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GPR109a agonists. Part 2: Pyrazole-acids as agonists of the human orphan G-protein coupled receptor GPR109a

Jason E. Imbriglio [a,*], Sookhee Chang [a], Rui Liang [a], Subharekha Raghavan [a], Darby Schmidt [a], Abby Smenton [a], Scott Tria [a], Thomas O. Schrader [d], Jae-Kyu Jung [d], Craig Esser [a], Tom G. Holt [b], Michael S. Wolff [b], Andrew K. P. Taggart [c], Kang Cheng [c], Ester Carballo-Jane [c], M. Gerard Waters [c], James R. Tata [a], Steven L. Colletti [a]

[a] Department of Medicinal Chemistry, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065-0900, United States
[b] Department of Drug Metabolism, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065-0900, United States
[c] Department of Cardiovascular Diseases, Merck Research Laboratories, Merck & Co., Inc., PO Box 2000, Rahway, NJ 07065-0900, United States
[d] Department of Medicinal Chemistry, Arena Pharmaceuticals, 6166 Nancy Ridge Drive, San Diego, CA 92121, United States

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ABSTRACT

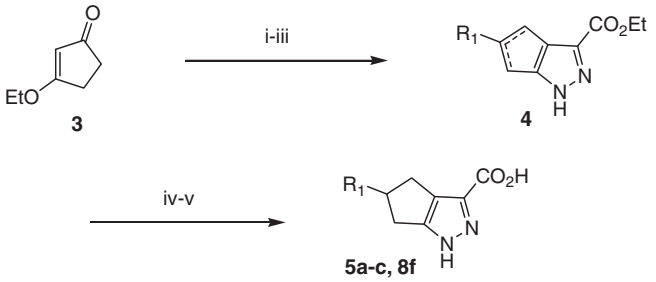
5-Alkyl and aryl-pyrazole-acids have been identified as a new class of selective, small-molecule, agonists of the human orphan G-protein-coupled receptor GPR109a, a high affinity receptor for the HDL-raising drug nicotinic acid.

Nicotinic acid (niacin) **1** has been a leading treatment for dyslipidemia and for the prevention of atherosclerosis for over 40 years.[1] Long term clinical studies have demonstrated niacin's ability to reduce mortality from coronary heart disease.[2] In spite of niacin's clinical significance, patients treated with niacin show low compliance of use due to an intense flushing side effect.[3,4] As a result, a number of drug discovery programs have focused on the development of a 'flush-free' niacin-like therapy. Despite considerable effort in the field, the absence of a niacin-related target and/or mechanism of action, has limited such investigations.

Recently, a G-protein-coupled receptor, GPR109a, was identified as a molecular target for niacin.[5] Following this breakthrough, our group initiated a drug discovery program focused on the development of a high affinity 'flush-free' niacin-like agonist. Previously, we reported on the identification of a pyrazole-tetrazole agonist **2a**, a compound that showed potential as a 'flush-free' agonist of GPR109a.[6] The intriguing pharmacology of compound **2a** inspired continued interests within this structure class. Subsequent work in the group showed that C5-alkyl- and aryl-substituted pyrazole-tetrazole derivatives had improved in vitro affinities and similar pharmacology to **2a**.[7]

With a continued interest in this structure class, we proceeded to explore further structure based improvements. In this effort, we discovered that the tetrazole moiety of compound **2a** could be suitably replaced with a carboxylic acid group. Curious as to the effect of this functional group exchange on the pharmacological profile for the class, we proceeded to develop this class of pyrazole-carboxylic acid derivatives.

Initially, we focused our effort on synthesis of the C5-alkyl and aryl derived pyrazole–acids. In this regard, generation of the series of C5-alkyl pyrazole-acids **5a–c** and the *N*-methyl pyrazole derivative **8f** was accomplished in a linear fashion from the commercially available ethoxy-cyclopentenone **3** (Scheme 1). Addition of the



Scheme 1. Reactions and conditions: (i) R^1Li; (ii) ^tBuOK, diethyl oxalate; (iii) NH_2NH_2–HCl; (iv) HCO_2NH_4, Pd–C; (v) LiOH.

* Corresponding author.
E-mail address: jason_imbriglio@merck.com (J.E. Imbriglio).

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desired alkyl lithium or the lithiated *N*-methyl pyrazole to **3** installed the desired C5-alkyl and *N*-methyl pyrazole moiety. Further elaboration of the core to the pyrazole derivative **4** was achieved via acylation with diethyl oxalate followed by condensation with hydrazine–HCl. Transfer hydrogenation reduced the olefin and saponification successfully converted the ester to the desired carboxylic acid to afford the C5-pyrazole derivatives **5a–c** and **8f**.

Syntheses of the C5-aryl-pyrazole-acids **8a**–**e** were accomplished via the readily available iodocyclopentenone **6** (Scheme 2). Suzuki coupling of the corresponding aryl boronic acid to enone **6** afforded the desired aryl-substituted cyclopentenone **7**. Conversion of enone **7** to the desired pyrazole-acids was achieved, following previously outlined conditions, via acylation of the enone with diethyl oxalate, condensation with hydrazine–HCl, transfer hydrogenation, and a final saponification.

The preparation of N-linked pyrazole and triazole derivatives **11a** and **11b** is outlined in Scheme 3. Treatment of commercially available cyclopentenone **9** with either commercially available pyrazole or triazole afforded the desired adduct **10**. Following previously described conditions, ketone **10** was further elaborated to the desired class of C5-substituted pyrazole-acids.

As illustrated in Table 1, the in vitro affinities for this pyrazole-acid series compared favorably with the similar class of pyrazole-tetrazoles. In this regard, *n*-propyl derivative **5a** (0.25 μM and 0.38 μM) showed good affinity on both the human receptor (GPR109a, hNBA) and murine receptor (PUMA-G, mNBA), while the branched alkyl derivatives **5b** (0.99 μM and 1.7 μM) and **5c** (1.1 μM and 1.3 μM) showed only modest affinity for the niacin receptor.

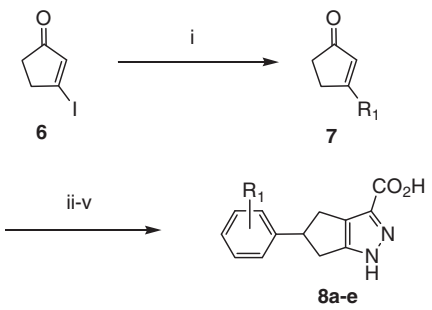
Further studies into the C5 phenyl series of molecules showed parallel trends to the pyrazole-tetrazole class. As demonstrated in Table 1, the phenyl substituted pyrazole-acid **8a** (0.15 μM and 0.20 μM) showed improved affinity for both mouse and human receptors.

The 2,3,5-trifluoro analog **8b** (0.03 μM and 0.02 μM), showed excellent intrinsic affinity for GPR109a, and a marked improvement over the pyrazole-tetrazole derivative **2b**. However, despite the promising intrinsic activity of compound **8b**, when screened in our competition binding assay in the presence of 4% human serum, compound **8b** showed an eightfold reduction in affinity for the receptor. The intrinsic affinity of pyrazole-tetrazole derivative **2b** was similarly affected by the presence of serum. Concerned with the role this serum shift effect may have on the in vivo efficacy, our focus turned towards identifying a *low-serum shifted* agonist.

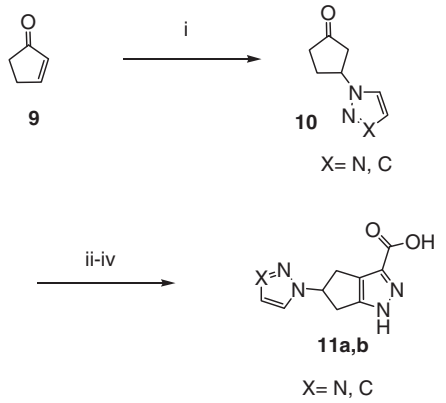
With this goal in mind, we proceeded to explore the C5-heteroaryl class of pyrazole-acids. Initial efforts, focused on a thiophene replacement, demonstrated little improvement. The 2-thiophene derivative **8c** (0.25 μM and 0.24 μM), a surrogate to the phenyl moiety, demonstrated only a modest boost in activity, when compared to **2a**. In addition, compound **8c** demonstrated a further reduction in affinity when assayed in the presence of human serum. Similarly, while thiophene analog **8d** (0.08 μM and 0.09 μM) showed improved intrinsic affinity for GPR109a, when compared with **2a**, compound **8d** also demonstrated reduced in vitro activity when assayed in the presence of human serum.

We proceeded to explore the C5 *N*-methyl pyrazole derivatives. While the 4-*N*-methyl pyrazole derivative, **8e** (1.6 μM and 2.1 μM), showed only modest intrinsic affinity for the niacin receptor, more intriguing was the limited effect serum had on the compound's intrinsic affinity. Even more promising was the 5-*N*-methyl pyrazole-acid **8f** (0.45 μM and 0.39 μM) which showed good intrinsic affinity and nearly comparable activity in the presence of serum. Finally, the C-5-*N*-pyrazole and *N*-triazole derivatives **11a** (3.4 μM and 1.9 μM) and **11b** (5.2 μM and 4.0 μM) demonstrated only modest affinity for the receptor, despite a minimal serum shift effect.

In light of the promising in vitro activity for the series, we proceeded to investigate the ADME properties of select members of the class. In this regard, the mouse pharmacokinetic (mPK) profiles

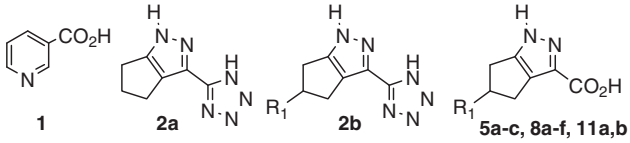


Scheme 2. Reactions and conditions: (i) $RB(OH)_2$, $Pd(dppf)Cl_2$; (ii) ^tBuOK, diethyl oxalate; (iii) NH_2NH_2–HCl; (iv) HCO_2NH_4, Pd–C; (v) LiOH.



Scheme 3. Reactions and conditions: (i) pyrazole or triazole, 70 °C; (ii) ^tBuOK, diethyl oxalate; (iii) NH_2NH_2–HCl; (iv) LiOH.

Table 1
Affinity of C5 substituted pyrazole-acids for GPR109[a]



Compds	R_1	IC_{50}[b] (μM)	
		mNBA	hNBA
1	—	0.14	0.14(0.14)[c]
2a	—	1.2	1.5
2b	*ent*-2,3,5-F-Ph	0.07	0.08(4.0)[c]
5a	*n*-Propyl	0.25	0.38(0.75)[c]
5b	*i*-Propyl	0.99	1.7(>1 μM)[c]
5c	*sec*-Butyl	1.1	1.3(>1 μM)[c]
8a	Ph	0.15	0.20(2.7)[c]
8b	2,3,5-F-Ph	0.03	0.02(0.15)[c]
8c	2-Thiophene	0.25	0.24(1.0)[c]
8d	3-Thiophene	0.08	0.09(1.0)[c]
8e	4-*N*-Methyl pyrazole	1.6	2.1(2.3)[c]
8f	*ent*-5-*N*-Methyl pyrazole	0.45	0.39(0.45)[c]
11a	*N*-Pyrazole	3.4	1.9(2.0)[c]
11b	*N*-Triazole	5.2	4.0(5.3)[c]

[a] Values are an average of two or greater. Individual assays.
[b] [^{3}H]-Nicotinic acid binding competition assay.
[c] [^{3}H]-Nicotinic acid binding competition assay with 4% human serum.

Table 2
Mouse[a] pharmacokinetics of pyrazole-acids

Compds	F[b] (%)	Cl_p (mL/kg/min)	V_{dss} (L/kg)	$t_{1/2}$[c] (h)
Niacin	100	145	1.0	0.02
2b	10	27	1.1	2.4
8b	53	24	9.3	—
8f	27	86	4.2	2.3

[a] C57BL/6-mice.
[b] Dose: 1 mg/kg iv; 2 mg/kg po.
[c] $t_{1/2}$ = plasma half-life$_{(0-8\ h)}$.

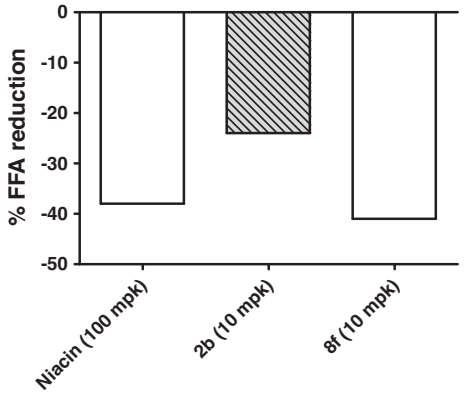


Figure 1. Mouse pFFA reduction studies.

of lead candidates **8b**, a compound with excellent intrinsic affinity but an eightfold serum shift effect and compound **8f**, a compound with good intrinsic affinity and minimal serum-effect, were studied.

As illustrated in Table 2, both **8b** and **8f** showed mPK profiles that compared favorably with niacin and pyrazole-tetrazole **2b**. The high affinity agonist **8b** demonstrated good bioavailability and low clearance when compared to niacin. Similarly, agonist **8f** with a promising in vitro profile and low-serum shift effect, showed modest results across all parameters.

In an effort to understand the effect this serum shift might be having on the in vivo efficacy, we performed a head-to-head comparison of compounds **2b** and **8f** in our mouse PD assay. In this regard, we dosed compound **8f** in our mouse plasma free fatty acid assay (pFFA) and our mouse vasodilation assay (mVD). As illustrated in Figure 1, six male C57 B1/6 mice were each dosed at 10 mpk (IP) for 15 min with **8f** and compared to mice dosed, 10 mpk (IP) of **2b**, and 100 mpk (IP) with niacin and the characteristic reduction in plasma free fatty acids was measured. In the case of compound **8f**, the mice that were treated showed a 41% reduction in plasma free fatty acids at 10 mpk, compared to a 21% reduction in plasma free fatty acid upon administration of **2b** and a 38% reduction with niacin.

Having demonstrated the ability of agonist **8f** to effectively lower plasma free fatty acids in our mouse PD model, further investigations hinged on whether or not this class of agonists would elicit a flushing response in our mouse vasodilation assay. With this goal in mind, compound **8f** was administered to eight mice at 30 mpk

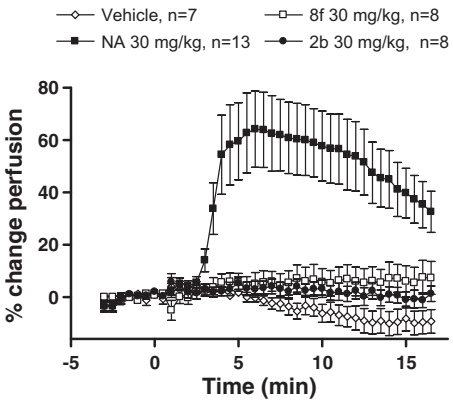


Figure 2. Mouse vasodilation (mVD).

(IP) for 15 min, three times the dose for FFA reduction. As illustrated in Figure 2, niacin administered in 13 mice at 30 mpk (IP) showed an 80% change in perfusion,[8] characteristic of a flushing response in the mouse. In contrast, compound **8f** showed no change in perfusion under similar experimental conditions.

In summary, we have identified a new class of pyrazole-acids that act as selective agonists of GPR109a. In particular, optimization of the pyrazole-acid series resulted in the identification of compound **8f**, a potent, low-serum shift, and flush-free agonists of GPR109a that demonstrated superior in vivo efficacy when compared to previous members of the class. Further investigations are currently underway.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.06.041.

References and notes

1. Carlson, L. A. *J. Int. Med.* **2005**, *258*, 94.
2. Tavintharan, S.; Kashyap, M. L. *Curr. Atheroscler. Rep.* **2001**, *3*, 74.
3. Knopp, R. H. *Am. J. Cardiol.* **2000**, *86*, 51L.
4. For a discussion on the clinical use of the D_2 receptor antagonist laropripant as a means of suppressing the nicotinic acid-induced vasodilation in humans, refer to: Paolini, J. F.; Mitchel, Y. B.; Reyes, R.; Kher, U.; Lai, E.; Watson, D. J.; Norquist, J. M.; Meehan, A. G.; Bays, H. E.; Davidson, M.; Ballantyne, C. M. *Am. J. Cardiol.* **2008**, *101*, 625.
5. (a) Lorenzen, A.; Stannek, C.; Lang, H.; Andrianov, V.; Kalvinsh, I.; Schwabe, U. *Mol. Pharmacol.* **2001**, *59*, 349; (b) Wise, A.; Foord, S. M.; Fraser, N. J.; Barnes, A. A.; Elshourbagy, N.; Eilert, M.; Ignar, D. M.; Murdock, P. R.; Steplewski, K.; Green, A.; Brown, A. J.; Dowell, S. J.; Szekeres, P. G.; Hassall, D. G.; Marshall, F. H.; Wilson, S.; Pike, N. B. *J. Biol. Chem.* **2003**, *278*, 9869; (c) Soga, T.; Kamohara, M.; Takasaki, J. M.; Shun-Ichiro, S.; Tetsu, O.; Takahide, H.; Hideki, M. A.; Matsushime, H.; Furuichi, K. *Biochem. Biophys. Res. Commun.* **2003**, *303*, 364.
6. Semple, G.; Skinner, P. J.; Gharbaoui, T.; Shin, Y. J.; Jung, J. K.; Cherrier, M. C.; Webb, P. J.; Tamura, S. Y.; Boatman, P. D.; Sage, C. R.; Schrader, T. O.; Chen, R.; Colletti, S. L.; Tata, J. R.; Waters, G.; Cheng, K.; Taggart, A. K.; Cai, T. Q.; Jane, E. C.; Behan, D. P.; Connolly, D. T.; Richman, J. G. *J. Med. Chem.* **2008**, *51*, 5105.
7. Imbriglio, J. E.; Chang, S.; Liang, R.; Raghavan, S.; Schmidt, D.; Smenton, A.; Tria, S.; Schrader, T. O.; Jung, J. K.; Esser, C.; Taggart, A. K. P.; Cheng, K.; Carballo-Jane, E.; Waters, M. G.; Tata, J. R.; Colletti, S. L. *Bioorg. Med. Chem. Lett.* **2009**, 2121.
8. Measured using a Periscan PIMII Laser Doppler Perfusion Imager system.