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Pyrido pyrimidinones as selective agonists of the high affinity niacin receptor GPR109A: Optimization of in vitro activity

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ABSTRACT

Pyrido pyrimidinones are selective agonists of the human high affinity niacin receptor GPR109A (HM74A). They show no activity on the highly homologous low affinity receptor GPR109B (HM74). Starting from a high throughput screening hit the in vitro activity of the pyrido pyrimidinones was significantly improved providing lead compounds suitable for further optimization.

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Niacin, a vitamin of the B complex, has been used for almost 50 years as an anti-dyslipidemic drug with a favorable profile for all lipoprotein classes. In particular, niacin is the most potent agent to raise high density lipoprotein cholesterol (HDL-c).[1–3] Numerous clinical studies have shown the beneficial effects of niacin, namely a reduction of coronary artery disease and overall mortality.[4,5] However, extensive use of niacin is limited due to transient skin vasodilatation (flushing) affecting most of the patients.[6] Extended release formulations of niacin (e.g., Niaspan®) show a reduction in flushing events, but are not able to overcome this side effect completely.[4,7] In addition, doses of extended release niacin formulations are limited due to hepatotoxicity caused by niacin metabolites.[8,9] It has been proposed that niacin's main mode of action is inhibiting lipolysis in the adipose tissue.[2] As a consequence, free fatty acid (FFA) levels in plasma and liver are lowered leading to a decreased production of very low density lipoprotein cholesterol (VLDL-c). This results in a reduction of total plasma cholesterol (TC), triglyceride (TG), and LDL-c levels. Due to the lower number of TG rich lipoprotein particles in plasma, fewer modifications of the HDL-c particles via the cholesteryl ester transfer protein (CETP) occur, which leads to a decrease in HDL-c catabolism.[10,11] A niacin-mediated direct inhibition of lipoprotein A-I HDL-c (LpAI-HDL-c) particle uptake by the liver, which would contribute to the overall HDL-c raising properties of niacin, has also been proposed.[12] In addition, the anti-dyslipidemic effects of niacin are discussed in the context of its diacylglycerol acyltransferase 2 (DGAT2) inhibitory effects.[3]

In 2003, three independent groups identified GPR109A (HM74A) and GPR109B (HM74), two GPCRs, as the receptors for niacin.[13–15] GPR109A, which is present in all species, is a high affinity receptor for niacin.[14,16] GPR109B, which is only present in human and chimpanzee, is a low affinity receptor for niacin.[17,18] The lack of this ortholog in rodents suggests that GPR109A is sufficient for the anti-lipolytic activity of niacin in vivo.[14,19] However, deletion of the GPR109A-receptor in mice showed that this receptor can be responsible for both effects of niacin: lipid lowering as well as prostaglandin-mediated transient skin vasodilation.[20] Several approaches to dissect the desired dyslipidemic effects from the undesired flushing effect are under discussion: (i) avoid high c_{max} values (e.g., like with immediate release niacin)[21,22] and strive for low c_{max}/c_{trough} ratios (e.g., slow release niacin)[22] assuming that c_{max} drives the flushing; (ii) combine niacin or a novel GPR109A agonist with aspirin or a prostaglandin D2 inhibitor;[23] (iii) use positive allosteric agonists;[24] (iv) develop partial GPR109A agonists.[25] Supported by the comparison of immediate release niacin versus sustained release niacin, we

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hypothesized that a pharmacokinetic profile which is characterized by a low c_{max}/c_{trough} ratio, a very low volume of distribution and a very low clearance is essential to achieve a separation between desired and side effect. Immediate release niacin (high c_{max}/c_{trough}) causes flushing in >90% of all patients whereas sustained release also called 'no flush' niacin (low c_{max}/c_{trough}) avoids flushing but leads to severe liver toxicity.[26] Since this liver toxicity is linked to a niacin specific metabolite we were confident to overcome this issue with a structurally different GPR109A agonist. To probe the PK hypothesis a chemistry program based on the high throughput screening hit **1** was initiated. The optimization of the in vitro activity of these pyrido pyrimidinones on GPR109A will be described in this Letter.

Receptor-based modeling driven mutational studies supported the medicinal chemistry efforts. Niacin and pyrido pyrimidinone **1** were docked into a 3D receptor pharmacophore model of the GPR109A transmembrane binding pocket (Fig. 1). The binding mode hypothesis of niacin is in agreement with the work of Tunaru et al.[17] and in-house site-directed mutagenesis studies. It proposes an interaction of the carboxyl group of nicotinic acid with R111$^{3.36}$ at TM3 and a hydrogen bond between the nitrogen of the pyridine ring and the hydroxyl group of the S178$^{45.51}$ at EC2. The pyridine ring is embedded between TM2/EC1 and TM7 (Y284$^{7.43}$). The additional critical determinants, F276$^{7.35}$ and amino acids in the EC1 (N86, W91), of the niacin binding pocket are in close proximity to the hypothesized binding mode of niacin, but are not shown due to reasons of clarity. In addition, a possible binding mode for pyrido pyrimidinone **1** is presented. The nitrogens of the pyridine and pyrimidinone ring mimic the carboxyl group of the nicotinic acid interacting with R111$^{3.36}$ at TM3 and the carbonyl group of the pyrimidinone forms a hydrogen bond with the hydroxyl group of the S178$^{45.51}$ at EC2. The trifluoro substituent points towards the binding pocket arranged by TM5 and TM6 demonstrates the possibility to extend this exit vector.

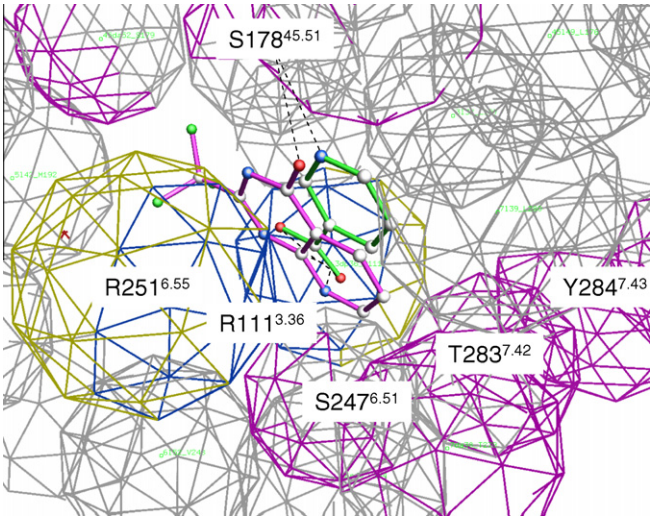


Figure 1. 3D receptor pharmacophore model of the GPR109A transmembrane binding pocket. The binding pocket is docked with niacin (green) and pyrido pyrimidinone **1** (magenta). For illustration purposes, the two compounds are not completely overlaid rather shown at parallel positions. Important residues are labeled in Ballesteros–Weinstein nomenclature in addition to the one letter amino acid code. The amino acids of the GPR109A transmembrane binding pocket are shown as spheres, whereas the size corresponds to the size of the side chain of the amino acids. The pharmacophoric spheres are colored according to their pharmacophoric properties. Hydrophobic amino acids (F, P, M, A, L, I, G, V, and W) gray, H-donor/acceptor (Y, T, S, H, C, N, and Q) magenta, H-bond donors with a positive charge (R) yellow/blue. Possible H-bond interactions are presented as dotted lines. C atoms of niacin and pyrido pyrimidinone **1** are displayed in white, oxygen in red, nitrogen in blue, and fluorine in green.

HTS hit **1** already has interesting binding affinities to the human and rat receptor as well as good functional activity (Table 1).

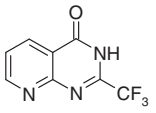
Unfortunately, clearance determined in vitro from rat liver microsome incubations was high. This translated also into a high clearance in vivo which was accompanied by a short plasma half-life in rat after iv dosing leading overall to a high c_{max}/c_{trough} value. Therefore, further in vivo profiling was prohibited and an in vitro optimization program was initiated. As expected from the proposed binding mode derived from the mutational studies, the pyrido pyrimidinone scaffold is essential for activity. Replacement of any of the nitrogen atoms by a carbon atom or alkylation of the pyrimidinone-NH rendered the scaffold significantly less active or even inactive (data not shown). Moreover, the trifluoromethyl group could not be replaced with small alkyl, acyl, aryl, alkoxy, and alkylamino groups without substantial loss of activity. Based on the modeling hypothesis, the possibility to extend this exit vector was probed and substituents containing a phenyl group attached to a simple alkyl-chain linker were identified as suitable replacements for the trifluoro-methyl group (Table 2).

A linker length of 4 and 5 atoms was found to be optimal (**5** and **6**) compared to the only weakly active compounds with longer linkers (**7** and **8**) or the inactive compounds with shorter linker chains (**2**–**4**). In a next step incorporation of hetero-atoms in the linker was explored (Table 3). An amide linker as in **14** and different ether linkers improved affinity compared to **5** and **6** with the most interesting compounds being **10** and **13**.

To further improve the activity of compounds **10** and **13** the influence of substitution at the phenyl ring was investigated with small substituents. Whereas the introduction of methoxy-groups was not beneficial, chlorine or fluorine substitution in *ortho* or *meta* position led to compounds with very high affinity to the GPR109A-receptor such as **13**-*o*-Cl and **10**-*m*-Cl (Tables 4 and 5).

These compounds also exhibited very good functional activity at the human and rat receptor. Unfortunately, their in vitro microsomal clearance was not improved compared to **1** (Table 6). Therefore, the slightly less potent but metabolically more stable compound **10**-*p*-F was selected for in vivo PK profiling. Surprisingly, the half-life after iv dosing was even shorter than that of **1**, despite lower clearance in microsomes. Partly, this can be ex-

Table 1
In vitro pharmacology and PK profile of HTS hit **1**

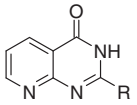


1

IC_{50}[a,b] (hGPR109A)	1.3 μM
IC_{50}[a,b] (hGPR109B)	>50 μM
EC_{50}[c] (GTPγS, hGPR109A)	1.7 μM
IC_{50}[a,b] (rGPR109A)	0.4 μM
EC_{50}[c] (GTPγS, rGPR109A)	0.06 μM
CL_{int}[d] (*h*, μl/min/mg)	4.9
CL_{int}[e] (*r*, μl/min/mg)	58
CL[f] (ml/min/kg)	84
c_{max}[f] (ng/ml)	8800
V_{ss}[f] (l/kg)	0.4
$t_{1/2}$[f] (h)	0.5

[a] Inhibition of radioligand binding.
[b] The variability of the IC_{50} determinations was on average ±10%.
[c] All GTPγS measurements were performed at least in duplicates.
[d] From incubations with human liver microsomes; mg = mg of protein.
[e] Rat liver microsomes.
[f] The HTS hit **1** was administered to Wistar rats for intravenous bolus administration. Rats ($N = 2$ per dose) were dosed intravenously with 5 mg/kg and blood samples were taken up to 24 h by jugular vein cannulation.

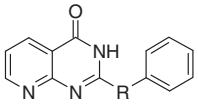
Table 2
Replacement of the CF_3 group of **1**

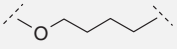
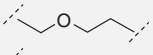
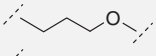
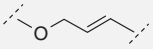
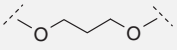
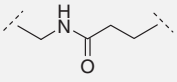


Compounds	R	IC_{50}[a] (μM)
2	$-(CH_2)$Ph	>50
3	$-(CH_2)_2$Ph	>50
4	$-(CH_2)_3$Ph	>50
5	$-(CH_2)_4$Ph	4.4
6	$-(CH_2)_5$Ph	5.9
7	$-(CH_2)_6$Ph	19
8	$-(CH_2)_7$Ph	48

[a] Inhibition of radioligand binding.

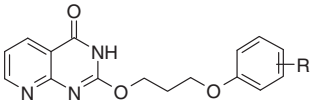
Table 3
Exploration of linker chain analogs of **5** and **6**



Compound	R=	IC_{50}[a] (μM)
9		0.84
10		0.67
11		>50
12		0.37
13		0.13
14		0.92

[a] Inhibition of radioligand binding.

Table 4
SAR exploration of aromatic ring substituents in **13** (inhibition of radioligand binding, μM)



13
13 (R = H): 0.13

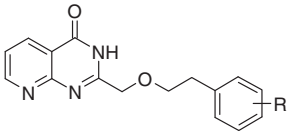
R=	F	Cl	Me	OMe
ortho	0.25	0.015	0.45	n.d.
meta	0.37	0.033	0.86	n.d.
para	1.1	0.23	4.7	6.3

n.d., not determined.

plained by a fivefold lower volume of distribution of compound **10**-*p*-F compared to compound **1**. Another reason however is a mismatch of microsomal and in vivo clearance that was later found to originate from efficient extra-hepatic metabolism; the elucidation of this elimination mechanism, and the further optimization of metabolic stability, will be the subject of a later publication.

Representative syntheses of pyrido pyrimidinones are outlined in Schemes 1–4 and follow two general routes. On one hand, side chains can be introduced by N-acylation of 2-amino-nicotinonitrile

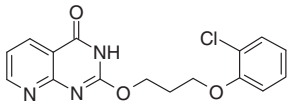
Table 5
SAR exploration of aromatic ring substituents in **10** (inhibition of radioligand binding, μM)



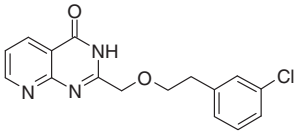
10
10 (R = H): 0.67

R=	F	Cl	Me	OMe
ortho	0.22	0.60	0.44	1.7
meta	0.23	0.05	0.41	1.5
para	0.63	1.2	4.3	4.4

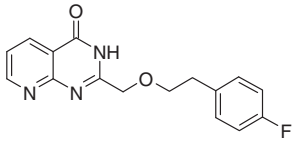
Table 6
In vitro pharmacology and PK profiles of compounds **13**-*o*-Cl, **10**-*m*-Cl, and **10**-*p*-F



13-o-Cl



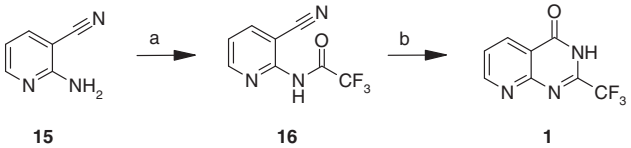
10-m-Cl



10-p-F

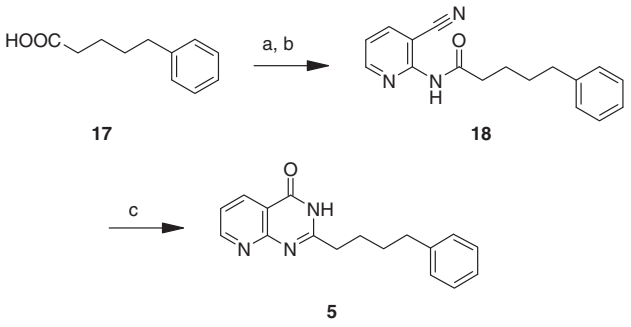
	13-*o*-Cl	**10**-*m*-Cl	**10**-*p*-F
IC_{50}[a] (hGPR109A, μM)	0.015	0.05	0.63
IC_{50}[a] (hGPR109B)	33 μM	n.d.	>50 μM
EC_{50} (GTPγS, hGPR109A, μM)	0.05	0.34	2.5
IC_{50}[a] (rGPR109A, μM)	1.4	0.64	2.7
EC_{50} (GTPγS, rGPR109A, μM)	0.19	0.14	1.6
CL_{int}[b] (*h*, μl/min/mg)	201	24	11
CL_{int}[c] (*r*, μl/min/mg)	165	60	18
CL[d] (ml/min/kg)	n.d.	n.d.	30
c_{max} (ng/ml)[d]	n.d.	n.d.	9700
V_{ss}[d] (l/kg)	n.d.	n.d.	0.07
$t_{1/2}$[d] (h)	n.d.	n.d.	0.05

n.d., not determined.
[a] Inhibition of radioligand binding.
[b] From incubations with human liver microsomes; mg = mg of protein.
[c] Rat liver microsomes.
[d] The compounds were administered to Wistar rats for intravenous bolus administration. Rats ($N = 2$ per dose) were dosed intravenously with 5 mg/kg and blood samples were taken up to 24 h by jugular vein cannulation.

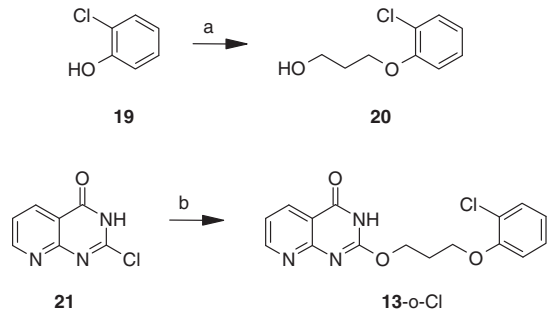


15 **16** **1**

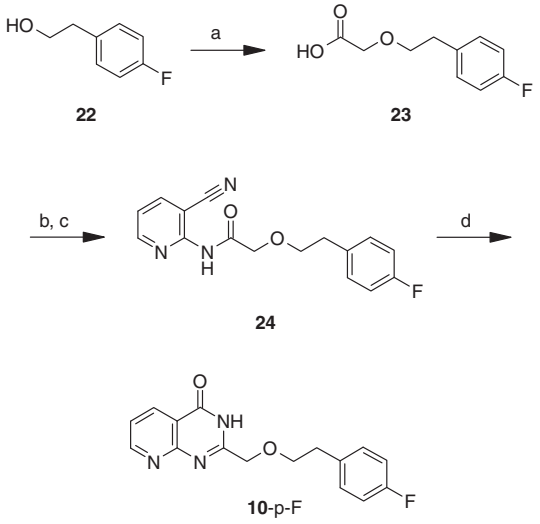
Scheme 1. Reagents and conditions: (a) $(CF_3CO)_2O$, pyridine, THF, 0 °C to rt o.n., 98%; (b) NaOH, H_2O_2, EtOH/H_2O, 4 h reflux then rt o.n., 76%.[27]



Scheme 2. Representative procedure for the preparation of 2-substituted pyrido pyrimidinones from carboxylic acids. Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, 2 h, rt; (b) add to **15**, pyridine, CH_2Cl_2, rt o.n., 75%; (c) NaOH, H_2O_2, EtOH/H_2O, 3 h reflux, 34%.[28]



Scheme 3. Representative procedure for the preparation of **13** from **21**.[29] Reagents and conditions: (a) $Cl(CH_2)_3OH$, K_2CO_3, DMF, 60 °C o.n., 76%; (b) **20**, KOtBu, DMSO, 120 °C o.n., 22%.[28,29]



Scheme 4. Representative procedure for the preparation of **10**. Reagents and conditions: (a) NaH, $ClCH_2COOH$, DMF, 1 h, 60 °C, 58%; (b) $(COCl)_2$, DMF, CH_2Cl_2, 2 h, rt; (c) add to **15**, pyridine, CH_2Cl_2, 0 °C to rt o.n., 49%; (d) K_2CO_3, H_2O_2, MeOH/DMSO, 0 °C to rt, 2.5 h, 56%.[28]

15 with the appropriate acid derivatives. The resulting amide derivatives **16**, **18**, or **24** can be cyclized to the corresponding pyrido pyrimidinones **1**, **5**, and **10**-*p*-F using hydrogen peroxide under basic conditions. On the other hand, oxygen-linked side chains can be introduced by nucleophilic substitution reaction using known chloro-derivative **21** and appropriate alcohols such as **20** to obtain compounds as **13**-*o*-Cl.

In summary, a novel class of agonists for the human GPCR, GPR109A (HM74A), the pyrido pyrimidinones has been discovered and optimized. These molecules show no activity on the highly homologous low affinity receptor GPR109B (HM74). Based on the high throughput screening hit **1** and supported by receptor-based modeling the key pharmacophore moieties of the pyrido pyrimidinones have been identified and a first comprehensive SAR study of such molecules was established making use of human GPR109A binding and GTPγS assays. Elongation at the 2-position of the pyrido pyrimidinone led to molecules with significantly improved in vitro activity. Although selected compounds of this class, for example, **10**-*p*-F, show an improved microsomal clearance compared to the HTS hit compound **1**, this is not mirrored by clearance and half-life in rat pharmacokinetic studies. Progress made to address this issue in order to come up with GPR109A agonists which avoid high c_{max} values, have low c_{max}/c_{trough} ratios and therefore might be able to dissect desired dyslipidemic effects from the undesired flushing effect will be reported in due course.

Acknowledgments

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