Bioorganic & Medicinal Chemistry Letters 23 (2013) 2560–2565

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

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

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ARTICLE INFO

Article history:
Received 9 January 2013
Revised 21 February 2013
Accepted 28 February 2013
Available online 7 March 2013

Keywords:
Fatty acid transport protein
High-throughput screening
Microsomal stability
Arylpiperazine

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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http://dx.doi.org/10.1016/j.bmcl.2013.02.116

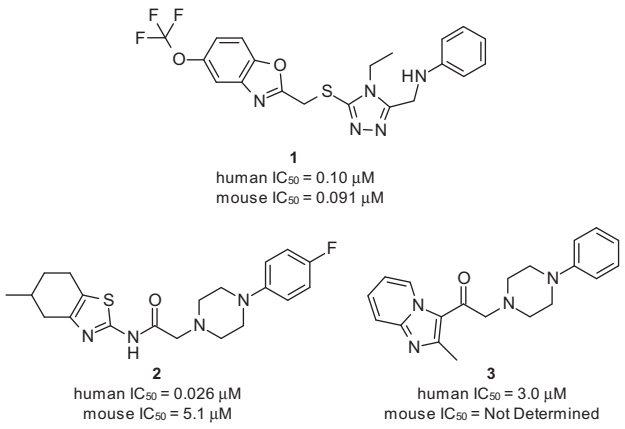


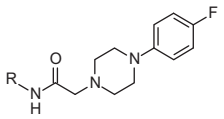
Figure 1. Triazole-based FATP1 inhibitor **1** and HTS hits **2** and **3** with FATP1 IC_{50} values.

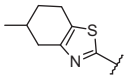
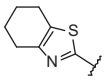
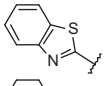
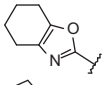
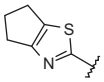
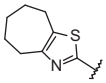
activity (compound **4d**). Tetrahydrobenzooxazole **4e**, an oxazole analogue of **4a**, retained fair human and mouse in vitro activity (0.18 and 5.4 μM, respectively). Compared to tetrahydrobenzothiazole **4a**, the five-membered ring derivative **4f** lost in vitro activity against mouse FATP1, and 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.