(S)-2-AMINO-6-((3-AMINOPROPYL)AMINO)HEXANOIC ACID (APL) FOR USE IN THE TREATMENT OF NON-ALCOHOLIC STEATOHEPATITIS (NASH), LIVER INFLAMMATION, HEPATOCELLULAR BALLOONING, LIVER FIBROSIS AND STEATOSIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims benefit of U.S. Provisional Application No. 63/015,175, filed April 24, 2020, which is incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] The invention relates to methods and compositions for the treatment of non-alcoholic steatohepatitis (NASH).

BACKGROUND

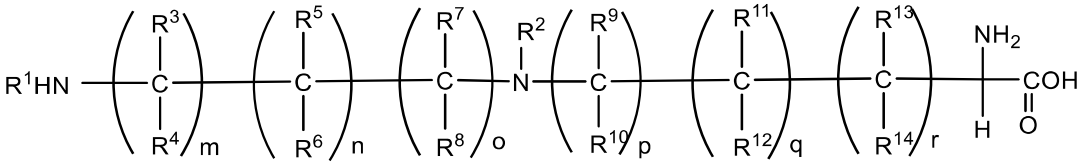
[0003] Non-alcoholic steatohepatitis (NASH) is a non-benign disorder characterized by substantial health risks. Subjects diagnosed with NASH are at significantly increased risk of morbidity and mortality. More specifically, NASH is characterized by increased risk of cardiovascular and liver-related mortality. NASH can lead to cirrhosis, which in turn can result in fluid retention, muscle wasting, bleeding from the intestines, and liver failure. Liver transplantation is the only treatment for advanced cirrhosis with liver failure, with NASH is currently the number two reason for liver transplants.

[0004] Accordingly, there is a continuing need for therapeutic agents for the treatment of NASH.

SUMMARY

[0005] Described herein in that are new methods for treating liver diseases and disorders, including non-alcoholic steatohepatitis (NASH).

[0005a] In one aspect, the present disclosure provides a use of a compound in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH) in a subject in need thereof, wherein said compound is a compound according to Formula I,



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2,
-NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$,
-SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13} and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

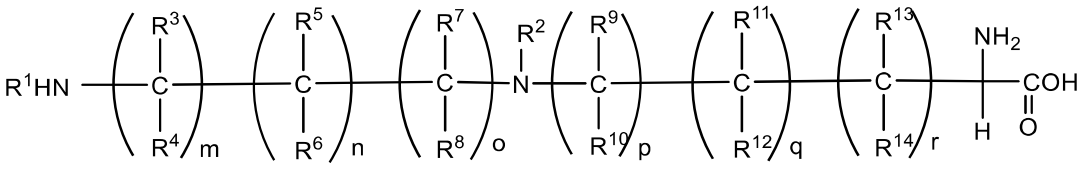
o is 0, 1, 2, 3 or 4;

p is 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4; and

r is 0, 1, 2, 3 or 4.

[0005b] In a further aspect, the present disclosure provides a use of a compound in the manufacture of a medicament for treating liver inflammation in a subject in need thereof wherein said compound is a compound according to Formula I,



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2,
-NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$,
-SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13} and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

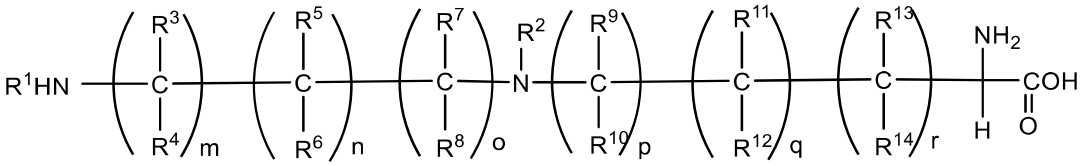
o is 0, 1, 2, 3 or 4;

p is 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4; and

r is 0, 1, 2, 3 or 4.

[0005c] In another aspect, the present disclosure provides a use of a compound in the manufacture of a medicament for treating hepatocellular ballooning in a subject in need thereof wherein said compound is a compound according to Formula I,



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2,
-NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$,
-SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13} and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

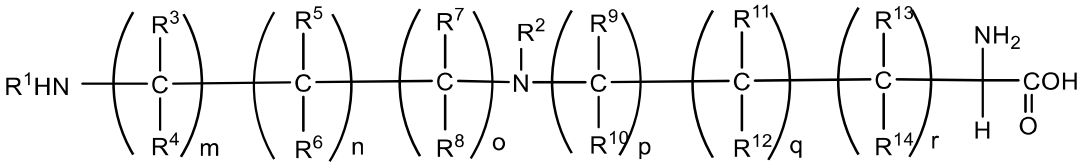
o is 0, 1, 2, 3 or 4;

p is 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4; and

r is 0, 1, 2, 3 or 4.

[0005d] In yet another aspect, the present disclosure provides a use of a compound in the manufacture of a medicament for treating liver fibrosis in a subject in need thereof, wherein said compound is a compound according to Formula I,



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2,
-NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -

NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$,
-SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13} and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

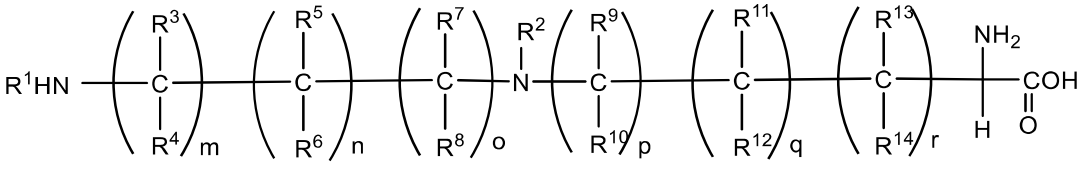
o is 0, 1, 2, 3 or 4;

p is 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4; and

r is 0, 1, 2, 3 or 4.

[0005e] In yet another aspect, the present disclosure provides a use of a compound in the manufacture of a medicament for treating steatosis in a subject in need thereof, wherein said compound is a compound according to Formula I,



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2,
-NH(C_1-C_6)alkyl, -$N[(C_1$-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-

C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl,
-$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$,
-SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13} and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

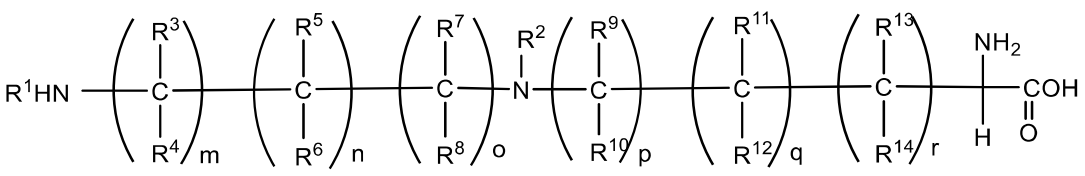
o is 0, 1, 2, 3 or 4;

p is 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4; and

r is 0, 1, 2, 3 or 4.

[0006] In one example, the disclosure features a method for treating non-alcoholic steatohepatitis (NASH), the method comprising administering to the subject in need thereof an effective amount of a compound according to Formula I,



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2, -NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2, -NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13}, and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is an integer from 1 to 4;

n is an integer from 0 to 4

o is an integer from 0 to 4;

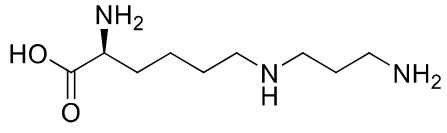
p is an integer from 1 to 4;

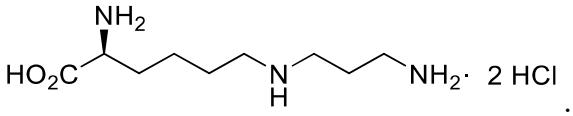
q is an integer from 0 to 4; and

r is an integer from 0 to 4.

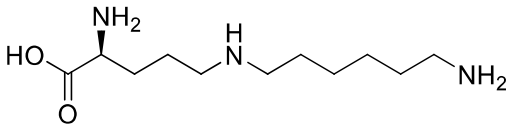
[0007] In another example, the disclosure features compounds according to Formula I, or a pharmaceutically acceptable salt thereof, for use in treating NASH in a subject.

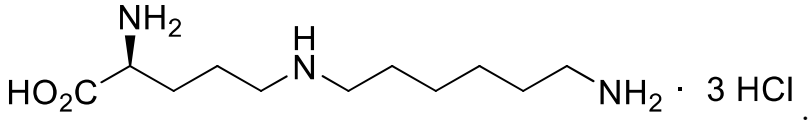
[0008] In another example, the disclosure features compounds of Formula I, or a pharmaceutically acceptable salt thereof, for preparation of a medicament for treatment of NASH.

[0009] In examples, a compound of Formula I is (*S*)-2-amino-6-((3-aminopropyl)amino)hexanoic acid,  (1), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula (I) is (S)-2-amino-6-((3-aminopropyl)amino)hexanoic acid dihydrochloride,

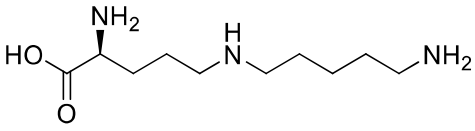


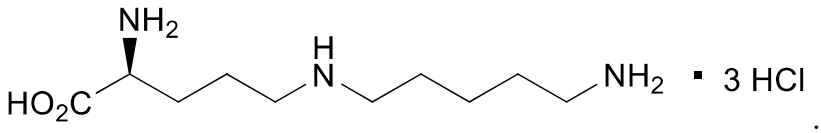
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[0010] In examples, a compound of Formula I is (*S*)-2-amino-5-((6-aminohexyl)amino)pentanoic acid,  (2), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula I is (*S*)-2-amino-5-((6-aminohexyl)amino)pentanoic acid trihydrochloride,



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[0011] In examples, a compound of Formula I is (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid,  (3), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula I is (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid trihydrochloride,



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[0012] In examples, R^1 and R^2 are independently selected from the group consisting of hydrogen and -(C_1-C_8)alkyl.

[0013] In examples, each of R^3, R^4, R^5, R^6, R^7 and R^8 is independently selected from hydrogen and -(C_1-C_8)alkyl.

[0014] In examples, each of R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from hydrogen and -(C_1-C_8)alkyl.

[0015] In examples, each of R^3, R^4, R^5, R^6, R^7 and R^8 is independently selected from hydrogen and -(C_1-C_8)alkyl; and each of R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} is independently selected from hydrogen and -(C_1-C_8)alkyl.

[0016] In examples, or a pharmaceutically acceptable salt thereof, the sum of m + n + o is in the range of from 2 to 10, and the sum of p + q + r is in the range of from 2 to 10.

[0017] In examples, m is 3; p is 4; each of n, o, q and r is zero. In examples, R^3, R^4, R^9, and R^{10} are independently selected from hydrogen and -(C_1-C_8)alkyl. In examples, R^1 and R^2 are independently selected from the group consisting of hydrogen and -(C_1-C_8)alkyl. In examples, R^1, R^2, R^3, R^4, R^9 and R^{10} are hydrogen.

[0018] In examples, m is 4; n is 2; o is zero; p is 3; q is 1; and r is zero. In examples, R^3, R^4, R^5, R^6 R^9, R^{10}, R^{11}, and R^{12} are independently selected from hydrogen and -(C_1-C_8)alkyl. In examples, R^1 and R^2 are independently selected from the group consisting of hydrogen and -(C_1-C_8)alkyl. In examples, R^1, R^2, R^3, R^4, R^5, R^6, R^9, R^{10}, R^{11}, and R^{12}, are hydrogen.

[0019] In examples, m is 4; n is 1; o is zero; p is 3; q is 1; and r is zero. In examples, R^3, R^4, R^5, R^6, R^9, R^{10}, R^{11} and R^{12} are independently selected from hydrogen and -(C_1-C_8)alkyl. In examples, R^1 and R^2 are independently selected from the group consisting of hydrogen and -(C_1-C_8)alkyl. In examples, R^1, R^2, R^3, R^4, R^5, R^6, R^9, R^{10}, R^{11}, and R^{12} are hydrogen.

[0020] In examples, a subject is a human.

[0021] In examples, a compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or any pharmaceutically acceptable salt thereof, is administered to a subject for a time period that is at least about four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, or sixteen weeks.

[0022] In examples, a compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or any pharmaceutically acceptable salt thereof, is administered to a subject for a time period that is at least about 4-6, 4-8, 4-10, 4-12, 4-14, or 4-16 weeks.

[0023] In examples, a compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or any pharmaceutically acceptable salt thereof, is administered to a subject at a dose of about 2-1000, 10-1000 or 10-100 mg/kg/day.

[0024] In examples, a compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or any pharmaceutically acceptable salt thereof, is administered to a subject at a dose that is about 10 mg/kg or greater per day.

[0025] In examples, a compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or any pharmaceutically acceptable salt thereof, is administered to a subject at a dose that is about 2 mg/kg or greater per day.

[0026] In examples, a compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or any pharmaceutically acceptable salt thereof, is administered to a subject at a total daily dose that is about 100-5000, 500-5000 or 600-3000 mg per day.

[0027] In examples, a compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or any pharmaceutically acceptable salt thereof, is orally administered to a subject.

[0028] In examples, a subject has a NAFLD Activity Score (NAS) of ≥ 4.

[0029] In examples, a subject has a NAFLD Activity Score (NAS) of ≥ 5.

[0030] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or any pharmaceutically acceptable salt thereof, results in a NAFLD Activity Score (NAS) of < 4.

[0031] In examples, a subject has non-cirrhotic NASH.

[0032] In examples, a subject has cirrhotic NASH.

[0033] In examples, a subject has liver inflammation. In examples, liver inflammation is lobular inflammation.

[0034] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or a pharmaceutically acceptable salt thereof results in a decrease in liver inflammation.

[0035] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or a pharmaceutically acceptable salt thereof results in a liver inflammation score of 0 or 1.

[0036] In examples, the liver of the subject is characterized by hepatocellular ballooning.

[0037] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or a pharmaceutically acceptable salt thereof results in a decrease in hepatocellular ballooning.

[0038] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or a pharmaceutically acceptable salt thereof results in ballooning score of 0.

[0039] In examples, a subject has elevated hepatic alanine aminotransferase (ALT) levels.

[0040] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or a pharmaceutically acceptable salt thereof results in decreased hepatic alanine aminotransferase (ALT) levels.

[0041] In examples, a subject has elevated hepatic aspartate aminotransferase (AST) levels.

[0042] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or a pharmaceutically acceptable salt thereof results in decreased hepatic aspartate aminotransferase (AST) levels.

[0043] In examples, a subject has liver fibrosis. In examples, a subject has stage 2, stage 3, or stage 4 liver fibrosis. In examples, a subject has cirrhosis.

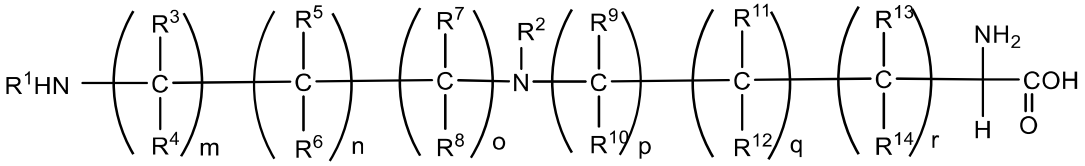
[0044] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or a pharmaceutically acceptable salt thereof results in stabilization of liver fibrosis in the subject.

[0045] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or a pharmaceutically acceptable salt thereof results in reversal of liver fibrosis in the subject.

[0046] In examples, a subject has a steatosis score of 1, 2, or 3.

[0047] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or a pharmaceutically acceptable salt thereof results in a decrease in liver hypertrophy in the subject.

[0048] In one example, the disclosure features a method for reducing liver inflammation, the method comprising administering to the subject in need thereof an effective amount of a compound according to Formula I,



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2, -NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2, -NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH,

thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13}, and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is an integer from 1 to 4;

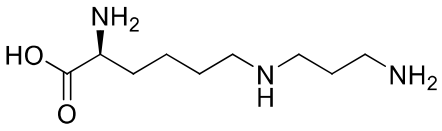
n is an integer from 0 to 4

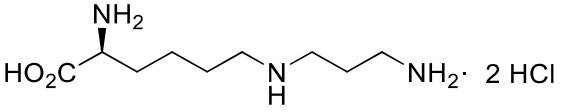
o is an integer from 0 to 4;

p is an integer from 1 to 4;

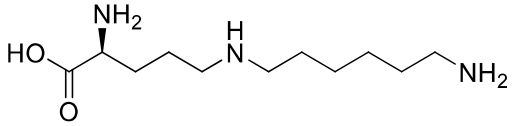
q is an integer from 0 to 4; and

r is an integer from 0 to 4.

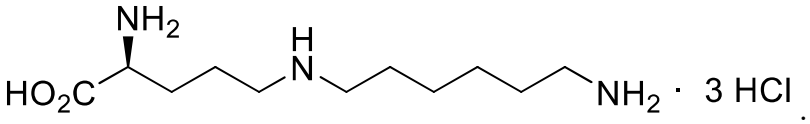
[0049] In examples, a compound of Formula I is (*S*)-2-amino-6-((3-aminopropyl)amino)hexanoic acid,  (1), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula (I) is (S)-2-amino-6-((3-aminopropyl)amino)hexanoic acid dihydrochloride,

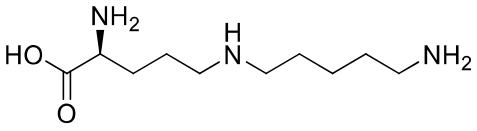


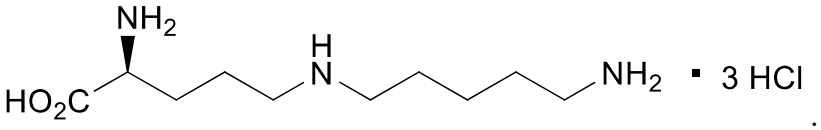
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[0050] In examples, a compound of Formula I is (*S*)-2-amino-5-((6-aminohexyl)amino)pentanoic acid,  (2), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula I is (*S*)-2-

amino-5-((6-aminohexyl)amino)pentanoic acid trihydrochloride,



[0051] In examples, a compound of Formula I is (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid,  (3), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula I is (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid trihydrochloride,

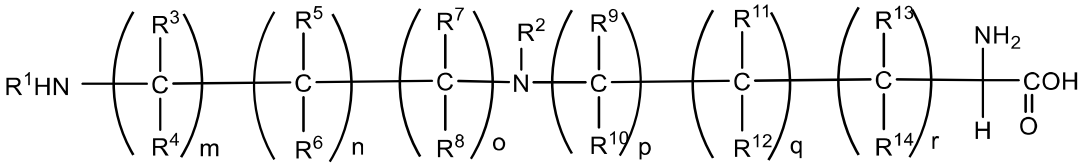


[0052] In examples, liver inflammation is lobular inflammation.

[0053] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)) or a pharmaceutically acceptable salt thereof results in a liver inflammation score of 0 or 1.

[0054] In examples, a subject has non-alcoholic steatohepatitis (NASH).

[0055] In one example, the disclosure features a method for reducing hepatocellular ballooning, the method comprising administering to the subject in need thereof an effective amount of a compound according to Formula I,



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2, -NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl,

-(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2, -NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13}, and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is an integer from 1 to 4;

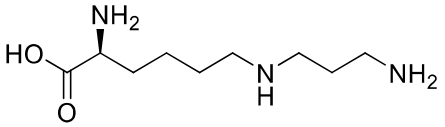
n is an integer from 0 to 4

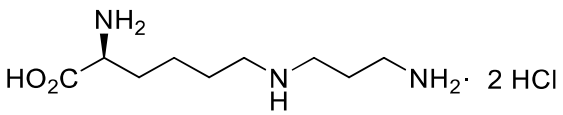
o is an integer from 0 to 4;

p is an integer from 1 to 4;

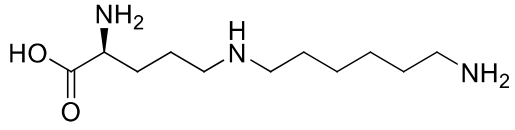
q is an integer from 0 to 4; and

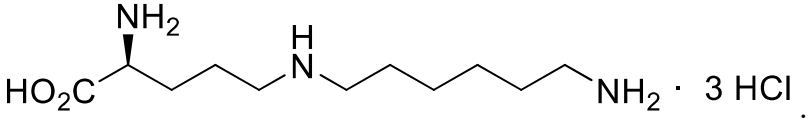
r is an integer from 0 to 4.

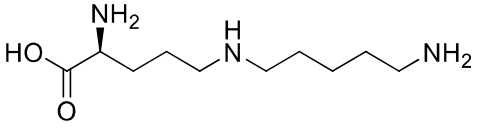
[0056] In examples, a compound of Formula I is (*S*)-2-amino-6-((3-aminopropyl)amino)hexanoic acid,  (1), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula (I) is (S)-2-amino-6-((3-aminopropyl)amino)hexanoic acid dihydrochloride,

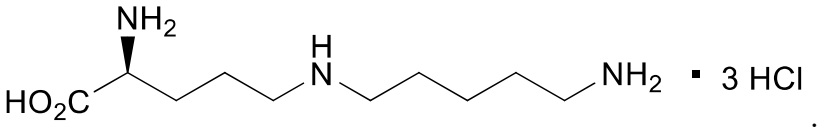


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[0057] In examples, a compound of Formula I is (*S*)-2-amino-5-((6-aminohexyl)amino)pentanoic acid,  (2), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula I is (*S*)-2-amino-5-((6-aminohexyl)amino)pentanoic acid trihydrochloride,



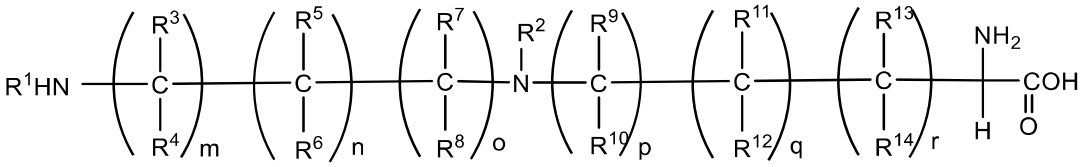
[0058] In examples, a compound of Formula I is (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid,  (3), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula I is (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid trihydrochloride,



[0059] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or a pharmaceutically acceptable salt thereof results in a ballooning score of 0.

[0060] In examples, a subject has non-alcoholic steatohepatitis (NASH).

[0061] In one example, the disclosure features a method for treating liver fibrosis, the method comprising administering to the subject in need thereof an effective amount of a compound according to Formula I,



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2, -NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2, -NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13}, and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is an integer from 1 to 4;

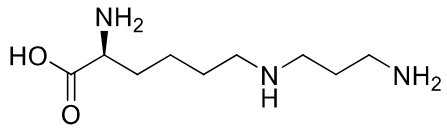
n is an integer from 0 to 4

o is an integer from 0 to 4;

p is an integer from 1 to 4;

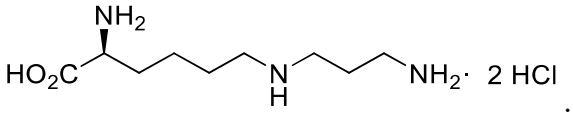
q is an integer from 0 to 4; and

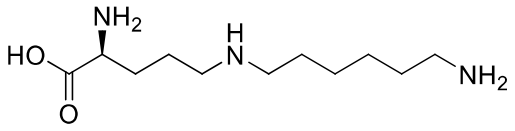
r is an integer from 0 to 4.

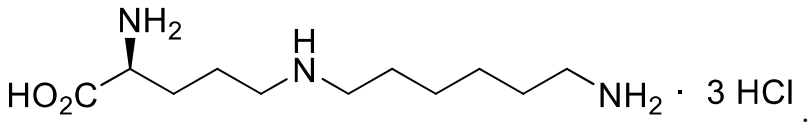
[0062] In examples, a compound of Formula I is (*S*)-2-amino-6-((3-aminopropyl)amino)hexanoic acid, 

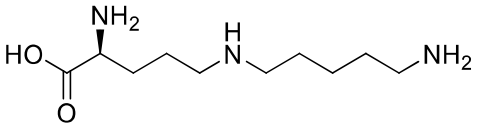
(1), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula (I) is (S)-

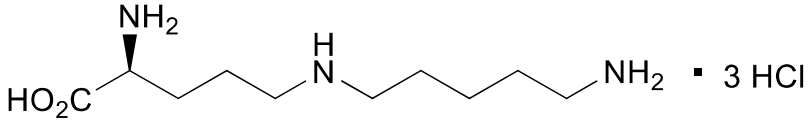
2-amino-6-((3-aminopropyl)amino)hexanoic acid dihydrochloride,



[0063] In examples, a compound of Formula I is (*S*)-2-amino-5-((6-aminohexyl)amino)pentanoic acid,  (2), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula I is (*S*)-2-amino-5-((6-aminohexyl)amino)pentanoic acid trihydrochloride,



[0064] In examples, a compound of Formula I is (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid,  (3), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula I is (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid trihydrochloride,



[0065] In examples, a subject has stage 2, stage 3, or stage 4 liver fibrosis.

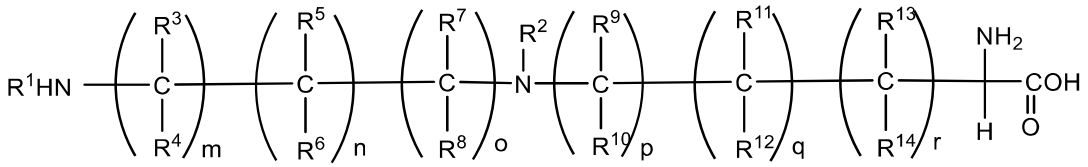
[0066] In examples, a subject has cirrhosis.

[0067] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or a pharmaceutically acceptable salt thereof results in stabilization of liver fibrosis in the subject.

[0068] In examples, administering of the compound of Formula I (*e.g.*, any one of Compounds (1), (2), and (3)), or a pharmaceutically acceptable salt thereof results in reversal of liver fibrosis in the subject.

[0069] In examples, a subject has non-alcoholic steatohepatitis (NASH).

[0070] In one example, the disclosure features a method for treating steatosis, the method comprising administering to the subject in need thereof an effective amount of a compound according to Formula I,



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2, -NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen,-CN, -NO_2, -NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13}, and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is an integer from 1 to 4;

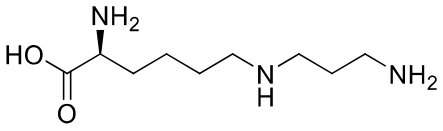
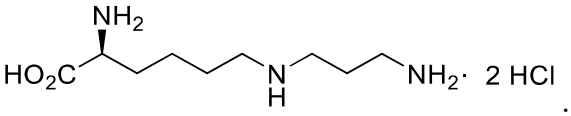
n is an integer from 0 to 4

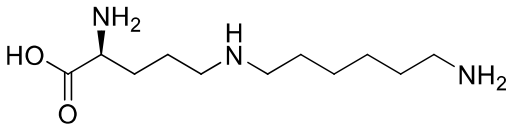
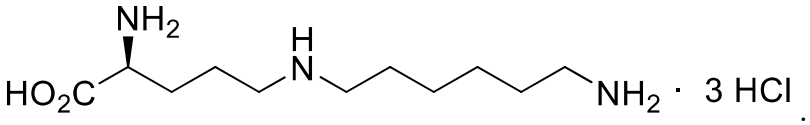
o is an integer from 0 to 4;

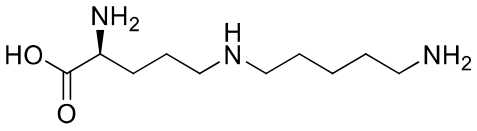
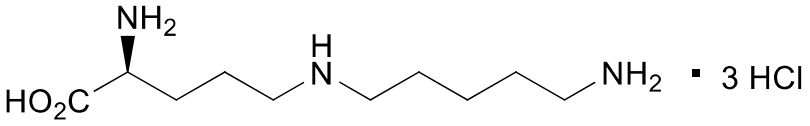
p is an integer from 1 to 4;

q is an integer from 0 to 4; and

r is an integer from 0 to 4.

[0071] In examples, a compound of Formula I is (*S*)-2-amino-6-((3-aminopropyl)amino)hexanoic acid,  (1), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula (I) is (S)-2-amino-6-((3-aminopropyl)amino)hexanoic acid dihydrochloride, .

[0072] In examples, a compound of Formula I is (*S*)-2-amino-5-((6-aminohexyl)amino)pentanoic acid,  (2), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula I is (*S*)-2-amino-5-((6-aminohexyl)amino)pentanoic acid trihydrochloride, .

[0073] In examples, a compound of Formula I is (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid,  (3), or a pharmaceutically acceptable salt thereof. In examples, a compound of Formula I is (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid trihydrochloride, .

[0074] In examples, a subject has a steatosis score of 1, 2, or 3.

[0075] In examples, administering of the compound of Formula I or a pharmaceutically acceptable salt thereof results in a decrease of steatosis in the subject.

[0076] In examples, a subject has non-alcoholic steatohepatitis (NASH).

[0077] As envisioned in the present disclosure with respect to the disclosed compositions of matter and methods, in one example the examples of the disclosure comprise the components and/or steps disclosed herein. In another example, the examples of the disclosure consist essentially of the components and/or steps disclosed herein. In yet another example, the examples of the disclosure consist of the components and/or steps disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0078] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0079] The accompanying drawings, which are included to provide a further understanding of the disclosure and are incorporated in and constitute a part of this specification, illustrate exemplary embodiments of the disclosure, and together with the description serve to explain the principles of the disclosure.

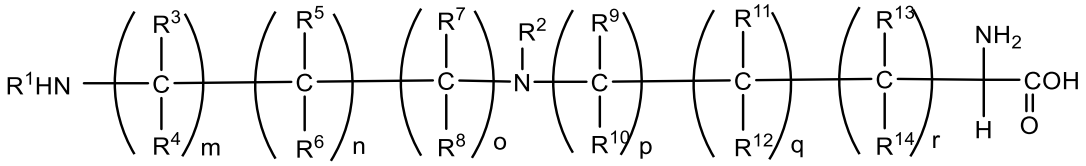
[0080] **Figure 1** depicts data regarding the effect of APL on impaired glucose tolerance in a rat model of NASH. Figure 1 is a plot of area under the curve (AUC) of a Glucose Tolerance Test (GTT) in Zucker lean (Fa/fa) and obese (fa/fa) rats treated twice daily for 78 days with either vehicle (positive control) or APL (treated). Two-way ANOVA and Bonferroni multiple comparison post tests were performed. A significant statistical difference was observed between positive control and treated groups (**$p<0.01$).

[0081] **Figure 2**, comprising **Fig. 2A** and **Fig. 2B**, depicts data regarding the effect of APL on impaired glucose tolerance in a diet induced mouse model of NASH. **Fig. 2A** is a plot of glucose levels in C57BL/6J mice fed either chow diet (CHOW) and vehicle (negative control); high fat/high fructose diet (HFD) and vehicle (positive control); or HFD and APL (treated) for 131 days, after which animals were fasted, glucose was administered orally (2

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a compound in the manufacture of a medicament for treating non-alcoholic steatohepatitis (NASH) in a subject in need thereof, wherein said compound is a compound according to Formula I,



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13} and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

o is 0, 1, 2, 3 or 4;

p is 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4; and

r is 0, 1, 2, 3 or 4.

2. The use of claim 1, wherein:

(i) the subject has a NAFLD Activity Score (NAS) of ≥ 4; and/or

(ii) the compound of Formula I or a pharmaceutically acceptable salt thereof results in a NAFLD Activity Score (NAS) of < 4.

3. The use of claim 1 or claim 2, wherein the subject has non-cirrhotic NASH or cirrhotic NASH.

4. The use of claim 1 or claim 2, wherein:

(i) the subject has liver inflammation, wherein optionally:

(a) the liver inflammation is lobular inflammation; and/or

(b) the compound of Formula I, or a pharmaceutically acceptable salt thereof, results in a decrease in liver inflammation; and/or

(c) the compound of Formula I or a pharmaceutically acceptable salt thereof, results in a liver inflammation score of 0 or 1; and/or

(ii) the liver of the subject is characterized by hepatocellular ballooning, and wherein optionally the compound of Formula I or a pharmaceutically acceptable salt thereof results in a decrease in

hepatocellular ballooning, optionally wherein the compound of Formula I or a pharmaceutically acceptable salt thereof results in a ballooning score of 0; and/or

(iii) the subject has elevated hepatic alanine aminotransferase (ALT) levels, wherein optionally wherein the compound of Formula I or a pharmaceutically acceptable salt thereof results in decreased hepatic alanine aminotransferase (ALT) levels; and/or

(iv) the subject has elevated hepatic aspartate aminotransferase (AST) levels, optionally wherein the compound of Formula I or a pharmaceutically acceptable salt thereof results in decreased hepatic aspartate aminotransferase (AST) levels; and/or

(v) the subject has liver fibrosis; optionally wherein

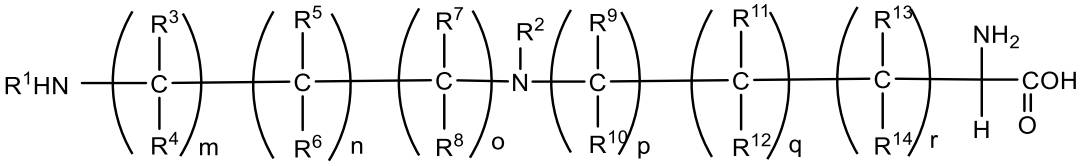
(a) the subject has stage 2, stage 3, or stage 4 liver fibrosis; and/or

(b) the compound of Formula I or a pharmaceutically acceptable salt thereof results in stabilization or reversal of liver fibrosis in the subject; and/or

(vi) the subject has a steatosis score of 1, 2, or 3, optionally wherein the compound of Formula I or a pharmaceutically acceptable salt thereof results in a decrease of steatosis in the subject; and/or

(vii) the compound of Formula I or a pharmaceutically acceptable salt thereof results in a decrease in liver hypertrophy in the subject.

5. Use of a compound in the manufacture of a medicament for treating liver inflammation in a subject in need thereof wherein said compound is a compound according to Formula I,



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13} and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

o is 0, 1, 2, 3 or 4;

p is 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4; and

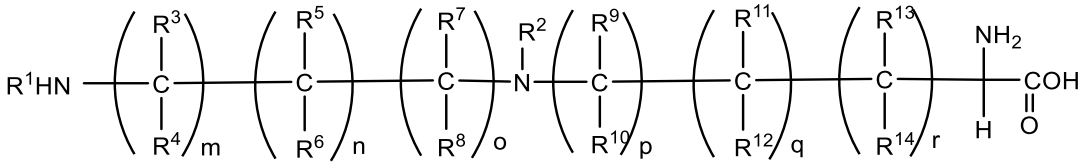
r is 0, 1, 2, 3 or 4.

6. The use of claim 5, wherein:

(i) said liver inflammation is lobular inflammation; and/or

(ii) the compound of Formula I or a pharmaceutically acceptable salt thereof results in a liver inflammation score of 0 or 1.

7. Use of a compound in the manufacture of a medicament for treating hepatocellular ballooning in a subject in need thereof wherein said compound is a compound according to Formula I,



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13} and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

o is 0, 1, 2, 3 or 4;

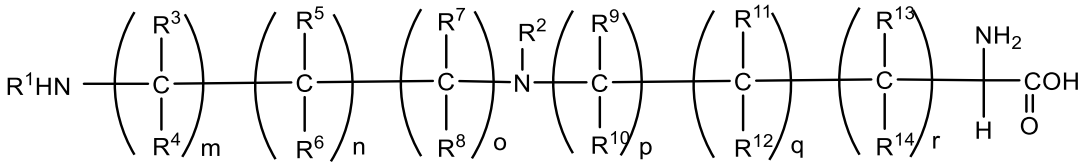
p is 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4; and

r is 0, 1, 2, 3 or 4.

8. The use of claim 7, wherein the compound of Formula I or a pharmaceutically acceptable salt thereof results in a ballooning score of 0.

9. Use of a compound in the manufacture of a medicament for treating liver fibrosis in a subject in need thereof, wherein said compound is a compound according to Formula I,



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13} and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

o is 0, 1, 2, 3 or 4;

p is 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4; and

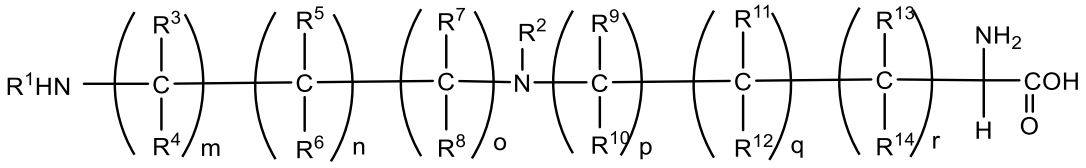
r is 0, 1, 2, 3 or 4.

10. The use of claim 9, wherein:

(i) the subject has (a) stage 2, stage 3, or stage 4 liver fibrosis or (b) cirrhosis; and/or

(ii) the compound of Formula I or a pharmaceutically acceptable salt thereof results in stabilization or reversal of liver fibrosis in the subject.

11. Use of a compound in the manufacture of a medicament for treating steatosis in a subject in need thereof, wherein said compound is a compound according to Formula I,



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -NH(C_1-C_6)alkyl, -N[(C_1-C_6)alkyl)]$_2$, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^2 is selected from the group consisting of hydrogen, -(C_1-C_8)alkyl, -(C_1-C_8)alkenyl, -(C_1-C_8)alkynyl, unsubstituted or substituted -ara(C_1-C_6)alkyl, unsubstituted or substituted -heteroara(C_1-C_6)alkyl, where the substituents on said substituted ara(C_1-C_6)alkyl and substituted heteroara(C_1-C_6)alkyl are selected from the group consisting of halogen, -CN, -NO_2,- NH_2, -OH, halo(C_1-C_6)alkyl, -(C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, -SH, thio(C_1-C_6)alkyl, -$SONH_2$, -SO_2NH_2, -SO-(C_1-C_6)alkyl, -SO_2-(C_1-C_6)alkyl, -$NHSO_2$(C_1-C_6)alkyl, and -$NHSO_2NH_2$;

R^3, R^4, R^7, R^8, R^9, R^{10}, R^{13} and R^{14} are independently selected from the group consisting of hydrogen and -(C_1-C_6)alkyl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^5 and R^6 cannot be –OH;

R^{11} and R^{12} are independently selected from the group consisting of hydrogen, -(C_1-C_6)alkyl and –OH, provided that both R^{11} and R^{12} cannot be –OH;

m is 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

o is 0, 1, 2, 3 or 4;

p is 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4; and

r is 0, 1, 2, 3 or 4.

12. The use of claim 11, wherein:

(i) the subject has a steatosis score of 1, 2, or 3; and/or

(ii) the compound of Formula I or a pharmaceutically acceptable salt thereof results in a decrease of steatosis in the subject.

13. The use of any one of claims 5-12, wherein the subject has non-alcoholic steatohepatitis (NASH).

14. The use of any one of the preceding claims, wherein:

(i) the subject is a human; and/or

(ii) the compound of Formula I, or a pharmaceutically acceptable salt thereof, is to be administered to the subject

(a) for a time period that is at least four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, or sixteen weeks;(b) for a time period that is at least 4-6, 4-8, 4-10, 4-12, 4-14, or 4-16 weeks;

(c) at a dose of 2-1000, 10-1000 or 10-100 mg/kg per day;

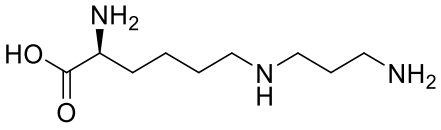
(d) at a dose that is about 10 mg/kg or greater per day; or

(e) at a total daily dose that is100-5000, 500-5000 or 600-3000 mg per day; and/or

(iii) the compound of Formula I is to be orally administered.

15. The use of any one of the preceding claims, wherein the compound is:

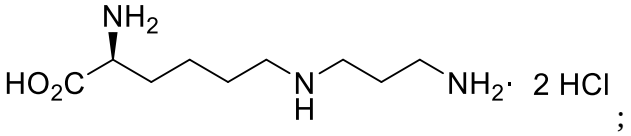
(i) (*S*)-2-amino-6-((3-aminopropyl)amino)hexanoic acid,



, or a pharmaceutically acceptable salt thereof,

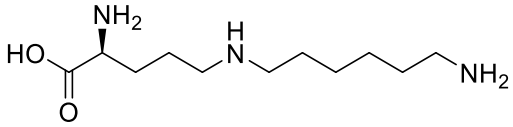
optionally wherein the compound is a hydrochloride salt of (S)-2-amino-6-((3-aminopropyl)amino)hexanoic acid,

optionally wherein the compound is (S)-2-amino-6-((3-aminopropyl)amino)hexanoic acid dihydrochloride,



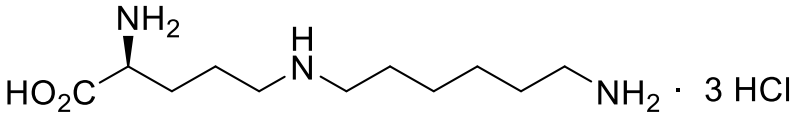
; or

(ii) (S)-2-amino-5-((6-aminohexyl)amino)pentanoic acid,



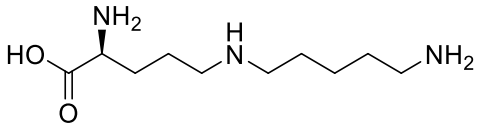
, or a pharmaceutically acceptable salt thereof, optionally wherein the compound is a hydrochloride salt of (*S*)-2-amino-5-((6-aminohexyl)amino)pentanoic acid,

optionally wherein the compound is (*S*)-2-amino-5-((6-aminohexyl)amino)pentanoic acid trihydrochloride,



; or

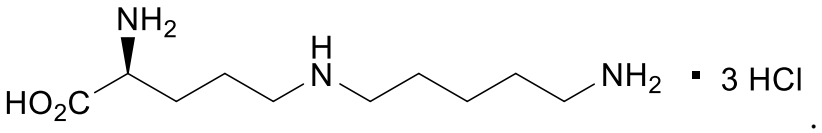
(iii) (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid,



, or a pharmaceutically acceptable salt thereof,

optionally wherein the compound is a hydrochloride salt of (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid,

optionally wherein the compound is (S)-2-amino-5-((5-aminopentyl)amino)pentanoic acid trihydrochloride,



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