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Miniperspective

Nicotinic Acid Receptor Agonists

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Nicotinic Acid: Use as an Antidyslipidemic in the Clinic

Nicotinic acid is one of the oldest drugs used to treat dyslipidemia.[1] It has gained significant favor over the years because of its versatility; nicotinic acid offers protection against a variety of known cardiovascular risk factors by lowering very low-density lipoprotein (VLDL[a])-cholesterol, low-density lipoprotein (LDL)-cholesterol, and lipoprotein(a) (Lp(a)) and is the most effective agent currently marketed for raising high-density lipoprotein (HDL)-cholesterol plasma concentrations.[2,3] Clinical trials have shown that nicotinic acid treatment can reduce the number of cardiac events and mortality resulting from heart disease.[4−7] Indeed, the Coronary Drug Project, a nationwide clinical study designed to determine whether specific therapeutic interventions could prevent further coronary heart disease (CHD) events and prolong the life of men with a previous history of myocardial infarction (MI), identified nicotinic acid (3 g/day) as capable of reducing the rate of nonfatal MI,[4,5] as well as decreasing total mortality, 9 years following the completion of the trial.[7,8] In addition, when given in combination with statins, nicotinic acid slowed the progression of atherosclerosis as well as decreased the number of cardiac events.[9] In a subsequent trial, nicotinic acid was added to the dosing regime of patients already on statin therapy and was shown to significantly slow the progression of atherosclerosis beyond the therapeutic benefit of statins alone.[10]

Despite these very encouraging data, the widespread therapeutic use of nicotinic acid has been hindered by reports of a number of potential liabilities including a short half-life (and hence the requirement for multiple doses per day), dyspepsia, hyperuricemia, a fatty acid rebound effect, and most notably its major side effect, an uncomfortable cutaneous flushing effect that manifests itself as a burning sensation, felt mainly on the face and upper body.[11,12] Niacin is approved and available in three general formulations: crystalline or immediate release niacin, slow-release niacin, and extended-release niacin. The slow-release formulations were developed in an attempt to alleviate the flushing and pruritis side effects of crystalline niacin but have occasionally resulted in elevated liver enzymes and even hepatotoxicity.[11,12] To address the hepatotoxicity and flushing side effects and provide a once daily formulation, an extended release formulation (Niaspan) was developed.[13] Unfortunately, the flushing side effect, while somewhat diminished in intensity, is still largely responsible for the lack of patient compliance. In a further attempt to improve compliance by alleviating the flushing side effect, Merck and Co. has demonstrated that a combination of extended-release nicotinic acid with laropiprant, an antagonist of the prostaglandin D2 (PGD_2) receptor, significantly lowered flushing symptom scores when compared to extended-release nicotinic acid alone, allowing for an accelerated dose advancement paradigm.[14] This finding has implications for the mechanism of action of nicotinic acid in both lipid remodeling and flushing, as will be discussed below.

Nicotinic Acid Receptor GPR109a

The identification of a high-affinity nicotinic acid binding site on rat adipocytes, macrophages, and spleen cells that had all the hallmarks of a G_i-protein-coupled receptor[15] led shortly thereafter to the identification of two orphan GPCRs that share 95% identity and that are both expressed in human adipocytes

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[a] Abbreviations: GPR109a, G-protein-coupled receptor 109a (also known as HM74a); GPR109b, G-protein-coupled receptor 109b (also known as HM74); PUMA-G, protein up-regulated in macrophages by interferon γ (the mouse orthologue of GPR109a); VLDL, very low-density lipoprotein; LDL, low-density lipoprotein; HDL, high density lipoprotein; Lp(a), lipoprotein(a); MI, myocardial infarction; PGD_2, prostaglandin D_2; (D)-β-OHB, (D)-β-hydroxybutyrate; PKA, protein kinase A; CHO cells, Chinese hamster ovary cells; TG, triglycerides; FFA, free fatty acids; cAMP, 3′,5′-cyclic adenosine monophosphate; MAPK, mitogen activated protein kinase.

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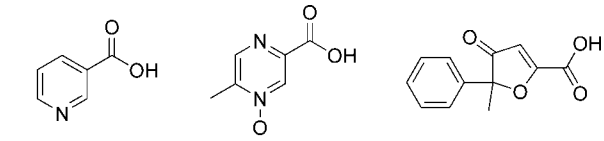


Figure 1. Structures of niacin, acipimox, and acifran.

as putative molecular targets for nicotinic acid. GPR109a (HM74a) is the human orthologue of the previously described mouse receptor (PUMA-G, called mGPR109a hereafter), whereas GPR109b (HM74) differs from hGPR109a and mGPR109a mainly in the intracellular C-terminal tail portion of the receptor and is not expressed in rodents.[16−18] Nicotinic acid was shown to activate hGPR109a in a guanine nucleotide exchange assay and displace ^{3}H-nicotinic acid from hGPR109a expressing CHO cell membranes with activity in the tens of nanomolar range but was a much weaker ligand for GPR109b.

Endogenous levels of nicotinic acid, while sufficient to serve as a vitamin cofactor to support energy homeostasis, are not sufficient to activate GPR109a, and nicotinic acid is therefore not the likely endogenous ligand for GPR109a. Taggart et al. identified the fatty acid derived ketone body (D)-β-hydroxybutyrate ((D)-β-OHB) as a potential natural ligand. Indeed, (D)-β-OHB specifically activates GPR109a at concentrations that are found physiologically under fasting conditions and inhibits mouse adipocyte lipolysis in a GPR109a dependent manner.[19]

Although the mechanisms by which nicotinic acid may raise HDL-cholesterol have not been clearly established, even after 50 years of clinical experience, the discovery of GPR109a has led to the generation of hypotheses involving activation of this receptor by niacin. Activation of GPR109a in adipose tissue mediates an antilipolytic response by lowering intracellular cAMP levels, thus leading to reduced protein kinase A (PKA) activity. This in turn results in a decrease in lipase activity, thereby reducing intracellular triglyceride (TG) hydrolysis and free fatty acid (FFA) secretion. It has been demonstrated in mGPR109a knockout mice that the FFA and triglyceride lowering effects of nicotinic acid in vivo are ablated in the absence of this receptor. One hypothesis for the mechanism by which nicotinic acid raises HDL is that it is an indirect consequence of nicotinic acid's ability to inhibit lipolysis in adipocytes via GPR109a, thus reducing the availability of FFA for delivery to the liver. The decreased availability of FFA in the liver reduces the synthesis of triglyceride and the subsequent packaging into VLDL. The attenuated synthesis of the triglyceride rich VLDL particles in the liver leads to a decreased rate of HDL metabolism via limiting the cholesterol ester transfer protein (CETP)-mediated exchange of cholesterol from HDL to VLDL and of TG from VLDL to HDL.[20−24] Another proposal is that nicotinic acid inhibits the uptake and subsequent catabolism of Apo-AI-containing HDL particles in hepatocytes.[25,26] Since there is little to no GPR109a receptor expression detected in hepatocytes, it is not clear what the molecular target of nicotinic acid might be in the liver. This second mechanism could operate in parallel to, or instead of, GPR109a mediated FFA lowering.

Data supporting the role of GPR109a in nicotinic acid's therapeutic activity come from the SAR profiles of various ligands for the receptor. Structurally dissimilar GPR109a agonists have antilipolytic effects and can also modulate lipid profiles. For example, acipimox and acifran (**1** and **2**, respectively, Figure 1) are two clinically tested compounds that were subsequently shown to activate GPR109a. Neither compound can support the vitamin role of nicotinic acid (formation of NAD for use in energy homeostasis), but both compounds have pharmacological characteristics similar to nicotinic acid.[27−29] Specifically, **1** (0.75 g daily) has been shown to lower VLDL and raise HDL to a similar extent as nicotinic acid (given at 3 g daily).[27] **2** was able to significantly lower plasma LDL-cholesterol and triglyceride levels and elevate HDL-cholesterol (300 mg t.i.d.).[29,30]

Recent work has begun to elucidate the mechanism by which nicotinic acid induces flushing.[31,32] Again, with the use of knockout mice, GPR109a has been shown to mediate nicotinic acid-induced flushing through release of PGD_2.[33,34] Further work has provided data showing that GPR109a receptors on Langerhans cells in the skin participate in nicotinic acid-induced flushing through increased generation of PGD_2.[33,35,36] It may be envisioned, therefore, that an ideal therapeutic would exhibit antilipolytic qualities while blocking the downstream effect of PGD_2 (for example, with the addition of a PGD_2 receptor antagonist, as discussed above) or by avoiding the release of PGD_2 from Langerhans cells. The latter option would at first glance seem somewhat unlikely, as both processes have been shown to be mediated by the same receptor, but as will be discussed below, multiple compounds from different series have been shown to lower FFA without inducing flushing in both animals and humans. However, because the therapeutic mechanism of action for nicotinic acid has not been established, if either prostaglandins or activation of the intracellular pathway leading to prostaglandin release plays a significant role in the antiatherogenic and antidyslipidemic response, elimination of the flushing response could abrogate the therapeutic effect.

Comparison of GPR109a and GPR109b

GPR109b appears to be the product of a very recent gene duplication of GPR109a. The two receptors are greater than 95% identical. GPR109b is found only in the human and chimpanzee genomes and may not have a physiologically relevant function or endogenous ligand. As a result of this limited species expression, the development of drugs targeting GPR109b will be challenging, as it will prove difficult to obtain appropriate animal pharmacology or safety information.

Despite the exceptionally high homology, highly selective agonists of each receptor have been identified, starting with the prototypical compound, nicotinic acid. The potency (in inhibition of forskolin stimulated cAMP production) of nicotinic acid is approximately 20 000 times greater in cells transfected with GPR109a than those transfected with GPR109b. Indeed, one of the few GPR109a modulators that have been clinically tested, **2**, has proven to be one of the few compounds disclosed that show comparable activity for both receptors (500 nM IC_{50} vs 3 μM IC_{50} at GPR109a and GPR109b in a cAMP assay, respectively).[37]

Mutagenesis and chimera studies have begun to determine the key binding pocket residues in the transmembrane (TM) domain of GPR109a and may help to elucidate the structural basis for the observed selectivity. Tunaru et al. have developed a model of the structural requirements of GPR109a for binding nicotinic acid (Figure 2).[38] They provide data supporting the requirement of the arginine 111 (Arg-111) in TM-3 for binding the carboxylate moiety of nicotinic acid and **1**, the aromatic ring being sandwiched between tryptophan 91 (Trp-91) and phenylalanine 276 or tyrosine 284 (Phe-276/Tyr-284) and the heterocyclic ring also forming a hydrogen-bonding interaction with serine 178 (Ser-178).

As may be inferred from the exceptionally high receptor identity, there are very few differences within the TM domains

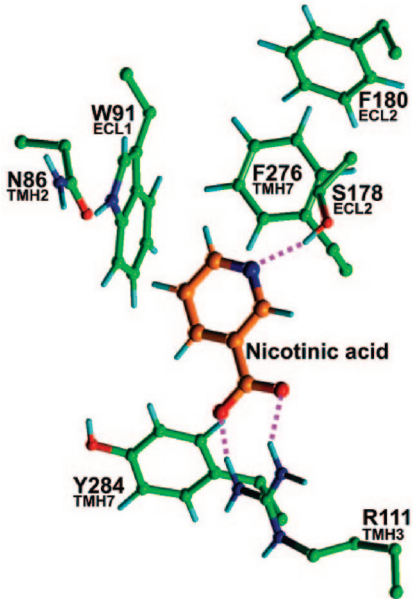


Figure 2. Predicted binding mode of nicotinic acid to the GPR109a receptor. Reproduced with permission from *Molecular Pharmacology* (Tunaru et al.).[39] Copyright 2005 American Society for Pharmacology and Experimental Therapeutics.

of GPR109a and GPR109b. However, adjacent to Arg-111, there is a single amino acid difference in the sequences between the two receptors. While the difference (Leu to Phe substitution) may be very subtle, it has been proposed that it could explain why GPR109b prefers somewhat larger (i.e., 6,5-fused bicyclic) ligands than GPR109a.[39] Conversely, smaller ligands such as nicotinic acid are preferred by GPR109a. The absence of other sequence differences adjacent to basic amino acid residues in the transmembrane regions makes the Tunaru model one of the few plausible explanations for the observed specificity. Interestingly, none of the GPR109b selective compounds showed any activation of the homologous mouse receptor, mGPR109a. This is also consistent with the proposed binding model, as the mouse receptor is identical to GPR109a and not GPR109b around the proposed key basic residue Arg-111, and thus, it too prefers smaller ligands such as nicotinic acid over fused bicyclic heterocycles.

Nicotinic Acid and Acipimox

Nicotinic acid is a structurally simple compound that has been difficult to optimize by medicinal chemistry methods. Conversion of nicotinic acid to the primary amide (nicotinamide) abolishes activity at GPR109a, emphasizing the importance of the carboxylic acid for binding. Homologation of nicotinic acid to 3-pyridylacetic acid resulted in a significant loss of potency as did the movement of the pyridyl nitrogen to any other position in the ring.[40,41] Older data derived from experiments in dog showing FFA lowering in vivo demonstrate that substitution of the ring was also poorly tolerated, although 5-fluoro- and 5-methylnicotinic acid had demonstrable effects on FFA, which were presumably via activation of GPR109a.[42]

Replacement of the carboxylic acid with an acid mimetic tetrazole (5-(3-pyridyl)tetrazole) provided a compound that was approximately 1000-fold less potent in inhibiting the release of free fatty acids in isolated adipocytes. However, in vivo the tetrazole had a much longer duration of action that was attributed to improved metabolic stability.[43] Unfortunately, tolerance developed in rats treated with high doses of the compound and its antilipolytic effects were no longer observed after 4 days.[44] The only structurally similar compound to be reported is **1**, discovered by Pharmacia (now Pfizer).[45,46] **1** was launched in Europe in 1985 for the treatment of hyperlipidemia. However, cutaneous flushing is a reported side effect, so the compound has no great advantage over nicotinic acid in that respect, and there are conflicting reports of whether it represents any improvement over nicotinic acid in the maintenance of glycemic control.[47,48]

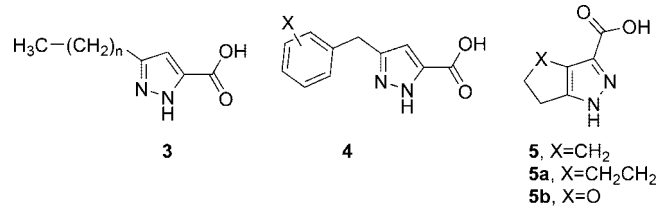


Figure 3. Antilipolytic pyrazole-3-carboxylic acids.

Pyrazoles and Isoxazoles

Long before identification of GPR109a as a receptor for nicotinic acid, other small heterocyclic acids were shown to inhibit lipolysis in vivo. Both 3,5-dimethylpyrazole[49] and 3,5-dimethylisoxazole[50] demonstrated potent antilipolytic effects in rats. It was soon discovered that metabolic oxidation to the corresponding 5-methylpyrazole-3-carboxylic and 3-methylisoxazole-5-carboxylic acids was necessary for activity. Since these early studies, it was clearly established that dosing these acids directly provided good in vivo efficacy. In particular, 5-methylisoxazole-3-carboxylic acid was highly potent at lowering free fatty acids in vivo; however, tachyphylaxis to this antilipolytic effect developed in rats and dogs upon repeated administration.[51] Such desensitization has evidently hindered the development of these compounds as therapeutic agents.

Following these initial studies, it was a number of years before reports of further study of pyrazolecarboxylate SAR emerged. Seki and co-workers reported hypolipidemic activity in rats for a number of 5-alkylpyrazolecarboxylic acid derivatives.[52] Generally, it was found that straight-chain alkyl groups with increasing chain length up 15 carbons demonstrated antilypolytic activity (**3**, Figure 3, $n = 14$). As with nicotinic acid, amide and ester derivatives were much less active, as were carbinols. Although it was not investigated, the weak activity shown by the carbinol compounds as well as the ester and amide derivatives may have been due to metabolic oxidation and hydrolysis (respectively) to the corresponding acids.

van Herk and co-workers reported receptor ligand binding assay data for some of the analogues reported by Seki as well as new analogues using radiolabeled nicotinic acid and spleen membrane preparations,[53] confirming binding of the pyrazolecarboxylic acids to the nicotinic acid receptor GPR109a. The most potent analogue, 5-butylpyrazole-3-carboxylic acid, had a K_i of 72 nM in this assay with the 5-propyl derivative only around 2-fold less potent. Branched alkyl, phenyl, and benzyl derivatives (**4**, Figure 3) were all less potent. Fused bicyclic derivatives also showed reasonable binding affinity, with the 5,5-fused pyrazole **5** ($K_i = 156$ nM) nearly equipotent with the propyl derivative. However, the 5,6-fused pyrazolecarboxylic acid (**5a**) was considerably less potent ($K_i = 3.5$ μM). Interestingly, replacement of one of the methylenes in compound **3** with an oxygen (**5b**) completely abolished activity. The increase in binding of [^{35}S]GTPγS by the GPR109a agonists in both rat spleen and adipocyte preparations was also examined. The partial agonist character of the pyrazole acids was revealed in

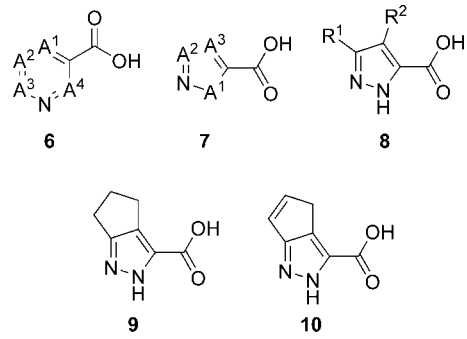


Figure 4. Nitrogen containing heterocyclic acids with activity at GPR109a.

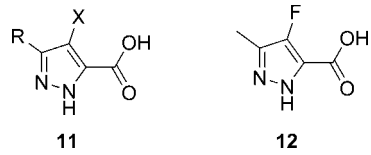


Figure 5. Halogenated pyrazole acids.

this assay system in that the intrinsic activities of pyrazole derivatives were all less than nicotinic acid and varied between 29% and 85%.[53]

Merck and Arena Pharmaceuticals have published patent applications that extend the scope of reported pyrazole carboxylic acid structures,[54−59] and some of this work has recently been described in the more detail. The first of these publications describes exploration of nitrogen containing heterocycles with a carboxylic acid three atoms away, depicted by the generic structures **6** and **7** (Figure 4).[40] None of the six-membered heterocycles investigated were more potent than nicotinic acid, and the extreme sensitivity of the receptor to small changes in the nicotinic acid core is evident from this work. A large number of five-membered heterocycles were investigated, and among these, the previously described pyrazole (**7**, $A^1 = N$, $A^2 = CCH_3$) and isoxazole (**7**, $A^1 = O$, $A^2 = CCH_3$) gave good receptor activity along with the previously untested thiazole carboxylic acid (**7**, $A^3 = S$, $A^2 = CCH_3$). A fairly extensive SAR study of 5-substituted pyrazole carboxylic acids was reported, with relatively modest activities for most analogues. 4,5-Disubstituted pyrazole acids, **8**, were inactive unless the substituents were tied back into a ring. Within this framework, 6,5-bicyclic pyrazole acids (**8**, R^1, $R^2 = (CH_2)_4$) were inactive whereas the 5,5-bicyclic pyrazole acids, **9**, were moderately active (low micromolar). In particular, the unsaturated analogue, **10**, was slightly more potent than its saturated counterpart; however, the double bond had a tendency to migrate.[40]

Skinner et al. followed this with a report of the synthesis and activities of several substituted pyrazole carboxylic acids incorporating halogen atoms at the 4-position (e.g., Figure 5, **11**, **12**).[60] The previously reported 5-methylpyrazole-3-carboxylic acid was one of the more potent compounds investigated, and additional substitution around the ring was generally not well tolerated. However, 4-fluoro-5-methylpyrazole-3-carboxylic acid was equipotent with the 4-hydrogen analogue, and 4-fluoro-5-ethylpyrazole-3-carboxylic acid appeared slightly more potent than its nonhalogenated counterpart at decreasing generation of cAMP in vitro. 4-Fluoro-5-methylpyrazole-3-carboxylic acid decreased free fatty acids when dosed orally in Sprague−Dawley rats, with efficacy equal to that of nicotinic acid but at a fraction of the dose (1 mg/kg vs 10 mg/kg), and appeared to demonstrate a decreased effect on vasodilation in a mouse model at doses of 100 mg/kg.[61]

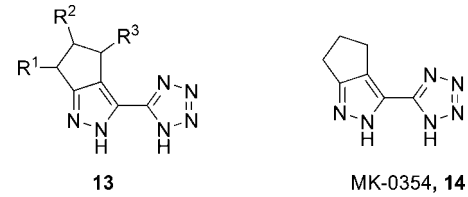


Figure 6. Pyrazole tetrazole analogues.

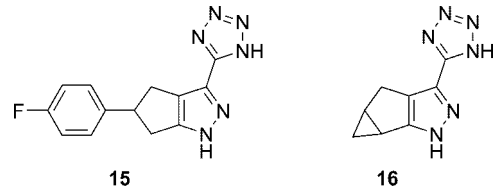


Figure 7. Patented pyrazolecarboxylic acid analogues.

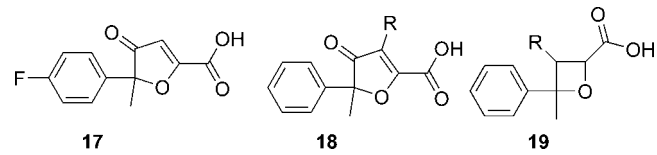


Figure 8. Analogues of acifran.

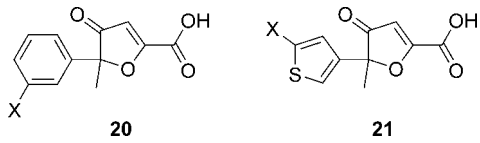
This work was followed by disclosure of the first clinical compound, MK-0354 (**14**, Figure 6), from the Arena/Merck collaboration. **14** was a partial GPR109a agonist chosen from a set of pyrazole compounds **13** in which a tetrazole was used as a carboxylic acid mimic. Interestingly, whereas the carboxylic acids induced vasodilation in mice, the tetrazole analogue did not, even at plasma concentrations that were more than 30 times higher than needed to reduce plasma free fatty acids. Additionally, it was demonstrated that **14** could block the vasodilation effect of nicotinic acid when dosed 5 min prior to administration of nicotinic acid, consistent with competitive antagonism of the nicotinic acid-induced flushing pathway by **14**.[62] Similar antilipolytic behavior for **14** was observed in rat and dog, although some modest vasodilation was observed in these species at high doses. Despite this, a significantly better therapeutic ratio than that observed for nicotinic acid was reported.[63]

Patent applications claiming further derivatives of **14** have been published, although detailed accounts of their discovery have not yet appeared in the literature. The Merck group has claimed derivatives with substitution on the cyclopentyl ring (**15**, Figure 7), and Arena has claimed derivatives modified with a fused cyclopropyl ring (**16**) with further optional substitutions at the cyclopropyl ring apex.[55,56]

Acifran

2 was developed by Ayerst Laboratories in the early 1980s as a lipid lowering agent.[64] Although the compound was effective at lowering circulating triglycerides in rats, few analogues were reported presumably because of difficulties in optimizing the chemical class without knowledge of the molecular target.

Mahboubi and co-workers reported on the exploration of a series of analogues of **2** (Figure 8).[65] By use of the original patent synthesis, 12 analogues were tested for their ability to decrease triglyceride in a fructose fed rat model. None of the analogues reported were more efficacious than **2**, with only one compound, the 4-fluorophenyl derivative (**17**), being essentially equipotent with the parent. Derivatives with substitution on the furan ring (**18**, R = Me, *i*-Pr) and four-membered ring analogues



20 **21**

Figure 9. Potent acifran analogues.

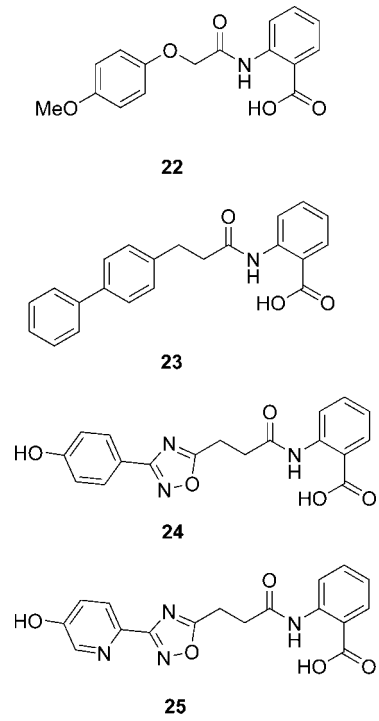
(**19**, R = *t*-Bu, 4-FPh) were all inactive or considerably less potent than **2**. Chiral versions of **2** were also prepared via a Sharpless asymmetric dihydroxylation, and all of the activity of racemic **2** could be assigned to the (*S*)-enantiomer, as the (*R*)-enantiomer was completely inactive.

Semple and co-workers have reported on a more extensive examination of the SAR of further analogues.[66] With development of improved synthetic methods to produce **2** and its analogues, the synthesis and activity of more than 30 compounds in a cAMP whole-cell assay were reported. Within the series, compounds with a meta halogen on the phenyl ring (Figure 9, **20**, X = Cl, Br) were generally more active than **2** (**20**, X = H, GPR109a EC_{50} = 1.3 μM, GPR109b EC_{50} = 4.2 μM), giving a 2- to 3-fold increase in potency. Other substituents at the meta position had little effect (fluorine and methyl) or decreased potency. Replacement of the phenyl with 2- and 3-thienyl also decreased potency. However, substituted thienyl analogues were considerably more potent than **2**. In particular, 5-chloro-3-thienyl (**21**, X = Cl) and 5-bromo-3-thienyl (**21**, X = Br) were 0.2 and 0.11 μM at GPR109a and moderately selective over GPR109b (1.72 and 1.47 μM, respectively). Additionally, a small number of analogues were separated into individual enantiomers, revealing that the (+)-enantiomers were consistently more active than the corresponding (−)-enantiomers. Although the absolute stereochemistry was not determined, it could be extrapolated that the (+)-enantiomers in this case correspond to the (*S*)-stereochemistry described by Mahboubi et al.

Anthranilic Acid Derivatives

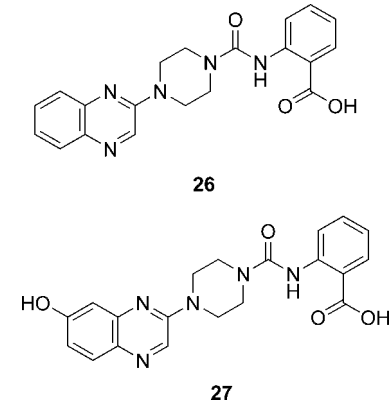
Publications describing the discovery and optimization of the anthranilic acid analogues developed at Merck have recently begun to appear. The first of these describes discovery of an anthranilic acid agonist of GPR109a (**22**, Figure 10) via high-throughput screening and the initial optimization of the phenyl side chain, resulting in compounds containing a biphenyl side chain. The biphenyl anthranilides, **23**, although more potent, suffered from relatively poor pharmacokinetic parameters as well as a significant shift of the EC_{50} in the presence of serum, suggesting that they would have weak activity in vivo. In addition, several examples were potent CYP2C8 and 2C9 inhibitors. Further optimization of the biphenyl compound led to series of biaryl agonists in which at least one aryl group was heterocyclic in order to reduce the cLogP, resulting in improved potency and PK and lowered serum shifts. The hydroxyphenyloxadiazole **24** and the hydroxypyridyloxadiazole **25** decreased plasma free fatty acids with an ED_{50} of 9 mg/kg and did not induce vasodilation at doses up to 100 mg/kg, giving a potential therapeutic index for flushing of greater than 70. This is a marked improvement over nicotinic acid, which showed an estimated therapeutic index close to 1.[67]

In a divergent optimization approach, the anthranilic acid hit led to a compound with a naphthalene substituent that demonstrated increased potency. This was further optimized by converting the linking group between the naphthyl and anthranilate portions to a piperazylurea and surveying heterocyclic replacements of the naphthalene. Because of the finding that a quinoxaline ring gave optimal activity, SAR of substitution



22 **23** **24** **25**

Figure 10. Early anthranilic acid analogies with GPR109a agonist activity.



26 **27**

Figure 11. Quinoxaline containing anthranilic acid analogues.

around the quinoxaline ring was investigated. Interestingly, as in the biaryl series, an appropriately positioned hydroxyl group gave the best inhibition of ^{3}H-nicotinic acid binding. The quinoxaline compound **27** (Figure 11) was also shown to suppress plasma free fatty acids in mice to levels lower than nicotinic acid when both were administered orally at 100 mg/kg. Again, no vasodilation was observed in mice at this dose, indicating that a therapeutic margin may exist for this class of compounds.[68]

These examples are the highest molecular weight ligands of GPR109a described to date and are redefining models of ligand binding, since it appears from activity data that the distal aromatic portion has a significant interaction with the receptor.

Merck and GlaxoSmithKline have each published patents on a series of anthranilic acid analogues as ligands for GPR109a (Figure 12).[54,59,69−73] The similarities in the structures claimed suggest that the two groups identified similar HTS derived molecular starting points. The compounds are generally anthranilic acids (**28**, **29**) or heterocyclic amino carboxylates (**30**) with an aromatic group attached to the amine via a spacer. A recent

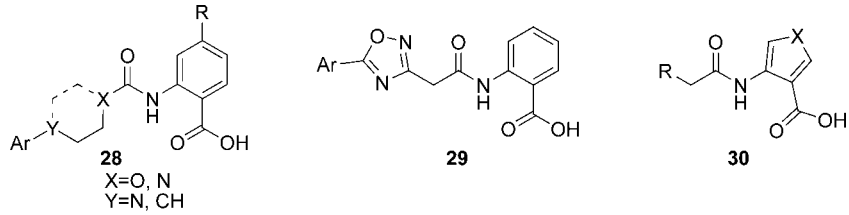


Figure 12. Further anthranilic acid derivatives with GPR109a activity.

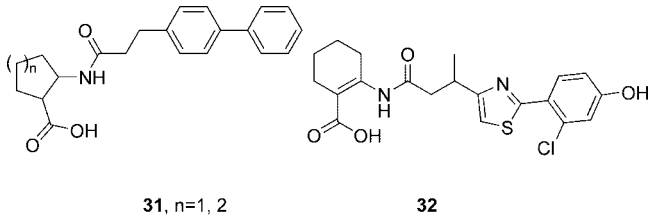


Figure 13. Anthranilic acid-like analogues.

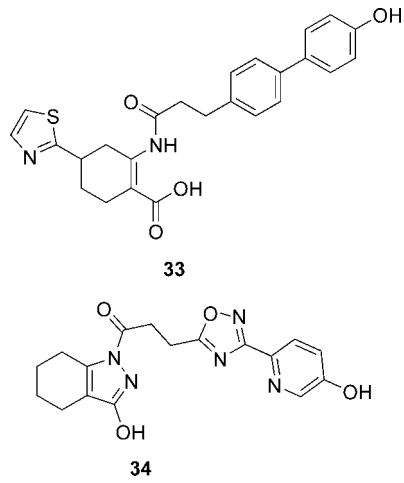


Figure 14. Further elaborations around the anthranilic acid series.

patent application from Incyte Corporation also claims thienyl analogues of the anthranilic acids as agonists of GPR109a.[74]

The most recent publication from the group at Merck gives an account of the effects of modification of the anthranilic acid core. The fully saturated cyclopentyl and cyclohexyl analogues **31** (Figure 13) were completely inactive in GPR109a receptor binding and functional assays. This was proposed to be due to the lack of a hydrogen bond between the amide NH and the carbonyl of the carboxylate. The importance of this hydrogen bond interaction was also demonstrated by the lack of activity for the *N*-methyl derivatives of the anthranilic acid compounds. However, synthesis of tetrahydroanthranilic acid analogues in which the amide and carboxylic acid remain coplanar provided compounds with good activity. The cyclohexene version **32** was around 4-fold more potent than the corresponding anthranilic acid, whereas the cyclopentene derivative was slightly less potent.

This modification provided a significant advantage over the anthranilic acids. Attachment of side chains that gave good activity in the anthranilic acid series to the tetrahydroanthranilic acid core produced compound **33** (Figure 14) with essentially equivalent potency at GPR109a but greatly reduced inhibition of P450 enzymes (CYP2C8 and -2C9 in particular) and improved pharmacokinetic properties.[75] The earlier anthranilic acid GPR109a agonists were reported to have high serum shifts, but no mention of improvement of this parameter was described for the tetrahydroanthranilic acid series. Additional patent applications originating from Merck have also been published, demonstrating a continued interest in anthranilic acid based agonists of GPR109a. These applications claim structures where the partially reduced anthranilic acid core has been further substituted.[76] This scaffold has been extended to an acylpyrazolone core (e.g., **34**), a potentially interesting acid mimetic.[77]

Other Series

As discussed above, since the discovery of GPR109a as a receptor for nicotinic acid, an increasing number of patents have appeared describing new chemical classes that interact with the receptor. Although there are not enough data reported in the applications to discern SAR, it is clear that medicinal chemistry efforts on the nicotinic acid receptor have greatly accelerated over the past few years. In addition to the anthranilate applications outlined above, Glaxo has published a number of patent applications covering multiple series of xanthine analogues (e.g., **35**, Figure 15).[78−80] An application from Schering Plough covering a series of compounds derived from barbituric acid has also published.[81] Most recently, applications from Incyte also cover a series of tricyclic compounds (**36** and **37**) derived from the corresponding xanthines.[82,83] The structural similarity of these classes of GPR109a ligands and apparent similarity in the range of substituents required for activity suggest that these classes of compounds most likely activate the receptor in a similar fashion. The lack of a carboxylic acid or obvious acid mimetic to interact with Arg-111 of the nicotinic acid receptor is notable in these classes of ligands, and at first glance, they do not appear to fit the Tunaru binding model. It is possible, however, that the nitrogen on the five-membered ring of the core structure of the xanthines is acidic enough to interact with Arg111 of GPR109A, particularly when the ring is halogenated, and that one of the ring heteroatoms forms a hydrogen bond with Ser178. For the barbituric acid derivatives, **38**, one can assume the most likely binding mode would arise from overlapping the required alkyl groups of the barbiturates (R group on **38**) and xanthines, which would provide an acidic N−H group in the former in approximately the same position as the acidic N−H in the xanthine series. However, no detailed literature reports exist to support this speculation.

GPR109b Ligands

Little medicinal chemistry has been reported on the related receptor GPR109b. The lack of suitable animal models for testing agents that act at the receptor has likely hampered development of GPR109b as a therapeutic target and decreased interest in the discovery and optimization of ligands for the receptor. Nonetheless, a few reports of GPR109b ligands have appeared in recent years. A patent from Aventis claimed a series of oxidecalincarboxylic acid derivatives **39** (Figure 16).[84] No receptor activity data were provided, and the claims broadly cover alkyl substitutions at both R_2 and R_3. Aventis has also claimed a series of substituted anthranilic acid derivatives (**40**)

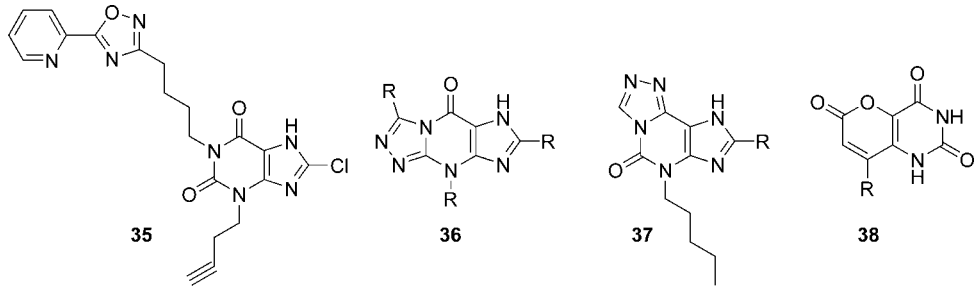


Figure 15. Xanthine and barbituric acid derivatives with GPR109A receptor activity.

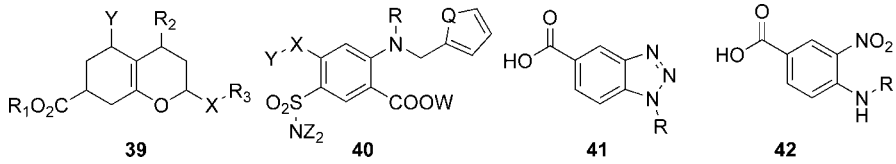


Figure 16. GPR109b ligands.

related to Furosamide as ligands of GPR109b. Again, no receptor activity data are given and the application broadly claims compounds with alkyl substitutions at positions Z and Y.[85]

A series of benzotriazolecarboxylic acids **41** has been reported by Semple and co-workers and includes the first detailed receptor activity data published.[39] 1-Isopropylbenzotriazole-5-carboxylic acid was discovered via high-throughput screening to inhibit forskolin induced cAMP production in cells stably transfected with GPR109b, with an EC_{50} of 400 nM. A number of analogues were prepared, indicating that branched chain alkyl and alkoxy containing substituents gave the highest receptor activity. Again, remarkably, none of the analogues reported had activity at GPR109a. This high degree of selectivity was rationalized in terms of the ligand size, as has been discussed above. In a followup paper, it was revealed that the synthetic intermediates in the preparation of the benzotriazole acid series, the 3-nitro-4-aminobenzoic acid analogues **42**, also had significant receptor activity.[86] The SAR in this series was somewhat similar to that observed in the benzotriazole series, suggesting that they may be making similar interactions with the receptor. Again, the compounds were devoid of activity at GPR109a. Finally, in the same paper the authors described the electronically isosteric replacement of the nitro group with a pyridyl moiety to produce 6-aminonicotinic acids. Examples from these two series are the most potent agonists of the GPR109a receptor described to date, with EC_{50} values in the 25−100 nM range, but no further pharmacology is described.

Summary

As has been discussed above, nicotinic acid has been used routinely in the treatment of dyslipidemia for several decades, despite its shortcomings. With the discovery of a GPCR with which nicotinic acid interacts (GPR109a), a flurry of effort was initiated in the search of more potent and selective agonists of the receptor. A significant amount of progress in the understanding of how to design compounds that avoid some or all of current liabilities associated with nicotinic acid therapies including flushing, fatty acid rebound, and desensitization has been made. Consequently a number of compounds that interact with the receptor but that have somewhat different profiles from nicotinic acid itself have been described. Several companies have now advanced compounds into early clinical development. The data that have been disclosed thus far could have profound implications for further progress in the field.

GlaxoSmithKline announced that the compound GSK-256073 had moved into phase I in late 2005.[87] While neither the structure of GSK-256073 nor any preclinical pharmacology has been disclosed, GSK has focused their patenting efforts around the anthranilic acid and xanthine series. GSK-256073 is being investigated for its ability to block nicotinic acid-induced flushing in healthy volunteers.[88] Such a study would imply that the compound alone did not produce flushing in humans in the initial phase I studies, and in accordance with the animal data with other nonflushing agonists described above, it might be expected that such a compound would competitively inhibit nicotinic acid-induced flushing.

14, developed jointly by Merck and Arena, entered the clinic in early 2006, and data from the phase I and phase II studies have recently been reported.[89] Single doses of **14** from 25 to 4000 mg and multiple doses (over 7 days) up to 3600 mg provided dose-related increases in plasma exposure and concomitant reductions in plasma FFA at doses above 300 mg. Single doses of 300 mg of **14** and 1 g of extended release niacin (Niaspan) provided comparable reductions in FFA. The observed FFA reductions were reproducible after 7 days of dosing, indicating there was no detectable tendency toward tachyphylaxis with this compound over the time period measured. In accordance with the preclinical data in rat and dog, treatment with **14** was well-tolerated, with only modest flushing seen at the highest doses. In the phase IIa study, **14** (2.5 g) again produced little flushing but, in contrast to historical data with extended-release niacin, showed no clinically meaningful effects on lipids or triglycerides after 4 weeks of dosing. As discussed above, decreased FFA flux to the liver has been postulated to play a key role in the beneficial lipid effects of nicotinic acid. One conclusion that could be derived from the clinical data is that a reduction in FFA alone is not sufficient to modulate global changes in plasma lipid levels over the time period tested. However, since plasma FFA levels were not measured at the end of the study, the possibility cannot be excluded that tachyphylaxis occurred between weeks 1 and 4 of dosing, although this explanation may be somewhat unlikely. Alternatively it may be postulated that differences between nicotinic acid and **14** in their ability to fully activate GPR109A contribute to the different pharmacological responses. The in vitro data clearly show that **14** is only a partial agonist and does not effectively activate MAPK pathways. If either full agonism or the ability to activate MAPK pathways or both are required for global lipid changes, these deficiencies could explain the

observed lack of clinical effect. Finally, another plausible explanation is that the activation of GPR109a is not involved in the beneficial lipid effects of nicotinic acid and that another target or combination of targets is involved. However, even with the current data, we cannot exclude the possibility that FFA lowering is required for lipid modulation but that multiple additional targets also need to be engaged. Clearly, further exploration of the mechanism by which nicotinic acid raises HDL-cholesterol is needed before we can make firm conclusions of whether other activators of GPR109a can have the same effect. Arena and Merck have recently moved a second candidate into phase I, although no details have been released as to how it may differ in profile from **14**.

In light of these initial negative data for HDL-cholesterol modulation using **14**, it is interesting that Incyte recently announced the progression of INCB-19602 (structure undisclosed) into clinical development. On the basis of the observation that infusions of FFAs in normal volunteers (to elevate blood levels to those seen in type 2 diabetes) show a dose-dependent decrease in insulin signaling in muscle with a concomitant decrease in insulin-stimulated glucose disposal, coupled with the observation that, like **14**, INCB-19602 lowered FFA in humans in phase I without rebound effects, the compound is being targeted toward type II diabetes.[90] The compound has been reported to be well-tolerated in human volunteers, without any significant flushing or drug-induced elevations of plasma prostaglandins, and had a $t_{1/2}$ of about 20 h and a steady state peak to trough ratio of about 2, thereby making it suitable for once daily administration. A phase II study in diabetic patients has recently been initiated.[91]

Further data from these and other studies will help to broaden our understanding of the key mechanism (or mechanisms) of action of nicotinic acid and GPR109A agonists and will help to determine whether the major molecular target of niacin has finally been identified or whether there are more targets remaining to be discovered.

Biographies

P. Douglas Boatman received his B.S. degree in Chemistry from Oregon State University in 1986 and his Ph.D. degree in Organic Chemistry from Texas Tech University in 1990 under the direction of Professor Robert Walkup. He did postdoctoral work culminating in the first total synthesis of Taxol at The Florida State University under the direction of Professor Robert Holton. He began his industrial career at Molecumetics, Ltd., in 1994 and focused on medicinal chemistry of peptide mimetic small molecules. In 2002 he moved to Arena Pharmaceuticals where he is currently Director of Medicinal Chemistry. His research is focused on small molecule drugs that act on G-protein-coupled receptors. He has coauthored more than 30 publications and patents.

Jeremy G. Richman has been working in the GPCR research field for a little over 19 years, starting with the cloning and characterization of opioid receptors in Henry I. Yamamura and William Roeske's laboratory at the University of Arizona. Moving to the study of the α_2-adrenergic receptors, he earned his Ph.D. in Pharmacology and Toxicology at the University of Arizona in 1998, under the guidance of John W. Regan. From there, he moved to the Vanderbilt University Medical Center for postdoctoral work characterizing GPCR nontraditional protein-interacting partners under the tutelage of Lee Limbird. He moved to Arena Pharmaceuticals in San Diego, CA, in December of 2000 where he works on the identification and characterization of GPCR modulators aimed at treating cardiovascular and metabolic diseases. He has coauthored over 20 publications and patents.

Graeme Semple received both his B.Sc. (1983) and his Ph.D. (1986) from the University of Warwick, U.K., the latter under the guidance of David Hutchinson. After postdoctoral appointments at the University of Oxford, U.K., under Gordon Lowe and the University of Bath, U.K., with Malcolm Campbell, he joined Ferring Research, Ltd., in 1989. He worked in the area of both GPCRs and enzyme inhibitors and published on modulators of the CCK and gastrin receptors and inhibitors of caspase-1. In 1998 he joined Astra Hässle in Sweden working in the gastrointestinal disease area where he stayed for 4 years, during which time the company became AstraZeneca. He joined Arena Pharmaceuticals in San Diego, CA, in 2002 where he has had a particular interest in orphan GPCRs. He is currently Vice-President of Discovery Chemistry at Arena.

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