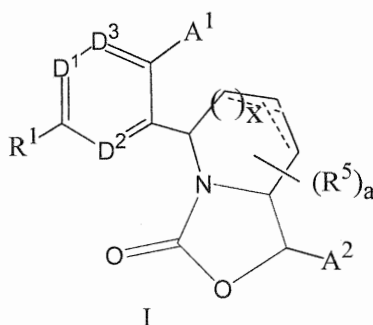


many of the highly lipophilic compounds that have so far been studied. "Food effect" refers to the variability in exposure to the active drug that occurs depending on when the patient had last eaten, whether or not the drug is administered with food, and the fat content of the food.

5 SUMMARY OF THE INVENTION

In a first aspect, there is provided a ~~The compound~~ compound of Formula I, or a pharmaceutically acceptable salt thereof, ~~is a potent CETP inhibitor~~, having the utilities described below:



In Formula I, R¹ is H, -C₁-C₅ alkyl, -OC₁-C₅ alkyl, -C₂-C₅ alkenyl, -OC₂-C₅ alkenyl, -C₂-C₅ alkynyl, -OC₂-C₅ alkynyl, -OH, halogen, -CN, -NR⁶R⁷, -CO₂R⁸, -C(O)NR⁶R⁷, -SO₂NR⁶R⁷, HET(3), or C₃-6 cycloalkyl optionally having 1-2 double bonds, wherein -C₁-C₅ alkyl, -OC₁-C₅ alkyl, -C₂-C₅ alkenyl, -OC₂-C₅ alkenyl, -C₂-C₅ alkynyl, and -OC₂-C₅ alkynyl are each 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, -C₁-C₃ alkyl, -OC₁-C₃ alkyl, -C₂-C₃ alkenyl, -OC₂-C₃ alkenyl, -C₂-C₃ alkynyl, or -OC₂-C₃ alkynyl, wherein -C₁-C₃ alkyl, -OC₁-C₃ alkyl, -C₂-C₃ alkenyl, -OC₂-C₃ alkenyl, -C₂-C₃ alkynyl, and -OC₂-C₃ alkynyl are each optionally substituted with 1-7 halogens;

R⁶ and R⁷ are each independently H or -C₁-C₅ alkyl;

R⁸ is H or -C₁-5alkyl optionally substituted with 1-7 halogens;

HET(3) is a 3-6 membered heterocyclic ring having 1-3 heteroatom groups which are each independently N, NH, O, S, S(O), or S(O)₂ and optionally having 1-3 double bonds;

x is 0 or 1;

The dashed lines in Formula I represent one optional double bond between 2 adjacent carbon atoms;

D¹ is N or CR²;

D² is N or CR³;

D³ is N or CR⁴;

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.

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 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 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:

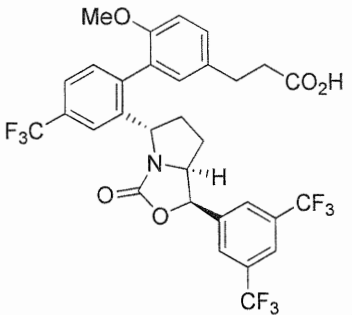
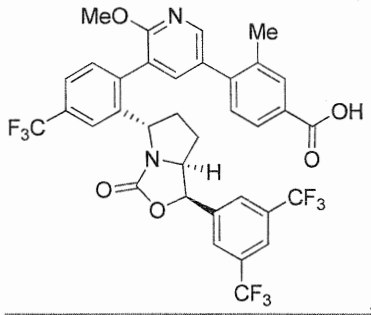
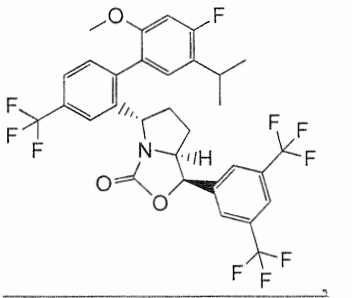
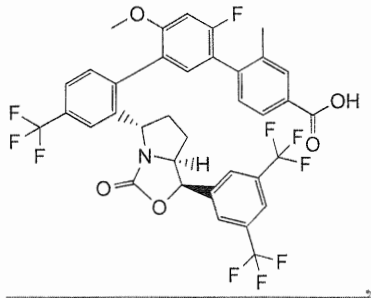
(i) HMG-CoA reductase inhibitors;

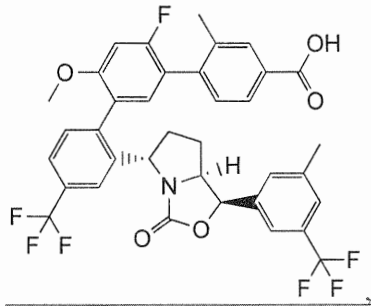
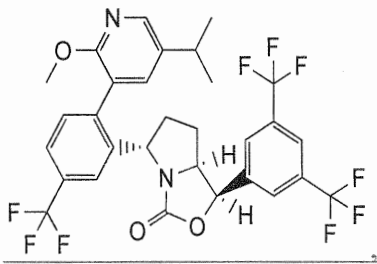
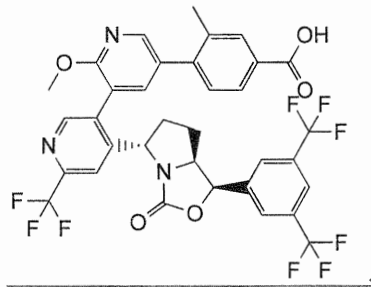
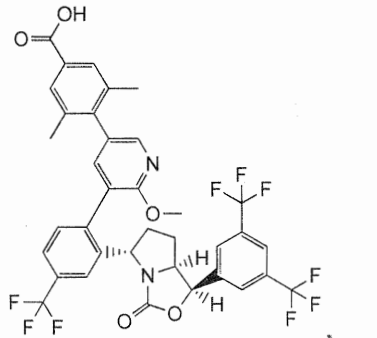
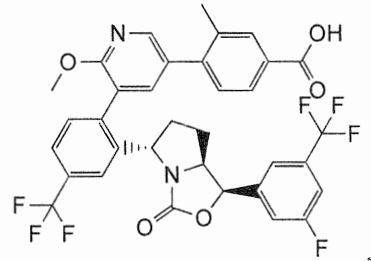
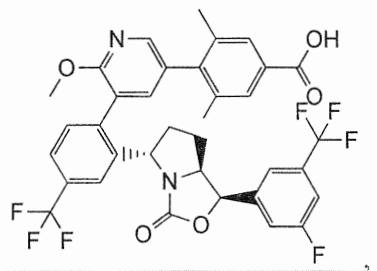
(ii) bile acid sequestrants;

(iii) niacin and related compounds;

- (iv) PPAR α agonists;
- (v) cholesterol absorption inhibitors;
- (vi) acyl CoA:cholesterol acyltransferase (ACAT) inhibitors;
- (vii) phenolic anti-oxidants;
- 5 (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;
- 10 (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
- 15 (xviii) niacin receptor agonists.

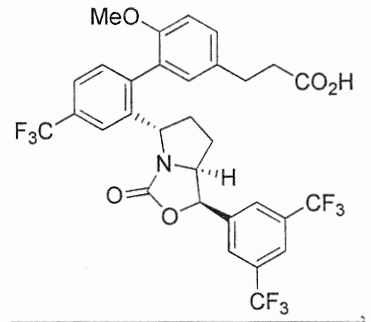
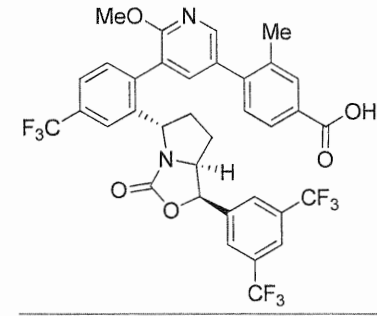
In an eighth aspect, there is provided a compound having the structure below:

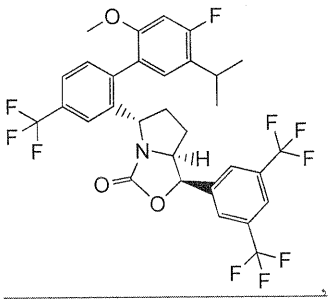
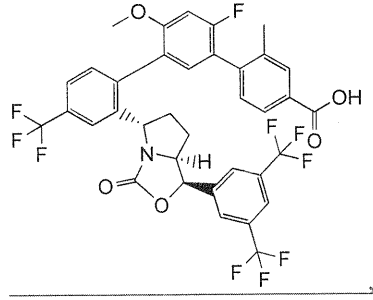
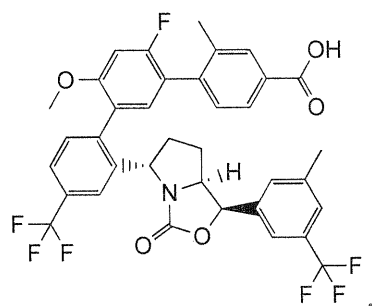
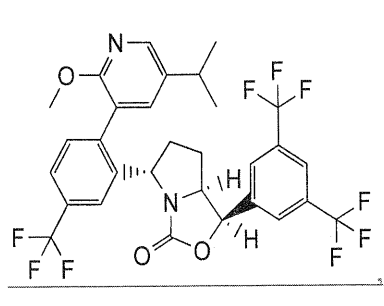
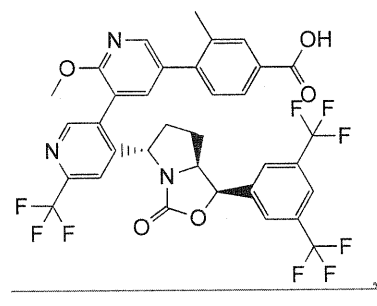
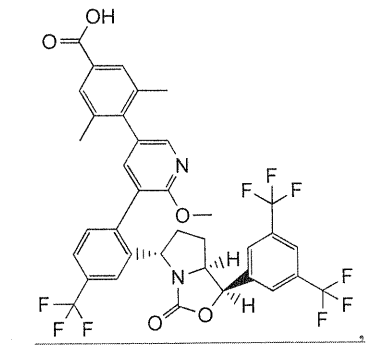
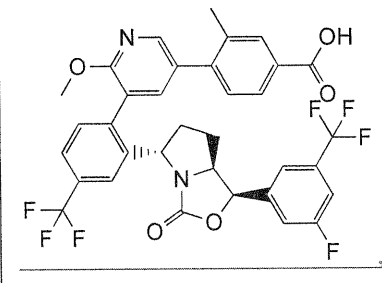
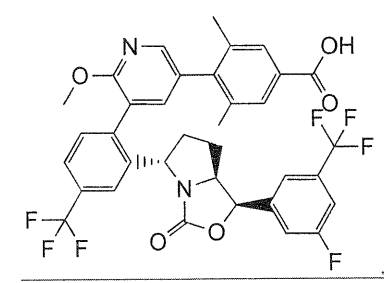
Ex. 2		Ex. 3	
Ex. 5		Ex. 7	

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

or a pharmaceutically acceptable salt thereof.

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

Ex. 2		Ex. 3	
-------	---	-------	--

<u>Ex. 5</u>		<u>Ex. 7</u>	
<u>Ex. 29</u>		<u>Ex. 45</u>	
<u>Ex. 54</u>		<u>Ex. 56</u>	
<u>Ex. 63</u>		<u>or</u> <u>Ex. 64</u>	

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.

5 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.

10 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.

15 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.

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