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Arylpiperazines as fatty acid transport protein 1 (FATP1) inhibitors with improved potency and pharmacokinetic properties

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ABSTRACT

The discovery and optimization of a novel series of FATP1 inhibitors are described. Through the derivatization process, arylpiperazine derivatives **5k** and **12a** were identified as possessing potent in vitro activity against human and mouse FATP1s as well as excellent pharmacokinetic properties. In vivo evaluation of triglyceride accumulation in the liver, white gastrocnemius muscle and soleus is also described.

Skeletal muscle is one of the most promising target tissues for the treatment of insulin resistance as it accounts for the largest proportion of body mass and uptakes glucose in an insulin-dependent manner. However, no drug acting directly on skeletal muscle is presently available for the treatment of insulin resistance. Fatty acid transport protein 1 (FATP1) is a transmembrane protein with acyl-CoA synthase activity, that is, highly expressed in skeletal muscle.[1] FATP1 is reported to play a major role in uptaking and metabolizing fatty acids through their conversion to the corresponding acyl-CoA in skeletal muscle. In FATP1-deficient mice, less accumulation of intramuscular fatty acyl-CoA was observed under a high-fat-diet (HFD)-fed condition, which made them less insulin resistant.[2] Therefore, the inhibition of FATP1 is an attractive therapeutic target for the treatment of insulin resistance. In a previous paper, we reported the potent triazole-based FATP1 inhibitor **1** (Fig. 1) with moderate pharmacokinetic parameters.[3] To acquire potent anti-insulin-resistance activity in vivo, further improvement of pharmacokinetic parameters was required. This led us to discover a new scaffold with an improved pharmacokinetic profile for the evaluation of in vivo efficacy. In this Letter, we describe the structure–activity relationship (SAR) of novel arylpiperazine derivatives as FATP1 inhibitors with improved pharmacokinetic parameters.

Through the high-throughput screening (HTS) of our corporate library, phenylpiperazine derivatives **2** and **3** were identified (Fig. 1). In an in vitro assay, to validate the direct inhibitory activity against FATP1, cell-free fatty acyl-CoA synthase (ACS) activity was evaluated with purified human or mouse FATP1 protein, because the transportation of fatty acid by FATP1 is known to involve ACS synthesis.[4] Although tetrahydrobenzothiazole **2** possessed potent in vitro activity against human FATP1, **2** showed moderate in vitro activity against mouse FATP1.[5] Furthermore, as the mouse microsomal stability of **2** was 30%,[6] it was also necessary to address this issue. On the other hand, imidazopyridine **3** was needed for the improvement of in vitro activity against both species. Thus, we initiated the derivatization of **2** and **3** to improve in vitro activity as well as microsomal stability.

First, the derivatization of compound **2** was commenced because of the potent in vitro inhibitory activity against human FATP1. Since the tetrahydrobenzothiazole moiety of compound **2** might cause microsomal instability, the attenuation of lipophilicity was examined, as described in Table 1. Simple removal of the methyl group in **2** maintained mouse in vitro activity of 4.0 μM with reduced activity against human FATP1 (compound **4a**). Since dimethyl derivative **4b** showed a further fivefold reduction of human in vitro activity, while thiazole **4c** lost its in vitro potency, the bicyclic structure in **4a** plays a major role for in vitro activity against human FATP1. Furthermore, partial saturation of the bicyclic ring in **4a** was also required, because the introduction of the benzothiazole ring led to the disappearance of mouse in vitro

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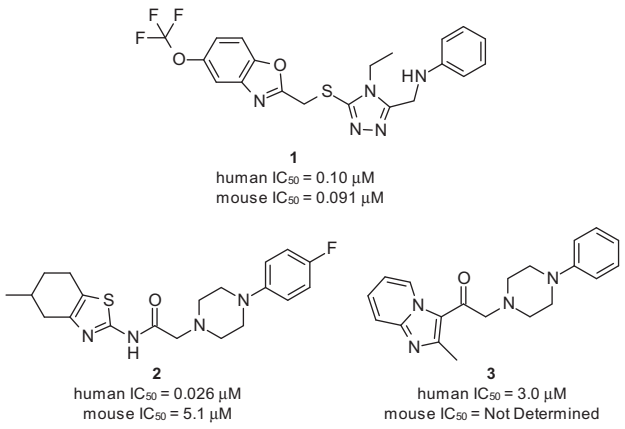


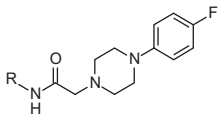
Figure 1. Triazole-based FATP1 inhibitor **1** and HTS hits **2** and **3** with FATP1 IC_{50} values.

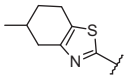
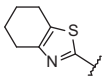
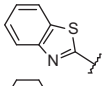
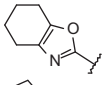
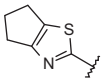
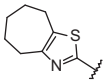
activity (compound **4d**). Tetrahydrobenzooxazole **4e**, an oxazole analogue of **4a**, retained fair human and mouse in vitro activity (0.18 and 5.4 μM, respectively). Compared to tetrahydrobenzothiazole **4a**, the five-membered ring derivative **4f** lost in vitro activity against mouse FATP1, and reduced human activity was observed in the seven-membered ring analogue **4g**. Thus, the tetrahydrobenzothiazole ring seemed to be the most suitable ring system in this position.

Then, further modifications of compound **4a** were performed, as indicated in Table 2. The 4-fluoro substituent on the phenyl ring is important for in vitro activity, because phenyl derivative **5a** showed decreased human and mouse in vitro activity and the 4-methyl substituent did not improve the activity (compound **5b**). Moreover, replacement with the 3-fluoro substituent resulted in a complete loss of in vitro potency (compound **5c**). Similarly, no in vitro activity was observed in the benzoyl and cyclohexyl derivatives (**5d** and **5e**). For further enhancement of in vitro activity and microsomal stability, the replacement of the benzene ring with heterocycles was also examined. Among pyridine derivatives **5f**, **5g** and **5h**, only 2-pyridyl derivative **5f** retained in vitro activity. Due to the fact that 2-thiazole **5j** also possessed moderate activity as with 2-pyridine **5f**, an aromatic nitrogen atom in this position can be installed. Nevertheless, 2-pyrimidyl derivative **5i** lost all in vitro activity. These results led us to synthesize fluoro-substituted 2-pyridyl compounds **5k** and **5l** to find a several-fold increase in in vitro activity against both species. Moreover, the microsomal stability of **5k** was improved to 63%.[6] Although the log*D* value of tetrahydrobenzooxazole **5l** was further reduced to 2.7, the microsomal stability was not improved compared to tetrahydrobenzothiazole **5k**. To improve the microsomal stability of **5k** by increasing the steric hindrance, *N*-alkyl derivatives **5m** and **5n** were synthesized. Methyl derivative **5m** retained in vitro potency with similar microsomal stability, while ethyl derivative **5n** indicated a sharp loss of in vitro activity.

The synthesis of arylpiperazine derivatives listed in Tables 1 and 2 (**4a–4g, 5a–5n**) is shown in Scheme 1. Compounds **4a–4e** (Table 1) were synthesized in two simple steps. After preparing thiazoyl or oxazoyl amine **6** in the known manner,[7] acylation with chloroacetyl chloride, followed by S_N2 reaction with 4-fluorophenylpiperazine **8** provided compounds **4a–4e**. Five- and seven-membered ring derivatives **4f** and **4g** were synthesized from carboxylic acid **9**. Starting from 4-fluorophenyl piperazine **8**, N-alkylation

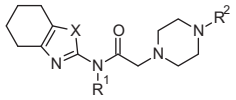
Table 1
IC_{50} values of FATP1 inhibitors **2** and **4a–4g**[4]

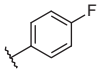
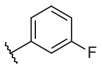
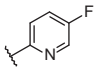
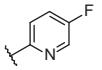
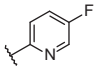
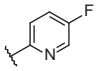


Compd	R	Human FATP1 IC_{50}[a] (μM)	Mouse FATP1 IC_{50}[a] (μM)	log*D*[b]	MS[c] (%)
2		0.026	5.1	5.1	30
4a		0.077	4.0	4.5	42
4b		0.43	1.7	3.7	56
4c		>1.0	>10	2.8	ND[d]
4d		0.49	>10	4.4	ND[d]
4e		0.18	5.4	3.0	53
4f		0.49	>10	4.0	ND[d]
4g		0.12	2.0	5.0	ND[d]

[a] Inhibition of recombinant human or mouse acyl-CoA synthetase activity of FATP1. The IC_{50} values represent the average of at least $n = 2$.
[b] The distribution coefficients (log*D*) were measured between 1-octanol and phosphate buffered saline (pH 7.4).
[c] Remaining (%) of the test compound after 0.5-h incubation with mouse liver microsome.
[d] Not determined.

Table 2
IC_{50} values of FATP1 inhibitors **4a** and **5a–5n**[4]



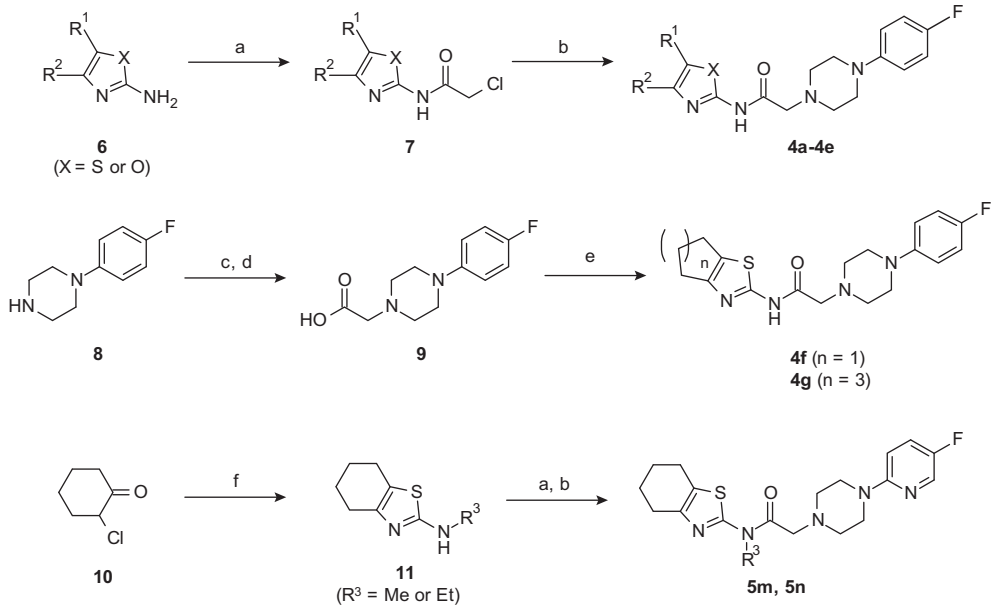
Compd	X	R^1	R^2	Human FATP1 IC_{50}[a] (μM)	Mouse FATP1 IC_{50}[a] (μM)	log*D*[b]	MS[c] (%)
4a	S	H		0.077	4.0	4.5	42
5a	S	H		0.28	9.0	4.3	ND[d]
5b	S	H		0.25	>10	4.8	ND[d]
5c	S	H		>1.0	>10	ND[d]	ND[d]
5d	S	H		>1.0	>10	2.1	ND[d]
5e	S	H		>1.0	>10	3.0	ND[d]
5f	S	H		0.20	4.9	3.9	ND[d]
5g	S	H		>1.0	>10	3.3	ND[d]
5h	S	H		>1.0	>10	2.0	ND[d]
5i	S	H		>1.0	>10	3.7	ND[d]
5j	S	H		0.52	7.9	3.8	ND[d]
5k	S	H		0.046	0.60	4.1	63
5l	O	H		0.10	1.7	2.7	63
5m	S	Me		0.041	0.62	3.9	65
5n	S	Et		0.78	>10	ND[d]	ND[d]

[a] Inhibition of recombinant human or mouse acyl-CoA synthetase activity of FATP1. The IC_{50} values represent the average of at least $n = 2$.
[b] The distribution coefficients (log*D*) were measured between 1-octanol and phosphate buffered saline (pH 7.4).
[c] Remaining (%) of the test compound after 0.5-h incubation with mouse liver microsome.
[d] Not determined.

with benzyl bromoacetate, followed by benzyl deprotection provided carboxylic acid **9**, which was condensed with the corresponding amines to furnish **4f** and **4g** with good yields. In the same manner, using the appropriate starting material and reagents, compounds **5a–5l** (Table 2) were synthesized.[8] *N*-alkyl amides **5m** and **5n** were synthesized from *N*-alkyl thiazoyl amine **11** derived from chlorocyclohexanone **10** and *N*-alkyl thiourea. In the same manner, acylation with chloroacetyl chloride, followed by S_N2 reaction with 1-(5-fluoropyridine-2-yl)piperazine hydrochloride[8] provided *N*-alkyl amides **5m** and **5n**, respectively.

Then, the derivatization of imidazopyridine **3** was focused on, as described in Table 3, because the structural similarity between **2** and **3** allowed us to utilize the structure–activity relationship of **2**. As expected, the replacement of the phenyl group in **3** with a fluoro-substituted 2-pyridyl group resulted in a dramatic enhancement of in vitro activity against both species compared to hit compound **3** (compound **12a**; human $IC_{50} = 0.43$ μM, mouse $IC_{50} = 0.39$ μM). Even compared to thiazole **5k**, imidazopyridine **12a** showed better mouse in vitro activity. Moreover, the elimination of the methyl group in imidazopyridine **12a** led to compound **12b**, which showed an enhancement of human and mouse in vitro activity (0.13 and 0.29 μM, respectively) as well as excellent mouse microsomal stability of 98%.[6] Although several imidazopyridine ring replacements were examined, only pyrazolopyridine **12e** and benzofuran **12g** indicated fair in vitro activity. On the other hand, tetrahydroimidazopyridines **12h** and **12i** showed enhanced in vitro potency, especially **12i**, which indicated the best in vitro activity against mouse FATP1 without an increase in lipophilicity.

Imidazopyridine derivatives and their analogs **12a–12i** were synthesized as illustrated in Scheme 2. Tetrahydroimidazopyridine **15** was synthesized via imidazopyridine **14** with partial hydrogenation under acidic conditions. The synthesis of other acetyl

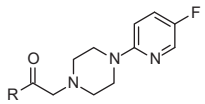


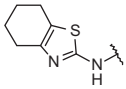
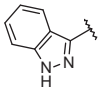
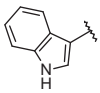
Scheme 1. Reagents and conditions: (a) chloroacetyl chloride, Et_3N, THF; (b) arylpiperazine, KI, DMF or THF, 80 °C, 2 steps, 14–82%; (c) benzyl bromoacetate, Et_3N, KI, THF, reflux, 97%; (d) H_2, Pd/C, EtOH, 86%; (e) thiazoyl amine, WSC·HCl, HOBt·H_2O, Et_3N, CH_2Cl_2, 71–74%; (f) methyl or ethyl thiourea, EtOH, reflux.

heterocycles is known.[9] Finally, after bromination of acetyl heterocycle **16**, S_N2 reaction with 1-(5-fluoropyridine-2-yl)piperazine hydrochloride[8] yielded compounds **12a–12i**.

Compounds **2**, **5k** and **12a** were selected to evaluate pharmacokinetic parameters in mice (Table 4). We believe that FATP1 inhibitors should be exposed in blood or skeletal muscle above the IC_{50} value to show sufficient in vivo efficacy. When hit compound **2** was orally administered to mice at 10 mg/kg, the C_{max} value was 1.8 μg/mL, which was comparable to its IC_{50} value against mouse FATP1 (2.0 μg/mL). Compound **2** showed high plasma protein binding (99.57%). Therefore, if protein binding was taken into account, only 0.0077 μg/mL of unbound **2** would be exposed in mouse plasma,

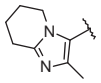
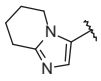
Table 3
IC_{50} values of FATP1 inhibitors **5k** and **12a–12i**[4]



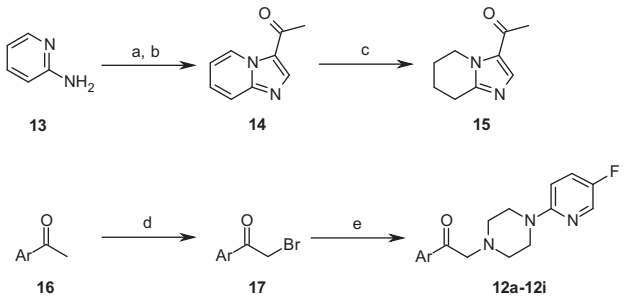
Compd	R	Human FATP1 IC_{50}[a] (μM)	Mouse FATP1 IC_{50}[a] (μM)	log *D*[b]	MS[c] (%)
5k		0.046	0.60	4.1	63
12a		0.43	0.39	2.8	52
12b		0.13	0.29	2.5	98
12c		>1	>10	ND[d]	ND[d]
12d		>1	>10	2.8	ND[d]
12e		0.33	1.1	2.5	84
12f		>1	>10	ND[d]	ND[d]
12g		0.47	1.9	3.9	76

(*continued on next page*)

Table 3 (*continued*)

Compd	R	Human FATP1 IC_{50}[a] (μM)	Mouse FATP1 IC_{50}[a] (μM)	log*D*[b]	MS[c] (%)
12h		0.19	0.40	2.5	55
12i		0.10	0.16	2.1	86

[a] Inhibition of recombinant human or mouse acyl-CoA synthetase activity of FATP1. The IC_{50} values represent the average of at least $n = 2$.
[b] The distribution coefficients (log*D*) were measured between 1-octanol and phosphate buffered saline (pH 7.4).
[c] Remaining (%) of the test compound after 0.5-h incubation with mouse liver microsome.
[d] Not determined.



Scheme 2. Reagents and conditions: (a) *N*,*N*-dimethylformamide dimethylacetal, toluene, reflux; (b) bromoacetone, ethanol, reflux, 18% (2 steps); (c) H_2 (50 psi), HCl, EtOH, rt, 59%; (d) bromine, HBr, AcOH, 96–100%; (e) 1-(5-fluoropyridine-2-yl)piperazine hydrochloride, Et_3N, DMF, rt, 24–92%.

which was much lower than its IC_{50} value. When thiazole **5k** was administered at the same dosage, improved pharmacokinetic parameters were observed, especially for clearance, which was reduced to 5.0 mL/min/kg. The C_{max} value of thiazole **5k** (5.5 μg/mL) was more than 20 times higher than its IC_{50} value of 0.22 μg/mL. However, unbound **5k** in mouse plasma was only 0.0083 μg/mL due to its high protein binding ability. The pharmacokinetic parameters were further improved in imidazopyridine **12a** with better solubility as well as lower plasma protein binding ability compared to that of **5k**. The free C_{max} value reached 0.61 μg/mL, which is above its in vitro IC_{50} of 0.14 μg/mL, even if the protein binding was considered. Therefore, imidazopyridine **12a** was expected to show the most potent in vivo efficacy among these compounds.

The soleus to plasma concentration ratio (K_p soleus) was also evaluated, as shown in Table 4. Although compound **1** showed a K_p value of 0.33, K_p soleus of **5k** was as low as 0.030. Since an excellent K_p soleus value was observed in imidazopyridine **12a**, **12a** was the most promising compound in this aspect, as well.

Then, to assess the in vivo inhibition of FATP1, we evaluated tissue triglyceride (TG) content in skeletal muscle and liver, as depicted in Figure 2, because TG is known as the storage form of fatty acid. When mice were fed with a high-fat diet (HFD) for 4 weeks, TG content in the liver increased by around threefold compared to the mice fed with a normal diet. The increase of TG content was also observed in the white gastrocnemius muscle of HFD-fed mice compared to the group fed with a normal diet, whereas TG content in the soleus muscle showed no difference. When 3, 10, 30 mg/kg of imidazopyridine **12a** was orally administered to mice fed with a HFD for 4 weeks, TG content of each tissue did not change at any dose. A similar result was observed with 10, 30, 100 mg/kg administration of **2**. When 1, 10, 100 mg/kg of thiazole **5k** was examined in the same manner for 3 weeks, a reduction of TG content in each tissue was not observed (data not shown).

In summary, the discovery and optimization of arylpiperazine derivatives as novel FATP1 inhibitors were described. The replacement of the 4-fluoro phenyl group with a fluoro-substituted 2-pyridyl group increased in vitro activity against human and mouse FATP1 to identify thiazole **5k**. With the improvement of physiological properties as well as microsomal stability, **5k** showed good pharmacokinetic parameters. A 2-amino tetrahydrobenzothiazole moiety can be replaced with an imidazopyridine ring, and imidazopyridine **12a** was found to possess reduced plasma protein binding ability with potent in vitro activity. When **5k** was orally administered at 10 mg/kg, the C_{max} value exceeded the mouse IC_{50} value without considering plasma protein binding. Moreover, oral administration of **12a** at 10 mg/kg showed a C_{max} value above the mouse IC_{50} value even though the free fraction was considered. When compounds **2**, **5k** and **12a** were orally administered to mice fed with a HFD, reduction of TG accumulation was not observed in the liver, white gastrocnemius muscle and soleus. Recently,

Table 4
Physical properties and mouse PK parameters of **2**, **5k** and **12a**

Compd	In vitro IC_{50} (μg/mL)	SolubilityJP1/JP2 (μg/mL)	PB free[a] (%)	T_{max}[b] (h)	C_{max}[b] (μg/mL)	Free C_{max}[c] (μg/mL)	AUC[b] (h μg/mL)	V_d[d] (L/kg)	Cl[d] (mL/min/kg)	*F* (%)	K_p soleus[e]
2	2.0	540/0.7	0.43	0.25	1.8	0.0077	2.3	1.5[f]	46[f]	62	0.33
5k	0.22	700/2.4	0.15	0.33	5.5	0.0083	36	0.57	5.0	100	0.030
12a	0.14	>700/350	27.5	0.33	2.2	0.61	5.5	0.20	6.4	21	1.1

[a] Unbound fractions (%) in mouse plasma.
[b] Average of three mice dosed at 10 mg/kg po in DMA/PG/(20%HPβCD/saline): 10/10/80.
[c] Free C_{max} = PB free (%) × in vitro IC_{50}.
[d] Average of two mice dosed at 1 mg/kg iv in DMA/PG/(20%HPβCD/saline): 10/10/80.
[e] Soleus to plasma concentration ratio. K_p value was determined after 1-week repeated administration of compounds at 10 mg/kg po to mice. The measurement of each concentration was conducted at 3 h after administration.
[f] Dosed at 5 mg/kg iv.

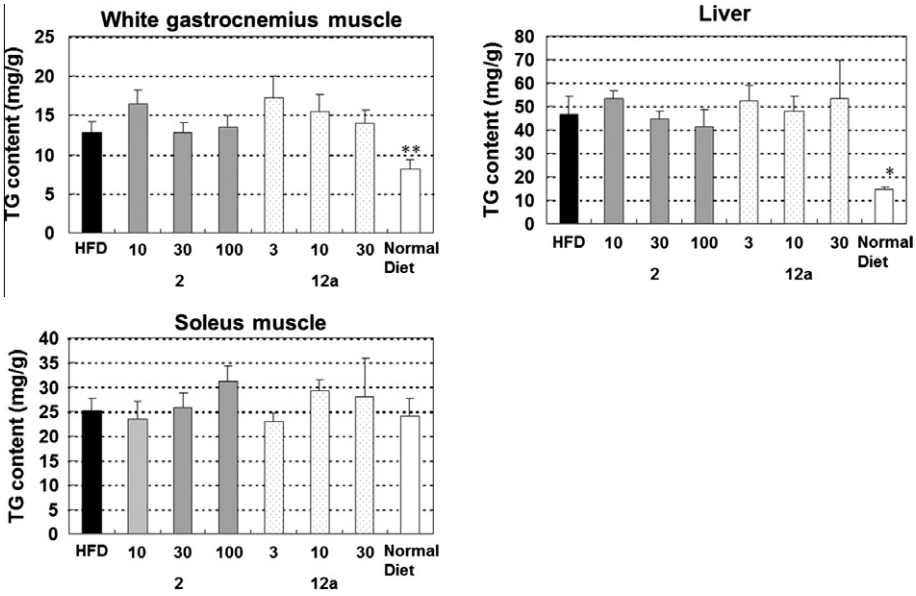


Figure 2. Inhibition of tissue TG accumulation in vivo (*P <0.05 versus HFD control. **P <0.01 versus HFD control).

Holloway et al. reported that FATP1 overexpression in mice muscle did not cause muscular TG accumulation or whole body insulin resistance.[10] Taken together, FATP1 inhibition alone may not have enough of an impact on fatty acid transport and/or metabolism to reduce tissue TG contents.

References and notes

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4. *The inhibition of human or mouse FATP1 was evaluated by cell-free ACS assay:* FLAG-tag fused human or mouse FATP1 protein was incubated with 10 μM [1-^{14}C] oleic acid and test compound in 100 mM Tris–HCl (pH 7.4), 30 mM NaCl, 0.5 mM ATP, 5 mM $MgCl_2$, 0.5 mM coenzyme A, 0.05% Triton-X 100, 2 mM dithiothreitol at 37 °C for 20 min. After the reaction, [1-^{14}C] oleoyl-CoA was extracted by successive additions of fivefold volume of 2-propanol/heptane/H_2SO_4 (40:10:1, v/v/v), threefold volume of heptane, and twofold volume of water. Phases were then separated by centrifugation, and the organic phase was removed. To remove [1−^{14}C] oleic acid completely, the aqueous phase was washed by heptane again. The aqueous phase was added Pico-Fluor 40 scintillation cocktail (PerkinElmer) and the radioactivity was measured by LSC-6100 scintillation counter (Aloka). The radioactivity of FLAG-tagged luciferase protein instead of FATP1 protein was deducted as background. The IC_{50} values represent the average of at least $n = 2$.
5. *The homology between human and mouse FATP1 is calculated to be 89% from NCBI reference sequence:* NP_940982.1 (human FATP1), NP_036107.1 (mouse FATP1).
6. Mouse microsomal stability was evaluated by measuring the remaining (%) of the test compound after 0.5-h incubation with mouse liver microsome.
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