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Exploration of phenylpropanoic acids as agonists of the free fatty acid receptor 4 (FFA4): Identification of an orally efficacious FFA4 agonist

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ABSTRACT

The long chain free fatty acid receptor 4 (FFA4/GPR120) has recently been recognized as lipid sensor playing important roles in nutrient sensing and inflammation and thus holds potential as a therapeutic target for type 2 diabetes and metabolic syndrome. To explore the effects of stimulating this receptor in animal models of metabolic disease, we initiated work to identify agonists with appropriate pharmacokinetic properties to support progression into in vivo studies. Extensive SAR studies of a series of phenylpropanoic acids led to the identification of compound **29**, a FFA4 agonist which lowers plasma glucose in two preclinical models of type 2 diabetes.

Free fatty acids play important roles in biological processes contributing to both health and disease. As essential nutritional components, free fatty acids are utilized as building blocks for energy storage and cell membrane integrity and as substrates for critical cellular pathways (i.e. Randle cycle[1]). In addition to these roles, free fatty acids have been recognized as important signaling molecules involved in a variety of physiological processes including inflammation and insulin resistance and hence contribute to the pathologies of type 2 diabetes and obesity.

Recently, numerous G-protein coupled receptors (GPCRs) have been identified that are activated by free fatty acids.[2–6] The GPCRs can be grouped according to the carbon chain length (short chain: <6 carbons; medium chain: 6–12 carbons; long chain: >12 carbons) and level of unsaturation of the fatty acids which activate the receptors, with free fatty acid receptor 2 (FFA2/GPR43) and free fatty acid receptor 3 (FFA3/GPR41) activated by short chain fatty acids, G-protein coupled receptor 84 (GPR84) activated by medium chain fatty acids, free fatty acid receptor 1 (FFA1/GPR40) activated by saturated and unsaturated long-chain fatty acids, and free fatty acid receptor 4 (FFA4/GPR120) activated by unsaturated long-chain fatty acids including omega-3 fatty acids (ω-3 FAs).[7,8]

Our interest in understanding the physiological processes governed by the long-chain fatty acid receptors led us to further consider FFA1 and FFA4 as candidates for small molecule drug discovery efforts. Previous reports have highlighted our group's efforts leading to the identification of the FFA1 biased agonist GW9508 (~100-fold selective for FFA1 over FFA4).[9,10] These studies provided the first evidence that small molecule mediated FFA1 agonism could be utilized for the pharmacological regulation of insulin secretion.[11] FFA1 is expressed highest in the pancreas, with insulin secreting β-cells abundantly expressing the receptor, and has also been shown to also be present in intestine and brain.[12,13] FFA1 amplified glucose-stimulated insulin secretion has been extensively studied and provides the basis for the current interest in FFA1 selective small molecule agonists for the treatment of type 2 diabetes.[14–18]

FFA4 has been less extensively studied but numerous recent reports highlight the receptor in several pathologies associated with type 2 diabetes and the components of metabolic syndrome.[8,19–21] FFA4 is abundantly expressed in several tissues including the intestine,[22] adipose,[23] and lung[24] and is present in a variety of cell types including proinflammatory macrophages,[8] intestinal L- and K-cells,[22,25] the mouse enteroendocrine STC-1 cell

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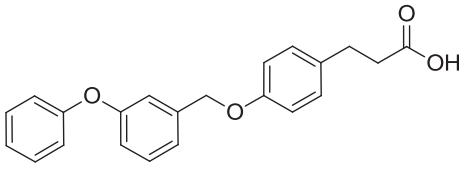
line,[26] and in the taste buds of the tongue.[27] This pattern of expression is consistent with the nutrient sensing and anti-inflammatory roles that have been reported for FFA4.[21,28–30] Indeed, seminal studies aimed at identifying the receptors involved in nutrient stimulated glucagon-like peptide-1 (GLP-1) secretion have identified FFA4 as a candidate GPCR involved in long-chain fatty acid stimulated GLP-1 secretion.[22] In addition the anti-inflammatory and insulin sensitizing effects of the ω-3 fatty acids DHA and EPA have been reported to occur through FFA4.[8,30–32] Further understanding of the therapeutic potential of FFA4 activation would be greatly aided by the identification of small molecule agonists with good pharmacokinetic properties.[33–40] With this goal in mind, efforts directed toward the identification of small molecule FFA4 agonists culminating in identification of phenylpropanoic acid agonists with pharmacokinetic properties appropriate for in vivo studies are described herein.

Compound **1** was identified as starting point for optimization following a cross-screening effort of our FFA1 program compounds (Fig. 1). The potency and efficacy of compound **1** was determined using a ten-point dose response curve in mammalian U2OS cells transiently expressing either human FFA1 or FFA4 using a FLIPR readout. The data revealed that compound **1** was 17-fold selective for FFA1 over FFA4. Thus, a primary goal of this exercise was to explore the SAR against both receptors while identifying compounds with selectivity for the FFA4 receptor.

In addition, several other considerations were made for the optimization exercise. While the structural features of the endogenous ligands for long-chain fatty acid receptors suggest obtaining orthosteric agonists with drug-like properties may be challenging, the optimization efforts were committed to maintaining molecular weight in the range of compound **1** (MW < 400) while hoping to realize high plasma drug concentrations, as plasma protein binding was expected to limit the free fraction of the drug. With these goals in mind, our efforts directed toward the identification of improved small molecule FFA4 agonists commenced.

The general synthesis of the phenylpropanoic acid agonists is shown in Scheme 1. Alkylation of substituted 4-hydroxyphenylpropanoic esters with substituted benzyl halides or benzyl alcohols followed by ester hydrolysis directly yielded the desired phenylpropanic acids. The ease of synthesis of the desired compounds coupled with the commercial availability of the starting materials allowed for rapid SAR generation.

Phenylpropanoic acid headgroups were prepared as shown in Scheme 2. In general, ketone or benzaldehyde derivatives (**I**) were olefinated and reduced to provide the corresponding propanoates (**III**), which in some cases required demethylation (BBr_3) to provide the desired phenols. Hydroxyl derivative **4** was obtained via the aldol reaction of the corresponding benzaldehyde derivative (**I**) with bis-lithiated species of acetic acid. The phenylpropanoic acid derivative for alcohol **13** was obtained from the corresponding



1

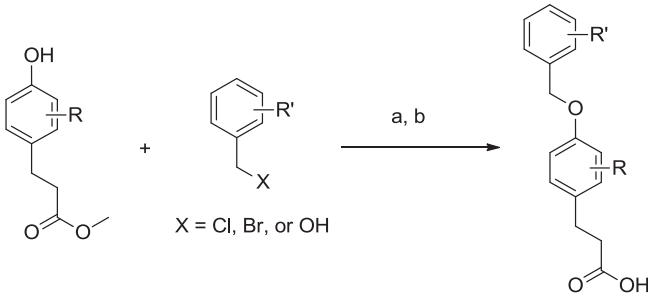
Human FFA4 EC_{50} = 968 nM

% Max Resp = 85 % ± 23

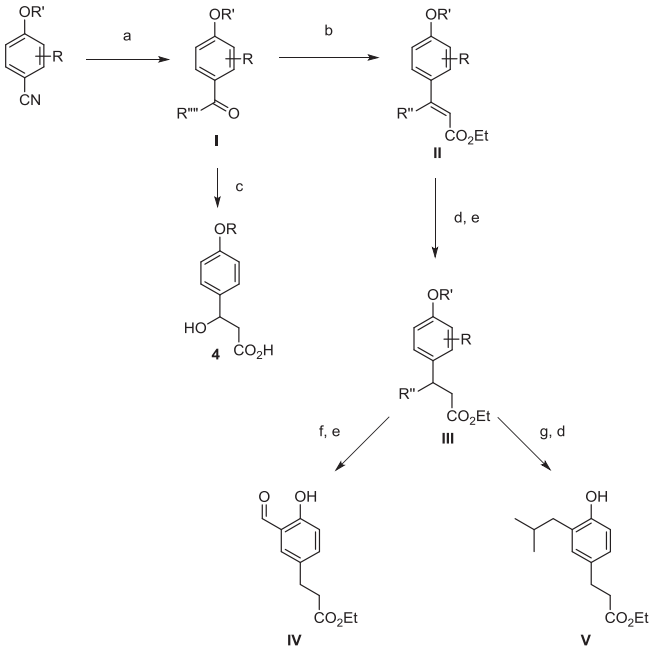
Human FFA1 EC_{50} = 57 nM

% Max Resp = 106 % ± 8

Fig. 1. In vitro profile of FFA1 agonist 1.



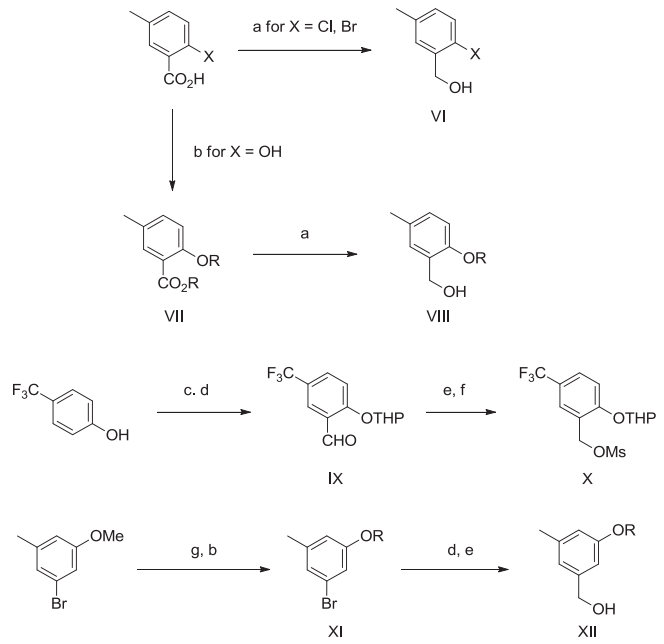
Scheme 1. General syntheses of the phenylpropanoic acids. Reagents and conditions: (a) K_2CO_3, DMF (X = Cl or Br) or DIAD, PPh_3 (X = OH); (b) NaOH or LiOH, THF/MeOH/H_2O.



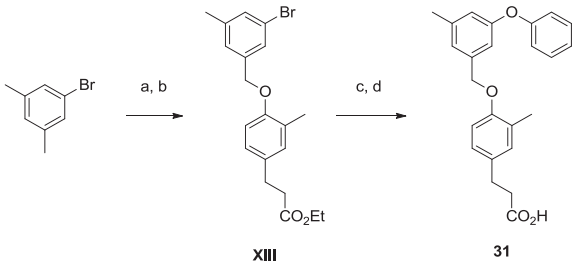
Scheme 2. General syntheses of the phenylpropanoic phenols. Reagents and conditions: (a) DIBAL-H, toluene; (b) NaH or *t*-BuOK, $(EtO)_2POCH_2CO_2R$, DMF; (c) *n*-BuLi, AcOH, THF; (d) 10% Pd/C, H_2, THF/MeOH or $NiCl_2$, $NaBH_4$, THF; (e) BBr_3, DCM (f) $TiCl_4$, $MeOCHCl_2$, DCM; (g) 2-methyl-2-propen-1-ol, DIAD, PPh_3, toluene, 250 °C.

aldehyde (**IV**) which in turn was prepared by a titanium-mediated formylation/deprotection sequence from **III**. Isobutyl derivative **14** was prepared by the Mitsunobu-initiated Claisen-rearrangement of the corresponding phenol (**III**, R′ = H) with 2-methyl-2-propenol followed by alkene reduction to afford intermediate **V**.

Benzyl alcohols and their activated derivatives were prepared as outlined in Scheme 3. Benzoic acids with the desired 2,5-disubstitution pattern were reduced directly to the desired benzyl alcohol derivatives (**VI**). Variation of ether group at the 2-position holding the 5-methyl substituent constant (**VII**) was accomplished starting from 5-methyl salicylic acid by simple alkylation followed by reduction. Formylation of 4-trifluoromethyl phenol followed by reduction and conversion to the mesylate derivative **X** allowed for incorporation of a trifluoromethyl group at the 5-position of the benzyl alcohol derivatives. 5-Methyl-3-alkoxy-disubstituted benzyl alcohols were prepared starting from 3-methoxy-5-bromobenzene utilizing a sequence consisting of deprotection followed by alkylation to furnish bromide **XI**, which underwent subsequent metal-halogen exchange and trapping to provide the intermediate aldehyde which was reduced to afford the desired benzyl alcohol derivatives (**XII**).



Scheme 3. General synthetic routes to benzyl alcohol derivatives. Reagents and conditions: (a) $LiAlH_4$ or BH_3●THF, THF; (b) RI, K_2CO_3, DMF; (c) 3,4-dihydro-2H-pyran, PPTS, DCM; (d) *n*-BuLi; DMF; (e) $NaBH_4$, MeOH; (f) MsCl, Et_3N, DCM; (g) BBr_3, DCM.



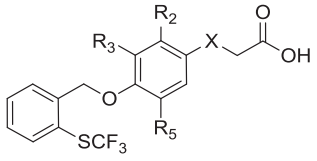
Scheme 4. Synthesis of compound **34**. Reagents and conditions: (a) NBS, CCl_4 (b) Ethyl 3-(4-hydroxy-3-methylphenyl)propanoate, K_2CO_3, DMF (c) Phenol, $Pd(OAc)_2$, di-*t*-BuXPhos, K_3PO_4, toluene (d) LiOH, 1,4-dioxane/H_2O.

Select compounds were derivatized following construction of the benzyl ether bond (Scheme 4), for instance, compounds containing 5-methyl-3-alkoxy substitution on the benzyl tail were prepared starting from 3,5-dimethylbromobenzene. Radical halogenation followed by benzyl ether formation provided the arylbromide intermediate **XIII** which underwent palladium catalyzed etherification[41] followed by saponification to provide the desired diphenylether **31**.

Our initial studies explored substitution about the phenylpropanoic acid headgroup while holding a 2-thiotrifluoromethylbenzyl tail constant (Table 1). Parent compound **2** provided a nearly balanced FFA1/FFA4 (2-fold selective for FFA4) starting point and it was hoped that further improvements in potency for FFA4 could be realized utilizing the benzyl tail of compound **2**. Addition of polarity (**3** & **4**) along the propanoic acid chain or simple substitution (**5**) eroded activity at both receptors. Incorporation of a methyl substituent at R2 (**6**) or dimethyl substitution at R3 and R5 (**8**) provided no improvement in potency, while methyl substitution at R3 (**7**) increased activity at FFA4 while diminishing FFA1 activity. Dimethyl substitution (**9**) provided a selective FFA4 agonist while growing the substitution in the form of a naphthalene ring (**10**) led to diminished activity at FFA4. Small nonpolar substituents at R3, such as the chloro group of **11**, provided a further improvement in FFA4 potency and afforded excellent selectivity over FFA1, which stands in contrast to the incorporation of more polar (**12** & **13**) or larger (**14**) R3 substituents which led to a reduction in activity at both receptors.

With the identification of small nonpolar substituents at R3 of the phenylpropanoic acid ring providing improved activity at FFA4, exploration of the benzyl SAR was undertaken (Table 2). Small substituents were well tolerated at both the *ortho* and *meta* positions (**15**–**23**) with the 2-bromo- (**19**), 2-isopropoxy- (**18**), and 3-methyl-substituents (**23**) providing potent and selective FFA4 agonists. In select cases incorporation of *ortho-meta*-disubstitution (2,5-orientation) and *meta-meta*-disubstitution (3,5-orientation) afforded equipotent agonists with the mono-substituted comparators (**24** vs. **23**; **27** vs. **18** & **23**) while for the majority of exemplars improved potency was realized (**25** vs. **19**; **26** vs. **23**; **28** vs. **23**; **29** vs. **21**) at FFA4. Benzyl disubstitution provided weak activity at FFA1. Unmasking polar functionality (**30** vs. **29**) provided a dramatic decrease in activity at FFA4, consistent with the lipophilic nature of the binding pocket and structures of the natural ligands.

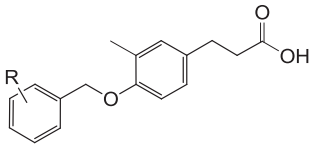
Table 1
In vitro FFA4 agonism: Phenylpropanoic acid SAR.



Cmpd	R2, R3, R5	X	hFFA4 EC_{50}[a] (% Max Resp.)	hFFA1 EC50 (% Max Resp.)
2	H, H, H	CH_2	681 (105)	1423 (77)
3	H, H, H	O	9977 (85)	>30,000
4	H, H, H	CHOH	>30,000	N.T.
5	H, H, H	$CHCH_3$	11,380 (97)	13,142 (109)
6	Me, H, H	CH_2	722 (90)	1544 (108)
7	H, Me, H	CH_2	201 (108)	8514 (81)
8	H, Me, Me	CH_2	660 (102)	21,777 (115)
9	Me, Me, H	CH_2	304 (77)	>30,000
10	-$(CH)_4$-, H	CH_2	2292 (105)	>30,000
11	H, Cl, H	CH_2	108 (80)	>10,000
12	H, OMe, H	CH_2	1992 (110)	>30,000
13	H, CH_2OH, H	CH_2	5911 (53)	>30,000
14	H, $CH_2CH(CH_3)_2$, H	CH_2	9660 (161)	>30,000

[a] Values are means of three experiments, see the supporting information for standard deviations (N.T. = not tested). EC_{50} reported in nM. See Ref. [38] for assay details.

Table 2
In vitro FFA4 agonism: benzyl substitution.



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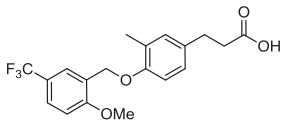
Cmpd	R	hFFA4 EC_{50}[a] (% Max Resp)	hFFA1 EC_{50}[a] (% Max Resp)
15	H	750 (83)	>30,000
16	2-Cl	972 (130)	11,588 (80)
17	2-CF_3	531 (103)	8600 (95)
18	2-OiPr	271 (118)	>30,000
19	2-Br	236 (116)	>30,000
20	3-Cl	362 (104)	10,268 (60)
21	3-CF_3	898 (117)	>30,000
22	3-OPh	556 (95)	3837 (90)
23	3-Me	275 (100)	>30,000
24	2-Cl-5-Me	188 (115)	18,051 (243)
25	2-Br-5-Me	53 (118)	>30,000
26	3,5-diMe	60 (66)	3782 (97)
27	2-OiPr-5-Me	172 (106)	19,588 (154)
28	3-OiPr-5-Me	60 (112)	>30,000
29	2-MeO-5-CF_3	299 (124)	11,803 (105)
30	2-OH-5-CF_3	10,000 (78)	N.T.
31	3-Me-5-OPh	40 (97)	1631 (85)

[a] Values are means of three experiments, see the supporting information for standard deviations (N.T. = not tested). EC_{50} reported in nM. See Ref. [38] for assay details.

Interestingly, combination of the biphenyl ether moiety of **1** with the *meta*-methyl (**22**) provided the most potent FFA4 agonist of the series (**31**).

With a series of FFA4 agonists with varying degrees of selectivity over FFA1 in hand, examination of the pharmacokinetic (PK) properties of select compounds in C57Bl6 mice was initiated (Table 3). In general, the compounds were characterized with low to moderate IV clearance, low volumes of distribution (V_{ss} < 2 L/kg), and rapid oral absorption (T_{max} values of 0.25–0.5 h). Compound **29** showed good oral exposure and high oral bioavailability with moderate half-life (t½ = 1.7 h). Examination of the protein binding of the compounds revealed all to be >99% bound in human plasma with 99.9% protein binding measured for compound **29**. Despite high protein binding, compound **29** was chosen as a tool molecule for in vivo studies based upon its superior oral exposure (C_{max} = 6779 ng/mL), potency at FFA4 (EC_{50} = 299 nM), and selectivity over human FFA1 (EC_{50} = 11.8 μM).

Prior to in vivo studies, the in vitro selectivity of compound **29** was evaluated in a panel of targets in both full curve binding and functional assays including the rodent ortholog assays for FFA1 and FFA4 and additional members of the free fatty acid receptor family (Fig. 2). Increased selectivity (>85-fold) for both rat and mouse FFA4 over FFA1 was realized relative to the human



29

FFA4 (GPR120):
Human EC_{50} = 299 nM, % Max Resp = 124 ± 24 %
Mouse EC_{50} = 70 nM, Max Resp = 108 ± 32 %
Rat EC_{50} = 230 nM, Max Resp = 110 ± 41 %

FFA1 (GPR40):
Human EC_{50} = 11,803 nM, Max Resp = 105 ± 36 %
Mouse EC_{50} = 6,213 nM, Max Resp = 83 ± 2 %
Rat EC_{50} > 30,000 nM

FFA2 (GPR43) human EC_{50} = 25,312 nM, Max Resp = 59 ± 37 %
FFA3 (GPR41) human EC_{50} > 50,000 nM

Fig. 2. In vitro profile of FFA1 agonist **29**.

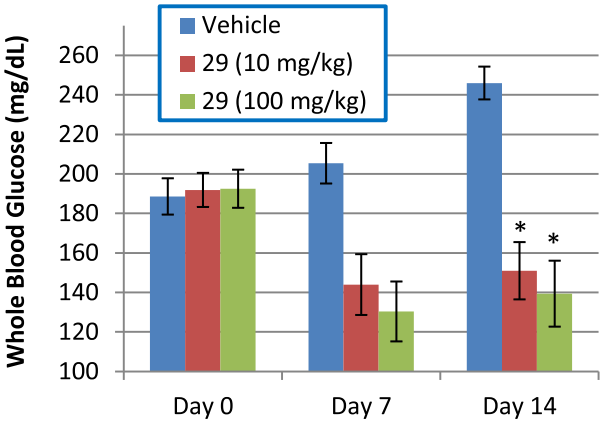


Fig. 3. Effect of FFA4 agonist **29** on plasma glucose in 8-week old male ZDF rats (n = 8) treated orally twice a day at the indicated doses for 14 days. *p < 0.05 vs vehicle.

receptors (40-fold). With respect to activity on the remaining members of the free fatty acid family, compound **29** showed weak partial agonism of the FFA2 receptor and profiled as inactive against FFA3 in FLIPR based assays. The remainder of the panel included a mixture of GPCR, ion channel, and enzyme assays with compound **29** showing robust selectivity against the panel.

Investigation of the anti-diabetic properties of compound **29** was undertaken in Zucker Diabetic Fatty (ZDF) rats, an established preclinical model of type 2 diabetes. Compound **29** was administered to 8-week old male ZDF rats at doses of 10 and 100 mg/kg twice daily for 14 days with plasma glucose concentrations determined at baseline, 7 and 14 days.

Table 3
DMPK profiles of selected FFA4 agonists in C57BL/6 J mice.[a]

Cmpd	IV Cl (mL/min/kg)	IV AUC (hr*ng/mL)	PO Cmax (ng/mL)	PO AUC (hr*ng/mL)	% F
23	12	4105	3083	5353	39
24	18	2859	3028	4403	46
26	35	1416	2627	2596	55
28	43	1171	687	767	20
29*	20	3618	6779	9438	110

[a] C57BL/6 J Mice (n = 2), Oral dose = 10 mg/kg, IV dose = 3 or 4.2* mg/kg. PO formulation: 0.5% HMPC: 0.1% Tween suspension; IV formulation: 2% DMSO, 5% solutol.

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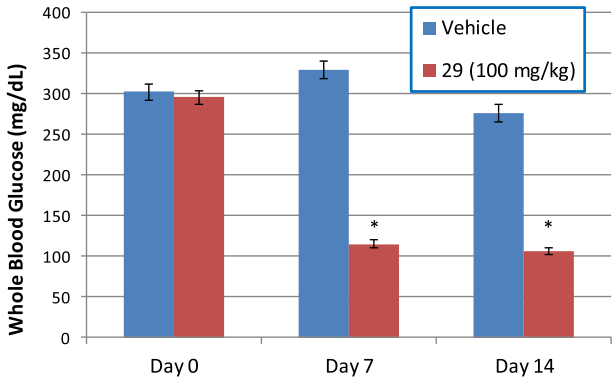

Fig. 4. Effect of compound **29** on blood glucose in db/db mice (n = 10) dosed at 100 mg/kg BID as compared to vehicle. $^{*}p < 0.05$ vs vehicle.

All groups of ZDF rats had comparable levels of plasma glucose, insulin, and HbA_{1c} prior to treatment. As illustrated in Fig. 3, the vehicle-treated animals showed a progressive hyperglycemia with plasma glucose rising from baseline values of 188 to 245 mg/dL. In contrast, plasma glucose for compound **29** treated animals was reduced to 151 and 139 mg/dL at the 10 and 100 mg/kg doses, respectively, from a starting average of 192 mg/dL.

With positive effects on plasma glucose measured in the ZDF rat, compound **29** was progressed into a second rodent model of type 2 diabetes, the db/db mouse. In this model fed db/db mice were orally administered either vehicle or compound **29** (100 mg/kg) twice a day and blood glucose was measured before and after 1 and 2 weeks of treatment. In addition, HbA_{1c} levels were measured before and after 2 weeks of treatment. As shown in Fig. 4, compound **29** gave a robust response, normalizing blood glucose after 1 week of treatment. Glucose lowering was maintained through the end of the study with levels for the compound **29** treated animals finishing at 106 mg/dL versus 276 mg/dL for vehicle controls. Compound **29** also robustly lowered HbA_{1c} levels by 1.6% to a final value of 5.8% with the vehicle control group finishing the study at 7.8%.

In summary, the SAR of a series of phenylpropanoic acid-free fatty acid receptor agonists is described which resulted in the identification of potent FFA4 agonists. The superior pharmacokinetic properties of compound **29** led to its selection as an in vivo tool compound which afforded robust efficacy in two rodent models of type 2 diabetes. In vivo results with compound **29** detail the potential for FFA4 agonists as treatments for type 2 diabetes and additional factors associated with metabolic syndrome.

A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2017.01.034.

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