 (t, J=9.0 Hz, 2H), 1.70 (sext, J=6.0 Hz, 2H), 1.02 (t, J=7.3 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.34, 143.96, 129.10, 118.90, 115.38, 112.60, 38.10, 24.46, 13.93.

2-((3-Propylphenyl)amino)benzoic acid (19). 3-Propylaniline **61** (106 mg, 0.784 mmol) was reacted with methyl 2-bromobenzoate (327 mg, 1.52 mmol) according to general procedure C. The crude compound was used without any purification. Its saponification was performed according to general procedure D to afford **19** (160 mg, 0.627 mmol, 80%) as a yellow solid without the need of any purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.29 (s(br), 1H), 8.03 (dd, J=8.1, 1.6 Hz, 1H), 7.35 (ddd, J=8.6, 7.0, 1.6 Hz, 1H), 7.31–7.27 (m, 1H), 7.25–7.20 (m, 1H), 7.09 (d, J=7.4 Hz, 2H), 6.96 (d, J=7.6 Hz, 1H), 6.78–6.71 (m, 1H), 2.59 (t, J=9.0 Hz, 2H), 1.66 (sext, J=7.4 Hz, 2H), 0.96 (t, J=7.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.67, 149.27, 144.40, 140.32, 135.31, 132.74, 129.32, 124.55, 123.49, 120.62, 117.12, 114.25, 38.12, 24.64, 13.99; HRMS (ESI) $[M+H]^+$ calcd for $C_{16}H_{17}NO_2$: 256.13321, found 256.13422; HPLC purity: >99%..

1-(Buta-1,3-dien-1-yl)-3-nitrobenzene (62). To a solution of 3-nitrobenzaldehyde (1.02 g, 6.75 mmol) in dry THF (25 mL) was added allyltriphenylphosphonium bromide (3.10 g, 8.09 mmol) under argon atmosphere. Potassium *tert*-butoxide (960 mg, 8.56 mmol) was added portionwise at 0 °C. The mixture was stirred at 0 °C for 15 min and then was allowed to warm up to room temperature for 16 h, after which it was concentrated under reduced pressure. The residue was dissolved in EtOAc. The organic phase was washed with H_2O (3×50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc 95:5) provided 1-(buta-1,3-dien-1-yl)-3-nitrobenzene **62** (548 mg, 3.13 mmol, 46%) as a yellow oil. A 1:1 mixture of *E/Z* isomers was obtained. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (dt, J=24.0, 2.0 Hz, 1H), 8.08 (dddd, J= 11.3, 8.1, 2.3, 1.1 Hz, 1H), 7.65 (ddt, J=18.6, 7.7, 1.5 Hz, 1H), 7.49 (dt, J=9.7, 7.9 Hz, 1H), 6.96–6.71 (m, 1H), 6.63–6.45 (m, 1H), 6.45–6.34 (m, 1H), 5.52–5.40 (m, 1H), 5.38–5.26 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.06, 139.02, 136.43, 134.97, 133.27, 132.61, 132.25, 132.03, 130.24, 129.62, 129.30, 127.69, 123.70, 122.14, 122.13, 121.91, 120.93, 120.19.

3-Butylaniline (63). To a solution of 1-(buta-1,3-dien-1-yl)-3-nitrobenzene **62** (567 mg, 3.24 mmol) in EtOAc (12 mL) was added Pd/C 10% (10 mg). The reaction vessel was evacuated under vacuum and filled back with hydrogen. The cycle was repeated twice and the suspension was stirred at room temperature for 16 h under H_2 atmosphere. The mixture was then filtered over a plug of celite, rinsed with DCM and concentrated under reduced pressure to give 3-butylaniline **63** (461 mg, 3.09 mmol, 95%) as an orange oil without any purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25–7.18 (m, 1H), 6.76 (d, J=7.5 Hz, 1H), 6.64–6.57 (m, 2H), 3.69 (s(br), 2H), 2.69 (t, J=9.0 Hz, 2H), 1.83–1.68 (m, 2H), 1.61–1.47 (sext, J=7.3 Hz, 2H), 1.12 (t, J=7.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.32, 143.81, 128.84, 118.42, 115.06, 112.31, 35.48, 33.37, 22.24, 13.79.

2-((3-Butylphenyl)amino)benzoic acid (20). 2-Bromobenzoic acid (300 mg, 1.49 mmol) was reacted with 3-butylaniline **63** (298 mg, 2.00 mmol) according to general procedure F to afford product **20** (104 mg, 0.386 mmol, 26%) as a brown solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.25 (s(br), 1H), 8.01 (dd, J=8.1, 1.6 Hz, 1H), 7.32 (ddd, J=8.6, 7.0, 1.7 Hz, 1H), 7.27–7.21 (m, 1H), 7.19 (dd, J=8.5, 0.7 Hz, 1H), 7.06 (dd, J=6.7, 1.0 Hz, 2H), 6.93 (d, J=7.6 Hz, 1H), 6.71 (ddd, J=8.1, 7.1, 1.0 Hz, 1H), 2.58 (t, J=9.0 Hz, 2H), 1.66–1.52 (m, 2H), 1.42–1.27(sext, J=7.3 Hz, 2H), 0.91 (t, J=7.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.59, 149.28, 144.63, 140.33, 135.32, 132.73, 129.32, 124.51, 123.46, 120.58, 117.11, 114.26, 110.38, 35.73, 33.70, 22.53, 14.10; HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{19}NO_2$: 270.1489, found 270.1493; HPLC purity: 97%..

1-Nitro-3-(pent-1-en-1-yl)benzene (64). To a solution of 3-nitrobenzaldehyde (1.22 g, 8.07 mmol) in dry THF (30 mL) was added *n*-butyltriphenylphosphonium iodide (4.31 g, 9.66 mmol) under argon atmosphere. Potassium *tert*-butoxide (1.09 g, 9.71 mmol) was added portionwise at 0 °C. The mixture was stirred at 0 °C for 15 min and then was allowed to warm up to room temperature over 16 h, after which it was concentrated under reduced pressure. The residue was dissolved in EtOAc. The organic phase was washed with H_2O (3×50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc 95:5) provided 1-nitro-3-(pent-1-en-1-yl)benzene **64** (651 mg, 3.40 mmol, 42%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10–7.91 (m, 2H), 7.55 (dd, J=11.8, 7.8 Hz, 1H), 7.47–7.34 (m, 1H), 6.36 (dd, J=13.4, 7.9 Hz, 1H), 5.78 (dt, J=11.7, 7.3 Hz, 1H), 2.25 (qd, J=7.4, 1.8 Hz, 2H), 1.45 (dd, J=14.7, 7.4 Hz, 2H), 0.90 (t, J=7.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.07, 139.23, 135.70, 134.59, 128.92, 126.68, 123.18, 121.11, 30.47, 22.83, 13.62..

3-Pentylaniline (65). To a solution of 1-nitro-3-(pent-1-en-1-yl) benzene **64** (371 mg, 1.94 mmol) in EtOAc (10 mL) was added Pd/C 10% (6 mg). The reaction vessel was evacuated under vacuum and filled back with hydrogen. The cycle was repeated twice and the suspension was stirred at room temperature for 16 h under H_2 atmosphere. The mixture was filtered over a plug of celite, rinsed with DCM and concentrated under reduced pressure to give 3-pentylaniline **65** (268 mg, 1.64 mmol, 85%) as an orange oil without any purification. Spectral data are consistent with literature values[59] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.15 (m, 1H), 6.73 (d, J=7.6 Hz, 1H), 6.60 (dd, J=7.8, 1.4 Hz, 2H), 3.64 (s(br), 2H), 2.65 (t, J=9.0 Hz, 2H), 1.80–1.66 (m, 2H), 1.53–1.42 (m, 4H), 1.05 (t, J=6.9 Hz, 3H).

2-((3-Pentylphenyl)amino)benzoic acid (21). 3-Pentylaniline **65** (149 mg, 0.913 mmol) was reacted with methyl 2-bromobenzoate (304 mg, 1.41 mmol) according to general procedure C. The crude compound was used without any purification. Its saponification was performed according to general procedure D to afford **21** (186 mg, 0.656 mmol, 72%) was obtained as a yellow solid without the need of any purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.42 (s(br), 1H), 8.16 (dd, J=8.0, 1.2 Hz, 1H), 7.45–7.37 (m, 1H), 7.33 (t, J=7.1 Hz, 2H), 7.21–7.15 (m, 2H), 7.05 (d, J=7.5 Hz, 1H), 6.82 (t, J=7.2 Hz, 1H), 2.70 (t, J=9.0 Hz, 2H), 1.74 (quint. J=6.0 Hz, 2H), 1.49–1.40 (m, 4H), 1.01 (t, J=6.8 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 174.43, 149.23, 144.56, 140.27, 135.29, 132.75, 129.28, 124.43, 123.36, 120.50, 117.08, 114.20, 110.46, 35.98, 31.64, 31.21, 22.68, 14.18; HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{21}NO_2$: 284.1645, found 284.1658; HPLC purity: >99%.

***n*-Pentyltriphenylphosphonium iodide (66)**. To a solution of triphenylphosphine (5.00 g, 19.1 mmol) in dry toluene (30 mL) was added 1-iodopentane (4.24 mL, 32.5 mmol). The reaction mixture was stirred at 110 °C for 48 h under argon atmosphere. After cooling down to room temperature, the precipitate was filtered and dried to yield to product **66** (8.78 g, 19.1 mmol, 99%) as a white powder. Spectral data are consistent with literature values[60] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.85–7.75 (m, 9H), 7.74–7.66 (m, 6H), 3.69–3.56 (m, 2H), 1.70–1.54 (m, 4H), 1.30 (sext, J=7.3 Hz, 2H), 0.81 (t, J=7.3 Hz, 3H).

1-(Hex-1-en-1-yl)-3-nitrobenzene (67). To a solution of 3-nitrobenzaldehyde (2.46 g, 16.29 mmol) in dry THF (65 mL) was added **66** (9.00 g, 19.55 mmol) under argon atmosphere. Potassium *tert*-butoxide (2.19 g, 19.52 mmol) was added portionwise at 0 °C. The mixture was stirred at 0 °C for 15 min and then was allowed to warm up to room temperature for 16 h, after which it was concentrated under reduced pressure. The residue was dissolved in EtOAc. The organic phase was washed with H_2O (3×50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc 95:5) provided **67** (1.89 g, 9.21 mmol, 57%) as a yellow oil. Spectral data are consistent with literature values.[61] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15 (dt, J=17.2, 1.7 Hz, 1H), 8.09–8.00 (m, 1H), 7.64–7.54 (m, 1H), 7.52–7.41 (m, 1H), 6.43 (d, J=12.9 Hz, 1H), 5.83 (dt, J=11.7, 7.4 Hz, 1H), 2.36–2.26 (m 2H), 1.51–1.42 (m, 2H), 1.42–1.31 (m, 2H), 0.90 (t, J=7.2 Hz, 3H).

3-Hexylaniline (68). To a solution of **67** (563 mg, 2.74 mmol) in EtOAc (10 mL) was added Pd/C 10% (15 mg). The reaction vessel was evacuated under vacuum and filled with hydrogen. The cycle was repeated twice and the suspension was stirred at room temperature for 16 h under H_2 atmosphere. The mixture was then filtered over a plug of celite, rinsed with DCM and concentrated under reduced pressure to afford 3-hexylaniline **68** (429 mg, 2.42 mmol, 88%) as a yellow oil which was used directly in the next step. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.08 (td, J=7.7, 1.0 Hz, 1H), 6.61 (d, J=7.7 Hz, 1H), 6.55–6.49 (m, 2H), 3.60 (s, 2H), 2.53 (t, J=7.6 Hz, 2H), 1.61 (quint, J=7.5 Hz, 2H), 1.40–1.29 (m, 6H), 0.90 (t, J=6.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.34, 144.27, 129.15, 118.89, 115.35, 112.58, 36.06, 31.83, 31.42, 29.14, 22.69, 14.18.

2-((3-Hexylphenyl)amino)benzoic acid (22). 2-Bromobenzoic acid (109 mg, 0.54 mmol) was reacted with **68** (125 mg, 0.71 mmol) according to general procedure F to afford product **22** (24 mg, 0.081 mmol, 15%) as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.28 (s(br), 1H), 8.04 (dd, J=8.1, 1.5 Hz, 1H), 7.35 (ddd, J=8.6, 7.0, 1.6 Hz, 1H), 7.28 (d, J=8.7 Hz, 1H), 7.25–7.19 (m, 1H), 7.13–7.05 (m, 3H), 6.96 (d, J=7.6 Hz, 1H), 6.80–6.68 (m, 1H), 2.61 (t, J=9.0 Hz, 2H), 1.69–1.57 (m, 2H), 1.41–1.27 (m, 6H), 0.89 (t, J=6.7 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.97, 149.26, 144.66, 140.32, 135.28, 132.69, 129.33, 124.49, 123.44, 120.56, 117.09, 114.24, 110.28, 36.05, 31.87, 31.53, 29.15, 22.77, 14.25; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{23}NO_2$: 298.1802, found 298.1796; HPLC purity: 96%.

1-(Hept-1-yn-1-yl)-3-nitrobenzene (69). To a solution of 1-iodo-3-nitrobenzene (500 mg, 2.0 mmol) in dry THF (5 mL) was added $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (8 mg, 0.04 mmol), DIPEA (1.1 mL, 6.3 mmol) and hept-1-yne (0.29 mL, 2.2 mmol). The reaction mixture was stirred at 50 °C for 16 h under argon atmosphere,

then cooled down to room temperature and diluted with EtOAc and H_2O. The aqueous phase was extracted with EtOAc (3×20 mL) and the combined organic phases were washed with brine (1× 60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) provided **69** (436 mg, 2.0 mmol, >99%) as an orange oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.23 (t, J=1.9 Hz, 1H), 8.10 (ddd, J=8.3, 2.3, 1.0 Hz, 1H), 7.68 (dt, J=7.7, 1.2 Hz, 1H), 7.45 (t, J=8.0 Hz, 1H), 2.42 (t, J=7.1 Hz, 2H), 1.63 (quint, J=7.1 Hz, 2H), 1.48–1.30 (m, 4H), 0.93 (t, J=7.1 Hz, 3H); ^{13}C-NMR (151 MHz, $CDCl_3$) δ 148.21, 137.43, 129.25, 126.52, 126.10, 122.33, 93.78, 78.63, 31.24, 28.30, 22.34, 19.47, 14.10.

3-(Hept-1-yn-1-yl)aniline (70). The reduction of the nitro group in **69** (200 mg, 0.921 mmol) was performed according to general procedure A. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) provided **70** (156 mg, 0.833 mmol, 90%) as an orange oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.08 (t, J=7.8 Hz, 1H), 6.84 (d, J=7.6 Hz, 1H), 6.74 (s, 1H), 6.59 (dd, J=8.0, 2.5 Hz, 1H), 3.62 (s(br), 2H), 2.41 (t, J=7.1 Hz, 2H), 1.63 (quint.J=6.9 Hz, 2H), 1.51–1.34 (m, 4H), 0.96 (t, J=7.0 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.27, 129.12, 124.77, 121.93, 117.91, 114.61, 89.88, 80.80, 31.15, 28.52, 22.28, 19.38, 14.04..

3-Heptylaniline (71). To a solution of **70** (189 mg, 1.0 mmol) in EtOAc (5 mL) was added Pd/C 10% (5 mg). The reaction vessel was evacuated under vacuum and filled back with hydrogen. The cycle was repeated twice and the suspension was stirred at room temperature for 16 h under H_2 atmosphere. The mixture was then filtered over a plug of celite, rinsed with DCM and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 70/30) provided **71** (131 mg, 0.68 mmol, 68%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (t, J=7.6 Hz, 1H), 6.64 (d, J=7.4 Hz, 1H), 6.59–6.50 (m, 2H), 3.62 (s(br), 2H), 2.56 (t, J=9.0 Hz, 2H), 1.70–1.56 (m, 2H), 1.41–1.29 (m, 8H), 0.94 (t, J=6.7 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.38, 144.29, 129.16, 118.90, 115.35, 112.58, 36.07, 31.91, 31.48, 29.44, 29.29, 22.76, 14.19.

Methyl 2-((3-heptylphenyl)amino)benzoate (72). 3-Heptylaniline **71** (70 mg, 0.37 mmol) was reacted with methyl 2-bromobenzoate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) provided product **72** (102 mg, 0.31 mmol, 84%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.45 (s(br), 1H), 7.97 (dd, J=8.0, 1.4 Hz, 1H), 7.35–7.26 (m, 2H), 7.24 (d, J=7.4 Hz, 1H), 7.11–7.05 (m, 2H), 6.92 (d, J=7.5 Hz, 1H), 6.78–6.67 (m, 1H), 3.91 (s, 3H), 2.60 (t, J=9.0 Hz, 2H), 1.69–1.55 (m, 2H), 1.36–1.26 (m, 8H), 0.89 (t, J=6.7 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.08, 148.28, 144.53, 140.72, 134.20, 131.73, 129.24, 123.95, 122.83, 119.90, 117.00, 114.21, 111.87, 51.87, 36.05, 31.96, 31.54, 29.42, 29.32, 22.81, 14.24.

2-((3-Heptylphenyl)amino)benzoic acid (23). Methyl 2-((3-heptylphenyl)amino)benzoate **72** (102 mg, 0.31 mmol) was saponified according to general procedure D to afford **23** (93 mg, 0.30 mmol, 97%) as a yellow solid without the need of any purification. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 7.96 (dd, J=8.0, 1.5 Hz, 1H), 7.27–7.21 (m, 1H), 7.20–7.13 (m, 2H), 7.03–6.94 (m, 2H), 6.83 (d, J=7.6 Hz, 1H), 6.67 (ddd, J=8.1, 6.9, 1.3 Hz, 1H), 2.51 (t, J=9.0 Hz, 2H), 1.55 (quint, J=7.1 Hz, 2H), 1.33–1.19 (m, 8H), 0.85 (t, J=6.8 Hz, 3H); ^{13}C-NMR (75 MHz, Methanol-d4) δ 171.84, 149.38, 145.39, 141.98, 134.99, 133.26, 130.18, 124.60, 123.15, 120.32, 117.89, 114.80, 113.26, 36.83, 32.97, 32.55, 30.27, 23.68, 14.48; HRMS (ESI) $[M+H]^+$ calcd for $C_{20}H_{25}NO_2$: 312.1958, found 312.1965; HPLC purity: >99%.

2-((3-Isopropylphenyl)amino)benzoic acid (24). 2-Bromobenzoic acid (210 mg, 1.04 mmol) was reacted with 3-isopropylaniline (198 mg, 1.46 mmol) according to general procedure F to afford product **24** (56 mg, 0.22 mmol, 21%) as a light yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.35 (s(br), 1H), 8.11 (dd, J=8.1, 1.5 Hz, 1H), 7.44–7.33 (m, 2H), 7.29 (t, J=8.8 Hz, 1H), 7.20–7.12 (m, 2H), 7.07 (d, J=7.6 Hz, 1H), 6.85–6.74 (m, 1H), 2.97 (sept, J=6.9 Hz, 1H), 1.33 (d, J=6.9 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 174.25, 150.65, 149.32, 140.34, 135.36, 132.77, 129.40, 122.54, 121.62, 120.77, 117.11, 114.22, 110.41, 34.24, 29.85, 24.09; HRMS (ESI) $[M+H]^+$ calcd for $C_{16}H_{17}NO_2$: 256.1332, found 256.1339; HPLC purity: >99%.

Methyl 2-((3-(*tert*-butyl)phenyl)amino)benzoate (73). 3-(*Tert*-butyl) aniline (300 mg, 2.0 mmol) was reacted with methyl 2-bromobenzoate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 95:5) provided product **73** (485 mg, 1.72 mmol, 86%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.48 (s(br), 1H), 7.97 (dd, J=8.1, 1.3 Hz, 1H), 7.35–7.23 (m, 4H), 7.19–7.06 (m, 2H), 6.76–6.67 (m, 1H), 3.91 (s, 3H), 1.33 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.12, 152.84, 148.39, 140.46, 134.23, 131.75, 129.00, 120.87, 120.30, 119.77, 116.93, 114.07, 111.76, 51.87, 34.86, 31.44.

2-((3-(*Tert*-butyl)phenyl)amino)benzoic acid (25). Methyl 2-((3-(*tert*-butyl)phenyl)amino)benzoate **73** (200 mg, 0.71 mmol) was saponified according to general procedure D to afford **25** (188 mg, 0.70 mmol, 99%) was obtained without the need of any purification as a brown solid. Spectral data are consistent with literature values.[62] ^{1}H-NMR (300 MHz, Methanol-d_4) δ 7.97 (dd, J=8.0, 1.5 Hz, 1H), 7.28 (ddd, J=8.6, 5.3, 1.6 Hz, 1H), 7.25–7.21 (m, 2H), 7.23–7.14 (m, 2H), 7.15–7.06 (m, 1H), 7.03 (ddd, J=7.9, 2.1, 0.9 Hz, 1H), 6.76–6.64 (m, 1H), 1.31 (s, 9H); HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{19}NO_2$: 270.1489, found 270.15013; HPLC purity: >99%.

2-([1,1′-Biphenyl]-3-ylamino)benzoic acid (26). 2-Bromobenzoic acid (200 mg, 0.99 mmol) was reacted with 3-aminobiphenyl (235 mg, 1.39 mmol) according to general procedure F to afford product **26** (47 mg, 0.16 mmol, 16%) as a beige powder. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.40 (s(br), 1H), 8.08 (dd, J=8.1, 1.4 Hz, 1H), 7.65–7.58 (m, 2H), 7.51 (t, J=1.7 Hz, 1H), 7.45 (td, J=7.5, 2.1 Hz, 3H), 7.42–7.33 (m, 3H), 7.35–7.26 (m, 2H), 6.84–6.73 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.62, 148.99, 142.84, 140.96, 140.85, 135.44, 132.81, 129.96, 128.95, 127.68, 127.28, 123.07, 121.96, 118.56, 117.49, 114.36, 110.67; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{15}NO_2$: 290.1176, found 290.1182; HPLC purity: 98%.

Methyl 2-bromo-3-fluorobenzoate (74). Esterification of 2-bromo-3-fluorobenzoic acid (300 mg, 1.37 mmol) was performed according to general procedure E to afford **74** (236 mg, 1.01 mmol, 74%) as a colorless oil without the need of any purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58–7.53 (m, 1H), 7.32 (td, J=8.0, 5.1 Hz, 1H), 7.23 (td, J=8.3, 1.7 Hz, 1H), 3.93 (s, 3H); ^{19}F-NMR (282 MHz, $CDCl_3$) δ −102.88, −102.88, −102.90, −102.90, −102.91, −102.91, −102.93, −102.93; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 165.93, 165.89, 161.25, 157.98, 134.39, 128.58, 128.47, 126.66, 126.61, 119.36, 119.05, 109.65, 109.35, 52.76.

Methyl 3-fluoro-2-((3-hexylphenyl)amino)benzoate (75). 3-Hexylaniline **68** (100 mg, 0.56 mmol) was reacted with **74** according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) provided product **75** (78 mg, 0.24 mmol, 42%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.87 (s(br), 1H), 7.83–7.78 (m, 1H), 7.29–7.23 (m, 1H), 7.19 (t, J=8.7 Hz, 1H), 6.91 (td, J=8.0, 4.6 Hz, 1H), 6.85 (d, J=7.6 Hz, 1H), 6.79 (dd, J=8.0, 2.9 Hz, 2H), 3.91 (s, 3H), 2.59 (t, J=7.0 Hz, 2H), 1.69–1.59 (m, 2H), 1.38–1.29 (m, 6H), 0.92 (t, J=6.7 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 182.37, 168.23, 151.98, 147.24, 143.76, 128.55, 126.94, 122.35, 121.00, 120.73, 119.66, 118.98, 116.06, 52.36, 36.11, 31.88, 31.49, 29.17, 22.76, 14.25; ^{19}F-NMR (282 MHz, $CDCl_3$) δ −115.20, −115.21, −115.22, −115.23, −115.24, −115.25.

3-Fluoro-2-((3-hexylphenyl)amino)benzoic acid (31). Methyl 3-fluoro-2-((3-hexylphenyl)amino)benzoate **75** (78 mg, 0.24 mmol)

was saponified according to general procedure D to afford **31** (60 mg, 0.19 mmol, 79%) as a brown oil without the need of any purification. ^{1}H-NMR (300 MHz, Methanol-d$_4$) δ 7.84 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.26 (ddd, *J* = 12.1, 8.1, 1.5 Hz, 1H), 7.10 (td, *J* = 7.7, 1.8 Hz, 1H), 6.95 (td, *J* = 8.0, 4.7 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.71–6.64 (m, 2H), 2.52 (t, *J* = 9.0 Hz, 2H), 1.65–1.49 (m, 2H), 1.37–1.24 (m, 6H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 174.30, 156.45, 153.16, 143.80, 143.19, 133.45, 133.29, 128.59, 127.17, 124.07, 121.86, 120.51, 120.39, 119.98, 119.71, 118.26, 115.62, 36.04, 31.84, 31.46, 29.20, 22.76, 14.22; ^{19}F-NMR (282 MHz, Methanol-d$_4$) δ −118.95, −118.96, −118.98, −118.99, −119.00, −119.02, −119.03; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{22}FNO_2$: 316.1707, found 316.1720; HPLC purity: 99%.

Methyl 2-bromo-4-fluorobenzoate (76). Esterification of 2-bromo-4-fluorobenzoic acid (2.00 g, 9.13 mmol) was performed according to general procedure E to afford **76** (1.92 g, 8.25 mmol, 44%) as a colorless oil without the need of any purification. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.89 (dd, *J* = 8.7, 6.0 Hz, 1H), 7.43 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.09 (td, *J* = 8.2, 2.5 Hz, 1H), 3.94 (s, 3H); ^{13}C-NMR (151 MHz, CDCl$_3$) δ 165.66, 164.80, 163.10, 133.52, 133.46, 128.11, 128.09, 123.28, 123.21, 122.09, 121.93, 114.71, 114.57, 52.63; ^{19}F-NMR (282 MHz, CDCl$_3$) δ −105.73, −105.75, −105.76, −105.78, −105.78, −105.81..

Methyl 4-fluoro-2-((3-hexylphenyl)amino)benzoate (77). 3-Hexylaniline **68** (121 mg, 0.68 mmol) was reacted with **76** according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 95:5) provided product **77** (211 mg, 0.64 mmol, 94%) as a yellow oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 9.65 (s(br), 1H), 7.98 (dd, *J* = 9.0, 6.8 Hz, 1H), 7.29 (td, *J* = 7.4, 1.3 Hz, 1H), 7.11–7.06 (m, 2H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.87 (dd, *J* = 12.2, 2.5 Hz, 1H), 6.45–6.37 (m, 1H), 3.91 (s, 3H), 2.67–2.59 (t, *J* = 7.5 Hz, 2H), 1.71–1.58 (m, 2H), 1.41–1.30 (m, 6H), 0.96–0.88 (m, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 168.61, 168.42, 165.28, 150.89, 150.73, 144.73, 139.85, 134.38, 134.23, 129.40, 124.84, 123.54, 120.62, 107.96, 104.73, 104.43, 100.07, 99.72, 51.84, 35.99, 31.85, 31.46, 29.10, 22.73, 14.21; ^{19}F-NMR (282 MHz, CDCl$_3$) δ −103.31, −103.32, −103.34, −103.34, −103.35, −103.36, −103.37, −103.38, −103.39, −103.41, −103.41.

4-Fluoro-2-((3-hexylphenyl)amino)benzoic acid (32). Saponification of methyl 4-fluoro-2-((3-hexylphenyl)amino)benzoate **77** (200 mg, 0.61 mmol) was performed according to general procedure D to afford **32** (95 mg, 0.30 mmol, 49%) as a yellow solid without the need of any purification. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 9.43 (s(br), 1H), 8.04 (dd, *J* = 8.7, 6.9 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.12–7.05 (m, 2H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.80 (dd, *J* = 12.1, 2.2 Hz, 1H), 6.48–6.38 (m, 1H), 2.68–2.56 (t, *J* = 7.5 Hz, 2H), 1.71–1.55 (m, 2H), 1.41–1.24 (m, 6H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 172.87, 169.39, 166.04, 151.91, 151.75, 144.91, 139.47, 135.57, 135.41, 129.52, 125.38, 124.10, 121.23, 105.21, 104.90, 100.18, 99.83, 36.01, 31.86, 31.50, 29.13, 22.75, 14.24; ^{19}F-NMR (282 MHz, CDCl$_3$) δ −101.57, −101.59, −101.61, −101.63, −101.66; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{22}FNO_2$: 316.1707, found 316.1722; HPLC purity: >99%.

Methyl 2-bromo-5-fluorobenzoate (78). Esterification of 2-bromo-5-fluorobenzoic acid (300 mg, 1.37 mmol) was performed according to general procedure E to afford **78** (262 mg, 1.13 mmol, 82%) as a colorless oil without the need of any purification. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.60 (dt, *J* = 7.9, 2.5 Hz, 1H), 7.51 (dt, *J* = 8.7, 2.9 Hz, 1H), 7.10–7.00 (m, 1H), 3.93 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 165.47, 163.06, 159.76, 135.97, 135.87, 133.56, 133.46, 120.23, 119.93, 118.79, 118.46, 116.19, 116.15, 52.82; ^{19}F-NMR (282 MHz, CDCl$_3$) δ −113.95, −113.96, −113.97, −113.98, −113.99, −113.99, −114.00, −114.02.

Methyl 5-fluoro-2-((3-hexylphenyl)amino)benzoate (79). 3-Hexylaniline **68** (100 mg, 0.56 mmol) was reacted with **78** according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) provided product **79** (93 mg, 0.28 mmol, 50%) as a yellow oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 9.25 (s(br), 1H), 7.66 (dd, *J* = 9.5, 3.1 Hz, 1H), 7.29–7.21 (m, 2H), 7.11–7.03 (m, 3H), 6.93 (d, *J* = 7.6 Hz, 1H), 3.92 (s, 3H), 2.61 (t, *J* = 9.0 Hz, 2H), 1.70–1.58 (m, 2H), 1.42–1.27 (m, 6H), 0.92 (t, *J* = 6.7 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 168.11, 168.08, 155.87, 152.74, 144.85, 144.83, 144.61, 140.91, 129.31, 123.88, 122.39, 122.01, 121.71, 119.43, 117.00, 116.69, 115.91, 115.82, 112.24, 112.16, 52.08, 36.03, 31.85, 31.48, 29.12, 22.74, 14.21; ^{19}F-NMR (282 MHz, CDCl$_3$) δ −126.87, −126.88, −126.89, −126.90, −126.91, −126.92, −126.93, −126.94.

5-Fluoro-2-((3-hexylphenyl)amino)benzoic acid (33). Saponification of methyl 5-fluoro-2-((3-hexylphenyl)amino)benzoate **79** (74 mg, 0.22 mmol) was performed according to general procedure D to afford **33** (66 mg, 0.21 mmol, 95%) as a yellow solid without the need of any purification. ^{1}H-NMR (300 MHz, Methanol-d$_4$) δ 7.62 (dd, *J* = 9.6, 3.1 Hz, 1H), 7.25–7.17 (m, 1H), 7.17 (dd, *J* = 2.6, 2.0 Hz, 1H), 7.08 (ddd, *J* = 9.3, 7.7, 3.1 Hz, 1H), 7.00–6.95 (m, 2H), 6.86 (d, *J* = 7.6 Hz, 1H), 2.55 (t, *J* = 9.0 Hz, 2H), 1.64–1.52 (m, 2H), 1.33–1.26 (m, 6H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C-NMR (75 MHz, Methanol-d$_4$) δ 170.68, 157.09, 153.98, 146.04, 145.59, 142.26, 130.29, 124.62, 122.88, 122.24, 120.02, 118.25, 116.75, 36.85, 32.86, 32.57, 30.03, 23.69, 14.43; ^{19}F-NMR (282 MHz, Methanol-d$_4$) δ −128.98, −129.00, −129.01, −129.01, −129.02, −129.03, −129.04, −129.06; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{22}FNO_2$: 316.1707, found 316.1718; HPLC purity: >99%.

Methyl 2-bromo-6-fluorobenzoate (80). Esterification of 2-bromo-6-fluorobenzoic acid (300 mg, 1.4 mmol) was performed according to general procedure E to afford **80** (140 mg, 0.6 mmol, 43%) as a colorless oil without the need of any purification. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.38 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.30–7.20 (m, 1H), 7.11–7.02 (m, 1H), 3.96 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 164.43, 161.34, 157.97, 132.11, 131.99, 128.71, 128.67, 124.78, 124.51, 120.39, 120.34, 115.17, 114.89, 53.11; ^{19}F-NMR (282 MHz, CDCl$_3$) δ −111.50, −111.52, −111.54, −111.56.

Methyl 2-fluoro-6-((3-hexylphenyl)amino)benzoate (81). 3-Hexylaniline **68** (100 mg, 0.56 mmol) was reacted with **80** according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) provided product **81** (162 mg, 0.49 mmol, 88%) as a yellow oil. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 9.09 (s(br), 1H), 7.28–7.14 (m, 2H), 7.06–7.01 (m, 2H), 6.98 (d, *J* = 8.6 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.46 (ddd, *J* = 11.2, 8.1, 1.0 Hz, 1H), 3.94 (s, 3H), 2.59 (t, *J* = 9.0 Hz, 2H), 1.65–1.58 (m, 2H), 1.37–1.27 (m, 6H), 0.93–0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 167.86, 165.14, 161.75, 149.02, 144.64, 140.54, 133.87, 129.32, 124.27, 122.86, 119.96, 110.12, 105.22, 52.28, 36.02, 31.85, 31.48, 29.12, 22.75, 14.23; ^{19}F-NMR (282 MHz, CDCl$_3$) δ −105.83, −105.85, −105.87, −105.89.

2-Fluoro-6-((3-hexylphenyl)amino)benzoic acid (34 = LM98). Methyl 2-fluoro-6-((3-hexylphenyl)amino)benzoate **81** (100 mg, 0.30 mmol) was saponified according to general procedure D to afford **34** (**LM98**) (57 mg, 0.18 mmol, 60%) as a brown solid without the need of any purification. ^{1}H-NMR (300 MHz, Methanol-d$_4$) δ 7.25–7.11 (m, 2H), 6.99–6.85 (m, 4H), 6.43 (ddd, *J* = 11.2, 8.1, 0.7 Hz, 1H), 2.57–2.49 (t, *J* = 7.5 Hz, 2H), 1.56 (quint, *J* = 7.6 Hz, 2H), 1.33–1.23 (m, 6H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, Methanol-d$_4$) δ 169.79, 166.44, 163.06, 150.11, 150.05, 145.55, 141.87, 134.66, 134.51, 130.27, 124.98, 123.36, 120.56, 110.85, 110.81, 105.94, 105.62, 104.96, 104.77, 36.80, 32.83, 32.52, 30.00, 23.66, 14.44; ^{19}F-NMR (282 MHz, Methanol-d$_4$) δ −107.32, −107.34, −107.36, −107.38; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{22}FNO_2$: 316.1707, found 316.1722; HPLC purity: >99%.

2-Iodo-6-methylbenzoic acid (82). To a solution of 2-methylbenzoic acid (500 mg, 3.67 mmol) in dry DMF (12 mL) was added *N*-iodosuccinimide (NIS) (826 mg, 3.67 mmol) and $Pd(OAc)_2$ (83 mg, 0.37 mmol). The reaction mixture was stirred at 100 °C for 2 h, cooled down to room temperature and concentrated under vacuum. The residue was dissolved in DCM, washed with saturated aqueous solution of brine (2×15 mL), dried over Na_2SO_3 and concentrated under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc 98:2 to 85:15) provided product **82** (681 mg, 2.60 mmol, 71%) as a white solid. Spectral data are consistent with literature values.[63] ^{1}H-NMR (300 MHz, Chloroform-d) δ 7.70 (d, *J*=7.9 Hz, 1H), 7.22 (d, *J*=7.7 Hz, 1H), 7.03 (t, *J*=7.8 Hz, 1H), 2.45 (s, 3H).

2-((3-Hexylphenyl)amino)-6-methylbenzoic acid (35). 3-Hexylaniline **68** (100 mg, 0.56 mmol) was reacted with **82** according to general procedure B to afford product **35** (32 mg, 0.10 mmol, 18%) as a brown solid without any need for further purification. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.95 (s(br), 1H), 7.18 (t, *J*=7.8 Hz, 1H), 7.12 (t, *J*=7.7 Hz, 1H), 7.06 (d, *J*=8.2 Hz, 1H), 6.87–6.83 (m, 2H), 6.77 (d, *J*=7.4 Hz, 1H), 6.71 (d, *J*=7.5 Hz, 1H), 2.35 (s, 3H), 1.53 (quint, *J*=7.3 Hz, 2H), 1.30–1.22 (m, 8H), 0.85 (t, *J*=6.7 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 169.97, 143.43, 142.98, 142.44, 137.51, 130.36, 128.99, 122.93, 122.60, 120.91, 118.34, 115.70, 115.61, 35.19, 31.10, 30.80, 28.33, 22.06, 21.09, 13.95; HRMS (ESI) $[M+H]^+$ calcd for $C_{20}H_{25}NO_2$: 312.1958, found 312.1963; UPLC-MS purity: 93%.

Methyl 2-((4-hexylphenyl)amino)benzoate (83). 4-Hexylaniline (300 mg, 1.69 mmol) was reacted with methyl 2-bromobenzoate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) provided product **83** (174 mg, 0.56 mmol, 33%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.47 (s(br), 1H), 8.02 (dd, *J*=8.1, 1.7 Hz, 1H), 7.38–7.28 (m, 2H), 7.24–7.21 (m, 4H), 6.79–6.72 (m, 1H), 3.96 (s, 3H), 2.66 (dd, *J*=8.7, 6.7 Hz, 2H), 1.68 (quint, *J*=7.5 Hz, 2H), 1.46–1.34 (m, 6H), 0.98 (t, *J*=6.0, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.07, 148.71, 138.75, 138.28, 134.20, 131.69, 129.38, 129.16, 128.35, 123.23, 116.70, 113.91, 111.51, 51.81, 35.55, 31.88, 31.68, 29.14, 22.76, 14.24.

2-((4-Hexylphenyl)amino)benzoic acid (36). Saponification of **83** (75 mg, 0.24 mmol) was performed according to general procedure D to afford **36** (48 mg, 0.16 mmol, 67%) as a brown solid without the need of any purification. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 7.95 (dd, *J*=8.0, 1.7 Hz, 1H), 7.29 (ddd, *J*=8.7, 7.0, 1.7 Hz, 1H), 7.19–7.09 (m, 5H), 6.73–6.64 (m, 1H), 2.58 (t, *J*=7.4 Hz, 2H), 1.61 (quint, *J*=7.5 Hz, 2H), 1.39–1.29 (m, 6H), 0.95–0.85 (t, *J*=6.8 Hz, 3H); ^{13}C-NMR (75 MHz, Methanol-d_4) δ 171.91, 149.89, 139.71, 139.57, 135.09, 133.23, 130.35, 123.68, 117.67, 114.57, 112.99, 36.36, 32.90, 32.78, 30.05, 23.69, 14.42; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{23}NO_2$: 298.1802, found 298.1815; HPLC purity: 99%.

Methyl 2-((4-(*tert*-butyl)phenyl)amino)benzoate (84). 4-*Tert*-butylaniline (0.32 mL, 2.01 mmol) was reacted with methyl 2-bromobenzoate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) provided product **84** (422 mg, 1.49 mmol, 74%) as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.41 (s(br), 1H), 7.95 (dd, *J*=8.1, 1.6 Hz, 1H), 7.40–7.34 (m, 2H), 7.33–7.27 (m, 1H), 7.24–7.16 (m, 3H), 6.74–6.65 (m, 1H), 3.90 (s, 3H), 1.34 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.08, 148.60, 146.86, 138.12, 134.21, 131.71, 126.33, 122.76, 116.78, 114.04, 111.61, 51.86, 34.52, 31.58.

2-((4-(*Tert*-butyl)phenyl)amino)benzoic acid (37). Methyl 2-((4-(*tert*-butyl)phenyl)amino)benzoate **84** (100 mg, 0.35 mmol) was saponified according to general procedure D to afford **37** (82 mg, 0.30 mmol, 86%) as a yellow solid without the need of any purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, *J*=8.1, 1.7 Hz, 1H), 7.42–7.30 (m, 3H), 7.23–7.15 (m, 3H), 6.77–6.69 (m, 1H), 1.34 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.63, 149.52, 147.40, 137.73, 135.29, 132.71, 126.42, 123.27, 116.92, 114.14, 110.20, 34.57, 31.57; HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{19}NO_2$: 270.1489, found 270.1499; UPLC-MS purity: >99%.

Methyl 2-([1,1′-biphenyl]-4-ylamino)benzoate (85). 4-Aminobiphenyl (300 mg, 1.77 mmol) was reacted with methyl 2-bromobenzoate according to general procedure C. Purification by flash column chromatography (DCM 100%) provided product **85** (536 mg, 1.77 mmol, >99%) as an orange solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.55 (s(br), 1H), 7.99 (dt, *J*=8.0, 1.1 Hz, 1H), 7.63–7.55 (m, 4H), 7.48–7.41 (m, 2H), 7.37–7.29 (m, 5H), 6.81–6.72 (m, 1H), 3.92 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.06, 147.79, 140.79, 140.27, 136.34, 134.26, 131.80, 128.91, 128.11, 127.08, 126.88, 122.50, 117.45, 114.42, 112.28, 51.95.

2-([1,1′-Biphenyl]-4-ylamino)benzoic acid (38). 85 (114 mg, 0.376 mmol) was saponified according to general procedure D to afford **38** (68 mg, 0.24 mmol, 64%) as a light yellow solid without the need of any purification. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.75 (s(br), 1H), 7.92 (dd, *J*=8.1, 1.7 Hz, 1H), 7.68–7.64 (m, 4H), 7.48–7.40 (m, 3H), 7.36–7.30 (m, 4H), 6.81 (t, *J*=7.5 Hz, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 169.93, 146.54, 140.12, 139.67, 134.48, 134.10, 131.90, 128.96, 128.91, 127.63, 126.94, 126.15, 121.21, 117.72, 114.20; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{15}NO_2$: 290.1176, found 290.1183; UPLC-MS purity: 95%.

N-(4-((3r,5r,7r)-adamantan-1-yl)phenyl)acetamide (86). To a solution of 1-bromoadamantane (250 mg, 1.16 mmol) in dichloroethane (10 mL) was added acetanilide (157 mg, 1.16 mmol). The reaction mixture was stirred for 5 min under argon atmosphere before $ZnCl_2$ (32 mg, 0.23 mmol) was added. The mixture was then heated at 75 °C for 16 h. EtOAc was added (100 mL) and the organic phase was washed with H_2O (50 mL) and a saturated aqueous solution of brine (50 mL). The organic phase was dried over Na_2SO_4 and evaporated. The crude material was purified by flash column chromatography (hexanes/EtOAc 95:5 to 40:60) to give **86** (199 mg, 0.739 mmol, 64%) as a white powder. Spectral data are consistent with literature values.[65] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J*=8.7 Hz, 2H), 7.31 (d, *J*=8.7 Hz, 2H), 7.07 (s(br), 1H), 2.16 (s, 3H), 2.12–2.06 (m, 3H), 1.90–1.86 (m, 6H), 1.83–1.69 (m, 6H).

4-((3r,5r,7r)-adamantan-1-yl)aniline hydrochloride (87). To a solution of **86** (70 mg, 0.26 mmol) in MeOH/H_2O (3:1) (4 mL) was added concentrated HCl (0.4 mL). The reaction mixture was stirred at 80 °C for 16 h, cooled back to room temperature and evaporated. The crude compound **87** (69 mg, 0.26 mmol, >99%) was used in the next step without further purification. Spectral data are consistent with literature values.[65] ^{1}H-NMR (300 MHz, Methanol-d_4) δ 7.52–7.45 (m, 2H), 7.26–7.20 (m, 2H), 2.13–2.06 (m, 3H), 1.95–1.91 (m, 6H), 1.90–1.75 (m, 6H).

Methyl 2-((4-((3r,5r,7r)-adamantan-1-yl)phenyl)amino)benzoate (88). 87 (100 mg, 0.379 mmol) was reacted with methyl 2-bromobenzoate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) followed by prep-TLC (hexanes/EtOAc 95:5) provided product **88** (87 mg, 0.24 mmol, 63%) as a beige powder. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 9.40 (s(br), 1H), 7.95 (d, *J*=8.1 Hz, 1H), 7.33 (d, *J*=6.8 Hz, 2H), 7.23–7.17 (m, 4H), 6.69 (s(br), 1H), 3.89 (s, 3H), 2.14–2.07 (m, 3H), 1.96–1.88 (m, 6H), 1.82–1.73 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.00, 148.53, 147.09, 138.11, 134.14, 131.67, 129.13, 128.32, 125.84, 122.70, 116.72, 114.00, 111.53, 51.77, 43.36, 36.90, 35.97, 29.08.

2-((4-((3r,5r,7r)-Adamantan-1-yl)phenyl)amino)benzoic acid (39). 88 (34 mg, 0.094 mmol) was saponified according to general procedure D to afford **39** (30 mg, 0.087 mmol, 93%) as a white powder without the need of any purification. ^{1}H-NMR (300 MHz,

Acetone-d_6) δ 8.45 (dd, J = 8.0, 1.6 Hz, 1H), 7.86–7.79 (m, 3H), 7.70–7.63 (m, 3H), 7.20 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 2.58–2.53 (m, 3H), 2.42–2.37 (m, 6H), 2.29–2.21 (m, 6H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 170.07, 147.53, 146.01, 137.81, 134.13, 131.88, 129.49, 125.68, 121.54, 121.37, 116.93, 113.46, 112.10, 42.71, 36.21, 35.39, 28.37; HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{25}NO_2$: 348.1958, found 348.1969; HPLC purity: 97%.

Methyl 2-((4-cyclohexylphenyl)amino)benzoate (89). 4-Cyclohexylaniline (300 mg, 1.71 mmol) was reacted with methyl 2-bromobenzoate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) provided product **89** (402 mg, 1.30 mmol, 76%) as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.61 (s(br), 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.41–7.30 (m, 2H), 7.30–7.27 (m, 4H), 6.83–6.74 (m, 1H), 3.96 (s, 3H), 2.66–2.53 (m, 1H), 2.07–1.91 (m, 4H), 1.92–1.83 (m, 1H), 1.59–1.47 (m, 4H), 1.46–1.37 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.84, 148.50, 143.64, 138.28, 134.02, 131.56, 127.60, 122.93, 116.57, 113.76, 111.34, 51.55, 44.00, 34.57, 26.93, 26.17.

2-((4-Cyclohexylphenyl)amino)benzoic acid (40). 89 (200 mg, 0.646 mmol) was saponified according to general procedure D to afford **40** (93 mg, 0.31 mmol, 48%) as a light yellow solid without the need of any purification. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 13.01 (s(br), 1H), 9.58 (s(br), 1H), 7.88 (dd, J = 7.9, 1.7 Hz, 1H), 7.36 (ddd, J = 8.7, 7.0, 1.7 Hz, 1H), 7.21 (d, J = 8.5 Hz, 2H), 7.18–7.13 (m, 3H), 6.76–6.71 (m, 1H), 2.49–2.44 (m, 1H), 1.84–1.75 (m, 4H), 1.73–1.66 (m, 1H), 1.45–1.30 (m, 4H), 1.29–1.19 (m, 1H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 169.98, 147.55, 142.77, 138.09, 134.15, 131.83, 127.61, 121.90, 116.92, 113.44, 112.09, 43.16, 34.06, 26.38, 25.60; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{21}NO_2$: 296.1645, found 296.1652; UPLC-MS purity: >99%. Compound **40** has been recrystallized by the solvent diffusion technique. Coordinates for X-ray structure of **40** have been deposited in the Cambridge Crystallographic Date Centre (CCDC) under the number 2054155.

3-Nitrophenol (90). To (3-nitrophenyl)boronic acid (1.00 g, 5.99 mmol) and Cu_2O (26 mg, 0.18 mmol) was added a solution of hydrogen peroxide at 30% (3.6 mL). The reaction mixture was stirred at room temperature for 15 min, after which H_2O and Et_2O were added. The aqueous phase was extracted with Et_2O (3× 40 mL) and the combined organic phases were washed with 20% aqueous solution of NH_4OAc (1×60 mL), brine (1×60 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product **90** (833 mg, 5.99 mmol, >99%) was obtained as a yellow solid and used without further purification. Spectral data are consistent with literature values.[66] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.82 (ddd, J = 8.2, 2.1, 0.8 Hz, 1H), 7.69 (t, J = 2.3 Hz, 1H), 7.41 (t, J = 8.2 Hz, 1H), 7.17 (ddd, J = 8.2, 2.5, 0.8 Hz, 1H).

1-Nitro-3-(pentyloxy)benzene (91). To a solution of **90** (833 mg, 5.99 mmol) in dry DMF (30 mL) were added 1-iodopentane (0.86 mL, 6.6 mmol) and NaH dry 90% (175 mg, 6.59 mmol). The reaction mixture was stirred at 80 °C for 16 h under argon atmosphere, cooled down to room temperature, diluted with DCM and H_2O. The aqueous phase was extracted with DCM (3×50 mL) and the combined organic phases were washed with H_2O (3× 50 mL), brine (1×50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (DCM 100%) provided product **91** (545 mg, 2.60 mmol, 43%) was obtained as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79 (ddd, J = 8.1, 2.1, 0.8 Hz, 1H), 7.71 (t, J = 2.3 Hz, 1H), 7.40 (t, J = 8.2 Hz, 1H), 7.21 (ddd, J = 8.3, 2.5, 0.8 Hz, 1H), 4.02 (t, J = 6.5 Hz, 2H), 1.90–1.75 (m, 2H), 1.51–1.34 (m, 4H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.83, 149.34, 129.97, 121.82, 115.64, 108.81, 68.87, 28.83, 28.22, 22.53, 14.11.

3-(Pentyloxy)aniline (92). Nitro reduction of **91** (97 mg, 0.46 mmol) was performed according to general procedure A. Purification by flash column chromatography (DCM 100%) provided **92** (82 mg, 0.46 mmol, >99%) as a dark brown oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.05 (t, J = 8.0 Hz, 1H), 6.33 (ddd, J = 8.2, 2.3, 0.7 Hz, 1H), 6.28 (ddd, J = 7.8, 2.1, 0.8 Hz, 1H), 6.25 (t, J = 2.2 Hz, 1H), 3.92 (t, J = 6.6 Hz, 2H), 3.60 (s(br), 2H), 1.84–1.70 (m, 2H), 1.49–1.32 (m, 4H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.45, 147.85, 130.15, 107.85, 104.76, 101.81, 67.90, 29.13, 28.35, 22.59, 14.15.

Methyl 2-((3-(pentyloxy)phenyl)amino)benzoate (93). 3-(Pentyloxy)aniline **92** (82 mg, 0.46 mmol) was reacted with methyl 2-bromobenzoate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) followed by preparative TLC (hexanes/EtOAc 95:5) provided product **93** (46 mg, 0.15 mmol, 32%) as a white powder. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.45 (s(br), 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 3.6 Hz, 2H), 7.23 (dd, J = 13.9, 5.7 Hz, 1H), 6.85–6.77 (m, 2H), 6.77–6.70 (m, 1H), 6.64 (d, J = 8.2 Hz, 1H), 3.94 (t, J = 6.6 Hz, 2H), 3.90 (s, 3H), 1.78 (quint, J = 6.0 Hz, 2H), 1.48–1.35 (m, 4H), 0.93 (t, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.06, 160.32, 147.89, 142.15, 134.22, 131.73, 130.10, 117.32, 114.63, 114.59, 112.19, 109.88, 108.62, 68.19, 51.91, 29.12, 28.35, 22.61, 14.16.

2-((3-(Pentyloxy)phenyl)amino)benzoic acid (47). Methyl 2-((3-(pentyloxy)phenyl)amino)benzoate **93** (46 mg, 0.15 mmol) was saponified according to general procedure D to afford **47** (16 mg, 0.054 mmol, 36%) as a beige powder without the need of any purification. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 7.97 (dd, J = 8.0, 1.5 Hz, 1H), 7.36–7.25 (m, 2H), 7.20 (t, J = 8.1 Hz, 1H), 6.80–6.70 (m, 3H), 6.61 (ddd, J = 8.4, 2.4, 0.7 Hz, 1H), 3.94 (t, J = 6.5 Hz, 2H), 1.76 (quint, J = 6.0 Hz, 2H), 1.49–1.36 (m, 4H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, Methanol-d_4) δ 170.42, 160.24, 147.65, 142.08, 133.68, 131.87, 129.70, 116.89, 113.89, 113.57, 112.27, 109.03, 107.59, 67.61, 28.74, 28.00, 22.16, 12.99; HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{21}NO_3$: 300.1594, found 300.1608; HPLC purity: 98%..

(3-Nitrophenyl)methanol (94). To a solution of 3-nitrobenzaldehyde (750 mg, 4.96 mmol) in EtOH (4 mL) at room temperature was added a suspension of $NaBH_4$ (124 mg, 3.27 mmol) in EtOH (4 mL). The reaction mixture was stirred at room temperature for 30 min, after which an aqueous solution of NaOH 10% was added (10 mL). After stirring the resulting mixture at room temperature for 5 min, it became limpid. EtOH was removed in vacuo and DCM was added. The aqueous phase was extracted with DCM (3×10 mL) and the combined organic phases were washed with saturated aqueous solution of $NaHCO_3$ (1×30 mL), brine (1×30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Product **94** (694 mg, 4.53 mmol, 91%) was obtained as a yellow oil and used in the following step without further purification. Spectral data are consistent with literature values.[57] ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.22 (d, J = 1.4 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 7.9 Hz, 1H), 4.80 (s, 2H).

1-(Butoxymethyl)-3-nitrobenzene (95). To a solution of **94** (350 mg, 2.29 mmol) in dry DMF (5 mL) were added 1-iodobutane (0.29 mL, 2.5 mmol) and NaH dry 90% (61 mg, 2.5 mmol). The reaction mixture was stirred at 80 °C for 16 h under argon atmosphere, cooled down to room temperature, diluted with DCM and quenched with H_2O. The aqueous phase was extracted with DCM (3×10 mL) and the combined organic phases were washed with H_2O (3×30 mL), brine (1×30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (DCM 100%) provided product **95** (205 mg, 0.980 mmol, 43%) was obtained as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 4.58 (s, 2H), 3.52 (t, J = 6.5 Hz, 2H), 1.67–1.56 (m, 2H), 1.49–1.33 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C-

NMR (75 MHz, $CDCl_3$) δ 148.47, 141.18, 133.38, 129.41, 122.56, 122.29, 71.70, 70.97, 31.88, 19.48, 14.02.

3-(Butoxymethyl)aniline (96). Nitro reduction of **95** (205 mg, 0.980 mmol) was performed according to general procedure A. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 70:30) provided **96** (158 mg, 0.881 mmol, 90%) as a dark brown oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.12 (t, J=7.7 Hz, 1H), 6.74–6.66 (m, 2H), 6.60 (dd, J=7.9, 1.7 Hz, 1H), 4.42 (s, 2H), 3.58 (s(br), 2H), 3.47 (t, J=6.6 Hz, 2H), 1.67–1.53 (m, 2H), 1.48–1.33 (m, 2H), 0.93 (t, J=7.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 146.61, 140.08, 129.34, 117.93, 114.36, 114.31, 72.92, 70.27, 31.96, 19.48, 14.04.

Methyl 2-((3-(butoxymethyl)phenyl)amino)benzoate (97). 3-(Butoxymethyl)aniline **96** (158 mg, 0.881 mmol) was reacted with methyl 2-bromobenzoate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) provided product **97** (203 mg, 0.648 mmol, 74%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.58 (s(br), 1H), 8.04–7.95 (m, 1H), 7.37–7.26 (m, 4H), 7.20 (d, J=7.9 Hz, 1H), 7.09 (d, J=7.5 Hz, 1H), 6.79–6.71 (m, 1H), 4.51 (s, 2H), 3.90 (s, 3H), 3.52 (t, J=6.5 Hz, 2H), 1.71–1.59 (m, 2H), 1.53–1.39 (m, 2H), 0.97 (t, J=7.3 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.75, 147.76, 140.80, 140.22, 133.98, 131.55, 129.21, 122.53, 121.26, 121.18, 117.06, 114.01, 111.86, 72.53, 70.24, 51.60, 31.82, 19.37, 13.90.

2-((3-(Butoxymethyl)phenyl)amino)benzoic acid (48). Methyl 2-((3-(butoxymethyl)phenyl)amino)benzoate **97** (90 mg, 0.29 mmol) was saponified according to general procedure D to afford **48** (28 mg, 0.095 mmol, 33%) as a beige solid without the need of any purification. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.67 (s(br), 1H), 7.90 (dd, J=7.9, 1.7 Hz, 1H), 7.39 (ddd, J=8.6, 7.1, 1.7 Hz, 1H), 7.32 (t, J=7.7 Hz, 1H), 7.23 (dd, J=8.5, 1.1 Hz, 1H), 7.20–7.12 (m, 2H), 7.01 (dt, J=7.7, 1.3 Hz, 1H), 6.78 (ddd, J=8.0, 7.1, 1.1 Hz, 1H), 4.44 (s, 2H), 3.43 (t, J=6.5 Hz, 2H), 1.57–1.48 (m, 2H), 1.40–1.29 (m, 2H), 0.87 (t, J=7.4 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 169.91, 146.86, 140.52, 140.33, 134.05, 131.87, 129.34, 121.90, 120.04, 119.87, 117.47, 113.84, 112.79, 71.48, 69.32, 31.28, 18.89, 13.74; HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{21}NO_3$: 300.1594, found 300.1603; UPLC-MS purity: >99%.

Methyl 2-((3-hexylphenyl)amino)nicotinate (98). 3-Hexylaniline **68** (200 mg, 1.13 mmol) was reacted with methyl 2-bromonicotinate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 80:20) provided **98** (276 mg, 0.883 mmol, 79%) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.23 (s(br), 1H), 8.40 (dd, J=4.8, 2.0 Hz, 1H), 8.21 (dd, J=7.8, 2.0 Hz, 1H), 7.74–7.68 (m, 1H), 7.50 (t, J=1.9 Hz, 1H), 7.30 (t, J=7.8 Hz, 1H), 6.93 (d, J=7.7 Hz, 1H), 6.68 (dd, J=7.8, 4.7 Hz, 1H), 3.91 (s, 3H), 2.67 (t, J=7.6 Hz, 2H), 1.70 (quint, J=7.6 Hz, 2H), 1.46–1.35 (m, 6H), 0.94 (t, J=6.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.86, 156.16, 153.17, 143.54, 140.01, 139.61, 128.57, 122.99, 120.81, 118.18, 112.98, 106.71, 52.04, 36.05, 31.77, 31.40, 29.05, 22.63, 14.11.

2-((3-Hexylphenyl)amino)nicotinic acid (49). Methyl 2-((3-hexylphenyl)amino)nicotinate **98** (126 mg, 0.403 mmol) was saponified according to general procedure D to afford **49** (72 mg, 0.24 mmol, 60%) as a light yellow solid without the need of any purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.98 (s(br), 1H), 8.40 (dd, J=4.7, 1.8 Hz, 1H), 8.29 (dd, J=7.8, 1.8 Hz, 1H), 7.51 (d, J=8.0 Hz, 1H), 7.38 (s, 1H), 7.30–7.22 (m, 1H), 6.92 (d, J=7.5 Hz, 1H), 6.74 (dd, J=7.8, 4.8 Hz, 1H), 6.17 (s(br), 1H), 2.61 (t, J=9.0 Hz, 2H), 1.68–1.54 (m, 2H), 1.40–1.27 (m, 6H), 0.88 (t, J=6.6 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.81, 156.69, 153.70, 144.04, 141.77, 139.04, 128.89, 124.11, 122.14, 119.48, 113.37, 106.62, 36.16, 31.89, 31.55, 29.21, 22.77, 14.25; HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{22}N_2O_2$: 299.1754, found 299.1752; HPLC purity: 97%.

Methyl 2-((3-(pentyloxy)phenyl)amino)nicotinate (99). 3-(Pentyloxy)aniline **92** (40 mg, 0.22 mmol) was reacted with methyl 2-bromonicotinate according to general procedure C. Purification by flash column chromatography (DCM 100%) provided product **99** (57 mg, 0.18 mmol, 82%) as a brown oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.18 (s(br), 1H), 8.39 (dd, J=4.8, 2.0 Hz, 1H), 8.23 (dd, J=7.8, 2.0 Hz, 1H), 7.42 (t, J=1.6 Hz, 1H), 7.24–7.19 (m, 2H), 6.71 (dd, J=7.8, 4.8 Hz, 1H), 6.65–6.57 (m, 1H), 3.98 (t, J=6.6 Hz, 2H), 3.92 (s, 3H), 1.80 (quint, J=6.7 Hz, 2H), 1.53–1.32 (m, 4H), 0.94 (t, J=7.0 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.03, 159.81, 156.20, 153.25, 140.92, 140.31, 129.53, 113.35, 113.27, 109.17, 107.42, 107.17, 68.08, 52.34, 29.14, 28.36, 22.61, 14.16.

2-((3-(Pentyloxy)phenyl)amino)nicotinic acid (50). Methyl 2-((3-(pentyloxy)phenyl)amino)nicotinate **99** (57 mg, 0.18 mmol) was saponified according to general procedure D to afford **50** (33 mg, 0.11 mmol, 61%) as a light yellow solid without the need of any purification. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 8.31 (dd, J=7.7, 1.9 Hz, 1H), 8.26 (dd, J=4.9, 1.8 Hz, 1H), 7.40 (t, J=2.1 Hz, 1H), 7.18 (t, J=8.1 Hz, 1H), 7.05 (dd, J=8.0, 1.0 Hz, 1H), 6.78 (dd, J=7.7, 4.9 Hz, 1H), 6.59 (dd, J=8.1, 1.8 Hz, 1H), 3.94 (t, J=6.5 Hz, 2H), 1.75 (quint, J=6.0 Hz, 2H), 1.50–1.35 (m, 4H), 0.93 (t, J=7.1 Hz, 3H); ^{13}C-NMR (75 MHz, Methanol-d_4) δ 170.50, 161.13, 157.24, 152.60, 142.40, 141.84, 130.52, 114.47, 114.16, 110.14, 109.78, 108.37, 68.95, 30.14, 29.39, 23.54, 14.40; HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{20}N_2O_3$: 301.1547, found 301.1557; HPLC purity: >99%.

Methyl 2-((4-((3r,5r,7r)-adamantan-1-yl)phenyl)amino)nicotinate (100). 87 (70 mg, 0.27 mmol) was reacted with methyl 2-bromonicotinate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 95:15) provided product **100** (76 mg, 0.21 mmol, 78%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.10 (s(br), 1H), 8.37 (dd, J=4.7, 2.0 Hz, 1H), 8.22 (dd, J=7.8, 2.0 Hz, 1H), 7.68–7.57 (m, 2H), 7.41–7.30 (m, 2H), 6.68 (dd, J=7.8, 4.7 Hz, 1H), 3.92 (s, 3H), 2.16–2.07 (m, 3H), 1.97–1.89 (m, 6H), 1.86–1.72 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.01, 156.38, 153.42, 146.24, 140.22, 137.05, 128.90, 125.31, 121.04, 121.00, 112.98, 106.74, 52.22, 43.35, 36.93, 35.89, 29.09.

2-((4-((3r,5r,7r)-Adamantan-1-yl)phenyl)amino)nicotinic acid (51). Saponification of **100** (77 mg, 0.21 mmol) was performed according to general procedure D to afford **51** (11 mg, 0.032 mmol, 15%) as a white solid without the need of any purification. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.54 (s(br), 1H), 8.33 (dd, J=4.8, 2.0 Hz, 1H), 8.22 (dd, J=7.7, 2.1 Hz, 1H), 7.61 (d, J=8.7 Hz, 2H), 7.29 (d, J=8.7 Hz, 2H), 6.81 (dd, J=7.7, 4.7 Hz, 1H), 2.09–2.04 (m, 3H), 1.87–1.83 (m, 6H), 1.75–1.72 (m, 6H); ^{13}C-NMR (151 MHz, DMSO-d_6) δ 169.34, 155.95, 152.78, 145.18, 140.67, 137.38, 125.09, 120.19, 113.79, 107.93, 42.93, 36.40, 35.48, 28.53; HRMS (ESI) $[M+H]^+$ calcd for $C_{22}H_{24}N_2O_2$: 349.1911, found 349.1911; UPLC-MS purity: 96%.

1-Nitro-4-(pentyloxy)benzene (101). To a solution of 4-nitrophenol (500 mg, 3.59 mmol) in MeCN (9 mL) were added K_2CO_3 (1.99 g, 14.4 mmol) and 1-iodopentane (0.52 mL, 4.0 mmol). The reaction mixture was stirred at 82 °C for 16 h, cooled down to room temperature, diluted with EtOAc and H_2O. The aqueous phase was extracted with EtOAc (3×30 mL) and the combined organic phases were washed with brine (1×50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Product **101** (751 mg, 3.59 mmol, >99%) was obtained as a yellow oil and used without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.22–8.14 (m, 2H), 6.96–6.89 (m, 2H), 4.04 (t, J=6.5 Hz, 2H), 1.82 (quint, J=6.0 Hz, 2H), 1.50–1.32 (m, 4H), 0.93 (t, J=7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.38, 141.43, 126.01, 114.51, 69.01, 28.78, 28.17, 22.50, 14.08.

4-(Pentyloxy)aniline (102). Nitro reduction of **101** (751 mg, 3.59 mmol) was performed according to general procedure A to afford product **102** (626 mg, 3.49 mmol, 97%) as a dark brown oil

which was used in the following step without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.77–6.71 (m, 2H), 6.66–6.60 (m, 2H), 3.88 (t, J=6.6 Hz, 2H), 3.23 (s(br), 2H), 1.74 (quint, J=6.0 Hz, 2H), 1.47–1.32 (m, 4H), 0.92 (t, J=7.0 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 152.47, 139.87, 116.55, 115.78, 68.81, 29.24, 28.34, 22.59, 14.1.

Methyl 2-((4-(pentyloxy)phenyl)amino)benzoate (103). 4-(Pentyloxy)aniline **102** (127 mg, 0.708 mmol) was reacted with methyl 2-bromobenzoate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 95:5 to 90:10) provided product **103** (220 mg, 0.702 mmol, >99%) as a yellow solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.31 (s(br), 1H), 7.96 (dd, J=8.1, 1.7 Hz, 1H), 7.27 (ddd, J=8.7, 7.0, 1.7 Hz, 1H), 7.21–7.15 (m, 2H), 7.00 (dd, J=8.6, 1.1 Hz, 1H), 6.96–6.88 (m, 2H), 6.67 (ddd, J=8.1, 7.0, 1.1 Hz, 1H), 3.97 (t, J=6.5 Hz, 2H), 3.91 (s, 3H), 1.82 (quint, J=6.7 Hz, 2H), 1.57–1.36 (m, 4H), 0.97 (t, J=7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.49, 156.81, 150.14, 134.64, 133.66, 132.01, 126.42, 116.58, 115.75, 113.81, 111.23, 68.75, 52.11, 29.54, 28.74, 22.99, 14.54..

2-((4-(Pentyloxy)phenyl)amino)benzoic acid (52). 103 (215 mg, 0.686 mmol) was saponified according to general procedure D to afford **52** (143 mg, 0.478 mmol, 70%) as a light yellow solid without the need of any purification. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, J=8.1, 1.7 Hz, 1H), 7.34–7.23 (m, 1H), 7.18 (d, J=8.7 Hz, 2H), 7.00–6.85 (m, 3H), 6.69 (t, J=7.5 Hz, 1H), 3.97 (t, J=6.6 Hz, 2H), 1.81 (quint, J=6.7 Hz, 2H), 1.56–1.33 (m, 4H), 0.95 (t, J=7.0 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.61, 150.53, 135.25, 132.76, 132.52, 129.39, 126.41, 116.28, 115.35, 113.55, 103.20, 68.34, 29.03, 28.24, 22.50, 14.06; HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{21}NO_3$: 300.1594, found 300.1603; HPLC purity: >99%.

Methyl 2-((4-(pentyloxy)phenyl)amino)nicotinate (104). 4-(Pentyloxy)aniline **102** (40 mg, 0.22 mmol) was reacted with methyl 2-bromonicotinate according to general procedure C. Purification by flash column chromatography (DCM 100%) provided product **104** (58 mg, 0.18 mmol, 84%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.93 (s(br), 1H), 8.32 (dd, J=4.8, 2.0 Hz, 1H), 8.20 (dd, J=7.8, 2.0 Hz, 1H), 7.55–7.47 (m, 2H), 6.93–6.85 (m, 2H), 6.65 (dd, J=7.8, 4.8 Hz, 1H), 3.95 (t, J=6.6 Hz, 2H), 3.91 (s, 3H), 1.79 (quint, J=6.0 Hz, 2H), 1.49–1.36 (m, 4H), 0.94 (t, J=7.1 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.04, 156.69, 155.60, 153.40, 140.33, 132.45, 123.52, 114.92, 112.71, 106.55, 68.39, 52.22, 29.15, 28.33, 22.58, 14.14.

2-((4-(Pentyloxy)phenyl)amino)nicotinic acid (53). 104 (58 mg, 0.19 mmol) was saponified according to general procedure D to afford **53** (51 mg, 0.17 mmol, 89%) as a beige solid without the need of any purification. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 8.41 (dd, J=7.7, 1.9 Hz, 1H), 8.11 (dd, J=5.3, 1.9 Hz, 1H), 7.45–7.38 (m, 2H), 6.97–6.91 (m, 2H), 6.81 (dd, J=7.7, 5.3 Hz, 1H), 3.98 (t, J=6.5 Hz, 2H), 1.78 (quint, J=6.0 Hz, 2H), 1.50–1.39 (m, 4H), 0.96 (t, J=7.1 Hz, 3H); ^{13}C-NMR (75 MHz, Methanol-d_4) δ 169.93, 158.06, 156.81, 149.57, 143.95, 131.84, 125.67, 116.27, 113.80, 111.30, 69.31, 30.12, 29.37, 23.52, 14.40; HRMS (ESI) $[M+H]^+$ calcd for $C_{17}H_{20}N_2O_3$: 301.1547, found 301.1544; HPLC purity: >99%.

Ethyl 3-((3-(pentyloxy)phenyl)amino)benzoate (105). 3-(Pentyloxy) aniline **92** (40 mg, 0.22 mmol) was reacted with ethyl 3-iodobenzoate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 85:15) provided product **105** (50 mg, 0.15 mmol, 69%) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.74–7.70 (m, 1H), 7.59 (dt, J=7.1, 1.7 Hz, 1H), 7.34–7.27 (m, 2H), 7.17 (ddd, J=8.3, 7.3, 1.0 Hz, 1H), 6.67–6.62 (m, 2H), 6.51 (ddd, J=8.2, 2.2, 1.1 Hz, 1H), 5.82 (s, 1H), 4.36 (q, J=7.1 Hz, 2H), 3.92 (t, J=6.6 Hz, 2H), 1.77 (quint, J=6.7 Hz, 2H), 1.45–1.32 (m, 7H), 0.92 (t, J=7.0 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.71, 160.43, 143.95, 143.40, 131.81, 130.27, 129.39, 122.06, 121.93, 118.88, 110.58, 107.69, 104.56, 68.08, 61.10, 29.10, 28.34, 22.59, 14.45, 14.15.

3-((3-(Pentyloxy)phenyl)amino)benzoic acid (54). 105 (50 mg, 0.15 mmol) was saponified according to general procedure D to afford **54** (43 mg, 0.14 mmol, 96%) as a brown oil without the need of any purification. ^{1}H-NMR (300 MHz, Methanol-d_4) δ 7.75 (s(br), 1H), 7.51–7.45 (m, 1H), 7.29–7.24 (m, 2H), 7.10 (t, J=8.1 Hz, 1H), 6.70–6.65 (m, 1H), 6.64 (t, J=2.1 Hz, 1H), 6.42 (dd, J=8.1, 2.1 Hz, 1H), 3.89 (t, J=6.5 Hz, 2H), 1.77–1.67 (m, 2H), 1.43–1.33 (m, 4H), 0.92 (t, J=7.0 Hz, 3H); ^{13}C-NMR (75 MHz, Methanol-d_4) δ 170.81, 161.51, 145.77, 145.41, 133.54, 130.89, 130.07, 122.26, 122.12, 118.99, 111.08, 107.88, 104.99, 68.85, 30.10, 29.35, 23.50, 14.39; HRMS (ESI) $[M+H]^+$ calcd for $C_{18}H_{21}NO_3$: 300.1594, found 300.1587; HPLC purity: 95%.

Methyl 2-((3-(trifluoromethyl)phenyl)amino)nicotinate (106). 3-(Trifluoromethyl)aniline (0.15 mL, 1.2 mmol) was reacted with methyl 2-bromonicotinate according to general procedure C. Purification by flash column chromatography (hexanes/EtOAc 99:1 to 90:10) provided product **106** (350 mg, 1.18 mmol, 98%) as a transparent oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.40 (s(br), 1H), 8.41 (dd, J=4.8, 2.0 Hz, 1H), 8.24 (dd, J=7.8, 2.0 Hz, 1H), 8.15 (s, 1H), 7.90 (d, J=8.1 Hz, 1H), 7.44 (t, J=7.9 Hz, 1H), 7.30 (d, J=8.3 Hz, 1H), 6.77 (dd, J=7.8, 4.8 Hz, 1H), 3.94 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.96, 155.75, 153.08, 140.50, 140.27, 131.80, 131.37, 130.95, 130.53, 129.26, 126.15, 123.44, 122.54, 119.03, 118.98, 118.92, 118.87, 117.12, 117.06, 117.01, 116.96, 114.13, 107.48, 52.39; ^{19}F-NMR (282 MHz, $CDCl_3$) δ −62.62.

2-((3-(Trifluoromethyl)phenyl)amino)nicotinic acid (2) (Niflumic acid; NA). 106 (350 mg, 1.18 mmol) was saponified according to general procedure D to afford niflumic acid **2** (274 mg, 0.971 mmol, 82%) as a beige solid without the need of any purification. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.71 (s(br), 1H), 8.41–8.28 (m, 2H), 8.26 (dd, J=7.6, 2.1 Hz, 1H), 7.84 (dd, J=8.1, 2.1 Hz, 1H), 7.51 (t, J=8.0 Hz, 1H), 7.27 (d, J=7.6 Hz, 1H), 6.88 (dd, J=7.6, 4.8 Hz, 1H); ^{13}C-NMR (151 MHz, DMSO-d_6) δ 206.39, 155.38, 150.78, 141.22, 140.20, 129.69, 129.58, 129.37, 125.21, 123.41, 122.70, 117.29, 117.28, 114.82, 114.80, 114.79, 114.48, 30.64; ^{19}F-NMR (282 MHz, DMSO-d_6) δ −61.12; HRMS (ESI) $[M+H]^+$ calcd for $C_{13}H_9F_3N_2O_2$: 283.0689, found 283.0683; HPLC purity: 97%.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] K. Harvey, N. Tapon, *Nat. Rev. Cancer* **2007**, *7*, 182–191.
[2] L. Cairns, T. Tran, J. M. Kavran, *ACS Chem. Biol.* **2017**, *12*, 601–610.
[3] S. Piccolo, S. Dupont, M. Cordenonsi, *Physiol. Rev.* **2014**, *94*, 1287–1312.
[4] M. K. Kim, J. W. Jang, S. C. Bae, *BMB Rep.* **2018**, *51*, 126–133.
[5] S. Strano, E. Munarriz, M. Rossi, L. Castagnoli, Y. Shaul, A. Sacchi, M. Oren, M. Sudol, G. Cesareni, G. Blandino, *J. Biol. Chem.* **2001**, *276*, 15164–15173.
[6] H. Zhang, H. A. Pasolli, E. Fuchs, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 2270–2275.
[7] B. Zhao, L. Li, Q. Lei, K. L. Guan, *Genes Dev.* **2010**, *24*, 862–874.
[8] A. V. Pobbati, W. Hong, *Cancer Biol. Ther.* **2013**, *14*, 390–398.
[9] M. Z. Xu, S. W. Chan, A. M. Liu, K. F. Wong, S. T. Fan, J. Chen, R. T. Poon, L. Zender, S. W. Lowe, W. Hong, J. M. Luk, *Oncogene* **2011**, *30*, 1229–1240.
[10] D. Pan, *Dev. Cell.* **2010**, *19*, 491–505.
[11] A. A. Ahmed, A. D. Mohamed, M. Gener, W. Li, E. Taboada, *Mol. Cell. Oncol.* **2017**, *4*, e1295127.
[12] M. Corvaisier, M. Bauzone, F. Corfiotti, F. Renaud, M. El Amrani, D. Monté, S. Truant, E. Leteurtre, P. Formstecher, I. Van Seuningen, C. Gespach, G. Huet, *Oncotarget* **2016**, *7*, 56699–56712.
[13] L. Guo, L. Teng, *Int. J. Oncol.* **2015**, *46*, 1444–1452.
[14] J. F. Knight, C. J. Shepherd, S. Rizzo, D. Brewer, S. Jhavar, A. R. Dodson, C. S. Cooper, R. Eeles, A. Falconer, G. Kovacs, M. D. Garrett, A. R. Norman, J. Shipley, D. L. Hudson, *Br. J. Cancer.* **2008**, *99*, 1849–1858.
[15] T. Hucl, J. R. Brody, E. Gallmeier, C. A. Iacobuzio-Donahue, I. K. Farrance, S. E. Kern, *Cancer Res.* **2007**, *67*, 9055–9065.
[16] Y. Liu, G. Wang, Y. Yang, Z. Mei, Z. Liang, A. Cui, T. Wu, C. Y. Liu, L. Cui, *Oncogene* **2016**, *35*, 2789–2800.
[17] B. Lim, J. L. Park, H. J. Kim, Y. K. Park, J. H. Kim, H. A. Sohn, S. M. Noh, K. S. Song, W. H. Kim, Y. S. Kim, S. Y. Kim, *Carcinogenesis* **2014**, *35*, 1020–1027.
[18] R. Johnson, G. Halder, *Nat. Rev. Drug Discovery* **2014**, *13*, 63–79.
[19] B. Zhao, X. Ye, J. Yu, L. Li, W. Li, S. Li, J. Yu, J. D. Lin, C. Y. Wang, A. M. Chinnaiyan, Z. C. Lai, K. L. Guan *Genes Dev.* **2008**, *22*, 1962–1971.
[20] B. Zhao, J. Kim, X. Ye, Z. C. Lai, K. L. Guan, *Cancer Res.* **2009**, *69*, 1089–1098.
[21] J. Dong, G. Feldmann, J. Huang, S. Wu, N. Zhang, S. A. Comerford, M. F. Gayyed, R. A. Anders, A. Maitra, D. Pan, *Cell.* **2007**, *130*, 1120–1133.
[22] F. Zanconato, M. Cordenonsi, S. Piccolo, *Cancer Cell* **2016**, *29*, 783–803.
[23] J. S. A. Warren, Y. Xiao, J. M. Lamar, *Cancers* **2018**, *10*, 115–151.
[24] Y. Liu-Chittenden, B. Huang, J. Sup Shim, Q. Chen, S.-J. Lee, R. A. Anders, J. O. Liu, D. Pan, *Genes Dev.* **2012**, *26*, 1300–1305.
[25] Z. Li, B. Zhao, P. Wang, F. Chen, Z. Dong, H. Yang, K. L. Guan, Y. Xu, *Genes Dev.* **2010**, *24*, 235–240.
[26] Z. Zhou, T. Hu, Z. Xu, Z. Lin, Z. Zhang, T. Feng, L. Zhu, Y. Rong, H. Shen, J. M. Luk, X. Zhang, N. Qin, *FASEB J.* **2015**, *29*, 724–732.
[27] Z. Zhang, Z. Lin, Z. Zhou, H. C. Shen, S. F. Yan, A. V. Mayweg, Z. Xu, N. Qin, J. C. Wong, Z. Zhang, Y. Rong, D. C. Fry, T. Hu, *ACS Med. Chem. Lett.* **2014**, *5*, 993–998.
[28] P. Furet, B. Salem, Y. Mesrouze, T. Schmelzle, I. Lewis, J. Kallen, P. Chène, *Bioorg. Med. Chem. Lett.* **2019**, *29*, 2316–2319.
[29] Z. R. Crook, G. P. Sevilla, D. Friend, M. Y. Brusniak, A. D. Bandaranayake, M. Clarke, M. Gewe, A. J. Mhyre, D. Baker, R. K. Strong, P. Bradley, J. M. Olson, *Nat. Commun.* **2017**, *8*, 2244–2258.
[30] S. Jiao, H. Wang, Z. Shi, A. Dong, W. Zhang, X. Song, F. He, Y. Wang, Z. Zhang, W. Wang, X. Wang, T. Guo, P. Li, Y. Zhao, H. Ji, L. Zhang, Z. Zhou, *Cancer Cell* **2014**, *25*, 166–180.
[31] F. Gibault, M. Coevoet, M. Sturbaut, A. Farce, N. Renault, F. Allemand, J.-F. Guichou, A.-S. Drucbert, C. Foulon, R. Magnez, X. Thuru, M. Corvaisier, G. Huet, P. Chavatte, P. Melnyk, F. Bailly, P. Cotelle, *Cancers* **2018**, *10*, 140–153.
[32] S. A. Smith, R. B. Sessions, D. K. Shoemark, C. Williams, R. Ebrahimighaei, M. C. McNeill, M. P. Crump, T. R. McKay, G. Harris, A. C. Newby, M. Bond, *J. Med. Chem.* **2019**, *62*, 1291–1305.
[33] A. V. Pobbati, B. P. Rubin, *Molecules* **2020**, *25*, 6001–6017.
[34] Y. Li, S. Liu, E. Y. Ng, R. Li, A. Poulsen, J. Hill, A. V. Pobbati, A. W. Hung, W. Hong, T. H. Keller, C. Kang, *Biochem. J.* **2018**, *475*, 2043–2055.
[35] P. Chan, X. Han, B. Zheng, M. DeRan, J. Yu, G. K. Jarugumilli, H. Deng, D. Pan, X. Luo, X. Wu, *Nat. Chem. Biol.* **2016**, *12*, 282–289.
[36] C. L. Noland, S. Gierke, P. D. Schnier, J. Murray, W. N. Sandoval, M. Sagolla, A. Dey, R. N. Hannoush, W. J. Fairbrother, C. N. Cunningham, *Structure* **2016**, *24*, 179–186.
[37] Y. Mesrouze, M. Meyerhofer, F. Bokhovchuk, P. Fontana, C. Zimmermann, T. Martin, C. Delaunay, A. Izaac, J. Kallen, T. Schmelzle, D. Erdmann, P. Chène, *Protein Sci.* **2017**, *26*, 2399–2409.
[38] X. Wu, International Patent WO 2017/053706 A1, **2017**.
[39] N. G. Kim, B. M. Gumbiner, *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 9877–9882.
[40] A. V. Pobbati, X. Han, A. W. Hung, S. Weiguang, N. Huda, G. Y. Chen, C. Kang, C. S. B. Chia, X. Luo, W. Hong, A. Poulsen, *Structure* **2015**, *23*, 2076–2086.
[41] M. Barth, S. Contal, J. L. Junien, C. Massardier, C. Montalbetti, A. Soude, International Patent WO 2020/070181 A1, **2020**.
[42] J. K. Holden, J. J. Crawford, C. L. Noland, S. Schmidt, J. R. Zbieg, J. A. Lacap, R. Zang, G. M. Miller, Y. Zhang, P. Beroza, R. Reja, W. Lee, J. Y. W. K. Tom, R. Fong, M. Steffek, S. Clausen, T. J. Hagenbeek, T. Hu, Z. Zhou, H. C. Shen, C. N. Cunningham, *Cell Rep.* **2020**, *31*, 107809.
[43] V. B. K. Kunig, M. Potowski, M. Akbarzadeh, M. K. Škopić, D. Dos Santos Smith, L. Arendt, I. Dormuth, H. Adihou, B. Andlovic, H. Karatas, S. Shaabani, T. Zarganes-Tzitzikas, C. G. Neochoritis, R. Zhang, M. Groves, S. M. Guéret, C. Ottmann, J. Rahnenführer, R. Fried, A. Dömling, A. Brunschweiger, *Angew. Chem. Int. Ed. Engl.* **2020**, *59*, 20338–20342.
[44] W. Lu, J. Wang, Y. Li, H. Tao, H. Xiong, F. Lian, J. Gao, H. Ma, T. Lu, D. Zhang, X. Ye, H. Ding, L. Yue, Y. Zhang, H. Tang, N. Zhang, Y. Yang, H. Jiang, K. Chen, B. Zhou, C. Luo, *Eur. J. Med. Chem.* **2019**, *184*, 111767.
[45] K. Bum-Erdene, D. Zhou, H. Gonzalez-Gutierrez, M. K. Ghozayel, Y. Si, D. Xu, H. E. Shannon, B. J. Bailey, T. W. Corson, K. E. Pollok, C. D. Wells, S. O. Meroueh, *Cell Chem. Biol.* **2019**, *26*, 378–389.
[46] A. V. Pobbati, T. Mejuch, S. Chakraborty, H. Karatas, S. R. Bharath, S. M. Guéret, P. A. Goy, G. Hahne, A. Pahl, S. Sievers, E. Guccione, H. Song, H. Waldmann, W. Hong, *ACS Chem. Biol.* **2019**, *14*, 2909–2921.
[47] F. H. Niesen, H. Berglund, M. Vedadi, *Nat. Protoc.* **2007**, *2*, 2212–2221.
[48] M. Vedadi, F. H. Niesen, A. Allali-Hassani, O. Y. Fedorov, P. J. Finerty Jr, G. A. Wasney, R. Yeung, C. Arrowsmith, L. J. Ball, H. Berglund, R. Hui, B. D. Marsden, P. Nordlund, M. Sundstrom, J. Weigelt, A. M. Edwards, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 15835–15840.
[49] N. Igoe, E. D. Bayle, C. Tallant, O. Fedorov, J. C. Meier, P. Savitsky, C. Rogers, Y. Morias, S. Scholze, H. Boyd, D. Cunoosamy, D. M. Andrews, A. Cheasty, P. E. Brennan, S. Müller, S. Knapp, P. V. Fish, *J. Med. Chem.* **2017**, *60*, 6998–7011.
[50] A. N. Bullock, J. E. Debreczeni, O. Y. Fedorov, A. Nelson, B. D. Marsden, S. Knapp, *J. Med. Chem.* **2005**, *48*, 7604–7614.
[51] A. M. Omar, M. A. Elfaky, S. T. Arold, S. H. Soror, M. T. Khayat, H. Z. Asfour, F. H. Bamane, M. E. El-Araby, *Biomolecules* **2020**, *10*, 479–501.
[52] U. S. Hameed, I. Haider, M. Jamil, B. A. Kountche, X. Guo, R. A. Zarban, D. Kim, A. Al-Babili, S. T. Arold, *EMBO Rep.* **2018**, *19*, e45619.
[53] T. Sugiki, K. Furuita, T. Fujiwara, C. Kojima, *Molecules* **2018**, *23*, 148-174.
[54] C. Dalvit, A. Vulpetti, *J. Med. Chem.* **2019**, *62*, 2218–2244.
[55] S. Akoka, L. Barantin, M. Trierweiler, *Anal. Chem.* **1999**, *71*, 2554–2557.

[56] T. Machleidt, C. C. Woodroofe, M. K. Schwinn, J. Méndez, M. B. Robers, K. Zimmerman, P. Otto, D. L. Daniels, T. A. Kirkland, K. V. Wood, *ACS Chem. Biol.* **2015**, *10*, 1797–1804.
[57] S. Dupont, L. Morsut, M. Aragona, E. Enzo, S. Giulitti, M. Cordenonsi, F. Zanconato, J. Le Digabel, M. Forcato, S. Bicciato, N. Elvassore, S. Piccolo, *Nature* **2011**, *474*, 179–183.
[58] H. Andersson, H. Demaegdt, G. Vauquelin, G. Lindeberg, A. Karlén, M. Hallberg, *Bioorg. Med. Chem.* **2008**, *16*, 6924–6935.
[59] G. Ortar, M. Grazia Cascio, L. De Petrocellis, E. Morera, F. Rossi, A. Schiano-Moriello, M. Nalli, V. de Novellis, D. F. Woodward, S. Maione, V. Di Marzo, *J. Med. Chem.* **2007**, *50*, 6554–6569.
[60] B. Ringstrand, M. Oltmanns, J. A. Batt, A. Jankowiak, R. P. Denicola, P. Kaszynski, *Beilstein J. Org. Chem.* **2011**, *7*, 386–393.
[61] V. P. Prasad, S. Wagner, P. Keul, S. Hermann, B. Levkau, M. Schäfers, G. Haufe, *Bioorg. Med. Chem.* **2014**, *22*, 5168–5181.
[62] C. Féau, L. A. Arnold, A. Kosinski, F. Zhu, M. Connelly, R. K. Guy, *ACS Chem. Biol.* **2009**, *4*, 834–843.
[63] T. S. Mei, R. Giri, N. Maugel, J. Q. Yu, *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 5215–5219.
[64] D. S. Zurabishvili, M. O. Lomidze, S. A. Samsoniya, A. Wesquet, U. Kazmaier, *Chem. Heterocycl. Compd.* **2008**, *44*, 941–949.
[65] A. Koperniku, A. S. Foscolos, I. Papanastasiou, G. B. Foscolos, A. Tsotinis, D. Schols, *Lett. Org. Chem.* **2016**, *13*, 171–176.
[66] C. M. Rudzinski, A. M. Young, D. G. Nocera, *J. Am. Chem. Soc.* **2002**, *124*, 1723–1727.

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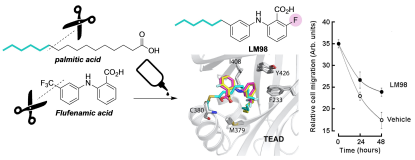
FULL PAPERS

Fusion chemistry: We report the design and development of LM98, a reversible TEAD inhibitor that originates from the fusion of flufenamic acid and palmitic acid. LM98 binds in the palmitic acid pocket of TEAD, preventing its autopalmitoylation and reducing the expression of associated genes. LM98 reduces TEAD activation, inhibits breast cancer cell migration and arrests cells in the S phase. Extensive SAR studies revealed new opportunities for future medicinal chemistry activities within this series.



*L. Mélin, S. Abdullayev, A. Fnaiche, Dr. V. Vu, N. González Suárez, H. Zeng, Dr. M. M. Szewczyk, Dr. F. Li, Dr. G. Senisterra, Dr. A. Allali-Hassani, I. Chau, Dr. A. Dong, Dr. S. Woo, Prof. B. Annabi, Dr. L. Halabelian, Prof. S. R. LaPlante, Prof. M. Vedadi, Dr. D. Barsyte-Lovejoy, Dr. V. Santhakumar, Prof. A. Gagnon**

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Development of LM98, a Small-Molecule TEAD Inhibitor Derived from Flufenamic Acid