

A² is phenyl or HET(1), wherein A² is optionally substituted with 1-3 substituent groups which are each independently -C₁-C₅ alkyl, -OC₁-C₅ alkyl, -C₂-C₅ alkenyl, -OC₂-C₅ alkenyl, -C₂-C₅alkynyl, -OC₂-C₅alkynyl, halogen, -CN, -OH, or C₃-6cycloalkyl, wherein -C₁-C₅ alkyl, -OC₁-C₅ alkyl, -C₂-C₅ alkenyl, -OC₂-C₅ alkenyl, -C₂-C₅alkynyl, and -OC₂-C₅alkynyl are optionally substituted with 1-7 halogens, and C₃-6cycloalkyl is optionally substituted with 1-3 substituents which are each independently halogen, -C₁-C₃ alkyl, or -OC₁-C₃ alkyl, wherein -C₁-C₃ alkyl and -OC₁-C₃ alkyl are each optionally substituted with 1-7 halogens; and a is 0 or an integer from 1-3.

The compound of Formula I, or a pharmaceutically acceptable salt thereof, is a potent CETP inhibitor.

In the compound of Formula I or Formula Ia, and in subgroups and other embodiments of the invention, alkyl groups and substituents based on alkyl groups, such as alkoxy, may be linear or branched unless otherwise indicated.

In general, references to the compound(s) of formula I or Ia are meant to also include subsets of compounds of formula I and Ia as may be defined herein, and also are meant to include the specific numbered examples provided herein.

In a second aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of the compound as defined above or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a third aspect, there is provided use of the compound as defined above or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of atherosclerosis.

In a fourth aspect, there is provided use of the compound as defined above or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for ~~raising HDL-C~~ in a patient the treatment or prevention of a disease or condition selected from the group consisting of peripheral vascular disease, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity, endotoxemia, metabolic syndrome, Alzheimer's disease, and other neurodegenerative diseases.

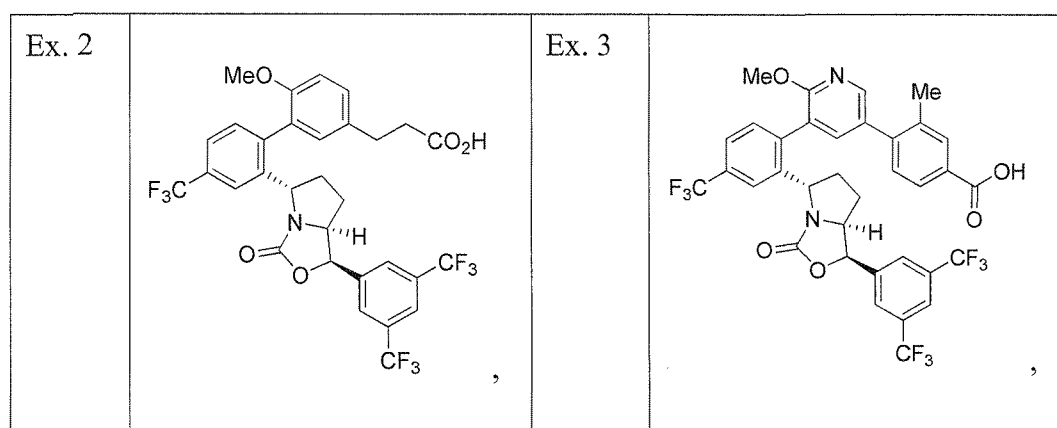
~~In a fifth aspect, there is provided use of the compound as defined above or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for lowering LDL-C in a patient.~~

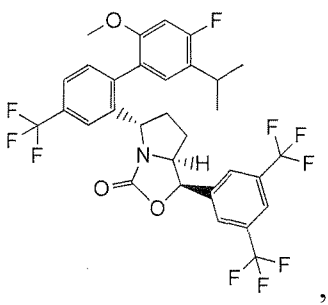
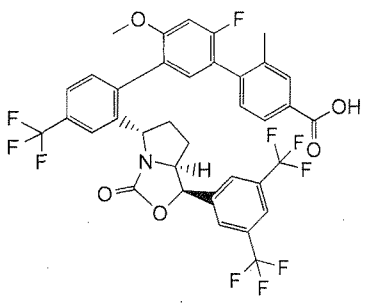
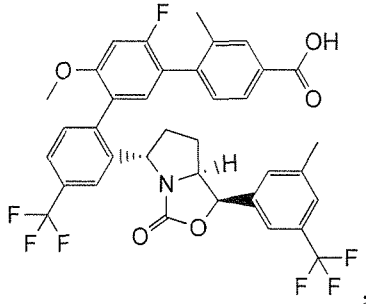
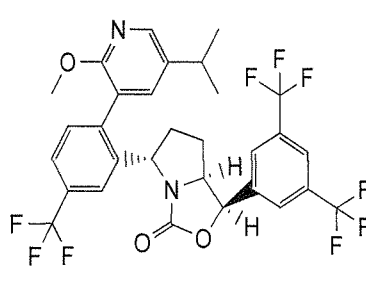
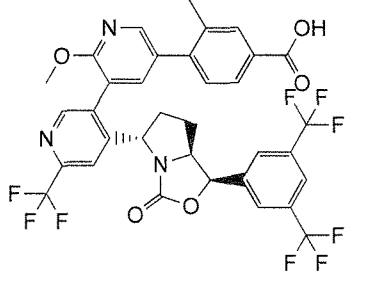
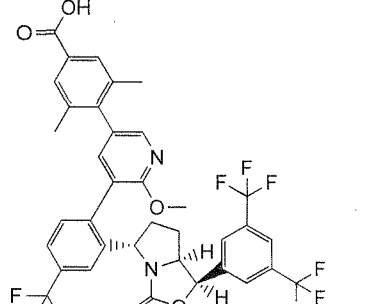
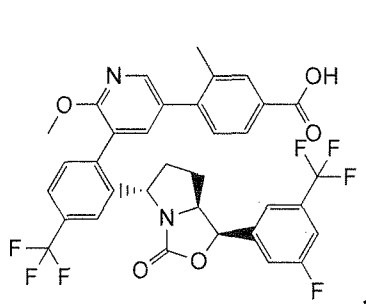
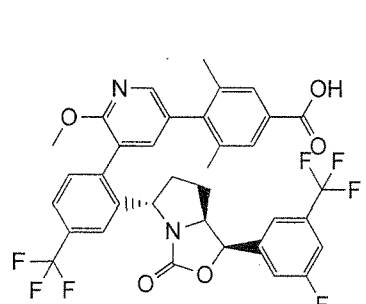
In a ~~sixth~~ fifth aspect, there is provided use of the compound as defined above or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of dyslipidemia.

In a ~~seventh~~ sixth aspect, there is provided a pharmaceutical composition comprising the compound as defined above or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and one or more active ingredients selected from the group consisting of:

- (i) HMG-CoA reductase inhibitors;
- (ii) bile acid sequestrants;
- (iii) niacin and related compounds;
- (iv) PPAR α agonists;
- (v) cholesterol absorption inhibitors;
- (vi) acyl CoA:cholesterol acyltransferase (ACAT) inhibitors;
- (vii) phenolic anti-oxidants;
- (viii) microsomal triglyceride transfer protein (MTP)/ApoB secretion inhibitors;
- (ix) anti-oxidant vitamins;
- (x) thyromimetics;
- (xi) LDL (low density lipoprotein) receptor inducers;
- (xii) platelet aggregation inhibitors;
- (xiii) vitamin B12 (also known as cyanocobalamin);
- (xiv) folic acid or a pharmaceutically acceptable salt or ester thereof;
- (xv) FXR and LXR ligands;
- (xvi) agents that enhance ABCA1 gene expression;
- (xvii) ileal bile acid transporters; and
- (xviii) niacin receptor agonists.

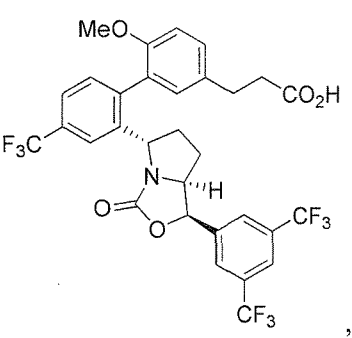
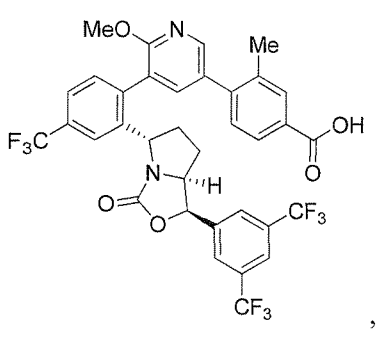
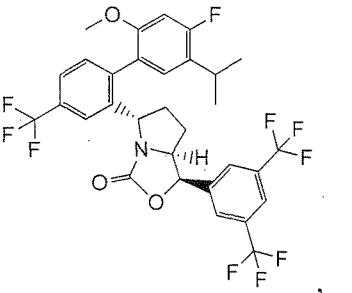
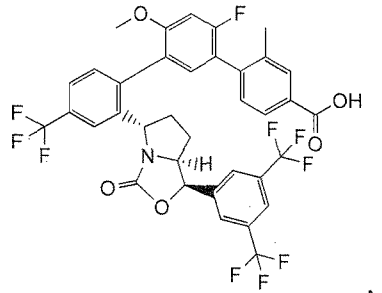
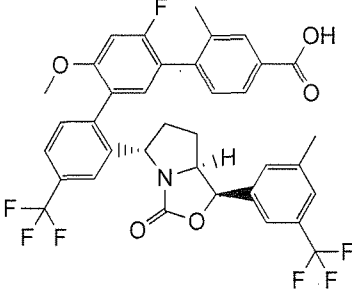
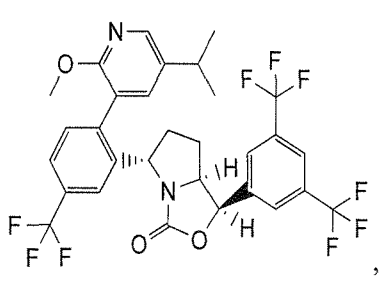
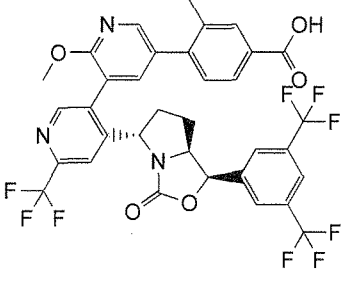
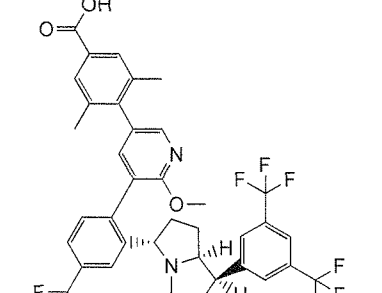
In an ~~eighth~~ seventh aspect, there is provided a compound having the structure below:

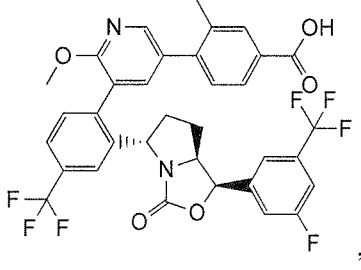
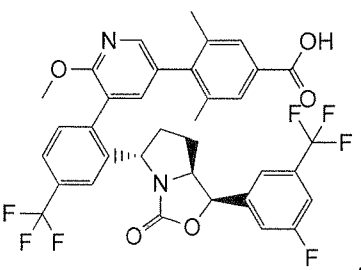


Ex. 5		Ex. 7	
Ex. 29		Ex. 45	
Ex. 54		Ex. 56	
Ex. 63		or Ex. 64	

or a pharmaceutically acceptable salt thereof.

In an ~~ninth~~ eighth aspect, there is provided a compound having the structure below:

Ex. 2		Ex. 3	
Ex. 5		Ex. 7	
Ex. 29		Ex. 45	
Ex. 54		Ex. 56	

Ex. 63		or Ex. 64	
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In a ninth aspect, there is provided the compound as defined herein for use in raising HDL-C in a patient.

In a tenth aspect, there is provided the compound as defined herein for use in lowering LDL-C in a patient.

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DETAILED DESCRIPTION OF THE INVENTION

In further embodiments of the invention, the substituent groups defined above may have alternative values independent of one another, as written below. Such embodiments include pharmaceutically acceptable salts when such salts are possible.

10 In many embodiments, R¹ is -C₁-C₅ alkyl, -OC₁-C₅ alkyl, halogen, -NR⁶R⁷, HET(3), or C₃-6 cycloalkyl optionally having 1-2 double bonds, wherein -C₁-C₅ alkyl and -OC₁-C₅ alkyl are optionally substituted with 1-7 halogens, and wherein HET(3) and C₃-6 cycloalkyl optionally having 1-2 double bonds are optionally substituted with 1-3 substituent groups which are each independently halogen, CH₃, CF₃, OCH₃, or OCF₃.

15 In many embodiments, R¹ is CH₃, CF₃, -OCH₃, -OCF₃, halogen, or -NR⁶R⁷.

In many embodiments, R¹ is CH₃, CF₃, -OCH₃, -OCF₃, F, Cl, or -NR⁶R⁷.

In many embodiments, R¹ is CF₃, F, or -N(CH₃)₂.

In many embodiments, R⁶ and R⁷ are each independently H or -C₁-C₃ alkyl.

In many embodiments, R⁶ and R⁷ are each independently H or -CH₃.

20 In many embodiments, R², R³, and R⁴ are each independently H, -C₁-C₅ alkyl, -OC₁-C₅ alkyl, or halogen, wherein -C₁-C₅ alkyl and -OC₁-C₅ alkyl are optionally substituted with 1-7 halogens.

In many embodiments, R², R³, and R⁴ are each independently H, C₁-3alkyl, -OC₁-3alkyl, or halogen, wherein -C₁-C₃ alkyl and -OC₁-C₃ alkyl are optionally substituted with 1-3 halogens.

25 In many embodiments, R², R³, and R⁴ are each independently of one another -C₁-3alkyl, F, or Cl.

Ex. 81		Ex. 82	
Ex. 83			

or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition comprising a therapeutically effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

9. Use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of atherosclerosis.

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10. Use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for raising HDL-C in a patient of a medicament for the treatment or prevention of a disease or condition selected from the group consisting of peripheral vascular disease, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, vascular complications of diabetes, obesity, endotoxemia, metabolic syndrome, Alzheimer's disease, and other neurodegenerative diseases.

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~~11. Use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for lowering LDL C in a patient.~~

5 | ~~1211.~~ Use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of dyslipidemia.

1312. A pharmaceutical composition comprising the compound of Claim 1 or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and one or more active ingredients selected from the group consisting of:

- (i) HMG-CoA reductase inhibitors;
- (ii) bile acid sequestrants;
- (iii) niacin and related compounds;
- (iv) PPAR α agonists;
- (v) cholesterol absorption inhibitors;
- (vi) acyl CoA:cholesterol acyltransferase (ACAT) inhibitors;
- (vii) phenolic anti-oxidants;
- (viii) microsomal triglyceride transfer protein (MTP)/ApoB secretion inhibitors;
- (ix) anti-oxidant vitamins;
- (x) thyromimetics;
- (xi) LDL (low density lipoprotein) receptor inducers;
- (xii) platelet aggregation inhibitors;
- (xiii) vitamin B12 (also known as cyanocobalamin);
- (xiv) folic acid or a pharmaceutically acceptable salt or ester thereof;
- (xv) FXR and LXR ligands;
- (xvi) agents that enhance ABCA1 gene expression;
- (xvii) ileal bile acid transporters; and
- (xviii) niacin receptor agonists.

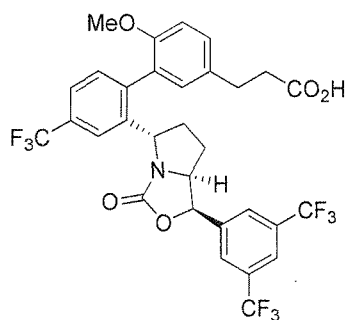
1413. A compound having the structure below:

Ex. 2		Ex. 3	
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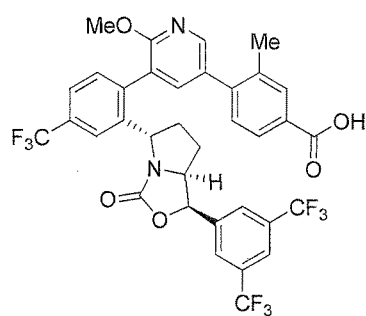
Ex. 63		or Ex. 64	
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or a pharmaceutically acceptable salt thereof.

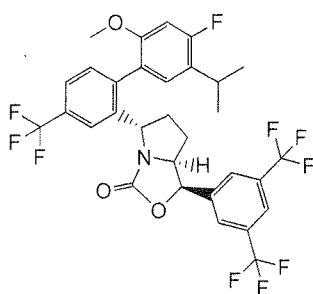
1414. The compound of Claim 1413, or a pharmaceutically acceptable salt thereof, having the structure:



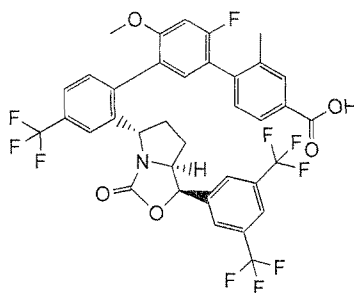
1415. The compound of Claim 1413, or a pharmaceutically acceptable salt thereof, having the structure:



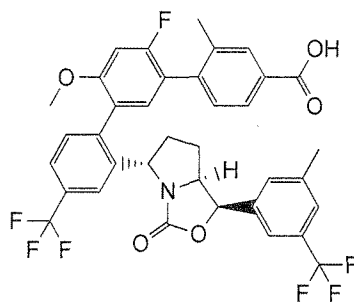
1416. The compound of Claim 1413, or a pharmaceutically acceptable salt thereof, having the structure:



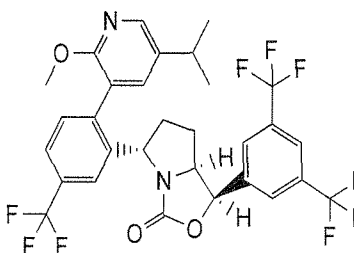
1817. The compound of Claim 1413, or a pharmaceutically acceptable salt thereof, having the structure:



1918. The compound of Claim 1413, or a pharmaceutically acceptable salt thereof, having the structure:

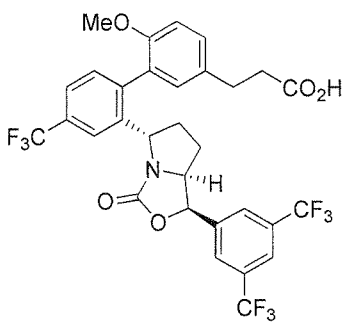
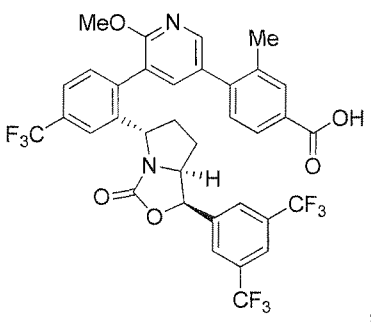
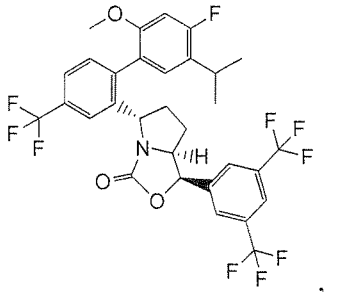
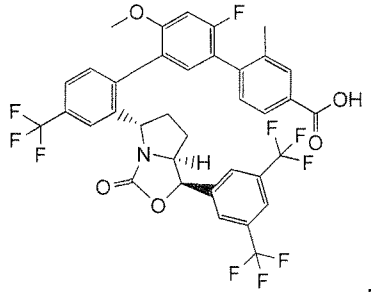
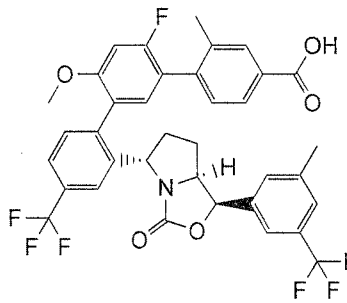
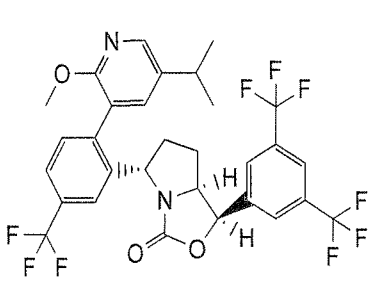
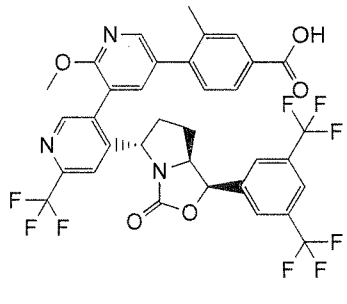
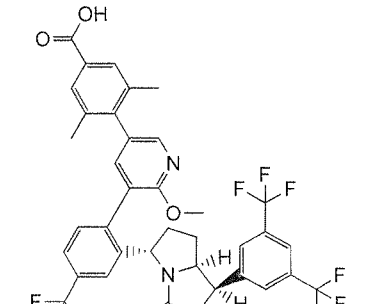


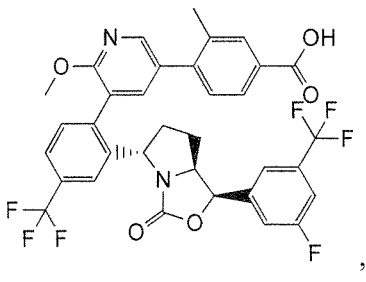
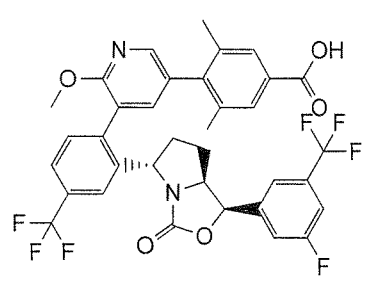
2019. The compound of Claim 1413, or a pharmaceutically acceptable salt thereof, having the structure:



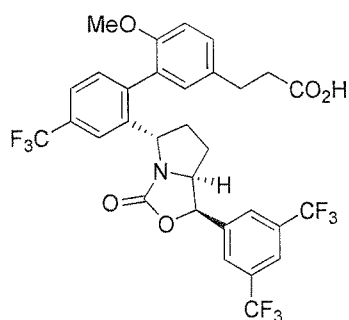
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2524. A compound having the structure below:

Ex. 2		Ex. 3	
Ex. 5		Ex. 7	
Ex. 29		Ex. 45	
Ex. 54		Ex. 56	

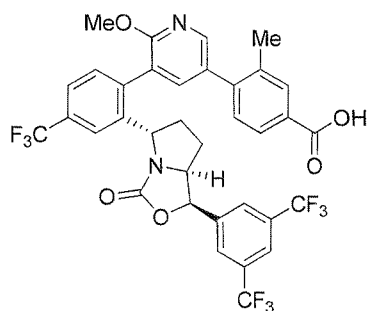
Ex. 63		or Ex. 64	
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2625. The compound of Claim ~~25~~ 24 having the structure:



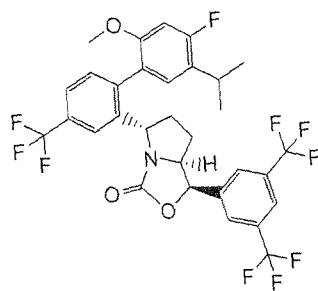
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2726. The compound of Claim ~~25~~ 24 having the structure:

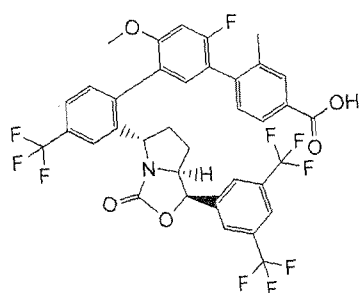


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2827. The compound of Claim ~~25~~ 24 having the structure:

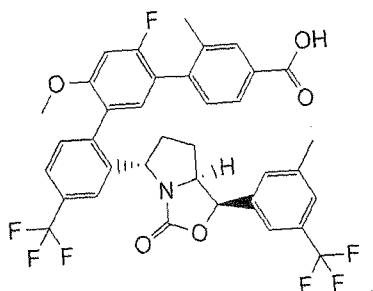


2928. The compound of Claim 25-24 having the structure:

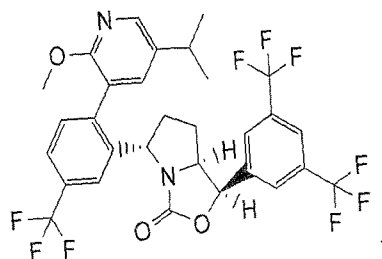


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3029. The compound of Claim 25-24 having the structure:

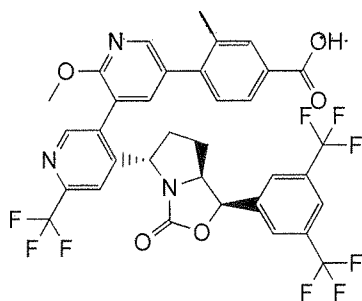


3130. The compound of Claim 25-24 having the structure:

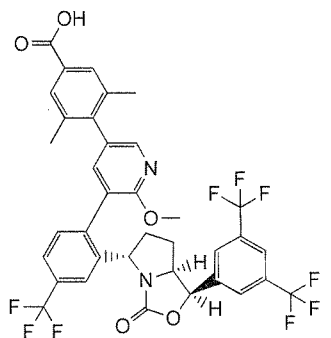


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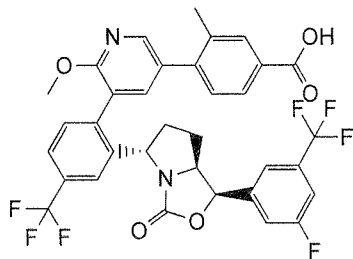
3231. The compound of Claim 25-24 having the structure:



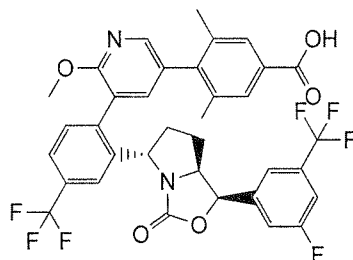
3332. The compound of Claim 25-24 having the structure:



3433. The compound of Claim 25-24 having the structure:



3534. The compound of Claim 25-24 having the structure:



35. The compound of any one of claims 1 to 7 or 13 to 35 for use in raising HDL-C in a patient.

36. The compound of any one of claims 1 to 7 or 13 to 35 for use in lowering LDL-C in a patient.