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Brief Article

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Free Fatty Acid Receptor 1 (FFA1/GPR40) Agonists: Mesylpropoxy Appendage Lowers Lipophilicity and Improves ADME Properties

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Supporting Information

ABSTRACT: FFA1 (GPR40) is a new target for treatment of type 2 diabetes. We recently identified the potent FFA1 agonist TUG-469 (**5**). Inspired by the structurally related TAK-875, we explored the effects of a mesylpropoxy appendage on **5**. The appendage significantly lowers lipophilicity and improves metabolic stability while preserving potency, resulting in discovery of the potent FFA1 agonist **13**.

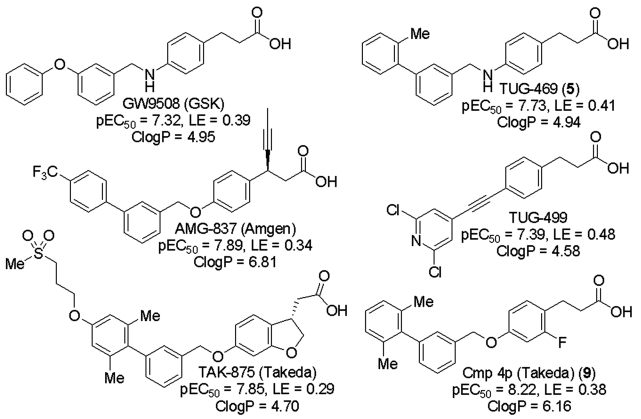
INTRODUCTION

Current methods used for design, synthesis, screening, and optimization in drug discovery tend to produce compounds with higher than ideal lipophilicity, a property that recently has been repeatedly pointed at as a critical factor for the success of new potential drugs in the development stages because high lipophilicity is associated with poor absorption, metabolic instability, high promiscuity, toxic effects, and consequently a higher risk of attrition in clinical trials.[1−7] To counteract this, concepts such as ligand efficiency (LE, free energy binding divided by the number of non-hydrogen atoms),[8] ligand lipophilicity efficiency (LLE, logarithmic potency subtracted by log *P* or log *D*)[1] and ligand efficiency-dependent lipophilicity (LELP, log *P* divided by LE)[7] have been introduced and are increasingly being implemented in drug discovery programs and useful in directing optimization away from oversized and highly lipophilic compounds.

The free fatty acid receptor 1 (FFA1, also known as GPR40) is activated by medium- and long-chain free fatty acids (FFAs), is highly expressed on pancreatic *β*-cells, and enhances glucose-stimulated insulin secretion.[9−11] This observation has attracted considerable attention to the receptor as a new potential target for improved therapeutics for treatment of type 2 diabetes, and several potent and selective FFA1 agonists are now known (Chart 1).[12−26] Many of these ligands have relatively high lipophilicity, most likely resulting from fatty acids being used as initial leads and from the lipophilic nature of the FFA1 binding site. We recently addressed this issue in our alkyne series, where we were able to lower the lipophilicity of the compounds by replacing the terminal benzene ring by aromatic nitrogen containing heterocycles (cf. TUG-499 in Chart 1).[22]

In our program aimed at discovery of potent and selective FFA1 (GPR40) agonists, we identified 4-benzyloxydihydrocinnamic acid (TUG-20) in screening of a focused library of constrained FFA analogues.[19] Inspired by the subsequent publication of the related potent FFA1 agonist GW9508,[12] we explored the structure−activity relationships (SAR) around these compounds and found that whereas the central ether is favored for small compounds, a central amine is preferred when the structures are more extended such as for GW9508 and TUG-469.[19] The central amine has the additional advantage that it provides less lipophilic compounds. Takeda recently published their clinical candidate TAK-875, corresponding to a conformationally constrained analogue of TUG-469 with an

Chart 1. Representative FFA1 Agonists[a]



[a]ClogP is calculated by ChemBioDraw.

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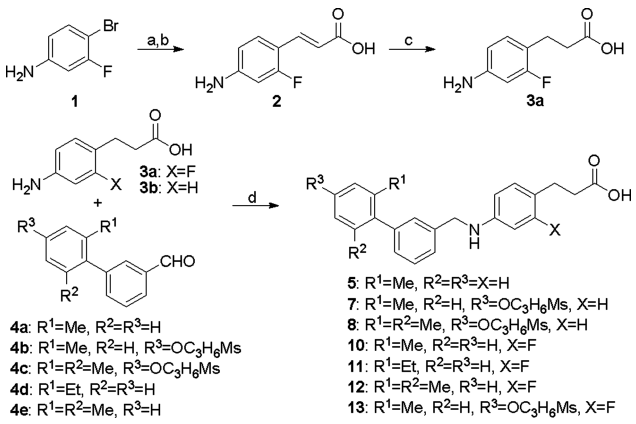
additional *ortho*-methyl and a *para*-mesylpropoxy chain on the biphenyl system and furthermore contains a central ether linker rather than the amine linker predicted by our SAR studies (Chart 1).[18] Calculations indicated that the mesylpropoxy appendage decrease lipophilicity by an order of magnitude. As the ClogP of **5** is in the uppermost part of the generally acceptable range, we were interested in exploring the effects of introducing a mesylpropoxy chain on this compound.

RESULTS AND DISCUSSION

Compounds **5**, **6**, and **9** were synthesized as described previously.[18−20] The mesylpropoxy-appended analogues **7** and **8** were synthesized as described for **5**[19] using the mesylpropoxy-substituted biphenyl building blocks **4b** and **4c**[18] (Scheme 1). The 2-fluoro substituted intermediate **3a** was prepared by a Heck coupling of **1** with ethyl acrylate followed by ester hydrolysis. Reductive amination of **2** with 2′-methylbiphenyl-3-carboxaldehyde followed by hydrogenation of the double bond over palladium provided **10** but in very poor yield (see Supporting Information (SI)). By swapping the first two steps and reducing **2** to **3a** followed by reductive coupling with **4d**, **4e**, and **4b**, compounds **11**−**13** were obtained, respectively, in moderate to good overall yields (Scheme 1).

Scheme 1[a]



[a]Reagents, conditions and yields: (a) ethyl acrylate, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, DIPEA, DMF, 80 °C, 4 h, 86%; (b) LiOH, THF, MeOH, H_2O, rt, 3 d, 99%; (c) Pd/C, MeOH, H_2, rt, 2 h, 73%; (d) $NaBH(OAc)_3$, CH_2Cl_2, AcOH (cat.), rt, 3−21 h, 38−67%.

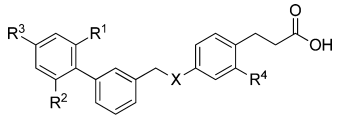
In our assay, **5** is somewhat more potent than **6** (racemic TAK-875) but also more lipophilic, giving **6** a slightly higher LLE (Table 1). The potency of EC_{50} = 26 nM found for **6** is in excellent agreement with the activity reported by Takeda for TAK-875 (EC_{50} = 14 nM), given that this enantiomer is primarily responsible for the activity.[18] Takeda has also reported the racemic analogue of TAK-875 lacking the mesylpropoxy substituent to have pEC_{50} = 7.66, i.e., equipotent with TAK-875 when it is taken into account that one enantiomer is mainly responsible for the activity.[18] Thus, the mesylpropoxy tail appears to improve ADME properties by lowering lipophilicity rather than to increase potency.

We proceeded by attaching a corresponding mesylpropoxy tail to **5**. The resulting **7** indeed turned out equipotent with **5** but had lipophilicity reduced by one log unit and thereby obtained a significant advantage in terms of LLE. Introducing the second *ortho*-methyl group in the biphenyl system (**8**) resulted in a barely significant increase in potency and a drop in LLE due to increased lipophilicity.

The values for **6**−**8** in Table 1 are in the presence of 0.05% BSA. In the absence of BSA, the values were significantly lower (pEC_{50} 6.85 ± 0.04 for **6**, 7.46 ± 0.06 for **7**, and 7.52 ± 0.04 for **8**). BSA often reduces the observed potency by competitive binding of the ligand but can also increase potency by increasing solubility, presumably the explanation of the effects observed here.[27]

The precursor in the development of TAK-875 is the highly potent and lipophilic **9** (Cmp 4p in Chart 1), which differs from **5** in having a second *ortho*-methyl substituent on the biphenyl system, a central ether linker, and a 2-fluoro

Table 1. Effects of *para*-Mesylpropoxy Chain and Substituents on FFA1 Agonist Activity and Lipophilicity



	R^1	R^2	R^3	R^4	X	FFA1 pEC_{50} (% efficacy)[a]	GPR120 pEC_{50} (% efficacy)	$LogD_{7.4}$ (ClogP)[b]	LE[c]	LLE[d]	HLM[e] (%)
5	Me	H	H	H	NH	7.73 ± 0.04 (114)	5.20 ± 0.02 (53)	2.49 ± 0.01 (4.9)	0.41	5.2 (2.8)	87
6[f]	Me	Me	MsC_3H_6O		O	7.59 ± 0.04 (91)[g]	n.t.[h]	2.24 ± 0.03 (4.7)	0.28	5.4 (2.9)	101
7	Me	H	MsC_3H_6O	H	NH	7.76 ± 0.03 (98)[g]	4.96 ± 0.07 (90)	1.43 ± 0.01 (3.9)	0.31	6.3 (3.8)	106
8	Me	Me	MsC_3H_6O	H	NH	7.83 ± 0.04 (92)[g]	n.t.[h]	1.77 ± 0.02 (4.4)	0.31	6.1 (3.7)	
9[i]	Me	Me	H	F	O	7.46 ± 0.04 (92)	5.08 ± 0.08 (82)	3.82 ± 0.13 (6.2)	0.37	3.6 (1.3)	42
10	Me	H	H	F	NH	8.03 ± 0.04 (102)	5.07 ± 0.04 (92)	2.86 ± 0.03 (5.4)	0.41	5.2 (2.7)	
11	Et	H	H	F	NH	7.63 ± 0.02 (101)	5.37 ± 0.08 (91)	2.88 ± 0.01 (5.9)	0.37	4.8 (1.7)	
12	Me	Me	H	F	NH	7.75 ± 0.02 (104)	4.03 ± 0.08 (78)	3.03 ± 0.04 (5.6)	0.38	4.7 (2.2)	
13	Me	H	MsC_3H_6O	F	NH	8.04 ± 0.02 (102)	4.36 ± 0.09 (66)	1.87 ± 0.01 (4.4)	0.32	6.2 (3.7)	100

[a]Efficacy is given as percentage of the full agonist TUG-20.[19] [b]$LogD_{7.4}$ values were determined by shake-flask procedure. ClogP values were calculated by the BioByte's algorithm as implemented in ChemBioDraw Ultra 12.0 (the "ClogP" option). [c]LE values were calculated by $-\Delta g = RT \ln K_D$, presuming $EC_{50} \approx K_D$.[8] [d]LLE values were calculated by the formula $pEC_{50} - LogD_{7.4}$ (values in parentheses were calculated by pEC_{50} − ClogP). [e]Stability toward human liver microsomes (HLM) was evaluated at Cerep Inc. (see the SI) [f]Racemic TAK-875 (structure in Chart 1). The pure (*S*)-enantiomer is previously reported by Takeda as with EC_{50} = 14 nM (pEC_{50} = 7.85) in a FLIPR assay with 0.1% BSA. [g]Tested with 0.05% BSA. [h]Not tested. [i]Previously reported by Takeda as an FFA1 agonist with EC_{50} = 5.7 nM (pEC_{50} = 8.22) in a FLIPR assay with 0.1% BSA.

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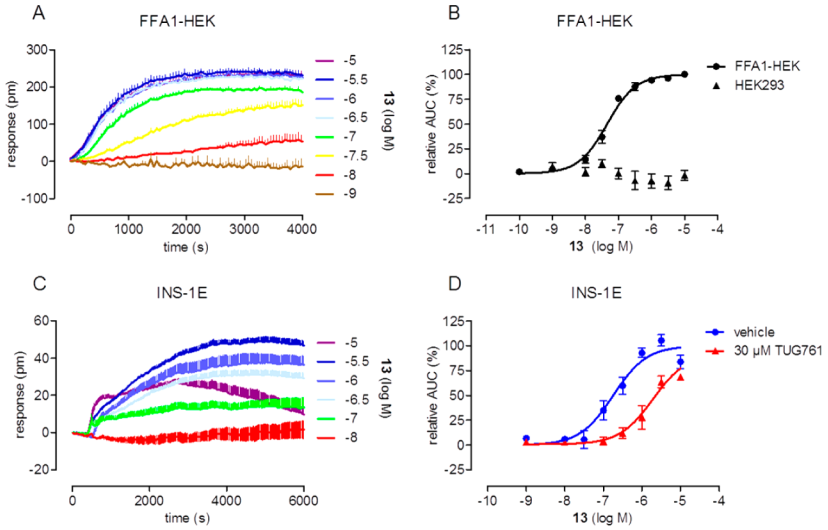

Figure 1. Activity of **13** on FFA1 transfected HEK293 cells and on the rat β-cell line INS-1E. (A) Representative traces (mean + SEM) from the dynamic mass redistribution (DMR) assay of HEK293 cells stably expressing the human FFA1 receptor (FFA1-HEK) and stimulated with the indicated concentrations of **13**. (B) Receptor activation in FFA1-HEK cells is concentration-dependent (pEC_{50}: 7.34 ± 0.06, n = 3); no activation is detectable in native HEK293 cells. (C) Representative traces from the DMR assay of INS-1E cells endogenously expressing FFA1. (D) Concentration-effect-curve of **13** on INS-1E cells (pEC_{50} = 6.74 ± 0.14, n = 6). Preincubation with the FFA1 antagonist TUG-761[22] (30 μM) resulted in a right-shifted curve (pEC_{50} = 5.71 ± 0.21, n = 3), confirming FFA1-dependent DMR responses.

substituent on the central benzene ring.[20] The compound surprisingly appeared significantly less potent in our assay than reported by Takeda. It is possible that the difference is related to Takeda using 0.1% BSA in the assay. We wished to explore the *ortho*-fluoro substituent, which was introduced by the Takeda group to resolve metabolic issues with preceding compounds but which also was found to slightly increase potency. Introducing the 2-fluoro substituent on **5** to give **10** indeed boosted potency to the single-digit nanomolar range but also increased lipophilicity correspondingly, leading to virtually unchanged or slightly decreased LE and LLE. Substituting the *ortho*-methyl for ethyl (**11**) gave a significant decrease in potency and a similar increase in lipophilicity. Surprisingly, a second *ortho*-methyl substituent (**12**) also resulted in decreased potency.

In an attempt to reach an optimal combination of high potency and moderate lipophilicity, the 2-fluoro substituent and the mesylpropoxy chain were introduced to **10** to give **13**. Again, whereas the two compounds exhibited identical potency, lipophilicity (ClogP and $logD_{7.4}$) was lowered by an order of magnitude. Despite the LE of **13** being significantly lower than **5** and **10** and that the compound exhibits an LLE value similar to **7** and **8**, we believe that **13** represents the optimal combination of high potency and acceptable lipophilicity in this series. In contrast to the other compounds with mesylpropoxy appendages, the potency of **13** was not affected by 0.05% BSA.

Lipophilicity is known to influence the metabolic stability by increasing interaction with enzymes. We found that **6** (racemic TAK-875), **7**, and **13** all were completely stable toward human liver microsomes, whereas the somewhat more lipophilic compound **5** had slightly reduced stability (Table 1). The significantly reduced stability of **9** (Chart 1) is in agreement with the higher lipophilicity of the compound.[24]

Compound **13** was examined further using a dynamic mass redistribution (DMR) assay, enabling real-time label-free detection of intracellular events.[28] Concentration dependent activation of hFFA1 transfected HEK293 cells was confirmed, with no detectable activity on native HEK293 cells (Figure 1). Likewise, **13** induced a concentration dependent response in insulin secreting rat β-cell line INS-1E endogenously expressing FFA1. Pretreatment with the FFA1 antagonist TUG-761[22] resulted in a right-shifted curve, and pretreatment with the selective FFA1 agonist TUG-499 (Chart 1 and ref 22) prevented activation by **13** (Figure S1, SI), demonstrating that the activity is mediated through FFA1. **13** was devoid of activity on the related receptors FFA2 and FFA3 (Figure S2, SI) and on nontransfected HEK293 cells in the DMR assays (Figure 1) and exhibited 4800-fold selectivity over GPR120, an order of magnitude higher than **5** (Table 1).

The pharmacokinetic properties of compounds **5** and **13** were investigated in mice. Both compounds were rapidly absorbed, and compound **13** exhibited twice as high exposure as **5** (Table 2). This effect can be rationalized by reduced first-pass metabolism due to the lower lipophilicity of **13**.

Table 2. Pharmacokinetic Parameters after Oral Dosing[a]

	C_{max} (ng/mL)	T_{max} (min)	AUC_{po} (ng·h/mL)
5	2360	15	2740
13	8748	15	5202

[a]Compounds were dosed p.o. at 10 mg/kg in mice (n = 3).

CONCLUSION

By combining features of the previously published compounds **5**, **6**, and **9**, we identified **13** as a compound with higher potency and lower lipophilicity than any previous FFA1 agonist. The 2-fluoro substituent increases both potency and lipophilicity by approximately the same degree and is therefore only an advantage as long as the compound is not already too lipophilic. The mesylpropoxy chain decreased lipophilicity by one log unit without affecting potency on FFA1. A consequence of the reduced lipophilicity was increased stability toward human liver microsomes. It seems possible that attachment of mesylalkoxy or similar groups can represent a general strategy for lowering the lipophilicity and thereby

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"rescuing" otherwise problematic compound series. The viability of this strategy is currently being explored on other compound series.

EXPERIMENTAL SECTION

All commercial starting materials and solvents were used without further purification unless otherwise stated. THF was freshly distilled from sodium/benzophenone. DIPEA was dried over 4 Å sieves, and anhydrous DMF was purchased from Sigma-Aldrich. Purification by flash chromatography was carried out using silica gel 60 (0.040−0.063 mm, Merck). ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 101 MHz, respectively, and calibrated relative to TMS internal standard or residual solvent peak. High-resolution mass spectra (HRMS) were obtained on a Bruker micrOTOF-Q II (ESI). HPLC analysis was performed using a Dionex 120 C18 column (5 μ, 4.6 × 150 mm^2); flow, 1 mL/min; 10% acetonitrile in water (0−1 min), 10−100% acetonitrile in water (1−10 min), 100% acetonitrile (11−15 min), with both solvents containing 0.05% TFA as modifier; UV detection at 254 nm. Purity was determined by HPLC analysis and confirmed by inspection of NMR spectra. All target compounds have >95% purity.

(*E*)-3-(4-Amino-2-fluorophenyl)acrylic Acid (2). Step 1: A dry Schlenk flask was charged with 4-bromo-3-fluoroaniline (1140 mg, 6.01 mmol), $Pd(OAc)_2$ (67 mg, 0.30 mmol), tris(2-methylphenyl)-phosphine (182 mg, 0.60 mmol), DMF (4.2 mL), and DIPEA (4.2 mL) under N_2-flow. The flask was evacuated and backfilled with argon before addition of ethyl acrylate (0.8 mL, 7.36 mmol) and heated to 80 °C for 4 h. The reaction was cooled to room temperature, added water, and extracted with EtOAc. The organic phase was washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:2) to give ethyl 4-amino-2-fluorocinnamate (1079 mg, 86%) as a yellow solid; R_f = 0.19 (EtOAc:petroleum ether, 1:2). ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 16.1 Hz, 1H), 7.31 (t, J = 8.3 Hz, 1H), 6.42 (dd, J = 8.4 Hz, 2.3 Hz, 1H), 6.35 (dd, J = 12.6 Hz, 2.1 Hz, 1H), 6.32 (d, J = 16.1 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.08 (s, 2H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 167.6, 162.8 (d, J = 253.5 Hz), 150.2 (d, J = 12.1 Hz), 137.7 (d, J = 2.4 Hz), 130.4 (d, J = 5.1 Hz), 116.0 (d, J = 7.1 Hz), 112.5 (d, J = 13.1 Hz), 110.9 (d, J = 2.0 Hz), 101.6 (d, J = 26.3 Hz), 60.3, 14.3. Step 2: A solution of ethyl 4-amino-2-fluorocinnamate (1002 mg, 4.79 mmol) in THF (32 mL) was added to a solution of $LiOH·H_2O$ (567 mg, 20.0 mmol) in H_2O (16 mL), and MeOH (5 mL) was added to give a homogeneous solution. The reaction was stirred at room temperature until complete hydrolysis, then added aqueous HCl (1 M) until pH <2 and extracted with EtOAc (×3). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated to give 858 mg (99%) of **2** as an orange solid; t_R = 8.03 min (HPLC). ^{1}H NMR (MeOH-d_4) δ 7.70 (d, J = 16.0 Hz, 1H), 7.36 (t, J = 8.5 Hz, 1H), 6.48 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 6.38 (dd, J = 13.5 Hz, 2.2 Hz, 1H), 6.26 (d, J = 16.0 Hz, 1H), 4.91 (s, 2H). ^{13}C NMR (MeOH-d_4) δ 171.4, 164.5 (d, J = 250.5 Hz), 154.5 (d, J = 13.3 Hz), 139.9 (d, J = 3.0 Hz), 131.3 (d, J = 5.1 Hz), 115.1 (d, J = 7.1 Hz), 111.8 (d, J = 1.8 Hz), 111.5 (d, J = 12.1 Hz), 101.3 (d, J = 26.3 Hz).

3-(4-Amino-2-fluorophenyl)propanoic Acid (3a). To a solution of **2** (388 mg, 2.14 mmol) in MeOH (15 mL) was added 10% Pd/C (35 mg). The reaction mixture was placed under argon, the argon was replaced with H_2, and the reaction mixture was stirred under ambient pressure. After 2 h, the reaction mixture was filtered through Celite, concentrated, and purified by flash chromatography (SiO_2, EtOAc) to give **3a** (285 mg, 73%) as a pale-brown solid; t_R = 4.88 min (HPLC). ^{1}H NMR (DMSO-d_6) δ 12.09 (s, 1H), 6.89 (t, J = 8.7 Hz, 1H), 6.39−6.23 (m, 2H), 5.19 (s, 2H), 2.65 (t, J = 7.6 Hz, 2H), 2.40 (t, J = 7.7 Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 173.7, 161.2 (d, J = 240.7 Hz), 149.0 (d, J = 11.5 Hz), 130.5 (d, J = 7.1 Hz), 113.3 (d, J = 16.5 Hz), 109.8 (d, J = 2.1 Hz), 100.2 (d, J = 25.0 Hz), 34.5, 23.2 (d, J = 2.1 Hz).

3-(2-Fluoro-4-(((2′-methyl-4′-(3-(methylsulfonyl)propoxy)-[1,1′-biphenyl]-3-yl)methyl)amino)-phenyl)propanoic Acid (13). A dry flask charged with 2′-methyl-4′-(3-(methylsulfonyl)-propoxy)-[1,1′-biphenyl]-3-carbaldehyde (**4b**, 35 mg, 0.11 mmol), 3-(4-amino-2-fluorophenyl)propanoic acid (**3a**, 19 mg, 0.11 mmol), CH_2Cl_2 (1 mL) and AcOH (1 drop) under argon was added $NaBH(OAc)_3$ (34 mg, 0.16 mmol) and stirred at room temperature until consumption of the starting material. The reaction mixture was quenched with water and aqueous HCl (1 M), and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (SiO_2, EtOAc:petroleum ether, 1:2) to give 30 mg (58%) of **13** as a light-brown foam; R_f = 0.54 (EtOAc) (purity 98.1% by HPLC). ^{1}H NMR (acetone-d_6) δ 7.40−7.29 (m, 3H), 7.22−7.07 (m, 2H), 7.05−6.94 (m, 1H), 6.90−6.78 (m, 2H), 6.48−6.32 (m, 2H), 4.40 (s, 2H), 4.18 (t, J = 6.1 Hz, 2H), 3.35−3.26 (m, 2H), 2.99 (s, 3H), 2.77 (t, J = 7.7 Hz, 2H), 2.49 (t, J = 7.7 Hz, 2H), 2.34−2.19 (m, 2H), 2.18 (s, 3H). ^{13}C NMR (acetone-d_6) δ 174.3, 163.8 (d, J = 241.4 Hz), 158.9, 150.1 (d, J = 11.1 Hz), 142.6, 140.7, 137.4, 135.5, 131.7 (d, J = 8.1 Hz), 131.5, 129.1, 128.6, 126.4, 117.3, 115.5 (d, J = 16.2 Hz), 112.7, 109.7 (d, J = 2.0 Hz), 100.0 (d, J = 26.3 Hz), 66.6, 52.0, 48.0, 40.8, 30.1, 24.5 (d, J = 2.0 Hz), 24.5, 23.5, 20.8. ESI-MS calcd for $C_{27}H_{30}FNO_5SNa$ (M + Na^+), 500.1901; found, 500.1916.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures and compound characterization, procedures for $logD_{7.4}$ determination and biological assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

ADME, absorption distribution metabolism excretion; AUC, area under the curve; BSA, bovine serum albumin; DIPEA, diisopropylethylamine; DMR, dynamic mass redistribution; FFA, free fatty acid; FFA1, free fatty acid receptor 1 (GPR40); HEK, human embryonic kidney; SAR, structure−activity relationships

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