2666 J. Med. Chem. 2010, 53, 2666–2670
DOI: 10.1021/jm100022r

Journal of Medicinal Chemistry
Brief Article

Discovery of a Biaryl Cyclohexene Carboxylic Acid (MK-6892): A Potent and Selective High Affinity Niacin Receptor Full Agonist with Reduced Flushing Profiles in Animals as a Preclinical Candidate

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Received January 8, 2010

Biaryl cyclohexene carboxylic acids were discovered as full and potent niacin receptor (GPR109A) agonists. Compound **1e** (MK-6892) displayed excellent receptor activity, good PK across species, remarkably clean off-target profiles, good ancillary pharmacology, and superior therapeutic window over niacin regarding the FFA reduction versus vasodilation in rats and dogs.

Introduction

Niacin (nicotinic acid, NA[a]) at high doses exerts favorable effects on lipid profiles in man. As the most efficacious registered drug for elevating HDL-C, NA also reduces total plasma cholesterol, TG, VLDL-C, LDL-C, and Lp(a), all of which are closely associated with coronary heart disease.[1] In human clinical trials,[2] NA has been shown to decrease the morbidity and mortality of patients with coronary heart disease and slow the progression of atherosclerosis. One of the major side effects of NA treatment is severe cutaneous flushing.

GPR109A, the high affinity NA receptor, has been discovered recently as a novel therapeutic target.[3] Although the precise mechanism of action of NA remains elusive, it has been known that NA binds to GPR109A on adipocytes and decreases the hydrolysis of adipocyte TG, thereby reducing the plasma FFA level. This likely results in a more sustained reduction in plasma TG and an elevation of HDL. The FFA reduction caused by NA has been shown to be GPR109A dependent. As such, FFA is selected as the proximal biomarker to interrogate the effects of agonists on this target. Since GPR109A is also expressed on immune cells, it is conceivable that some of NA's antiatherosclerotic effects could be derived from its modulation of vascular inflammation.

The discovery of GPR109A has stimulated interest in developing small molecule agonists to mimic the functions of NA.[4] While it is not obvious how to separate the desired pharmacological properties of NA from its GPR109A-dependent flushing side effect,[5] one strategy of reducing NA-induced flushing is to combine extended-release NA with a DP1-antagonist (laropiprant).[6] Alternatively, it is conceivable that GPR109A agonists with different tissue distribution and/or binding kinetics from NA could lead to a reduced flushing profile while maintaining the lipid effects. To test this hypothesis, we have discovered several cyclohexene carboxylic acid analogues as highly potent GPR109A agonists, of which compound **1e** indeed provided a superior therapeutic index in rats and dogs, regarding FFA reduction and flushing, relative to NA.

In Vitro SAR

On the basis of our recent discovery of biaryl anthranilide agonists for GPR109A,[7] tetrahydroanthranilide has been introduced as a surrogate of the anthranilide moiety (Scheme 1).[8] In this article the SAR is focused on the profound influence of linker region between the amide and oxadiazole on the potency, serum shift, and PK profiles. It is noted that **1a**−**k** were all characterized as orthosteric ligands, as they shared the receptor binding site of the endogenous ligand β-hydroxybutyrate (as defined by the fact that these compounds and β-hydroxybutyrate displace ^{3}H-NA).[9] The binding affinities of these analogues, as determined by ^{3}H-NA competition in the absence or presence of 4% human serum, were expressed as K_i. In the guanine nucleotide exchange (GTPγS) assays with membranes from CHO cells expressing the recombinant human GPR109A, the functional activity of GPR109A agonists was determined. The human GPR109A binding and functional data are summarized in Table 1.

As our benchmark compound, **1a** exhibited excellent activity in the ^{3}H-NA competitive binding assay (K_i = 4 nM) and GTPγS assay (EC_{50} = 27 nM).[7] The replacement of the phenyl group in **1a** with a cyclohexenyl moiety resulted in another potent analogue **1b** that matched the GPR109A activity of **1a**. The α-methyl substituted derivative of **1b** as

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[a] Abbreviations: NA, niacin or nicotinic acid; CYP, cytochrome P450; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; VLDL-C, very-low-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein a; GPCR, G-protein-coupled receptor; FFA, free fatty acid; DP1, prostagladin D2 receptor 1; SAR, structure−activity relationship; CHO, Chinese hamster ovary; WT, wild-type; PK, pharmacokinetics; mpk, mg/kg; PD, pharmacodynamics; AUCN, normalized area under curve; NMO, *N*-methylmorpholine *N*-oxide; PMB, *p*-methoxybenzyl.

 Published on Web 02/25/2010

Scheme 1

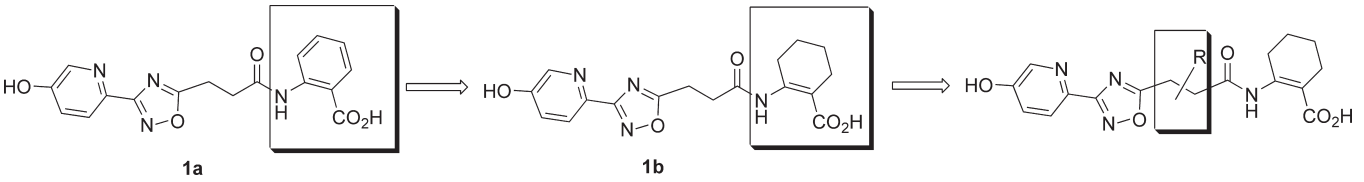
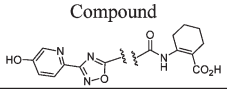
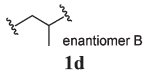
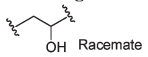
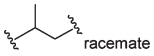


Table 1. K_i and GTPγS EC_{50} of Compounds on the Human GPR109A with and without 4% Human Serum[a]

Compound	K_i (nM)	K_i (nM) with 4% human serum	GTPγS EC_{50} (nM)
			
NA	82	104	527
1a	4.0	120	27
1b	3.0	150	21
 enantiomer A **1c**	8.0	240	25
 enantiomer B **1d**	4.0	230	22
 **1e (MK-6892)**	4.0	595	16
 **1f**	11	9130	-
 **1g**	360	1080	730
 OH Racemate **1h**	22	660	290
 racemate **1i**	29	1100	290
 **1j**	130	24700	6400
 **1k**	1.4	840	-

[a] On average, repeat determinations differed by ±20%.

either enantiomer (**1c** or **1d**) gave similar binding affinity, indicating that a gem-dimethyl analogue might be just as active. Indeed, analogue **1e**, like **1a**, **1b**, and **1d**, also had ~20-fold higher affinity for GPR109A than NA. However, the K_i values of **1a**−**e** for the GPR109A were increased ~100-fold in the presence of 4% human serum. Despite the increased serum shift of these compounds, the representative **1e** was highly potent in vivo (vide infra). Furthermore, these compounds had no activity on GPR109B and GPR81, the two most closely related GPCRs with ~96% and 50% sequence identity to GPR109A, respectively. The maximum level of the compound-induced guanine nucleotide exchange (a measure of G_α subunit activation) in human GPR109A-bearing membranes was equal to that obtained with NA, suggesting that these compounds were full agonists. They were also full agonists relative to NA on the mouse, rat, and dog NA receptors.

The introduction of the cyclopropyl group (**1f**) to rigidify the conformation of the linker gave lower activity (K_i = 11 nM) and surprisingly greater serum shift (K_i = 9130 nM with 4% human serum). On the other hand, unexpectedly, the cyclobutyl analogue (**1g**) reduced the serum shift to only 3-fold, despite the considerable loss of activity. The α-hydroxy analogue (**1h**) was reasonably potent, but it offered no advantages over alkyl-substituted analogues. The β-subsituted analogues (**1i**, **1j**) were much less active than their α-substituted counterparts. Finally, the tetrafluoro-substituted compound (**1k**) gave remarkable potency (K_i = 1.4 nM) but high serum shift (~600-fold).

Table 2. Rat and Dog PK of **1b**−**e**[a]

compd	F (%)	Cl ((mL/min)/kg)	V_d (L/kg)	$T_{1/2}$ (h)	$AUCN_{po}$ (μM·h·kg/mg)
1b (rat)	22	2.0	0.11	2.0	10
1b (dog)	33	1.3	0.18	2.1	11
1c (rat)	19	1.1	0.21	3.6	7.4
1d (rat)	23	1.1	0.25	4.1	8.9
1e (mouse)	45	1.3	0.2	6.4	15
1e (rat)	24	0.40	0.15	4.3	26
1e (dog)	90	1.8	0.27	7.6	21
1e (rhesus)	14	0.40	0.08	4.9	15

[a] Values are average of two or three animals. The iv doses at 1.0 mg/kg (mpk) were formulated in DMSO/Tween-80/water (5:10:85, v/v/v) for rats and in EtOH/PEG400/water (10:40:50, v/v/v) for dogs and monkeys. The oral doses at 2 mpk were formulated in 0.5% methylcellulose for rats and dogs.

Pharmacology

The PK profiles of **1b**−**e** were characterized by small volume of distribution, low clearance, and large normalized AUC (Table 2). The presence of one or two α-methyl groups (**1c**−**e**) correlated with longer half-life and lower clearance in rat. For example, the rat half-life of **1e** (4.3 h) was twice as long as that of **1b** (2.0 h), and the rat clearance of **1e** (0.4) was significantly lower than analogues **1b**−**d**. Furthermore, the bioavailability of **1e** was excellent in dog and mouse and moderate in rat and rhesus.

In order to test whether **1e** suppressed plasma FFA in vivo and whether this effect was NA receptor-dependent, NA or **1e** was orally administered to WT or NA receptor null mice on the same C57Bl/6 genetic background. After 15 min of 100 mpk dosing of NA or **1e** to fed WT or NA receptor null mice, the blood levels of **1e** at 15 min were 229 μM (~950-fold greater than the in vitro EC_{50} determined in mouse NA receptor GTPγS assay, which is 240 nM) in WT mice and 148 μM (~620-fold greater than the in vitro EC_{50}) in NA receptor null mice. Figure 1 showed that NA and **1e** effectively suppressed plasma FFA in the WT but not in the NA receptor null animals, indicating that the FFA reduction of **1e** was NA receptor-dependent.

To assess the potential of developing a NA receptor agonist with which the lipid and flushing adverse effects could be separated, rat and dog models were developed to measure FFA reduction and vasodilation.[10] Compound **1e** was selected for the studies because of its good PK and activity profiles in these two species (EC_{50} = 4.6 μM in the GTPγS assay for the rat NA receptor and 1.3 μM in the GTPγS assay

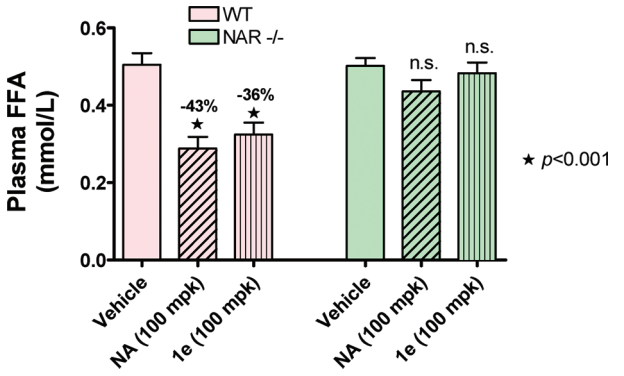


Figure 1. Reduction of plasma FFA levels by the treatment of NA and **1e** in WT and NA receptor null mice (n = 8/group) 15 min postdose (n.s. = not significant).

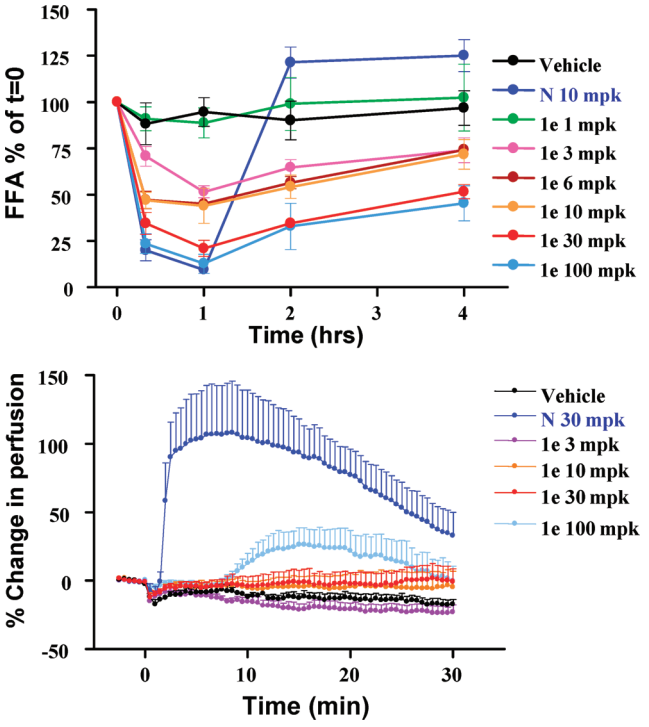


Figure 2. Comparison between reduction of plasma FFA relative to FFA level at t = 0 (top panel) and change of blood perfusion (bottom panel) in rats dosed with NA and **1e** ($n \geq 5$ for each group). NA controls (blue) were included in the experiments in both panels (N = niacin).

for the dog NA receptor). Despite the significant weaker activity of **1e** in rat and dog with respect to that in human, **1e** showed good activity in reducing FFA in rat and dog models.

Dose ranging studies in conscious rats were then conducted to compare the ability of NA and **1e** to reduce plasma FFA after oral administration (Figure 2, top panel). NA and **1e** effectively reduced plasma FFA levels by ~85%, and the magnitude and duration of this effect were dose-dependent between 1 and 100 mpk. Vasodilation was monitored on the ears of anesthetized rats by laser Doppler flowmetry after subcutaneous administration of compound in a separate dose ranging study (Figure 2, bottom panel). While NA induced intense flushing in the rat at doses of ≥3 mpk, only at the highest dose (100 mpk) of **1e** was flushing observed in 5 of the 10 rats. Furthermore, the average magnitude of vasodilation

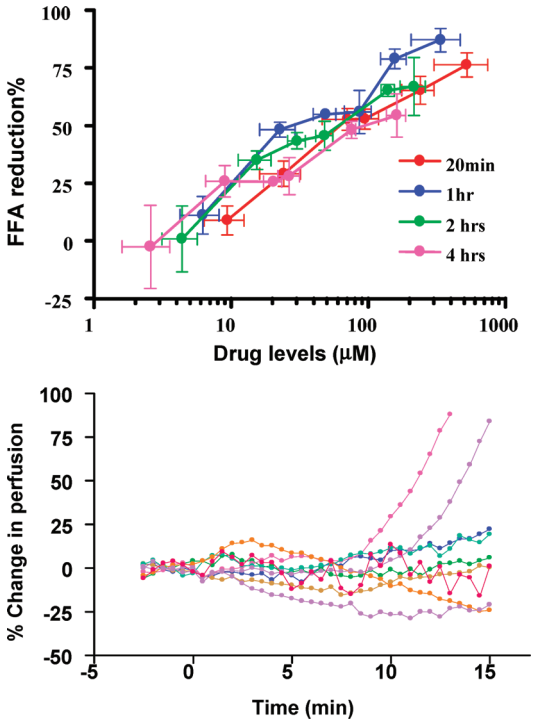


Figure 3. Plasma FFA reduction relative to FFA level at t = 0 vs drug levels at various times postdose for **1e** (top panel) and threshold dosing of **1e** for vasodilation (bottom panel, vasodilation at 100 mpk, ip dosing, n = 9; each line represents an individual rat dosed with **1e** at t = 0, and average peak plasma concentration of **1e** at this ip dose was 555 ± 82 μM).

Table 3. Calculated TI in Rats for NA and **1e** in Rats

	CVD (μM)	EC_{50} FFA (μM)	rat TI
NA	9.4	2.2	4.2
1e	560	67	8.4

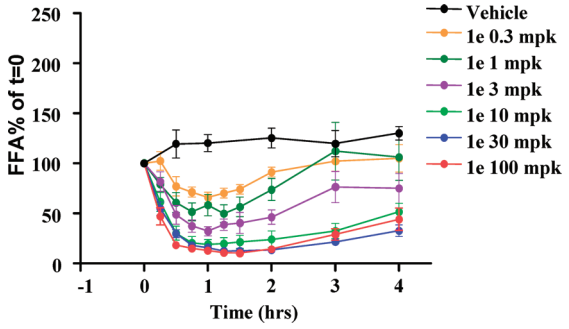


Figure 4. Reduction of plasma FFA levels after oral administration of **1e** to fasted dogs (n = 3−7 per group).

induced by **1e** at the highest 100 mkg dose was considerably less than that seen with NA at doses over 3 mpk.

To quantify the therapeutic indices, FFA reduction and vasodilation were measured as a function of plasma drug levels. For this purpose, two separate experiments under different routes of administration were conducted. The oral dose−response curves for FFA reduction were translated into concentration−response plots; representative data for **1e** are shown in Figure 3. Over the 4 h time course, the percentage of FFA reduction was solely dependent on the plasma levels of the compound (Figure 3, top panel). Apparently, there was no

time-dependent desensitization of the receptor after the treatment of **1e** within the studied time course. A similar analysis, however, was impossible for the vasodilation experiments described above, as for technical reasons blood could not be drawn during the time course of this assay. Instead, a separate experiment was performed in which NA and **1e** were administered (ip) at a relatively low "threshold" dose (100 mpk), which was shown to induce vasodilatation in half of the animals in previous experiments. Vasodilation was monitored and plasma drug levels were measured at a predetermined time point (e.g., 15 min for **1e**, corresponding to the T_{max} of **1e**) to yield an estimate of the threshold plasma level of drug required to trigger vasodilation. Representative data for **1e** are shown in the bottom panel of Figure 3, in which 2 of 9 animals experienced vasodilation. The average peak plasma level of **1e** at this threshold ip dose for vasodilation was 555 ± 82 μM, and no significant drug level difference between responders and nonresponders was observed.

Table 4. Dose Basis TI in Dogs Measured as Threshold Dose of Vasodilation (TDV) Divided by the Dose That Achieved Maximal FFA Suppression for NA and **1e**

	TDV (mpk)	FFA_{max} (mpk)	dog TI
NA	3	6	0.5
1e	100	10	10

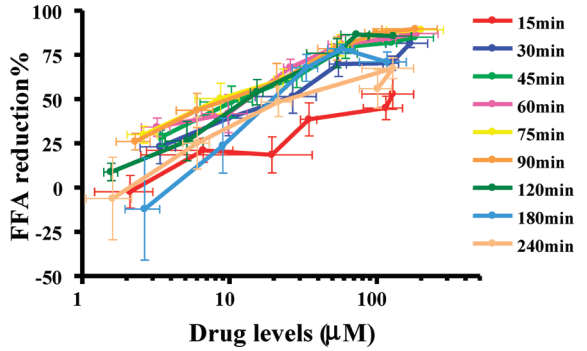


Figure 5. Plasma FFA reduction vs drug level for **1e** in dogs (100 mpk, po dosing).

Table 5. Calculated TI in dDogs for NA and **1e** on a Plasma Compound Level Basis

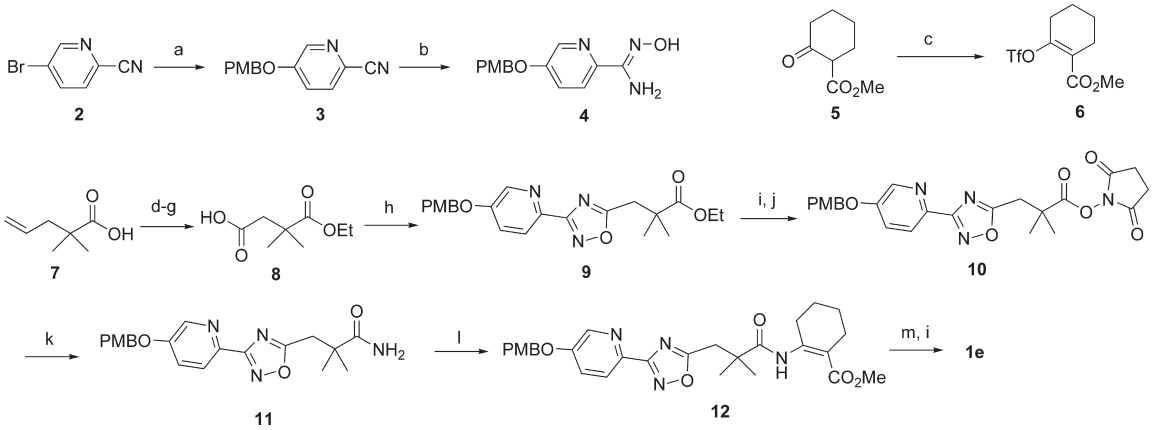
	C_{max} (TDV) (μM)	EC_{50} FFA (μM)	dog TI
NA	14.6	2.7	5.4
1e	182	16.5	11.0

A therapeutic index (TI) was estimated from these data according to the following formula: rat TI = CVD/EC_{50} (FFA) (Table 3). The in vivo EC_{50} (FFA) was generated from the plasma drug concentration−response plot, and CVD was defined as the average blood level at the threshold dose.

Since the fraction of animals experiencing vasodilation was not the same for each compound, the measured value for CVD did not necessarily represent the true threshold concentration for vasodilation. For example, since 8 of 10 animals experienced vasodilation with NA but only 2 of 9 experienced vasodilation with **1e**, the value for TI was presumably overestimated for NA and underestimated for **1e**. Regardless, on the basis of these data, **1e** had an index between PD efficacy and vasodilation that was superior to that of NA.

A dog model suitable for TI measurement was also developed. Importantly, the dog model allowed measurement of FFA suppression (Figure 4) and vasodilation in the same conscious dogs after oral compound administration. In dogs, both NA (see Supporting Information) and **1e** demonstrated dose-dependent antilipolytic activity resulting in 85−90% maximal FFA suppression, with a robust duration of action of >4 h (Figure 4). Furthermore, NA induced flushing in a dose-dependent manner (see Supporting Information), as measured by spectrocolorimetry of the ear and vocal and physical agitation of the dogs. At the highest dose of **1e**, only 1 of 4 dogs flushed, and the flush was relatively mild. Because FFA reduction and flushing were measured in the same conscious animal, it was possible to establish a therapeutic index on a dose basis, and this was defined as the threshold dose at which vasodilation occurred in a subset of the animals divided by the dose that gave maximal FFA suppression (Table 4). These data illustrated that **1e** had a superior TI to NA in the dog on a dose basis.

Scheme 2[a]



[a] Reaction conditions: (a) *p*-methoxybenzyl alcohol, NaH, DMF, 0 °C to room temp, 72%; (b) NH_2OH HCl salt, NaOH, EtOH, room temp, 100%; (c) NaH, Comins' reagent, 0 °C to room temp, 79%; (d) H_2SO_4, EtOH, 80 °C; (e) OsO_4, NMO, 0 °C to room temp; (f) $NaIO_4$, acetone, 0 °C to room temp; (g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *tert*-butanol, 0 °C to room temp, 94% over four steps; (h) $(COCl)_2$, cat. DMF, CH_2Cl_2, then **4**, 0 °C to room temp, 48%; (i) LiOH, THF/MeOH/water, room temp, 100%; (j) *N*-hydroxysuccinimide, EDC, CH_2Cl_2, room temp; (k) ammonia in water, 0 °C to room temp, 91% over two steps; (l) Pd_2dab_3, xantphos, Cs_2CO_3, dioxane, **6**, 80 °C, 92%; (m) TFA, *i*-Pr_3SiH, CH_2Cl_2, 0 °C to room temp, 79%.

The dog TI could also be expressed in terms of blood levels, as was done in the rat model. The FFA reduction caused by **1e** versus the plasma drug level is shown in Figure 5. On a drug level basis, dog TI = C_{max}(TDV)/EC_{50} (FFA), in which C_{max}(TDV) was the corresponding average maximal blood level of compound at the threshold dose of vasodilation, and the in vivo EC_{50} (FFA) was generated from the concentration−response plot (Table 5).

Through quantification of the TI in the rat and dog models, **1e** has a larger therapeutic index than NA, which could be attributed to different binding kinetics of compounds and/or tissue distribution profiles. Besides excellent receptor activity and PK profile, **1e** was remarkably clean in 166 different biological target counter-screening assays (IC_{50} > 10 μM) and CYP inhibition (IC_{50} > 100 μM for CYP2C8, 2D6, and 3A4; IC_{50} = 39 μM for CYP2C9). Furthermore, **1e** displayed no preliminary safety issues in ancillary pharmacological studies in CNS mouse, CV dog, GI motility, renal and respiratory dog models. Lastly, the presence of the hydroxypyridine group in **1e** did not introduce any in vivo or in vitro covalent binding issues, which is a common concern for bioactivated drugs containing a phenolic moiety.[11]

Chemistry

The preparation of **1e** is summarized in Scheme 2. This scalable and convergent route featured a nucleophilic aromatic substitution to afford **3**, an efficient cyclization to construct oxadiazole **9**, and a Pd-catalyzed C−N bond formation to generate intermediate **12**.[12]

Conclusion

In conclusion, we have identified **1e**, or 2-({3-[3-(5-hydroxypyridin-2-yl)-1,2,4-oxadiazol-5-yl]-2,2-dimethylpropanoyl}-amino)cyclohex-1-ene-1-carboxylic acid (MK-6892), as a potent, selective, and full agonist for the high affinity NA receptor GPR109A. In addition, **1e** demonstrated good PK, a remarkably clean off-target profile, and excellent ancillary pharmacology safety. On the basis of the FFA reduction and vasodilation studies in preclinical PD models, this compound exhibited a significantly larger therapeutic index than NA, suggesting a potentially useable window between lipid effects and flushing in humans. Therefore, **1e** has been selected as a preclinical candidate for further evaluation in humans.

Experimental Section

The synthetic procedures to prepare **1b-1k** are provided in the Supporting Information.

Supporting Information Available: Experimental procedures for compound preparation; characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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