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Letter

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Discovery of FDA-Approved Drugs as Inhibitors of Fatty Acid Binding Protein 4 Using Molecular Docking Screening

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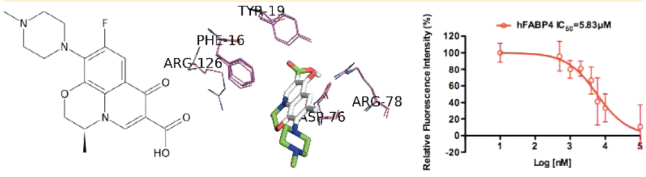
Supporting Information



Levofloxacin

ABSTRACT: We first identified fluorescein, ketazolam, antrafenine, darifenacin, fosaprepitant, paliperidone, risperidone, pimozide, trovafloxacin, and levofloxacin as inhibitors of fatty acid binding protein 4 using molecular docking screening from FDA-approved drugs. Subsequently, the biochemical characterizations showed that levofloxacin directly inhibited FABP4 activity in both the *in vitro* ligand displacement assay and cell-based function assay. Furthermore, levofloxacin did not induce adipogenesis in adipocytes, which is the major adverse effect of FABP4 inhibitors.

INTRODUCTION

Fatty acids are a class of carboxylic acids with a long aliphatic tail. Many fatty acids are derived from triglycerides or phospholipids; they serve as critical sources of fuel in our body. There is accumulating evidence showing that chronically elevated plasma fatty acid leads to pathophysiological disorders. The elevated fatty acid levels in circulation are associated with the pathogenesis of diabetes, obesity, and atherosclerosis (reviewed in refs 1−3). The intracellular trafficking of fatty acids requires a cluster of specific carrier proteins, named fatty acid-binding proteins (FABPs). Fatty acids directly bind to FABPs with high affinity, and the fatty acid-FABP complexes are transported in cytoplasm for metabolic process or storage.[4,5]

The adipocyte FABP, FABP4 (aP2), is highly expressed in adipocytes. FABP4 plays an important role in various aspects of metabolic disorders, including insulin resistance, diabetes, and atherosclerosis. Insulin resistance can be observed in high-fat diet-fed mice; deficiency of FABP4 partially protects these mice against the development of insulin resistance. In addition, FABP4-deficient mice exhibit better performances in both insulin and glucose tolerance tests.[6] Apart from genetic approaches, the blockade of FABP4 by small molecules could potentially mimic the phenotype of FABP4-deficient mice.[6] Therefore, pharmacological agents that inhibit FABP4-mediated responses might serve as potential candidates for the treatment of insulin resistance, diabetes, and atherosclerosis.[7]

FABP4 has recently been reported to interact directly with the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ), triggering ubiquitination and subsequent proteasomal degradation of PPARγ.[8] BMS309403, the well-characterized FABP4 inhibitor, up-regulated the basal protein levels of PPARγ.[9] The elevation of PPARγ induced adipogenesis in adipose tissue, which is a significant adverse effect of PPARγ activation.[10] The fatty acid binding pocket of FABP4 is distinct from the interaction site of FABP4 and PPARγ.[8] In this respect, BMS309403 binding to FABP4 might lead to an allosteric regulation of FABP4, therefore resulting in the elevation of PPARγ protein expression.[8]

The expenditure of research and development (R&D) increased dramatically over past two decades. The pharmaceutical industries are interested in several strategies to reduce the cost of new drug development. The strategy of the U.S. Food and Drug Administration (FDA)-approved drug repurposing aims to identify new uses for existing drugs. Given that favorable pharmacokinetic and toxicological profiles of existing drugs in human subjects have been well characterized, a collection of FDA-approved drugs can be powerful resources for new indication discoveries.[11−16] For example, ciclopirox olamine is a synthetic antifungal drug for topical dermatologic treatment of superficial mycoses. Recently, ciclopirox olamine has been identified as a novel intracellular iron chelator, which exhibited anticancer activity in both *in vitro* and *in vivo* studies.[17] The latest clinical trials reported that ciclopirox olamine displayed biological activity, which is now in a phase I study in patients with advanced hematologic malignancies.[18]

In the present study, a ligand library containing ∼1500 compounds from FDA-approved drugs was compiled to search for a ligand of human FABP4 for potential drugs of metabolic disorders.

RESULTS AND DISCUSSION

In this study, we employed molecular docking screening to identify novel FABP4 inhibitors from an FDA-approved drug database of ∼1500 compounds. The workflow chart is illustrated in Figure 1A. To reduce the false positive hit rate, we

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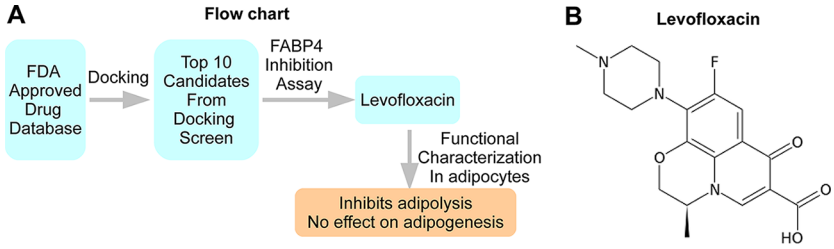

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Critical residues between ligands and FABP4

PDB	Benchmark			Levofloxacin		
	Docking score	Hydrogen bond	π-π interaction	Docking score	Hydrogen bond	π-π interaction
1TOU	-8.2	Tyr19, Arg126, Tyr128	None	-9.8	Tyr19, Asp76	Phe16
1TOW	-7.9	Ser53, Arg126, Tyr128	Phe16, Phe57	-10	Asp76, Arg126	Phe16
2NNQ	-11.1	Arg106, Arg126, Tyr128	Phe57	-10.7	Asp76, Arg78	Phe16
3FR5	-10	Ser55, Arg126, Tyr128	Phe16	-9.9	Tyr19, Arg78	Phe16

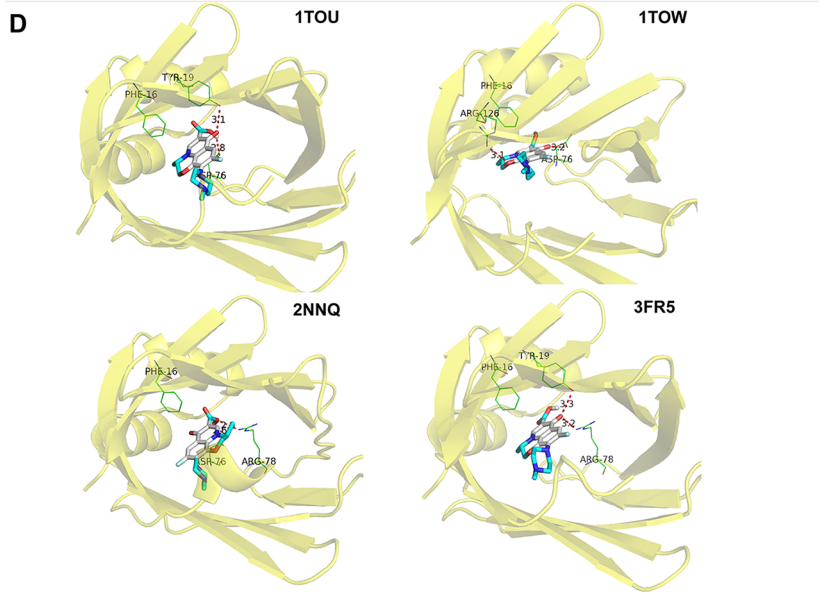

Figure 1. Levofloxacin is a FABP4 inhibitor identified by molecular docking. (A) Workflow chart of the analysis. (B) Chemical structure of levofloxacin. Critical residues for inhibitor binding are demonstrated. The inhibitors in each crystal structure were used as benchmarks. (D) Molecular docking analysis illustrates the favorable binding positions of levofloxacin with the lowest binding free energy in the inhibitor-binding site of human FABP4 (PDB codes: 1TOU, 1TOW, 2NNQ, and 3FR5). The three-dimensional diagrams show the interactions of levofloxacin (gray stick) to human FABP4 (yellow cartoon) with labeled amino residues.

incorporated different FABP4−inhibitor complex structures to partially compensate for target flexibility in our computational study. Generally, four human FABP4 models were selected for molecular docking screening, including 1TOU,[19] 1TOW,[7] 2NNQ,[20] and 3FR5[21] from the Protein Data Bank. The software AutoDock Vina v.1.0.2 was used for all dockings in this study. The docking parameters for AutoDock Vina were kept to their default values. The grid box was 20 Å × 14 Å × 12 Å, encompassing the inhibitor binding cavity of FABP4. The binding modes were clustered through the root-mean square deviation (RMSD) among the Cartesian coordinates of the ligand atoms. The docking results were ranked by the binding free energy. The complete docking ranking lists are summarized in the Supporting Information. A total of the top 30 ligands from each protein model were selected; and the average binding energies were calculated according to the scores of four different models. The top 10 candidates were filtered as potential FABP4 inhibitors from FDA-approved drugs and are summarized in the Supporting Information.

Among the top 10 ranked hits, fluorescein is extensively used as a fluorescent tracer in diagnostic applications. It is unlikely to be drug for disease treatment due to serious adverse reactions, including cardiac arrest and anaphylactic shock.[22] Ketazolam, a benzodiazepine derivative, is used for the treatment of anxiety. However, long-term administration of ketazolam results in tolerance and physical dependence. Currently, ketazolam is not approved for sale in Australia or the United Kingdom or United States.[23] Antrafenine, a phenylpiperazine derivative, is marketed as an analgesic and anti-inflammatory drug, but it is not widely used because it has been replaced by the next generation anti-inflammatory drugs.[24] Darifenacin and fosaprepitant are newly approved drugs that are not commercially available.

We therefore examined five chemicals. As shown in the Supporting Information, three antipsychotic drugs (paliper-

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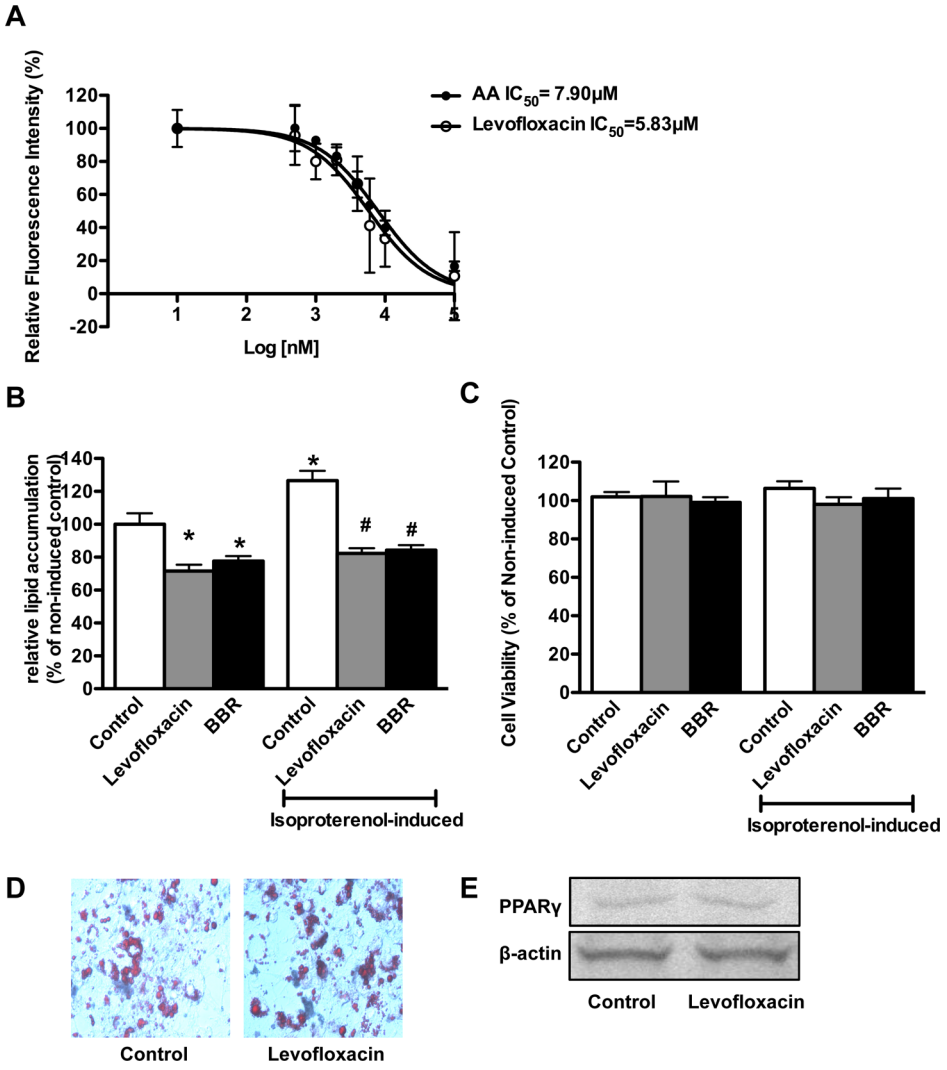

Figure 2. Levofloxacin inhibits FABP4 activity in cell-free and cell-based assays. (A) Dose−response curves of levofloxacin in FABP4 activity inhibition assay. Arachidonic acid was used as a positive control. The IC_{50} values were calculated using the inhibitor dose−response function in Prism 5. (B) Levofloxacin inhibits both basal and isoproterenol-stimulated adipolysis in 3T3-L1 cells. Benzbromarone (BBR) (10 μM) was used as a positive control. Results were repeated at least three times from three independent experiments and presented as mean ± SD, $n = 3$. The results were statistically analyzed by a one-way ANOVA test; ∗, $P < 0.05$; compared with the control group, and #, $P < 0.05$; compared with the isoproterenol-treated group. (C) There were no effects on the cell proliferation at 10 μM of levofloxacin in the presence or absence of isoproterenol. 3T3-L1 cells were treated with levofloxacin for 24 h followed by incubation with isoproterenol (100 nM) for another 24 h. Afterward the viability was detected by MTT. Results were repeated at least three times from three independent experiments and presented as mean ± SD, $n = 3$. The results were statistically analyzed by one-way ANOVA test. (D) Levofloxacin does not promote adipocyte differentiation. Confluent preadipocytes (day 0) were stimulated by the differentiation cocktail and cultured for 6 days in the absence or in the presence of levofloxacin (10 μM). At day 6, 3T3-L1 cells were stained with red oil and photographed macroscopically. Results were repeated at least three times from three independent experiments. (E) At day 6, the cells were harvested, and the total protein was collected for Western blot to measure PPARγ protein level. Results were repeated at least three times from three independent experiments.

idone, risperidone, and pimozide[25]) all exhibited high binding affinities to human FABP4 in our analysis of molecular docking, whereas only pimozide directly inhibits FABP4 activity by *in vitro* validations. Two antibiotics showed strong inhibitory effects on FABP4 activity. Trovafloxacin was a broad spectrum antibiotic that blocks the activity of DNA gyrase and topoisomerase IV in various bacteria.[26] Trovafloxacin inhibits 57.46 ± 12.18% FABP4 activity at 10 μM, indicating that it might function as a FABP4 inhibitor. The most potent FABP4 inhibitor from our screening is levofloxacin with 70.01 ± 12.15% inhibition on FABP4 activity at 10 μM.

Figure 1B shows the chemical structure of levofloxacin. Levofloxacin, a chiral-fluorinated carboxyquinolone, is the 3,9-enantiomer of the racemic drug ofloxacin. Levofloxacin is a broad spectrum antibiotic used to treat a series of infections, including respiratory tract infections, cellulitis, and urinary tract infections.[27,28] The new medical indication of levofloxacin has been reported. Levofloxacin significantly reduces pulmonary inflammation; therefore, its expanded indication could include asthma and cystic fibrosis.[29]

Levofloxacin binds to FABP4 with reasonable binding affinities in all of four protein models (Figure 1C,D). In the 1TOU model, the benchmark is 2-[4-hydroxy-6-(trifluoromethyl)pyrimidin-2-yl] sulfanyl-1-piperidin-1-yl-ethanone (B1V).[19] On the basis of our docking simulation, B1V formed three critical hydrogen bonds with Tyr19, Arg126, and Tyr128. The $\pi-\pi$ interaction cannot be observed in the B1V-FABP4 binding mode. Levofloxacin directly bound to Tyr19 and Asp79 through

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hydrogen bonds. In addition, levofloxacin also formed a $\pi-\pi$ interaction with Phe16. The calculated binding affinities of levofloxacin and B1V are −9.8 and −8.2 kcal/mol, respectively. In the 1TOW model, the benchmark is 4-carbazol-9-ylbutanoic acid (CRZ).[7] The docking simulation showed that CRZ interacted with FABP4 through hydrogen bonds with Arg126 and Tyr128 as well as $\pi-\pi$ interactions with Phe16 and Phe57. Levofloxacin formed hydrogen bonds with both Asp76 and Arg126. The $\pi-\pi$ interaction between benzoxazine of a ligand and a benzene ring of Phe16 contributed the high binding affinity of levofloxacin with FABP4. The benchmark of 2NNQ is 2-[3-[2-(5-ethyl-3,4-diphenyl-pyrazol-1-yl)phenyl]phenoxy]ethanoic acid (T4B).[20] The docking score of T4B is −11.1 kcal/mol, indicating that T4B might tightly bind to FABP4. The binding mode of T4B showed that Arg106, Arg126, and Tyr128 were key residues and formed hydrogen bonds with the ligand. Additionally, a strong $\pi-\pi$ interaction between T4B and Phe57 can be observed in the optimal binding mode. In the same protein model, levofloxacin bound to FABP4 with a high binding score (−10.7 kcal/mol) through a $\pi-\pi$ interaction with Phe16 as well as hydrogen bonds with Asp76 and Arg78, respectively. The benchmark of 3FR5 is 5-(3-carbamoylbenzyl)-5,6,7,8,9,10-hexahydrocyclohepta[b]indole-4-carboxylic acid (I4A).[21] I4A interacted with Ser55, Arg126, and Tyr128 through hydrogen bonds and formed $\pi-\pi$ interactions with Phe16. The docking simulation using the same protein model showed that levofloxacin formed hydrogen bonds with both Tyr19 and Arg78 as well as $\pi-\pi$ interactions with Phe16. Taken together, we noticed that Arg126 and Tyr128 are common residues to form hydrogen bonds with FABP4 ligands, whereas Phe16 and Phe57 are residues to form $\pi-\pi$ interactions with the ligands. However, levofloxacin is likely to form hydrogen bonds with Tyr19, Asp76, and Arg78. Furthermore, Phe16 has been identified as the most significant residue that can interact with levofloxacin through $\pi-\pi$ interactions in all of four FABP4 protein models.

The inhibitory effect of levofloxacin on FABP4 activity has been verified in binding assays. Levofloxacin directly inhibited FABP4 activity with the IC_{50} value of 5.83 μM. The inhibitory activity of levofloxacin is similar to that of arachidonic acid (IC_{50} value of 7.90 μM, an endogenous ligand of FABP4[30]) (Figure 2A).

The inhibition of FABP4 by both pharmacological agents and genetic approaches was reported to decrease adipolysis in 3T3-L1 cells. For example, benzbromarone is a newly identified FABP4 inhibitor, which inhibits adipolysis at 10 μM.[31] Thus, we assessed whether levofloxacin could modulate the levels of adipolysis in adipocytes. The results showed that levofloxacin (10 μM) inhibited both basal and isoproterenol-stimulated adipolysis in 3T3-L1 cells (Figure 2B). This result is consistent with levofloxacin as an inhibitor of FABP4. Additionally, we found levofloxacin has no effect on 3T3-L1 cells proliferation (Figure 2C).

Rising blood glucose and insulin levels have been identified as critical indicators of obesity-induced insulin resistance and type 2 diabetes. Obese wild-type mice exhibited higher blood glucose levels compared to lean controls. However, on the high-fat diet, FABP4-deficiency mice had significantly lower blood glucose concentrations compared to wild-type controls.[32] Interestingly, severe hypoglycemia has reported associated with levofloxacin treatment in type 2 diabetic patients receiving polytherapy.[33−35] We suggest levofloxacin-induced hypoglycemia in type 2 diabetic patients might be attributed to its FABP4 inhibitory effects.

A recent study demonstrated that BMS309403, a well-known FABP4 inhibitor, when binding to FABP4 might lead to an allosteric regulation of FABP4, therefore resulting in the elevation of PPARγ protein expression as well as the induction of adipogenesis in adipocytes.[9] Here, we tested whether levofloxacin can act as an allosteric inhibitor to promote adipogenesis in 3T3-L1 cells. We found that the levofloxacin did not induce lipid accumulation during adipocyte differentiation. Levofloxacin was added at the beginning of differentiation induction and kept in the medium throughout the differentiation period (days 0−6). At the end of treatment, the cells were fixed with formalin and stained with 0.5% Oil Red O. The lipid droplets in cells were characterized as red dots. As shown in Figure 2D, there is no significant difference in the red dots between the levofloxacin-induced group and control group, indicating that levofloxacin does not promote lipid accumulation in adipocytes.

We also investigated the effects of levofloxacin treatment on protein expression levels of PPARγ. However, the addition of levofloxacin did not increase protein expressions of PPARγ compared with vehicle control treatment. BMS309403 has been reported to elevate the basal protein levels of PPARγ in adipocytes.[9] These results indicate that levofloxacin treatment during adipocyte differentiation has no impact on adipogenesis in 3T3-L1 cells. Taken together, we postulated that levofloxacin directly binds to the fatty acid binding pocket and does not induce an allosteric regulation of FABP4 and up-regulation of PPARγ. We concluded that levofloxacin is not an allosteric inhibitor of FABP4.

In summary, we identified levofloxacin as a novel inhibitor of FABP4 from the database of FDA-approved drugs through molecular docking. Subsequently, the biochemical characterizations showed that levofloxacin directly inhibited FABP4 activity in both the *in vitro* ligand displacement assay and cell-based function assay. Furthermore, levofloxacin does not induce adipogenesis in adipocytes that is the major adverse effects of FABP4 inhibitors. We anticipate that levofloxacin could be further explored to act as a novel FABP4 inhibitor that is a potential candidate for metabolic disease treatment, such as insulin resistance, diabetes, and atherosclerosis.

■ ASSOCIATED CONTENT

Supporting Information

Materials and methods are given in the PDF. Complete docking ranking lists and top 10 candidates filtered as potential FABP4 inhibitors from FDA-approved drugs are summarized in the Excel spreadsheets. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

Y. Wang, W.-K. Law, and J.-S. Hu contributed equally to this work.

Notes

The authors declare no competing financial interest.

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