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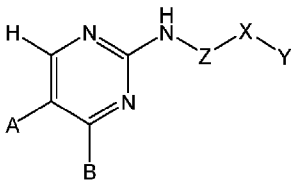
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(54) Title: PCSK9 INHIBITORS AND METHODS OF USE THEREOF

(57) Abstract: Disclosed herein are PCSK9 inhibitors. Also disclosed herein are methods of using PCSK9 inhibitors to treat certain diseases and disorders.



(I)

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PCSK9 INHIBITORS AND METHODS OF USE THEREOF

BACKGROUND

PCSK9, also referred to as "proprotein convertase subtilisin/kexin 9", is a member of the secretory proprotein convertase family and plays an important role in cholesterol metabolism. PCSK9 increases the levels of circulating LDL cholesterol via the enhanced degradation of the LDL receptors independently of its catalytic activity. Secreted PCSK9 binds to the Epidermal Growth Factor domain A (EGFA) of the LDL receptor (LDLR) at the cell surface and the PCSK9/LDL receptor complex is internalized into endosomal/lysosomal compartments. The enhanced binding affinity of PCSK9 to the LDL receptor at the acidic pH of late endosomes/lysosomes reduces LDL receptor recycling and instead targets LDL receptors for lysosomal degradation. Genetic association studies have demonstrated that loss-of-function mutations in PCSK9 are associated with low plasma LDL-C levels and a reduction in the incidence of adverse cardiovascular events.

Another biological pathway involving the effect of PCSK9 on LDL receptors is the onset of septic shock. Septic shock is an often fatal complication of a severe microbial infection (sepsis) that triggers an uncontrolled systemic inflammatory response and subsequent organ failure. Sepsis originates with the microbial cell walls that contain pathogenic lipid moieties such as lipopolysaccharide (LPS; Gram-negative bacteria). LPS are potent ligands for mammalian innate immune receptors [Toll-like receptors (TLRs)] and thus figure prominently in the septic inflammatory response (septic shock, or sepsis).

PCSK9 reduces LPS uptake by the liver's LDL receptors, such that free LPS overstimulates the body's immune response to the pathogen leading to sepsis. Thus, inhibiting PCSK9 is beneficial in retaining liver LDL receptors to effect systemic pathogen clearance and detoxification in response to sepsis. However, beyond antibiotic therapy, there are currently no effective treatments for sepsis or septic shock.

For cardiovascular disease, few options exist for inhibiting PCSK9. Statins actually upregulate PCSK9 in HepG2 cells and in human primary hepatocytes through the increased expression of SREBP-2, a transcription factor that upregulates both the LDLR and PCSK9 genes.

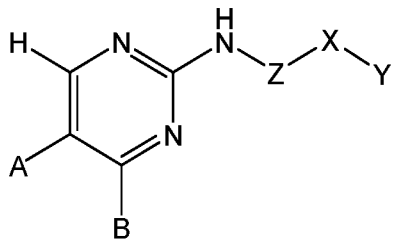
Since an elevated level of PCSK9 decreases the abundance of LDL receptor on the cell surface, increasing doses of statins have failed to achieve proportional LDL-cholesterol lowering effects.

Two monoclonal antibodies (mAbs) that bind selectively to extracellular PCSK9 and prevent its interaction with the LDL receptor, alirocumab and evolocumab, have recently received FDA approval for lowering LDL-C levels. In clinical trials, alirocumab showed an about 50% decrease in LDL levels compared to placebo. Elbitar et al., *Expert Opin Therapeutic Patents* 2016 26:1377-1392. Patients taking evolocumab showed an about 60-75% decrease in LDL levels. The potency of these drugs demonstrates the potential for inhibitors of PCSK9 to be effective treatments for those with hypercholesterolemia and other cardiovascular diseases. However, both antibody drugs require intravenous administration and can cause allergic reactions or other deleterious immune responses in the body.

Cardiovascular diseases often require management over a person's lifetime, unlike an infection that could be episodic. Thus, ease of dosing and administration become key factors to patient compliance with maintenance drug treatments. There is a need for PCSK9 inhibitors with increased efficacy and greater ease of administration, which can be achieved with small molecule PCSK9 inhibitors.

SUMMARY OF THE INVENTION

In one aspect, the present disclosure provides compounds with a structure represented by formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

A is selected from H, halo, hydroxy, alkyl, alkylthio, alkenyl, alkoxy, acyloxy, cyano, cycloalkyl, -C(O)OR^6, and -C(O)NR^{6}R^7;

B is selected from H, alkyl, and halo; or A and B are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered heteroaryl;

X is NR^5 or O;

Z is cycloalkyl, cycloalkenyl, aryl, heteroaryl, or heterocyclyl;

each R^6 and R^7 is independently H or alkyl;

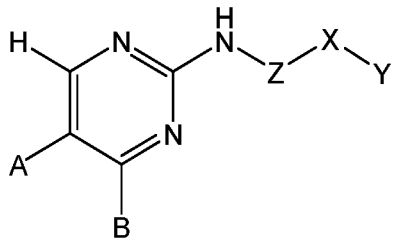
Y is selected from aryl, heteroaryl and heterocyclyl; and

n is 0 or 1.

In another aspect, the present disclosure relates to methods of treating certain diseases and disorders (e.g., cardiovascular disease or septic shock) with the compounds of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure relates to inhibitors PCSK9 and uses thereof. In one aspect, the present disclosure provides compounds with a structure represented by formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

A is selected from H, halo, hydroxy, alkyl, alkylthio, alkenyl, alkoxy, acyloxy, cyano, cycloalkyl, $-C(O)OR^6$, and $-C(O)NR^6R^7$;

B is selected from H, alkyl, and halo; or A and B are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered heteroaryl;

X is NR^5 or O;

Z is cycloalkyl, cycloalkenyl, aryl, heteroaryl, or heterocyclyl;

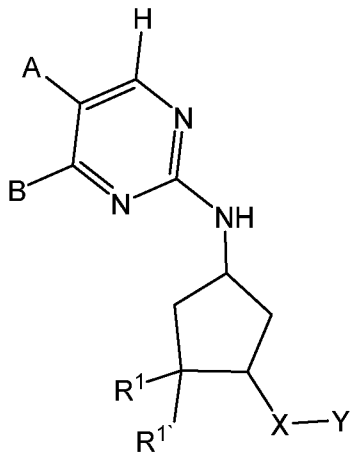
each R^6 and R^7 is independently H or alkyl;

Y is selected from aryl, heteroaryl and heterocyclyl; and

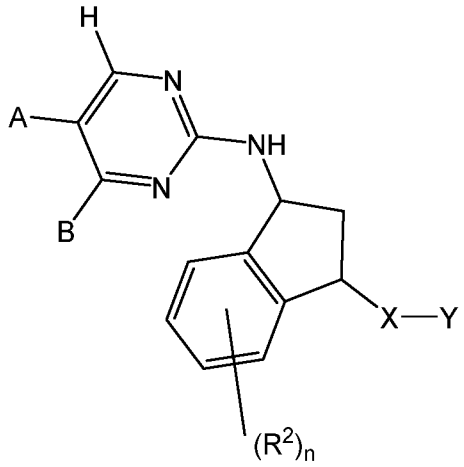
n is 0 or 1.

In certain preferred embodiments of formula I, Z is cycloalkyl.

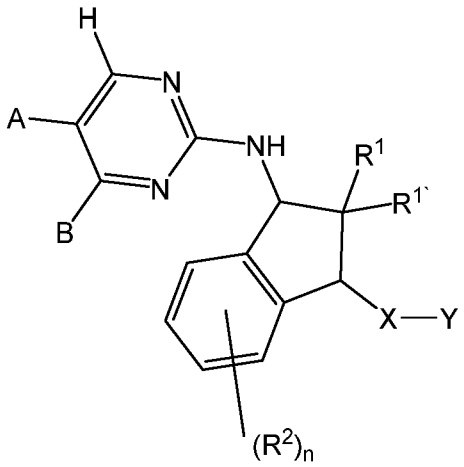
In certain embodiments of formula (I), the structure of the compound is represented by formula (Ia), (Ib), (Ic), or a pharmaceutically acceptable salt thereof:



(Ia)



(Ib)



(Ic)

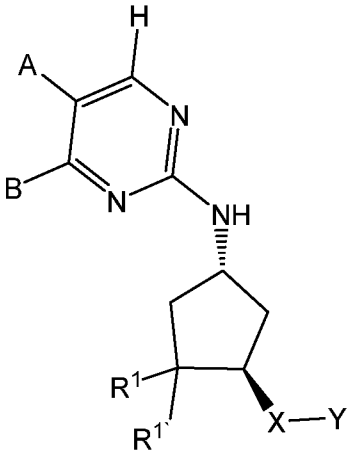
wherein

R^1 and $R^{1`}$ are each independently selected from alkyl, halo, hydroxyl, carboxyl, acyl, ester, thioester, alkoxy, phosphoryl, amino, amide, cyano, nitro, azido, alkylthio, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, heteroaralkyl, sulfonamide, aryl, heteroaryl, heterocyclyl, and aralkyl; or R^1 and $R^{1`}$ combine to form an alkylalkene, cycloalkyl, cycloalkene or heterocyclyl;

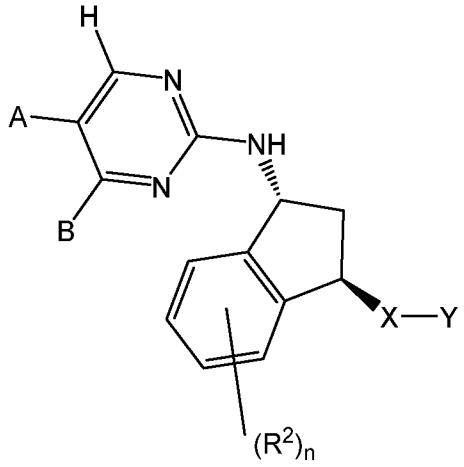
each R^2 is independently selected from alkyl, halo, hydroxyl, carboxyl, acyl, ester, thioester, alkoxy, phosphoryl, amino, amide, cyano, nitro, azido, alkylthio, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, heteroaralkyl, sulfonamide, aryl, heteroaryl, heterocyclyl, and aralkyl; and

n is 1, 2, 3, or 4.

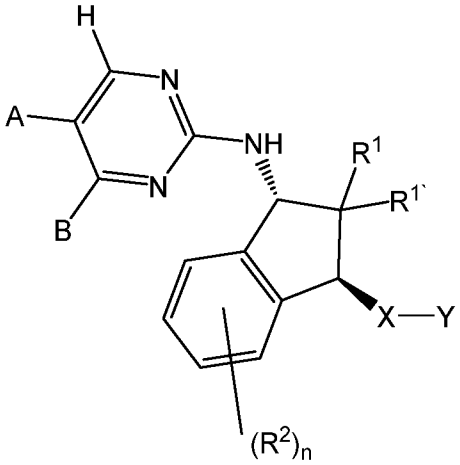
In certain embodiments of formula (I), (Ia), (Ib), or (Ic), the structure of the compound is represented by formula (IIa), (IIb), (IIc), or a pharmaceutically acceptable salt thereof:



(IIa)

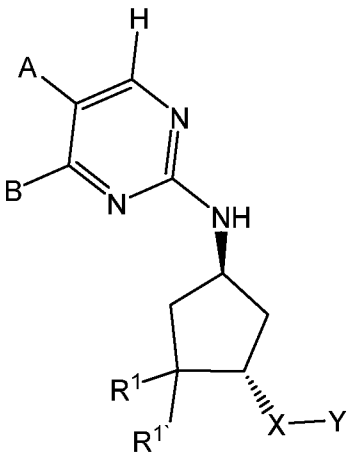


(IIb)

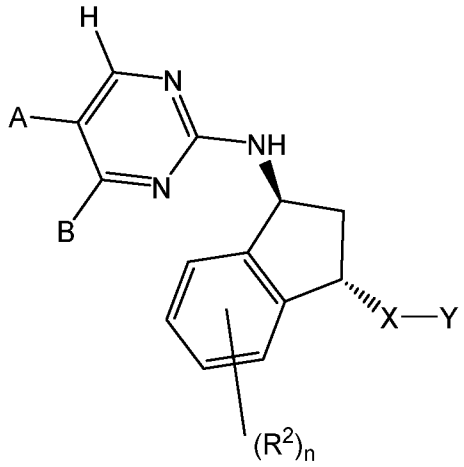


(IIc).

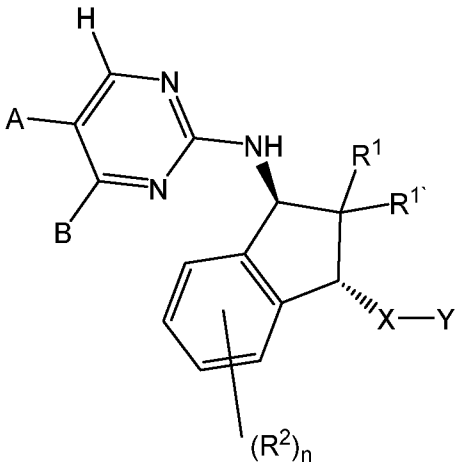
In other embodiments of formula (I), (Ia), (Ib), or (Ic), the structure of the compound is represented by formula (IIIa), (IIIb), (IIIc), or a pharmaceutically acceptable salt thereof:



(IIIa)



(IIIb)



(IIIc).

In certain embodiments of formula (I), (Ia), (Ib), (Ic), (IIa), (IIb), (IIc), (IIIa), (IIIb), or (IIIc), A is selected from H, halo, hydroxy, alkylthio, alkyl, alkoxy, acyloxy, cyano, cycloalkyl, -C(O)OR^6, and -C(O)NR^{6}R^7. In certain embodiments, A is H. In other embodiments, A is alkyl. In other embodiments, A is halo (e.g., chloro). In yet other embodiments, A is alkylthio. In yet other embodiments, A is alkoxy. In yet other embodiments A is cycloalkyl. In certain preferred embodiments, A is selected from -SCH_3, -$SCHF_2$, and -$OCHF_2$. In yet other embodiments, A and B are taken together with the carbon atoms to which they are attached to form a pyrrolyl or thienyl ring, which is unsubstituted or substituted with one or more alkyl.

In certain embodiments of formula (I), (Ia), (Ib), (Ic), (IIa), (IIb), (IIc), (IIIa), (IIIb), or (IIIc), B is H.

In certain embodiments of formula (I), (Ia), (Ib), (Ic), (IIa), (IIb), (IIc), (IIIa), (IIIb), or (IIIc), X is NR^5.

In certain embodiments of formula (I), (Ia), (Ib), (Ic), (IIa), (IIb), (IIc), (IIIa), (IIIb), or (IIIc), Y is heteroaryl or heterocyclyl, preferably monocyclic heteroaryl, e.g., pyridyl, pyridinyl, pyrazinyl, pyrimidinyl, or thiazolyl. In other embodiments, Y is a monocyclic heteroaryl selected from triazenyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, and triazolyl.

In certain such embodiments, the monocyclic heteroaryl is unsubstituted or substituted with one or more substituents selected from alkyl, alkylthio, alkoxy, alkoxycarbonyl, amido, carboxy, cyano, halo, aryl, heteroaryl, heterocyclyl, nitro, sulfonamido, and alkylthio. In certain embodiments, the monocyclic heteroaryl is substituted with a 6-membered aryl, heteroaryl or heterocyclyl selected from phenyl, pyridinyl, 2-hydroxypyridinyl, piperidinonyl, 2-hydroxy-1-methylpyridinyl, triazolyl, imidazolidinonyl, pyrimidonyl, 2-hydroxyisoquinolinyl, 3-hydroxypyridazinyl, pyrrolidinonyl, pyrazolyl, and morpholinonyl. In certain embodiments, the monocyclic heteroaryl is substituted with an heteroaryl or heterocyclyl that is substituted with one or more substituents selected from halo, CN, alkyl, alkoxy, hydroxy, carboxy, $-CO_2$alkyl, and tetrazolyl. In certain preferred embodiments, the substituent is disposed on the para position of Y relative to X.

In other embodiments, Y is bicyclic heteroaryl, such as benzothiazolyl, benzoxazolyl, benzimidazolyl, triazolopyridinyl, thiazolopyrindinyl, quinolinyl, or quinoxalinyl. In certain such embodiments, the bicyclic heteroaryl is unsubstituted, or substituted with one or more substituents selected from alkyl, haloalkyl, hydroxyalkyl, alkylthio, alkoxy, alkoxycarbonyl, amido, carboxy, cyano, halo, heteroaryl, nitro, and sulfonamido. In certain embodiments, the bicyclic heteroaryl is unsubstituted, or substituted with one or more substituents selected from alkylthio, alkoxycarbonyl, amido, carboxy, halo, and heteroaryl. In certain preferred embodiments, Y is substituted with an amido substituent of the formula $–C(O)NR^8R^9$ or $–NR^9C(O)R^{10}$, wherein

R^8 and R^9 are each independently selected from H, alkyl, heterocyclyl and heteroaryl; or

R^8 and R^9, taken together with the nitrogen atom to which they are attached, form a

4-, 5-, 6-, or 7-membered heterocyclic or heteroaryl ring; and

R^{10} is alkyl.

In other preferred embodiments, Y is substituted with a sulfonamido substituent of the formula $–S(O)_2NR^8R^9$ or $–NR^9S(O)_2R^{10}$; wherein

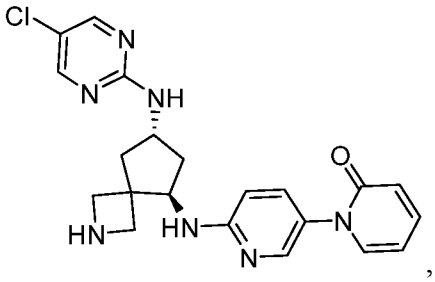
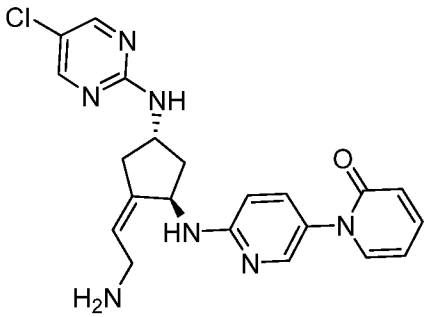
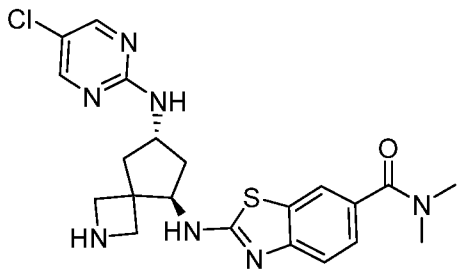
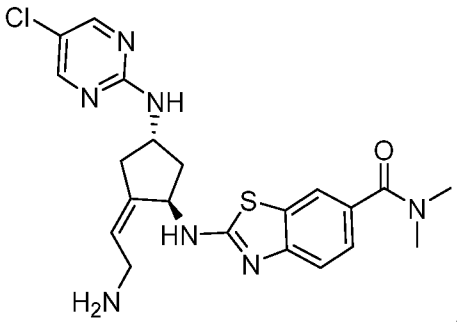
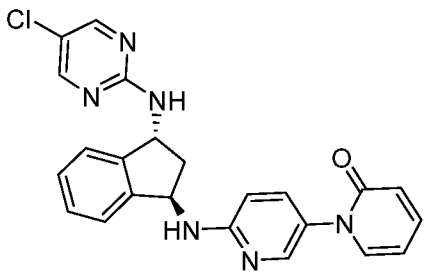
R^8 and R^9 are each independently selected from H, alkyl, and heteroaryl; or

R^8 and R^9, taken together with the nitrogen atom to which they are attached, form a 4-, 5-, 6-, or 7-membered heterocyclic ring; and

R^{10} is alkyl.

In certain embodiments of formula (I), (Ia), (Ib), (Ic), (IIa), (IIb), (IIc), (IIIa), (IIIb), or (IIIc), R^8 and R^9 are each independently selected from H, methyl, ethyl, triazolyl, and pyrazolyl. In certain embodiments, one or both of R^8 and R^9 are alkyl, and each alkyl is independently unsubstituted, or substituted with one or more substituents selected from methyl, methoxy, carboxy, cyano, hydroxy, dimethylamino, ethoxycarbonyl, phenyl, methoxyphenyl, oxadiazolyl, tetrazolyl, 2-methyl-tetrazolyl, triazolyl, 1-methyltriazolyl, 4-methyltriazolyl, and 2,4-dihydro-3H-1,2,4-triazol-3-onyl. In other embodiments, R^8 and R^9, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring selected from aziradine, isothiazolidine-1,1-dioxide, azetindine, thiazol-4(5Hn)-one, morpholine, piperidine, piperazine, pyrrolidine, thiomorpholine-1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane. In certain embodiments, R^8 and R^9, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring selected from 2,8-diazaspiro[5,5]undecene, tetrahydroimidazo[1,2-a]pyrazine, octahydropyrazino[2,1-c][1,4]oxazine, tetrahydropyrido[3,4-d]pyrimidine, 2-oxa-8-azaspiro[4.5]decane, tetrahydropyrrolo[3,4-c]pyrazole, thiomorpholine, 2-oxa-7-azaspiro[3.5]nonane, 2,8-diazaspiro[4.5]decan-3-one, tetrahydro-1,7-naphthyridine, 1-oxa-4,9-diazaspiro[5.5]undecan-3-one, tetrahydropyrrolo[3,4-d]imidazole, pyrimidine, 8-oxa-2-azaspiro[4.5]decane, hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one, 1-oxa-7-azaspiro[3.5]nonane, octahydrocyclopenta[c]pyrrole, tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, 2,7-diazaspiro[4.4]nonane, 2,6-diazaspiro[3.4]octane, 7-oxa-2-azaspiro[3.5]nonane, 1-oxa-8λ^2-azaspiro[4.5]decane, 2-oxa-6-azaspiro[3.3]heptane, tetrahydrofuran, oxadiazole, triazole, pyridinone, tetrahydro-[1,2,4]triazolo[4,3-a]pyrazin-3(2H)-one, piperidinone, 3,6-diazabicyclo[3.1.1]heptane, 5-oxa-2,7-diazaspiro[3.5]nonane, pyrazole, and pyridazin-3(2H)-one. In certain embodiments, the heterocyclic ring is unsubstituted, or substituted with one or more substituents selected from alkyl, alkoxycarbonyl, halo, hydroxy, cyano, carboxy, and heterocyclyl. In certain embodiments, the heterocyclic ring is unsubstituted, or substituted with one or more substituents selected from methyl, ethoxycarbonyl, halo, hydroxy, cyano, carboxy, and oxetanyl.

In certain embodiments of formula (I), (Ia), (Ib), (Ic), (IIa), (IIb), (IIc), (IIIa), (IIIb), or (IIIc), R^1 and $R^{1'}$ combine to form a heterocyclyl (e.g., azetidinyl). In other embodiments, R^1 and $R^{1'}$ combine to form an alkylalkene (e.g., aminoallyl).

In certain embodiments, the compound is selected from , , , , and ; or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides pharmaceutical composition comprising a compound of the disclosure (e.g., a compound of formula (I), (Ia), (Ib), (Ic), (IIa), (IIb), (IIc), (IIIa), (IIIb), or (IIIc)) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

In yet another aspect, the present disclosure provides methods of treating a cardiovascular disease or disorder in a subject, comprising administering a compound of the disclosure (e.g., a compound of formula (I), (Ia), (Ib), (Ic), (IIa), (IIb), (IIc), (IIIa), (IIIb), or (IIIc)) or a pharmaceutically acceptable salt thereof to the subject.

In certain embodiments, the cardiovascular disease is selected from hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, dyslipidemia, dyslipoproteinemia, atherosclerosis, hepatic steatosis, metabolic syndrome and coronary artery disease. In certain embodiments, the cardiovascular disease is familial hypercholesterolemia. In certain embodiments, the cardiovascular disease is autosomal dominant hypercholesterolemia. In certain embodiments, the level of circulating serum cholesterol is decreased in the subject. In certain embodiments, the level of circulating serum LDL-cholesterol is decreased in the subject. In certain embodiments, the level of circulating serum VLDL-cholesterol is decreased in the subject. In certain embodiments, the level of circulating serum triglycerides is decreased in the subject. In certain embodiments, the level of circulating serum lipoprotein A is decreased in the subject. In certain embodiments, the subject has atherosclerosis. In certain embodiments, atherosclerotic plaque formation is decreased in the subject. In certain embodiments, the subject has a gain-of-function mutation in *PCSK9* gene.

In certain embodiments, the method comprises administering one additional therapeutic agent. In certain embodiments, the method comprises administering two additional therapeutic agents. In certain embodiments, the method comprises administering three additional therapeutic agents. In certain embodiments, the method comprises administering four additional therapeutic agents.

In certain embodiments, the additional therapeutic agent is selected from HMG-CoA reductase inhibitor, a HMG-CoA synthase inhibitor, a HMG-CoA reductase gene expression inhibitor, a HMG-CoA synthase gene expression inhibitor, an MTP/Apo B secretion inhibitor, a CETP inhibitor, a bile acid absorption inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a squalene synthetase inhibitor, a squalene epoxidase inhibitor, a squalene cyclase inhibitor, a combined squalene epoxidase/squalene cyclase inhibitor, a fibrate, a niacin, a combination of niacin and lovastatin, an ion-exchange resin, an antioxidant, an ACAT inhibitor, a bile acid sequestrant, a PCSK9 translation inhibitor, an ATP citrate lyase inhibitor, an apoC3 inhibitor, an ANGPTL3 inhibitor, an omega-3 fatty acid, an Lp(a) inhibitor, an apoB inhibitor, an apoA1 inhibitor, a low-density lipoprotein receptor inhibitor, a low-density lipoprotein inhibitor, a diacylglycerol acyltransferase inhibitor, a lysosomal acid lipase inhibitor, and a lecithin cholesterol acyl transferase inhibitor. In certain embodiments, the additional therapeutic agent is an ATP citrate lyase inhibitor. In certain embodiments, the additional therapeutic agent is

an apoC3 inhibitor. In certain embodiments, the additional therapeutic agent is an ANGPTL3 inhibitor. In certain embodiments, the additional therapeutic agent is an omega-3 fatty acid. In certain embodiments, the additional therapeutic agent is an Lp(a) inhibitor. In certain embodiments, the additional therapeutic agent is an apoB inhibitor. In certain embodiments, the additional therapeutic agent is an apoA1 inhibitor. In certain embodiments, the additional therapeutic agent is a low-density lipoprotein receptor inhibitor. In certain embodiments, the additional therapeutic agent is a low-density lipoprotein inhibitor. In certain embodiments, the additional therapeutic agent is a diacylglycerol acyltransferase inhibitor. In certain embodiments, the additional therapeutic agent is a lysosomal acid lipase inhibitor. In certain embodiments, the additional therapeutic agent is a lecithin cholesterol acyl transferase inhibitor.

In certain embodiments, the additional therapeutic agent is selected from volanesorsen, evinacumab, IONIS-ANGPTL3-LRX, icosapent ethyl, icosapentaenoic acid, eicosapentaenoic acid ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid ethyl ester, docosahexaenoic acid, docosahexaenoic acid ester, docosahexaenoic acid methyl ester, docosahexaenoic acid ethyl ester, bempedoic acid, ezetimibe, IONIS-APO(a) RX, mipomersen, CSL-112, lomitapide, AAV8.TBG.hLDLR (RGX-501), alipogene tiparvovec, pradigastat, sebelipase, ACP-501/MEDI6012, OM3FA-EE, OM3FA-CA, OM3FA-IPE, alirocumab, evolocumab, bococizumab, RG7652, LY3015014, mAb316P, berberine, quercetin, ezetimbe, policosanol, BMS-962476, atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. In certain embodiments, the additional therapeutic agent is volanesorsen. In certain embodiments, the additional therapeutic agent is evinacumab. In certain embodiments, the additional therapeutic agent is IONIS-ANGPTL3-LRX. In certain embodiments, the additional therapeutic agent is icosapent ethyl. In certain embodiments, the additional therapeutic agent is eicosapentaenoic acid ethyl ester. In certain embodiments, the additional therapeutic agent is docosahexaenoic acid ethyl ester. In certain embodiments, the additional therapeutic agent is bempedoic acid. In certain embodiments, the additional therapeutic agent is ezetimibe. In certain embodiments, he additional therapeutic agent is IONIS-APO(a) RX. In certain embodiments, the additional therapeutic agent is mipomersen. In certain embodiments, the additional therapeutic agent is CSL-112. In certain embodiments, the additional therapeutic agent is lomitapide. In certain embodiments, the additional therapeutic agent is AAV8.TBG.hLDLR (RGX-501). In certain embodiments, the additional therapeutic agent is

alipogene tiparvovec. In certain embodiments, the additional therapeutic agent is pradigastat. In certain embodiments, the additional therapeutic agent is sebelipase. In certain embodiments, the additional therapeutic agent is ACP-501/MEDI6012. In certain embodiments, the additional therapeutic agent is OM3FA-EE. In certain embodiments, the additional therapeutic agent is OM3FA-CA. In certain embodiments, the additional therapeutic agent is OM3FA-IPE.

In certain embodiments, PCSK9 is over expressed in the subject. In certain embodiments, the subject is male. In certain embodiments, the subject is overweight or obese. In certain embodiments, the subject is African American. In certain embodiments, the subject is Caucasian. In certain embodiments, the subject is Hispanic.

In certain embodiments, the PCSK9 inhibitor and the one or more additional therapeutic agents are administered simultaneously. In other embodiments, the one or more additional therapeutic agents are administered within about 5 minutes to within about 168 hours prior to or after administration of the PCSK9 inhibitor.

In yet another aspect, the present disclosure provides methods of treating sepsis or septic shock in a subject, comprising administering a compound of the disclosure (e.g., a compound of formula (I), (Ia), (Ib), (Ic), (IIa), (IIb), (IIc), (IIIa), (IIIb), or (IIIc)) or a pharmaceutically acceptable salt thereof to the subject.

In certain embodiments, further comprising conjointly administering one or more additional therapeutic agents. In certain embodiments, the method comprises administering one additional therapeutic agent. In certain embodiments, the method comprises administering two additional therapeutic agents. In certain embodiments, the method comprises administering three additional therapeutic agents. In certain embodiments, the method comprises administering four additional therapeutic agents.

In certain embodiments, additional therapeutic agent is selected from kanamycin, amikacin, tobramycin, dibekacin, gentamicin, sisomicin, netilmicin, streptomycin, neomycins B, C, and E, imipenum, meropenum, ertapenem, doripenum, panipenum, biapenem, razupenum, tebipenum, lenapenum, tomopenum, thienpenum, ciprofloxacin, garenoxacin, gatifloxacin, gemifloxaicin, levofloxacin, cinoxacin, nalidixic acid, moxifloxacin, oxolinic acid, piromidic acid, pipemidic acid, rosoxacin, enoxacin, fleroxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pefloxacin, rufloxacin, balofloxacin, grepafloxacin, levofloxacin, pazufloxacin, sparfloxacin, temafloxacin, tosufloxacin, clinafloxacin, sitafloxacin, trovafloxacin, prulifloxacin,

delafloxacin, JNJ-Q2, nemonoxacin, zabofloxacin, doxycycline, tetracycline, chlortetracycline, oxytetracycline, demeclocycline, lymecycline, meclocycline, methacycline, minocycline, rolitetracycline, tigecycline, ampicillin, amoxicillin, augmentin, piperacillin, tazobactam, chloramphenicol, and ticarcillin.

Pharmaceutical Compositions

The compositions and methods of the present disclosure may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the invention and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In preferred embodiments, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule, lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as a lotion, cream, or ointment.

A pharmaceutically acceptable carrier can contain physiologically acceptable agents that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound of the invention. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier, including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a selfemulsifying drug delivery system or a selfmicroemulsifying drug delivery system. The pharmaceutical composition (preparation) also

can be a liposome or other polymer matrix, which can have incorporated therein, for example, a compound of the invention. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for application to the tongue); absorption through the oral mucosa (e.g., sublingually); subcutaneously; transdermally (for example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin). The compound may also be formulated for inhalation. In certain embodiments, a compound

may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the invention, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present disclosure with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present disclosure as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example,

carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active

ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present disclosure to the body. Such dosage forms can be made by dissolving or

dispersing the active compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend

upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

For use in The compounds of this invention, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Methods of introduction may also be provided by rechargeable or biodegradable devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs, including proteinaceous biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or

compound at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. By "therapeutically effective amount" is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with The method of the invention. A larger total dose can be delivered by multiple administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher et al. (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

In general, a suitable daily dose of an active compound used in the compositions and methods of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of the present disclosure, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

The patient receiving this treatment is any animal in need, including primates, in particular humans; and other mammals such as equines, cattle, swine, sheep, cats, and dogs; poultry; and pets in general.

In certain embodiments, compounds of the invention may be used alone or conjointly administered with another type of therapeutic agent.

The present disclosure includes the use of pharmaceutically acceptable salts of compounds of the invention in the compositions and methods of the present disclosure. In certain embodiments, contemplated salts of the invention include, but are not limited to, alkyl, dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, L-arginine, benenthamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol,

ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine, potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine, and zinc salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, l-ascorbic acid, l-aspartic acid, benzenesulfonic acid, benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), caprylic acid (octanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, d-glucoheptonic acid, d-gluconic acid, d-glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, l-malic acid, malonic acid, mandelic acid, methanesulfonic acid , naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, l-pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, l-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, trifluoroacetic acid, and undecylenic acid acid salts.

The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-

tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Definitions

Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, pharmacology, genetics and protein and nucleic acid chemistry, described herein, are those well known and commonly used in the art.

The compounds and techniques of the present disclosure are generally performed, unless otherwise indicated, according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout this specification. See, e.g. "Principles of Neural Science", McGraw-Hill Medical, New York, N.Y. (2000); Motulsky, "Intuitive Biostatistics", Oxford University Press, Inc. (1995); Lodish et al., "Molecular Cell Biology, 4th ed.", W. H. Freeman & Co., New York (2000); Griffiths et al., "Introduction to Genetic Analysis, 7th ed.", W. H. Freeman & Co., N.Y. (1999); and Gilbert et al., "Developmental Biology, 6th ed.", Sinauer Associates, Inc., Sunderland, MA (2000).

Chemistry terms used herein, unless otherwise defined herein, are used according to conventional usage in the art, as exemplified by "The McGraw-Hill Dictionary of Chemical Terms", Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985).

All of the above, and any other publications, patents and published patent applications referred to in this application are specifically incorporated by reference herein. In case of conflict, the present specification, including its specific definitions, will control.

The term "agent" is used herein to denote a chemical compound (such as an organic or inorganic compound, a mixture of chemical compounds), a biological macromolecule (such as a nucleic acid, an antibody, including parts thereof as well as humanized, chimeric and human antibodies and monoclonal antibodies, a protein or portion thereof, e.g., a peptide, a lipid, a carbohydrate), or an extract made from biological materials such as bacteria, plants, fungi, or animal (particularly mammalian) cells or tissues. Agents include, for example, agents whose structure is known, and those whose structure is not known. The ability of such agents to inhibit

AR or promote AR degradation may render them suitable as "therapeutic agents" in The compounds and compositions of this disclosure.

A "patient," "subject," or "individual" are used interchangeably and refer to either a human or a non-human animal. These terms include mammals, such as humans, primates, livestock animals (including bovines, porcines, etc.), companion animals (e.g., canines, felines, etc.) and rodents (e.g., mice and rats).

"Treating" a condition or patient refers to taking steps to obtain beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

The term "preventing" is art-recognized, and when used in relation to a condition, such as a local recurrence (e.g., pain), a disease such as cancer, a syndrome complex such as heart failure or any other medical condition, is well understood in the art, and includes administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, and/or delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, e.g., by a statistically and/or clinically significant amount.

"Administering" or "administration of" a substance, a compound or an agent to a subject can be carried out using one of a variety of methods known to those skilled in the art. For example, a compound or an agent can be administered, intravenously, arterially, intradermally, intramuscularly, intraperitoneally, subcutaneously, ocularly, sublingually, orally (by ingestion), intranasally (by inhalation), intraspinally, intracerebrally, and transdermally (by absorption, e.g., through a skin duct). A compound or agent can also appropriately be introduced by rechargeable or biodegradable polymeric devices or other devices, e.g., patches and pumps, or formulations, which provide for the extended, slow or controlled release of the compound or agent.

Administering can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

Appropriate methods of administering a substance, a compound or an agent to a subject will also depend, for example, on the age and/or the physical condition of the subject and the chemical and biological properties of the compound or agent (e.g., solubility, digestibility, bioavailability, stability and toxicity). In some embodiments, a compound or an agent is administered orally, e.g., to a subject by ingestion. In some embodiments, the orally administered compound or agent is in an extended release or slow release formulation, or administered using a device for such slow or extended release.

As used herein, the phrase "conjoint administration" refers to any form of administration of two or more different therapeutic agents such that the second agent is administered while the previously administered therapeutic agent is still effective in the body (e.g., the two agents are simultaneously effective in the patient, which may include synergistic effects of the two agents). For example, the different therapeutic compounds can be administered either in the same formulation or in separate formulations, either concomitantly or sequentially. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic agents.

A "therapeutically effective amount" or a "therapeutically effective dose" of a drug or agent is an amount of a drug or an agent that, when administered to a subject will have the intended therapeutic effect. The full therapeutic effect does not necessarily occur by administration of one dose, and may occur only after administration of a series of doses. Thus, a therapeutically effective amount may be administered in one or more administrations. The precise effective amount needed for a subject will depend upon, for example, the subject's size, health and age, and the nature and extent of the condition being treated, such as cancer or MDS. The skilled worker can readily determine the effective amount for a given situation by routine experimentation.

As used herein, the terms "optional" or "optionally" mean that the subsequently described event or circumstance may occur or may not occur, and that the description includes instances where the event or circumstance occurs as well as instances in which it does not. For example, "optionally substituted alkyl" refers to the alkyl may be substituted as well as where the alkyl is not substituted.

It is understood that substituents and substitution patterns on the compounds of the present disclosure can be selected by one of skill in the art to result in chemically stable compounds which

can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results.

As used herein, the term "optionally substituted" refers to the replacement of one to six hydrogen radicals in a given structure with the radical of a specified substituent including, but not limited to: hydroxyl, hydroxyalkyl, alkoxy, halogen, alkyl, nitro, silyl, acyl, acyloxy, aryl, cycloalkyl, heterocyclyl, amino, aminoalkyl, cyano, haloalkyl, haloalkoxy, -OCO-CH_2-O-alkyl, -OP(O)(O-alkyl)$_2$ or –CH_2-OP(O)(O-alkyl)$_2$. Preferably, "optionally substituted" refers to the replacement of one to four hydrogen radicals in a given structure with the substituents mentioned above. More preferably, one to three hydrogen radicals are replaced by the substituents as mentioned above. It is understood that the substituent can be further substituted.

As used herein, the term "alkyl" refers to saturated aliphatic groups, including but not limited to C_1-C_{10} straight-chain alkyl groups or C_1-C_{10} branched-chain alkyl groups. Preferably, the "alkyl" group refers to C_1-C_6 straight-chain alkyl groups or C_1-C_6 branched-chain alkyl groups. Most preferably, the "alkyl" group refers to C_1-C_4 straight-chain alkyl groups or C_1-C_4 branched-chain alkyl groups. Examples of "alkyl" include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, n-butyl, sec-butyl, tert-butyl, 1-pentyl, 2-pentyl, 3-pentyl, neo-pentyl, 1-hexyl, 2-hexyl, 3-hexyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 1-octyl, 2-octyl, 3-octyl or 4-octyl and the like. The "alkyl" group may be optionally substituted.

Moreover, the term "alkyl" as used throughout the specification, examples, and claims is intended to include both unsubstituted and substituted alkyl groups, the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc.

As used herein, the term "alkylene" refers to a bivalent saturated aliphatic group, including but not limited to C_1-C_{50} straight-chain alkylene groups or C_1-C_{50} branched-chain alkylene groups. Moreover, the term "alkylene" as used throughout the specification, examples, and claims is intended to include both unsubstituted and substituted alkylene groups, the latter of which refers to alkylene moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc.

As used herein, the term "heteroalkylene" refers to a bivalent aliphatic group wherein one or more of the carbon atoms has been replaced with a heteroatom such as N, O, or S, or a moiety such as (C=O). The term includes but is not limited to 2-50 atom straight-chain heteroalkylene groups or 2-50 atom branched-chain heteroalkylene groups. If a heteroalkylene comprises a N atom or another heteroatom that has three or more open valence positions, then the heteroatom atom may be unsubstituted (e.g., -N(H)-) or it may be substituted with substituents known to those with skill in the art (e.g., alkyl, aralkyl, aryl, etc. as further described herein), or all of the heteroatom's valencies may be occupied by its bonds to the chain of the heteroalkylene (e.g., -N= or =N-). Moreover, the term "heteroalkylene" as used throughout the specification, examples, and claims is intended to include both unsubstituted and substituted heteroalkylene groups, the latter of which refers to heteroalkylene moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc.

The term "acyl" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

The term "acylamino" is art-recognized and refers to an amino group substituted with an acyl group and may be represented, for example, by the formula hydrocarbylC(O)NH-.

The term "acyloxy" is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O-, preferably alkylC(O)O-.

The term "alkoxy" refers to an alkyl group having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

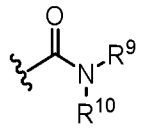
The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

The term "C_{x-y}" or "C_x-C_y", when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. C_0alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. A C_{1-6}alkyl group, for example, contains from one to six carbon atoms in the chain.

The term "alkylamino", as used herein, refers to an amino group substituted with at least one alkyl group.

The term "alkylthio", as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkylS-.

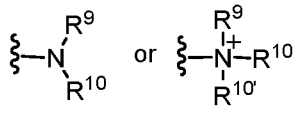
The term "amide", as used herein, refers to a group



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wherein R^9 and R^{10} each independently represent a hydrogen or hydrocarbyl group, or R^9 and R^{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by



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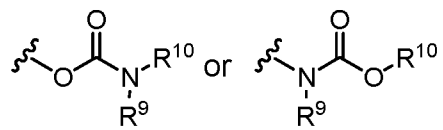
wherein R^9, R^{10}, and $R^{10'}$ each independently represent a hydrogen or a hydrocarbyl group, or R^9 and R^{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term "aminoalkyl", as used herein, refers to an alkyl group substituted with an amino group.

The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group.

The term "aryl" as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

The term "carbamate" is art-recognized and refers to a group



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wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl group.

The term "carbocyclylalkyl", as used herein, refers to an alkyl group substituted with a carbocycle group.

The term "carbocycle" includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused carbocycle" refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary "carbocycles" include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. "Carbocycles" may be substituted at any one or more positions capable of bearing a hydrogen atom.

The term "carbocyclylalkyl", as used herein, refers to an alkyl group substituted with a carbocycle group.

The term "carbonate" is art-recognized and refers to a group $-OCO_2-$.

The term "carboxy", as used herein, refers to a group represented by the formula $-CO_2H$.

The term "cycloalkyl" include substituted or unsubstituted non-aromatic single ring structures, preferably 4- to 8-membered rings, more preferably 4- to 6-membered rings. The term "cycloalkyl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is cycloalkyl and the substituent (e.g., R^{100}) is attached to the cycloalkyl ring, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, denzodioxane, tetrahydroquinoline, and the like.

The term "ester", as used herein, refers to a group $-C(O)OR^9$ wherein R^9 represents a hydrocarbyl group.

The term "ether", as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-heterocycle. Ethers include "alkoxyalkyl" groups, which may be represented by the general formula alkyl-O-alkyl.

The terms "halo" and "halogen" as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

The terms "hetaralkyl" and "heteroaralkyl", as used herein, refers to an alkyl group substituted with a hetaryl group.

The terms "heteroaryl" and "hetaryl" include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heteroaryl" and "hetaryl" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, pyrimidine, denzodioxane, tetrahydroquinoline ,and the like.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

The term "heterocyclylalkyl", as used herein, refers to an alkyl group substituted with a heterocycle group.

The terms "heterocyclyl", "heterocycle", and "heterocyclic" refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heterocyclyl" and "heterocyclic" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like.

The term "hydrocarbyl", as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and even trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocycle, alkyl, alkenyl, alkynyl, and combinations thereof.

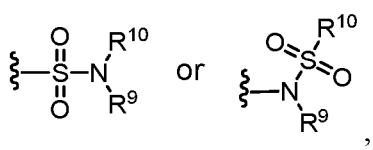
The term "hydroxyalkyl", as used herein, refers to an alkyl group substituted with a hydroxy group.

The term "lower" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer atoms in the substituent, preferably six or fewer. A "lower alkyl", for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

The terms "polycyclyl", "polycycle", and "polycyclic" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) in which two or more atoms are common to two adjoining rings, e.g., the rings are "fused rings". Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

The term "sulfate" is art-recognized and refers to the group $-OSO_3H$, or a pharmaceutically acceptable salt thereof.

The term "sulfonamide" is art-recognized and refers to the group represented by the general formulae



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wherein R^9 and R^{10} independently represents hydrogen or hydrocarbyl.

The term "sulfoxide" is art-recognized and refers to the group–S(O)-.

The term "sulfonate" is art-recognized and refers to the group SO_3H, or a pharmaceutically acceptable salt thereof.

The term "sulfone" is art-recognized and refers to the group $–S(O)_2-$.

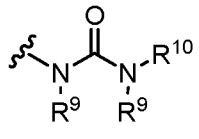
The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate.

The term "alkylthio", as used herein, refers to an alkyl group substituted with a thiol group.

The term "thioester", as used herein, refers to a group $-C(O)SR^9$ or $–SC(O)R^9$ wherein R^9 represents a hydrocarbyl.

The term "thioether", as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

The term "urea" is art-recognized and may be represented by the general formula



wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl.

The term "modulate" as used herein includes the inhibition or suppression of a function or activity (such as cell proliferation) as well as the enhancement of a function or activity.

The phrase "pharmaceutically acceptable" is art-recognized. In certain embodiments, the term includes compositions, excipients, adjuvants, polymers and other materials and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

"Pharmaceutically acceptable salt" or "salt" is used herein to refer to an acid addition salt or a basic addition salt which is suitable for or compatible with the treatment of patients.

The term "pharmaceutically acceptable acid addition salt" as used herein means any non-toxic organic or inorganic salt of any base compounds represented by Formula I. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acids, as well as metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids that form suitable salts include mono-, di-, and tricarboxylic acids such as glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, benzoic, phenylacetic, cinnamic and salicylic acids, as well as sulfonic acids such as p-toluene sulfonic and methanesulfonic acids. Either the mono or di-acid salts can be formed, and such salts may exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of compounds of Formula I are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms. The selection of the appropriate salt will be known to one skilled in the art. Other non-pharmaceutically acceptable salts, e.g., oxalates, may be used, for example, in the isolation of compounds of Formula I for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

The term "pharmaceutically acceptable basic addition salt" as used herein means any non-toxic organic or inorganic base addition salt of any acid compounds represented by Formula I or any of their intermediates. Illustrative inorganic bases which form suitable salts include lithium,

sodium, potassium, calcium, magnesium, or barium hydroxide. Illustrative organic bases which form suitable salts include aliphatic, alicyclic, or aromatic organic amines such as methylamine, trimethylamine and picoline or ammonia. The selection of the appropriate salt will be known to a person skilled in the art.

Many of the compounds useful in The compounds and compositions of this disclosure have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondence with the rules described in Pure Appl. Chem. (1976), 45, 11-30. The disclosure contemplates all stereoisomeric forms such as enantiomeric and diastereoisomeric forms of the compounds, salts, prodrugs or mixtures thereof (including all possible mixtures of stereoisomers). See, e.g., WO 01/062726.

Furthermore, certain compounds which contain alkenyl groups may exist as Z (zusammen) or E (entgegen) isomers. In each instance, the disclosure includes both mixture and separate individual isomers.

Some of the compounds may also exist in tautomeric forms. Such forms, although not explicitly indicated in the formulae described herein, are intended to be included within the scope of the present disclosure.

"Prodrug" or "pharmaceutically acceptable prodrug" refers to a compound that is metabolized, for example hydrolyzed or oxidized, in the host after administration to form The method of the present disclosure (e.g., compounds of formula I). Typical examples of prodrugs include compounds that have biologically labile or cleavable (protecting) groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, or dephosphorylated to produce the active compound. Examples of prodrugs using ester or phosphoramidate as biologically labile or cleavable (protecting) groups are disclosed in U.S. Patents 6,875,751, 7,585,851, and 7,964,580, the disclosures of which are incorporated herein by reference. The prodrugs of this disclosure are metabolized to produce a compound of Formula I. The present disclosure includes within its scope, prodrugs of the compounds described herein. Conventional procedures for the selection and preparation of suitable prodrugs are described, for example, in "Design of Prodrugs" Ed. H. Bundgaard, Elsevier, 1985.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filter, diluent, excipient, solvent or encapsulating material useful for formulating a drug for medicinal or therapeutic use.

The term "Log of solubility", "LogS" or "logS" as used herein is used in the art to quantify the aqueous solubility of a compound. The aqueous solubility of a compound significantly affects its absorption and distribution characteristics. A low solubility often goes along with a poor absorption. LogS value is a unit stripped logarithm (base 10) of the solubility measured in mol/liter.

As used herein, the term "interacts" in the context of an inhibitor in relation to one or more residues of PCSK9 refers to direct or indirect associations of the inhibitor with either the backbone of the enzyme or the side chain of any given residue. For example, interactions include covalent bonds, hydrogen bonds, hydrophobic attractions, cation-pi interactions, anion-pi interactions and others well known in the art.

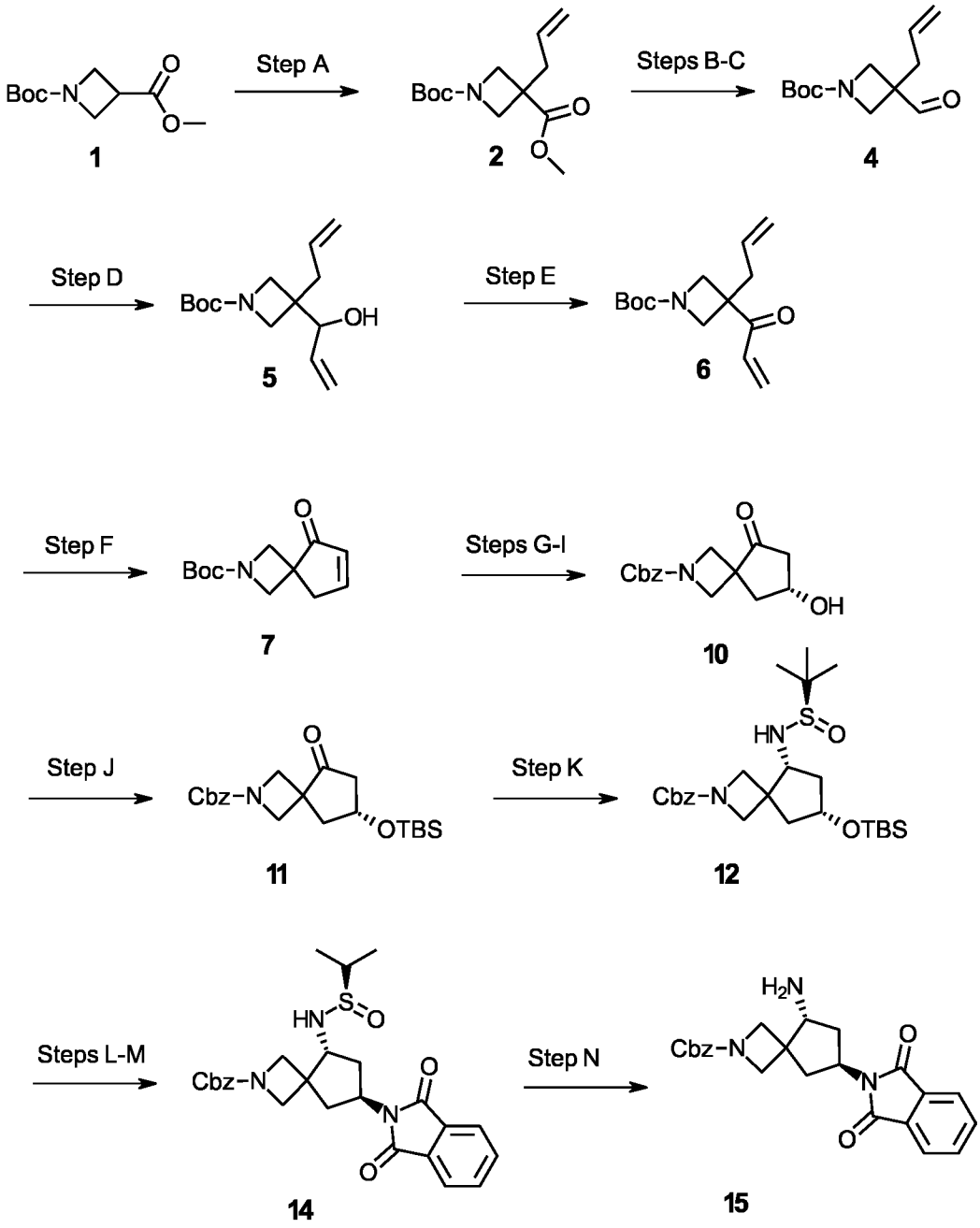
EXAMPLES

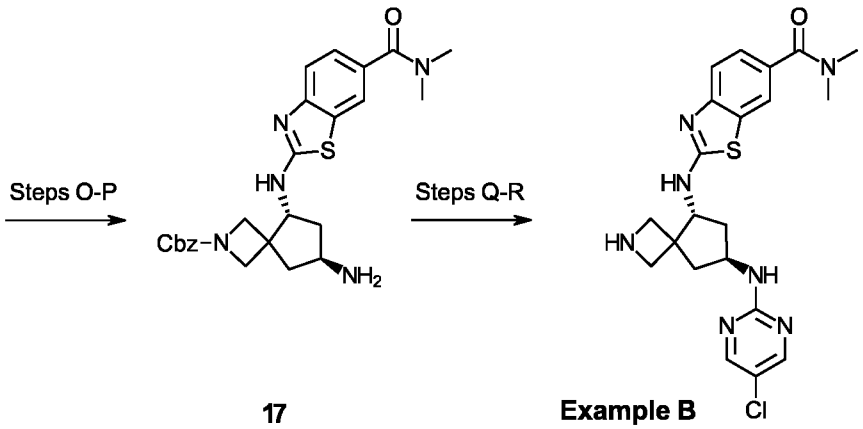
The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present disclosure, and are not intended to limit the invention.

Example 1: Preparation of Exemplary PCSK9 inhibitors

^{1}H NMR spectra were performed on a Varian MR-400 spectrometer operating at 400 MHz (proton frequency), equipped with: a self-shielded z-gradient coil 5 mm 1H/nX broad band probehead for reverse detection, deuterium digital lock channel unit, quadrature digital detection unit with transmitter offset frequency shift. Chemical shifts are reported as δ values in ppm relative to trimethylsilane (TMS) as an internal standard. Coupling constants (J values) are given in hertz (Hz) and multiplicities are reported using the following abbreviation (s= singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, nd=not determined).

Example B


Boc-N
O
O
Step A
Boc-N
O
O
Steps B-C
Boc-N
O
1
2
4
Step D
Boc-N
OH
Step E
Boc-N
O
5
6
Step F
Boc-N
O
Steps G-I
Cbz-N
O
OH
7
10
Step J
Cbz-N
O
OTBS
Step K
HN
S
O
Cbz-N
OTBS
11
12
Steps L-M
HN
S
O
Cbz-N
O
N
O
Step N
H2N
Cbz-N
O
N
O
14
15



17 Example B

Step A: 1-tert-butyl 3-methyl 3-allylazetidine-1,3-dicarboxylate (2)

To a stirred solution of 1-(tert-butyl) 3-methyl azetidine-1,3-dicarboxylate (19.3 g, 89.7 mmol) in dry THF (180 mL) at -78 °C, LiHMDS (1 M in THF, 179.5 mL,179.5 mmol) was added dropwise under nitrogen atmosphere. The reaction mixture was stirred for 1h at -78 °C, then allyl bromide (21.7 g, 179.5 mmol) was added to the above reaction mixture at -78 °C. The reaction mixture was slowly warmed to room temperature and stirred overnight. After completion, the reaction mixture was cooled to 0 °C, quenched with sat.aq. NH_4Cl (200 mL) and extracted with EA (150 mL × 3). The combined organic layers were washed with brine (250 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 1-(tert-butyl) 3-methyl 3-allylazetidine-1,3-dicarboxylate (crude, 22 g, yield: 90%) as a yellow oil, which was used directly for next step without further purification.

Step B: tert-butyl 3-allyl-3-(hydroxymethyl)azetidine-1-carboxylate (3)

To a stirred solution of 1-(tert-butyl) 3-methyl 3-allylazetidine-1,3-dicarboxylate (22 g, 86 mmol) in dry DCM (300 mL) at -78 °C was added DIBAl-H (1 M in toluene, 129 mL, 129 mmol) slowly and stirred at r.t for 2 h. After completion, the reaction mixture was cooled to 0 °C and quenched with NaOH (1 M in H_2O, 100 mL) and extracted with DCM (200 mL× 3). The combined organic layers were washed with brine (250 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 3-allyl-3-(hydroxymethyl)azetidine-1-carboxylate(crude, 15 g, yield: 77%) as a yellow oil, which was used directly for next step without further purification.

Step C: tert-butyl 3-allyl-3-formylazetidine-1-carboxylate (4)

To a stirred solution of tert-butyl 3-allyl-3-(hydroxymethyl)azetidine-1-carboxylate (15 g, 66 mmol) in dry DCM(500 mL) at 0 °C was added Dess–Martin (56 g, 132 mmol) and the mixture

was stirred at r.t for 2 h. The reaction mixture was quenched with Na_2SO_3 (10%, 200 mL) and aqueous $NaHCO_3$ (10%, 200 mL), extracted with DCM (200 mL× 3). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MTBE/PE=25%) to give tert-butyl 3-allyl-3-formylazetidine-1-carboxylate (9.2 g, yield: 46%, three steps) as a yellow oil.

Step D: tert-butyl 3-allyl-3-(1-hydroxyallyl)azetidine-1-carboxylate (5)

To a stirred solution of tert-butyl 3-allyl-3-formylazetidine-1-carboxylate (9.2 g, 40.8 mmol) in dry THF (200 mL) at -78 °C was added vinylmagnesium bromide (1 M in THF, 49 mL, 49 mmol) and the reaction mixture was stirred at r.t for 2 h. After completion, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl (200 mL) and extracted with EA (200 mL × 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give tert-butyl 3-allyl-3-(1-hydroxyallyl)azetidine-1-carboxylate (crude, 10 g, yield: 97%) as a yellow oil, which was used directly for next step without further purification.

Step E: tert-butyl 3-acryloyl-3-allylazetidine-1-carboxylate (6)

To a stirred solution of tert-butyl 3-allyl-3-(1-hydroxyallyl)azetidine-1-carboxylate (10 g, 39.5 mmol) in dry DCM (200 mL) at 0 °C was added Dess–Martin (25 g, 59 mmol) and the mixture was stirred at r.t for 2 h. The reaction mixture was quenched with Na_2SO_3 (10%, 100 mL) and aqueous $NaHCO_3$ (10%, 100 mL), extracted with DCM (100 mL× 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EA/PE=18%) to give tert-butyl 3-acryloyl-3-allylazetidine-1-carboxylate (4.2 g, yield: 42%, two steps) as a yellow oil.

Step F: tert-butyl 5-oxo-2-azaspiro[3.4]oct-6-ene-2-carboxylate (7)

To a stirred solution of tert-butyl 3-acryloyl-3-allylazetidine-1-carboxylate (4.2 g, 16.7 mmol) in toluene (200 mL) was added Grubbs-II catalyst (709 mg, 0.8 mmol) under nitrogen atmosphere. The mixture was stirred at 85 °C for 1h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MTBE/PE=35%) to give tert-butyl 5-oxo-2-azaspiro[3.4]oct-6-ene-2-carboxylate (3.1 g, yield: 83%) as a brown solid.

Step G: 2-azaspiro[3.4]oct-6-en-5-one (8)

To a stirred solution of tert-butyl 5-oxo-2-azaspiro[3.4]oct-6-ene-2-carboxylate (2 g, 9.0 mmol) in DCM (15 mL) was added TFA(5 mL) at 0 °C. The mixture was stirred at r.t for 1h. The reaction mixture was concentrated under reduced pressure to give 2-azaspiro[3.4]oct-6-en-5-one (2 g crude, quant.), which was used directly for next step without further purification.

Step H: benzyl 5-oxo-2-azaspiro[3.4]oct-6-ene-2-carboxylate (9)

To a stirred solution of 2-azaspiro[3.4]oct-6-en-5-one (1.1 g, 8.9 mmol) in THF(15 mL) was added TEA(2.7 g, 26.7 mmol) and Cbz-OSU(2.67 g, 10.7 mmol) at 0 °C. The mixture was stirred at r.t for 1h. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EA/PE=35%) to give benzyl 5-oxo-2-azaspiro[3.4]oct-6-ene-2-carboxylate (2 g, yield: 86%, two steps) as a yellow oil. LCMS $[M+1]^+$= 258.0

Step I: (R)-benzyl 7-hydroxy-5-oxo-2-azaspiro[3.4]octane-2-carboxylate (10)

A solution of CuC1 (46 mg, 0.47 mmol), (S)-TolBINAP (318 mg, 0.47 mmol), and sodium tert-butoxide (45 mg, 0.47 mmol) in THF (10 mL) was stirred for 30 min at r.t. Then bis(pinacolato)diboran (2.96 g, 11.7 mmol) in THF (20 mL) was added and the resulting mixture was stirred for 10 min at r.t. benzyl 5-oxo-2-azaspiro[3.4]oct-6-ene-2-carboxylate (2.0 g, 7.8 mmol) in THF(20 mL) was added to above solution followed by MeOH (500 mg, 15.6 mmol). The resulting mixture was stirred for 1h at r.t, then water (10 mL) was added followed by sodium perborate (6.0 g, 39 mmol) and the resulting mixture was vigorously stirred at r.t for 1h. The resulting green suspension was filtered through a pad of celite, poured into a separation funnel containing sat. aq. $NaHCO_3/Na_2SO_3$ (1/1,50 mL) and extracted with EA (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude benzyl (R)-7-hydroxy-5-oxo-2-azaspiro[3.4]octane-2-carboxylate (5.4 g, quant.), which was used directly for next step without further purification. LCMS $[M+1]^+$= 276.0

Step J: (R)-benzyl 7-((tert-butyldimethylsilyl)oxy)-5-oxo-2-azaspiro[3.4]octane-2-carboxylate (11)

To a stirred solution of benzyl (R)-7-hydroxy-5-oxo-2-azaspiro[3.4]octane-2-carboxylate(2.1 g, 7.8 mmol) in DCM (30 mL) was added imidazole (4.3 g, 31.2 mmol) and TBSCl

(2.3 g, 15.6 mmol) at 0°C. The resulting mixture was stirred for 3h at r.t. After completion, the mixture was diluted with water (50 mL) and extracted with DCM (30 mL× 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EA/PE=23%) to give benzyl (R)-7-((tert-butyldimethylsilyl)oxy)-5-oxo-2-azaspiro[3.4]octane-2-carboxylate (1.8 g, yield: 59%, two steps) as a yellow oil. LCMS $[M+1]^+$= 390.0

Step K: (5R,7R)-benzyl 7-((tert-butyldimethylsilyl)oxy)-5-((R)-1,1-dimethylethyl sulfinamido)-2-azaspiro[3.4]octane-2-carboxylate (12)

To a stirred solution of benzyl (R)-7-((tert-butyldimethylsilyl)oxy)-5-oxo-2-azaspiro[3.4]octane-2-carboxylate (1.7 g, 4.4 mmol) in dry THF (20 mL) was added (R)-2-methylpropane-2-sulfinamide (1.06 g, 8.7 mmol) and Titanium tetraisopropanolate (5 g, 17.6 mmol) at 0 °C. The resulting mixture was stirred overnight at 75 °C. The mixture was cooled to -78 °C, L-selectride (13.2 mL, 13.2 mmol) was added dropwise. After addition, the mixture was stirred for 3h at -78 °C. The mixture was quenched by sat.aq. NH_4Cl, filtered and extracted with EA (50 mL× 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EA/PE=40%) to give benzyl (5R,7R)-7-((tert-butyldimethylsilyl)oxy)-5-(((R)-tert-butylsulfinyl)amino)-2-azaspiro[3.4]octane-2-carboxylate (750 mg, yield: 35%) as a yellow oil. LCMS $[M+1]^+$= 495.0

Step L: (5R,7R)-benzyl 5-((R)-1,1-dimethylethylsulfinamido)-7-hydroxy-2-azaspiro[3.4]octane-2-carboxylate (13)

To a stirred solution of benzyl (5R,7R)-7-((tert-butyldimethylsilyl)oxy)-5-(((R)-tert-butylsulfinyl)amino)-2-azaspiro[3.4]octane-2-carboxylate (800 mg, 1.62 mmol) in THF (3 mL) was added TBAF (1M in THF, 2.42 mL, 2.42 mmol) at r.t. and stirred for 2h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM=3%) to give benzyl (5R,7R)-5-(((R)-tert-butylsulfinyl)amino)-7-hydroxy-2-azaspiro[3.4]octane-2-carboxylate (600 mg, yield: 97%) as a yellow oil. LCMS $[M+1]^+$= 381.0

Step M: (5R,7S)-benzyl 5-((R)-1,1-dimethylethylsulfinamido)-7-(1,3-dioxoisoindolin-2-yl)-2-azaspiro[3.4]octane-2-carboxylate (14)

To a stirred solution of benzyl (5R,7R)-5-(((R)-tert-butylsulfinyl)amino)-7-hydroxy-2-azaspiro[3.4]octane-2-carboxylate (600 mg, 1.58 mmol) in THF (15 mL) was added PPh_3 (828 mg, 3.16 mmol), isoindoline-1,3-dione (348 mg, 2.37 mmol) and DIAD (638 mg, 3.16 mmol) at 0 °C under nitrogen atmosphere. After addition, the mixture was stirred at r.t for 1h and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM=2%) to give (5R,7S)-benzyl 5-((R)-1,1-dimethylethylsulfinamido)-7-(1,3-dioxoisoindolin-2-yl)-2-azaspiro[3.4]octane-2-carboxylate (750 mg, yield: 93%) as a yellow oil. LCMS $[M+1]^+$= 510.0

Step N: (5R,7S)-benzyl 5-amino-7-(1,3-dioxoisoindolin-2-yl)-2-azaspiro[3.4]octane-2-carboxylate (15)

To a stirred solution of (5R,7S)-benzyl 5-((R)-1,1-dimethylethylsulfinamido)-7-(1,3-dioxoisoindolin-2-yl)-2-azaspiro[3.4]octane-2-carboxylate (600 mg, 1.2 mmol) in DCM (5 mL) was added HCl in dioxane (4M in dioxane, 5 mL) at 0 °C. The mixture was stirred at r.t for 30 min. The reaction mixture was concentrated under reduced pressure to give (5R,7S)-benzyl 5-amino-7-(1,3-dioxoisoindolin-2-yl)-2-azaspiro[3.4]octane-2-carboxylate (610 mg crude, quant.), which was used directly for next step without further purification. LCMS $[M+1]^+$= 406.0

Step O: (5R,7S)-benzyl 5-((6-(dimethylcarbamoyl)benzo[d]thiazol-2-yl)amino)-7-(1,3-dioxoisoindolin-2-yl)-2-azaspiro[3.4]octane-2-carboxylate (16)

To a stirred solution of (5R,7S)-benzyl 5-amino-7-(1,3-dioxoisoindolin-2-yl)-2-azaspiro[3.4]octane-2-carboxylate (350 mg, 0.86 mmol) in DMSO (3.5 mL) was added 2-chloro-N,N-dimethylbenzo[d]thiazole-6-carboxamide (312 mg, 1.3 mmol) and DIEA (333 mg, 2.58 mmol) at r.t. The resulting mixture was stirred overnight at 90 °C. The mixture was diluted with water (30 mL) and extracted with EA (30 mL× 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by by silica gel column chromatography (MeOH/DCM=2%) to give (5R,7S)-benzyl 5-((6-(dimethylcarbamoyl)benzo[d]thiazol-2-yl)amino)-7-(1,3-dioxoisoindolin-2-yl)-2-azaspiro[3.4]octane-2-carboxylate (300 mg, yield: 57%) as a yellow oil. LCMS $[M+1]^+$= 610.3

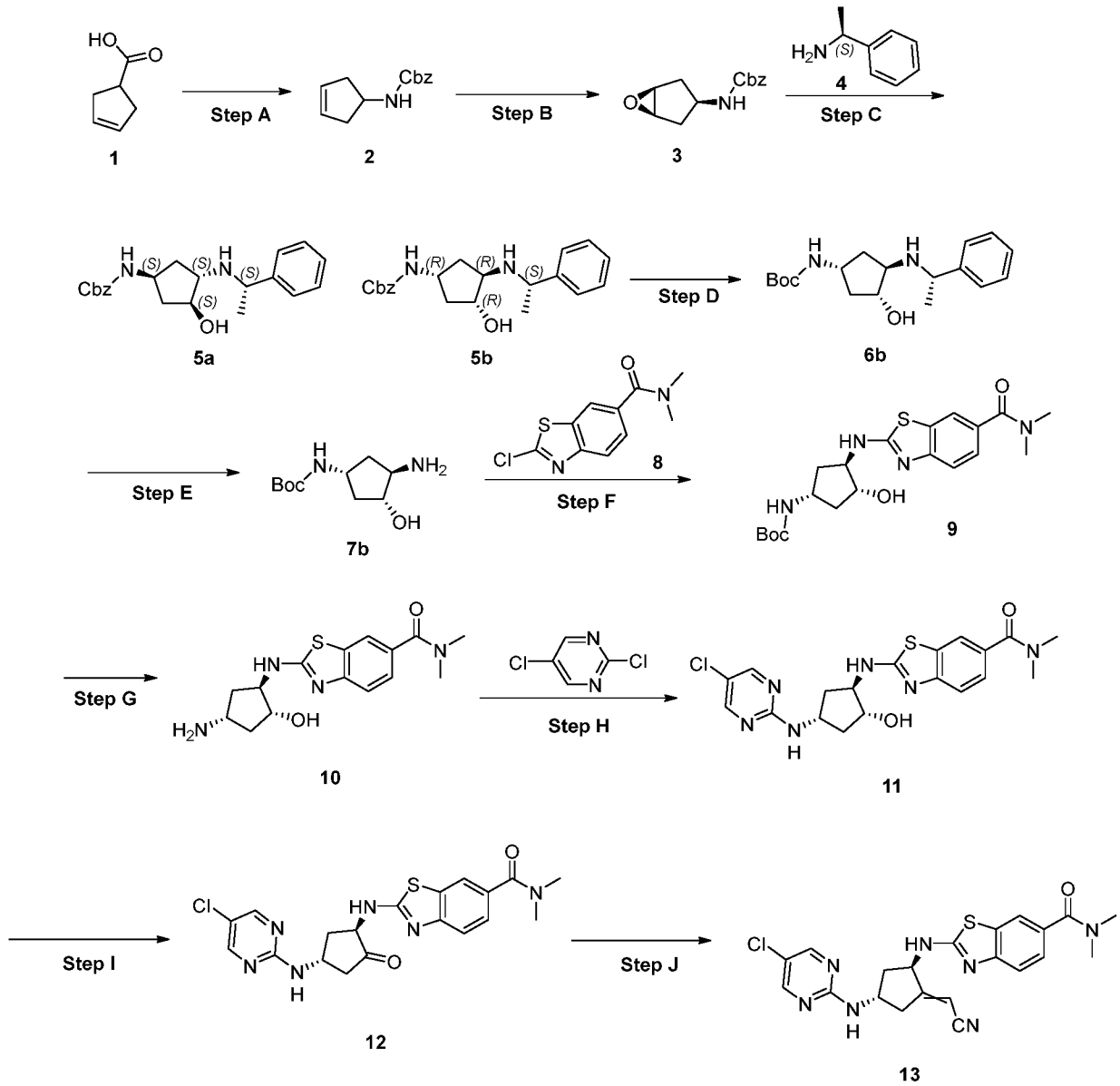
Step P: (5R,7S)-benzyl 7-amino-5-((6-(dimethylcarbamoyl)benzo[d]thiazol-2-yl)amino)-2-azaspiro[3.4]octane-2-carboxylate (17)

To a stirred solution of (5R,7S)-benzyl 5-((6-(dimethylcarbamoyl)benzo[d]thiazol-2-yl)amino)-7-(1,3-dioxoisoindolin-2-yl)-2-azaspiro[3.4]octane-2-carboxylate (300 mg, 0.49 mmol) in EtOH (3 mL) was added hydrazine hydrate (246 mg, 4.9 mmol) at r.t and stirred for 1h. After completion, the mixture was filtered and the filtrate was diluted with water (50 mL) and extracted with EA (30 mL× 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give (5R,7S)-benzyl 7-amino-5-((6-(dimethylcarbamoyl)benzo[d]thiazol-2-yl)amino)-2-azaspiro[3.4]octane-2-carboxylate (240 mg crude, quant.), which was used directly for next step without further purification. LCMS $[M+1]^+$= 480.3

Step Q and R: N,N-Dimethyl-2-{(5R,7S)-7-(5-chloro-2-pyrimidinylamino)-2-aza-5-spiro[3.4]octylamino}-1,3-benzothiazole-6-carboxamide (Example B)

To a stirred solution of (5R,7S)-benzyl 7-amino-5-((6-(dimethylcarbamoyl)benzo[d]thiazol-2-yl)amino)-2-azaspiro[3.4]octane-2-carboxylate (240 mg, 0.5 mmol) in DMSO (3 mL) was added 2,5-dichloropyrimidine (112 mg, 0.75 mmol) at r.t. The resulting mixture was stirred for 2h at 80 °C. After completion, the mixture was diluted with water (30 mL) and extracted with EA (50 mL× 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (MeOH/DCM=8%) to give (5R,7S)-benzyl 7-((5-chloropyrimidin-2-yl)amino)-5-((6-(dimethylcarbamoyl)benzo[d]thiazol-2-yl)amino)-2-azaspiro[3.4]octane-2-carboxylate (260 mg, yield: 88%) as a yellow solid. LCMS $[M+1]^+$= 592.0. Deprotection of the benzyl carbamate using standard conditions affords the title compound.

Example 13



Step A: benzyl cyclopent-3-en-1-ylcarbamate

To a solution of cyclopent-3-ene-1-carboxylic acid (51.8 g, 462.5 mmol) in toluene (780 mL) and Et_3N (56.1 g, 555.6 mmol) was added DPPA (140 g, 508.8 mmol) dropwise. The reaction mixture was stirred at room temperature for 2 hours, then BnOH (74.9 g, 693.8 mmol) was added dropwise to the mixture. The reaction mixture was heated to 90 °C and stirred overnight under nitrogen atmosphere. After cooling to room temperature, the reaction mixture was poured into water (3 L), extracted with ethyl acetate (500 mL x 3). The combined organic layers were washed with brine (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced

pressure to give benzyl cyclopent-3-en-1-ylcarbamate crude (126 g, quant.) as yellow oil. The crude was directly used for next step without further purification.

LCMS $[M+H]^+$=218.1.

Step B: benzyl ((1R,3r,5S)-6-oxabicyclo[3.1.0]hexan-3-yl)carbamate

To a solution of benzyl cyclopent-3-en-1-ylcarbamate (35 g, 161.3 mmol) in DCM (875 mL) was added *m*-CPBA (85%, 50 g, 290.3 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min. After completion, the reaction was quenched with Na_2SO_3 (aq) and $NaHCO_3$ (aq), extracted with DCM (800 mLx2). The combined organic phase were washed with brine (800 mLx2), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EA/PE=30%) to give benzyl ((1R,3r,5S)-6-oxabicyclo[3.1.0]hexan-3-yl)carbamate (32.5 g, 86.7%) as a white solid. LCMS $[M+H]^+$=234.1

Step C: benzyl ((1S,3S,4S)-3-hydroxy-4-(((S)-1-phenylethyl)amino)cyclopentyl) carbamate(5a) and benzyl ((1R,3R,4R)-3-hydroxy-4-(((S)-1phenylethyl)amino) cyclopentyl) carbamate (5b)

A mixture of benzyl ((1R,3r,5S)-6-oxabicyclo[3.1.0]hexan-3-yl)carbamate (32.5 g, 139.5 mmol) and (S)-1-phenylethan-1-amine (33.8 g, 279 mmol) was stirred at 120°C overnight, then MeOH (1.5 L) and $(Boc)_2O$ (30.4 g) were added. After stirring at room temperature for 30 min, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EA(3% NH_3.MeOH)/PE=78%) to give the mixture of 5a and 5b (18.2 g, 36.9%) as a yellow solid. LCMS $[M+H]^+$=355.3.

Step D: tert-butyl((1R,3R,4R)-3-hydroxy-4-(((S)-1-phenylethyl)amino)cyclopentyl) carbamate

To a solution of benzyl ((1R,3R,4R)-3-hydroxy-4-(((S)-1-phenylethyl)amino)cyclopentyl) carbamate (18.2 g, 51.4 mmol) in MeOH (360 mL) was added $(Boc)_2O$ (11.8 g, 54 mmol) and Pd/C (4.6 g). The reaction mixture was stirred at room temperature for 3 hours under hydrogen atmosphere. After completion, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EA/PE=78%) to give tert-butyl((1R,3R,4R)-3-hydroxy-4-(((S)-1-phenylethyl)amino)cyclopentyl)carbamate (8.5 g, 50%) as a colorless oil. LCMS $[M+H]^+$= 321.2

Step E: tert-butyl ((1R,3R,4R)-3-amino-4-hydroxycyclopentyl)carbamate

To a solution of tert-butyl((1R,3R,4R)-3-hydroxy-4-(((S)-1-phenylethyl)amino)cyclopentyl) carbamate (18.5 g, 57.8 mmol) in MeOH (360 mL) was added $Pd(OH)_2$ (6.17 g). The reaction mixture was stirred at 60 °C for 20 hours under hydrogen atmosphere. After completion, the reaction mixture was filtered and the filtrate was concentrated to give tert-butyl ((1R,3R,4R)-3-amino-4-hydroxycyclopentyl)carbamate (11 g, 88%) as a white solid. LCMS $[M+H]^+$= 217.1

Step F: tert-butyl ((1R,3R,4R)-3-((6-(dimethylcarbamoyl)benzo[d]thiazol-2-yl)amino)-4-hydroxycyclopentyl)carbamate

To a solution of tert-butyl ((1R,3R,4R)-3-amino-4-hydroxycyclopentyl)carbamate (700 mg, 3.22 mmol) in DMSO (15 mL) was added DIPEA (1.25 g, 9.66 mmol) and 2-chloro-N,N-dimethylbenzo[d]thiazole-6-carboxamide (931 mg, 3.85 mmol). The mixture was heated to 80 °C and stirred for 6 h under nitrogen atmosphere. After completion, the reaction mixture was diluted with water (30 mL), extracted with ethyl acetate (30 mLx3). The combined organic layers were washed with brine (30 mLx3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (DCM/ MeOH = 50/1to 20/1) to give tert-butyl ((1R,3R,4R)-3-((6-(dimethylcarbamoyl)benzo[d]thiazol-2-yl)amino)-4-hydroxycyclopentyl)carbamate (880 mg, 65%) as a light yellow solid. LCMS $[M+H]^+$=421.3

Step G: 2-(((1R,2R,4R)-4-amino-2-hydroxycyclopentyl)amino)-N,N-dimethylbenzo[d]thiazole-6-carboxamide

To a solution of tert-butyl ((1R,3R,4R)-3-((6-(dimethylcarbamoyl)benzo[d]thiazol-2-yl)amino)-4-hydroxycyclopentyl)carbamate (880 mg, 2.09 mmol) in DCM (25 mL) was added HCl in dioxane (2M, 5 mL) at room temperature. After addition, the reaction mixture was stirred at room temperature for 1 h. After completion, the mixture was concentrated under reduced pressure to give 2-(((1R,2R,4R)-4-amino-2-hydroxycyclopentyl)amino)-N,N-dimethylbenzo[d]thiazole-6-carboxamide (669 mg, quant.) as a HCl salt which was used for next step without further purification. LCMS $[M+H]^+$= 321.1

Step H: 2-(((1R,2R,4R)-4-((5-chloropyrimidin-2-yl)amino)-2-hydroxycyclopentyl) amino)-N,N-dimethylbenzo[d]thiazole-6-carboxamide

To a solution of 2-(((1R,2R,4R)-4-amino-2-hydroxycyclopentyl)amino)-N,N-dimethylbenzo[d]thiazole-6-carboxamide (669 mg, 2.09 mmol) in DMSO (10 mL) was added K_2CO_3 (865 mg, 6.27 mmol) and 2,5-dichloropyrimidine (309 mg, 2.09 mmol). The mixture was heated to 80 °C and stirred overnight under nitrogen atmosphere. After cooling to room temperature, the mixture was diluted with water (30 mL), extracted with ethyl acetate (20 mLx2). The combined organic layers were washed with brine (20 mLx3), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with DCM/ MeOH = 50/1 to 20/1) to give 2-(((1R,2R,4R)-4-((5-chloropyrimidin-2-yl)amino)-2-hydroxycyclopentyl)amino)-N,N-dimethylbenzo[d]thiazole-6-carboxamide (600 mg, 66.4%) as a white solid. LCMS $[M+H]^+$=433.3

Step I: 2-(((1R,4R)-4-((5-chloropyrimidin-2-yl)amino)-2-oxocyclopentyl)amino)-N,N-dimethylbenzo[d]thiazole-6-carboxamide

To a solution of 2-(((1R,2R,4R)-4-((5-chloropyrimidin-2-yl)amino)-2-hydroxycyclopentyl)amino)-N,N-dimethylbenzo[d]thiazole-6-carboxamide (600 mg, 1.39 mmol) in DCM (40 mL) was added Dess-martin periodinane (1.18 g, 2.78 mmol) portion wise at 0 °C. After addition, the mixture was stirred at 0°C for 1h. After completion, the mixture was added 10% Na_2SO_3 solution, extracted with ethyl acetate (40 mLx2). The combined organic layers were washed with saturated sodium bicarbonate aqueous (20 mLx2) and brine (20 mLx2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with DCM/ MeOH = 50/1 to 20/1) to give 2-(((1R,4R)-4-((5-chloropyrimidin-2-yl)amino)-2-oxocyclopentyl)amino)-N,N-dimethylbenzo[d]thiazole-6-carboxamide (280 mg, 46.8%) as a yellow solid. LCMS $[M+H]^+$=431.0

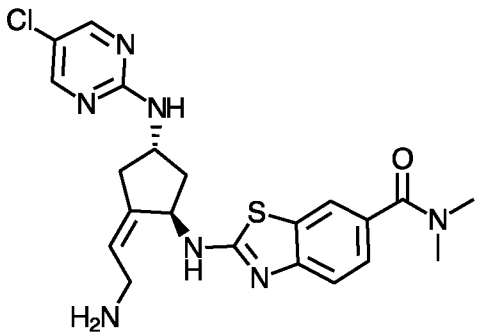
Step J: 2-(((1R,4S)-4-((5-chloropyrimidin-2-yl)amino)-2-(cyanomethylene)cyclopentyl) amino)-N,N-dimethylbenzo[d]thiazole-6-carboxamide

To a solution of diethyl (cyanomethyl)phosphonate (230.7 mg, 1.3 mmol) in THF (3.2 mL) was added NaH (52 mg, 1.3 mmol) at 0 °C. After addition, the mixture was stirred at 0°C for 30 mins. Then 2-(((1R,4R)-4-((5-chloropyrimidin-2-yl)amino)-2-oxocyclopentyl)amino)-N,N-dimethylbenzo[d]thiazole-6-carboxamide (280 mg, 0.65 mmol) in THF (3.2 mL) was added dropwise and the mixture was stirred at 0°C for 30 min. After completion, the mixture was diluted with water (10 mL), extracted with ethyl acetate (15 mLx2). The combined organic layers were

washed with brine (15 mLx2), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluted with DCM/ MeOH = 50/1 to 20/1) to give 2-(((1R,4S)-4-((5-chloropyrimidin-2-yl)amino)-2-(cyanomethylene)cyclopentyl)amino)-N,N-dimethylbenzo[d]thiazole-6-carboxamide (190 mg, yield: 64.5%) as a yellow solid. LCMS $[M+H]^+$=454.3 ^{1}HNMR (400 MHz, DMSO-d_6) δ: 9.05-9.00 (s, 1H), 8.39-8.29 (m, 2H), 7.88-7.81 (m, 2H), 7.51-7.43 (m, 1H), 7.34-7.31 (m, 1H), 5.76-5.68 (m, 1H), 5.29-5.09 (m, 1H), 4.41-4.34 (m, 1H), 3.18-3.09 (m, 1H), 2.96 (s, 6H), 2.75-2.58 (m, 2H), 2.33-1.71(m, 1H).

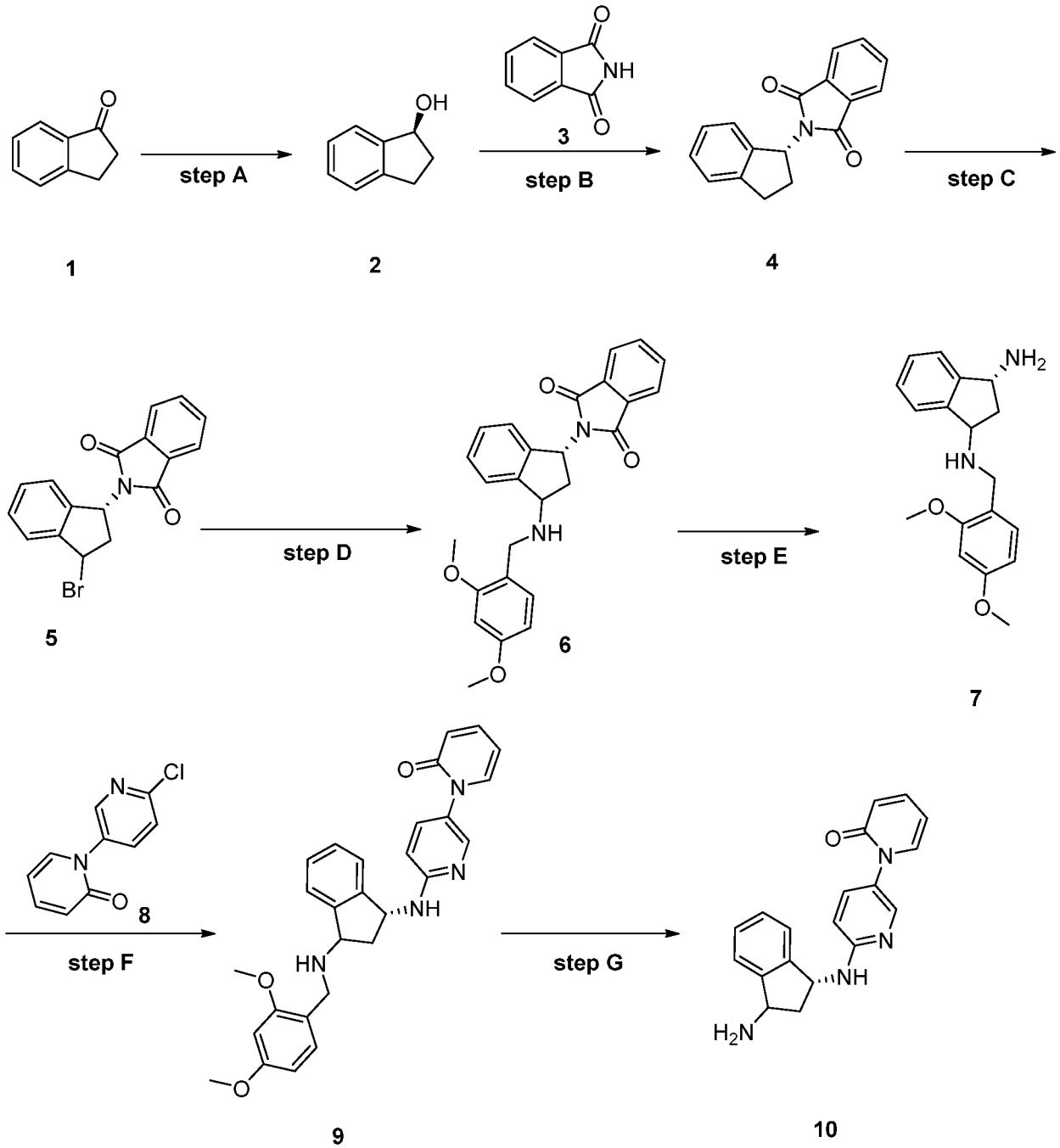
Example D

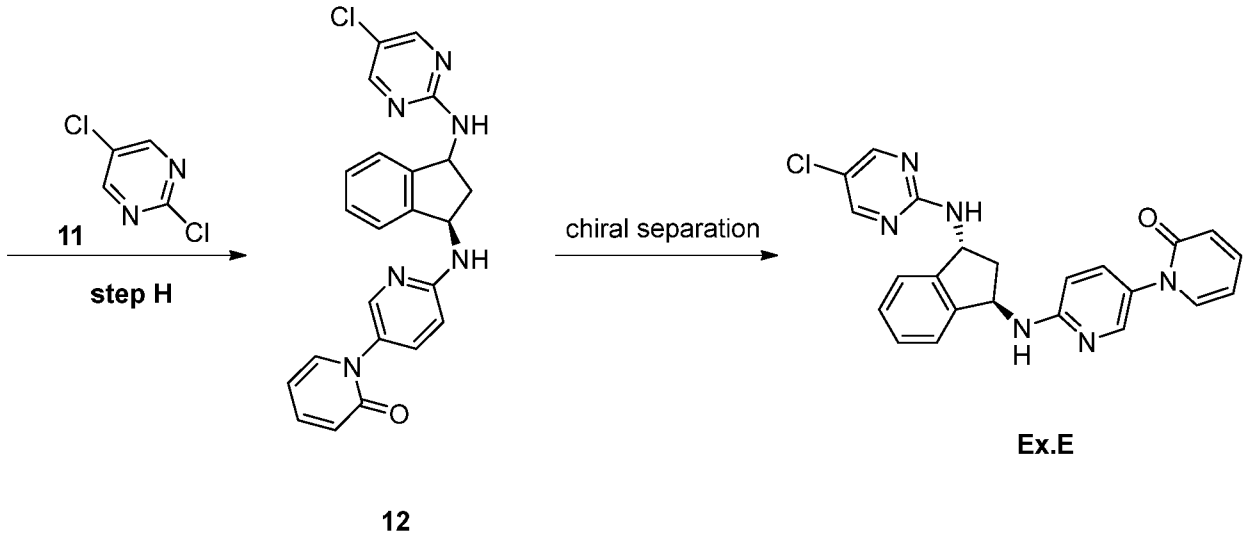
N,N-Dimethyl-2-[(1R,4S)-(Z)-2-(2-aminoethylidene)-4-(5-chloro-2-pyrimidinylamino) cyclopentylamino]-1,3-benzothiazole-6-carboxamide



Using 2-(((1R,4S)-4-((5-chloropyrimidin-2-yl)amino)-2-(cyanomethylene)cyclopentyl)amino) -N,N-dimethylbenzo[d]thiazole-6-carboxamide, the title compound can be prepared by using reductive conditions.

Example E


step A
step B
step C
step D
step E
step F
step G
1
2
3
4
5
6
7
8
9
10



Step A: (S)-2,3-dihydro-1H-inden-1-ol (2)

A solution of R-CBS (1.4 g, 5.15 mmol) and $(CH_3)_2S$-BH_3 (0.48 mL, 0.95 mmol) was stirred at room temperature for 10 minute under nitrogen atmosphere. Then DCM (33 mL) and $(CH_3)_2S$-BH_3 (28.4 mL, 56.82 mmol) were added to this solution at -5 °C. A solution of 2,3-dihydro-1H-inden-1-one (**1**) (5 g, 37.88 mmol) in DCM (30 mL) was added dropwise to the above solution while maintaining the reaction temperature under 0 °C. After addition, the reaction mixture was stirred at -5 °C for 2 hours. The mixture was quenched by CH_3OH (40 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with EtOAc/petroleum ether = 0%-10% to give (S)-2,3-dihydro-1H-inden-1-ol (**2**) (4.9 g, 96%) as a colorless oil. LCMS $[M+H-OH]^+$= 117.3. ^1H NMR (400 MHz, DMSO-d_6) δ 7.34-7.31 (m, 1H), 7.23-7.16 (m, 3H), 5.20 (br., s., 1H), 5.04 (t, J = 6.8 Hz, 1H), 2.94-2.87 (m, 1H), 2.74-2.66 (m, 1H), 2.36-2.28 (m, 1H), 1.81-1.72 (m, 1H).

Step B: (R)-2-(2,3-dihydro-1H-inden-1-yl)isoindoline-1,3-dione (4)

To a solution of (S)-2,3-dihydro-1H-inden-1-ol (**2**) (4.9 g, 36.57 mmol), isoindoline-1,3-dione (**3**) (6.99 g, 47.5 mmol) and PPh_3 (14.4 g, 54.8 mmol) in THF (102 mL) was added DIAD (11.1 g, 54.8 mmol) dropwise at 0 °C under nitrogen atmosphere. After addition, the reaction mixture was stirred at room temperature overnight. Then the reaction solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with ^{t}BuOMe/ petroleum ether = 0%-11% to give (R)-2-(2,3-dihydro-1H-inden-1-yl)isoindoline-1,3-dione (**4**) (3.3 g, 34%) as a yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 (s, 4H), 7.29 (d,

J = 7.6 Hz, 1H), 7.24-7.20 (m, 1H), 7.13-7.11 (m, 2H), 5.74 (t, J = 8.0 Hz, 1H), 3.18-3.14 (m, 1H), 2.96-2.92 (m, 1H), 2.47-2.40 (m, 2H).

Step C: 2-((1R)-3-bromo-2,3-dihydro-1H-inden-1-yl)isoindoline-1,3-dione (5)

To a solution of (R)-2-(2,3-dihydro-1H-inden-1-yl)isoindoline-1,3-dione (**4**) (3.3 g, 12.5 mmol) and NBS (2.45 g, 13.8 mmol) in CCl_4 (32 mL) was added AIBN (0.2 g, 1.25 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 80 °C for 2 hours. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with EtOAc/petroleum ether = 0%-9% to give 2-((1R)-3-bromo-2,3-dihydro-1H-inden-1-yl)isoindoline-1,3-dione (**5**) (3.2 g, 75%) as a yellow oil.

Step D: 2-((1R)-3-((2,4-dimethoxybenzyl)amino)-2,3-dihydro-1H-inden-1-yl)isoindoline-1,3-dione (6)

To a solution of 2-((1R)-3-bromo-2,3-dihydro-1H-inden-1-yl)isoindoline-1,3-dione (**5**) (3.2 g, 9.38 mmol) and $DMBNH_2$ (3.13 g, 18.77 mmol) in DCM (40 mL) was added Et_3N (0.69 mL, 9.38 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with DCM (20 mL) and washed with brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with 50% NH_3-CH_3OH/DCM = 0%-3% to give 2-((1R)-3-((2,4-dimethoxybenzyl)amino)-2,3-dihydro-1H-inden-1-yl)isoindoline-1,3-dione **(6)** (1.3 g, 32%) as a yellow solid. LCMS $[M+H]^+$= 429.5.

Step E: (3R)-N1-(2,4-dimethoxybenzyl)-2,3-dihydro-1H-indene-1,3-diamine (7)

To a solution of 2-((1R)-3-((2,4-dimethoxybenzyl)amino)-2,3-dihydro-1H-inden-1-yl)isoindoline-1,3-dione **(6)** (1.3 g, 3 mmol) in THF (20 mL) and CH_3OH (20 mL) was added N_2H_4-H_2O (1.82 mL, 30 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved with DCM (50 mL) and washed with water (30 mL), sat.$NaHCO_3$ aqueous (30 mL) and brine (30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatograph on silica gel, eluting with 50% NH_3-CH_3OH/DCM = 0%-6% to give (3R)-N^1-(2,4-dimethoxybenzyl)-2,3-dihydro-1H-indene-1,3-diamine **(7)** (700 mg, 78%) as yellow oil. LCMS $[M+H]^+$= 299.5.

Step F: 6'-(((1R)-3-((2,4-dimethoxybenzyl)amino)-2,3-dihydro-1H-inden-1-yl)amino)-2H-[1,3'-bipyridin]-2-one (9)

To a solution of (3R)-N^1-(2,4-dimethoxybenzyl)-2,3-dihydro-1H-indene-1,3-diamine **(7)** (400 mg, 1.34 mmol), 6'-chloro-2H-[1,3'-bipyridin]-2-one (**8**) (277 mg, 1.34 mmol) and t-BuONa (258 mg, 2.68 mmol) in DMA (5 mL) was added ^{t}BuxPhosPdG3 (119 mg, 0.134 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 100 °C overnight. After cooling to room temperature, the mixture was diluted with water (30 mL) and extracted with EtOAc (20 mL x3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with CH_3OH/DCM = 0%-7% to give 6'-(((1R)-3-((2,4-dimethoxybenzyl)amino)-2,3-dihydro-1H-inden-1-yl)amino)-2H-[1,3'-bipyridin]-2-one **(9)** (440 mg, 70%) as a brown solid.LCMS $[M+H]^+$= 469.6. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 2.8 Hz, 1H), 7.65-7.63 (m, 1H), 7.51-7.43 (m, 3H), 7.34-7.22 (m, 5H), 6.65 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.52-6.46 (m, 2H), 6.31-6.28 (m, 1H), 5.45-5.39 (m, 1H), 4.16 (t, J = 7.6 Hz, 1H), 3.78 (s, 3H), 3.76-3.72 (m, 5H), 2.89-2.82 (m, 1H), 1.70-1.62 (m, 1H).

Step G: 6'-(((1R)-3-amino-2,3-dihydro-1H-inden-1-yl)amino)-2H-[1,3'-bipyridin]-2-one (10)

A solution of 6'-(((1R)-3-((2,4-dimethoxybenzyl)amino)-2,3-dihydro-1H-inden-1-yl)amino)-2H-[1,3'-bipyridin]-2-one **(9)** (440 mg, 0.94 mmol) in CF_3COOH (6 mL) was stirred at 80 °C for 48 hours. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was diluted with water (10 mL) and extracted with DCM (10 mL x2). The aqueous layer was adjusted to PH=8 with sat. $NaHCO_3$ solution and extracted with DCM (10 mL x5). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude product (290 mg) was used for next step without further purification. LCMS $[M+H]^+$= 319.5.

Step H: 6'-(((1R)-3-((5-chloropyrimidin-2-yl)amino)-2,3-dihydro-1H-inden-1-yl)amino)-2H-[1,3'-bipyridin]-2-one (12)

To a solution of 6'-(((1R)-3-amino-2,3-dihydro-1H-inden-1-yl)amino)-2H-[1,3'-bipyridin]-2-one **(10)** (crude, 290 mg, 0.91 mmol) and 2,5-dichloropyrimidine **(11)** (150 mg, 1 mmol) in DMSO (5 mL) was added K_2CO_3 (377 mg, 2.73 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at 80 °C for 3 hours. After cooling to room

temperature, the mixture was diluted with water (40 mL) and extracted with EtOAc (20 mL x3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with CH_3OH/DCM = 0%-3% to give 6'-(((1R)-3-((5-chloropyrimidin-2-yl)amino)-2,3-dihydro-1H-inden-1-yl)amino)-2H-[1,3'-bipyridin]-2-one **(12)** (120 mg, 31%) as a yellow solid. LCMS $[M+H]^+$= 431.5. Example E can be separated from its isomers by chromatography.

Example 2: Biological Activity of Exemplary PCSK9 inhibitors

Human recombinant PCSK9 was expressed as follows:

Protein sequence:

QEDEDGDYEELVLALRSEEDGLAEAPEHGTTATFHRCAKDPWRLPGTYVVVLK
EETHLSQSERTARRLQAQAARRGYLTKILHVFHGLLPGFLVKMSGDLLELALKLPHVDY
IEEDSSVFAQSIPWNLERITPPRYRADEYQPPDGGSLVEVYLLDTSIQSDHREIEGRVMVT
DFENVPEEDGTRFHRQASKCDSHGTHLAGVVSGRDAGVAKGASMRSLRVLNCQGKGT
VSGTLIGLEFIRKSQLVQPVGPLVVLLPLAGGYSRVLNAACQRLARAGVVLVTAAGNFR
DDACLYSPASAPEVITVGATNAQDQPVTLGTLGTNFGRCVDLFAPGEDIIGASSDCSTCF
VSQSGTSQAAAHVAGIAAMMLSAEPELTLAELRQRLIHFSAKDVINEAWFPEDQRVLTP
NLVAALPPSTHGAGWQLFCRTVWSAHSGPTRMATAVARCAPDEELLSCSSFSRSGKRR
GERMEAQGGKLVCRAHNAFGGEGVYAIARCCLLPQANCSVHTAPPAEASMGTRVHCH
QQGHVLTGCSSHWEVEDLGTHKPPVLRPRGQPNQCVGHREASIHASCCHAPGLECKVK
EHGIPAPQEQVTVACEEGWTLTGCSALPGTSHVLGAYAVDNTCVVRSRDVSTTGSTSEG
AVTAVAICCRSRHLAQASQELQSGSGGLNDIFEAQKIEWHENLYFQGHHHHHH

The following assay method was used to identify and evaluate PCKS9 inhibitors that are effective in inhibiting PCSK9 function.

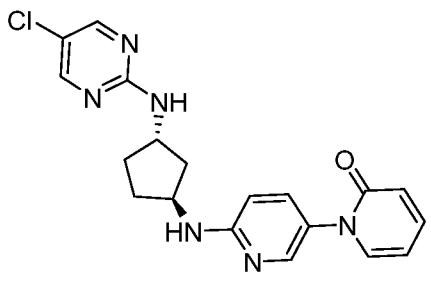
Example: PCSK9 SPR Assay

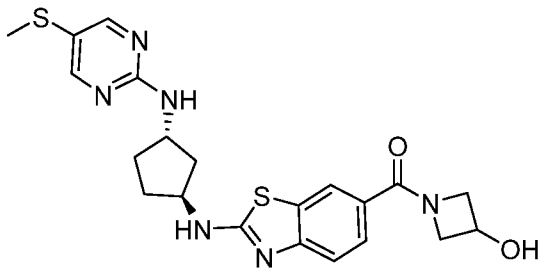
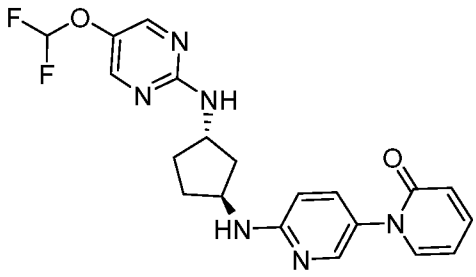
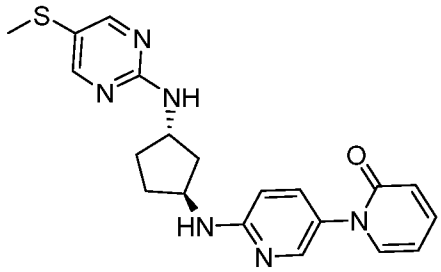
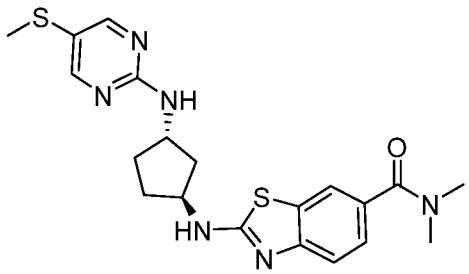
Surface plasmon resonance data was collected on a Biacore™ T200 or 3000 system (GE Healthcare) at 25°C. Streptavidin was immobilized on a CM5 (GE Healthcare) or CMD500d sensor chip (XanTec Bioanalytics) using standard amine-coupling chemistry at 25°C with HBS-N (10 mM HEPES, 0.15 M NaCl, pH 7.4) as the running buffer. Briefly, the carboxymethyl dextran surface was activated with a 12 min injection of a 1:1 ratio of 0.4 M 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC)/0.1 M *N*-hydroxy succinimide (NHS)

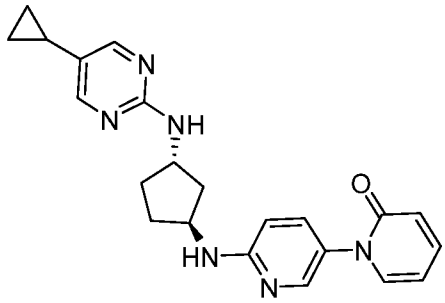
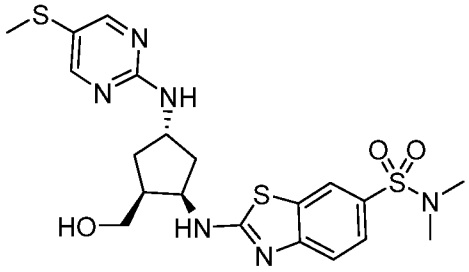
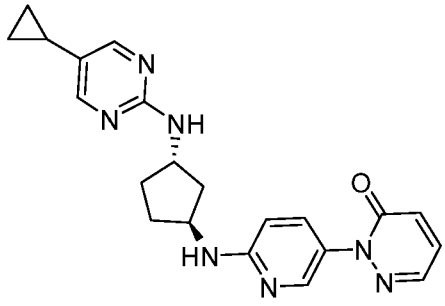
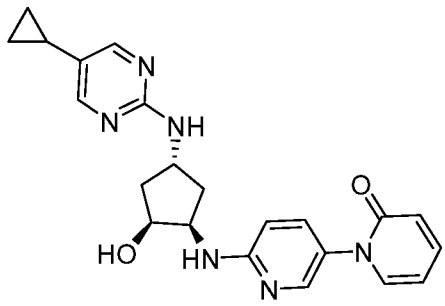
at a flow rate of 10 µL/min. For capture of streptavidin, protein was diluted to 0.2 mg/mL in 10 mM sodium acetate (pH 4.5) and captured by injecting 100 µL onto the activated chip surface. Residual activated groups were blocked with a 7 min injection of 1 M ethanolamine (pH 8.5). Avi-tagged PCSK9 protein was captured on the streptavidin surface by injection of 150 µL of protein diluted to 16 µg/mL in HBS-N, 0.05% tween-20, 0.1 mM $CaCl_2$. Typical surface densities obtained were 8000-10000 RU. SPR binding data were obtained using an appropriate dilution series of each compound at a flow rate of 30 µL/ min, with a capture time of 100 s and dissociation times of 300 s. Running buffer for compound binding studies was HBS-N, 0.05% tween-20, 0.1 mM $CaCl_2$, 4% DMSO. Data were corrected for DMSO excluded volume effects. All data were double-referenced for blank injections and reference surface using standard processing procedures and data processing and kinetic fitting were performed using Scrubber software, version 2.0c (BioLogic Software). Data were fitted using a simple 1:1 binding model to determine k_a, k_d and K_D values.

The ability of PCSK9 inhibitors the disclosure pharmaceutically acceptable salts thereof to bind and inhibit PCSK9 was established with the representative PCSK9 inhibitors of the disclosure listed in the table below:

PCSK9 Affinity (nM)	Category
K_D = 2,000 - 20,000 nM	+
K_D = 200 – 2,000 nM	++
K_D < 200 nM	+++

Example #	Structure	K_d
493		+++

Example #	Structure	K_d
335		+++
458B		+++
458		+++
310		+++

Example #	Structure	K_d
474		+++
309		++
468		+++
506		+++

INCORPORATION BY REFERENCE

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to

be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

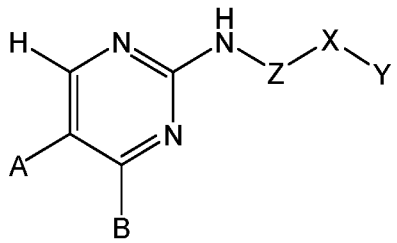
EQUIVALENTS

While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

CLAIMS

We claim:

1. A compound with a structure represented by formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

A is selected from H, halo, hydroxy, alkyl, alkylthio, alkenyl, alkoxy, acyloxy, cyano, cycloalkyl, -C(O)OR^6, and -C(O)NR^{6}R^7;

B is selected from H, alkyl, and halo; or A and B are taken together with the carbon atoms to which they are attached to form a 5- or 6-membered heteroaryl;

X is NR^5 or O;

Z is cycloalkyl, cycloalkenyl, aryl, heteroaryl, or heterocyclyl;

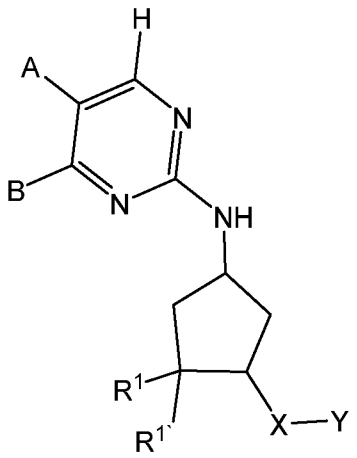
each R^6 and R^7 is independently H or alkyl;

Y is selected from aryl, heteroaryl and heterocyclyl; and

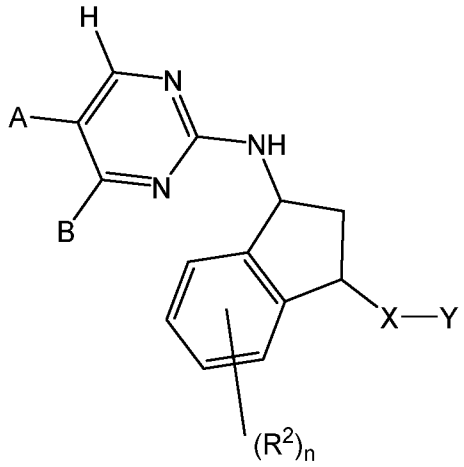
n is 0 or 1.

2. The compound of claim 1, wherein Z is cycloalkyl.

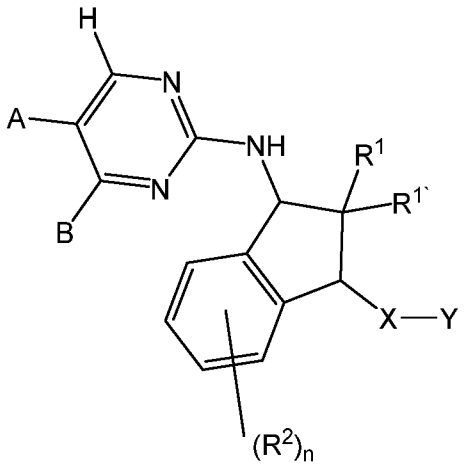
3. The compound of claim 1 or 2, wherein the structure of the compound is represented by formula (Ia), (Ib), (Ic), or a pharmaceutically acceptable salt thereof:



(Ia)



(Ib)



(Ic)

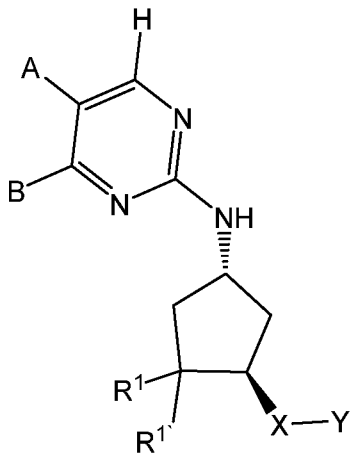
wherein

R^1 and $R^{1`}$ are each independently selected from alkyl, halo, hydroxyl, carboxyl, acyl, ester, thioester, alkoxy, phosphoryl, amino, amide, cyano, nitro, azido, alkylthio, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, heteroaralkyl, sulfonamide, aryl, heteroaryl, heterocyclyl, and aralkyl; or R^1 and $R^{1`}$ combine to form an alkylalkene, cycloalkyl, cycloalkene or heterocyclyl;

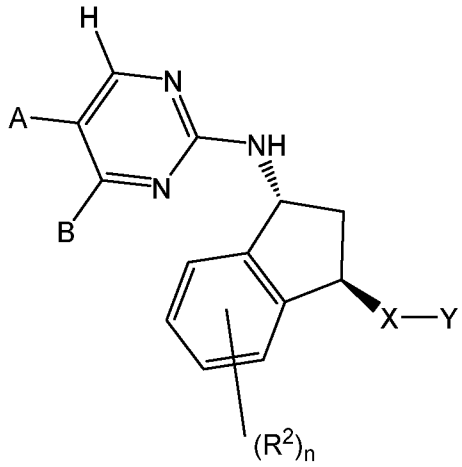
each R^2 is independently selected from alkyl, halo, hydroxyl, carboxyl, acyl, ester, thioester, alkoxy, phosphoryl, amino, amide, cyano, nitro, azido, alkylthio, alkenyl, alkynyl, cycloalkyl, heterocyclylalkyl, heteroaralkyl, sulfonamide, aryl, heteroaryl, heterocyclyl, and aralkyl; and

n is 1, 2, 3, or 4.

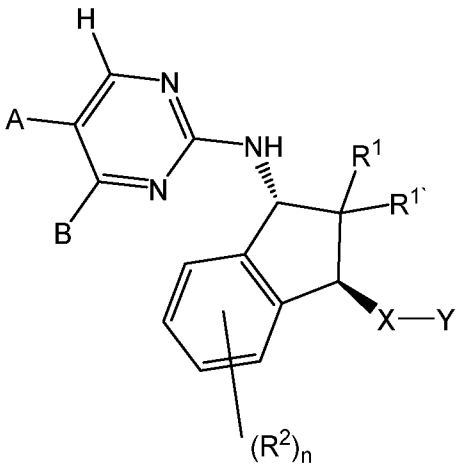
4. The compound of claim 3, wherein the structure of the compound is represented by formula (IIa), (IIb), (IIc), or a pharmaceutically acceptable salt thereof:



(IIa)

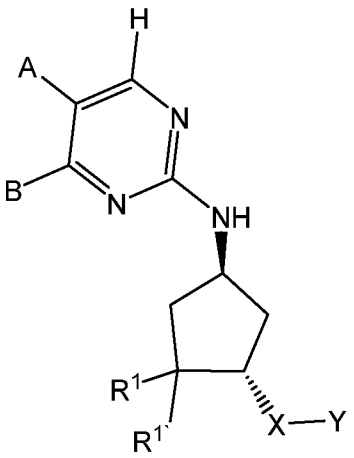


(IIb)

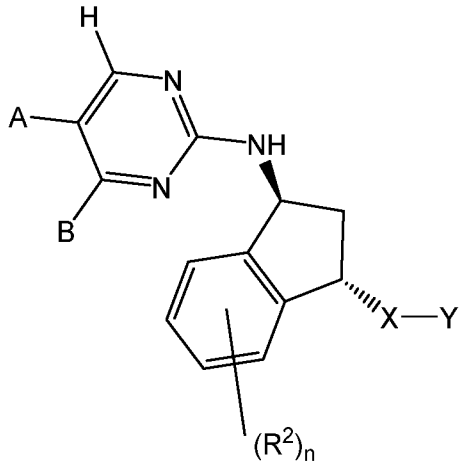


(IIc).

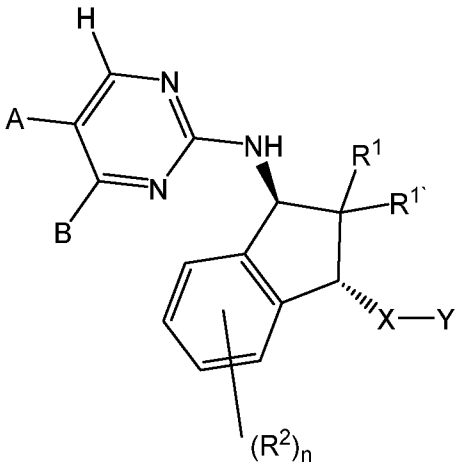
5. The compound of claim 3, wherein the structure of the compound is represented by formula (IIIa), (IIIb), (IIIc), or a pharmaceutically acceptable salt thereof:



(IIIa)



(IIIb)



(IIIc).

6. The compound of any one of claims 1-5, wherein A is selected from H, hydroxy, alkylthio, alkyl, alkoxy, acyloxy, cyano, cycloalkyl, -C(O)OR^6, and -C(O)NR^{6}R^7.

7. The compound of claim 6, wherein A is H.

8. The compound of claim 6, wherein A is alkyl.

9. The compound of claim 6, wherein A is alkylthio.

10. The compound of claim 6, wherein A is alkoxy.

11. The compound of claim 6, wherein A is cycloalkyl.

12. The compound of claim 6, wherein A is selected from $-SCH_3$, $-SCHF_2$, and $-OCHF_2$.

13. The compound of claim 6, wherein A is halo (e.g., chloro).

14. The compound of claim 6, wherein A and B are taken together with the carbon atoms to which they are attached to form a pyrrolyl or thienyl ring, which is unsubstituted or substituted with one or more alkyl.

15. The compound of any one of claims 1-14, wherein B is H.

16. The compound of any one of claims 1-15, wherein X is NR^5.

17. The compound of any one of claims 1-16, wherein Y is heteroaryl or heterocyclyl.

18. The compound of any one of claims 1-17, wherein Y is monocyclic heteroaryl.

19. The compound of claim 18, wherein Y is selected from pyridyl, pyridonyl, pyridinyl, pyrazinyl, pyrimidinyl, and thiazolyl.

20. The compound of claim 18, wherein Y is selected from triazenyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, and triazolyl.

21. The compound of any one of claims 18-20, wherein the monocyclic heteroaryl is unsubstituted or substituted with one or more substituents selected from alkyl, alkylthio, alkoxy, alkoxycarbonyl, amido, carboxy, cyano, halo, aryl, heteroaryl, heterocyclyl, nitro, sulfonamido, and alkylthio.

22. The compound of claim 21, wherein the monocyclic heteroaryl is substituted with a 6-membered aryl, heteroaryl or heterocyclyl selected from phenyl, pyridinyl, 2-hydroxypyridinyl, piperidinonyl, 2-hydroxy-1-methylpyridinyl, triazolyl, imidazolidinonyl, pyrimidonyl, 2-hydroxyisoquinolinyl, 3-hydroxypyridazinyl, pyrrolidinonyl, pyrazolyl, and morpholinonyl.

23. The compound of claim 21, wherein the monocyclic heteroaryl is substituted with an heteroaryl or heterocyclyl that is substituted with one or more substituents selected from halo, CN, alkyl, alkoxy, hydroxy, carboxy, -CO_2alkyl, and tetrazolyl.

24. The compound of any one of claims 21-23, wherein the substituent is disposed on the para position of Y relative to X.

25. The compound of any one of claims 1-17, wherein Y is bicyclic heteroaryl.

26. The compound of claim 25, wherein Y is selected from benzothiazolyl, benzoxazolyl, benzimidazolyl, triazolopyridinyl, thiazolopyrindinyl, quinolinyl, and quinoxalinyl.

27. The compound of claim 25 or 26, wherein the bicyclic heteroaryl is unsubstituted, or substituted with one or more substituents selected from alkyl, haloalkyl, hydroxyalkyl, alkylthio, alkoxy, alkoxycarbonyl, amido, carboxy, cyano, halo, heteroaryl, nitro, and sulfonamido.

28. The compound of claim 25 or 26, wherein the bicyclic heteroaryl is unsubstituted, or substituted with one or more substituents selected from alkylthio, alkoxycarbonyl, amido, carboxy, halo, and heteroaryl.

29. The compound of any one of claims 1-28, wherein Y is substituted with an amido substituent of the formula $–C(O)NR^8R^9$ or $–NR^9C(O)R^{10}$, wherein
R^8 and R^9 are each independently selected from H, alkyl, heterocyclyl and heteroaryl; or
R^8 and R^9, taken together with the nitrogen atom to which they are attached, form a
4-, 5-, 6-, or 7-membered heterocyclic or heteroaryl ring; and
R^{10} is alkyl.

30. The compound of any one of claims 1-28, wherein Y is substituted with a sulfonamido substituent of the formula $–S(O)_2NR^8R^9$ or $–NR^9S(O)_2R^{10}$; wherein
R^8 and R^9 are each independently selected from H, alkyl, and heteroaryl; or
R^8 and R^9, taken together with the nitrogen atom to which they are attached, form a
4-, 5-, 6-, or 7-membered heterocyclic ring; and

R^{10} is alkyl.

31. The compound of claim 29 or 30, wherein R^8 and R^9 are each independently selected from H, methyl, ethyl, triazolyl, and pyrazolyl.

32. The compound of any one of claims 29-31, wherein one or both of R^8 and R^9 are alkyl, and each alkyl is independently unsubstituted, or substituted with one or more substituents selected from methyl, methoxy, carboxy, cyano, hydroxy, dimethylamino, ethoxycarbonyl, phenyl, methoxyphenyl, oxadiazolyl, tetrazolyl, 2-methyl-tetrazolyl, triazolyl, 1-methyltriazolyl, 4-methyltriazolyl, and 2,4-dihydro-3H-1,2,4-triazol-3-onyl.

33. The compound of claim 29 or 30, wherein R^8 and R^9, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring selected from aziradine, isothiazolidine-1,1-dioxide, azetindine, thiazol-4(5Hn)-one, morpholine, piperidine, piperazine, pyrrolidine, thiomorpholine-1,1-dioxide, 2-oxa-6-azaspiro[3.3]heptane.

34. The compound of claim 29 or 30, wherein R^8 and R^9, taken together with the nitrogen atom to which they are attached, form a heterocyclic ring selected from 2,8-diazaspiro[5,5]undecene, tetrahydroimidazo[1,2-a]pyrazine, octahydropyrazino[2,1-c][1,4]oxazine, tetrahydropyrido[3,4-d]pyrimidine, 2-oxa-8-azaspiro[4.5]decane, tetrahydropyrrolo[3,4-c]pyrazole, thiomorpholine, 2-oxa-7-azaspiro[3.5]nonane, 2,8-diazaspiro[4.5]decan-3-one, tetrahydro-1,7-naphthyridine, 1-oxa-4,9-diazaspiro[5.5]undecan-3-one, tetrahydropyrrolo[3,4-d]imidazole, pyrimidine, 8-oxa-2-azaspiro[4.5]decane, hexahydro-3H-oxazolo[3,4-a]pyrazin-3-one, 1-oxa-7-azaspiro[3.5]nonane, octahydrocyclopenta[c]pyrrole, tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine, 2,7-diazaspiro[4.4]nonane, 2,6-diazaspiro[3.4]octane, 7-oxa-2-azaspiro[3.5]nonane, 1-oxa-8λ^2-azaspiro[4.5]decane, 2-oxa-6-azaspiro[3.3]heptane, tetrahydrofuran, oxadiazole, triazole, pyridinone, tetrahydro-[1,2,4]triazolo[4,3-a]pyrazin-3(2H)-one, piperidinone, 3,6-diazabicyclo[3.1.1]heptane, 5-oxa-2,7-diazaspiro[3.5]nonane, pyrazole, and pyridazin-3(2H)-one.

35. The compound of claim 33 or 34, wherein the heterocyclic ring is unsubstituted, or substituted with one or more substituents selected from alkyl, alkoxycarbonyl, halo, hydroxy, cyano, carboxy, and heterocyclyl.

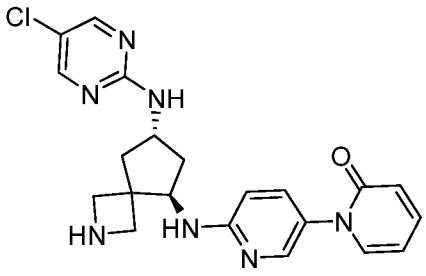
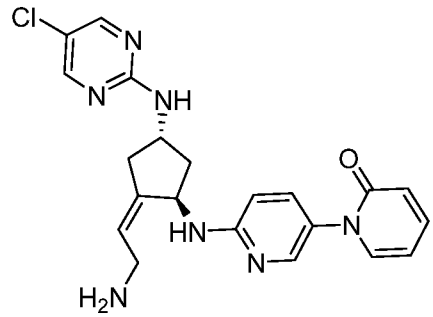
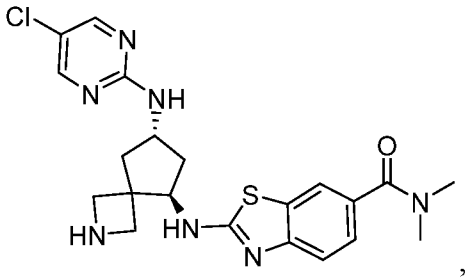
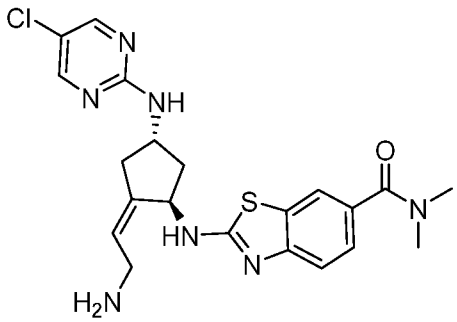
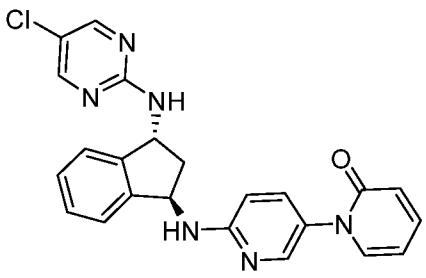
36. The compound of claim 33 or 34, wherein the heterocyclic ring is unsubstituted, or substituted with one or more substituents selected from methyl, ethoxycarbonyl, halo, hydroxy, cyano, carboxy, and oxetanyl.

37. The compound of any one of claims 2-36, wherein R^1 and $R^{1'}$ combine to form a heterocyclyl (e.g., azetidinyl).

38. The compound of any one of claims 2-36, wherein R^1 and $R^{1'}$ combine to form an alkylalkene (e.g., aminoallyl).

39. The compound of any one of claims 2-38, wherein n is 0.

40. The method of claim 1, wherein the compound is selected from


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, and

; or a pharmaceutically acceptable salt thereof.

41. A pharmaceutical composition comprising a compound of any one of claims 1-40 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

42. A method of treating cardiovascular disease or disorder in a subject, comprising administering a compound according to any one of claims 1-40 or a pharmaceutically acceptable salt thereof to the subject.

43. The method of claim 42, wherein the cardiovascular disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, dyslipidemia, dyslipoproteinemia, atherosclerosis, hepatic steatosis, metabolic syndrome and coronary artery disease.

44. The method of claim 42 or 43, wherein the cardiovascular disease or disorder is familial hypercholesterolemia.

45. The method of claim 42 or 43, wherein the cardiovascular disease or disorder is autosomal dominant hypercholesterolemia.

46. The method of any one of claims 42-45, wherein the level of circulating serum cholesterol is decreased in the subject.

47. The method of any one of claims 42-46, wherein the level of circulating serum LDL-cholesterol is decreased in the subject.

48. The method of any one of claims 42-47, wherein the level of circulating serum VLDL-cholesterol is decreased in the subject.

49. The method of any one of claims 42-48, wherein the level of circulating serum triglycerides is decreased in the subject.

50. The method of any one of claims 42-49, wherein the level of circulating serum lipoprotein A is decreased in the subject.

51. The method of any one of claims 42-50, wherein the subject has atherosclerosis.

52. The method of any one of claims 42-51, wherein atherosclerotic plaque formation is decreased in the subject.

53. The method of any one of claims 42-52, wherein the subject has a gain-of-function mutation in *PCSK9* gene.

54. The method of any one of claims 42-53, further comprising conjointly administering one or more additional therapeutic agents.

55. The method of claim 54, wherein the method comprises administering one additional therapeutic agent.

56. The method of claim 54, wherein the method comprises administering two additional therapeutic agents.

57. The method of claim 54, wherein the method comprises administering three additional therapeutic agents.

58. The method of any one of claims 54-57, wherein the additional therapeutic agent is selected from a HMG-CoA reductase inhibitor, a HMG-CoA synthase inhibitor, a HMG-CoA reductase gene expression inhibitor, a HMG-CoA synthase gene expression inhibitor, an MTP/Apo B secretion inhibitor, a CETP inhibitor, a bile acid absorption inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a squalene synthetase inhibitor, a squalene epoxidase inhibitor, a squalene cyclase inhibitor, a combined squalene epoxidase/squalene cyclase inhibitor, a fibrate, a niacin, a combination of niacin and lovastatin, an ion-exchange resin, an antioxidant, an ACAT inhibitor, a bile acid sequestrant, a PCSK9 translation inhibitor, an ATP citrate lyase inhibitor, an apoC3 inhibitor, an ANGPTL3 inhibitor, an omega-3 fatty acid, an Lp(a) inhibitor, an apoB inhibitor, an apoA1 inhibitor, a low-density lipoprotein receptor inhibitor, a low-density lipoprotein inhibitor, a diacylglycerol acyltransferase inhibitor, a lysosomal acid lipase inhibitor, and a lecithin cholesterol acyl transferase inhibitor.

59. The method of any one of claims 54-58, wherein the additional therapeutic agent is an ATP citrate lyase inhibitor.

60. The method of any one of claims 54-58, wherein the additional therapeutic agent is an apoC3 inhibitor.

61. The method of any one of claims 54-58, wherein the additional therapeutic agent is an ANGPTL3 inhibitor.

62. The method of any one of claims 54-58, wherein the additional therapeutic agent is an omega-3 fatty acid.

63. The method of any one of claims 54-58, wherein the additional therapeutic agent is an Lp(a) inhibitors.

64. The method of any one of claims 54-58, wherein the additional therapeutic agent is an apoB inhibitor.

65. The method of any one of claims 54-58, wherein the additional therapeutic agent is an apoA1 inhibitor.

66. The method of any one of claims 54-58, wherein the additional therapeutic agent is a low-density lipoprotein receptor inhibitor.

67. The method of any one of claims 54-58, wherein the additional therapeutic agent is a low-density lipoprotein inhibitor.

68. The method of any one of claims 54-58, wherein the additional therapeutic agent is a diacylglycerol acyltransferase inhibitor.

69. The method of any one of claims 54-58, wherein the additional therapeutic agent is a lysosomal acid lipase inhibitor.

70. The method of any one of claims 54-58, wherein the additional therapeutic agent is a lecithin cholesterol acyl transferase inhibitor.

71. The method of any one of claims 54-70, wherein the additional therapeutic agent is selected from volanesorsen, evinacumab, IONIS-ANGPTL3-LRX, icosapent ethyl, icosapentaenoic acid, eicosapentaenoic acid ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid ethyl ester, docosahexaenoic acid, docosahexaenoic acid ester, docosahexaenoic acid methyl ester, docosahexaenoic acid ethyl ester, bempedoic acid, ezetimibe,

IONIS-APO(a) RX, mipomersen, CSL-112, lomitapide, AAV8.TBG.hLDLR (RGX-501), alipogene tiparvovec, pradigastat, sebelipase, ACP-501/MEDI6012, OM3FA-EE, OM3FA-CA, OM3FA-IPE, alirocumab, evolocumab, bococizumab, RG7652, LY3015014, mAb316P, berberine, quercetin, ezetimbe, policosanol, BMS-962476, atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

72. The method of claim 71, wherein the additional therapeutic agent is volanesorsen.

73. The method of claim 71, wherein the additional therapeutic agent is evinacumab.

74. The method of claim 71, wherein the additional therapeutic agent is IONIS-ANGPTL3-LRX.

75. The method of claim 71, wherein the additional therapeutic agent is icosapent ethyl.

76. The method of claim 71, wherein the additional therapeutic agent is eicosapentaenoic acid ethyl ester.

77. The method of claim 71, wherein the additional therapeutic agent is docosahexaenoic acid ethyl ester.

78. The method of claim 71, wherein the additional therapeutic agent is bempedoic acid.

79. The method of claim 71, wherein the additional therapeutic agent is ezetimibe.

80. The method of claim 71, wherein the additional therapeutic agent is IONIS-APO(a) RX.

81. The method of claim 71, wherein the additional therapeutic agent is mipomersen.

82. The method of claim 71, wherein the additional therapeutic agent is CSL-112.

83. The method of claim 71, wherein the additional therapeutic agent is lomitapide.

84. The method of claim 71, wherein the additional therapeutic agent is AAV8.TBG.hLDLR (RGX-501).

85. The method of claim 71, wherein the additional therapeutic agent is alipogene tiparvovec.

86. The method of claim 71, wherein the additional therapeutic agent is pradigastat.

87. The method of claim 71, wherein the additional therapeutic agent is sebelipase.

88. The method of claim 71, wherein the additional therapeutic agent is ACP-501/MEDI6012.

89. The method of claim 71, wherein the additional therapeutic agent is OM3FA-EE.

90. The method of claim 71, wherein the additional therapeutic agent is OM3FA-CA.

91. The method of claim 71, wherein the additional therapeutic agent is OM3FA-IPE.

92. The method of any one of claims 42-91, wherein the disease or disorder is associated with PCSK9.

93. The method of any one of claims 42-92, wherein PCSK9 is over expressed in the subject.

94. The method of any one of claims 42-93, wherein the subject is male.

95. The method of any one of claims 42-94, wherein the subject is overweight or obese.

96. The method of any one of claims 42-95, wherein the subject is African American.

97. The method of any one of claims 42-95, wherein the subject is Caucasian.

98. The method of any one of claims 42-95, wherein the subject is Hispanic.

99. The method of any one of claims 42-98, wherein the PCSK9 inhibitor and the one or more additional therapeutic agents are administered simultaneously.

100. The method of claim 100, wherein the one or more additional therapeutic agents are administered within about 5 minutes to within about 168 hours prior to or after administration of the PCSK9 inhibitor.

101. A method of treating sepsis or septic shock in a subject, comprising administering a compound according to any one of claims 1-40 to the subject.

102. The method of claim 101, further comprising conjointly administering one or more additional therapeutic agents.

103. The method of claim 102, wherein the method comprises administering one additional therapeutic agent.

104. The method of claim 102, wherein the method comprises administering two additional therapeutic agents.

105. The method of claim 102, wherein the method comprises administering three additional therapeutic agents.

106. The method of any one of claims 102-105, wherein the additional therapeutic agent is selected from kanamycin, amikacin, tobramycin, dibekacin, gentamicin, sisomicin, netilmicin, streptomycin, neomycins B, C, and E, imipenum, meropenum, ertapenem, doripenum, panipenum, biapenem, razupenum, tebipenum, lenapenum, tomopenum, thienpenum, ciprofloxacin, garenoxacin, gatifloxacin, gemifloxaicin, levofloxacin, cinoxacin, nalidixic acid, moxifloxacin, oxolinic acid, piromidic acid, pipemidic acid, rosoxacin, enoxacin, fleroxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pefloxacin, rufloxacin, balofloxacin, grepafloxacin, levofloxacin, pazufloxacin, sparfloxacin, temafloxacin, tosufloxacin, clinafloxacin, sitafloxacin, trovafloxacin, prulifloxacin, delafloxacin, JNJ-Q2, nemonoxacin, zabofloxacin, doxycycline, tetracycline, chlortetracycline, oxytetracycline, demeclocycline,

lymecycline, meclocycline, methacycline, minocycline, rolitetracycline, tigecycline, ampicillin, amoxicillin, augmentin, piperacillin, tazobactam, chloramphenicol, and ticarcillin; or a combination thereof.

107. The method of any one of claims 102-106, wherein the PCSK9 inhibitor and the one or more additional therapeutic agents are administered simultaneously.

108. The method of any one of claims 102-106, wherein the one or more additional therapeutic agents are administered within about 5 minutes to within about 168 hours prior to or after administration of the PCSK9 inhibitor.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2023/069263

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed.

   b. ☒ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      ☒ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/069263

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D417/14 A61P9/00 A61K31/506
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2020/150473 A2 (DOGMA THERAPEUTICS INC [US]) 23 July 2020 (2020-07-23) page 263 - page 272; claim 52; examples 170-173, 250, 308-368, 371-403, 459A	1-108
X	WO 2020/193474 A1 (BAYER AG [DE]) 1 October 2020 (2020-10-01) page 27 - page 31; examples I-203, I-373, 3-28, 3-29	1-18
X	WO 2013/012827 A1 (BRISTOL MYERS SQUIBB CO [US]; EWING WILLIAM R [US] ET AL.) 24 January 2013 (2013-01-24) example 196	1-18
X	WO 2019/143675 A1 (VERTEX PHARMA [US]) 25 July 2019 (2019-07-25) examples 6, 233, 485	1-18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2023	26/09/2023

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Fazzi, Raffaella

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2023/069263

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