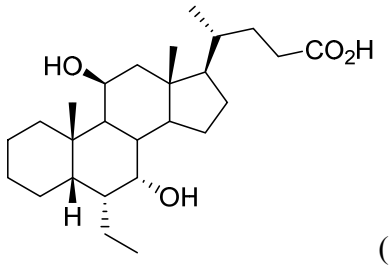
include ursodeoxycholic acid, vitamins E and C, and pentoxifylline, amongst others. Weight-loss agents such as Orlistat have had no significant benefit compared to just the use of diet and exercise to achieve weight loss alone. Most weight-loss studies in NAFLD/NASH have been pilot studies of short duration and limited success, reporting only a modest improvement in necroinflammation or fibrosis. Moreover, an investigational new drug encounters a variety of obstacles that may prevent its further development. Such obstacles may include poor tissue distribution, a non-suitable pharmacokinetic profile, safety issues such as toxicity, and/or undesirable drug-drug interactions. Despite ongoing efforts, there remains a significant unmet clinical need for an effective and well-tolerated compound that can treat or slow down the progression of NAFLD and NASH.

The present invention addresses these needs. Therefore, it is the object of the present invention to provide a novel therapeutic agent to treat liver disorders such as NAFLD and NASH while exhibiting physicochemical, *in vitro* and/or *in vivo* ADME (adsorption, distribution, metabolism and excretion) properties superior to known compounds and/or superior pharmacokinetics *in vivo*.

SUMMARY

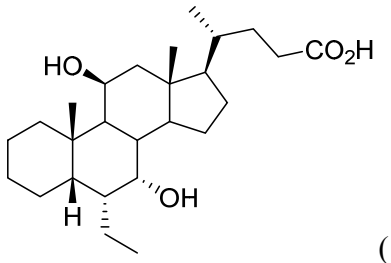
An objective of the present disclosure is to provide a compound that activates the Farnesoid X receptor (FXR) and is therefore useful to treat FXR related disorders including NAFLD and NASH. Accordingly, the present disclosure provides Compound 1:



(1),

or a pharmaceutically acceptable salt or amino acid conjugate thereof.

In one aspect of the present disclosure, there is provided a compound of structure:



(1),

or a pharmaceutically acceptable salt or amino acid conjugate thereof.

In another aspect of the present disclosure, there is provided a free acid of the compound disclosed herein.

In a further aspect of the present disclosure, there is provided a pharmaceutically acceptable salt of the compound disclosed herein.

In another aspect of the present disclosure, there is provided an amino acid conjugate of the compound disclosed herein, wherein the amino acid is glycine or sarcosine.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein and a pharmaceutically acceptable carrier or excipient.

In another aspect of the present disclosure, there is provided a compound disclosed herein for use in treating or preventing a disease or condition activated by FXR, wherein the disease or condition activated by FXR is selected from cardiovascular disease, chronic liver disease, lipid disorder, gastrointestinal disease, renal disease, metabolic disease, cancer, and neurological disease.

In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating or preventing a disease or condition activated by FXR, wherein the disease or condition activated by FXR is selected from cardiovascular disease, chronic liver disease, lipid disorder, gastrointestinal disease, renal disease, metabolic disease, cancer, and neurological disease.

The present disclosure further provides a pharmaceutical composition comprising Compound 1 or a pharmaceutically acceptable salt or amino acid conjugate thereof, and a pharmaceutically acceptable carrier or excipient.

The present disclosure also provides a method for treating or preventing a disease or condition activated by FXR, comprising administering to a subject in need thereof an

effective amount of Compound 1 or a pharmaceutically acceptable salt or amino acid conjugate thereof.

The present disclosure also provides for the manufacture of a medicament for treating or preventing a disease or condition activated by FXR, wherein the medicament comprises Compound 1 or a pharmaceutically acceptable salt or amino acid conjugate thereof.

The present disclosure further provides compositions, including pharmaceutical compositions, for use in treating or preventing a disease or condition activated by FXR, wherein the composition comprises Compound 1 or a pharmaceutically acceptable salt or amino acid conjugate thereof.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. The materials, methods, and examples are illustrative only and are not intended to be limiting. Other features and advantages of the invention will be apparent from the following detailed description.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the expression levels of FXR Target Gene Panel.

DETAILED DESCRIPTION

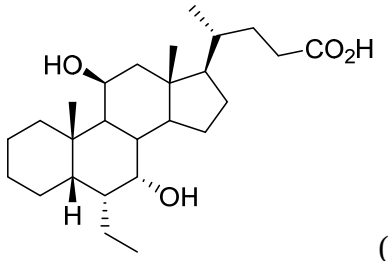
The present invention is based on the discovery that Compound 1 is a potent and selective activator of the Farnesoid X receptor (FXR). FXR is a nuclear receptor which acts as a key regulator of cholesterol homeostasis, triglyceride synthesis and lipogenesis (Crawley, Expert Opinion Ther. Patents 2010, 20, 1047-1057). This receptor is expressed in various organs and shown to be involved in many diseases and conditions, including liver diseases, lung diseases, renal diseases, intestinal diseases, and heart diseases, and biological processes, such as glucose metabolism, insulin metabolism, and lipid metabolism.

Definitions

As used herein, "Compound 1" or "a compound of the invention" refers to 7α,11β-dihydroxy-6α-ethyl-5β-cholan-24-oic acid which has the following chemical structure:

Claims:

1. A compound of structure:



(1),

or a pharmaceutically acceptable salt or amino acid conjugate thereof.

2. The free acid of the compound of claim 1.

3. The pharmaceutically acceptable salt of the compound of claim 1.

4. The amino acid conjugate of the compound of claim 1, wherein the amino acid is glycine or sarcosine.

5. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or excipient.

6. A compound of claim 1 for use in treating or preventing a disease or condition activated by FXR, wherein the disease or condition activated by FXR is selected from cardiovascular disease, chronic liver disease, lipid disorder, gastrointestinal disease, renal disease, metabolic disease, cancer, and neurological disease.

7. Use of a compound of claim 1 in the manufacture of a medicament for treating or preventing a disease or condition activated by FXR, wherein the disease or condition activated by FXR is selected from cardiovascular disease, chronic liver disease, lipid disorder, gastrointestinal disease, renal disease, metabolic disease, cancer, and neurological disease.