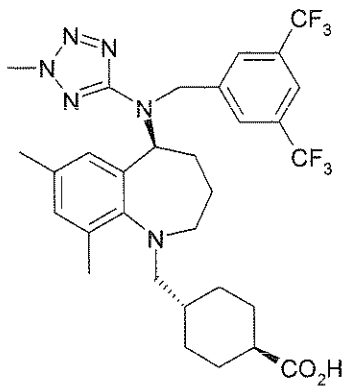
Further once administered, the compounds need to exhibit sufficiently high bioavailability and/or oral exposure for greater efficacious treatment.

The present ~~invention~~disclosure addresses these needs and provides a compound suitable for treatment of cardiovascular diseases including, but not limited to, dyslipidemia and atherosclerosis. The present ~~invention~~disclosure provides a compound exhibiting particularly advantageous and unexpected properties. The physical and pharmacological properties of the presently claimed compound make it particularly suitable for formulating into tablets for oral dosing. The particular advantageous properties include, among others, greater stability, solubility, and/or bioavailability.

The present ~~invention~~disclosure provides a compound which is *trans*-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid, (identified according to its Chemical Abstracts Index Name (referred to herein as BCCA) having the structure of Formula I illustrated below, and pharmaceutically acceptable salts of this compound.



I

The compound, BCCA, can be a free acid (referred to herein as BCCA free acid), or a pharmaceutically acceptable salt thereof, as a solvate (referred herein as BCCA•solvate) and a hydrate (referred to herein as BCCA•hydrate). The solvate molecules include water (as the hydrate), methanol, ethanol, formic acid, acetic acid, and isopropanol.

In one aspect, there is provided a compound which is *trans*-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid, a hydrate, or a pharmaceutically acceptable salt of said compound.

The present ~~invention~~disclosure provides a compound which is BCCA, a pharmaceutically acceptable salt thereof, or a hydrate or solvate thereof. In one form the compound BCCA is provided as a free acid. In other forms, BCCA is provided BCCA•hydrate or BCCA (either as a free acid or salt)•solvate in crystalline form. In still other forms, the present

~~invention~~disclosure provides BCCA from BCCA•hydrate or BCCA•solvate to an amorphous solid form.

The present ~~invention~~disclosure provides a compound which is BCCA•hydrate in crystalline form characterized by an X-ray powder diffraction pattern obtained from a CuKα source (λ=1.54056 Å), which comprises peaks at: a) 7.5, 9.2, 10.7, and 15.5 +/- 0.2 in 2θ; b) 7.5, 9.2, 10.7, 13.8, 15.0, 15.5, and 19.5 +/-0.2 in 2θ; or c) 7.5, 9.2, 10.7, 13.8, 11.3, 15.0, 15.5, 17.7, 19.5, and 25.1 +/-0.2 in 2θ.

In another form, the present ~~invention~~disclosure provides a compound which is BCCA•hydrate in crystalline form characterized by a solid state NMR spectrum that comprises peaks referenced to adamantane (δ = 29.5 ppm) at: a) 175.6, 168.0 61.1, 21.2, and 18.3 +/- 0.2 ppm; b) 175.6, 168.0, 145.6, 144.8, 61.1, 45.0, 21.2, and 18.3 +/- 0.2 ppm; or c) 175.6, 168.0, 145.6, 144.8, 139.9, 136.3, 61.1, 53.0, 49.8, 45.0, 21.2, and 18.2 +/- 0.2 ppm.

In still other forms, BCCA is provided as BCCA•hydrate in crystalline form as characterized by at least one of the following: a) a X-ray powder diffraction pattern obtained from a CuKα source (λ=1.54056 Å) which comprises peaks at 7.5, 9.2, 10.7, and 15.5 ±0.2 in 2θ or b) a solid state NMR spectrum which comprises peaks referenced to adamantine (δ = 29.5 ppm) at 175.6, 168.0, 61.1, 21.2, and 18.3 +/- 0.2 ppm.

In another aspect, there is~~The present invention~~ provide~~s~~d a compound which is *trans*-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid ~~BCCA~~• hemi-*tert*-butylamine salt• hemi ethanol solvate in crystalline form characterized by an X-ray powder diffraction pattern obtained from a CuKα source (λ=1.54056 Å)~~,~~ which comprises peaks at: a) 5.5, 9.0, 14.3, 22.0, and 22.5 +/-0.2 in 2θ; or b) 5.5, 9.0, 14.3, 17.5, 18.2, 19.4, 20.6, 22.0, and 22.5 +/-0.2 in 2θ; or c) 5.5, 9.0, 13.2, 13.6, 14.3, 15.2, 17.5, 18.2, 19.4, 19.8, 20.6, 22.0, and 22.5 +/-0.2 in 2θ.

In another aspect, there is~~The present invention~~ provides~~d~~ a compound which is *trans*-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid ~~BCCA~~•formic acid solvate in crystalline form characterized by an X-ray powder diffraction pattern obtained from a CuKα source (λ=1.54056 Å)~~,~~ which comprises peaks at: a) 15.4, 16.9, 18.2, and 18.6 +/-0.2 in 2θ; or b) 15.4, 15.7, 16.9, 18.2, 18.6, 19.5, 22.8, 25.7, and 25.5 +/-0.2 in 2θ; or c) 13.0, 13.9, 15.4, 15.7, 16.9, 16.4, 18.2, 18.6, 19.5, 20.8, 22.8, 25.7, and 25.5 +/-0.2 in 2θ.

In another aspect, there is~~The present invention~~ provided a compound which is *trans*-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid ~~BCCA~~•acetic acid solvate in crystalline form characterized by an X-ray powder diffraction pattern obtained from a CuKα source (λ=1.54056 Å), which comprises peaks at: a) 12.9, 15.1, 18.4, 19.4, and 20.8 +/-0.2 in 2θ; or b) 12.9, 13.8, 15.1, 16.4, 17.8, 18.4, 19.4, 20.1, and 20.8 +/-0.2 in 2θ; or c) 11.00, 12.9, 13.8, 15.1, 15.6, 16.4, 17.8, 18.4, 19.4, 20.1, 20.8, and 21.7 +/-0.2 in 2θ.

In another aspect, there is~~The present invention~~ provided a compound which is *trans*-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid • ~~BCCA~~ *tert* butylamine salt•isopropanol solvate in crystalline form characterized by an X-ray powder diffraction pattern obtained from a CuKα source (λ=1.54056 Å), which comprises peaks at: a) 5.6, 11.3, 12.6, and 17.9 +/-0.2 in 2θ; or b) 5.6, 8.0, 11.3, 12.6, 17.9, 20.4, and 24.1 +/-0.2 in 2θ.

In another aspect, there is provided a composition comprising *trans*-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid, hydrate, or hydrate in crystalline form, as defined above.

In another form, the present ~~invention~~disclosure provides a BCCA, or a pharmaceutically acceptable salt thereof, as a solvate where the solvate is selected from: water (also referred to as a hydrate), methanol, ethanol, isopropanol, formic acid, or acetic acid. The BCCA to solvate molar ratio can be from about 1:0.3 to about 1:1, more preferable between about 1:0.5 to about 1:1 +/- 0.2 (BCCA or salt:solvate). Preferred solvates include water, isopropanol and ethanol.

In another form the present ~~invention~~disclosure provides BCCA as a pharmaceutically acceptable salt. Preferred cations for the pharmaceutically acceptable salt can be selected from: sodium, potassium, magnesium, calcium, zinc, or a *tert*-butylamine (or *tert*-butyl ammonium). More preferred cations are sodium, calcium and *tert*-butylamine.

The present ~~invention~~disclosure provides substantially pure BCCA as BCCA free acid or pharmaceutically acceptable salts thereof, BCCA•hydrate, BCCA•solvate (or BCCA•hydrate) and the BCCA salt•solvate in crystalline form (individually the "referenced BCCA form"). As used herein the term "substantially pure" refers to a composition comprising greater than 80% w/w of the referenced BCCA form, preferable greater than 95 % w/w of the referenced BCCA form, and yet more preferable, greater than 98 % w/w of referenced BCCA form. In a particularly preferred ~~aspect~~embodiment, the present ~~invention~~disclosure provides substantially pure BCCA•hydrate in crystalline form.

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above, and at least one of a pharmaceutically acceptable: carrier, excipient or diluent.

The present ~~invention~~disclosure provides a pharmaceutical composition comprising BCCA, or a pharmaceutically acceptable salt thereof, and at least one of a pharmaceutically acceptable: carrier, excipient or diluent. In selected forms the pharmaceutical

composition comprises substantially pure BCCA as BCCA free acid or a pharmaceutically acceptable salt thereof, BCCA•solvate BCCA salt•solvate or BCCA•hydrate in crystalline form. In a particularly preferred ~~aspect~~embodiment, the pharmaceutical composition comprising substantially pure BCCA•hydrate in crystalline form.

The present ~~invention~~disclosure also provides a method of treating a patient for cardiovascular disease, wherein the method comprises administering an effective amount of BCCA to the patient. In preferred forms, the method comprises administering BCCA as BCCA•hydrate. In still other forms, the method comprises administering BCCA•solvate in crystalline form or BCCA•hydrate in crystalline form.

The present ~~invention~~disclosure provides for the use of BCCA (as BCCA free acid or its pharmaceutically acceptable salt, BCCA salt•solvate, BCCA•hydrate, or BCCA•solvate in crystalline form, or BCCA•hydrate in crystalline form) according to the present ~~invention~~disclosure for the manufacture of a medicament for the treatment of cardiovascular diseases including but not limited to dyslipidemia and atherosclerosis.

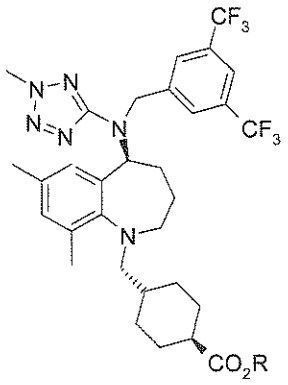
In another aspect, there is provided the use of a compound as defined above for the manufacture of a medicament for the treatment of dyslipidemia.

In another aspect, there is provided the use of a compound as defined above for the manufacture of a medicament for the treatment of arthrosclerosis.

The present ~~invention~~disclosure provides BCCA (as BCCA free acid; BCCA salt •solvate, BCCA•hydrate, or BCCA•solvate in crystalline form according to the present ~~invention~~disclosure) as a medicament. The present ~~invention~~disclosure also provides BCCA (as BCCA free acid; or BCCA salt•solvate, BCCA•hydrate, BCCA•solvate in crystalline form, in crystalline form according to the present ~~invention~~disclosure) for use in therapy.

The present ~~invention~~disclosure provides BCCA (as BCCA free acid; or BCCA•hydrate, BCCA salt•solvate, or BCCA•solvate in crystalline form according to the present ~~invention~~disclosure) for use in the treatment of cardiovascular diseases including but not limited to dyslipidemia and atherosclerosis.

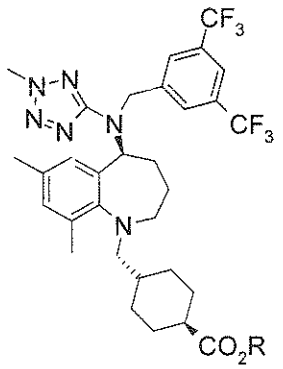
The present ~~invention~~disclosure also provides a compound having a structure illustrated below:



II;

wherein R is selected from a C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} alkyl-C_{3-6} cycloalkyl, phenyl, and C_{1-5} alkylphenyl to provide a compound of formula I, or a pharmaceutically acceptable salt thereof. Preferred R groups include C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkyl-C_{3-6} cycloalkyl, phenyl, and C_{1-5} alkylphenyl. Particularly preferred R groups include methyl, ethyl, phenyl and benzyl.

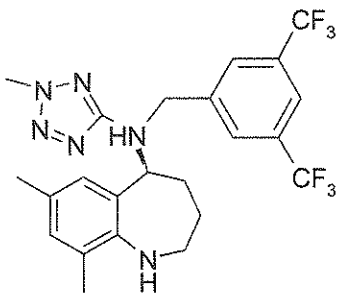
In another aspect, there is provided a compound having a structure illustrated below:



II

wherein R is selected from: C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkyl-C_{3-6}cycloalkyl, phenyl, or C_{1-5} alkylphenyl.

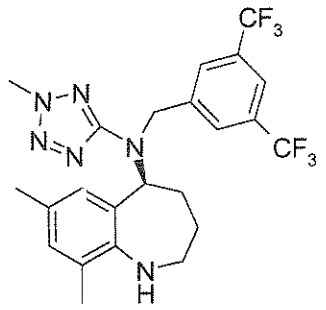
In another aspect, there is provided a compound having a structure illustrated below:



III.

The term C_{1-4} alkyl or C_{1-5} alkyl as referred to herein includes a straight or branched alkyl chain having from 1 to 4 carbon atoms or 1 to 5 carbon atoms, respectively. The term haloalkyl refers an alkyl group having the one or more halogens attached to one or more carbon atoms. As noted above the alkyl group can be a straight or branched chain. Preferred halogens are fluorine, chlorine and bromine. Fluorine is particularly preferred.

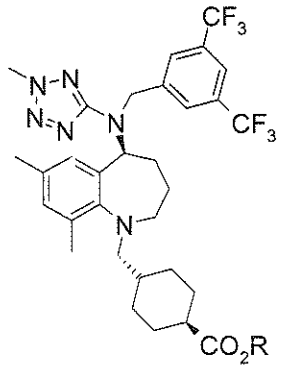
In still yet another form, the present ~~invention~~disclosure provides a compound which is



III

or a pharmaceutically acceptable salt thereof.

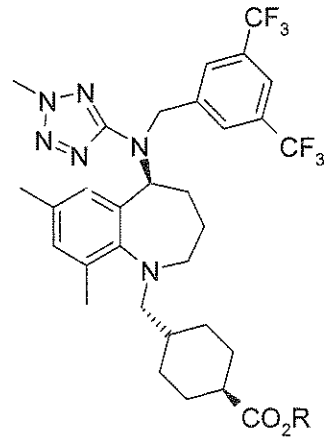
The present ~~invention~~disclosure provides a method of preparing BCCA. The method includes de-esterifying a compound of the formula II below:



II

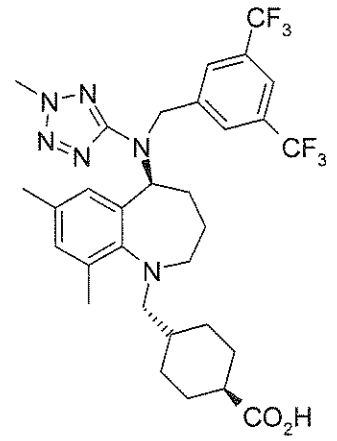
wherein R is selected from a C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkyl-C_{3-6} cycloalkyl, phenyl, or C_{1-5} alkylphenyl to provide a compound of formula I, or a pharmaceutically acceptable salt thereof to provide BCCA or a pharmaceutically acceptable salt thereof. Preferred R groups include C_{1-4} alkyl, phenyl, and C_{1-5} alkylphenyl. Particularly preferred R groups include methyl, ethyl, phenyl and benzyl.

In another aspect, there is provided a method of preparing *trans*-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid, or a pharmaceutically acceptable salt thereof, said method comprising de-esterifying a compound of formula II:



II;

where R is selected from a C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6}cycloalkyl, C_{1-4} alkyl-C_{3-6}cycloalkyl, phenyl, or C_{1-5} alkylphenyl to provide a compound of formula I, or a pharmaceutically acceptable salt thereof



I.

The method can also include deprotecting a protected carboxylic acid substituent on the cyclohexyl group. Examples of various acid protecting functionalities, methods of preparing the protected acids, and methods for deprotecting the acids can be found in "Protecting Groups in Organic Synthesis", 3rd Ed. Greene, T.W., Wuts, P.G.M., Eds., John Wiley and Sons, New York, 1999. It will be recognized by those skilled in the art that in addition to the carboxylic acid and protected carboxylic acid other functional groups that can be readily converted to a carboxylic acid can be used in place the carboxylic acid or protected acid. Such functional groups, preparations, and transformations of these groups to carboxylic acids can be found in "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" by Larock. R.C, Wiley VCH, 1999 and in "March's Advanced Organic Chemistry, Reactions, Mechanisms and Structure" Smith, M.B., and March, J., Wiley-Interscience, 6th Ed. 2007.

In still yet another form, the present ~~invention~~disclosure provides a method as described above and further including condensing a compound of the formula III below

tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid, hydrate, or hydrate in crystalline form, according to any one of claims 1 to ~~4~~5.

7. A composition according to claim 6 comprising *trans*-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid • hydrate in crystalline form.

8. A composition according to claim 6 comprising greater than 80 % *trans*-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid • hydrate in crystalline form.

9 A compound according to claim 5 comprising:

trans-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid, or a pharmaceutically acceptable salt thereof; and

a solvate molecule selected from: water, methanol, ethanol, isopropanol, formic acid, or acetic acid.

10. A compound according to claim 9 wherein the *trans*-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid, or a pharmaceutically acceptable salt thereof, and the solvate molecule is in a molar ratio of between about 1:0.3 to about 1:1 +/- 0.2 (acid or salt:solvate molecule).

11. A compound which is *trans*-4-[[(5*S*)-5-[[[3,5-bis(trifluoromethyl)phenyl]methyl] (2-methyl-2*H*-tetrazol-5-yl)amino]-2,3,4,5-tetrahydro-7,9-dimethyl-1*H*-1-benzazepin-1-yl]methyl]-cyclohexanecarboxylic acid • hemi-*tert*-butyl amine salt • hemi ethanol solvate in crystalline form characterized by an X-ray powder diffraction pattern obtained from a CuKα source (λ=1.54056 Å) which comprises peaks at: