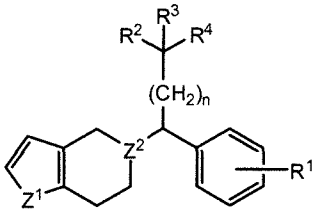
Claims

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein

each of R^1, R^2, and R^3 is independently -H, -OH, $-NH_2$, -NH(alkyl), -N(alkyl)(alkyl), hydrocarbyl, -O-hydrocarbyl, aryl, -O-aryl, aralkyl, -O-aralkyl, heteroaryl, -O-heteroaryl, heterocyclyl, -O-heterocyclyl, halo, $-OCF_3$, -C(O)O(alkyl), -OC(O)(alkyl), $-C(O)NH_2$, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), -OC(O)O(alkyl), $-OC(O)NH_2$, -OC(O)NH(alkyl), -OC(O)N(alkyl)(alkyl), -CHNH, -CHN(alkyl), or $-SO_2NH_2$;

R^4 is -H, -OH, -COOH, $-NH_2$, -NH(alkyl), -N(alkyl)(alkyl), -hydrocarbyl, -O-hydrocarbyl, -aryl, -O-aryl, -aralkyl, -O-aralkyl, -heteroaryl, -O-heteroaryl, -heterocyclyl, -O-heterocyclyl, -halo, -C(O)O(alkyl), -OC(O)(alkyl), $-C(O)NH_2$, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), -OC(O)O(alkyl), $-OC(O)NH_2$, -OC(O)NH(alkyl), or -OC(O)N(alkyl)(alkyl);

Z^1 is CH_2, S, O, NH, N-hydrocarbyl, N-aryl, N-heteroaryl, or N-heterocyclyl;

Z^2 is CH or N; and

n is an integer from 1-6.

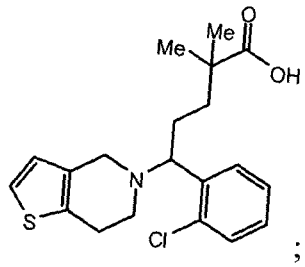
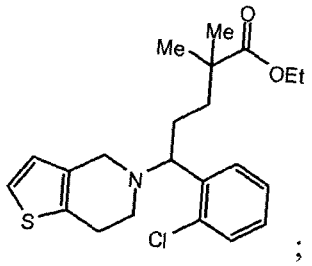
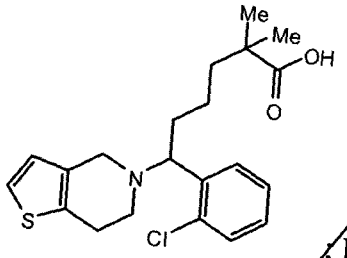
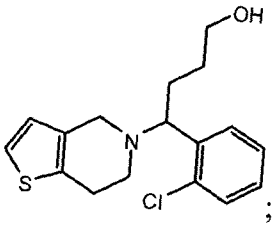
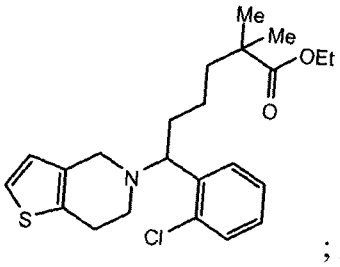
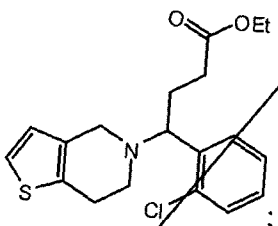
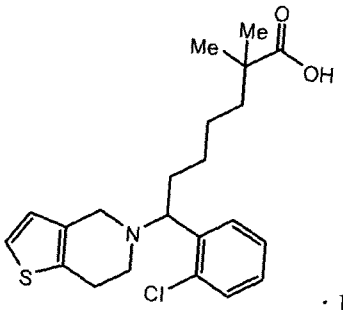
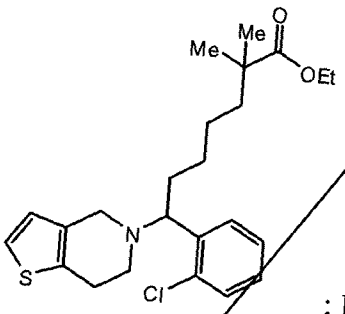
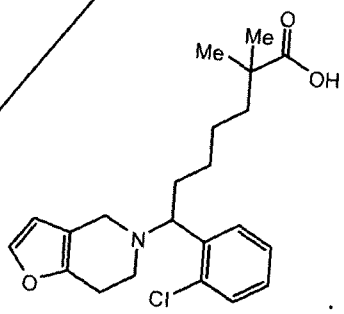
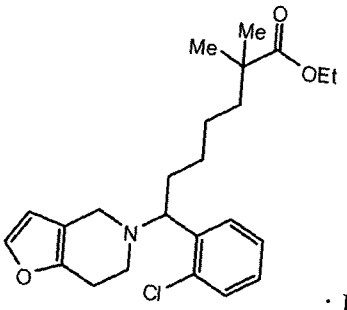
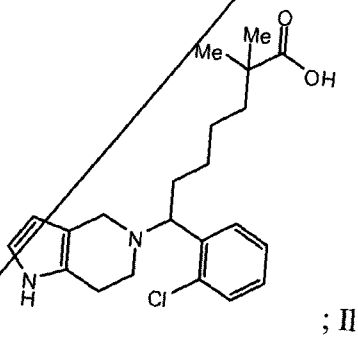
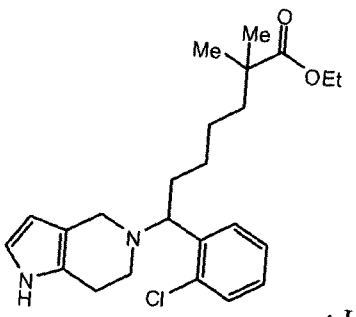
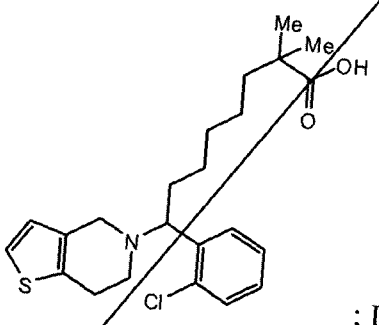
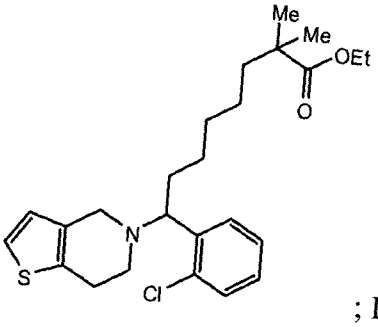
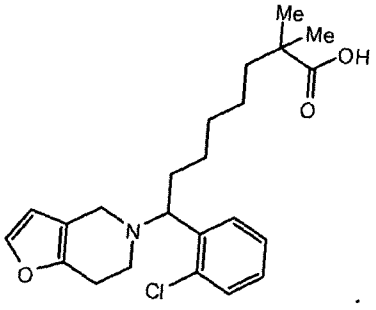
2. The compound or pharmaceutically acceptable salt of claim 1, wherein Z^2 is N.

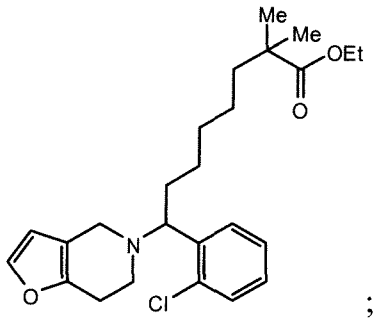
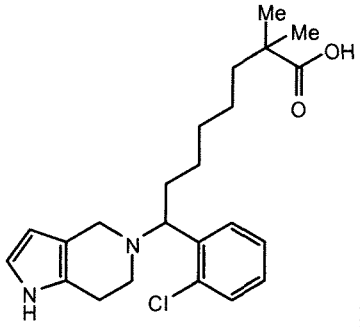
3. The compound or pharmaceutically acceptable salt of claim 2, wherein R^4 is OH, COOH, or an alkyl ester group.

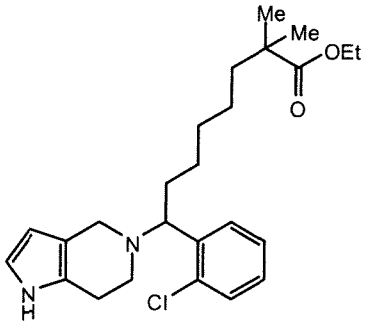
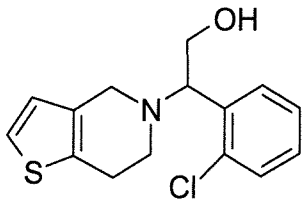
4. The compound or pharmaceutically acceptable salt of claim 3, wherein R^1 is 2-halo.

5. The compound or pharmaceutically acceptable salt of claim 4, wherein each of R^2 and R^3 is independently H or alkyl.

6. The compound of claim 1, wherein the compound is:

Ia:  ; Ib:  ; Ic:  ; Id:  ; Ie:  ; If:  ; Ig:  ; Ih:  ; Ii:  ; Ij:  ; Ik:  ; Il:  ; Im:  ; In:  ; Io:  ;

Ip:  ; Iq:  ; Ir:

 or Is:  or a pharmaceutically acceptable salt of any of the foregoing.

7. A composition comprising an effective amount of a compound or pharmaceutically acceptable salt of the compound of claim 1 and a pharmaceutically acceptable vehicle or carrier.

8. The composition of claim 7, wherein the composition is formulated for oral administration.

9. The composition of claim 7, wherein the composition is in the form of a tablet or capsule.

10. The composition of claim 7, wherein the compound or salt thereof is present in an amount of about 1 mg to about 1,000 mg.

11. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 6, in the preparation of a medicament for treating or preventing a disorder of lipoprotein metabolism.

12. The use of claim 11, wherein the disorder of lipoprotein metabolism is dyslipidemia, dyslipoproteinemia, lipoprotein overproduction or deficiency, elevation of total cholesterol,

elevation of low density lipoprotein concentration, elevation of triglyceride concentration, lipid elimination in bile, metabolic disorder, phospholipid elimination in bile, oxysterol elimination in bile, or peroxisome proliferator activated receptor-associated disorder.

13. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 6, in the preparation of a medicament for treating a disorder of glucose metabolism.

14. The use of claim 13, wherein the disorder of glucose metabolism is insulin resistance, impaired glucose tolerance, impaired fasting glucose levels in blood, diabetes mellitus, lipodystrophy, central obesity, peripheral lipoatrophy, diabetic nephropathy, diabetic retinopathy, renal disease, or speticemia.

15. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 6, in the preparation of a medicament for treating a cardiovascular disorder.

16. The use of claim 15, wherein the cardiovascular disorder or related vascular disorders is hypertension, coronary artery disease, myocardial infarcation, arrhythmia, atrial fibrillation, heart valve disease, heart failure, cardiomyopathy, or pericarditis.

17. The use of claim 15 or 16, wherein the method provides relief from at least one symptom of the cardiovascular disorder.

18. The use of claim 17, wherein the symptom is impotence.

19. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 6, in the preparation of a medicament for treating inflammation.

20. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 6, in the preparation of a medicament for treating ischemic necrosis.

21. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 6, in the preparation of a medicament for treating colon cancer, lung cancer, breast cancer, or skin cancer.

22. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 6, in the preparation of a medicament for treating a thrombotic disorder.

23. Use of of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 6, in the preparation of a medicament for treating Alzheimer's Disease.

24. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 6, in the preparation of a medicament for treating Parkinson's Disease.

25. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 6, in the preparation of a medicament for treating pancreatitis.

26. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 6, in the preparation of a medicament for treating abnormal bile production.

27. A method of monitoring the progress of therapy for a cardiovascular disorder in a subject, the method comprising:

a. determining the level of free cholesterol in the high-density lipoprotein in the blood of the subject;

b. administering to the subject a compound of any one of claims 1 to 6 or the composition of any one of claims 7 to 10;

c. monitoring the level of free cholesterol in the blood of the subject for a period of time after administration of the compound; and

d. evaluating the level of improvement in the subject based on a comparison of the results of steps a. and c.

28. The method of claim 27, wherein the cardiovascular disorder is reverse cholesterol transport from artery to liver or cholesterol elimination in bile acids.

29. A method of determining the level of P2Y13 activity in a subject, the method comprising:

a. determining the level of free cholesterol in the high-density lipoprotein in the blood of the subject;

b. administering to the subject a compound of any one of claims 1 to 6 or a composition of any one of claims 7 to 10;

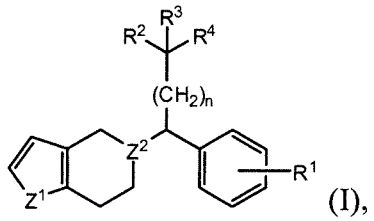
c. monitoring the level of free cholesterol in the blood of the subject for a period of time after administration of the compound; and

d. evaluating the level of P2Y13 activity in the subject based on a comparison of the results of steps a. and c.

30. The compound of any one of claims 1 to 6 or the composition to any one of claims 7 to 10, for use in treating or preventing a disorder of lipoprotein metabolism, treating a disorder of glucose metabolism, treating a cardiovascular disorder, treating inflammation, treating ischemic necrosis, treating colon cancer, lung cancer, breast cancer, or skin cancer, treating a thrombotic disorder, treating Alzheimer's Disease, treating Parkinson's Disease, treating pancreatitis, and/or treating abnormal bile production.

Claims

1. A compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein

each of R^1, R^2, and R^3 is independently H, -OH, $-NH_2$, -NH(alkyl), -N(alkyl)(alkyl), hydrocarbyl, -O-hydrocarbyl, aryl, -O-aryl, aralkyl, -O-aralkyl, heteroaryl, -O-heteroaryl, heterocyclyl, -O-heterocyclyl, halo, $-OCF_3$, -C(O)O(alkyl), -OC(O)(alkyl), $-C(O)NH_2$, -C(O)NH(alkyl), -C(O)N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), -OC(O)O(alkyl), $-OC(O)NH_2$, -OC(O)NH(alkyl), -OC(O)N(alkyl)(alkyl), -CHNH, -CHN(alkyl), or $-SO_2NH_2$;

R^4 is -OH, -COOH, or -C(O)O(alkyl);

Z^1 is CH_2, S, O, NH, N-hydrocarbyl, N-aryl, N-heteroaryl, or N-heterocyclyl;

Z^2 is N; and

n is an integer from 1-6;

wherein

each alkyl is independently -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, n-heptyl, -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, cyclohexyl, cyclopentyl, or cyclopropyl;

each hydrocarbyl is independently -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, n-heptyl, -isopropyl, -sec-butyl, -isobutyl, -tert-butyl, -isopentyl, -neopentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, cyclohexyl, cyclopentyl, cyclopropyl, ethylene, propylene, 1-butylene, 2-butylene, isobutylene, sec-butylene, 1-pentene, 2-pentene, isopentene, 1-hexene, 2-hexene, 3-hexene, isohexene, acetylene, propyne, 1-butyne, 2-butyne, isobutyne, sec-butyne, 1-pentyne, 2-pentyne, isopentyne, 1-hexyne, 2-hexyne, 3-hexyne, isohexyne, phenyl, naphthyl, pyridyl, phenanthryl, anthryl, furanyl, azolyl, imidazolyl, indolyl, benzyl, picolyl, or naphthylmethyl;

each aryl is independently phenyl, naphthyl, pyridyl, phenanthryl, anthryl, furanyl, azolyl, imidazolyl, or indolyl;

each aralkyl is independently benzyl, picolyl, or naphthylmethyl;

each heteroaryl is independently pyridyl, furanyl, azolyl, imidazolyl, thiophenyl, or indolyl;

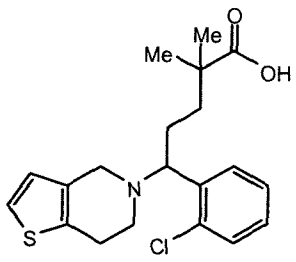
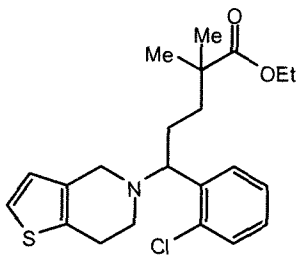
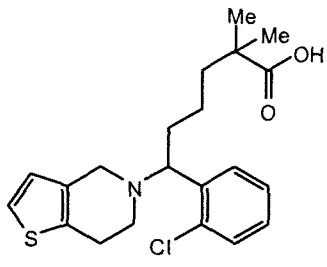
each heterocyclyl is independently furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, isothiazolyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiomorpholinyl, thiophenyl, triazinyl, or triazolyl;

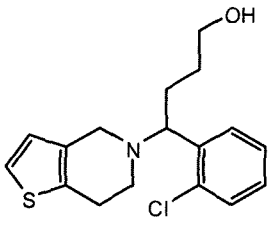
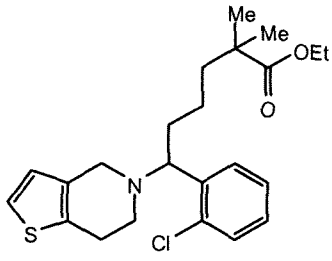
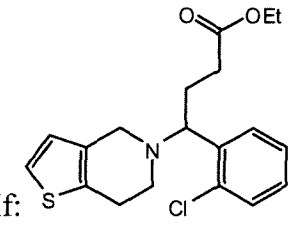
wherein each phenyl, naphthyl, pyridyl, phenanthryl, anthryl, furanyl, azolyl, imidazolyl, indolyl, pyridyl, furanyl, azolyl, imidazolyl, thiophenyl, indolyl, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, isothiazolyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiomorpholinyl, thiophenyl, triazinyl, and triazolyl is independently and optionally substituted with one or more of the following groups: -halo, -O- (C_1-C_6 alkyl), -OH, -CN, -COOR', -OC(O)R', -N(R')$_2$, -NHC(O)R' or -C(O)NHR' groups, wherein each R' is independently -H or unsubstituted –C_1-C_6 alkyl.

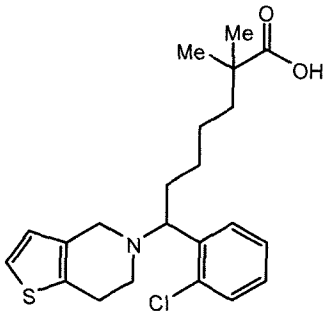
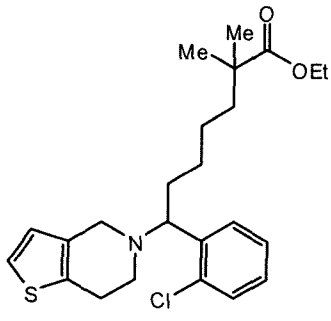
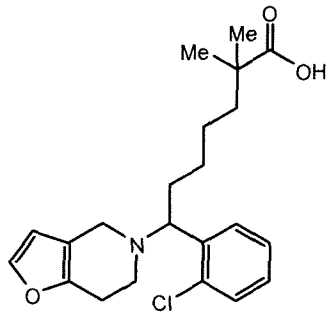
2. The compound or pharmaceutically acceptable salt of claim 1, wherein R^1 is 2-halo.

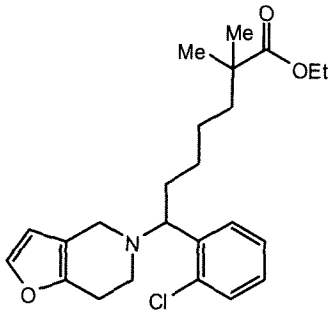
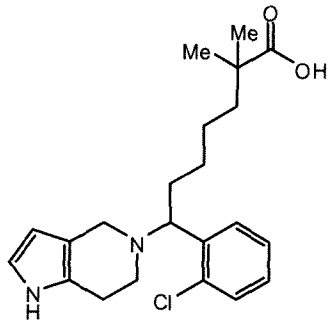
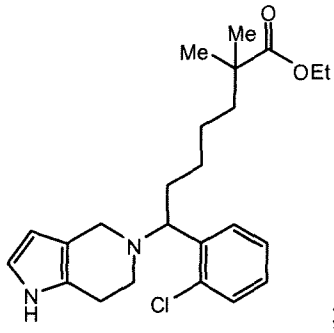
3. The compound or pharmaceutically acceptable salt of claim 2, wherein each of R^2 and R^3 is independently H or alkyl.

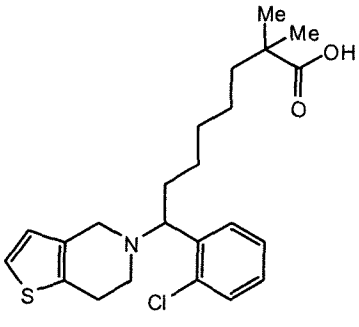
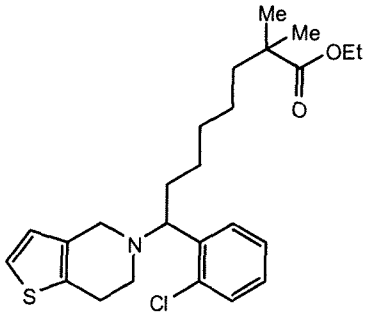
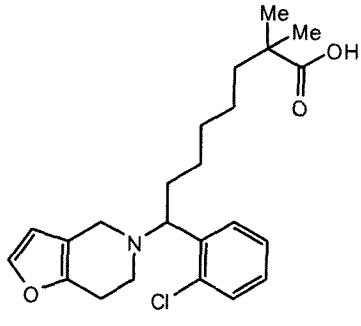
4. The compound of claim 1, wherein the compound is:

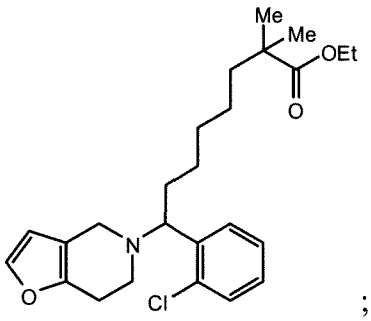
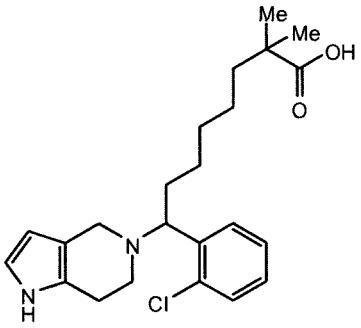
Ia:  ; Ib:  ; Ic:  ; Id:

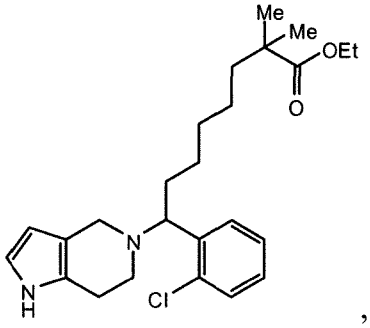
 ; Ie:  ; If:  ; Ig:

 ; Ih:  ; Ii:  ; Ij:

 ; Ik:  ; Il:  ; Im:

 ; In:  ; Io:  ;

Ip:  ; Iq:  ; or Ir:



, or a pharmaceutically acceptable salt of any of the foregoing.

5. A composition comprising an effective amount of a compound or pharmaceutically acceptable salt of the compound of claim 1 and a pharmaceutically acceptable vehicle or carrier.

6. The composition of claim 5, wherein the composition is formulated for oral administration.

7. The composition of claim 5, wherein the composition is in the form of a tablet or capsule.

8. The composition of claim 5, wherein the compound or salt thereof is present in an amount of about 1 mg to about 1,000 mg.

9. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 4 and 18 to 20, in the preparation of a medicament for treating or preventing a disorder of lipoprotein metabolism,

wherein the disorder of lipoprotein metabolism is dyslipidemia, dyslipoproteinemia, lipoprotein overproduction or deficiency, elevation of total cholesterol, elevation of low density lipoprotein concentration, elevation of triglyceride concentration, lipid elimination in bile,

metabolic disorder, phospholipid elimination in bile, oxysterol elimination in bile, or peroxisome proliferator activated receptor-associated disorder.

10. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 4 and 18 to 20, in the preparation of a medicament for treating a disorder of glucose metabolism,

wherein the disorder of glucose metabolism is insulin resistance, impaired glucose tolerance, impaired fasting glucose levels in blood, diabetes mellitus, lipodystrophy, central obesity, peripheral lipoatrophy, diabetic nephropathy, diabetic retinopathy, renal disease, or septicemia.

11. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 4 and 18 to 20, in the preparation of a medicament for treating a cardiovascular disorder,

wherein the cardiovascular disorder is hypertension, coronary artery disease, myocardial infarcation, arrhythmia, atrial fibrillation, heart valve disease, heart failure, cardiomyopathy, or pericarditis.

12. The use of claim 11, wherein the medicament provides relief from impotence.

13. Use of a compound or pharmaceutically acceptable salt of the compound of any one of claims 1 to 4 and 18 to 20, in the preparation of a medicament for treating abnormal bile production.

14. A method of monitoring the progress of therapy for a cardiovascular disorder in a subject, the method comprising:

a. determining the level of free cholesterol in the high-density lipoprotein in the blood of the subject;

b. administering to the subject a compound of any one of claims 1 to 4 and 18 to 20 or the composition of any one of claims 5 to 8;

c. monitoring the level of free cholesterol in the blood of the subject for a period of time after administration of the compound; and

d. evaluating the level of improvement in the subject based on a comparison of the results of steps a. and c.

15. The method of claim 14, wherein the cardiovascular disorder is reverse cholesterol transport from artery to liver or cholesterol elimination in bile acids.

16. A method of determining the level of P2Y13 activity in a subject, the method comprising:

a. determining the level of free cholesterol in the high-density lipoprotein in the blood of the subject;

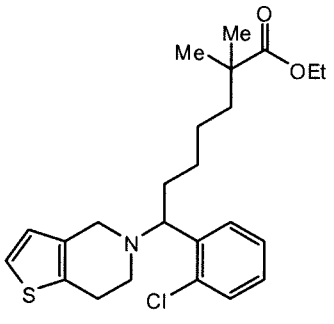
b. administering to the subject a compound of any one of claims 1 to 4 and 18 to 20 or a composition of any one of claims 5 to 8;

c. monitoring the level of free cholesterol in the blood of the subject for a period of time after administration of the compound; and

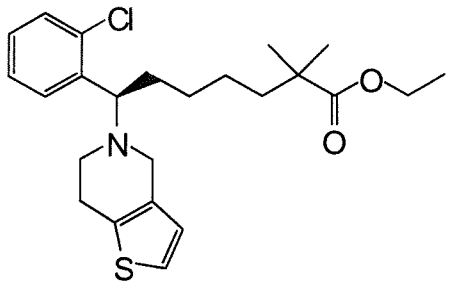
d. evaluating the level of P2Y13 activity in the subject based on a comparison of the results of steps a. and c.

17. The compound of any one of claims 1 to 4 and 18 to 20 or the composition to any one of claims 5 to 8, for use in treating or preventing a disorder of lipoprotein metabolism, treating a disorder of glucose metabolism, treating a cardiovascular disorder, treating inflammation, treating ischemic necrosis, treating colon cancer, lung cancer, breast cancer, or skin cancer, treating a thrombotic disorder, treating Alzheimer's Disease, treating Parkinson's Disease, treating pancreatitis, and/or treating abnormal bile production.

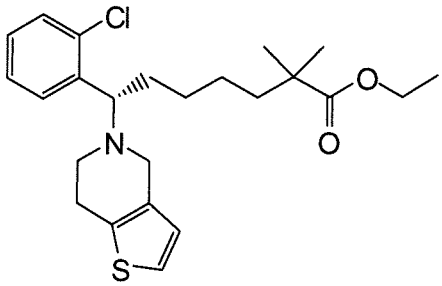
18. The compound of claim 1, wherein the compound is:

Ih (racemate):  or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1, wherein the compound is:

Ih (R-isomer):  or a pharmaceutically acceptable salt thereof.

20. The compound of claim 1, wherein the compound is:

Ih (S-isomer):  or a pharmaceutically acceptable salt thereof.