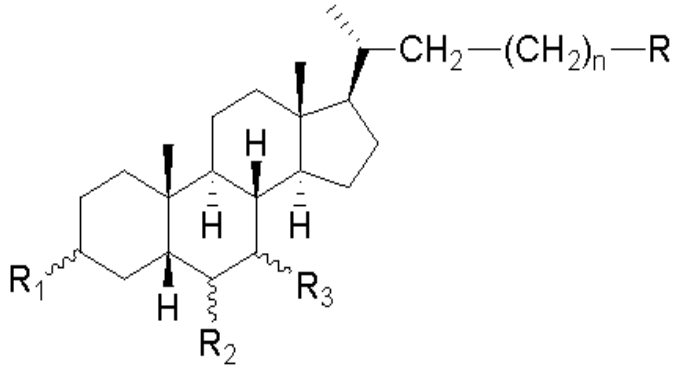
CLAIMS

1. A compound of formula (I)



(I)

wherein

R_1 is OH or H;

R_2 is Et or =CH-CH_3;

R_3 is OH or H;

n is 0, 1, or 3;

R is CH_2OH, COOH, CH_2OSO_3H, or CN;

proviso that

when R_2 is Et or =CH-CH_3 and R_3 is OH:

if n is 0 or 1 then R is CH_2OH or CN when R_1 is alpha-OH or R is COOH, CH_2OH or CH_2OSO_3H when R_1 is beta-OH or H;

if n is 3 then R_1 and R are as defined above;

including inorganic and organic pharmaceutically acceptable salts, solvates or amino acid conjugates thereof;

excluding a compound wherein

compund ID	N	R_1	R_2	R_3	R
BAR504	1	alpha-OH	alpha-Et	alpha-OH	CH2OH
BAR502	0	alpha-OH	alpha-Et	alpha-OH	CH2OH

2. The compound according to claim 1 wherein R_2 is Et or =CH-CH_3, R_3 is OH and

if n is 0 or 1, then R is CH_2OH or CN when R_1 is alpha-OH or R is CH_2OH, CH_2OSO_3H or COOH when R_1 is beta-OH or H;

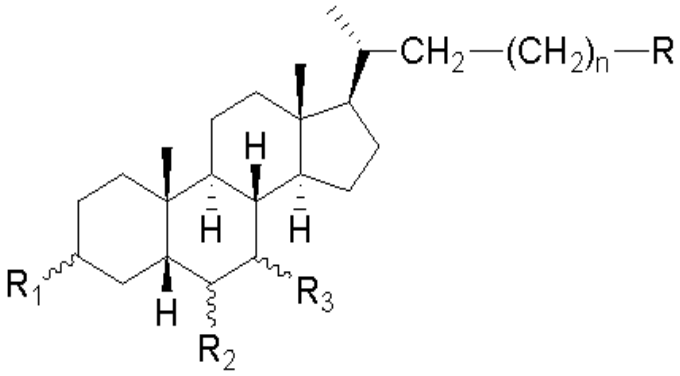
if n is 3 then R_1, R_3 and R are as defined above.

3. The compound according to claim 2 wherein

n is 0 or 1, R is CH_2OH or CN and R_1 is alpha-OH or n is 0 or 1, R is COOH, CH_2OH or CH_2OSO_3H and R_1 is beta-OH or H.

4. The compound according to claim 2 wherein R_2 is Et, n is 3, R_1 is alpha-OH and R_3 is alpha-OH.

5. A method for the prevention and/or treatment of diseases responsive to FXR and/or TGR5/GPBAR1 modulation selected from the group of gastrointestinal disorders, liver diseases, cardiovascular diseases, atherosclerosis, metabolic diseases, infectious diseases, cancer, renal disorders, inflammatory disorders, and neurological disorders, comprising administration of a compound of formula (I)



(I)

wherein

R_1 is OH or H;

R_2 is Et or =CH-CH_3;

R_3 is OH or H;

n is 0, 1, or 3;

R is CH_2OH, COOH, CH_2OSO_3H, or CN;

proviso that

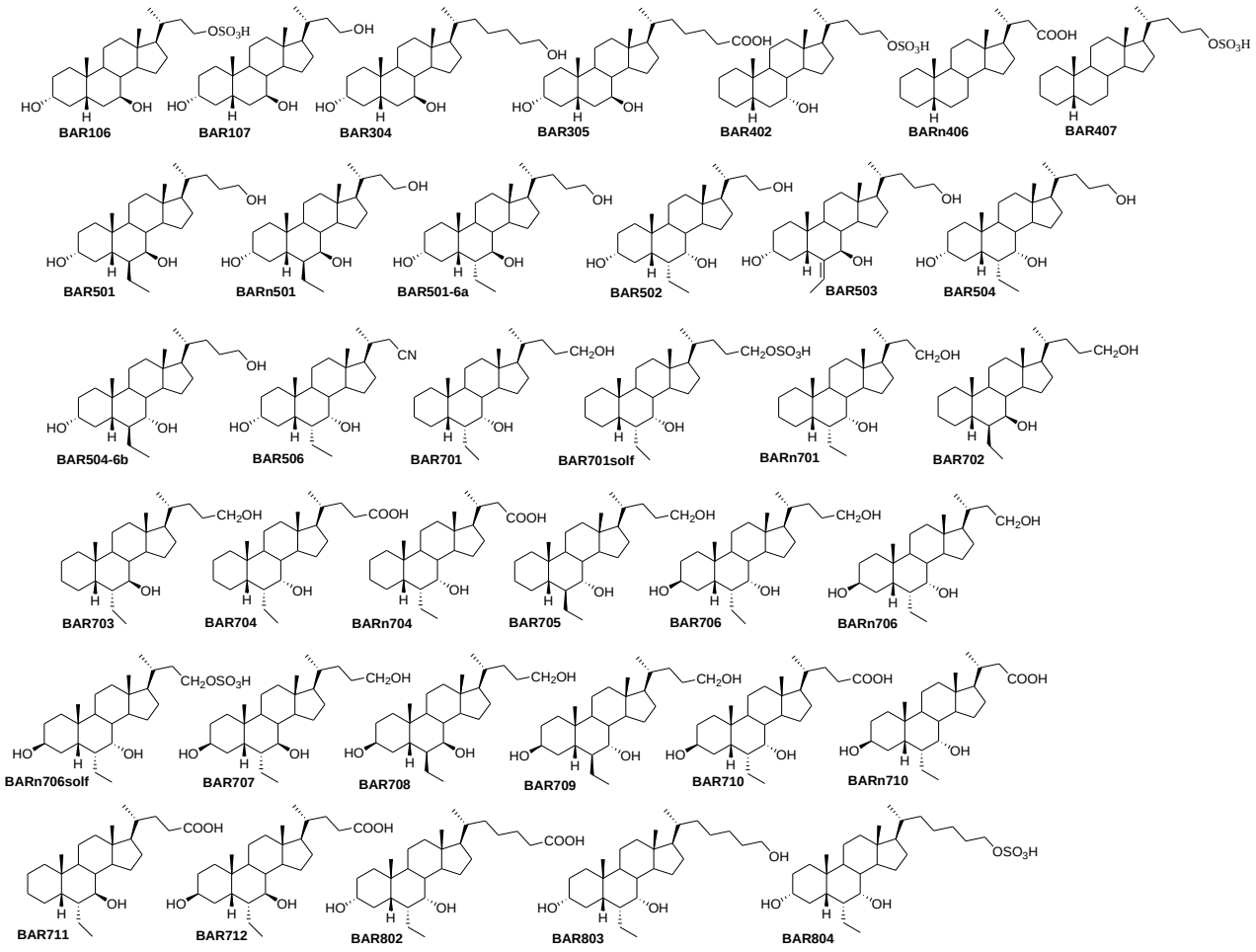
when R_2 is Et or =CH-CH_3 and R_3 is OH:

if n is 0 or 1 then R is CH_2OH or CN when R_1 is alpha-OH or R is CH_2OH, CH_2OSO_3H or COOH when R_1 is beta-OH or H;

if n is 3 then R_1 and R are as defined above;

including inorganic and organic pharmaceutically acceptable salts, solvates or amino acid conjugates thereof.

6. The method according to claim 5 wherein said compound of formula (I) is selected from the group consisting of

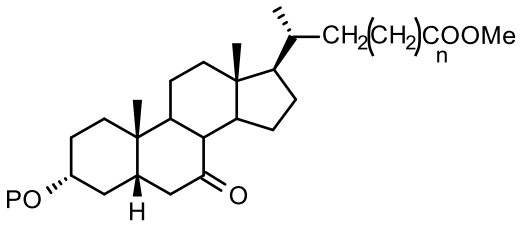


7. The method according to claim 5 or 6 wherein the compound of formula (I) is administered with at least another pharmaceutical ingredient.

8. Use of a compound of formula (I) according to any one of claims 1-6 in the preparation of a medicament for the prophylactic and/or treatment of diseases responsive to FXR and/or TGR5/GPBAR1 modulation selected from the group of gastrointestinal disorders, liver diseases, cardiovascular diseases, atherosclerosis, metabolic diseases, infectious diseases, cancer, renal disorders, inflammatory disorders, and neurological disorders.

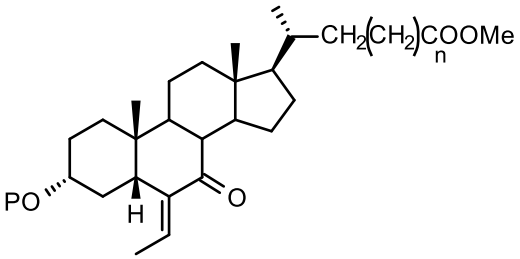
9. The use according to claim 8 wherein the medicament additionally comprises at least one other pharmaceutical ingredient.

10. A process for preparing a compound of formula (I), according to any one of claims 1-6, wherein R_2 is $=CH\text{-}CH_3$ or Et and R_3 is not H, said process comprising subjecting a compound of formula (VIII) to an aldol condensation thus contacting a compound of formula (VIII)



(VIII)

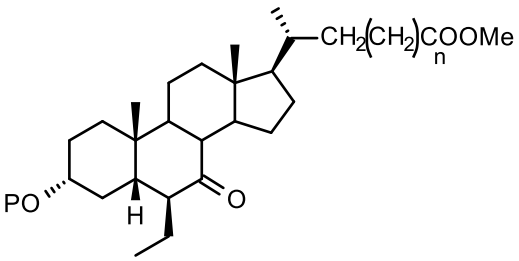
wherein n is 0 or 1, P is an hydroxyl protecting group, with alkyl lithium, such as nBuLi, and subsequently with acetaldehyde, preferably in presence also of $BF_3(OEt)_2$, for obtaining a compound of formula (IX)



(IX)

wherein n and P are as above described and

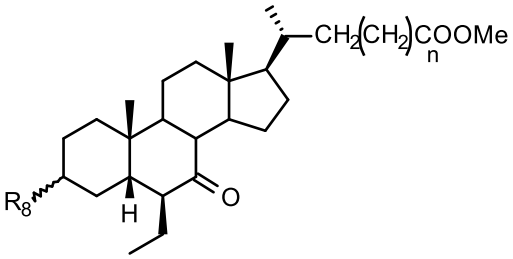
wherein the compound of formula (IX) is subjected to a catalytic hydrogenation, for obtaining a compound of formula (X)



(X).

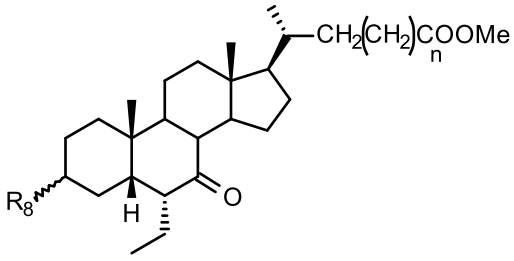
11. The process according to claim 10 wherein the compound of formula (X) is subjected to reduction of carbonyl at C7 by contacting the compound of formula (X) with $NaBH_4$ or $Ca(BH_4)_2$ for obtaining a mixture of alpha-OH and beta-OH at C7; and subsequently subjected to a treatment with $LiBH_4$ which completely reduces the methyl ester function on side chain to $–CH_2OH$.

12. A process for preparing a compound of formula (I), according to any one of claims 1-6, wherein R_2 is alpha-Et, said process comprising contacting with MeONa/MeOH a compound of formula (XIV)



(XIV)

wherein n is 0 or 1, R_8 is beta-OH, OAc or H for obtaining epimerization of the C6 stereocenter thus obtaining a compound of formula (XI)

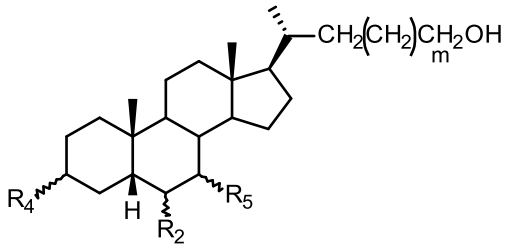


(XI)

wherein, in case R_8 is OAc the treatment with MeONa/MeOH affords simultaneously the C3 acetoxy group hydrolysis.

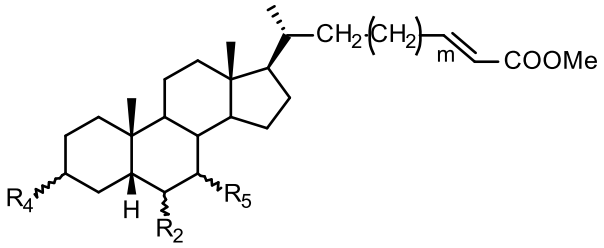
13. The process according to claim 12 wherein a reduction of carbonyl at C7 is obtained contacting a compound of formula (XI) or corresponding compound having COOH at the side chain, with $LiBH_4$ obtaining almost exclusively alpha-OH at C7; wherein the treatment with $LiBH_4$ simultaneously reduces, if present, the methyl ester function on side chain to –CH2OH and de-protects OAc if present at C3.

14. A process for preparing a compound of formula (I), according to any one of claims 1-2 or any one of claims 4-6, wherein n= 3 said process comprising subjecting a corresponding compound of formula (IV)



(IV)

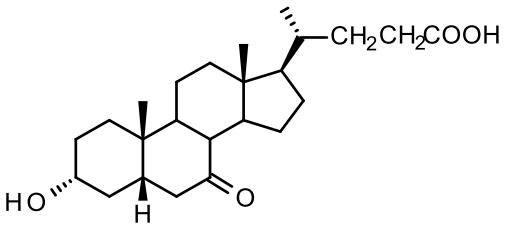
wherein m=n-2=1, R_4 and R_5, if other than H, are OP, wherein P is an alcoholic protecting function, and R_2 is H or Et, to a one pot Swern oxidation/Wittig C2 homologation for obtaining a protected methyl ester of formula (V)



(V)

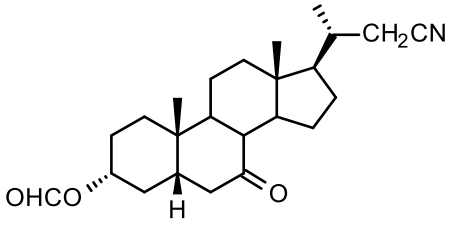
wherein m=1, R_2 is as defined in claim 1, R_4 and R_5, if other than H, are OP, wherein P is an alcoholic protecting function.

15. A process for preparing a compound of formula (I), according to any one of claims 1-3 or any one of claims 5-6, wherein n=0, said process comprising contacting a compound of formula (XII)



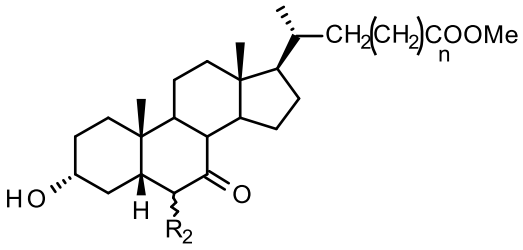
(XII)

with HCOOH and $HClO_4$ and subsequently contacting the resulting compound with TFA, trifluoroacetic anhydride and $NaNO_2$ for obtaining a compound of formula (VII)



(VII)

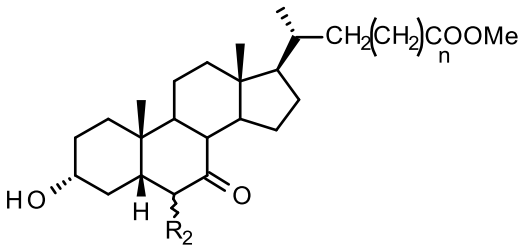
16. A process for preparing a compound of formula (I), according to any one of claims1-6, wherein R_1 is beta-OH, said process comprising starting from a compound having formula (XIII)



(XIII)

wherein R_2 is Et, n is 0 or 1 and inverting the C3 hydroxyl configuration by treatment with tosyl chloride in presence of a base then followed by a treatment with CH_3COOK.

17. A process for preparing a compound of formula (I), according to any one of claims 1-6, wherein R_1 is H, said process comprising subjecting a compound of formula (XIII)



(XIII)

wherein n is 0 or 1, R_2 Et or H, to tosylation and elimination at C-3 hydroxyl group followed by double bond reduction by way of a catalytic hydrogenation.