Discovery of Biaryl Anthranilides as Full Agonists for the High Affinity Niacin Receptor

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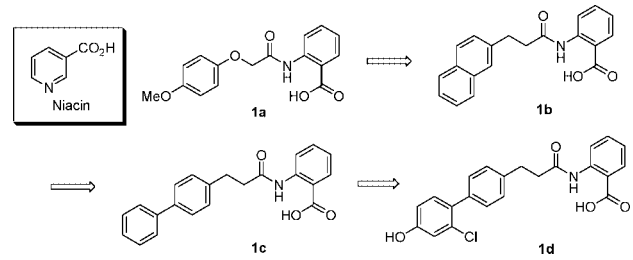
Abstract: Biaryl anthranilides are reported as potent and selective full agonists for the high affinity niacin receptor GPR109A. The SAR presented outlines approaches to reduce serum shift and both CYPCYP2C8 and CYP2C9 liabilities, while improving PK and maintaining excellent receptor activity. Compound **2i** exhibited good in vivo antilipolytic efficacy while providing a significantly improved therapeutic index over vasodilation (flushing) with respect to niacin in the mouse model.

Niacin (nicotinic acid, Scheme 1), a group B vitamin, serves as a precursor for NAD^+ and $NADP^+$ and is physiologically active at >15–20 mg/day.[1] As an antidyslipidemic drug dosed 500–2000 mg/day, niacin demonstrates its pharmacological utility by modifying various lipid profiles.[2] Particularly, niacin elevates HDL-C,[a] reduces total plasma cholesterol, TG, VLDL-C, LDL-C, and Lp(a).[3] In a series of clinical studies, including the Coronary Drug Project (CDP),[4] Stockholm Ischemeic Heart Disease Study,[5] HATS trial,[6] and ARBITER 2 trial, [7] niacin significantly decreased the morbidity and mortality of patients with coronary heart disease and slowed the progression of atherosclerosis by monotherapy or combination therapy with simvastatin. However, cutaneous flushing is a major adverse effect of niacin therapy, which results in lowered patient compliance.

GPR109A (HM74A in humans and PUMA-G in mice), the high affinity niacin receptor, was recently discovered.[8] Coupled to G_i proteins, GPR109A is expressed mainly on adipocytes and immune cells. Two other receptors related to GPR109A are GPR109B and GPR81. Interestingly, niacin has over a 1000-fold higher affinity for GPR109A than GPR109B despite the high identity between these two receptors (~90%). Niacin is not active against GPR81, which has <50% identity with GPR109A and GPR109B. Given the beneficial role of niacin, the discovery of GPR109A has stirred the interests of both academia[9] and the pharmaceutical industry[10] in pursuing agonists as potential therapeutic agents for cardiovascular disease devoid of the side effects of niacin.

Scheme 1



Regarding niacin's mechanism of action, it is known that niacin binds to GPR109A found on adipocytes and decreases the hydrolysis of adipocyte TG, thereby resulting in a transient reduction of plasma free FFA concentration. There has been a hypothesis in the literature that the reduction of FFA leads to sustained plasma TG reduction and HDL-C elevation. Moreover, because GPR109A is also expressed on immune cells, it is possible that some of its antiatherosclerotic effects derive from modulation of vascular inflammation. [3b]

To measure the activity of our compounds against GPR109A, a [^{3}H]-niacin competition binding assay in either the absence or the presence of 4% human serum and a guanine nucleotide exchange assay (GTPγS) were employed. In both assays, membranes from CHO cells expressing the recombinant human GPR109A were utilized. All active analogs described in this paper had a similar maximum level of response as niacin in the GTPγS assay and were, therefore, characterized as full agonists. High-throughput screening identified compound **1a** as a hit with moderate activity (Table 1). A rapid optimization led to the discovery of compound **1b** with improved activity similar to niacin in both binding and hGTPγS assays. It was then envisioned that the methoxyphenyl group in **1a** or naphthyl group of **1b** could be replaced by a biphenyl structure, thus providing a readily accessible and modular scaffold (Scheme 1). Indeed, biphenyl analog **1c** showed similar activity against human GPR109A ([^{3}H]-niacin IC_{50} = 93 nM and hGTPγS EC_{50} = 0.59 μM) as niacin. The SAR on the length of the linker between the amide and the biphenyl moiety, the alignment pattern of the biphenyl group, and the SAR surrounding both the inner and the terminal phenyl group led to a potent analog **1d** ([^{3}H]-niacin IC_{50} = 4 nM and hGTPγS EC_{50} = 0.045 μM). Despite its excellent activity, **1d** suffered from poor bioavailability, high clearance, low oral exposure, high serum shift (~8000-fold), and potent CYP2C8 and 2C9 inhibition (EC_{50} < 0.4 μM for both enzymes). To overcome these issues that were common for the biphenyl class, biaryl anthranilides containing one or two heterocycles were discovered.

The terminal and inner rings of the biaryl system were systematically modified and studied for their impact on activity and serum shift (Tables 1–3). A subset of these compounds were tested and found inactive against GPR109B and GPR81 indicating that they were selective for GPR109A. Several compounds were further profiled in CYP2C8 and 2C9 inhibition assays (Table 4), and mouse PK studies (Table 5).

First, after systematic modification of the terminal ring with various pyridine, pyrimidine, and pyrazine regioisomers (data not shown), analog **2a** gave the best activity matching that of the niacin control. The installation of the terminal hydroxyl group (**2b**) improved the affinity 10-fold. However, the large serum shift of **2b** had to be reduced. The amino substitution at

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[a]Abbreviations: 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; PUMG-G, protein-upregulated in macrophages by interferon γ; FFA, free fatty acid; CHO, Chinese hamster ovary; SAR, structure–activity relationship; DMAP, 4-dimethylaminopyridine; PK, pharmacokinetics; PD, pharmacodynamics.

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Table 1. In Vitro SAR of Biaryl Anthranilide Analogs to Optimize the Terminal Ring for Human GPR109A[a]

Cmpd	^{3}H Niacin IC_{50} (μM)	Serum shift[b] (fold)	GTPγS EC_{50} (μM)
niacin	0.14	0	1.0
1a	>2.5	-	6.0
1b	0.14	-	1.0
1c	0.094	-	0.59
1d	0.004	8000	0.045
2a	0.12	-	0.97
2b	0.009	5000	0.086
2c	-	-	>20
2d	-	-	3.4
2e	0.35	-	2.1

[a] On average, repeat determinations differed by 120%. [b] The binding assay was performed in the presence of 4% of human serum to calculate the serum shift.

Table 2. In Vitro SAR of Biaryl Anthranilide Analogs Containing an Inner Heterocycle for Human GPR109A[a]

Cmpd	^{3}H Niacin IC_{50} (μM)	Serum shift[b] (fold)	GTPγS EC_{50} (μM)	hadipocyte IC_{50} (μM)
niacin	0.14	0	1.0	0.07
2f	0.008	3200	0.077	-
2g	0.001	340	0.006	-
2h	0.024	60	0.093	0.04
2i	0.010	40	0.12	0.03
2j	0.33	-	>20	-

[a] On average, repeat determinations differed by 120%. [b] The binding assay was performed in the presence of 4% of human serum to calculate the serum shift.

the same position of a hydrogen bond donor (**2c**) resulted in a loss of activity. Five-membered heterocycles such as isoxazole (**2d**) and pyrole (**2e**) were inferior compared to **2a**.

Then the inner heterocycle was explored (Table 2). The thiophene isostere of the phenyl group (**2f**) yielded a marginal improvement of the serum shift yet similar activity compared to **1d**.

More polar heterocycles were designed to attempt to reduce serum shift. Indeed, thiazole analog **2g** lowered the serum shift to 340-fold and offered single digit nanomolar activity in the binding and functional assays. Next we examined compounds containing pyrazole, imidazole, isoxazole, oxazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,4-oxadiazole, or 1,3,4-oxadiazole as the inner ring, and compounds **2h** and **2i** were identified for their relatively low serum shift and good activity. In the human adipocyte assay in which the inhibition of lipolysis in human adipocytes was measured, **2h** and **2i** reduced FFA more effectively than niacin. Interestingly, **2j**, a regioisomer of **2i**, was 30-fold less active against GPR109A.

Table 3. In Vitro SAR of Biheteroaryl Anthranilide Analogs for Human GPR109A[a]

Cmpd	^{3}H Niacin IC_{50} (μM)	Serum shift[b] (fold)	GTPγS EC_{50} (μM)	hadipocyte IC_{50} (μM)
2k	0.020	500	0.24	-
2l	0.026	100	0.43	-
2m	0.051	330	0.93	-
2n	0.058	170	1.3	-
2o	0.004	30	0.027	0.005

[a] On average, repeat determinations differed by 120%. [b] The binding assay was performed in the presence of 4% of human serum to calculate the serum shift.

Table 4. Human CYP2C8 and 2C9 Inhibition Profiles[a]

cmpd	CYP2C8, IC_{50} (μM)	CYP2C9, IC_{50} (μM)
1d	<0.4	<0.4
2b	8.9	1.6
2g	1.2	2.8
2h	19	15
2l	20.3	5.7
2m	9.3	4.2
2o	>100	42

[a] The CYP2C8 inhibition assay in human liver microsomes used taxol and montelukast as the substrate and positive control, respectively. The CYP2C9 inhibition assay in human liver microsomes used diclofenac and sulfaphenazole as the substrate and positive control, respectively.

Lastly, our attention was turned to biheteroaryl analogs (Table 3). Hydroxypyrazole **2k** recapitulated the finding that a terminal hydroxyl group improved affinity. The combination of the optimized hydroxypyridine as the terminal ring, and the inner heterocycles with good properties in Table 2, produced thiazole (**2l** and **2m**) and pyrazole (**2n**) analogs with modest activities and over 100-fold serum shift. In contrast, compound **2o** displayed low nanomolar activity and a much lower serum shift (~30 fold). In the human adipocyte assay, **2o** effectively suppressed lipolysis with a 10-fold greater activity than niacin.

Not only did the lead compound **1d** have issues with serum shift, it was also a potent inhibitor of both CYP2C8 and 2C9 isozymes. Guided by the SAR, polar heterocycles helped to eliminate CYP liabilities.

The replacement of the terminal phenol with a hydroxypyridine (**2b**) or the inner phenyl group with a thiazole (**2g**) reduced both CYP2C8 and 2C9 inhibition (Table 4) compared to **1d**. The combination of hydroxypyridine and thiazole (**2l** and **2m**) was synergistic on reduction of CYP2C8 and 2C9 inhibition

Table 5. Mouse PK Profiles[a]

cmpd	*F*%	Cl (mL/min /kg)	Vd_{ss} (L/kg)	C_{max} (μM)	$T_{1/2}$ (h)	AUC_{po}(μM·h·kg/mg)
1d	5	18	0.35	0.96	2.0	0.11
2b	57	0.38	0.11	5.0	5.3	15
2g	37	7.3	0.37	2.1	1.6	2.1
2h	2.5	26	0.88	0.03	1.1	0.1
2i	6	34	1.66	0.12	1.3	0.18
2l	27	8.5	0.62	0.52	2.2	1.5

[a] Values are an average of three mice. IV dose, 1 mg/kg; PO dose, 2 mg/kg. Vehicle: DMSO/PEG400/water (5:40:55 v:v:v).

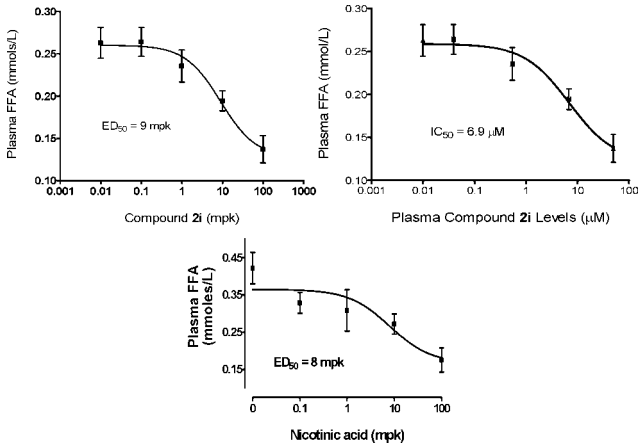


Figure 1. The FFA lowering effect of **2i** and niacin by p.o. dosing (mpk = mg/kg). Compound **2i** for mouse GPR109A: ^{3}H-niacin binding IC_{50} = 0.46 μM, GTPγS EC_{50} = 1.6 μM; niacin for mouse GPR109A: ^{3}H-niacin binding IC_{50} = 0.14 μM, GTPγS EC_{50} = 0.27 μM. Compound and FFA plasma levels were measured at 15 min post-dosing.

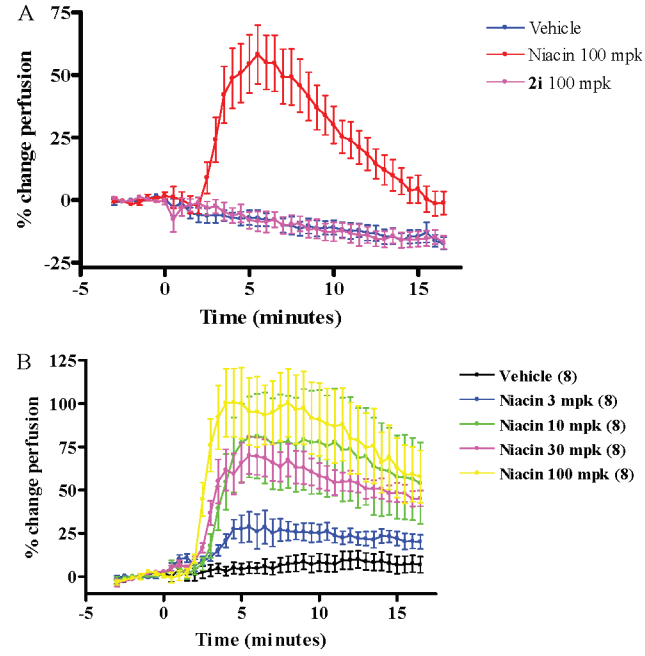


Figure 2. The mouse ear vasodilation effect of **2i** and niacin (i.p. dosing) in 5% DMSO/40% PEG400/55% water (mpk = mg/kg).

and gave higher IC_{50}s for both enzymes. The pyrazole ring was unique in that the IC_{50}s of **2h** against CYP2C8 and 2C9 were above 10 μM for both enzymes despite the presence of the phenol group. Compound **2o** completely eliminated the CYP2C8 and 2C9 inhibition concern by incorporating the hydroxypyridine and 1,3,4-oxadiazole combination.

In addition to its good activity, **2b** has a remarkable PK profile (Table 5) in sharp contrast to **1d**. As the most potent compound in this report, **2g** also provided a good PK profile exemplified by lower clearance, higher AUC, and bioavailability than **1d**. Compounds **2h** and **2i** represented breakthroughs in serum shift but were inferior in PK with poor bioavailability, high clearance, and low oral exposure. It was suspected that the presence of the phenol might be detrimental based upon the observation of the superior PK of **2b** over **1d**. By replacing the phenol with a hydroxypyridine, the bioavailability, clearance, C_{max}, and normalized AUC of **2l** were all significantly improved over **2h** and **2i**.

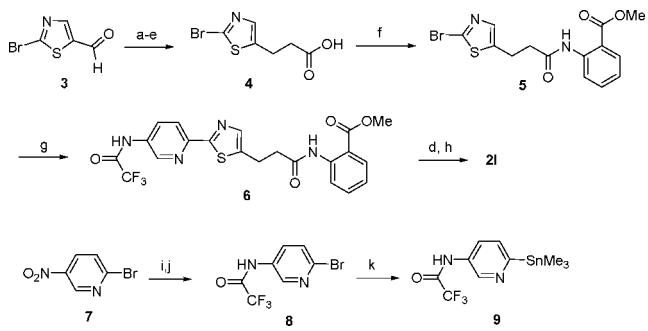
Niacin has been known to induce FFA reduction in mice and this effect was niacin receptor dependent.[8b] It was anticipated that the lipid effect of niacin treatment was mediated through GPR109A, and the reduction of FFA in adipocytes eventually led to TG reduction and HDL-C elevation.[3b] In mice (p.o. dosing), **2i** was as efficacious in lowering plasma FFA as niacin (Figure 1) on a dose basis (ED_{50} = 9 and 8 mg/kg, respectively). Furthermore, the in vivo IC_{50} of **2i** was 6.9 μM, whereas the drug level of niacin at 10 mg/kg p.o. dose in the same FFA reduction experiment was ~20 μM. It was estimated that the in vivo IC_{50} of niacin in mouse FFA reduction was close to 20 μM. Our PD observation indicated that the in vitro mouse activity, serum shift, and PK of **2i** were sufficient to elicit acute FFA reduction, which might result in other favorable lipid effects via GPR109A agonism.

To assess the flushing potential of our compounds, a mouse model was adopted to measure the extent of vasodilation by the change in blood perfusion in the mouse ear using laser Doppler flowmetry.[11] In the experiment shown in Figure 2A, **2i** failed to induce any vasodilation at the maximum feasible dose of 100 mg/kg (i.p.). At 15 min post 100 mg/kg dose (i.p.), the plasma compound level of **2i** was 490 μM. The therapeutic index (TI) could be defined as the minimum drug level that induces flushing over the IC_{50} for FFA reduction. Therefore, the TI of **2i** should be over 70 (490 μM/6.9 μM), given that **2i** did not induce flushing even at 490 μM. In contrast, niacin induced vasodilation at only 3 mpk (i.p.) (Figure 2B), which corresponded to an 18 μM plasma concentration of niacin at 5 min post-dosing. The time point chosen here corresponded to the maximum flushing observed at the T_{max} for niacin. Thus, the TI for niacin was virtually 1 (18 μM /20 μM). Compound **2i** demonstrated a significantly improved TI with respect to niacin in mice.

The benchmark compound **2l** offered a significant improvement in mouse PK and CYP2C8/2C9 profiles.[12] The key step in the preparation of **2l** was the Stille coupling of bromothiazole **5** and 2-trimethylstannyl pyridine **9** (Scheme 2). The desired product **6** was deprotected and the amino group was converted to the hydroxyl group via the hydrolysis of the diazonium salt to accomplish the synthesis of **2l**.

In summary, several highly potent biaryl anthranilide derivatives were discovered as agonists of GPR109A with 10–100-fold more activity than niacin in vitro. We successfully removed CYP2C8 and 2C9 inhibition, significantly reduced serum shift, and improved the PK profile of some members of the series

Scheme 2[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 94%; (b) CBr_4, PPh_3, CH_2Cl_2, 0 °C to rt, 82%; (c) dimethyl malonate, NaH, THF, 0 °C, 83%; (d) LiOH, THF/MeOH/water (3:1:1), rt, 100%; (e) DMF, 170 °C, 99%; (f) MsCl, Et_3N, CH_2Cl_2, then anthranilic acid methyl ester; 0 °C to rt, 33%; (g) $Pd(PPh_3)_4$, CuI, **9**, toluene, 120 °C, 79%; (h) $NaNO_2$, H_2SO_4, 0 °C−73 °C, 13%; (i) $SnCl_2$, EtOH, reflux, 38%; (j) trifluoroacetic anhydride, DMAP, CH_2Cl_2, 0 °C to rt, 81%; (k) $Pd(PPh_3)_4$, $(Me_3Sn)_2$, THF, 80 °C, 50%.

via introduction of five-membered heterocycles in conjunction with a terminal hydroxypyridine ring. One representative analog **2i** showed in vivo FFA reduction efficacy while failing to induce vasodilation in mice. Our initial studies of the biaryl anthranilide class demonstrated the possibility of developing niacin receptor agonists with good efficacy on the proximal biomarker, FFA, and an improved therapeutic index with respect to niacin-induced flushing.

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

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(12) See Supporting Information for the detailed preparation of all analogs.

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