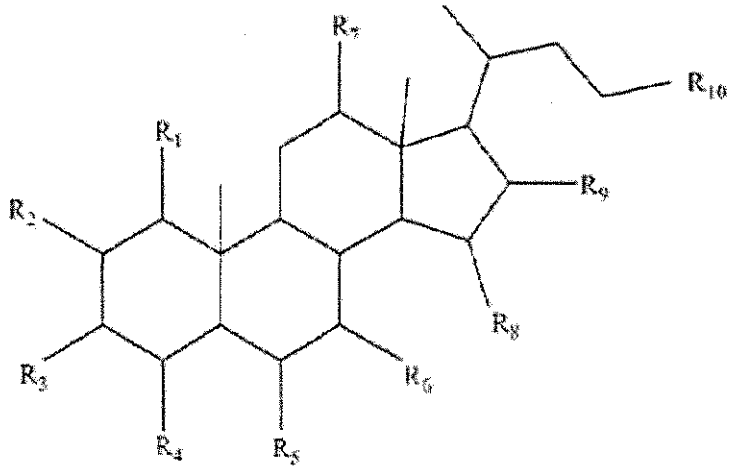
SUMMARY ~~OF THE INVENTION~~

[0010] The present disclosure~~invention~~ provides, in part, polyhydroxylated bile acids for treating biliary disorders, for example, biliary disorders arising out of cholestasis or portal hypertension, or for stimulating bile flow in for example normal subjects or subjects not diagnosed with a biliary disorder.

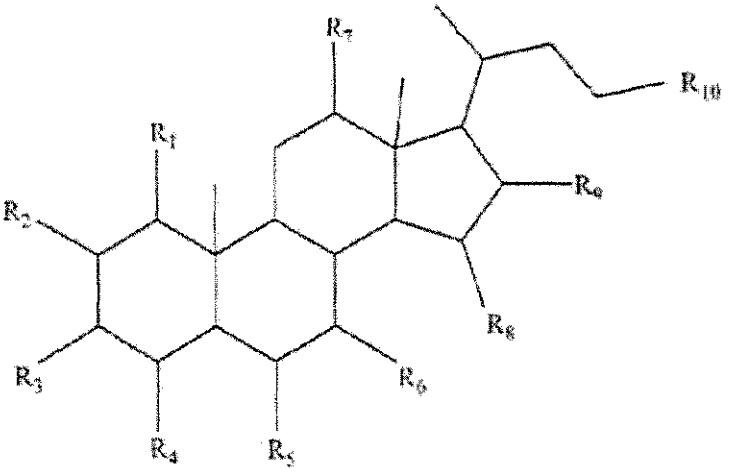
[0010a] In a first aspect, there is provided the use of a compound according to Formula I:



or a pharmaceutically-acceptable derivative thereof, wherein any one of R_1 to R_9 may be -H or -OH, provided that at least four of R_1 to R_9 are -OH; and

R_{10} is -COOH or $-CH_2OH$; in the manufacture of a medicament for treating a biliary disorder or stimulating bile flow in a subject in need thereof.

[0010b] In a second aspect, there is provided a pharmaceutical or nutritional composition comprising a compound according to Formula I:



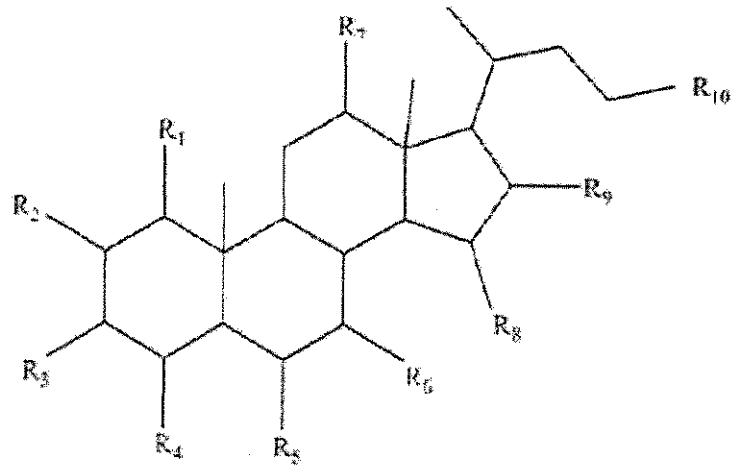
or a pharmaceutically-acceptable derivative thereof, together with a pharmaceutically acceptable carrier, wherein

any one of R_1 to R_9 may be -H or -OH, provided that at least four of R_1 to R_9 are -OH; and

R_{10} is -COOH or $-CH_2OH$.

[0010c] In a third aspect, there is provided the use of the composition as defined above for the preparation of a medicament for treating a biliary disorder or stimulating bile flow in a subject in need thereof.

[0010d] In a fourth aspect, there is provided an article of manufacture comprising a compound according to Formula I:



or a pharmaceutically-acceptable derivative thereof, together with instructions for use in treating biliary discorder or stimulating bile flow, wherein

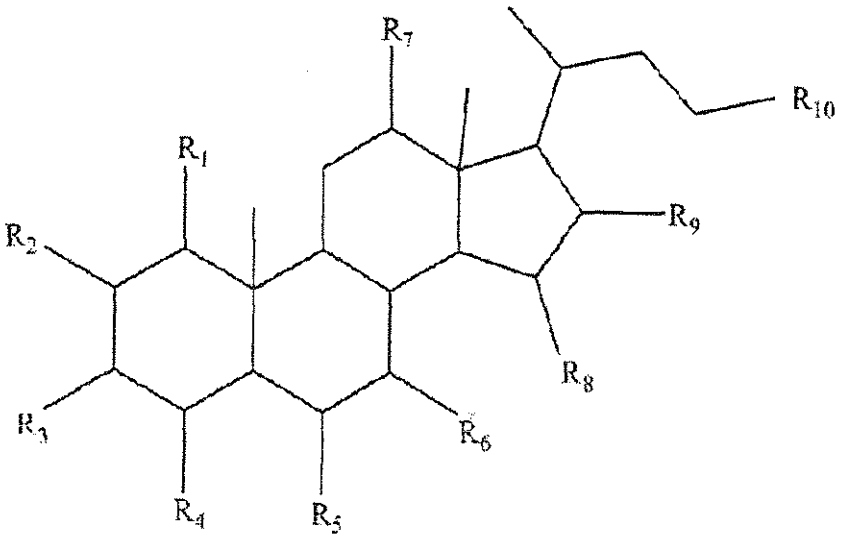
any one of R_1 to R_9 may be –H or –OH, provided that at least four of R_1 to R_9 are –OH; and

R_{10} is -COOH or $–CH_2OH$.

[0010e] In a fifth aspect, there is provided a 2α,3α,7α,12α-tetrahydroxy-5β-cholanoic acid.

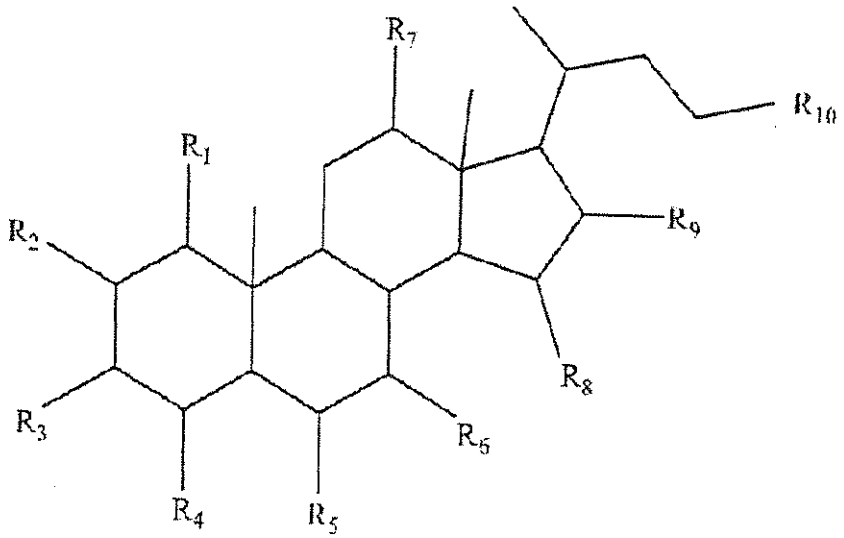
[0010f] In a sixth aspect, there is provided a 3α,4α,7α,12α-tetrahydroxy-5β-cholanoic acid.

[0011] In one embodiment~~aspect~~, the present disclosure~~invention~~ provides a method of treating a bile disorder in a subject in need thereof or of stimulating bile flow in a subject, the method comprising administering an effective amount of a compound according to Formula I:



or a derivative thereof, wherein any one of R_1 to R_9 may be –H or –OH, provided that at least four of R_1 to R_9 are –OH; and R_{10} may be –COOH or $-CH_2OH$.

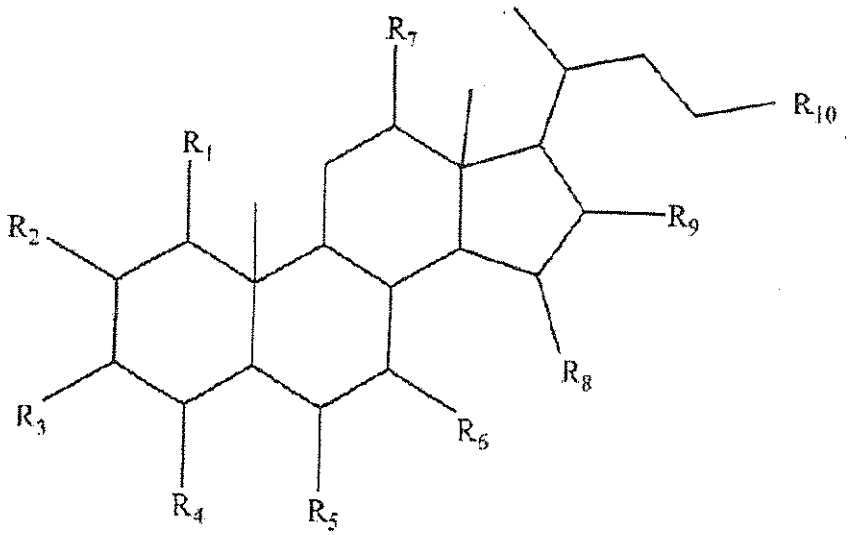
[0012] In ~~an~~ another~~lternative~~ embodiment~~aspect~~, the present disclosure~~invention~~ provides a pharmaceutical or nutritional composition comprising a compound according to Formula I:



or a derivative thereof, together with a pharmaceutically or physiologically or nutritionally acceptable carrier, wherein any one of R_1 to R_9 may be –H or –OH, provided that at least four of R_1 to R_9 are –OH; and R_{10} may be –COOH or $-CH_2OH$.

[0013] In ~~an~~ another embodiment~~alternative aspect~~, the present disclosure~~invention~~ provides the use of a pharmaceutical or nutritional composition as disclosed herein~~according to the invention~~ for the preparation of a medicament for treating a biliary disorder or stimulating bile flow.

[0014] In ~~an~~ another embodiment~~alternative aspect~~, the present disclosure~~invention~~ provides an article of manufacture comprising a compound according to Formula I:



[0023] In alternative embodiments, the compound may be a conjugated compound, e.g., a taurine or a glycine conjugate e.g., tauryl or glycyl conjugate of a 3α, 6β, 7α, 12β-tetrahydroxy-5β-cholan-24-oic acid, a tauryl or glycyl conjugate of a 3α, 6β, 7β, 12β-tetrahydroxy-5β-cholan-24-oic acid, a tauryl conjugate of a 3α, 6β, 7α, 12α-tetrahydroxy-5β-cholan-24-oic acid, or tauryl conjugate of a 3α, 6β, 7β, 12α-tetrahydroxy-5β-cholan-24-oic acid.

[0024] In alternative embodiments, the method may comprise administering at least one other therapeutic or prophylactic agent e.g., an agent having preferential affinity for BSEP, or at least one other nutritional supplement. The therapeutic or prophylactic agent or nutritional supplement may be ursodeoxycholate or a variant or derivative thereof.

[0025] In alternative embodiments, the biliary disorder may be benign biliary strictures, benign pancreatic disease cysts, diverticulitis, liver fibrosis, liver damage, common bile duct stones, pancreatitis, pancreatic cancer or pseudocyst, periampullary cancer, bile duct carcinoma, primary sclerosing cholangitis, autoimmune cholangitis, extrinsic duct compression (e.g., compression due to a mass or tumor on a nearby organ), viral hepatitis, sepsis, bacterial abscess, use of drugs e.g., drug-induced idiosyncratic hepatotoxicity, lymphoma, tuberculosis, metastatic carcinoma, sarcoidosis, amyloidosis, intravenous feeding, primary biliary cirrhosis, primary sclerosing cholangitis, alcoholic hepatitis with or without cirrhosis, nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, chronic hepatitis with or without cirrhosis, intrahepatic cholestasis of pregnancy, biliary calculosis, biliary dyscinesia, Sjogren syndrome, Wilson's disease, ischemia, toxins, alcohol, acute liver failure, α1-antitrypsin deficiency, PFIC2, Benign Recurrent Intrahepatic Cholestasis, hepatocellular carcinoma, portal hypertension, veno-occlusive disease, or hepatic vein thrombosis. The biliary disorder may arise or potentially arise from cholestasis.

[0026] In alternative embodiments, the subject may be a human.

[0027] This summary ~~of the invention~~ does not necessarily describe all features of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] **FIGURE 1** shows the cholestatic phenotype of the triple knockout (mdr1$1^{-/-}$/$mdr1a^{-/-}$/$1b^{-/-}$) mice: a) A view of abdomens showing liver enlargement of a TKO mouse in comparison with b) a wildtype mouse; c) Periportal fibrosis in the livers of a two month old male TKO mouse (Masson trichrome staining), 40x; d) Ultrastructual changes in hepatocytes, showing dilated

27. The composition of any one of claims 17 to 26, further comprising at least one other therapeutic agent.

28. The composition of claim 27, wherein said other therapeutic agent has a preferential affinity for Bile Salt Export Protein (BSEP/ABCB11/SPGP).

29. The composition of claim 27, wherein said other therapeutic agent is ursodeoxycholate.

30. Use of the composition of any one of claims 17 to 29 for the preparation of a medicament for treating a biliary disorder or stimulating bile flow in a subject in need thereof.

31. The use of claim 30 wherein said biliary disorder is selected from the group consisting of benign biliary strictures, benign pancreatic disease cysts, diverticulitis, liver fibrosis, liver damage, common bile duct stones, pancreatitis, pancreatic cancer or pseudocyst, periampullary cancer, bile duct carcinoma, primary sclerosing cholangitis, autoimmune cholangitis, extrinsic duct compression (e.g., compression due to a mass or tumor on a nearby organ, viral hepatitis, sepsis, bacterial abscess, use of drugs e.g., drug-induced idiosyncratic hepatotoxicity, lymphoma, tuberculosis, metastatic carcinoma, sarcoidosis, amyloidosis, intravenous feeding, primary biliary cirrhosis, primary sclerosing cholangitis, alcoholic hepatitis with or without cirrhosis, nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, chronic hepatitis with or without cirrhosis, intrahepatic cholestasis of pregnancy, biliary calculosis, biliary dyscinesia, Sjogren syndrome, Wilson's disease, ischemia, toxins, alcohol, acute liver failure, a 1 -antitrypsin deficiency, PFIC2, Benign Recurrent Intrahepatic Cholestasis, hepatocellular carcinoma, portal hypertension, veno-occlusive disease, and hepatic vein thrombosis.

32. The use of claim ~~26~~ 30 wherein said biliary disorder arises from cholestasis.

33. The use of any one of claims 30 to 32 wherein said subject is a human.

34. An article of manufacture comprising a compound according to Formula I: