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Letter

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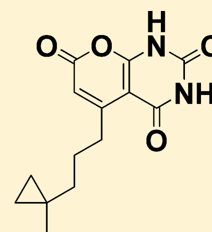
Discovery of SCH 900271, a Potent Nicotinic Acid Receptor Agonist for the Treatment of Dyslipidemia

Anandan Palani,*[,†] Ashwin U. Rao,*[,†] Xiao Chen,[†] Xianhai Huang,[†] Jing Su,[†] Haiqun Tang,[†] Ying Huang,[†] Jun Qin,[†] Dong Xiao,[†] Sylvia Degrado,[†] Michael Sofolarides,[†] Xiaohong Zhu,[†] Zhidan Liu,[†] Brian McKittrick,[†] Wei Zhou,[†] Robert Aslanian,[†] William J. Greenlee,[†] Mary Senior,[†] Boonlert Cheewatrakoolpong,[‡] Hongtao Zhang,[‡] Constance Farley,[‡] John Cook,[‡] Stan Kurowski,[‡] Qiu Li,[‡] Margaret van Heek,[‡] Gangfeng Wang,[§] Yunsheng Hsieh,[§] Fangbiao Li,[§] Scott Greenfeder,[‡] and Madhu Chintala[‡]

[†]Department of Medicinal Chemistry, [‡]Department of Biology, and [§]Department of Drug Metabolism & Pharmacokinetics, Merck Research Laboratories, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033, United States

Supporting Information

ABSTRACT: Structure-guided optimization of a series of C-5 alkyl substituents led to the discovery of a potent nicotinic acid receptor agonist SCH 900271 (**33**) with an EC_{50} of 2 nM in the hu-GPR109a assay. Compound **33** demonstrated good oral bioavailability in all species. Compound **33** exhibited dose-dependent inhibition of plasma free fatty acid (FFA) with 50% FFA reduction at 1.0 mg/kg in fasted male beagle dogs. Compound **33** had no overt signs of flushing at doses up to 10 mg/kg with an improved therapeutic window to flushing as compared to nicotinic acid. Compound **33** was evaluated in human clinical trials.



KEYWORDS: *Nicotinic acid receptor (NAR) agonist, flushing, dyslipidemia, FFA, LDL-C, VLDL-C, TG, HDL-C, CAD*

Morbidity and mortality associated with coronary artery disease (CAD) are significant problems around the world. Elevated low-density lipoprotein cholesterol (LDL-C) and plasma triglycerides (TG) and low levels of high-density lipoprotein cholesterol (HDL-C) are considered risk factors for the development of CAD. An improvement in all of these risk factors would reduce the risk for developing CAD. Nicotinic acid (NA, niacin) has been used clinically for decades to favorably alter plasma lipids.[1] NA reduces plasma free fatty acid (FFA), very low-density lipoprotein cholesterol (VLDL-C), LDL-C, plasma TG, and lipoprotein a (Lp-a), while increasing HDL-C.[2−7] Despite this attractive profile, physician adoption and patient compliance with NA are limited due to intense cutaneous flushing at therapeutic concentrations, a difficult dose titration schedule to avoid this side effect, and large doses.[8,9] An extended release formulation of NA (NIASPAN) is available by prescription.[10] This formulation has a reduced incidence of flushing, but patients must undergo a complicated titration schedule to approach maximally efficacious doses and often do not achieve desired lipid goals due to tolerability issues. In addition, studies have shown that patients taking a combination of extended release NA and an antagonist of the prostaglandin D2 antagonist (DP) (TREDAPTIVE) show reduced flushing symptoms as compared to taking NA alone.[11]

The molecular target for NA was discovered in 2003. NA binds with high affinity to and activates the G-protein coupled receptor GPR109a, expressed primarily in human adipose tissue. NA also binds with low affinity to the homologous receptor GPR109b, which shares ~95% identity to GPR109a and is only expressed in the human and chimpanzee.[12−16] Activation of GPR109a in adipose tissue mediates an antilipolytic response by lowering intracellular 3′-5′-cyclic adenosine monophosphate (cAMP) levels, leading to reduced protein kinase A activity. This in turn results in a decrease in lipase activity and a reduction in intracellular TG hydrolysis. A reduction in intracellular lipolysis decreases FFA secretion into plasma and ultimately reduces the hepatic FFA pool available for TG resynthesis. It has been postulated that the decreased availability of FFA in the liver directly reduces the production of hepatic TG and VLDL.[17−21] What is much less clear is whether the acute effects on plasma FFA and TG can eventually lead to an increase in HDL-C levels and other associated lipid and lipoprotein changes.[22,23]

Since the discovery of NA receptors (NAR), extensive efforts have been devoted to NAR agonists.[24−27] Our lead identification strategy, which involved an extensive structure−activity relationship (SAR) investigation of the C-2 region of a thiobarbituric acid core, had been shown to activate the receptor and has been reported previously.[28] Further screening and elaboration of both the C-2 and the C-5 regions provided a pyranopyrimidinedione series suitable for optimization as NAR agonists. A comparison of the in vitro activity data of the compounds synthesized is shown in Table 1. When the thiol

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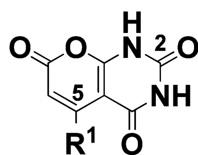
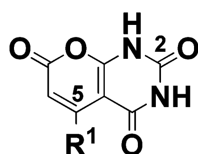
Table 1. Potency of Compounds in the hu-GPR109a cAMP Assay



compd	R^1	EC_{50} (nM)[a]	compd	R^1	EC_{50} (nM)[a]
1	Et	31 ± 18	**7**	CH_2CF_3	1600 ± 720
2	Me	290 ± 14	**8**	Ph	>10000
3	*n*-Pr	99 ± 58	**9**	CO_2Me	>10000
4	*n*-Bu	17 ± 5.0	**10**	CH_2CO_2Me	930 ± 230
5	*i*-Pr	220 ± 44	**11**	4−F-$C_6H_4CH_2$	170 ± 54
6	CF_3	>10000	**12**	CH(OH)Me	1300 ± 240

[a]Data represent an average of multiple determinations ($n \geq 3$) ± standard deviations.

Table 2. Potency of Compounds in the hu-GPR109a cAMP Assay



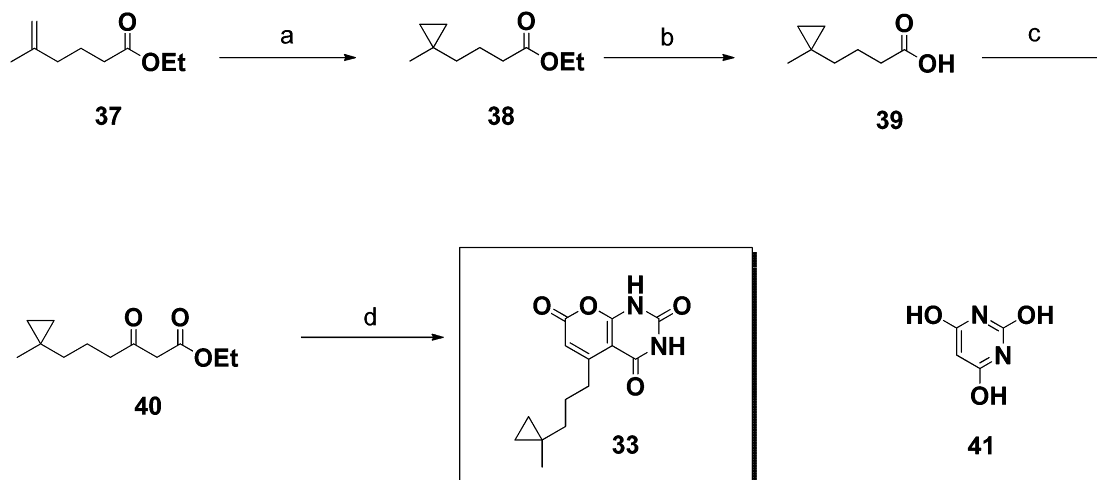
Compound	R^1	EC_{50} (nM)[a]	Compound	R^1	EC_{50} (nM)[a]
13	Ph	6100 ± 3900	**25**		5.0 ± 3.0
14	S	26 ± 6.0	**26**	F F	3.0 ± 1.0
15	S	47 ± 17	**27**	F_3C	10 ± 3.0
16		19 ± 8.0	**28**		13 ± 5.0
17		28 ± 14	**29**		1.0 ± 0.30
18	O	110 ± 24	**30**		4.0 ± 2.0
19	S	11 ± 3.0	**31**		39 ± 5.0
20	O S O	470 ± 140	**32**		10.0 ± 1.00
21		230 ± 99	**33**		2.0 ± 0.60
22		310 ± 48	**34**		16 ± 7.0
23		4.0 ± 2.0	**35**	Cl	7.0 ± 1.0
24		>10000	**36**	F	16 ± 5.0

[a]Data represent an average of multiple determinations ($n \geq 3$) ± standard deviations.

group (vide supra) was changed to a carbonyl group (**1**), while maintaining the ethyl group at the C-5 position, significant improvement in potency was observed. Compounds **2** and **3**, incorporating methyl and *n*-propyl groups, respectively, were 3−9-fold less active in the cAMP assay. Interestingly, the *n*-butyl analogue **4** showed moderate activity equivalent to that of **1**. Changing R^1 from ethyl (**1**) to isopropyl (**5**) was less tolerated, with 7-fold loss in activity. Fluoroalkyl derivatives were less tolerated with significant loss in activity (**6** and **7**). When R^1 was substituted with phenyl (**8**) or an ester (**9**), there was complete loss in activity. One carbon homologation of **8** and **9** as in **10** and **11** or introduction of polar functional group (**12**) resulted in decreased activity.

Having identified the optimal R^1 linker length, we undertook additional SAR studies on the C-5 region having longer side chain with different alkyl and aryl substituents (Table 2). Although the phenyl group in **13** had a negative effect on activity, the thiophene derivatives (**14** and **15**) retained better in vitro activity. Compounds **16** and **17** with longer alkyl side chains retained activity similar to that of **4**. Introduction of heteroatoms, for example **18**, showed much weaker activity, whereas the thio analogue **19** showed excellent activity. However, oxidation of **19** to the sulfone **20** was detrimental to activity. Meanwhile, the effect of branching on compound **4** was studied, which showed some interesting results. The α- and β-methyl group (with respect to C-5) in **21** and **22** showed significant loss in potency, while the γ-methyl improved the potency in the hu-GPR109a assay by 4-fold (**23**, EC_{50} = 4.0 nM). Introduction of another methyl substituent at the gamma position (**24**) resulted in complete loss of activity, indicating

Scheme 1. Synthesis of Compound 33[a]



[a]Reagents and conditions: (a) Et_2Zn, CH_2I_2, TFA, CH_2Cl_2, 0 °C to room temperature, 12 h, 99%. (b) NaOH, EtOH, room temperature, 12 h, 93%. (c) Ethyl potassium malonate, CDI, $MgCl_2$, THF, room temperature, 12 h, 99%. (d) Compound **41**, glacial AcOH, 110 °C, 24 h, 15%.

Table 3. In Vitro and in Vivo Potencies of NAR Agonists and NA

	4	23	26	29	30	33	NA
hu-GPR109a EC_{50} (nM)[a]	17	4.0	3.0	1.0	4.0	2.0	99 ± 15
hu-GPR109b EC_{50} (nM)[a]	190	1300	59	67	140	96	>10000
rat-GPR109a EC_{50} (nM)[a]	8.0	4.0	2.0	5.0	2.0	8.0	39 ± 10
m-GPR109a EC_{50} (nM)[a]	12	ND[b]	5.0	4.0	ND[b]	6.0	29 ± 5.0
dog-GPR109a EC_{50} (nM)[a]	16	ND[b]	3.0	ND[b]	1.0	5.0	31 ± 13
rat FFA reduction (1 h post 1.0 mg/kg dosing) (%)	−29	−15[c]	ND[b]	−50	−58	−53	−80[d]
rat TG reduction (1 h post 1.0 mg/kg dosing) (%)	−40	−16[c]	−59	−31	−49	−53	−60[d]
dog FFA reduction (1 h post 1.0 mg/kg dosing) (%)	−90[e]	ND[b]	−80[c]	ND[b]	−80[f]	−50	−38[c]

[a]Data represent an average of multiple determinations ($n \geq 3$) ± standard deviations. [b]ND, not determined. [c]3.0 mg/kg dosing. [d]10.0 mg/kg dosing. [e]0.3 mg/kg dosing. [f]2.0 mg/kg dosing.

the role of steric hindrance in cAMP activity. Homologation of **23** to **25** retained the best in vitro activity with an EC_{50} of 5.0 nM. Interestingly, fluoroalkyl derivatives **26** and **27** showed good activity with the difluoromethyl analogue (**26**) having an EC_{50} of 3.0 nM. An attempt was made to introduce small cycloalkyl groups given the promising data of analogues **23** and **25**. The cyclopropyl ring (**28**) was 3-fold less potent than **23**. However, the cyclobutyl ring (**29**) showed excellent activity (EC_{50} = 1.0 nM). Increasing the linker length had an opposite effect on activity (**30**, EC_{50} = 4.0 nM, vs **31**, EC_{50} = 39 nM). Further extending the linker length (**32**) led to decreased activity. Elaboration of SAR on compound **30** with substituents on the cyclopropyl ring was investigated with the identification of compound SCH 900271 (**33**) with excellent activity (EC_{50} = 2.0 nM). The substitution on the ipso position of cyclopropyl played an important role in activity, although the ethyl (**34**) and the halogens (**35** and **36**) showed a slight decrease in activity. SAR studies of the C-5 region eventually led to the discovery of several compounds with potent in vitro activity. Compounds tested active as GPR109a agonists are full agonists and showed much weaker agonist potency for the GPR109b (vide infra). The presence of the NH is important for GPR109a activity, and the acidic N1−H bond mimics the role of NA. The substitution of small alkyl groups on either N1 or N3 led to several fold loss in agonist potency.[29]

The synthetic route to pyranopyrimidinedione **33** as a representative example is summarized in Scheme 1. Starting with ethyl 5-methylhex-5-enoate **37**, cyclopropanation followed by basic hydrolysis afforded 4-(1-methylcyclopropyl)butanoic acid **39**. The acid **39** was then converted to the *β*-keto ester **40** followed by condensation of barbituric acid **41** in refluxing acetic acid to afford **33**. This sequence was adopted to prepare most of the analogues in this series.

Following these initial studies, several compounds were dosed orally in a rat in vivo model designed to measure reductions in FFA and TG (Table 3). Compound **4** demonstrated excellent efficacy in vivo (rat FFA, −29%; TG, −40%, 1 h post 1.0 mg/kg po dosing). Compound **4** also exhibited a dose-dependent reduction in plasma FFA and achieved 90% FFA reduction at 0.3 mg/kg dose in dogs. Only a very modest reduction of FFA and TG was observed following oral administration of 3.0 mg/kg of **23**, which was not statistically significant. Excellent in vivo efficacy was observed with compound **26** (TG, −59%, 1 h post 1.0 mg/kg po dosing). In dogs, **26** suppressed plasma FFA (80%); however, 4 h postdosing, FFA rebounded to levels markedly above baseline, a phenomenon not seen with other compounds in this series. The observed FFA reduction was also accompanied by modest flushing seen at 3.0 mg/kg also not seen with other compounds in this series. It is of interest to note the potential link between flushing and FFA rebound with compound **26**, which is reminiscent of the clinical profile of niacin. The reason for flushing behavior shown by compound **26** is not clear, and we speculate that it could be due to differences in free drug

concentration in plasma.[30] Reduction of FFA and TG levels by **29** and **30** was also measured in rats and dogs. Significant reductions in plasma FFA and TG were observed that were essentially equal in magnitude to the response elicited by a 10 mg/kg dose of NA. However, further evaluation of compound **4** was discontinued as it was found to cause acute renal necrosis in mice. Serum blood urea nitrogen (BUN) and creatinine were markedly elevated in mice at 100 mg/kg. Profound nephrotoxicity was also observed with a few other compounds in this series, including compounds **29** and **30**. Similar toxicity was not observed in rats, thereby suggesting that this phenomenon is likely species specific. The mechanism of this observed side effect is yet to be determined. Compound **33** was profiled further to assess its potential as a drug candidate.

Additionally, compound **33** was assessed for the reduction in FFA and TG in fasted rats (Table 3). Compound **33** was dosed orally in fasted rats, which demonstrated robust efficacy in vivo (rat FFA, −53%; TG, −53%, 1 h post 1.0 mg/kg po dosing) as compared to **4**. Compound **33** had good plasma exposure in rat $AUC_{0-24\ h}$ = 7.6 μM h, 5 mg/kg po dosing, and F = 76%. A head-to-head study between **33** and NA demonstrated that **33** also had improved potency as compared to NA in vitro and in vivo (see the Supporting Information). Compound **33** dose dependently reduced rat plasma FFA and TG with an ED_{50} of approximately 0.5 mg/kg and a maximally effective dose of 3.0 mg/kg. The ED_{50} for NA on plasma FFA was difficult to calculate due to its steep dose response effect in this model. The maximally effective dose for NA on plasma FFA was 10 mg/kg. A time−course study of **33** in rat at 3.0 mg/kg showed that it reduced FFA and plasma TG 0.5, 1, and 2 h after dosing but had no activity at later time points. In comparison, the duration of activity with NA at 10 mg/kg treatment did not extend beyond 2 h after dosing. Compound **33** was studied for efficacy and flushing profile in fasted male beagle dogs and exhibited dose-dependent inhibition of plasma FFA with 50% FFA reduction at 1.0 mg/kg (Figure 1). At this dose and up to 10 mg/kg, dogs had no overt signs of flushing, as determined by quantification of changes in cutaneous blood flow and/or changes in skin color and behavior (Figure 2). In contrast, NA achieved similar reduction of FFA at 30 mg/kg dose, but this dose produced a pronounced flushing response in 9 of 13 dogs, observed as an average of a 5-fold increase in cutaneous blood flow from baseline as well as behavioral responses characterized by head shaking and ear scratching. There was no incidence of nephrotoxicity with **33** in mice at 100 mg/kg po for 5 days. This compound also demonstrated a good pharmacokinetic (PK) profile in the dog (dog $AUC_{0-24\ h}$ = 7.2 μM h, 1.0 mg/kg po dosing, and F = 40%). Compound **33** had no effect on hERG at concentrations up to 10 μM,[31] representing a 1400-fold multiple of the projected free human C_{max} required for efficacy, was not an inhibitor of human CYPs 1A2, 2C9, 2D6, or 3A4 (IC_{50} > 50 μM), and did not show induction of CYP3A4 in the human PXR assay up to 10 μM. No significant activity was observed for **33** in various counter screens. The CL_{int} value of compound **33** in human/rat/dog/mouse is 1.6/10/<1/8.7 μL/min/10^6 cells.

In summary, we have identified a potent NAR agonist **33**, which demonstrated excellent in vivo activity in animal models. In addition, the incidence and magnitude of cutaneous blood

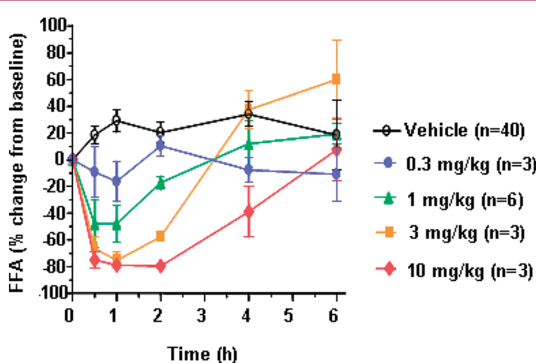


Figure 1. Acute FFA reduction of compound **33** in dogs.

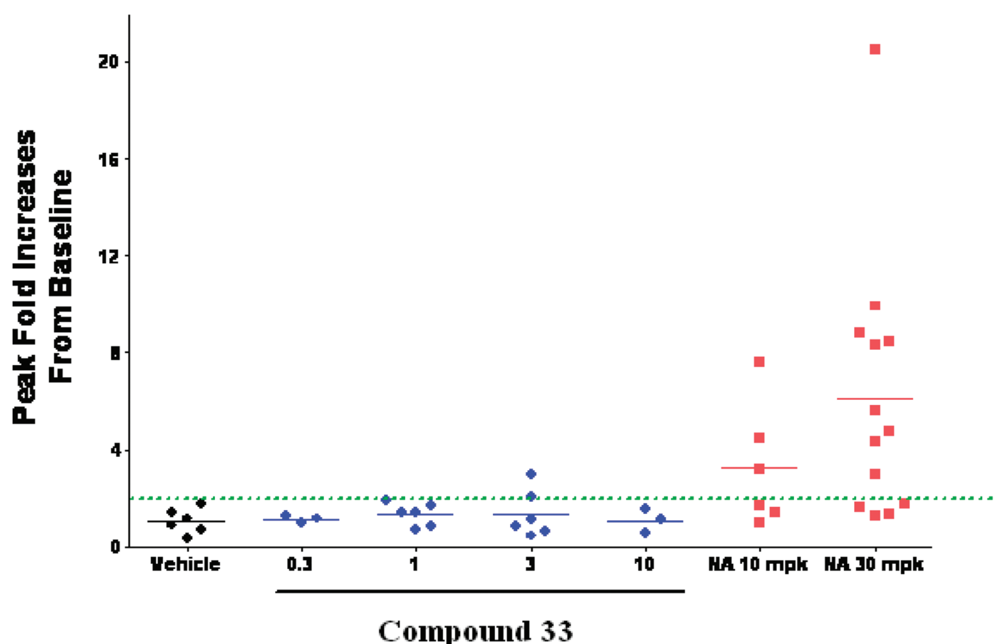


Figure 2. Peak fold increase from baseline in cutaneous blood flow in dogs dosed with compound **33** (0.3−10 mg/kg, po), NA, or vehicle (data for individual dogs).

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flow increases (flushing) observed with NA in the dog models were not observed with compound **33**, suggesting that it has an improved therapeutic window to flushing as compared to NA. This compound was investigated and developed further for its clinical potential.[32] Data from the phase I and phase II studies will be the subject of future publications.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for assay protocols, in vivo studies, and synthesis and characterization of compounds **1**−-**36**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: 908-740-7158. Fax: 908-740-7664. E-mail: anandan.palani@merck.com (A.P.). Tel: 908-740-5527. Fax: 908-740-7664. E-mail: ashwin.rao@merck.com (A.U.R.).

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

NA, nicotinic acid; FFA, free fatty acid; VLDL-C, very low-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; Lp-a, lipoprotein a; HDL-C, high-density lipoprotein cholesterol; CAD, coronary artery disease; NAR, nicotinic acid receptor; GPR, G-protein coupled receptor; cAMP, 3′-5′-cyclic adenosine monophosphate; PK, pharmacokinetic; CYP, cytochrome P450; BUN, blood urea nitrogen; TFA, trifluoroacetic acid; CDI, 1,1′-carbonyldiimidazole

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(29) The EC_{50} in the hu-GPR109a assay of N1 and N3 methyl analogues of compound **30** are 2700 ± 1500 and 250 ± 56 nM, respectively.

(30) We compared both flushing and non-flushing compounds in in vitro macrophage models to evaluate the ability to elicit the release of prostaglandin (a key driver of flushing).[2,8,11] No difference was found in that all compounds tested elicited the release of prostaglandins to a similar degree (data not shown). Given the similar activity of these compounds to cause release of a potential driver of flushing (prostaglandin), we speculate that the differences between compounds in this series to cause flushing are more likely related to physicochemical and/or pharmacokinetic properties. In dogs, the free drug concentration (at t_{max}) in plasma of compound **26** is 206.2 ng/mL and 83.9% protein bound whilst the free drug concentration for **33** is 26.1 ng/mL and 99% protein bound.

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