



HU000029402T2

(19) **HU**(11) Lajstromszám: **E 029 402**(13) **T2****MAGYARORSZÁG**
Szellemi Tulajdon Nemzeti Hivatala**EURÓPAI SZABADALOM**
SZÖVEGÉNEK FORDÍTÁSA(21) Magyar ügyszám: **E 13 712102**
(22) A bejelentés napja: **2013. 03. 14.**(51) Int. Cl.: **C07D 487/04** (2006.01)
A61K 3150/25 (2006.01)
A61P 3/06 (2006.01)(96) Az európai bejelentés bejelentési száma:
EP 20130712102(86) A nemzetközi (PCT) bejelentési szám:
PCT/US 13/031242(97) Az európai bejelentés közzétételi adatai:
EP 2825541 A1 **2013. 09. 19.**

(87) A nemzetközi közzétételi szám:

(97) Az európai szabadalom megadásának meghirdetési adatai:
EP 2825541 B1 **2016. 06. 22.****WO 13138565**(30) Elsőbbségi adatok:
201261612051 P **2012. 03. 16.** **US**(73) Jogosult(ak):
Vitae Pharmaceuticals, Inc., Fort Washington,
PA 19034 (US)(72) Feltaláló(k):
DONG, Chengguo, Staten Island, NY 10305 (US)
FAN, Yi, Doylestown, PA 18901 (US)
Leftheris, Katerina, San Diego California 92121 (US)
LOTESTA, Stephen, Burlington, NJ 08016 (US)
SINGH, Suresh, B., Kendall Park, NJ 08824 (US)
TICE, Colin, Ambler, PA 19002 (US)
ZHAO, Wei, North Potomac Maryland 20878 (US)
ZHENG, Yajun, Hockessin, DE 19707 (US)
ZHUANG, Linghang, Chalfont, PA 18914 (US)(74) Képvisező:
Advopatent Szabadalmi és Védjegy Iroda,
Budapest

(54)

Máj X receptor modulátorok

Az európai szabadalom ellen, megadásának az Európai Szabadalmi Közlönyben való meghirdetésétől számított kilenc hónapon belül, felszólalást lehet benyújtani az Európai Szabadalmi Hivatalnál. (Európai Szabadalmi Egyezmény 99. cikk(1))

A fordítást a szabadalmas az 1995. évi XXXIII. törvény 84/H. §-a szerint nyújtotta be. A fordítás tartalmi helyességét a Szellemi Tulajdon Nemzeti Hivatala nem vizsgálta.



(11) **EP 2 825 541 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention
of the grant of the patent:
22.06.2016 Bulletin 2016/25

(51) Int Cl.:
C07D 487/04 ^(2006.01) **A61K 31/5025** ^(2006.01)
A61P 3/06 ^(2006.01)

(21) Application number: **13712102.6**

(86) International application number:
PCT/US2013/031242

(22) Date of filing: **14.03.2013**

(87) International publication number:
WO 2013/138565 (19.09.2013 Gazette 2013/38)

(54) **LIVER X RECEPTOR MODULATORS**

LEBER-X-REZEPTORMODULATOREN

MODULATEURS DU RÉCEPTEUR X DU FOIE

(84) Designated Contracting States:
**AL AT BE BG CH CY CZ DE DK EE ES FI FR GB
GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO
PL PT RO RS SE SI SK SM TR**
Designated Extension States:
BA ME

(30) Priority: **16.03.2012 US 201261612051 P**

(43) Date of publication of application:
21.01.2015 Bulletin 2015/04

(73) Proprietor: **Vitae Pharmaceuticals, Inc.**
Fort Washington, PA 19034 (US)

(72) Inventors:
• **DONG, Chengguo**
Staten Island, NY 10305 (US)
• **FAN, Yi**
Doylestown, PA 18901 (US)
• **LEFTHERIS, Katerina**
San Diego
California 92121 (US)

- **LOTESTA, Stephen**
Burlington, NJ 08016 (US)
- **SINGH, Suresh, B.**
Kendall Park, NJ 08824 (US)
- **TICE, Colin**
Ambler, PA 19002 (US)
- **ZHAO, Wei**
North Potomac
Maryland 20878 (US)
- **ZHENG, Yajun**
Hockessin, DE 19707 (US)
- **ZHUANG, Linghang**
Chalfont, PA 18914 (US)

(74) Representative: **Potter Clarkson LLP**
The Belgrave Centre
Talbot Street
Nottingham NG1 5GG (GB)

(56) References cited:
WO-A1-2009/086129 CN-A- 101 456 863

EP 2 825 541 B1

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description**REFERENCE TO RELATED APPLICATIONS**

5 [0001] This application claims the benefit of the filing date of U.S. Provisional Application No. 61/612,051, filed on March 16, 2012.

FIELD OF THE INVENTION

10 [0002] The present invention relates to compounds that modulate the activity of liver X receptors.

BACKGROUND OF THE INVENTION

15 [0003] Atherosclerosis is the leading cause of death in the developed world, and atherosclerosis is predicted to be the leading cause of death in the developing world in the 21st century. Liver X receptors (LXRs) are ligand-activated transcription factors that play a crucial role in regulating the expression of genes involved in lipid metabolism and cellular cholesterol homeostasis. LXR agonists have been shown to enhance reverse cholesterol transport (RCT), facilitating cholesterol trafficking from the periphery back to the liver for processing and excretion. RCT occurs via upregulation of cholesterol transporters (ATP-Binding Cassettes: ABCA1 and ABCG1) in peripheral macrophages. Active RCT has the potential to inhibit the progression of atherosclerosis.

20 [0004] There are two isoforms of LXR, LXR α (NR1H3) and LXR β (NR1H2) that are encoded by separate genes. LXR α expression is tissue-selective, detectable in liver, intestine, kidney, adipose tissue and adrenal glands, all of which are important for lipid homeostasis, whereas LXR β is expressed ubiquitously. Both LXRs require the retinoid X receptor (RXR) as an obligate heterodimer partner to recognize and bind cooperatively to LXR response elements (LXREs) consisting of two direct repeats of a core hexameric sequence spaced by four nucleotides (DR4). The ligand binding domains of the two LXRs are fairly well conserved (~ 78% amino acid homology) and respond to endogenous ligands consisting of oxidized derivatives of cholesterol (oxysterols) that serve as intermediates in steroid hormone and bile acid synthesis. Among them, 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, and 24(S), 25-epoxycholesterol are the most potent. These data suggested that LXRs are likely to play an important role in cholesterol regulation, which was later confirmed through gene knock-out studies in mice. Non-steroidal ligands have also been identified, and, using these as chemical probes many LXR-regulated genes have been discovered. Several LXRE-containing genes are involved in cholesterol metabolism, reverse cholesterol transport (RCT) and lipogenesis. Other genes involved in inflammation and carbohydrate metabolism lack LXREs, but are repressed by LXRs in a ligand-dependent manner. Based on these discoveries, the liver X receptors have recently emerged as unprecedented targets acting as intracellular cholesterol sensors, providing the basis for the treatment of a variety of diseases, including atherosclerosis, diabetes, Alzheimer's disease, skin disorders, reproductive disorders and cancer (Viennois et al., 2011, Expert Opin. Ther. Targets, 15(2):219-232). Additionally, it has been determined that LXR agonists modulate intestinal and renal sodium phosphate (NaPi) transporters and, in turn, serum phosphate levels (Caldas et al., 2011, Kidney International, 80:535-544). Thus, LXR is also a target for kidney disorders, and particularly for the prevention of hyperphosphatemia and associated cardiovascular complications. Recently, LXRs have been identified as targets in the treatment of osteoporosis and related diseases (Kleyer et al., 2012, J. Bone Miner. Res., 27(12):2442-51).

35 [0005] Alzheimer's disease is one of the most common forms of dementia, characterized by the accumulation and deposition of amyloid-beta (A β) peptides in the brain, leading to the perturbation of synaptic function and neuronal loss in the brains of affected individuals. Neurons in the brain produce A β peptides via cleavage of amyloid precursor protein (APP), and A β peptides are normally cleared through efflux into the peripheral circulation and by degradation by proteinases within the brain.

40 [0006] Apolipoprotein E (apoE) is associated with age-related risk for Alzheimer's disease and plays critical roles in A β homeostasis. LXR increases the expression of apoE and increases the lipidation of apoE. Degradation of A β both intra- and extracellularly is enhanced by lipidated apoE. LXR agonist treatment stimulated proteolytic degradation of A β , reduced plaque pathology, and improved memory in APP-expressing transgenic mice (Jiang et al., 2008, Neuron, 58:681-693).

55 [0007] In skin, keratinocytes are a critical component of the epidermis. The outer layer, stratum corneum, is primarily responsible for the permeability barrier to water and electrolyte transit. Keratinocytes in the epidermis undergo differentiation which culminates in keratinocyte cornification ("the bricks") and in formation of the extracellular lipid-enriched lamellar membranes ("the mortar") in the stratum corneum. Both LXR α and LXR β are expressed in keratinocytes, and LXR expression and activation promotes epidermis barrier function. Activation of LXR is involved in keratinocyte differentiation, formation of the lamellar membrane and overall improvement of epidermal barrier function. Thus, LXR activation is expected to result in increased keratinocyte differentiation, increased lipid secretion (via ABCA1, ABCA12), and

increased lamellar body formation, leading to a healthy epidermis (smooth skin).

[0008] The potential therapeutic utility of LXR agonists has led to the development of several high affinity LXR ligands with potent agonism for both receptor subtypes. The therapeutic utility of LXR agonists is constrained by their potential to induce lipogenic genes including sterol response element binding protein-1c (SREBP1c) and fatty acid synthase (FAS). Preclinical studies have demonstrated that synthetic modulators of LXRs reduce lesion progression in murine models of atherosclerosis with limited increase in hepatic lipogenesis. There is a clear need for new LXR chemotypes that retain the anti-atherosclerotic efficacy of current LXR agonists but are devoid of lipogenic activity. Compounds exhibiting a pharmacological profile with positive effects on RCT while being neutral or suppressive on lipogenic genes will be valuable therapeutic agents in patients with atherosclerotic dyslipidemia. { - }

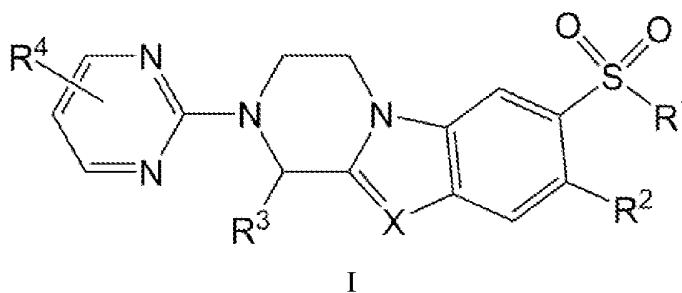
[0009] The present invention provides compounds that are liver X receptor agonists and are useful as therapeutic agents for the promotion of reverse cholesterol transport and the suppression of hepatic lipogenesis, and for the prevention, amelioration or treatment of diseases or disorders including atherosclerosis, Alzheimer's disease, dermatitis, and dyslipidemia in a patient.

SUMMARY OF THE INVENTION

[0010] Disclosed are LXR modulators that are useful as therapeutic agents for the promotion of reverse cholesterol transport and the suppression of hepatic lipogenesis, and for the prevention, amelioration or treatment of diseases or disorders including atherosclerosis and dyslipidemia in a subject. The disclosed LXR modulators are selective for the LXR β subtype over the LXR α subtype (see e.g., Example 2, isomer 1 and Example 4, isomer 1).

[0011] {WO2009/086129 describes pyrazolo [1, 5-a] pyrimidine-based modulators of Liver X receptors.}

[0012] One embodiment of the invention is a compound represented by structural formula I:



or a pharmaceutically acceptable salt thereof.

X is N or CR^c.

R¹ is alkyl or -NR^aR^b.

R² is H; halogen; -CN; -NRC(O)R; -C(O)OR; -C(O)NR^aR^b; monocyclic heteroaromatic optionally substituted with one or more groups selected from alkyl, -CN, -NRC(O)R, -C(O)OR, -C(O)NR^aR^b and halogen; monocyclic non-aromatic heterocycle optionally substituted with one or more groups selected from alkyl, halogen, -CN and =O; or alkyl optionally substituted by one or more groups selected from halogen, hydroxy, alkoxy, -NR^aR^b, -NRC(O)R, -NRC(O)O(alkyl), -NRC(O)N(R)₂, -C(O)OR, thiol, alkylthiol, nitro, -CN, =O, -OC(O)H, -OC(O)(alkyl), -OC(O)O(alkyl), -OC(O)N(R)₂ and -C(O)NR^aR^b.

R³ is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, monocyclic non-aromatic heterocycle, monocyclic heteroaromatic or phenyl, wherein the phenyl, monocyclic non-aromatic heterocycle and monocyclic heteroaromatic group represented by R³ are optionally substituted with one or more groups selected from alkyl, halogen, haloalkyl, alkoxy, haloalkoxy, nitro and -CN;

R⁴ is halogen, -CN, -OR, -SR, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)O(alkyl), -C(O)O(haloalkyl), -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(alkyl), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂, -NRSO₂N(R)₂, haloalkyl, haloalkoxy, cycloalkoxy, cycloalkyl, monocyclic non-aromatic heterocycle, monocyclic heteroaromatic or alkyl, wherein the monocyclic non-aromatic heterocycle, monocyclic heteroaromatic and alkyl group represented by R⁴ are optionally substituted with one or more group selected from -CN, -OR, -SR, -N(R)₂, =O, -C(O)R, -C(O)OR, -C(O)O(haloalkyl), -OC(O)R, -OC(O)O(alkyl), -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(alkyl), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂ and -NRSO₂N(R)₂.

Each R independently is H or alkyl.

R^a and R^b are independently H, alkyl or R^a and R^b can be taken together with the nitrogen to which they are attached to form a monocyclic non-aromatic heterocycle.

R^c is H, alkyl, or halogen.

[0013] Another aspect of the invention is a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or diluent. The application further illustrates a method of treating a subject with a disease or disorder that is treatable by upregulating LXR activity. The method comprises administering an effective amount of a compound of the invention or a pharmaceutically acceptable salt thereof to the subject in need thereof.

[0014] Also provided in the invention is the use of a compound of the invention for the manufacture of a medicament for treating a subject with a disease or disorder that is treatable by upregulating LXR activity in a subject in need thereof.

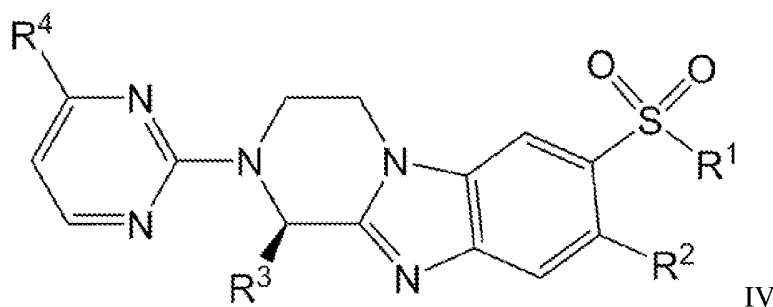
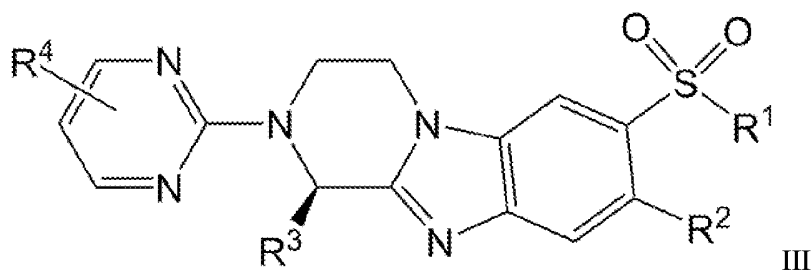
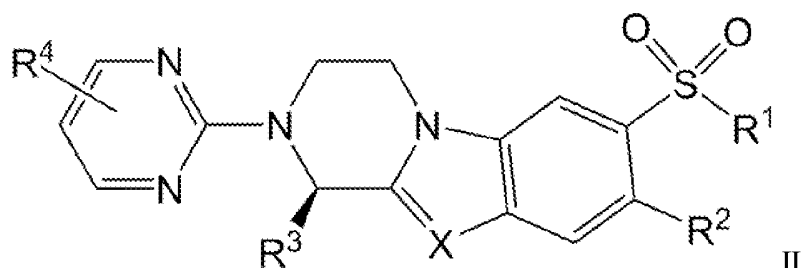
[0015] Disclosed herein is also a compound of the invention for use in treating a disease or disorder that is treatable by upregulating LXR activity in a subject in need thereof

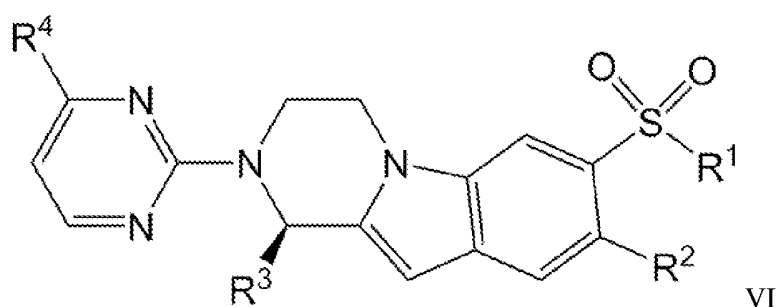
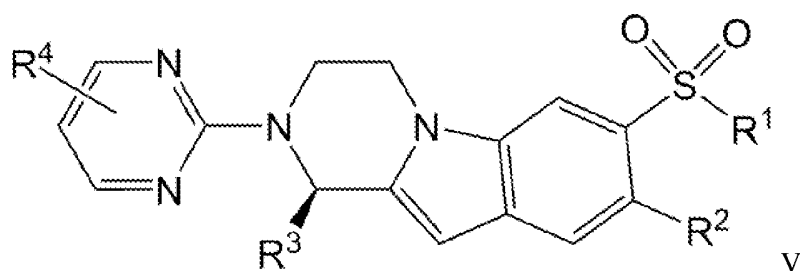
DETAILED DESCRIPTION OF THE INVENTION

A. COMPOUNDS

[0016] The compound(s) of the invention provided herein include both the neutral form and a pharmaceutically acceptable salt thereof.

[0017] In one embodiment, the compound is represented by structural formula II, III, IV, V, or VI, wherein the values for the variables are as defined for Formula I above.





[0018] In a first alternative embodiment of any compound of formulas I through VI, the variables are defined as follows:

R³ is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl or phenyl, wherein the phenyl represented by **R³** is optionally substituted with one or more groups selected from alkyl, halogen, haloalkyl, alkoxy, haloalkoxy, nitro and -CN; and **R⁴** is halogen, -CN, -OR, -SR,

- N(R)₂, -C(O)R, -C(O)OR, -OC(O)O(alkyl), -C(O)O(haloalkyl), -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(alkyl), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂, -NRSO₂N(R)₂, haloalkyl, haloalkoxy, cycloalkoxy, cycloalkyl or alkyl, wherein the alkyl group represented by **R⁴** is optionally substituted with one or more groups selected from -CN, -OR, -SR, -N(R)₂, =O, -C(O)R, -C(O)OR, -C(O)O(haloalkyl), -OC(O)R, -OC(O)O(alkyl), -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(alkyl), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂ and -NRSO₂N(R)₂.

[0019] The values for the remaining variables are as defined for Formula I.

[0020] In a second alternative embodiment of any compound of formulas I through VI, the variables are defined as follows.

R¹ is methyl or -NH₂.

R² is H or methyl, wherein the methyl group represented by **R²** is optionally substituted with one or more groups selected from halogen hydroxyl, alkoxy, -NR^aR^b, -NRC(O)R, -NRC(O)O(alkyl), -NRC(O)N(R)₂, -C(O)OR, thiol, alkylthiol, nitro, -CN, =O, -OC(O)H, -OC(O)(alkyl), -OC(O)O(alkyl), -C(O)NR^aR^b and -OC(O)N(R)₂. Preferably, **R²** is H or -CH₂OH.

R³ is methyl, ethyl, propyl, isopropyl, *tert*-butyl, *sec*-butyl, *iso*-butyl, -CH₂CF₃, -CH(CH₂F)₂, -CH(CHF₂)₂, -CH(CF₃)₂, -CF(CH₃)₂, -CF₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -C(OH)(CH₃)₂, -CH(OH)(CH₃), or phenyl, wherein the phenyl group represented by **R³** is optionally substituted with one or more groups selected from alkyl, halogen, haloalkyl, alkoxy, haloalkoxy, nitro and -CN.

R^c, where present, is H.

[0021] The values for the remaining variables are as defined for Formula I or in the first alternative embodiment.

[0022] In a third alternative embodiment of any compound of formulas I through VI, **R¹** is methyl; **R²** is -CH₂OH; and **R³** is isopropyl. The values for the remaining variables are as defined for Formula I or for the first or second alternative embodiment.

[0023] In a fourth alternative embodiment of any compound of formulas I through VI, **R⁴** is halogen, hydroxy, alkyl, cycloalkyl, cycloalkoxy, alkoxy, haloalkoxy, haloalkyl, -N(R)₂, -C(O)OH, -C(O)O(alkyl), -C(O)O(haloalkyl), -C(O)(alkyl), -C(O)N(R)₂, -NRC(O)R, -SO₂N(R)₂, -OC(O)N(R)₂, -CN, hydroxyalkyl or dihydroxyalkyl. The values for the remaining variables are as defined for Formula I or for the first, second or third alternative embodiments.

[0024] In a fifth alternative embodiment of any compound of formulas I through VI, **R⁴** is alkyl, haloalkyl, cycloalkyl, alkoxy, or haloalkoxy. The values for the remaining variables are as defined for Formula I or for the first, second or third alternative embodiments.

[0025] In a sixth alternative embodiment of any compound of formulas I through VI, **R⁴** is methyl, ethyl, hydroxy, -CF₃,

EP 2 825 541 B1

isopropyl, cyclopropyl, -CH₂OH, -CH(OH)(CH₂)(OH), -C(OH)(CH₃)₂, -CH(OH)(CH₃), -CH(OH)(CH₂)(CH₃), -CH(OH)(CH₂)₂(CH₃), -C(O)NH₂, -C(O)N(CH₃)₂, -C(O)OH, -C(O)NH(CH₃), -C(O)CH₃, -C(O)CH₂CH₃, -C(O)O(CH₂)(CH₃), -C(O)O(tert-butyl), -C(O)O(C)(CH₃)₂(CF₃), -NHC(O)CH₃, -OCHF₂, -OCF₃, -OCH₂CH₃, -OCH(CH₃)₂ or -OCH₃. Preferably, R⁵ is -C(CH₃)₂OH. The values for the remaining variables are as defined for Formula I or for the first, second or third embodiments.

[0026] In a seventh alternative embodiment of any compound of formulas I through VI, R⁴ is methyl, halogenated methyl, cyclopropyl, -OCHF₂ or -OCH₃. Preferably, R⁴ is CF₃. The values for the remaining variables are as defined for Formula I or for the first, second or third alternative embodiments.

[0027] Another embodiment of the invention is a compound represented by formula I, II, III, IV, V or VI or a pharmaceutically acceptable salt thereof, wherein the variables are as defined for formula (I) or in the first, second or third alternative embodiments, provided that the compound comprises at least one group represented by -C(O)OR.

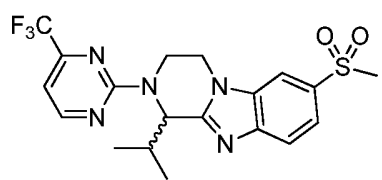
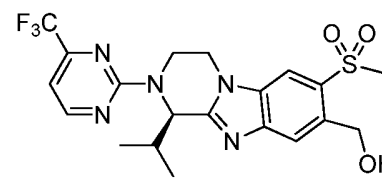
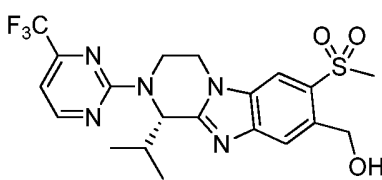
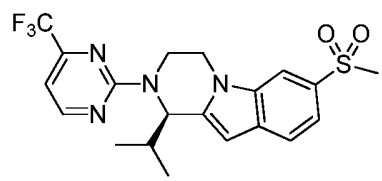
[0028] Another embodiment of the invention is a compound represented by formula I, II, III, IV V or VI or a pharmaceutically acceptable salt thereof, wherein the variables are as defined for formula (I) or in the first, second, third, fourth, fifth, sixth or seventh alternative embodiment, provided that the compound comprises no groups represented by -C(O)OR.

[0029] The compounds of the invention contain at least one chiral center and, therefore, exist as enantiomers. When compounds of the invention are depicted or named without indicating the stereochemistry, it is to be understood that enantiomerically pure forms and mixtures of enantiomers, including racemic mixtures, are encompassed.

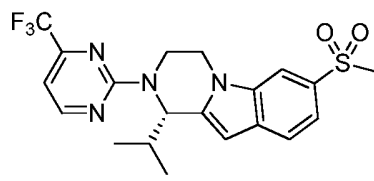
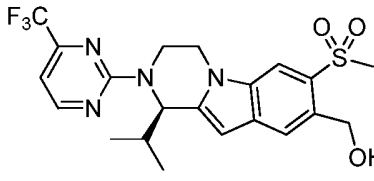
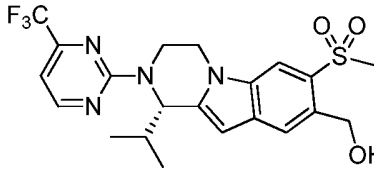
[0030] When a compound is designated by a name or structure that indicates a single enantiomer, unless indicated otherwise, the compound is at least 50%, 60%, 70%, 80%, 90%, 95%, 99%, 99.5% or 99.9% optically pure (also referred to as "enantiomerically pure"). Optical purity is the weight in the mixture of the named or depicted enantiomer divided by the total weight in the mixture of both enantiomers.

[0031] In a seventh alternative embodiment, a compound of the invention is depicted by a compound in Table 1 or a pharmaceutically acceptable salt thereof.

Table 1.

Compound No.	Example No.	Structure
E1	Example 1	
E2a	Example 2, isomer 1	
E2b	Example 2, isomer 2	
E3a	Example 3, isomer 1	

(continued)

Compound No.	Example No.	Structure
E3b	Example 3, isomer 2	
E4a	Example 4, isomer 1	
E4b	Example 4, isomer 2	

B. DEFINITIONS

[0032] Unless otherwise specified, the below terms used herein are defined as follows.

[0033] "Subject", "patient" and "mammal" are used interchangeably herein. In one embodiment, the subject is a non-human animal such as a non-human primate (e.g., a monkey, chimpanzee), a farm animal (e.g., a horse, cow, pig, chicken, or sheep), a laboratory animal (e.g., a rat or mouse), or a companion animal (e.g., dog, cat, guinea pig or rabbit). In a preferred embodiment, the subject is a human.

[0034] "Compound(s) of the invention" refers to compounds represented by Structural Formula I, II, III, VI, V, VI; a compound depicted in Table 1; a compound named or depicted in the examples herein as the final compound(s) of the examples; or a pharmaceutically acceptable salt thereof. "Compound(s) of the invention" also includes the neutral form of the compounds as depicted herein.

[0035] "Pharmaceutically acceptable" refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of the subject, such as humans and other mammals, without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio.

[0036] Included in the invention are pharmaceutically acceptable salts of the compounds disclosed herein. The disclosed compounds have basic amine groups and therefore can form pharmaceutically acceptable salts with pharmaceutically acceptable acid(s). Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention include salts of inorganic acids (such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids) and of organic acids (such as, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p- toluenesulfonic, and tartaric acids). Compounds of the invention with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts). Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Company, Easton, PA, 1990, p 1445.

[0037] "Liver X receptors or LXRs" includes both the α and β subtypes of the liver X receptor. In one embodiment, the disclosed compounds selectively bind and upregulate the activity of the LXR subtype over the LXR α subtype. To "modulate" a receptor means that there is a change or alteration in the activity of a molecule of interest, e.g., the biological activity of liver X receptor. Modulation may be an upregulation (increase) or a downregulation (decrease) in the magnitude of a certain activity or function of the molecule of interest. Exemplary activities and functions of a molecule include, but are not limited to, binding characteristics, enzymatic activity, cell receptor activation, transcriptional activity, and signal transduction. In an embodiment, the compounds of the invention are LXR agonists that, for example, upregulate or downregulate genes which are transcriptional targets of LXR (i.e., "LXR target genes").

[0038] "Treat" or "treating" include both therapeutic and prophylactic treatments and mean to ameliorate, decrease,

suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease.

[0039] "Disease" or "disorder" means any condition that is modulated or otherwise affected by LXR activity or in which LXR activity is implicated. The diseases or disorders include those which are associated with, or symptoms arising from the complications of, altered cholesterol transport, cholesterol reverse transport, fatty acid metabolism, cholesterol absorption, cholesterol re-absorption, cholesterol secretion, cholesterol excretion, or cholesterol metabolism.

[0040] "Effective amount" is the quantity of the compound which is sufficient to treat (therapeutically or prophylactically) the target disorder or in which a beneficial clinical outcome is achieved when the compound is administered to a subject in a proper dosing regimen. Effective doses will also vary, as recognized by one of ordinary skill in the art, depending on the disease being treated, the severity of the disease, the route of administration, the sex, age and general health condition of the patient, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician or other medical provider. For example, an effective amount is sufficient to reduce or ameliorate the severity, duration or progression of the disorder being treated, prevent the advancement of the disorder being treated, cause the regression of the disorder being treated, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy. For example, when a compound of the invention is administered to a subject with a cancer, a "beneficial clinical outcome" includes a reduction in tumor mass, a reduction in metastasis, a reduction in the severity of the symptoms associated with the cancer and/or an increase in the longevity of the subject compared with the absence of the treatment. When a compound of the invention is administered to a subject with a disorder such as atherosclerosis, a "beneficial clinical outcome" includes reduction in the severity or number of symptoms associated with the disorder, lower cholesterol, or increase in the longevity of the subject compared with the absence of the treatment. The recommended dosages of agents currently used for the treatment of a disorder can be obtained from various references in the art including, but not limited to, Hardman et al., eds., 1996, Goodman & Gilman's The Pharmacological Basis Of Basis Of Therapeutics 9th Ed, Mc-Graw-Hill, New York; Physician's Desk Reference (PDR) 57th Ed., 2003, Medical Economics Co., Inc., Montvale, NJ. In certain embodiments, an effective amount of a compound of this invention is in the range of from 0.5 mg to 2000 mg, or from 0.5 mg to 1000 mg, or from 0.5 mg to 500 mg, or from 0.5 mg to 100 mg, or from 100 mg to 1000 mg, or from 20 mg to 2000 mg per treatment. Treatment typically is administered from one to three times daily.

[0041] "Halo" or "halogen" means chloro, bromo, fluoro, or iodo. In one embodiment, halo is fluoro.

[0042] "Alkyl" means a straight or branched hydrocarbon group having 1 to 15 carbon atoms in the chain. In one embodiment, alkyl groups have 1 to 12 carbon atoms in the chain. In another embodiment, alkyl groups have 1 to 6 carbon atoms. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, *tert*-butyl, *sec*-butyl, n-pentyl, 3-pentyl, heptyl, octyl, nonyl, decyl, and dodecyl.

[0043] "Alkoxy" is an alkyl group which is attached to another moiety via an oxygen linker (-O(alkyl)). Non-limiting examples include methoxy, ethoxy, propoxy, and butoxy.

[0044] "Haloalkyl" or "halogenated alkyl" means an alkyl group in which one or more, including all, of the hydrogen radicals are replaced by a halo group, wherein each halo group is independently selected from -F, -Cl, -Br, and -I. For example, the term "halomethyl" or "halogenated methyl" means a methyl in which one to three hydrogen radical(s) have been replaced by a halo group. Representative haloalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, bromomethyl, 1,2-dichloroethyl, 4-iodobutyl, 2-fluoropentyl, and the like. Other examples include groups such as but are not limited to -CH₂CF₃, -CH(CH₂F)₂, -CH(CHF₂)₂, -CH(CF₃)₂, -CF(CH₃)₂, -CF₃.

[0045] "Haloalkoxy" is a haloalkyl group which is attached to another moiety via an oxygen linker such as but are not limited to -OCHCF₂ or -OCF₃.

[0046] "Alkoxyalkyl" is an alkoxy group which is attached to another moiety via an alkyl linker. "Hydroxyalkyl" or "dihydroxyalkyl" is one or two hydroxy groups, respectively, which are attached to another moiety via an alkyl linker. Representative "hydroxyalkyl" or "dihydroxyalkyl" include -CH₂OH, -CH(OH)(CH₂)(OH), -C(OH)(CH₃)₂, -CH(OH)(CH₃), -CH(OH)(CH₂)(CH₃), -CH(OH)(CH₂)₂(CH₃), -C(CH₃)₂(OH), and the like. 12

[0047] "Cycloalkyl" means a non-aromatic monocyclic ring system of 3 to 10 carbon atoms. In one embodiment, the cycloalkyl group has 3 to 6 carbon atoms. Exemplary cycloalkyl rings include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0048] "Cycloalkoxy" means a cycloalkyl group which is attached to another moiety via an oxygen linker (-O(cycloalkyl)).

[0049] "Monocyclic non-aromatic heterocycle" means a single saturated heterocyclic ring, typically having 3- to 10-members and more typically 3 to 7-members in the ring, wherein at least one atom in the ring is a heteroatom such as, for example, nitrogen, oxygen, sulfur, including sulfoxide and sulfone. A 3- to 4-membered monocyclic non-aromatic heterocycle can contain up to 2 heteroatoms; a 5-6 membered monocyclic heterocycle can contain up to 3 heteroatoms and a 7- to 10-membered monocyclic non-aromatic heterocycle can contain up to 4 heteroatoms. The monocyclic non-aromatic heterocycle may be attached to another group via any heteroatom or carbon atom of the monocyclic non-aromatic heterocycle. Representative monocyclic non-aromatic heterocycles include morpholinyl, thiomorpholinyl, pyr-

rolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isothiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. In one embodiment, a monocyclic non-aromatic heterocycle is a heterocyclic ring of 4, 5, 6, or 7 members.

5 **[0050]** "Monocyclic heteroaromatic" comprises carbon atom ring members and one or more heteroatom ring members. Each heteroatom is independently selected from nitrogen, oxygen, and sulfur, including sulfoxide and sulfone. The point of attachment of a monocyclic heteroaromatic ring to another group may be at either a carbon atom or a heteroatom of the heteroaromatic. In one embodiment, the monocyclic heteroaromatic ring is selected from 5 to 8 membered monocyclic heteroaromatic rings. Representative monocyclic heteroaromatic groups include pyridyl, 1-oxo-pyridyl, furanyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, a triazinyl, triazolyl, thiadiazolyl, and tetrazolyl.

C. PHARMACEUTICAL COMPOSITIONS, FORMULATIONS AND DOSAGES In one embodiment, provided herein is a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or diluent.

15 **[0051]** In the pharmaceutical compositions of the invention, the compound of the invention is present in an effective amount. The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., *Cancer Chemother. Rep*, 1966, 50: 219. Body surface area may be determined approximately from height and weight of the patient. See, e.g., *Scientific Tables*, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

20 **[0052]** The LXR modulators herein (e.g., compound(s) of the invention) can be formulated as pharmaceutical compositions and administered to a subject, such as a human, in a variety of forms adapted to the chosen route of administration. Typical routes of administering such pharmaceutical compositions include, without limitation, oral, topical, buccal, transdermal, inhalation, parenteral, sublingual, rectal, vaginal, and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrathecal, intrasternal injection or infusion techniques. Methods of formulating pharmaceutical compositions are well known in the art, for example, as disclosed in "Remington: The Science and Practice of Pharmacy," University of the Sciences in Philadelphia, ed., 21st edition, 2005, Lippincott, Williams & Wilkins, Philadelphia, PA. Each of the LXR modulators may be used alone or in combination as a part of a pharmaceutical composition of the invention.

30 **[0053]** The pharmaceutical compositions of the invention can be prepared by combining a compound of the invention with an appropriate pharmaceutically acceptable carrier, diluent or excipient, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants, gels, microspheres, and aerosols. Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable excipient such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

35 **[0054]** Suitable tablets may be obtained, for example, by mixing one or more compounds of the invention with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants. The tablets may also consist of several layers.

40 **[0055]** The compounds of the invention can be suitably formulated into pharmaceutical compositions for administration to a subject. The pharmaceutical compositions of the invention optionally include one or more pharmaceutically acceptable carriers and/or diluents therefor, such as lactose, starch, cellulose and dextrose. Other excipients, such as flavoring agents; sweeteners; and preservatives, such as methyl, ethyl, propyl and butyl parabens, can also be included. More complete listings of suitable excipients can be found in the *Handbook of Pharmaceutical Excipients* (5th Ed., Pharmaceutical Press (2005)). A person skilled in the art would know how to prepare formulations suitable for various types of administration routes. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in *Remington's Pharmaceutical Sciences* (2003 - 20th edition) and in *The United States Pharmacopeia: The National Formulary (USP 24 NF19)* published in 1999. The carriers, diluents and/or excipients are "acceptable" in the sense of being compatible with the other ingredients of the pharmaceutical composition and not deleterious to the recipient thereof.

50 **[0056]** Typically, for oral therapeutic administration, a compound of the invention may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

55 **[0057]** Typically for parenteral administration, solutions of a compound of the invention can generally be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[0058] Typically, for injectable use, sterile aqueous solutions or dispersion of, and sterile powders of, a compound of the invention for the extemporaneous preparation of sterile injectable solutions or dispersions.

[0059] For nasal administration, the compounds of the invention can be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas such as compressed air or an organic propellant such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer.

[0060] For buccal or sublingual administration, the compounds of the invention can be formulated with a carrier such as sugar, acacia, tragacanth, or gelatin and glycerine, as tablets, lozenges or pastilles.

[0061] For rectal administration, the compounds of the invention can be formulated in the form of suppositories containing a conventional suppository base such as cocoa butter.

[0062] Topical and/or local administration of the compounds of the invention can be achieved in a variety of ways including but not limited to ointments, lotions, pastes, creams, gels, powders, drops, sprays, solutions, inhalants, patches, suppositories, retention enemas, chewable or suckable tablets or pellets and aerosols. Topical and/or local administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. For topical and/or local administration, the compounds of the invention can be formulated as ointments, creams, milks, salves, powders, impregnated pads, syndets, solutions, gels, sprays, foams, suspensions, lotions, sticks, shampoos or washing bases. Compounds of the invention may also be administered in the form of suspensions of lipid or polymer vesicles or nanospheres or microspheres or polymer patches and hydrogels for controlled release.

D. METHODS OF TREATMENT AND USE OF THE LXR MODULATORS

[0063] Provided herein is a method of treating a subject with a disease or disorder that is treatable by modulation of LXR. In one embodiment, LXR is modulated by upregulating LXR activity. The method comprises administering an effective amount of the compound of the invention. Moreover, provided herein is the use of a compound of the invention for the manufacture of a medicament for treating a subject with a disease or disorder that is treatable by upregulating LXR activity in a subject in need thereof.

[0064] The methods provided herein may be useful for disorders treatable with LXR modulation, in particular LXR agonism.

[0065] Compounds of the invention are useful for the treatment or prevention of diseases or disorders associated with altered cholesterol transport, reverse cholesterol transport, fatty acid metabolism, cholesterol absorption, cholesterol re-absorption, cholesterol secretion, cholesterol excretion, or cholesterol metabolism. Representative diseases or disorders include, but are not limited to, a lipid disorder; cancer, particularly hormone-dependent cancers, including ovarian, breast and prostate cancer; acneiform skin condition; skin inflammatory disease; immunological disorder; condition characterized by a perturbed epidermal barrier function; condition of disturbed differentiation or excess proliferation of the epidermis or mucous membrane; cardiovascular disease; reproductive tract disorders; optic nerve and retinal pathology; degenerative neuropathy occurring in a disease; autoimmune disease; traumatic damage to the central or peripheral nervous system; neurodegenerative disease; a degenerative process due to aging; diseases or disorders of the kidney; and osteoporosis and related diseases.

[0066] In another embodiment, the disease or disorder is hyperlipidemia, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hepatic steatosis, nonalcoholic steatohepatitis (NASH), nonalcoholic fatty liver disease (NAFLD), hyperglycemia, insulin resistance, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, dermatitis (including but not limited to, psoriasis, contact dermatitis, atopic dermatitis, and eczema), skin wounds, skin aging, photoaging, wrinkling, diabetes, Niemann-Pick disease type C, Parkinson's disease, Alzheimer's disease, inflammation, xanthoma, obesity, metabolic syndrome, syndrome X, stroke, peripheral occlusive disease, memory loss, diabetic neuropathies, proteinuria, glomerulopathies (including but not limited to, diabetic nephropathy, hypertensive nephropathy, IGA nephropathy, focal segmental glomerulosclerosis), hyperphosphatemia, cardiovascular complications of hyperphosphatemia, cancer, multiple sclerosis, or osteoporosis.

[0067] In another embodiment, the disease or disorder is common acne; comedones; polymorphs; rosacea; nodulocystic acne; acne conglobate; senile acne; secondary acne, including but not limited to solar, medicinal and occupational acne; ichthyosis; ichthyosiform conditions; Darier's disease; palmoplantar keratoderma; leukoplakia; leukoplakiform conditions; cutaneous or mucous (oral) lichen; dermatological conditions or afflictions with an inflammatory immunological component, with or without a cellular proliferation disorder, including but not limited to cutaneous psoriasis, mucous psoriasis, unguinal psoriasis, psoriatic rheumatism, cutaneous atopy, including eczema, respiratory atopy and gingival hypertrophy; benign or malignant dermal or epidermal proliferations, of viral or non-viral origin, including but not limited

to common warts, flat warts, epidermodysplasia verruciformis, oral or florid papillomatosis, and T lymphoma or cutaneous T-cell lymphoma; proliferations that may be induced by ultraviolet light, including but not limited to basocellular epithelioma and spinocellular epithelioma; precancerous skin lesions, including but not limited to keratoacanthomas; immune dermatitides, including but not limited to lupus erythematosus; bullous immune diseases; collagen diseases, including but not limited to scleroderma; dermatological or systemic conditions or afflictions with an immunological component; skin disorders due to exposure to UV radiation; photo-induced or chronological aging of the skin; actinic pigmentations; keratosis; pathology associated with chronological or actinic aging, including but not limited to xerosis; sebaceous function disorders, including but not limited to hyperseborrhoea of acne, simple seborrhoea and seborrhoeic dermatitis; cicatrization disorders, including but not limited to stretch marks; pigmentation disorders, including but not limited to hyperpigmentation, melasma, hypopigmentation, and vitiligo; and alopecia, including but not limited to chemotherapy-associated alopecia and radiation-associated alopecia.

[0068] In an embodiment, the disease or disorder is hypercholesterolemia, atherosclerosis or dyslipidemia. In another embodiment, the disease or disorder is atherosclerosis or dyslipidemia. In yet another embodiment, the disease or disorder is atherosclerosis, Alzheimer's disease or dermatitis.

[0069] The application further illustrates a method for increasing reverse cholesterol transport and/or for inhibiting the progression of or promoting the regression of atherosclerosis.

[0070] The application further illustrates a method of treating diseases or disorders associated with a need for increasing high density lipoprotein (HDL)-cholesterol levels comprising the administration of an effective amount of a compound of the invention to a mammal (particularly a human) in need thereof.

[0071] The application further illustrates a method of treating a disease or disorder associated with a need for decreasing low density lipoprotein (LDL)-cholesterol levels comprising the administration of an effective amount of a compound of the invention to a mammal (particularly a human) in need thereof.

[0072] Additionally, provided herein is a method of increasing the expression of an ATP-Binding Cassette protein in a subject's cells, thereby increasing reverse cholesterol transport in a subject using the compounds of the invention and compositions provided herein.

[0073] Standard physiological, pharmacological and biochemical procedures are known to the art and are available for evaluating compounds of the present invention for the ability to modulate LXR activity. Such assays include, for example, binding assays, fluorescence polarization assays, FRET based co-activator recruitment assays, and cell-based co-transfection assays. Compounds of the present invention can be evaluated for their ability to modulate the expression of genes known to be modulated by LXR. Established animal models can be used to study the profiles of compounds of the present invention in relation to parameters directly relevant to diseases or disorders, including atherosclerosis, Alzheimer's disease, and skin conditions. Thus, compounds of the present invention can be tested *in vivo* in animal models by a variety of routes of administration, for example, oral gavage. Typically, *in vivo* compound exposure can be examined in plasma and in tissues of interest. LXR activity (as detected by gene expression of LXR-responsive genes) can be examined in whole blood and tissues of interest. Lipids can be quantified in the plasma and the liver.

[0074] In particular, compounds of the present invention can be tested for their activity on ATP-Binding Cassette (ABC) cholesterol transporters, such as ABCA1 and ABCG1, and on lipogenic markers, such as SREBP1c at the gene and protein expression level. The functional consequences of ABC transporter induction can be examined in cellular models for cholesterol efflux and in animal models for the reverse cholesterol pathway and atherosclerosis. Lipogenic markers can be examined in animal models by measuring plasma and liver triglyceride levels.

[0075] The compounds of the present invention can be used alone (*i.e.*, as a monotherapy) or in combination with one or more other therapeutic agent effective for treating any of the above indications. The pharmaceutical compositions can comprise the disclosed compounds alone as the only pharmaceutically active agent or can comprise one or more additional pharmaceutically active agents.

[0076] The application further illustrates a combination therapy for treating or ameliorating a disease or a disorder described herein. In some embodiments, the combination therapy comprises administering at least one compound represented by Structural Formula I, II, III, IV, V, or VI in combination with one or more agents for treating or ameliorating a disease or a disorder described herein. In some embodiments, the combination therapy comprises administering at least one compound represented by Structural Formula I, II, III, IV, V, or VI in combination with one or more agents for the treatment of diseases including hyperlipidemia, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hepatic steatosis, NASH, NAFLD, hyperglycemia, insulin resistance, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, dermatitis (including but not limited to, psoriasis, contact dermatitis, atopic dermatitis, and eczema), skin wounds, skin aging, photoaging, wrinkling, diabetes, Niemann-Pick disease type C, Parkinson's disease, Alzheimer's disease, inflammation, xanthoma, obesity, metabolic syndrome, syndrome X, stroke, peripheral occlusive disease, memory loss, diabetic neuropathies, proteinuria, glomerulopathies (including but not limited to, diabetic nephropathy, hypertensive nephropathy, IGA nephropathy, focal segmental glomerulosclerosis), hyperphosphatemia, cardiovascular complications of hyperphosphatemia, cancer, multiple sclerosis or osteoporosis.

[0077] In some embodiments, the compounds of the invention are used in combination with one or more additional

agents for the treatment of diabetes, dyslipidemia, cardiovascular disease, hypertension, or obesity. Agents for the treatment of diabetes include insulins, such as Humulin® (Eli Lilly), Lantus® (Sanofi Aventis), Novolin® (Novo Nordisk), and Exubera® (Pfizer); PPAR gamma agonists, such as Avandia® (rosiglitazone maleate, GSK) and Actos® (pioglitazone hydrochloride, Takeda/Eli Lilly); sulfonyleureas, such as Amaryl® (glimepiride, Sanofi Aventis), Diabeta® (glyburide, Sanofi Aventis), Micronase® /Glynase® (glyburide, Pfizer), and Glucotrol® /Glucotrol XL® and (glipizide, Pfizer); meglitinides, such as Prandin®/NovoNorm® (repaglinide, Novo Nordisk), Starlix® (nateglinide, Novartis), and Glufast® (mitiglinide, Takeda); biguanides, such as Glucophage®/Glucophage XR® (metformin HCl, Bristol Myers Squibb) and Glumetza® (metformin HCl extended release tablets, Depomed); thiazolidinediones; amylin analogs, GLP-1 analogs or agonists (including Byetta® (exenatide, Amylin/Eli Lilly) and Victoza® (recombinant liraglutide, Novo Nordisk)); DPP-IV inhibitors including Tradjenta™ (Eli Lilly/Boehringer Ingelheim), Januvia® (Merck), Galvus® (Novartis), and Onglyza® (Bristol-Myers Squibb/AstraZeneca); PTB-1 B inhibitors; protein kinase inhibitors (including AMP-activated protein kinase inhibitors); glucagon antagonists, glycogen synthase kinase-3 beta inhibitors; glucose-6-phosphatase inhibitors; glycogen phosphorylase inhibitors; sodium glucose co-transporter inhibitors, and alpha-glucosidase inhibitors, such as Precose®/Glucobay®/Prandase®/Glucor® (acarbose, Bayer) and Glyset® (miglitol, Pfizer). Agents for the treatment of dyslipidemia and cardiovascular disease include statins, fibrates, and ezetimibe. Agents for the treatment of hypertension include alpha-blockers, beta-blockers, calcium channel blockers, diuretics, angiotensin converting enzyme (ACE) inhibitors, dual ACE and neutral endopeptidase (NEP) inhibitors, angiotensin-receptor blockers (ARBs), aldosterone synthase inhibitors, aldosterone-receptor antagonists, or endothelin receptor antagonists. Agents for the treatment of obesity include orlistat, phentermine, sibutramine and rimonabant.

[0078] The application further illustrates the administration of an LXR modulator compound of the invention or composition thereof in a combination therapy with combination products, such as Avandamet® (metformin HCl and rosiglitazone maleate, GSK); Avandaryl® (glimepiride and rosiglitazone maleate, GSK); Metaglip® (glipizide and metformin HCl, Bristol Myers Squibb); and Glucovance® (glyburide and metformin HCl, Bristol Myers Squibb).

[0079] In some embodiments, the combination therapy comprises administering at least one compound of the invention in combination with one or more compound selected from the group of, for example, beta secretase (BACE1) inhibitors; gamma-secretase inhibitors; amyloid aggregation inhibitors (e.g., ELND-005); directly or indirectly acting neuroprotective and/or disease-modifying substances; anti-oxidants (e.g., vitamin E or ginkgolide); anti-inflammatory substances (e.g., Cox inhibitors, NSAIDs); HMG-CoA reductase inhibitors (statins); acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine, tacrine, galantamine, memantine; tacrine); NMDA receptor antagonists (e.g., memantine); AMPA receptor agonists; AMPA receptor positive modulators, AMPAkinases, monoamine receptor reuptake inhibitors, substances modulating the concentration or release of neurotransmitters; substances inducing the secretion of growth hormone (e.g., ibutamoren mesylate and capromorelin); CB-1 receptor antagonists or inverse agonists; antibiotics (e.g., minocyclin or rifampicin); PDE2, PDE4, PDE5, PDE9, PDE10 inhibitors, GABAA receptor inverse agonists, GABAA receptor antagonists, nicotinic receptor agonists or partial agonists or positive modulators, alpha4beta2 nicotinic receptor agonists or partial agonists or positive modulators, alpha7 nicotinic receptor agonists or partial agonists or positive modulators; histamine H3 antagonists, 5 HT-4 agonists or partial agonists, 5HT-6 antagonists, alpha2-adrenoreceptor antagonists, calcium antagonists, muscarinic receptor M1 agonists or partial agonists or positive modulators, muscarinic receptor M2 antagonists, muscarinic receptor M4 antagonists, metabotropic glutamate-receptor 5 positive modulators, antidepressants, such as citalopram, fluoxetine, paroxetine, sertraline and trazodone; anxiolytics, such as lorazepam and oxazepam; antipsychotics, such as aripiprazole, clozapine, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone, and other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced. The compounds according to the invention may also be used in combination with immunotherapies for the treatment of a disease or disorder disclosed herein.

[0080] Combination therapy includes co-administration of a compound of the invention and one or more other agent, sequential administration of a compound of the invention and one or more other agent, administration of a composition containing a compound of the invention and one or more other agent, or simultaneous administration of separate compositions containing a compound of the invention and one or more other agent.

E. EXEMPLARY SYNTHESIS

GENERAL DESCRIPTION OF SYNTHETIC METHODS

[0081] The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. Many of the reactions can also be carried out under microwave conditions or using conventional heating or utilizing other technologies such as solid phase reagents/scavengers or flow chemistry. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned

EP 2 825 541 B1

in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to a person of ordinary skill in the art in light of the following reaction schemes and examples. In cases where synthetic intermediates and final products contain potentially reactive functional groups, for example amino, hydroxy, thiol and carboxylic acid groups, that may interfere with the desired reaction, it may be advantageous to employ protected forms of the intermediate. Methods for the selection, introduction and subsequent removal of protecting groups are well known to those skilled in the art. In the discussion below X, R¹, R², R³ and R⁴ have the meanings indicated above unless otherwise indicated. The abbreviations used in these experimental details are listed below and additional ones should be known to a person skilled in the art of synthesis. In addition one can refer to the following references for suitable methods of synthesis as described in March, *Advanced Organic Chemistry*, 3rd edition, John Wiley & Sons, 1985, Greene and Wuts, *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley & Sons, 1991, and Richard Larock, *Comprehensive Organic Transformations*, 4th edition, VCH publishers Inc., 1989.

[0082] Generally, reagents in the reaction schemes are used in equimolar amounts; however, in certain cases it may be desirable to use an excess of one reagent to drive a reaction to completion. This is especially the case when the excess reagent can be readily removed by evaporation or extraction. Bases employed to neutralize HCl in reaction mixtures are generally used in slight to substantial excess (1.05 - 5 equivalents).

[0083] Where NMR data are presented, spectra were obtained on a Varian 400 (400 MHz) or 300 (300 MHz) and are reported as ppm downfield from tetramethylsilane with number of proton, multiplicities and coupling constants indicated parenthetically along with reference to deuterated solvent.

[0084] LC-MS data were obtained by utilizing one or more of the following chromatographic conditions:

Method 1 (10-80, 2 min)

Column	Xtimate™ C18 2.1*30mm, 3μm		
Mobile Phase	A: water (4 L) + TFA (1.5 mL) B: acetonitrile (4 L) + TFA (0.75 mL)		
	TIME(min)	A%	B%
	0	90	10
	0.9	20	80
	1.5	20	80
	1.51	90	10
	2	90	10
Flow Rate	1.2 mL/min		
wavelength	UV 220nm		
Oven Temp	50 °C		
MS ionization	ESI		

Method 2 (30-90, 2 min)

Column	Xtimate™ C18 2.1*30mm, 3μm		
Mobile Phase	A: water (4 L) + TFA (1.5 mL) B: acetonitrile (4 L) + TFA (0.75 mL)		
	TIME(min)	A%	B%
	0	70	30
	0.9	10	90
	1.5	10	90
	1.51	70	30
	2	70	30
Flow Rate	1.2 mL/min		

EP 2 825 541 B1

(continued)

	TIME(min)	A%	B%
wavelength	UV 220nm		
Oven Temp	50 °C		
MS ionization	ESI		

Method 3 (0-60, 2 min)

Column	Xtimate™ C18 2.1*30mm, 3µm		
Mobile Phase	A: water (4 L) + TFA (1.5 mL) B: acetonitrile (4 L) + TFA (0.75 mL)		
	TIME(min)	A%	B%
	0	100	0
	0.9	40	60
	1.5	40	60
	1.51	100	0
	2	100	0
Flow Rate	1.2 mL/min		
wavelength	UV 220nm		
Oven Temp	50 °C		
MS ionization	ESI		

Method 4:

HPLC System: Waters ACQUITY; Column: Waters ACQUITY CSH™ C18 1.7 µM

Guard column: Waters Assy. Frit, 0.2µM, 2.1 mm; Column tem: 40 °C.

Mobile Phase: A: TFA: Water (1:1000, v:v) Mobile phase B: TFA: ACN (1:1000, v:v); Flow Rate: 0.65 mL/min; Injection Volume: 2 µL; Acquisition time: approximately 1.5 minute.

Gradient Program:

Time (min)	B%
0	10
0.8	90
1.20	90
1.21	10

Mass Spectrometer Parameters

[0085] Mass Spectrometer: Waters SQD; Ionization: Positive Electrospray Ionization (ESI); Mode Scan (100-1400 m/z in every 0.2 second); ES Capillary Voltage: 3.5 kv; ES Cone Voltage: 25 v Source Temperature : 120 °C; Desolvation Temperature: 500 °C; Desolvation Gas Flow: Nitrogen Setting 650 (L/hr); Cone Gas Flow: Nitrogen Setting 50 (L/hr).

[0086] SFC separation of compounds of the invention were carried out under the following methods.

Method A:

Instrument: Thar SFC 80; Column: AD 250mm*30mm, 5µm; Mobile phase: A: Supercritical CO₂, B: IPA (0.05% DEA), A: B =80:20 at 60ml/min; Column Temp: 38°C; Nozzle Pressure: 100 Bar; Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220nm.

EP 2 825 541 B1

Method B:

Instrument: SFC MG2; Column: OJ 250mm*30mm, 5 μ m; Mobile phase: A: Supercritical CO₂, B: MeOH(0.05% DEA), A:B =90:10 at 70ml/min; Column Temp: 38 °C; Nozzle Pressure: 100 Bar Nozzle Temp: 60 °C; Evaporator Temp: 20 °C; Trimmer Temp: 25 °C; Wavelength: 220nm.

5

[0087] The chiral purity of compounds of the invention was determined by analytical chiral HPLC, which was carried out using Chiralcel® or Chiralpak® columns, using CO₂, together with from 5% to 40% methanol, ethanol or isopropanol, containing 0.05% DEA as eluents.

10

Analytical Chiral HPLC

Method	Detailed information
OJ-H_3_5_40_2.35ML	Column: Chiralcel® OJ-H 250x4.6mm I.D., 5 μ m Mobile phase: methanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.35 mL/min Wavelength: 220nm
OJ-H_3_5_40_2.5ML	Column: Chiralcel® OJ-H 250x4.6mm I.D., 5 μ m Mobile phase: methanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.5m L/min Wavelength: 220nm
AS-H_3_5_40_2.35ML	Column: Chiralpak® AS-H 250x4.6mm I.D., 5 μ m Mobile phase: methanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.35 mL/min Wavelength: 220nm
AS-H_4_5_40_2.5ML	Column: Chiralpak® AS-H 250x4.6mm I.D., 5 μ m Mobile phase: iso-propanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.5mL/min Wavelength: 220nm
AS-H_5_5_40_2.35ML	Column: Chiralpak® AS-H 250x4.6mm I.D., 5 μ m Mobile phase: ethanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.35mL /min Wavelength: 220nm
AS-H_3_5_40_2.5ML	Column: Chiralpak® AS-H 250x4.6mm I.D., 5 μ m Mobile phase: methanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.5m L/min Wavelength: 220nm
AD-H_3_5_40_2.35ML	Column: Chiralpak® AD-H 250x4.6mm I.D., 5 μ m Mobile phase: methanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.35 mL/min Wavelength: 220nm
AD-H_5_5_40_2.35ML	Column: Chiralpak® AD-H 250x4.6mm I.D., 5 μ m Mobile phase: ethanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.35mL /min Wavelength: 220nm
OD-3_3_5_40_2.5ML	Column: Chiralcel® OD-3 150x4.6mm I.D., 3 μ m Mobile phase: methanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.5m L/min Wavelength: 220nm
OD-3_4_5_40_2.5ML	Column: Chiralcel® OD-3 150x4.6mm I.D., 3 μ m Mobile phase: iso-propanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.5mL/min Wavelength: 220nm
OD-3_5_5_40_2.5ML	Column: Chiralcel® OD-3 150x4.6mm I.D., 3 μ m Mobile phase: ethanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.5mL/ min Wavelength: 220nm
AD-3_3_5_40_2.5ML	Column: Chiralpak® AD-3 150x4.6mm I.D., 3 μ m Mobile phase: methanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.5m L/min Wavelength: 220nm
AD-3_4_5_40_2.5ML	Column: Chiralpak® AD-3 150x4.6mm I.D., 3 μ m Mobile phase: iso-propanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.5 mL/min Wavelength: 220nm
AD-3_5_5_40_2.5ML	Column: Chiralpak® AD-3 150x4.6mm I.D., 3 μ m Mobile phase: ethanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.5mL/ min Wavelength: 220nm
OD-H_3_5_40_2.35ML	Column: Chiralcel® OD-H 250x4.6mm I.D., 5 μ m Mobile phase: methanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.35m L/min Wavelength: 220nm
OD-H_5_5_40_2.35ML	Column: Chiralcel® OD-H 250x4.6mm I.D., 5 μ m Mobile phase: ethanol (0.05% DEA) in CO ₂ from 5% to 40% Flow rate: 2.35mL /min Wavelength: 220nm

55

[0088] The invention is illustrated by way of the following examples, in which the following abbreviations may be employed:

Abbreviation	Meaning
ACN, MeCN, CH ₃ CN	acetonitrile

EP 2 825 541 B1

(continued)

Abbreviation	Meaning
Aq	aqueous
Boc	<i>tert</i> -butoxy carbonyl or <i>t</i> -butoxy carbonyl
brine	saturated aqueous NaCl
Cbz	benzyloxy carbonyl
CeCl ₃	ceric chloride
Cs ₂ CO ₃	cesium carbonate
CuI	cuprous iodide
DCM or CH ₂ Cl ₂	methylene chloride
DIEA	diisopropyl ethyl amine
DMF	dimethyl formamide
DMS/Me ₂ S	dimethyl sulfide
DMSO	dimethyl sulfoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Etl	ethyl iodide
Et	ethyl
Et ₂ O	ethyl ether
Et ₃ SiH	triethylsilane
Et ₃ N	triethylamine
EtOAc , EA, AcOEt	ethyl acetate
EtOH	ethanol
FeCl ₃	ferric chloride
h, hr	hour(s)
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate
HBTU	O-Benzotriazole-1-yl-N,N,N',N'-tetramethyluronium-hexafluorophosphate
HCl	hydrochloric acid
H ₂ O	water
H ₂ O ₂	hydrogen peroxide
HPLC	high performance liquid chromatography
i-BuOCOCI	iso-butoxycarbonyl chloride
ICI	iodochloride
K ₂ CO ₃	potassium carbonate
K ₃ PO ₄	tripotassium phosphate
LC-MS	liquid chromatography-mass spectrometry
LDA	lithium diisopropylamide
LiCl	lithium chloride
LiOH	lithium hydroxide
MCPBA, m-CPBA	meta-chloroperoxybenzoic acid
MeOH	methanol

EP 2 825 541 B1

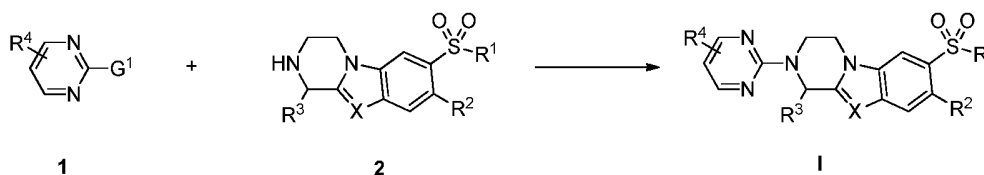
(continued)

Abbreviation	Meaning
MeI	methyl iodide
Me	methyl
mg	milligram
Mg ₂ SO ₄	magnesium sulfate (anhydrous)
min	minute(s)
mL	milliliters
mmol	millimoles
mp, m.p.	melting point
MS	mass spectrometry
MW	microwave
NaBH ₄	sodium borohydride
NaBH ₃ CN	sodium cyanoborohydride
NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
NaOH	sodium hydroxide
NaOMe	sodium methoxide
Na ₂ S ₂ O ₃	sodium thiosulfate
Na ₂ S ₂ O ₅	sodium dithionate
Na ₂ SO ₄	sodium sulfate
NH ₄ OH	ammonium hydroxide
(NH ₄) ₂ CO ₃	ammonium carbonate
NH ₄ Cl	ammonium chloride
Na ₂ CO ₃	sodium carbonate
NaHCO ₃	sodium bicarbonate
NaH	sodium hydride
<i>n</i> -BuLi	<i>n</i> -butyllithium
NMM	<i>N</i> -methyl-morpholine
NMP	<i>N</i> -methyl-pyrrolidin-2-one
OTf	trifluoromethanesulfonate
OTs	tosylate
PdCl ₂ dppf	[1,1-bis(diphenylphosphino)ferrocene] dichloropalladium(ii)
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
PE	petroleum ether
rt	room temperature
sat.	saturated
SFC	supercritical fluid chromatography
<i>t</i> -BuOK	potassium tert butoxide
<i>t</i> -BuLi	tert butyl lithium

(continued)

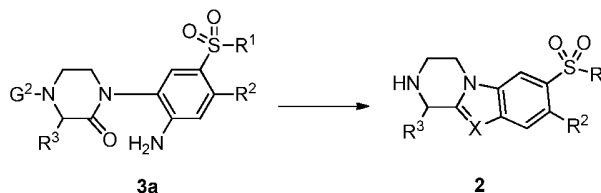
Abbreviation	Meaning
<i>t</i> -BuOOH	tert butyl peroxide
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Ti(OEt) ₄	titanium tetra ethoxide
Zn	zinc
Zn(CN) ₂	zinc cyanide

[0089] In the first process, a compound of Formula I can be prepared by S_NAr or palladium catalyzed reactions of reagents of **1**, where G¹ is Cl, Br, I, OTf or OTs, with intermediates of Formula **2**. Reagents **1** are either commercially available or can be prepared readily from commercially available precursors based on literature precedents.

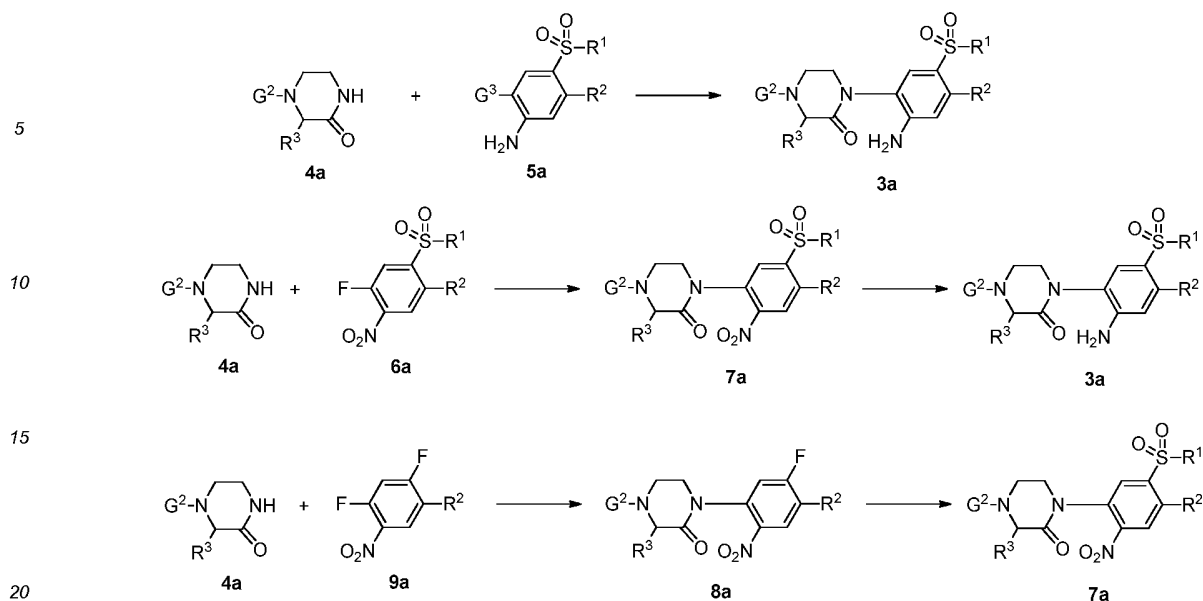


[0090] Intermediates **2** can be prepared by one of the several different methods depicted below.

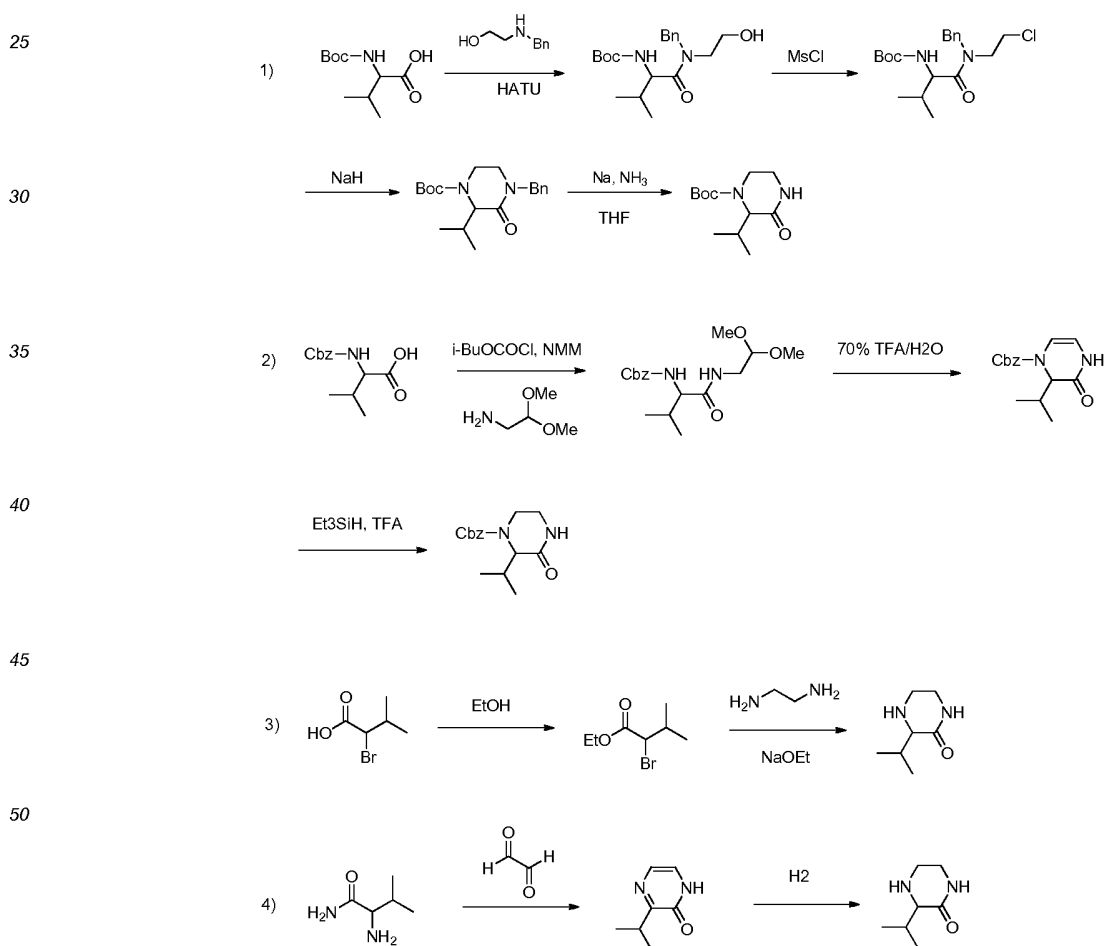
[0091] When X = N, intermediates of Formula **2** can be prepared by cyclization of intermediates of Formula **3a** followed by removal of G² when G² is not hydrogen. G² is an amine protecting group, such as Boc, Cbz and trifluoroacetamide, etc.



[0092] Intermediates of Formula **3a** can be prepared by one of the two methods: 1) copper mediated coupling of piperazinone **4a** and aniline **5a**, where G³ is Br, I, Cl or OTf; 2) S_NAr reaction between **4a** and fluorinated nitrobenzene **6a** to give intermediate of Formula **7a** followed by reduction of the nitro group. The intermediate **7a** can also be prepared from an intermediate of Formula **8a** by displacement of fluorine with either sodium alkanesulfinate (R¹SO₂Na) or sodium alkylsulfide (R¹SNa) followed by oxidation of the resulting thioether. The intermediate **8a** in turn can be prepared from piperazinone **4a** and difluoro nitrobenzene **9a**, which are either commercially available or can be readily prepared from commercial precursors based on literature procedures, well known to those of ordinary skill in the art.

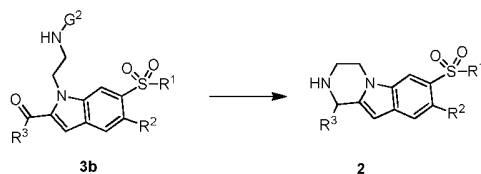


[0093] For example, when R^3 = isopropyl, piperazinone **4a** can be prepared by one of the methods presented below.



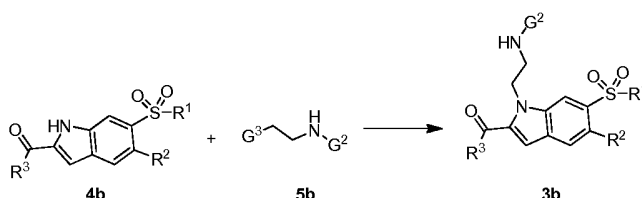
[0094] When X = CH, intermediates of Formula **2** can be prepared from intermediates of Formula **3b** by deprotection of G^2 followed by reductive amination. G^2 are amine protecting groups, such as Boc, Cbz and trifluoroacetamide etc.

5

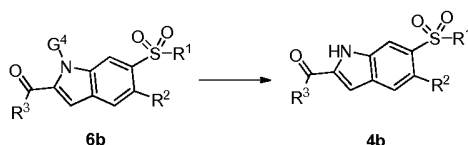


[0095] Intermediates of Formula **3b** can be prepared by N-alkylation of indole **4b** with commercially available alkyl halide **5b**, where G^3 is Br or I. Intermediates of Formula **4b** can be prepared by removal of G^4 from intermediates of Formula **6b**, where G^4 is methanesulfonate or phenylsulfonate.

15



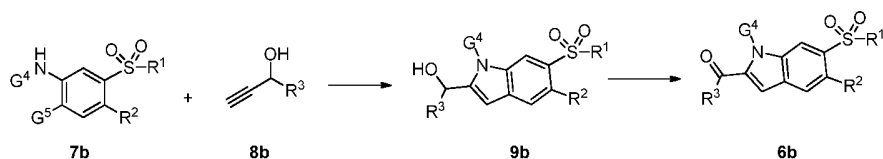
20



25

[0096] Intermediates of Formula **6b** can be prepared by sequential Sonogashira coupling reaction between aryl halides **7b** (where G^5 is Br or I) and propargyl alcohols **8b**, followed by cyclization, to give intermediates of Formula **9b**, followed by oxidation of the alcohol.

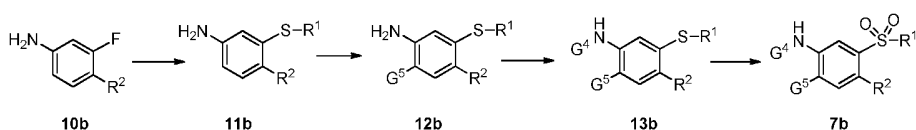
30



35

[0097] Intermediates of Formula **7b** can be prepared from commercially available aniline **10b** via the following transformations: 1) Displacement of fluorine with sodium alkyl sulfide R^1SNa (yielding **11b**); 2) Halogenation (yielding **12b**); 3) Protection of aniline (yielding **13b**); 4) Oxidation of sulfide (yielding **7b**).

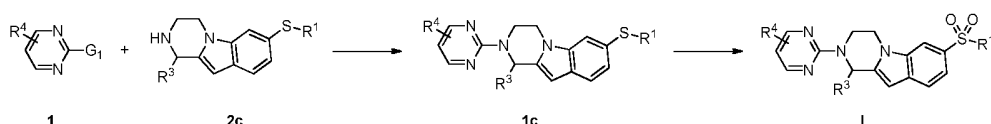
40



45

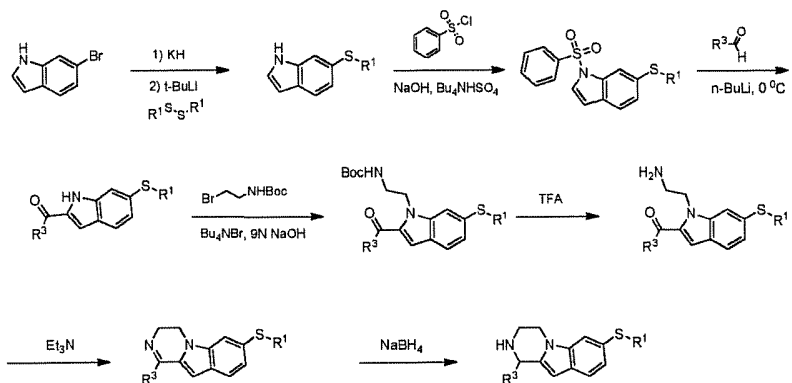
[0098] In the second process, a compound of Formula I, where R^1 = alkyl, R^2 = H and X = CH, can be prepared by oxidation of the thioether group in intermediates of Formula **1c**. Intermediate **1c** in turn can be prepared from coupling of reagents **1** and intermediates of Formula **2c** via S_NAr or palladium catalyzed reactions.

50



55

[0099] Intermediates **2c** can be prepared according to following scheme.

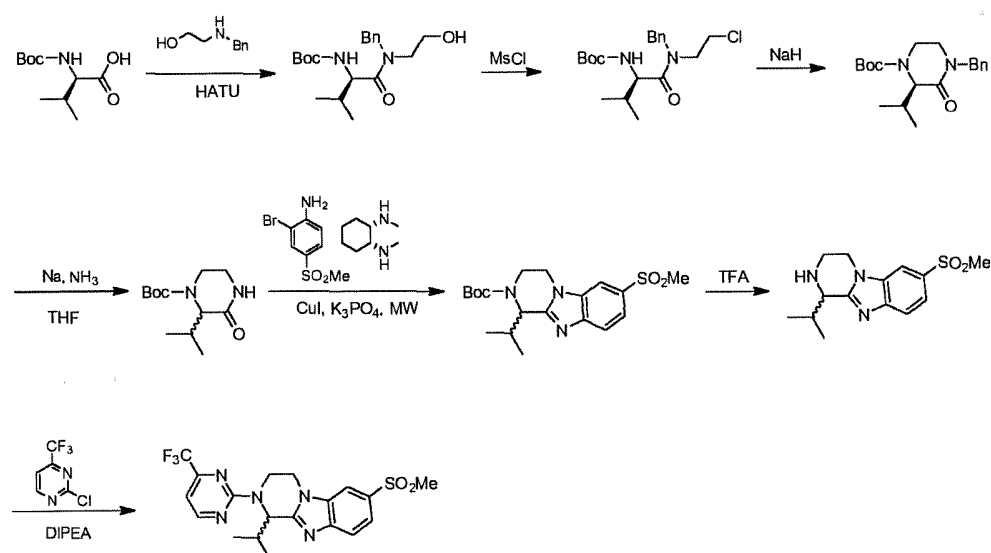


[0100] The invention will be further described by reference to the following detailed examples, which are given for illustration of the invention, and are not intended to be limiting thereof.

Example 1

1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine

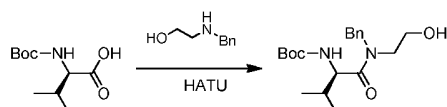
[0101]



Racemization occurred during the course of synthesis

Step 1:

[0102]



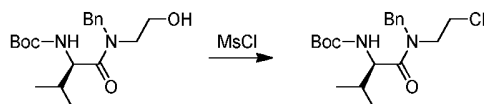
[0103] To a solution of (R)-2-((tert-butoxycarbonyl)amino)-3-methylbutanoic acid (2.0 g, 9.20 mmol) in CH_2Cl_2 (40 mL) were added 2-(benzylamino)ethanol (1.3 g, 8.80 mmol), HATU (5.30 g, 13.8 mmol) and Et_3N (2.80 g, 27.6 mmol) under N_2 . The mixture was stirred at rt overnight. The mixture was added water (20 mL) and extracted with EtOAc (3 \times 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered, con-

EP 2 825 541 B1

centrated and then purified by column chromatography on silica gel to afford (R)-tert-butyl (1-(benzyl(2-hydroxyethyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (2.80 g, 88% yield) as a white solid. **LC-MS** m/z 351.2 [M+H]⁺.

Step 2:

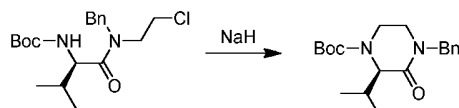
[0104]



[0105] To a solution of (R)-tert-butyl (1-(benzyl(2-hydroxyethyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (2.80 g, 8.0 mmol) in CH₂Cl₂ (20 mL) was added Et₃N (1.60 g, 16 mmol) and MsCl (1.40 g, 12.0 mmol) dropwise at -10 °C under N₂. The mixture was stirred at rt overnight. The mixture was quenched with water (20 mL) and extracted with CH₂Cl₂ (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na₂SO₄, filtered, concentrated to afford (R)-tert-butyl (1-(benzyl(2-chloroethyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (3.0 g, 100% yield) as a yellow solid, which was used for the next step without further purification. **LC-MS** m/z 369.2 [M+H]⁺. **¹H NMR** (CDCl₃ 400MHz): δ 7.37-7.28 (m, 3H), 7.22-7.20 (m, 2H), 5.27-5.18 (m, 1H), 4.93-4.86 (m, 1H), 4.64-4.39 (m, 2H), 3.85-3.66 (m, 2H), 3.61-3.39 (m, 2H), 2.03-1.97 (m, 1H), 1.45 (s, 9H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H).

Step 3:

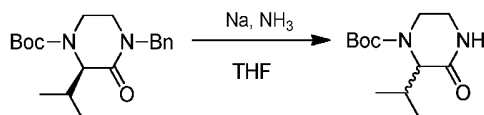
[0106]



[0107] To a solution of (R)-tert-butyl (1-(benzyl(2-chloroethyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (2.0 g, 5.40 mmol) in DMF (30 mL) was added NaH (1.0 g, 27.0 mmol, 60 % in mineral oil) at 0 °C under N₂. The mixture was stirred at rt for 2 h. The mixture was quenched with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na₂SO₄, filtered, concentrated and purified by column chromatography to afford (R)-tert-butyl 4-benzyl-2-isopropyl-3-oxopiperazine-1-carboxylate (1.13 g, 63% yield) as a white solid. **LC-MS** m/z 277.1 [M-56+H]⁺. **¹H NMR** (CDCl₃ 400MHz): δ 7.38-7.29 (m, 3H), 7.29-7.22 (m, 2H), 5.02-4.86 (m, 1H), 4.49-4.39 (m, 1H), 4.31-4.06 (m, 2H), 3.41-3.18 (m, 3H), 2.42-2.31 (m, 1H), 1.46 (s, 9H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H).

Step 4:

[0108]

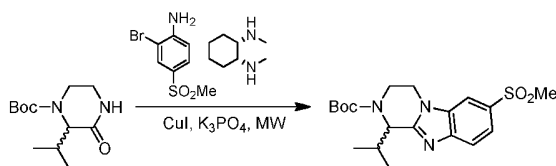


[0109] To a three-necked bottle containing THF (10 mL) was bubbled with NH₃ (gas) at -78 °C for 5 mins. Then Na (300 mg, 13.0 mmol) was added to the mixture slowly at -78 °C. After stirring for 30 min, (R)-tert-butyl 4-benzyl-2-isopropyl-3-oxopiperazine-1-carboxylate (700 mg, 2.11 mmol) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 30 min. The mixture was quenched with sat. aq. NH₄Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, filtered, concentrated and purified by preparative TLC with petroleum ether / EtOAc 1/1 to afford tert-butyl 2-isopropyl-3-oxopiperazine-1-carboxylate (300 mg, 59% yield) as a white solid. The product was found to be a racemic mixture. The cause of racemization was not investigated. **LC-MS** m/z 187.1 [M-56+H]⁺, 265.1 [M+Na]⁺. **¹H NMR** (CDCl₃ 400MHz): δ 6.29 (s, 1H), 4.55-3.99 (m, 2H), 3.51-3.36 (m, 1H), 3.32-3.12 (m, 2H), 2.34-2.29 (m, 1H), 1.46 (s, 9H), 1.09 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 7.2 Hz, 3H).

Step 5:

[0110]

5



10

[0111] To a solution of tert-butyl 2-isopropyl-3-oxopiperazine-1-carboxylate (200 mg, 0.83 mmol) in NMP (3 mL) were added 2-bromo-4-(methylsulfonyl)aniline (207 mg, 0.83 mmol), (1R,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (12.0 mg, 0.08 mmol), $K_3PO_4 \cdot 3H_2O$ (660 mg, 2.48 mmol) and CuI (16 mg, 0.08 mmol). The mixture was stirred at 150 °C for 1 h in a microwave oven. The mixture was diluted with water (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated and purified by preparative TLC with CH_2Cl_2 / MeOH 35/1 to afford tert-butyl 1-isopropyl-7-(methylsulfonyl)-3,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrazine-2(1H)-carboxylate (110 mg, 34% yield) as a white solid. **LC-MS** m/z 394.1 $[M+H]^+$. **1H NMR** ($CDCl_3$ 400MHz): δ 7.94 (s, 1H), 7.83-7.76 (m, 2H), 5.35-5.17 (m, 1H), 4.73-4.42 (m, 1H), 4.22-4.12 (m, 1H), 4.11-3.99 (m, 1H), 3.53-3.37 (m, 1H), 3.03 (s, 3H), 2.38-2.27 (m, 1H), 1.42 (s, 9H), 1.19 (d, $J = 6.8$ Hz, 3H), 0.97 (d, $J = 6.8$ Hz, 3H).

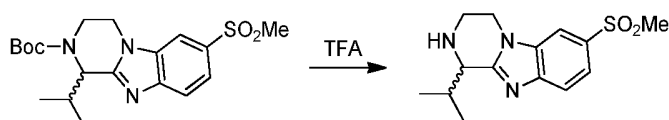
15

20

Step 6:

[0112]

25



30

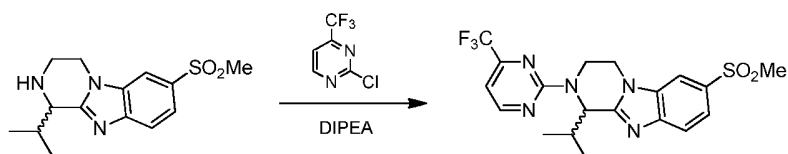
[0113] To a solution of tert-butyl 1-isopropyl-7-(methylsulfonyl)-3,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrazine-2(1H)-carboxylate (20 mg, 0.05 mmol) in CH_2Cl_2 (1 mL) was added TFA (0.3 mL) under N_2 . The mixture was stirred at rt for 1 h. The mixture was concentrated to afford 1-isopropyl-7-(methylsulfonyl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine (20 mg, TFA salt, 100% yield) as a yellow solid, which was used for the next step without further purification. **LC-MS** m/z 352.1 $[M+H]^+$.

35

Step 7:

[0114]

40



45

[0115] To a solution of 1-isopropyl-7-(methylsulfonyl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine (15 mg, 0.05 mmol) in DMSO (3 mL) was added 2-chloro-4-(trifluoromethyl)pyrimidine (19 mg, 0.10 mmol) and DIEA (20 mg, 0.15 mmol) under N_2 . The mixture was stirred at 100 °C for 2 h. Water (10 mL) was added and the mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 , filtered, concentrated and then purified by preparative TLC to afford 1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine (5.10 mg, 23% yield) as a white solid. **LC-MS** m/z 440.2 (MH^+). **1H NMR** ($CDCl_3$ 400MHz): δ 8.58 (d, $J = 4.8$ Hz, 1H), 8.01 (d, $J = 0.8$ Hz, 1H), 7.90-7.81 (m, 2H), 6.89 (d, $J = 4.8$ Hz, 1H), 6.12 (d, $J = 8.0$ Hz, 1H), 5.39 (dd, $J = 4.0$ and 14.0 Hz, 1H), 4.34-4.30 (m, 1H), 4.23-4.16 (m, 1H), 3.83-3.75 (m, 1H), 3.09 (s, 3H), 2.55-2.49 (m, 1H), 1.33 (d, $J = 6.8$ Hz, 3H), 1.09 (d, $J = 6.8$ Hz, 3H).

50

55

Example 2

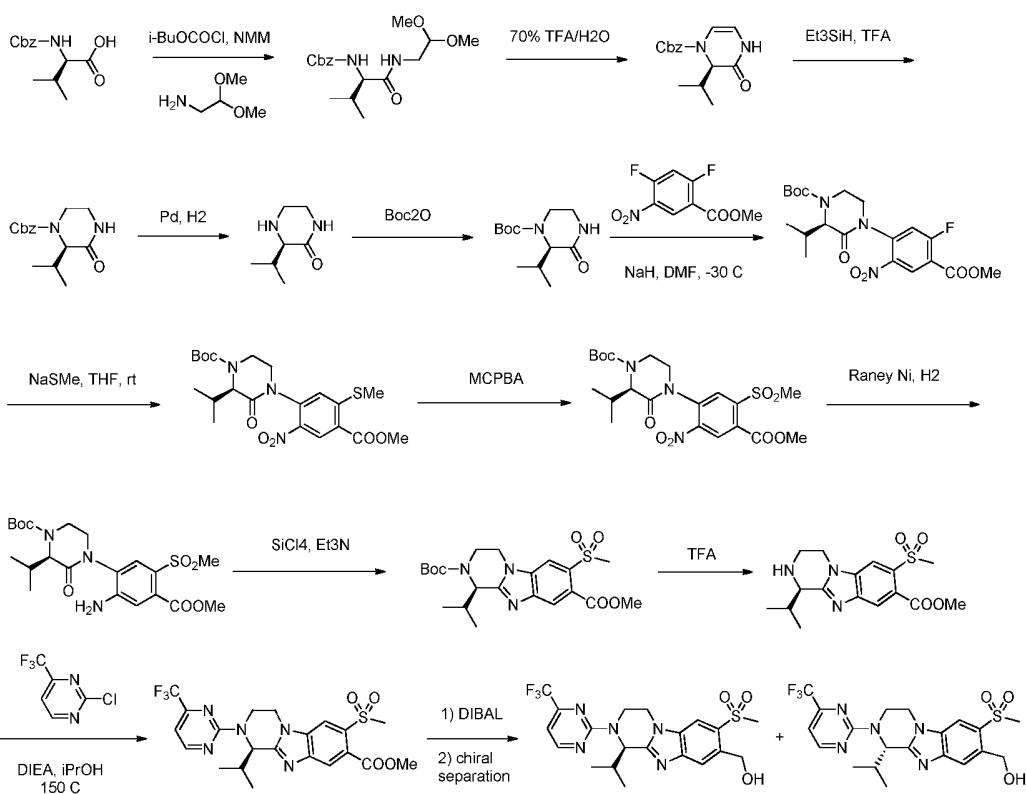
(R)-(1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-8-yl)methanol and

5

(S)-(1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-8-yl)methanol

[0116]

10



15

20

25

30

35

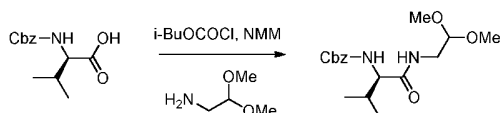
Racemization occurred during the course of synthesis

40

Step 1:

[0117]

45



50

[0118] A solution of Cbz-D-Valine (500 g, 1.99 mol) and N-methylmorpholine (201.8 g, 1.99 mol) in anhydrous THF (8 L) was cooled to -15°C and *i*-butyl chloroformate (299 g, 2.19 mol) was added dropwise under stirring. After 30 min, a solution of 1-amino-2,2-dimethoxyethane (209.5 g, 1.99 mol) in THF (1 L) was added slowly and the temperature was maintained at -15°C for 2 h. The reaction mixture was washed with brine (2 L) and the organic phase was concentrated to remove the THF. The residue was diluted with EtOAc (4 L), washed with 1N aq HCl (2 X 2 L), sat. aq. NaHCO_3 (2 L) and sat. aq. Na_2CO_3 (2 L) and brine (1.5 L). After drying over Na_2SO_4 , the organic solvent was removed under reduce pressure to afford (R)-benzyl (1-((2,2-dimethoxyethyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate as a white solid (670 g, yield 99.5%), which was used for next step without further purification. **LC-MS** m/z 360.9 $[\text{M}+\text{Na}]^+$.

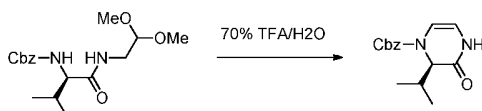
55

$^1\text{H NMR}$ (CD_3OD 300MHz): δ 7.35-7.30 (m, 5H), 5.08 (s, 2H), 4.45-4.35 (m, 1H), 3.95-3.85 (m, 1H), 3.34-3.25 (m, 8H),

2.10-1.90 (m, 1H), 0.94-0.91 (m, 6H).

Step 2:

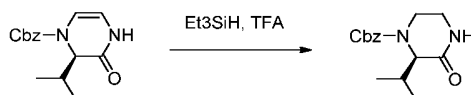
5 [0119]



10 [0120] (R)-benzyl 1-((2,2-dimethoxyethyl)amino)-3-methyl-1-oxobutan-2-ylcarbamate (335 g, 0.99 mol) was added in portions to a cooled TFA-H₂O (temperature < 5 °C, V_{TFA}/V_{H₂O}=7 / 3, 2 L), and the solution was stirred at rt for 12 h. The solution was added slowly into stirring cooled sat. aq. Na₂CO₃ (2.5 L) to keep the pH > 8. The mixture was extracted with EtOAc (5 X 2 L). The combined organic layers were washed with brine (2 L), dried over anhydrous Na₂SO₄, filtered and evaporated in *vacuo* to give (R)-benzyl 2-isopropyl-3-oxo-3,4-dihydropyrazine-1(2H)-carboxylate as a white solid (259 g, 95.4%), which was used for next step without further purification. **LC-MS** m/z 274.9 [M+H]⁺. **¹H NMR** (CD₃OD 300MHz): δ 7.36-7.34 (m, 5H), 6.33-6.30 (m, 1H), 5.79-5.68 (m, 1H), 5.26-5.13 (m, 2H), 4.38-4.29 (m, 1H), 2.01-1.96 (m, 1H), 1.00-0.84 (m, 6H).

Step 3:

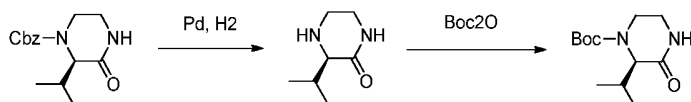
25 [0121]



30 [0122] To a stirring solution of (R)-benzyl 2-isopropyl-3-oxo-3,4-dihydropyrazine-1(2H)-carboxylate (400 g, 1.46 mol) in DCE (2 L) was added Et₃SiH (424 g, 3.65 mol) and TFA (665 g, 5.8 mol) at rt. The reaction was stirred under reflux for 36 h. After cooling to rt, the solution was concentrated to remove the solvent. The residue was diluted with EtOAc (2 L), and added slowly into stirring cooled sat. aq. NaHCO₃ (2 L) to make sure that the pH > 8. The mixture was extracted with EtOAc (2 X 2.5 L). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give (R)-benzyl 2-isopropyl-3-oxopiperazine-1-carboxylate (402 g, yield 99.75%), which was used for next step without further purification. **LC-MS** m/z 276.9 [M+H]⁺. **¹H NMR** (DMSO-*d*₆ 400MHz): δ 7.93 (s, 1H), 7.39-7.31 (m, 5H), 5.09 (s, 2H), 4.06-4.01 (m, 1H), 3.99-3.92 (m, 1H), 3.23-3.14 (m, 3H), 2.20-2.12 (m, 1H), 0.96-0.94 (m, 3H), 0.85 (d, *J* = 6.0 Hz, 3H).

Step 4:

45 [0123]



50 [0124] To a 1 L round-bottom flask containing (R)-benzyl 2-isopropyl-3-oxopiperazine-1-carboxylate (50 g, 0.181 mol) in MeOH (800 mL) was added Pd/C (dry, w/w 15%, 5 g). The mixture was stirred at rt under H₂ (1 atm, 1,013 bar) overnight. When TLC and LC-MS showed that the starting material was consumed, (Boc)₂O (76.74 g, 0.352 mol) was added to the reaction mixture, and the mixture was stirred at rt overnight until the intermediate (R)-3-isopropylpiperazine-2-one was consumed. The mixture was filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluting with petroleum: EtOAc = 3:1) to give (R)-tert-butyl 2-isopropyl-3-oxopiperazine-1-carboxylate as a white solid (26 g, yield 61%).

55 [0125] For (R)-3-isopropyl-piperazin-2-one:

EP 2 825 541 B1

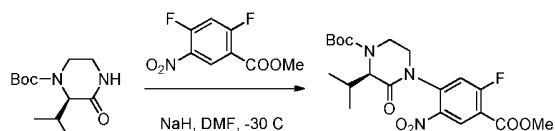
LC-MS m/z 143.2 $[M+H]^+$. **¹H NMR** (HCl salt, CD₃OD 400MHz): δ 3.95 (d, J = 3.6 Hz, 1H), 3.65-3.39 (m, 4H), 2.63-2.54 (m, 1H), 1.15 (d, J = 6.8 Hz, 3H), 1.09 (d, J = 7.2 Hz, 3H).

[0126] For (R)-tert-butyl 2-isopropyl-3-oxopiperazine-1-carboxylate:

LC-MS m/z 186.9 $[M-56+H]^+$. **¹H NMR** (DMSO-*d*₆ 400MHz): δ 7.93 (s, 1H), 4.02-3.82 (m, 2H), 3.17-3.15 (m, 3H), 2.16 (s, 1H), 1.41 (s, 9H), 0.98 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H).

Step 5:

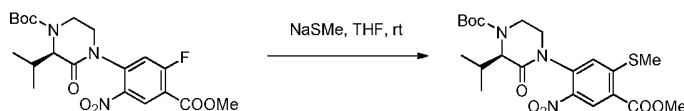
[0127]



[0128] Under N₂ atmosphere, NaH (8.8 g, 0.22 mol, 60 % in mineral oil, 1.1 eq.) was added in portions at - 10°C to a 1 L three-neck flask containing (R)-tert-butyl 2-isopropyl-3-oxopiperazine-1-carboxylate (26.66 g, 0.11 mol) in DMF (300 mL). The mixture was stirred at - 10°C for 30 min. Then the mixture was added dropwise to a 1 L three-neck flask containing methyl 2,4-difluoro-5-nitrobenzoate (26.3 g, 0.121 mol, 1.1 eq.) in DMF (200 mL) at - 20 °C over 10 min. After addition, the resulting mixture was stirred between - 20 °C and - 30 °C for another 10 min. The reaction was quenched with sat. aq. NH₄Cl (200 mL) and then water (800 mL). The aqueous layer was extracted with EtOAc (3 X 1 L). The combined organic layers were washed with water (3 X 1 L) and brine, and dried over anhydrous Na₂SO₄. The mixture was filtered and the filtrate was evaporated under vacuum. The residue was purified by column chromatography on silica gel eluting with petroleum ether : EtOAc 8:1~4:1 to give (R)-tert-butyl 4-(5-fluoro-4-(methoxycarbonyl)-2-nitrophenyl)-2-isopropyl-3-oxopiperazine-1-carboxylate (32 g, 66.3% yield) as a yellow solid. **LC-MS** MS (ESI) m/z 384.1 $[M - 56 + H]^+$, 462.1 $[M + Na]^+$. **¹H NMR** (CDCl₃ 300MHz): δ 8.63 (d, J = 6.9 Hz, 1H), 7.16 (d, J = 10.2 Hz, 1H), 4.61-4.30 (m, 2H), 3.97-3.89 (m, 4H), 3.62-3.48 (m, 2H), 2.40-2.34 (m, 1H), 1.49 (s, 9H), 1.08 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H).

Step 6:

[0129]



[0130] To a 1 L round-bottom flask containing (R)-tert-butyl 4-(5-fluoro-4-(methoxycarbonyl)-2-nitrophenyl)-2-isopropyl-3-oxopiperazine-1-carboxylate was added NaSMe (14.3 g, 0.204 mmol, 3 eq.). The mixture was stirred at rt for 1 h. Water (500 mL) was added and the mixture was concentrated under vacuum to remove THF. The aqueous layer was extracted with EtOAc (3 X 800 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to give (R)-tert-butyl 2-isopropyl-4-(4-(methoxycarbonyl)-5-(methylthio)-2-nitrophenyl)-3-oxopiperazine-1-carboxylate (31.9 g, 100% yield) as a yellow solid. The residue was used directly for the next step without further purification. **LC-MS** MS (ESI) m/z 412.1 $[M - 56 + H]^+$, 490.2 $[M + Na]^+$.

Step 7:

[0131]



[0132] To a 2 L round-bottom flask containing (R)-tert-butyl 2-isopropyl-4-(4-(methoxycarbonyl)-5-(methylthio)-2-ni-

EP 2 825 541 B1

trophenyl)-3-oxopiperazine-1-carboxylate (crude 91.7 g, 0.196 mol) in CH₂Cl₂ (1 L) was added *m*-CPBA (84.6 g, 0.49 mmol, 2.5 eq). The mixture was stirred at rt overnight. Sat. Na₂S₇O₃ solution was added slowly to quench the reaction. The mixture was extracted with CH₂Cl₂ (4 X 3 L). The combined organic layers were washed successively with Na₂S₇O₃ solution (500 mL), NaHCO₃ solution (500 mL) and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel eluting with dichloromethane to give (R)-tert-butyl 2-isopropyl-4-(4-(methoxycarbonyl)-5-(methylsulfonyl)-2-nitrophenyl)-3-oxopiperazine-1-carboxylate (83.7 g, 85.4% yield) as a yellow solid. **LC-MS** MS (ESI) m/z 444.0 [M - 56 + H]⁺, 522.1 [M + Na]⁺. **¹H NMR** (CDCl₃ 300MHz): δ 8.29 (s, 1H), 8.12 (s, 1H), 4.61-4.17 (m, 2H), 4.00-3.94 (m, 4H), 3.70-3.60 (m, 1H), 3.51-3.43 (m, 4H), 2.39-2.32 (m, 1H), 1.50 (s, 9H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H).

Step 8:

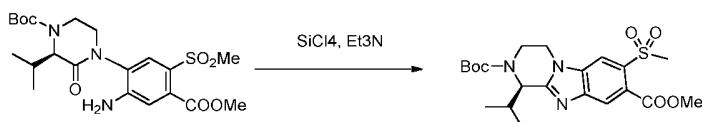
[0133]



[0134] To a 1 L round-bottom flask containing (R)-tert-butyl 2-isopropyl-4-(4-(methoxycarbonyl)-5-(methylsulfonyl)-2-nitrophenyl)-3-oxopiperazine-1-carboxylate (26.3 g, 0.0526 mol) in THF (200 mL) and methanol (200 mL) was added Raney Nickel (in H₂O, 4 g). The mixture was stirred under H₂ (30 psi, 2,07 bar) at rt overnight. The mixture was filtered and concentrated under vacuum to give (R)-tert-butyl 4-(2-amino-4-(methoxycarbonyl)-5-(methylsulfonyl)phenyl)-2-isopropyl-3-oxopiperazine-1-carboxylate (24.7 g, 100% yield) as a yellow solid. The residue was used directly for the next step without further purification. **LC-MS** MS (ESI) m/z 414.0 [M - 56 + H]⁺, 492.0 [M + Na]⁺. **¹H NMR** (CDCl₃ 300MHz): δ 7.77 (brs, 1H), 7.04 (s, 1H), 4.68-4.45 (m, 1H), 4.45-4.38 (m, 2H), 3.92 (s, 3H), 3.70-3.58 (m, 1H), 3.58-3.41 (m, 1H), 3.30 (s, 3H), 2.49-2.25 (m, 1H), 1.50 (s, 9H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H).

Step 9:

[0135]

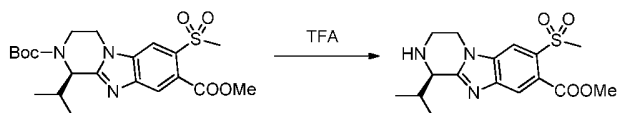


[0136] To a 1 L round-bottom flask containing (R)-tert-butyl 4-(2-amino-4-(methoxycarbonyl)-5-(methylsulfonyl)phenyl)-2-isopropyl-3-oxopiperazine-1-carboxylate (25 g, 0.0532 mol) in dichloromethane (500 mL) were added Et₃N (64.5 g, 0.638 mol, 12 eq.) and SiCl₄ (27.1 g, 0.160 mol, 3 eq.). The mixture was stirred at rt overnight. The mixture was added dropwise to aq. NaHCO₃ solution (54.1 g in 1 L of water, 0.644 mol, 12.1 eq.) at 0 °C slowly and adjusted to pH = 8. The mixture was filtered and the aqueous layer was extracted with dichloromethane (3 X 600 mL). The combined organic layers were washed with brine, and then dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated under vacuum to give the residue. The residue was purified by column chromatography on silica gel eluting with petroleum ether : EtOAc 2:1 to give (R)-2-tert-butyl 8-methyl 1-isopropyl-7-(methylsulfonyl)-3,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrazine-2,8(1H)-dicarboxylate (13.2 g, 55% yield) as a pale yellow solid. **Analytical chiral HPLC**: t_R = 9.03 min in 15 min chromatography (Method: OD-3_3_5_40_2.5ML). **LC-MS** MS (ESI) m/z 452.2 [M + H]⁺. **¹H NMR** (CD₃OD 400MHz): δ 8.31 (s, 1H), 8.01 (s, 1H), 5.30-5.18 (m, 1H), 4.70-4.52 (m, 1H), 4.47 (dd, *J* = 3.2 and 12.4 Hz, 1H), 4.18 (dt, *J* = 5.2 and 11.6 Hz, 1H), 3.98 (s, 3H), 3.70-3.52 (m, 1H), 3.44 (s, 3H), 2.50-2.38 (m, 1H), 1.53 (s, 9H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H).

Step 10:

[0137]

EP 2 825 541 B1



5

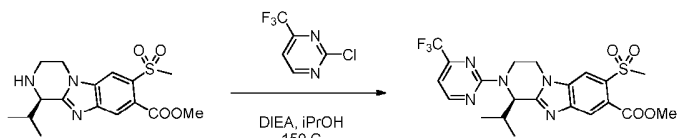
[0138] TFA (4 mL) was added dropwise to a solution of containing (R)-2-tert-butyl 8-methyl 1-isopropyl-7-(methylsulfonyl)-3,4-dihydrobenzo[4,5]imidazo[1,2-a]pyrazine-2,8(1H)-dicarboxylate (2.0 g, 4.4 mmol) in DCM (20 mL) at rt over 2 min. The mixture was stirred at rt for 3 h. TLC showed the starting material was consumed completely. The solvent was removed in vacuo at 30 °C, and then DCM (10 mL) was added. The mixture was neutralized with sat. aq. NaHCO₃ to pH=7. The mixture was extracted with DCM (3 X 20 mL) and the combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford (R)-methyl 1-isopropyl-7-(methylsulfonyl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine-8-carboxylate (1.5 g, 96.4% yield) as a white solid. **LC-MS** m/z 351.9 [M+H]⁺, 374.0 [M+Na]⁺. **¹H NMR** (CDCl₃ 300MHz): δ 8.15 (s, 1H), 8.07 (s, 1H), 4.26-4.05 (m, 3H), 3.97 (s, 3H), 3.63-3.50 (m, 1H), 3.44 (s, 3H), 3.32-3.16 (m, 1H), 2.85-2.66 (m, 1H), 1.16 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H).

10

15

Step 11:

[0139]



20

25

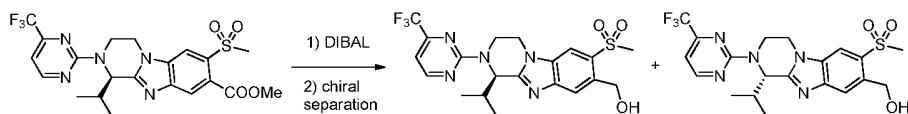
[0140] A mixture of (R)-methyl 1-isopropyl-7-(methylsulfonyl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine-8-carboxylate (0.9 g, 2.56 mmol), 2-chloro-4-(trifluoromethyl)pyrimidine (1.0 g, 5.1 mmol, 2 eq.) and DIEA (1.0 g, 7.7 mmol, 3 eq.) in *i*-PrOH (6 mL) was stirred in a microwave oven at 150 °C for 2 h. TLC showed the starting material was consumed completely (PE : EtOAc = 3 : 1). The solvent was removed in *vacuo* at 40 °C, and the residue was purified by column chromatography on silica gel eluting with PE / EtOAc = 6 / 1 to give (R)-methyl 1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine-8-carboxylate (1.0 g, 78% yield) as a white solid. **LC-MS** m/z 498.1 [M+H]⁺. **¹H NMR** (CDCl₃ 300MHz): δ 8.52 (d, J = 4.8 Hz, 1H), 8.13 (s, 1H), 8.06 (s, 1H), 6.83 (d, J = 4.8 Hz, 1H), 6.06 (d, J = 7.8 Hz, 1H), 5.39-5.28 (m, 1H), 4.33-4.24 (m, 1H), 4.20-4.12 (m, 1H), 3.93 (s, 3H), 3.77-3.65 (m, 1H), 3.39 (s, 3H), 2.52-2.38 (m, 1H), 1.25 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.6 Hz, 3H).

30

35

Step 12 :

[0141]



40

45

[0142] To a solution of (R)-methyl 1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine-8-carboxylate (1.3 g, 2.6 mmol) in DCM (15 mL) was added DIBAL-H (1M in toluene, 10.4 mL, 10.4 mmol, 4 eq.) at -78 °C. The mixture was stirred at -78 °C for 2 h. Sat. aq. NH₄Cl (25 mL) was added and the mixture was filtered. The aqueous layer was extracted with DCM (3 X 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel eluting with DCM / MeOH = 30 / 1 to give a partially racemized mixture (1.1 g, 91.6% yield) as a white solid. The racemized mixture was purified by SFC separation on a chiral column to give (R)-(1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-8-yl)methanol (**Isomer 1**) (0.65 g, 54.1% yield) as a white solid and (S)-(1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-8-yl)methanol (**Isomer 2**) (0.15 g, 12.5% yield) as a white solid.

50

55

Isomer 1: (R)-(1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imi-

EP 2 825 541 B1

dazo[1,2-a]pyrazin-8-yl)methanol:

Analytical chiral HPLC: $t_R = 8.768$ min in 15 min chromatography (Method: AD-H_5_5_40_2.35ML). **LC-MS** m/z 470.1 $[M+H]^+$. **1H NMR** ($CDCl_3$ 400MHz): δ 8.58 (d, $J = 4.8$ Hz, 1H), 8.13 (s, 1H), 7.89 (s, 1H), 6.89 (d, $J = 4.8$ Hz, 1H), 6.12 (d, $J = 8.0$ Hz, 1H), 5.40-5.36 (m, 1H), 5.06-5.03 (m, 2H), 4.35-4.31 (m, 1H), 4.21-4.16 (m, 1H), 3.82-3.76 (m, 1H), 3.23 (s, 3H), 3.09 (t, $J = 6.8$ Hz, 1H), 2.52-2.50 (m, 1H), 1.32 (d, $J = 6.8$ Hz, 3H), 1.08 (d, $J = 6.8$ Hz, 3H). **1H NMR** (CD_3OD 400 MHz): δ 8.69 (d, $J = 4.8$ Hz, 1H), 8.22 (s, 1H), 7.94 (s, 1H), 7.02 (d, $J = 4.8$ Hz, 1H), 6.05 (d, $J = 8.0$ Hz, 1H), 5.34 (d, $J = 10.0$ Hz, 1H), 5.10 (s, 2H), 4.50 (dd, $J_1 = 12.0$ Hz, $J_2 = 3.6$ Hz, 1H), 4.22 (td, $J_1 = 12.0$ Hz, $J_2 = 5.2$ Hz, 1H), 3.88 (dddd, $J_1 = 14.4$ Hz, $J_2 = 10.0$ Hz, $J_3 = 4.4$ Hz, 1H), 3.26 (s, 3H), 2.60 - 2.52 (m, 1H), 1.28 (d, $J = 6.8$ Hz, 3H), 1.06 (d, $J = 6.8$ Hz, 3H).

Isomer 1 was recrystallized as a crystalline solid by following procedure:

(R)-(1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-8-yl)methanol (470 mg) was dissolved into EtOAc (3.0 mL) followed by slow addition of hexanes (ca. 5 mL) until the solution turns cloudy. Several drops of EtOAc were added to cause the cloudiness to disappear. The solution was allowed to stand at rt until crystals formed. The crystalline solid was collected by filtration. m.p. 188-189 °C.

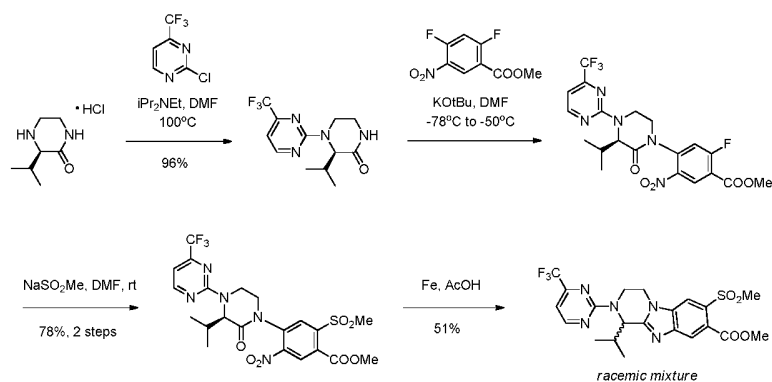
Isomer 2: (S)-(1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazin-8-yl)methanol:

Analytical chiral HPLC: $t_R = 7.780$ min in 15 min chromatography (Method: AD-H_5_5_40_2.35ML). **LC-MS** m/z 470.1 $[M+H]^+$. **1H NMR** ($CDCl_3$ 400MHz): δ 8.58 (d, $J = 5.2$ Hz, 1H), 8.12 (s, 1H), 7.88 (s, 1H), 6.89 (d, $J = 4.8$ Hz, 1H), 6.11 (d, $J = 8.0$ Hz, 1H), 5.40-5.35 (m, 1H), 5.04-5.00 (m, 2H), 4.34-4.31 (m, 1H), 4.21-4.16 (m, 1H), 3.82-3.75 (m, 1H), 3.22 (s, 3H), 2.52-2.50 (m, 1H), 1.31 (d, $J = 6.8$ Hz, 3H), 1.08 (d, $J = 6.8$ Hz, 3H).

[0143] Alternatively, a racemic mixture of methyl 1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine-8-carboxylate was prepared by the following method.

(rac)-methyl 1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine-8-carboxylate

[0144]

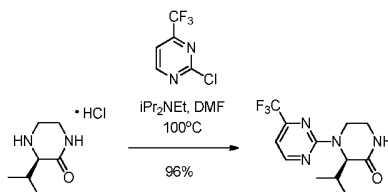


Step 1:

[0145]

EP 2 825 541 B1

5



10

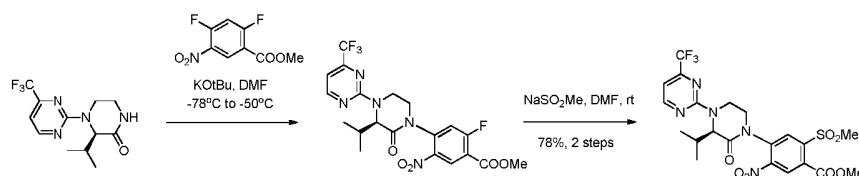
[0146] To a solution of (R)-3-isopropylpiperazin-2-one hydrochloride (2.61 g, 14.62 mmol) and iPr_2NEt (7.60 mL, 43.86 mmol) in DMF (20 mL) was added a solution of 2-chloro-4-(trifluoromethyl)pyrimidine (3.47 g, 19.00 mmol) in DMF (2 mL). The resulting solution was stirred at 100 °C under N_2 for 3 h at which point the reaction was deemed complete by LC-MS. Sat. aq. NH_4Cl (30 mL) was added to quench the reaction, followed by addition of EtOAc (30 mL). The EtOAc layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The EtOAc layers were combined, dried using Na_2SO_4 and evaporated to give nearly pure crude product. Purification on a silica cartridge using ISCO FCC eluting with 100% EtOAc gave 4.03 grams of (R)-3-isopropyl-4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-2-one (96%) as a slightly orange thick oil. LC-MS m/z 289.17 $[M + H]^+$. 1H NMR ($CDCl_3$, 400MHz): δ 8.52 (d, $J = 4.8$ Hz, 1H), 6.82 (d, $J = 4.4$ Hz, 1H), 6.56 (br, 1H), 5.20 (d, $J = 6.8$ Hz, 1H), 4.83-4.77 (m, 1H), 3.55-3.37 (m, 3H), 2.49-2.41 (m, 1H), 1.15 (d, $J = 6.8$ Hz, 3H), 1.04 (d, $J = 6.8$ Hz, 3H).

15

20 **Steps 2 and 3:**

[0147]

25



30

[0148] To a solution of (R)-3-isopropyl-4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-2-one (986 mg, 3.42 mmol) in DMF (5 mL) was added a 2 M solution of KOtBu in THF (2.14 mL, 4.28 mmol) dropwise at 0 °C. The reaction stirred for 1 h at 0 °C and was then cooled to -78 °C. In a separate flask, a solution of methyl 2,4-difluoro-5-nitrobenzoate (928 mg, 4.28 mmol) in DMF (15 mL) was cooled to -78 °C. To this solution was added a solution of the above anion via cannula at -78 °C over a 5 min period. The reaction was allowed to warm to -50 °C and stirred at this temperature for 2 h. Sat. aq. NH_4Cl (20 mL) was added to quench the reaction, followed by EtOAc (30 mL). The EtOAc layer was separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The EtOAc layers were combined, dried and evaporated to give crude (R)-methyl-2-fluoro-4-(3-isopropyl-2-oxo-4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)-5-nitrobenzoate which was taken on directly for the next step without further purification.

35

LC-MS m/z 486.20 $[M + H]^+$.

[0149] To a solution of the above crude (R)-methyl 2-fluoro-4-(3-isopropyl-2-oxo-4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)-5-nitrobenzoate in DMF (15 mL) was added $NaSO_2Me$ (1.05 g, 10.30 mmol) in one portion at rt. After stirring for 3 h, the reaction was deemed complete by LC-MS analysis. Water (100 mL) was added and the mixture stirred vigorously for 20 minutes before filtering off the solid material. To this solid material was added 20% EtOAc in Hexanes and the mixture stirred vigorously for 10 minutes. The EtOAc/Hexanes filtrate was collected and evaporated to give 1.45 g of (R)-methyl 4-(3-isopropyl-2-oxo-4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)-2-(methylsulfonyl)-5-nitrobenzoate as an off-white solid (78%, 2 steps). **LC-MS** m/z 546.27 $[M + H]^+$. 1H NMR ($CDCl_3$, 400MHz): δ 8.59 (d, $J = 4.4$ Hz, 1H), 8.32 (s, 1H), 8.14 (s, 1H), 6.92 (d, $J = 5.2$ Hz, 1H), 5.32 (d, $J = 6.8$ Hz, 1H), 5.04-5.00 (m, 1H), 4.12-4.02 (m, 1H), 4.03 (s, 3H), 3.88-3.80 (m, 2H), 3.44 (s, 3H), 2.55-2.50 (m, 1H), 1.15 (d, $J = 6.8$ Hz, 3H), 1.06 (d, $J = 6.8$ Hz, 3H).

40

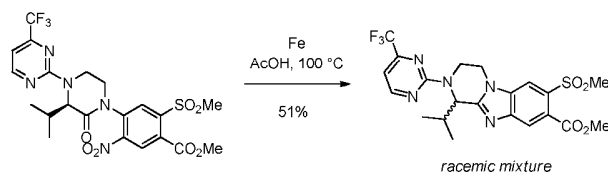
50

Step 4:

[0150]

55

5



10

To a solution of (R)-methyl-4-(3-isopropyl-2-oxo-4-(4-(trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)-2-(methylsulfonyl)-5-nitrobenzoate (1.45 g, 2.66 mmol) in glacial acetic acid (17 mL) was added iron powder (445 mg, 7.97 mmol). The mixture was heated to 100 °C. After 5 min, the suspended iron dissolved into solution. The mixture was stirred at 100 °C for 48 h, at which point the flask was cooled to rt and the contents were poured into ice. The mixture was extracted with EtOAc (2 x 75 mL), then the combined organic layers were washed with water (2 x 50 mL) and brine (50 mL). The solution was dried over MgSO₄, filtered through cotton, and concentrated *in vacuo*. The residue was purified on a silica cartridge (0% EtOAc in hexanes, then 50%) to yield 680 mg of methyl-1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyrazine-8-carboxylate as a racemic mixture (51%). **LC-MS:** m/z 498.32 (M + H)⁺. **¹H NMR** (CDCl₃, 400 MHz): δ 8.58 (d, *J* = 4.8 Hz, 1H), 8.20 (s, 1H), 8.12 (s, 1H), 6.90 (d, *J* = 4.8 Hz, 1H), 6.13 (d, *J* = 8.4 Hz, 1H), 5.39 (dd, *J* = 4.8 Hz, 14.4 Hz, 1H), 4.35 (ddd, *J* = 1.2 Hz, 4.4 Hz, 12.0 Hz, 1H), 4.21 (dt, *J* = 4.8 Hz, 12.0 Hz, 1H), 4.00 (s, 3H), 3.78 (ddd, *J* = 4.4 Hz, 11.6 Hz, 14.4 Hz, 1H), 3.45 (s, 3H), 2.48 (sept, *J* = 7.2 Hz, 1H), 1.32 (d, *J* = 6.4 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H).

20

Example 3

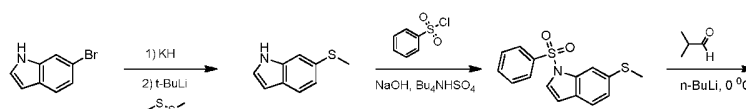
(R)-1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole and

25

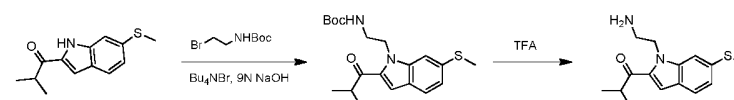
(S)-1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole

[0151]

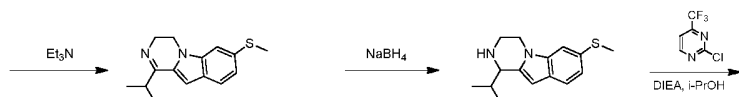
30



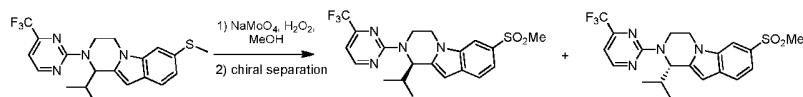
35



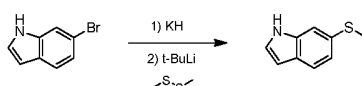
40



45

**Step 1:**

50

[0152]

55

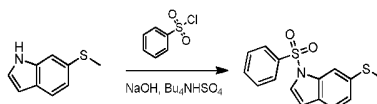
[0153] To a solution of 6-bromo-1H-indole (5 g, 25.50 mmol) in anhydrous THF (60 mL) at 0 °C was added KH (6.80 g, 51.00 mmol, 30% wt in mineral oil). After stirring for 30 min, the mixture was cooled to -78 °C and *t*-BuLi (39.23 mL, 51.0 mmol, 1.3 M) was added under nitrogen. After 30 min, 1,2-dimethyldisulfane (4.80 g, 51.0 mmol) was added to the

EP 2 825 541 B1

5 mixture. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and quenched with *sat.* aq NH_4Cl (30 mL) at $-78\text{ }^{\circ}\text{C}$ slowly (Caution: flame), adjusted pH = 7 with 1 N aqueous phosphoric acid and extracted with EtOAc (50 mL X 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, concentrated and purified by column chromatography on silica gel eluted with (petroleum ether / EtOAc 10:1) to give 6-(methylthio)-1H-indole (3.9 g, 93.67% yield) as a grey solid. **LC-MS** MS (ESI) m/z 164.1 $[\text{M} + \text{H}]^+$. **$^1\text{H NMR}$** (CDCl_3 400MHz): δ 8.14 (brs, 1H), 7.56 (d, $J = 8.0$ Hz, 1H), 7.37 (s, 1H), 7.18-7.11 (m, 1H), 6.56-6.51 (m, 1H), 2.52 (s, 3H).

Step 2:

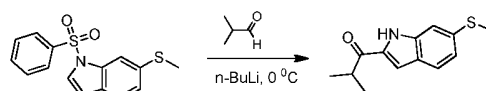
10 **[0154]**



20 **[0155]** To a solution of 6-(methylthio)-1H-indole (1 g, 6.13 mmol), NaOH (4.90 g, 122.6 mmol) and Bu_4NHSO_4 (207.8 mg, 0.613 mmol) in dichloromethane (20 mL) was added benzenesulfonyl chloride (1.29 g, 7.36 mmol). The reaction mixture was stirred at rt overnight. The mixture was quenched with water (30 mL) and extracted with CH_2Cl_2 (30 mL X 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, concentrated and purified by column chromatography on silica gel eluted with (petroleum ether / EtOAc 10:1) to afford 6-(methylthio)-1-(phenylsulfonyl)-1H-indole (1.1 g, 59.18% yield) as a white solid. **LC-MS** MS (ESI) m/z 304.0 $[\text{M} + \text{H}]^+$. **$^1\text{H NMR}$** (CDCl_3 400MHz): δ 7.93-7.75 (m, 3H), 7.58-7.41 (m, 5H), 7.17 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.6$ Hz, 1H), 6.63-6.60 (m, 1H), 2.53 (s, 3H).

Step 3:

25 **[0156]**

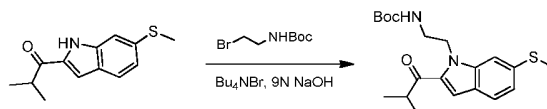


35 **[0157]** To a solution of 6-(methylthio)-1-(phenylsulfonyl)-1H-indole (890 mg, 2.93 mmol) in anhydrous THF (10 mL) at $0\text{ }^{\circ}\text{C}$ under nitrogen was added $n\text{-BuLi}$ (5.86 mL, 14.65 mmol, 2.5 M). After stirring for 30 min, isobutyraldehyde (1.05 g, 14.65 mmol) was added. The reaction mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 1 h and quenched with *sat.* aq NH_4Cl (10 mL) at $0\text{ }^{\circ}\text{C}$ and extracted with EtOAc (20 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, concentrated and purified by column chromatography on silica gel eluted with (petroleum ether / EtOAc 20:1) to give 2-methyl-1-(6-(methylthio)-1H-indol-2-yl)propan-1-one (440 mg, 64.28% yield) as a colorless oil.

40 **LC-MS** MS (ESI) m/z 234.1 $[\text{M} + \text{H}]^+$. **$^1\text{H NMR}$** (CDCl_3 400 MHz): δ 8.86 (brs, 1H), 7.52 (d, $J = 8.4$ Hz, 1H), 7.19 (s, 1H), 7.14-7.11 (m, 1H), 7.01 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.6$, 1H), 3.42-3.38 (m, 1H), 2.47 (s, 3H), 1.20 (d, $J = 6.8$ Hz, 6H).

Step 4:

45 **[0158]**



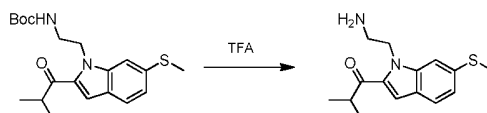
55 **[0159]** To a solution of 2-methyl-1-(6-(methylthio)-1H-indol-2-yl)propan-1-one (600 mg, 2.57 mmol) and Bu_4NBr (4.12 g, 12.85 mmol) in 9 N NaOH (10 mL, cooled) was added tert-butyl (2-bromoethyl)carbamate (2.87 g, 12.85 mmol). The reaction mixture was stirred at rt for 72 h. The mixture was diluted with water (20 mL) at $0\text{ }^{\circ}\text{C}$ and extracted with EtOAc (20 mL X 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, concentrated and purified by column chromatography on silica gel eluting with (petroleum ether / EtOAc 10:1) to afford tert-butyl (2-(2-isobutyryl-6-(methylthio)-1H-indol-1-yl)ethyl)carbamate (200 mg, 20.66% yield) as a colorless oil. **LC-MS** MS (ESI) m/z 321.1 $[\text{M} - 56 + \text{H}]^+$, 277.1 $[\text{M} - 100 + \text{H}]^+$. **$^1\text{H NMR}$** (CDCl_3 400 MHz): δ 7.57 (d, $J = 8.4$ Hz, 1H), 7.38 (s, 1H), 7.29 (s, 1H), 7.10

EP 2 825 541 B1

(d, $J = 8.4$ Hz, 1H), 4.80 (brs, 1H), 4.62 (t, $J = 6.4$ Hz, 2H), 3.58-3.42 (m, 3H), 2.58 (s, 3H), 1.38 (s, 9H), 1.24 (d, $J = 6.8$ Hz, 6H).

Step 5:

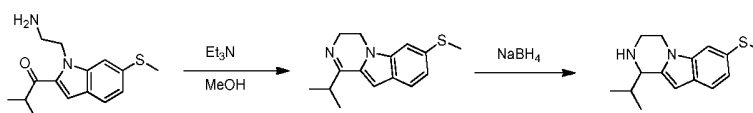
[0160]



[0161] To a solution of tert-butyl (2-(2-isobutyryl-6-(methylthio)-1H-indol-1-yl)ethyl)carbamate (200 mg, 0.53 mmol) in CH_2Cl_2 (9 mL) at 0°C was added TFA (1 mL). The reaction mixture was stirred at rt for 1 h. The mixture was concentrated ($T < 25^\circ\text{C}$), treated with water (5 mL), adjusted to pH=11 with sat. NaHCO_3 and extracted with EtOAc (20 mL X 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, concentrated to afford 1-(1-(2-aminoethyl)-6-(methylthio)-1H-indol-2-yl)-2-methylpropan-1-one (210 mg, 100% yield) as a colorless oil. **LC-MS** MS (ESI) m/z 258.8 $[\text{M}-18+\text{H}]^+$.

Step 6:

[0162]

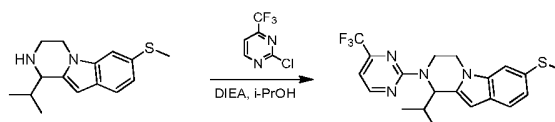


[0163] To a solution of 1-(1-(2-aminoethyl)-6-(methylthio)-1H-indol-2-yl)-2-methylpropan-1-one (200 mg, 0.724 mmol) in MeOH (5 mL) was added Et_3N (219.3 mg, 2.172 mmol). The reaction mixture was stirred at 60°C for 1 h. NaBH_4 (82.53 mg, 2.172 mmol) was added. The mixture was stirred at 60°C for 1 h. The mixture was concentrated, treated with water (10 mL) and extracted with EtOAc (20 mL X 3). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered, concentrated and purified by preparative TLC on silica gel eluted with (petroleum ether / EtOAc 1:1) to afford 1-isopropyl-7-(methylthio)-1,2,3,4-tetrahydropyrazino[1,2-a]indole (80 mg, 42.46% yield, store at 0°C) as a colorless oil.

LC-MS of 1-Isopropyl-7-methylsulfanyl-3,4-dihydro-pyrazino[1,2-a]indole MS (ESI) m/z 259.1 $[\text{M} + \text{H}]^+$. **LC-MS** of 1-isopropyl-7-(methylthio)-1,2,3,4-tetrahydropyrazino[1,2-a]indole MS (ESI) m/z 261.2 $[\text{M} + \text{H}]^+$. **$^1\text{H NMR}$** (CDCl_3 400 MHz): δ 7.41 (d, $J = 8.4$ Hz, 1H), 7.20 (s, 1H), 7.05 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.6$ Hz, 1H), 6.12 (s, 1H), 4.02-3.97 (m, 2H), 3.86-3.80 (m, 1H), 3.46-3.42 (m, 1H), 3.16-3.10 (m, 1H), 2.48 (s, 3H), 2.32-2.27 (m, 1H), 1.09 (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H).

Step 7:

[0164]

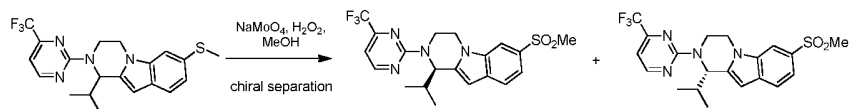


[0165] To a solution of 1-isopropyl-7-(methylthio)-1,2,3,4-tetrahydropyrazino[1,2-a]indole (50 mg, 0.19 mmol) in $i\text{PrOH}$ (2 mL) was added 2-chloro-4-(trifluoromethyl)pyrimidine (105 mg, 0.58 mmol) and DIEA (185 mg, 0.96 mmol). The mixture was stirred at 100°C for 4 h. The mixture was concentrated under *vacuum* and the residue was purified by preparative TLC to afford 1-isopropyl-7-(methylthio)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole (45 mg, 57.7% yield) as a yellow oil. **LC-MS** MS (ESI) m/z 407.1 $[\text{M} + \text{H}]^+$.

Step 8:

[0166]

5



10 **[0167]** To a solution of 1-isopropyl-7-(methylthio)-1,2,3,4-tetrahydropyrazino[1,2-a]indole (45 mg, 0.11 mmol) in MeOH (1 mL) was added NaMoO₄·2H₂O (61 mg, 0.33 mmol) and 30% H₂O₂ (67 mg, 0.55 mmol) at 0 °C. The mixture was stirred at rt for 2 h. Sat. Na₂S₂O₃ (5 mL) was added and the mixture was concentrated under *vacuum*. The aqueous layer was extracted with EtOAc (3 X 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under *vacuum*. The residue was purified by preparative TLC and SFC separation on a chiral column to afford **isomer 1** (20.10 mg, 46.6% yield) as a white solid and **isomer 2** (20.30 mg, 47.1% yield) as a white solid.

15 **Isomer 1: Analytical chiral HPLC:** $t_R = 6.64$ min in 15 min chromatography (Method: AD-H_5_5_40_2.35ML). **LC-MS** MS (ESI) m/z 439.0 [M + H]⁺. **¹H NMR** (CD₃OD 300MHz): δ 8.63 (d, $J = 4.8$ Hz, 1H), 7.98 (s, 1H), 7.69 (d, $J = 8.4$ Hz, 1H), 7.57 (dd, $J = 1.5$ and 8.4 Hz, 1H), 6.94 (d, $J = 4.8$ Hz, 1H), 6.50 (s, 1H), 5.88 (d, $J = 8.4$ Hz, 1H), 5.11-5.07 (m, 1H), 4.45-4.38 (m, 1H), 4.05 (dt, $J = 4.8$ and 11.4 Hz, 1H), 3.91-3.83 (m, 1H), 3.11 (s, 3H), 2.35-2.27 (m, 1H), 1.14 (d, $J = 6.6$ Hz, 3H), 1.01 (d, $J = 6.6$ Hz, 3H).

20 **Isomer 2: Analytical chiral HPLC:** $t_R = 7.37$ min in 15 min chromatography (Method: AD-H_5_5_40_2.35ML). **LC-MS** MS (ESI) m/z 439.0 [M + H]⁺, 461.0 [M + Na]⁺. **¹H NMR** (CD₃OD 300MHz): δ 8.63 (d, $J = 4.5$ Hz, 1H), 7.98 (s, 1H), 7.68 (d, $J = 8.4$ Hz, 1H), 7.57 (dd, $J = 1.5$ and 8.4 Hz, 1H), 6.94 (d, $J = 4.8$ Hz, 1H), 6.49 (s, 1H), 5.87 (d, $J = 8.1$ Hz, 1H), 5.10-5.06 (m, 1H), 4.44-4.37 (m, 1H), 4.03 (dt, $J = 4.8$ and 11.4 Hz, 1H), 3.90-3.80 (m, 1H), 3.11 (s, 3H), 2.34-2.26 (m, 1H), 1.14 (d, $J = 6.6$ Hz, 3H), 1.00 (d, $J = 6.6$ Hz, 3H).

Example 4

30

(R)-(1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-8-yl)methanol and

35

(S)-(1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-8-yl)methanol

[0168]

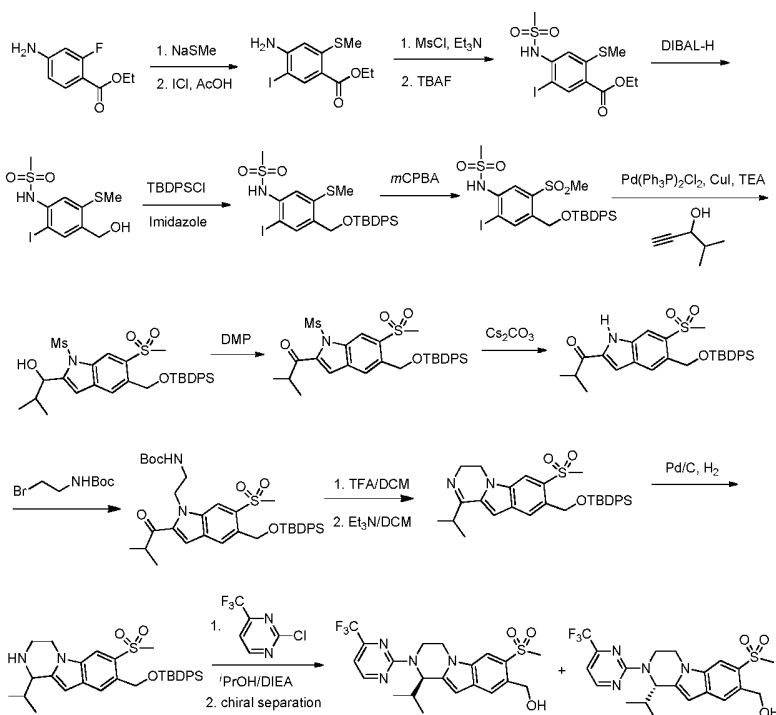
40

45

50

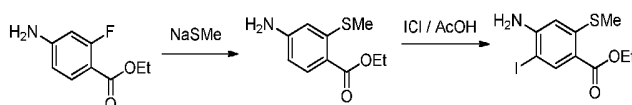
55

EP 2 825 541 B1



Step 1:

[0169]



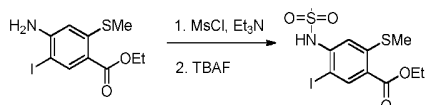
[0170] To a solution of ethyl 4-amino-2-fluorobenzoate (12 g, 65.5 mmol) in DMF (100 mL) was added NaSMe (9.17 g, 131 mmol) and the mixture was stirred at 60°C for 20 h. After cooling to rt the reaction was diluted with H₂O and extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to afford ethyl 4-amino-2-(methylthio)benzoate.

[0171] To a pre-heated, 60°C solution of ethyl 4-amino-2-(methylthio)benzoate (65 mmol) in acetic acid (150 mL) was added ICl/AcOH solution (1M, 72 mL, 72 mmol) dropwise during 40 min and the temperature was maintained at 60°C for 3 h. After cooling to rt the reaction was diluted with EtOAc (500 mL), washed with 5% Na₂S₂O₃ solution (3 x 100mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (0-20% EtOAc/Hexanes) afford ethyl 4-amino-5-iodo-2-(methylthio)benzoate (13.67 g, 53% yield).

For ethyl 4-amino-2-(methylthio)benzoate: **LC-MS** m/z 212 [M+H]⁺. For ethyl 4-amino-5-iodo-2-(methylthio)benzoate: **LC-MS** m/z 338 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 8.2 (s, 1H), 6.47 (s, 1H), 4.49 (br s, 2H), 4.31 (q, J = 7.2 Hz, 2H), 2.38 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H).

Step 2:

[0172]



[0173] To a solution of ethyl 4-amino-5-iodo-2-(methylthio)benzoate (13.6 g, 40 mmol) in DCM (100 mL) was added

EP 2 825 541 B1

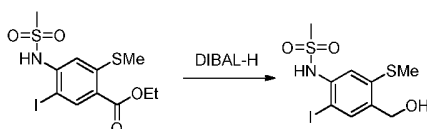
Et₃N (13.8 mL, 100 mmol), followed by MsCl (7.7 mL, 100 mmol) at 0°C. After addition the mixture was stirred at rt for 2 h. 1N HCl solution (50 mL) was added to the mixture and the aqueous phase was extracted with DCM (1 x 100mL). The organic solution was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give ethyl 5-iodo-4-(N-(methylsulfonyl)methylthio)benzoate.

5 The crude reaction mixture above was dissolved into 100 mL THF. To this solution was added TBAF solution in THF (1 M, 100 mL) and the mixture was stirred at rt for 2 h. H₂O was added to the mixture and the aqueous phase was extracted with EtOAc (3x 100 mL). The combined organic solution was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to afford ethyl 5-iodo-4-(methylthio)benzoate. It was used for next step without further purification. For ethyl 5-iodo-4-(N-(methylsulfonyl)methylthio)benzoate: **LC-MS** m/z 494 [M+H]⁺. For ethyl 5-iodo-4-(methylthio)benzoate: **LC-MS** m/z 415 [M+H]⁺.

Step 3:

[0174]

15



20

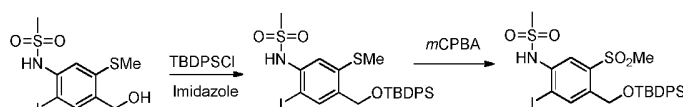
[0175] To a solution of ethyl 5-iodo-4-(methylthio)benzoate (crude, from step 2) in dry toluene (200 mL) at 0°C was added diisobutylaluminum hydride (1.0 M in toluene, 100 mL, 100 mmol) slowly. After addition, the mixture was stirred at 0°C for 3 h and quenched with methanol/H₂O (1/1). The reaction mixture was poured into a vigorously stirred solution of potassium sodium tartrate (1M, 300 mL) and stirred vigorously for 2 h, after which time it settled to two clear phases. The organic layer was separated, and the aq layer was extracted with EtOAc (3 x 200 mL). The combined organic solution was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (0-40% EtOAc/Hexanes) afford N-(4-(hydroxymethyl)-2-iodo-5-(methylthio)phenyl)methanesulfonamide (11.9 g, 80% yield for two steps). **LC-MS** m/z 356 [M+H]⁺. **¹H NMR** (400 MHz, CDCl₃): δ 7.82 (s, 1H), 7.49 (s, 1H), 4.67 (s, 2H), 2.99 (s, 3H), 2.50 (s, 3H).

30

Step 4:

[0176]

35



40

[0177] To a stirred solution of N-(4-(hydroxymethyl)-2-iodo-5-(methylthio)phenyl)methanesulfonamide (6.4 g, 17.2 mmol) and imidazole (1.76 g, 25.8 mmol) in CH₂Cl₂ (100 mL) and DMF (50 mL) at 0 °C was added tert-butyldiphenylsilyl chloride (5.8 mL, 22.4 mmol). The mixture was allowed to stir at rt overnight. The mixture was diluted with CH₂Cl₂ (100 mL), washed with 1N HCl solution, sat. aq. NaHCO₃ and brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to afford N-(4-((tert-butyldiphenylsilyloxy)methyl)-2-iodo-5-(methylthio)phenyl)methanesulfonamide. It was used for next step without further purification.

45

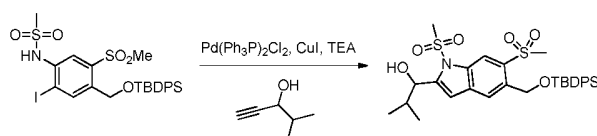
[0178] A suspension of crude N-(4-((tert-butyldiphenylsilyloxy)methyl)-2-iodo-5-(methylthio)phenyl)methanesulfonamide and mCPBA (8.9 g, 51.6 mmol) in CH₂Cl₂ (100 mL) was stirred for 2 h at rt. Sat. aq. NaHCO₃ (50 mL) and Na₂S₂O₃ (50 mL) were added and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel eluting with EtOAc/hexanes (3/7) to provide N-(4-((tert-butyldiphenylsilyloxy)methyl)-2-iodo-5-(methylsulfonyl)phenyl)methanesulfonamide (8.8 g, 80% yield for two steps). For N-(4-((tert-butyldiphenylsilyloxy)methyl)-2-iodo-5-(methylthio)phenyl)methanesulfonamide: **LC-MS** m/z 612 [M+H]⁺. For N-(4-((tert-butyldiphenylsilyloxy)methyl)-2-iodo-5-(methylsulfonyl)phenyl)methanesulfonamide: **LC-MS** m/z 644 [M+H]⁺. **¹H NMR** (400 MHz, CDCl₃): δ 8.25 (s, 1H), 8.08 (s, 1H), 7.67 - 7.65 (m, 4H), 7.46 - 7.37 (m, 6H), 6.77 (s, 1H), 5.05 (s, 2H), 3.11 (s, 3H), 2.83 (s, 3H), 1.12 (s, 9H).

55

Step 5:

[0179]

5



10

[0180] PdCl₂(PPh₃)₂ (277 mg, 0.38 mmol) and CuI (73 mg, 0.38 mmol) were added to a solution of N-(4-(((tert-butylidiphenylsilyloxy)methyl)-2-iodo-5-(methylsulfonyl)phenyl)methanesulfonamide (2.45 g, 3.8 mmol) in THF (20 mL) and Et₃N (10 mL). The mixture was purged with nitrogen for 10 min followed by addition of 4-methylpent-1-yn-3-ol (745 mg, 7.6 mmol) and stirred at 65°C for 8 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with 1N HCl (50 mL). The organic layer was separated, and the aq layer was extracted with EtOAc (3 x 50 mL). The combined organic solution was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel eluting with EtOAc/hexanes (3/7) to provide 1-(5-(((tert-butylidiphenylsilyloxy)methyl)-1,6-bis(methylsulfonyl)-1H-indol-2-yl)-2-methylpropan-1-ol (2.1 g, 90% yield). **LC-MS** m/z 614 [M+H]⁺. **¹H NMR** (400 MHz, CDCl₃): δ 8.68 (s, 1H), 7.90 (s, 1H), 7.71 - 7.67 (s, 4H), 7.46 - 7.35 (m, 6H), 6.77 (s, 1H), 5.21 (d, J = 3.2 Hz, 2H), 6.94 (t, J = 6.8 Hz, 1H), 3.22 (s, 3H), 2.90 (s, 3H), 2.61 (d, J = 6.8 Hz, 1H), 2.37 - 2.32 (m, 1H), 1.12 (s, 9H), 1.05 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 147.25, 135.54, 135.28, 135.00, 133.66, 133.00, 132.89, 129.96, 127.85, 121.68, 115.96, 108.69, 72.30, 62.98, 44.33, 41.59, 32.88, 26.89, 20.23, 19.30, 17.61.

15

20

Step 6:

[0181]

30



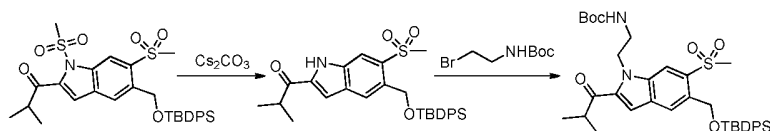
[0182] To a stirred solution of 1-(5-(((tert-butylidiphenylsilyloxy)methyl)-1,6-bis(methylsulfonyl)-1H-indol-2-yl)-2-methylpropan-1-ol (2.3 g, 3.8 mmol) in dry CH₂Cl₂ (25 mL) was added Dess-Martin periodinane (1.94 g, 4.56 mmol) in one portion. The mixture was allowed to stir at rt for 2 h. The reaction was quenched with a solution of Na₂S₂O₃ (5 g in 30 mL H₂O) and sat. aq. NaHCO₃ (40 mL). The mixture was extracted with EtOAc (3 x 80 mL). The combined organic solution was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel eluting with EtOAc/hexanes (2/8) to provide 1-(5-(((tert-butylidiphenylsilyloxy)methyl)-1,6-bis(methylsulfonyl)-1H-indol-2-yl)-2-methylpropan-1-one (2.0 g, 86% yield). **LC-MS** m/z 612 [M+H]⁺. **¹H NMR** (400 MHz, CDCl₃): δ 8.69 (s, 1H), 8.03 (s, 1H), 7.70 - 7.68 (m, 4H), 7.46 - 7.36 (m, 6H), 7.22 (s, 1H), 5.20 (s, 2H), 3.80 (s, 3H), 3.36 (m, 1H), 2.89 (s, 3H), 1.29 (d, J = 6.8 Hz, 6H), 1.13 (s, 9H). **¹³C NMR** (100 MHz, CDCl₃): δ 197.83, 141.53, 136.69, 136.05, 135.50, 135.04, 132.81, 131.14, 129.99, 127.88, 123.17, 117.12, 114.21, 62.87, 44.19, 44.03, 39.09, 26.88, 19.30, 18.41.

45

Step 7:

[0183]

50



55

[0184] To a stirred solution of 1-(5-(((tert-butylidiphenylsilyloxy)methyl)-1,6-bis(methylsulfonyl)-1H-indol-2-yl)-2-methylpropan-1-one (780 mg, 1.27 mmol) in THF / methanol (15 mL / 15 mL) was added Cs₂CO₃ (1.25 g, 3.83 mmol) in one portion. The mixture was allowed to stir at rt for 4 h and concentrated *in vacuo* to afford the crude product 1-(5-(((tert-

EP 2 825 541 B1

butyldiphenylsilyloxy)methyl)-6-(methylsulfonyl)-1H-indol-2-yl)-2-methylpropan-1-one. It was used for the next step reaction without further purification. To a solution of crude 1-(5-(((tert-butylidiphenylsilyloxy)methyl)-6-(methylsulfonyl)-1H-indol-2-yl)-2-methylpropan-1-one, 2-(Boc-amino)ethyl bromide (2.8 g, 12 mmol), tetrabutylammonium iodide (235 mg, 0.63 mmol) in CH₂Cl₂ / toluene (2 mL / 4 mL) was added 40% NaOH aqueous solution (20 mL). The mixture was allowed to stir at rt for 20 h. The reaction mixture was diluted with CH₂Cl₂ (40 mL) and washed with H₂O (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (4 x 50 mL). The combined organic solution was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel eluting with CH₂Cl₂ /Methanol (95/5) to provide tert-butyl (2-(5-(((tert-butylidiphenylsilyloxy)methyl)-2-isobutyryl-6-(methylsulfonyl)-1H-indol-1-yl)ethyl)carbamate (300 mg, 35% yield for two steps).

For 1-(5-(((tert-butylidiphenylsilyloxy)methyl)-6-(methylsulfonyl)-1H-indol-2-yl)-2-methylpropan-1-one: **LC-MS** m/z 556 [M+Na]⁺.

[0185] For tert-butyl (2-(5-(((tert-butylidiphenylsilyloxy)methyl)-2-isobutyryl-6-(methylsulfonyl)-1H-indol-1-yl)ethyl)carbamate: **LC-MS** m/z 699 [M+Na]⁺. **¹H NMR** (400 MHz, CDCl₃): δ 8.20 (s, 1H), 7.93 (s, 1H), 7.72 (dd, J₁ = 8.0 Hz, J₂ = 1.6 Hz, 4H), 7.47 - 7.35 (m, 7H), 5.21 (s, 2H), 4.72 (d, J = 6.8 Hz, 2H), 3.55 (d, J = 6.8 Hz, 2H), 3.33 - 3.26 (m, 1H), 3.00 (s, 3H), 1.46 (s, 9H), 1.30 (d, J = 6.4 Hz, 3H), 1.28 (d, J = 6.4 Hz, 3H), 1.11 (s, 9H).

Step 8:

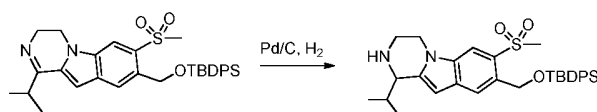
[0186]



[0187] To a solution of tert-butyl (2-(5-(((tert-butylidiphenylsilyloxy)methyl)-2-isobutyryl-6-(methylsulfonyl)-1H-indol-1-yl)ethyl)carbamate (250 mg, 0.37 mmol) in CH₂Cl₂ (5.0 mL) was added trifluoroacetic acid (1.0 mL) and the mixture was allowed to stir at rt for 1 h. The excess amount of TFA was removed by azeotropic evaporation with toluene under reduced pressure. The residue was redissolved in CH₂Cl₂ (5 mL) and Et₃N (0.5 mL) was added. The reaction mixture was stirred at rt for 45 min and concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel eluting with CH₂Cl₂ /methanol (98/2) to provide 8-(((tert-butylidiphenylsilyloxy)methyl)-1-isopropyl-7-(methylsulfonyl)-3,4-dihydropyrazino[1,2-a]indole (135 mg, 65% yield). **LC-MS** m/z 559 [M+H]⁺.

Step 9:

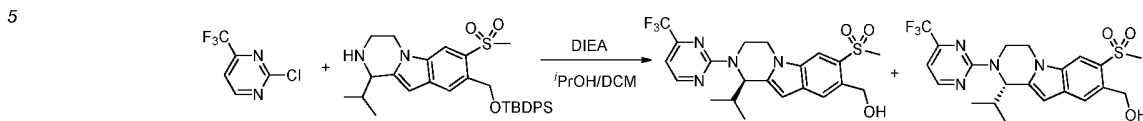
[0188]



[0189] A solution of 8-(((tert-butylidiphenylsilyloxy)methyl)-1-isopropyl-7-(methylsulfonyl)-3,4-dihydropyrazino[1,2-a]indole (140 mg, 0.25 mmol), 10% palladium on charcoal (37 mg, 0.025 mmol), and methanol (5 mL) was stirred at rt under 1 atmosphere of hydrogen for 3 h. The mixture was filtered through Celite® and the Celite® was washed thoroughly with methanol. Combined solvent was removed under reduced pressure to afford 8-(((tert-butylidiphenylsilyloxy)methyl)-1-isopropyl-7-(methylsulfonyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole. It was used directly without further purification. A small portion of product was purified by chromatography for characterization. **LC-MS** m/z 561 [M+H]⁺. **¹H NMR** (400 MHz, CD₃OD): δ 8.00 (s, 1H), 7.73 - 7.70 (m, 5H), 7.47 - 7.40 (m, 6H), 6.36 (s, 1H), 5.20 (d, J = 2.0 Hz, 2H), 4.24 - 4.19 (m, 1H), 4.11 - 4.00 (m, 2H), 3.52 - 3.47 (m, 1H), 3.20 - 3.13 (m, 1H), 3.03 (s, 3H), 2.47 - 2.39 (m, 1H), 1.18 (d, J = 6.8 Hz, 3H), 1.09 (s, 9H), 0.96 (d, J = 6.8 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃): δ 143.06, 135.68, 134.04, 133.31, 131.52, 130.26, 129.79, 129.51, 127.77, 121.39, 111.22, 97.14, 63.76, 59.28, 45.00, 42.94, 42.47, 31.55, 26.94, 19.72, 19.31, 16.49.

Step 10:

[0190]



10 **[0191]** A mixture of 2-chloro-4-(trifluoromethyl)pyrimidine (80 mg, 0.44 mmol), 8-(((tert-butyl)diphenylsilyloxy)methyl)-1-isopropyl-7-(methylsulfonyl)-1,2,3,4-tetrahydropyrazino[1,2-a]indole (crude, from step 9), and DIEA (115 μ L, 0.66 mmol) in *i*-PrOH / CH_2Cl_2 (2 mL / 1 mL) was stirred at 110°C for 30 h. The solvent was removed under reduced pressure and the crude residue was purified by silica chromatography and SFC separation on a chiral column to give isomers of (1-isopropyl-7-(methylsulfonyl)-2-(4-(trifluoromethyl)pyrimidin-2-yl)-1,2,3,4-tetrahydropyrazino[1,2-a]indol-8-yl)methanol (75 mg, 72% yield for two steps).

15 **Isomer 1: Analytical chiral HPLC:** $t_R = 11.8$ min in 15 min chromatography (Method: AD-H_5_5_40_2.35ML). **LC-MS** m/z 469 $[\text{M}+\text{H}]^+$. **$^1\text{H NMR}$** (400 MHz, CD_3OD): δ 8.65 (d, $J = 4.8$ Hz, 1H), 8.10 (s, 1H), 7.78 (s, 1H), 6.95 (d, $J = 4.8$ Hz, 1H), 6.52 (s, 1H), 5.91 - 5.89 (m, 1H), 5.14 - 5.09 (m, 1H), 5.06 (s, 2H), 4.47 - 4.42 (m, 1H), 4.12 - 4.05 (m, 1H), 3.94 - 3.86 (m, 1H), 3.26 (s, 3H), 2.37 - 2.29 (m, 1H), 1.17 (d, $J = 6.8$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H).

20 **Isomer 2: Analytical chiral HPLC:** $t_R = 9.7$ min in 15 min chromatography (Method: AD-H_5_5_40_2.35ML). **LC-MS** m/z 469 $[\text{M}+\text{H}]^+$. **$^1\text{H NMR}$** (400 MHz, CD_3OD): δ 8.65 (d, $J = 4.8$ Hz, 1H), 8.10 (s, 1H), 7.78 (s, 1H), 6.95 (d, $J = 4.8$ Hz, 1H), 6.52 (s, 1H), 5.91 - 5.89 (m, 1H), 5.14 - 5.09 (m, 1H), 5.06 (s, 2H), 4.47 - 4.42 (m, 1H), 4.12 - 4.05 (m, 1H), 3.94 - 3.86 (m, 1H), 3.26 (s, 3H), 2.37 - 2.29 (m, 1H), 1.17 (d, $J = 6.8$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H).

25

Example 5

LXR α/β radioligand binding assay

30 **[0192]** Compounds of the invention were assessed in a competition binding assay where different concentrations of compounds were incubated with the LXR ligand binding domain (LBD) in the presence of radiolabeled LXR ligand [^3H] TO901317. The amount of the LXR-LBD that complexed with [^3H]TO901317 was measured by scintillation proximity assay (SPA) employing non-specific binding of LXR-LBD to poly-lysine coated Yttrium silicate beads. Partially purified LXR α or β LBD protein (15-45 nM) was incubated at rt for 30 min with 15 nM [^3H]TO901317 (25-40 Ci/mmol) and different

35 concentrations of test compounds in 80 μ L of phosphate buffered saline (PBS) buffer containing 2.5% DMSO, 1% glycerol, 2mM EDTA, 2mM CHAPS and 5mM DTT in 96-well plates. Poly-lysine SPA beads (50 μ g) were added to each well and the total volume was adjusted to 120 μ L. The plates were shaken on an orbital shaker for 20 min and then allowed to settle for 10 more minutes at rt before a brief centrifugation at 2,000 rpm for 1 min. The SPA signal was measured on a MicroBeta[®] liquid scintillation counter (Perkin Elmer, Waltham, MA), and the results were used for

40 calculating IC50 values based on the total binding (DMSO control) and non-specific binding (5 μ M of unlabeled TO901317) controls. The K_i values were calculated according to equation 1, where [RL] is the final concentration of [^3H]TO901317 in the assay, and the K_d values of 20 nM and 10 nM of TO901317 for LBDs of LXR α and LXR β , respectively, were determined by direct titration of the radioligand with these proteins.

45

$$K_i = \frac{IC50}{\left(1 + \frac{[RL]}{K_d}\right)} \quad (1)$$

50 Example 6

LXR Luciferase Transcriptional Reporter Gene Assay

55 **[0193]** The LXR luciferase transcriptional reporter gene assay measures the ability of LXR ligands to promote transcriptional activation via the ligand binding domain (LBD) of LXR. HEK293 cells were grown in DMEM medium containing 10% FBS (Gibco[®], #11995-065) and 1xPenStrep (Gibco[®], #15140) at 37°C in 5% CO_2 atmosphere. 90% confluent cells from a 150mm dish were seeded in six 100mm dishes. The cells were batch-transfected with an expression plasmid containing the Gal4 DNA binding domain fused to either the LBD of LXR α or LXR β and a luciferase reporter plasmid

EP 2 825 541 B1

pG5-Luc (Promega, Madison, WI), which has Gal4 response elements upstream of firefly luciferase gene (luc+). Transfection was accomplished with Lipofectamine™ 2000 (Gibco®) according to the manufacturer's suggested protocol. Five h following transfection, 15 mL of 10% charcoal-treated FBS (Hyclone, #SH30070.03) in DMEM were added to the transfected dishes without removing transfection media, and then incubate the cells at 37°C overnight. The next day, the cells from the transfected dish were trypsinized, washed with PBS, resuspended in 10% charcoal-treated DMEM media and plated into 96-well plates with 60,000 cells/100 µL per well. The cells were incubated at 37°C for ~4 h before addition of 100 µL of test compound or control ligand at different concentrations (final DMSO concentration at 0.2%). Following incubation of the cells for 16 h with substances, the culture media were dumped and Bright-Glo™ luciferase reagent (Promega, Cat. #E2610) was added to lyse the cells and initiate the luciferase reaction. Luminescence, as a measure of luciferase activity, was detected in a plate reader (Victor2, PE-Wallac). Transcriptional activation in the presence of a test substance was expressed as fold-change in luminescence compared to that of cells incubated in the absence of the substance. EC₅₀ values were calculated using the XLfit™ program (IDBS, Guilford, UK).

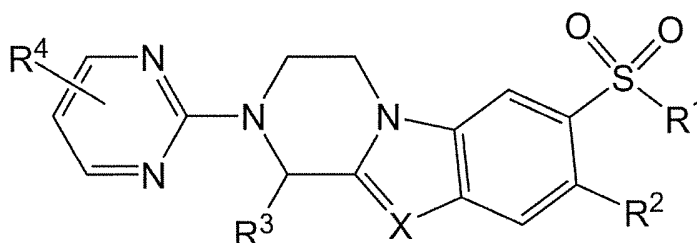
Example 7

[0194] Compounds of the invention were tested as described in Examples 5 and 6. The biological data are presented in the table below.

Compound No.	Example No.	LXR α BINDING K _i (nM)	LXR β BINDING K _i (nM)	LXR α CELL EC ₅₀ (nM)	LXR β CELL EC ₅₀ (nM)
E1	Example 1	1770	256	3370	313
E2a	Example 2, isomer 1	318	20	340	13
E2b	Example 2, isomer 2	> 3330	> 2500	17300	6940
E3a	Example 3, isomer 1	398	27	1100	87
E3b	Example 3, isomer 2	> 3330	1750	> 20000	> 20000
E4a	Example 4, isomer 1	43	4	163	10
E4b	Example 4, isomer 2	> 3330	846	> 20000	> 20000

Claims

1. A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

X is N or CR^c;

R¹ is alkyl or -NR^aR^b;

R² is H; halogen; -CN; -NRC(O)R; -C(O)OR; -C(O)NR^aR^b; monocyclic heteroaromatic optionally substituted with one or more groups selected from alkyl, -CN, -NRC(O)R, -C(O)OR, -C(O)NR^aR^b and halogen; monocyclic

non-aromatic heterocycle optionally substituted with one or more groups selected from alkyl, halogen, -CN and =O; or alkyl optionally substituted by one or more groups selected from halogen, hydroxy, alkoxy, -NR^aR^b, -NRC(O)R, -NRC(O)O(alkyl),

-NRC(O)N(R)₂, -C(O)OR, thiol, alkylthiol, nitro, -CN, =O, -OC(O)H, -OC(O)(alkyl), -OC(O)O(alkyl), -OC(O)N(R)₂ and -C(O)NR^aR^b;

R³ is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, monocyclic non-aromatic heterocycle, monocyclic heteroaromatic or phenyl, wherein the phenyl, monocyclic non-aromatic heterocycle, and monocyclic heteroaromatic group represented by R³ are optionally substituted with one or more groups selected from alkyl, halogen, haloalkyl, alkoxy, haloalkoxy, nitro and -CN;

R⁴ is halogen, -CN, -OR, -SR, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)O(alkyl), -C(O)O(haloalkyl), -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(alkyl), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂, -NRSO₂N(R)₂, haloalkyl, haloalkoxy, cycloalkoxy, cycloalkyl, monocyclic non-aromatic heterocycle, monocyclic heteroaromatic or alkyl, wherein the monocyclic non-aromatic heterocycle, monocyclic heteroaromatic and alkyl group represented by R⁴ are optionally substituted with one or more groups selected from -CN, -OR, -SR, -N(R)₂, =O, -C(O)R, -C(O)OR, -C(O)O(haloalkyl), -OC(O)R, -OC(O)O(alkyl), -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(alkyl), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂ and -NRSO₂N(R)₂;

Each R independently is H or alkyl;

R^a and R^b are independently H, alkyl or R^a and R^b can be taken together with the nitrogen to which they are attached to form a monocyclic non-aromatic heterocycle; and

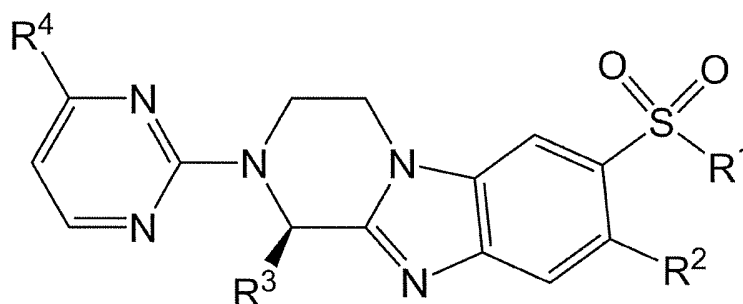
R^c is H, alkyl, or halogen.

2. The compound of claim 1, wherein:

R³ is alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl or phenyl, wherein the phenyl represented by R³ is optionally substituted with one or more groups selected from alkyl, halogen, haloalkyl, alkoxy, haloalkoxy, nitro and -CN;

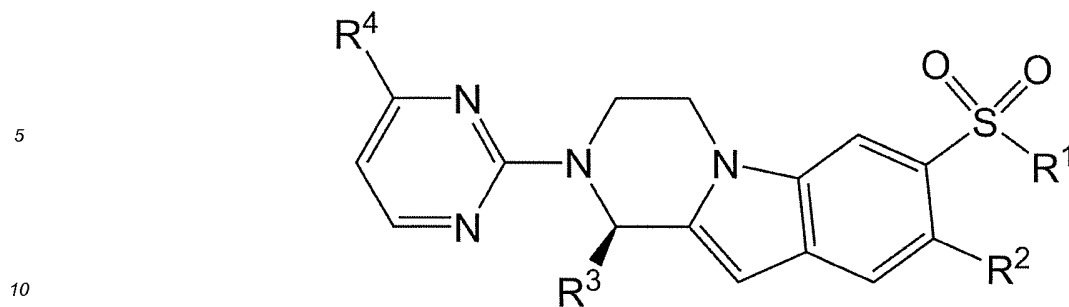
R⁴ is halogen, -CN, -OR, -SR, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)O(alkyl), -C(O)O(haloalkyl), -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(alkyl), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂, -NRSO₂N(R)₂, haloalkyl, haloalkoxy, cycloalkoxy, cycloalkyl or alkyl, wherein the alkyl group represented by R⁴ is optionally substituted with one or more groups selected from -CN, -OR, -SR, -N(R)₂, =O, -C(O)R, -C(O)OR, -C(O)O(haloalkyl), -OC(O)R, -OC(O)O(alkyl), -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(alkyl), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂ and -NRSO₂N(R)₂.

3. The compound of claim 1 or 2, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1 or 2, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

- 15 5. The compound of any one of the preceding claims, wherein:

R¹ is methyl or -NH₂;

R² is H or methyl, wherein the methyl group represented by R² is optionally substituted with one or more groups selected from halogen, hydroxy, alkoxy, -NR^aR^b, -NRC(O)R, -NRC(O)O(alkyl), -NRC(O)N(R)₂, -C(O)OR, thiol, alkylthiol, nitro, -CN, =O, -OC(O)H, -OC(O)(alkyl), -OC(O)O(alkyl), -C(O)NR^aR^b and -OC(O)N(R)₂;

20 R³ is methyl, ethyl, propyl, isopropyl, tert-butyl, sec-butyl, iso-butyl, -CH₂CF₃, -CH(CH₂F)₂, -CH(CHF₂)₂, -CH(CF₃)₂, -CF(CH₃)₂, -CF₃, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, -C(OH)(CH₃)₂, -CH(OH)(CH₃), or phenyl, wherein the phenyl group represented by R³ is optionally substituted with one or more groups selected from alkyl, halogen, haloalkyl, alkoxy, haloalkoxy, nitro and -CN; and R^c, where present, is H.

- 25 6. The compound of any one of the preceding claims, wherein:

R¹ is methyl;

R² is -CH₂OH;

R³ is isopropyl; and

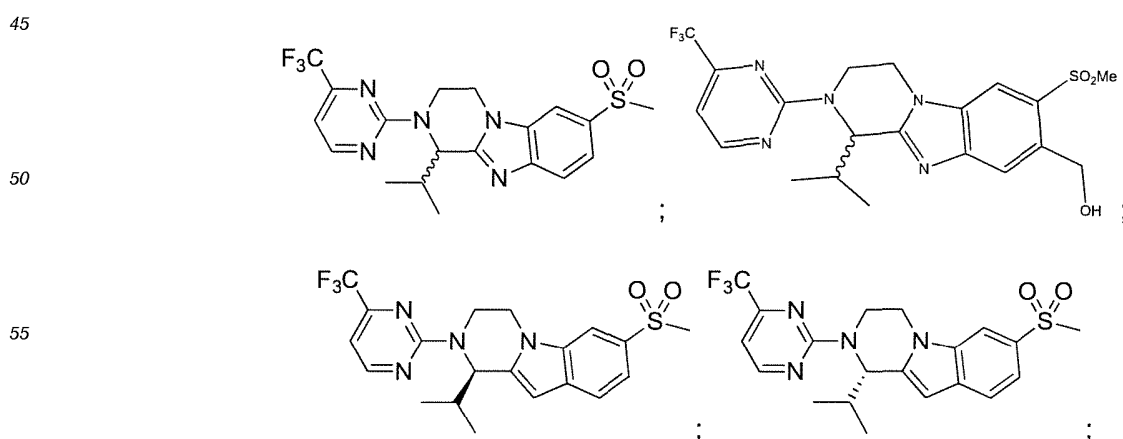
30 R⁴ is halogen, hydroxy, alkyl, cycloalkyl, cycloalkoxy, alkoxy, haloalkoxy, haloalkyl, -N(R)₂, -C(O)OH, -C(O)O(alkyl), -C(O)O(haloalkyl), -C(O)(alkyl), -C(O)N(R)₂, -NRC(O)R, -SO₂N(R)₂, -OC(O)N(R)₂, -CN, hydroxyalkyl or dihydroxyalkyl.

- 35 7. The compound of any one of the preceding claims, wherein R⁴ is methyl, ethyl, hydroxy, CF₃, isopropyl, cyclopropyl, CH₂OH, -CH(OH)(CH₂)(OH), -C(OH)(CH₃)₂, -CH(OH)(CH₃), -CH(OH)(CH₂)(CH₃), -CH(OH)(CH₂)₂(CH₃), -C(O)NH₂, C(O)N(CH₃)₂, -C(O)OH, -C(O)NH(CH₃), C(O)CH₃, C(O)CH₂CH₃, C(O)O(CH₂)(CH₃), -C(O)O (tert-butyl), -C(O)O(C)(CH₃)₂(CF₃), -NHC(O)CH₃, -OCHF₂, -OCF₃, -OCH₂CH₃, -OCH(CH₃)₂ or -OCH₃.

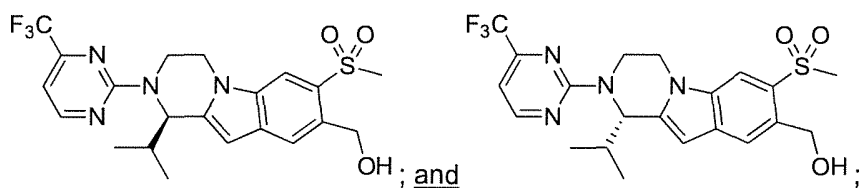
- 40 8. The compound of any one of the preceding claims, wherein R⁴ is methyl, CF₃, cyclopropyl, -OCHF₂ or -OCH₃.

- 45 9. The compound of any one of the preceding claims, wherein R⁴ is CF₃.

- 50 10. The compound of claim 1, wherein the compound is represented by a structural formula selected from:



5

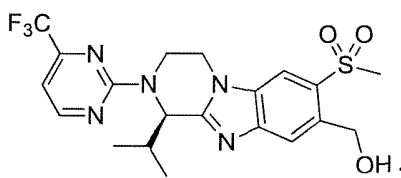


10

or a pharmaceutically acceptable salt of any of the foregoing.

11. The compound of claim 10, wherein the compound is represented by the following structural formula:

15



20

or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a pharmaceutical carrier or diluent and the compound of any one of claims 1 to 11.

25

13. A compound according to any one of claims 1 to 11 for use in treating a subject with a disease or disorder that is treatable by upregulating LXR activity.

30

14. The compound for use of claim 13, wherein the disease or disorder is hyperlipidemia, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hepatic steatosis, nonalcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), hyperglycemia, insulin resistance, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, dermatitis, psoriasis, contact dermatitis, atopic dermatitis, eczema, skin wounds, skin aging, photoaging, wrinkling, diabetes, Niemann-Pick disease type C, Parkinson's disease, Alzheimer's disease, inflammation, xanthoma, obesity, metabolic syndrome, syndrome X, stroke, peripheral occlusive disease, memory loss, diabetic neuropathies, proteinuria, glomerulopathies, diabetic nephropathy, hypertensive nephropathy, IGA nephropathy, focal segmental glomerulosclerosis, hyperphosphatemia, cardiovascular complications of hyperphosphatemia, cancer or multiple sclerosis.

35

15. The compound for use of claim 14 wherein the disease or disorder is atherosclerosis, Alzheimer's disease, eczema, psoriasis, or dermatitis, such as atopic dermatitis or contact dermatitis.

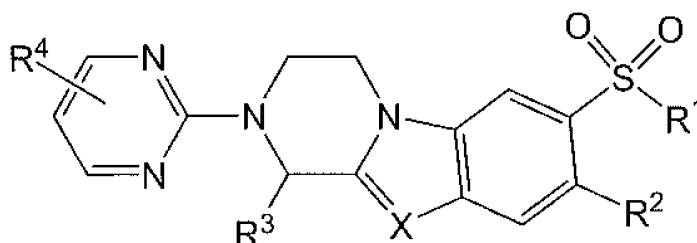
40

Patentansprüche

45

1. Verbindung, dargestellt durch die folgende Strukturformel:

50



55

oder ein pharmazeutisch unbedenkliches Salz davon, wobei:

X N oder CR^c ist;
R¹ Alkyl oder -NR^aR^b ist,

R² H, Halogen, -CN, -NRC(O)R, -C(O)OR, -C(O)NR^aR^b, ein monocyclischer Heteroaromat, gegebenenfalls mit einer oder mehreren Gruppen substituiert, die aus Alkyl, -CN, -NRC(O)R, -C(O)OR, -C(O)NR^aR^b und Halogen ausgewählt sind, ein monocyclischer nichtaromatischer Heterocyclus, der gegebenenfalls mit einer oder mehreren Gruppen substituiert ist, die aus Alkyl, Halogen, -CN und =O ausgewählt sind, oder Alkyl ist, das gegebenenfalls mit einer oder mehreren Gruppen substituiert ist, die aus Halogen, Hydroxy, Alkoxy, -NR^aR^b, -NRC(O)R, -NRC(O)O(Alkyl), -NRC(O)N(R)₂, -C(O)OR, Thiol, Alkylthiol, Nitro, -CN, =O, -OC(O)H, -OC(O)(Alkyl), -OC(O)O(Alkyl), -OC(O)N(R)₂ und -C(O)NR^aR^b ausgewählt sind, R³ Alkyl, Halogenalkyl, Hydroxyalkyl, Alkoxyalkyl, Cycloalkyl, ein monocyclischer nichtaromatischer Heterocyclus, ein monocyclischer Heteroaromat oder Phenyl ist, wobei das Phenyl, der monocyclische nichtaromatische Heterocyclus und die monocyclische heteroaromatische Gruppe, die durch R³ dargestellt sind, gegebenenfalls mit einer oder mehreren Gruppen substituiert ist, die aus Alkyl, Halogen, Halogenalkyl, Alkoxy, Halogenalkoxy, Nitro und -CN ausgewählt sind,

R⁴ Halogen, -CN, -OR, -SR, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)O(Alkyl), -C(O)O(Halogenalkyl), -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(Alkyl), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂, -NRSO₂N(R)₂, Halogenalkyl, Halogenalkoxy, Cycloalkoxy, Cycloalkyl, ein monocyclischer nichtaromatischer Heterocyclus, ein monocyclischer Heteroaromat oder Alkyl ist, wobei der monocyclische nichtaromatische Heterocyclus, der monocyclische Heteroaromat und die Alkylgruppe, die durch R⁴ dargestellt sind, gegebenenfalls mit einer oder mehreren Gruppen substituiert sind, die aus -CN, -OR, -SR, -N(R)₂, =O, -C(O)R, -C(O)OR, -C(O)O(Halogenalkyl), -OC(O)R, -OC(O)O(Alkyl), -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(Alkyl), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂ und -NRSO₂N(R)₂ ausgewählt sind, jedes R unabhängig H oder Alkyl ist,

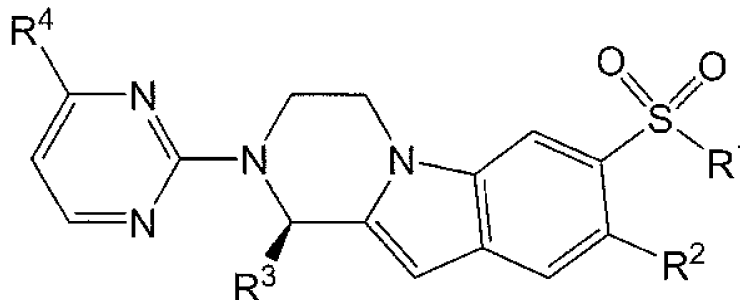
R^a und R^b unabhängig H, Alkyl sind oder R^a und R^b mit dem Stickstoff, an das sie gebunden sind, zusammengekommen werden können, um einen monocyclischen, nichtaromatischen Heterocyclus zu bilden, und R^c H, Alkyl oder Halogen ist.

2. Verbindung nach Anspruch 1, wobei:

R³ Alkyl, Halogenalkyl, Hydroxyalkyl, Alkoxyalkyl, Cycloalkyl oder Phenyl ist, wobei das Phenyl, das durch R³ dargestellt ist, gegebenenfalls mit einer oder mehreren Gruppen substituiert ist, die aus Alkyl, Halogen, Halogenalkyl, Alkoxy, Halogenalkoxy, Nitro und -CN ausgewählt sind,

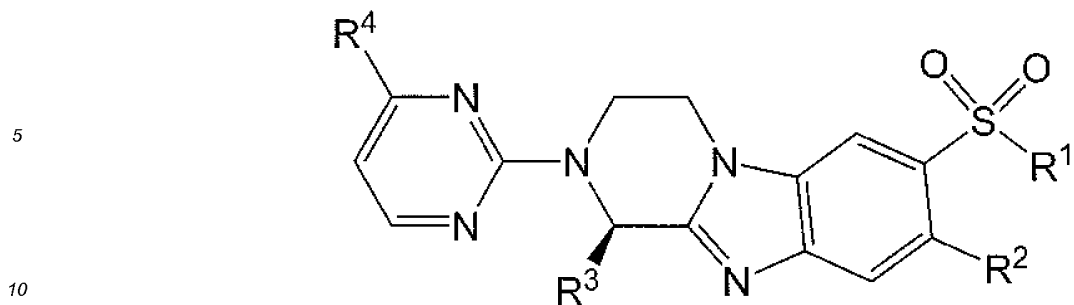
R⁴ Halogen, -CN, -OR, -SR, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)O(Alkyl), -C(O)O(Halogenalkyl), -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(Alkyl), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂, -NRSO₂N(R)₂, Halogenalkyl, Halogenalkoxy, Cycloalkoxy, Cycloalkyl oder Alkyl ist, wobei die Alkylgruppe, die durch R⁴ dargestellt ist, gegebenenfalls mit einer oder mehreren Gruppen substituiert ist, die aus -CN, -OR, -SR, -N(R)₂, =O, -C(O)R, -C(O)OR, -C(O)O(Halogenalkyl), -OC(O)R, -OC(O)O(Alkyl), -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(Alkyl), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂ und -NRSO₂N(R)₂ ausgewählt sind.

3. Verbindung nach Anspruch 1 oder 2, wobei die Verbindung durch die folgende Strukturformel dargestellt ist:



oder ein pharmazeutisch unbedenkliches Salz davon.

4. Verbindung nach Anspruch 1 oder 2, wobei die Verbindung durch die folgende Strukturformel dargestellt ist:



oder ein pharmazeutisch unbedenkliches Salz davon.

- 15 5. Verbindung nach einem der vorhergehenden Ansprüche, wobei:

R¹ Methyl oder -NH₂ ist,

R² H oder Methyl ist, wobei die durch R² dargestellte Methylgruppe gegebenenfalls mit einer oder mehreren Gruppen substituiert ist, die aus Halogen, Hydroxy, Alkoxy, -NR^aR^b, -NRC(O)R, -NRC(O)O(Alkyl), -NRC(O)N(R)₂, -C(O)OR, Thiol, Alkylthiol, Nitro, -CN, =O, -OC(O)H-OC(O)(Alkyl), -OC(O)O(Alkyl), -C(O)NR^aR^b und -OC(O)N(R)₂ ausgewählt sind, R³ Methyl, Ethyl, Propyl, Isopropyl, *tert*-Butyl, *sec*-Butyl, Isobutyl, -CH₂CF₃, -CH(CH₂F)₂, -CH(CHF₂)₂, -CH(CF₃)₂, -CF(CH₃)₂, -CF₃, Cyclopropyl, Cyclobutyl, Cyclopentyl, Cyclohexyl, -C(OH)(CH₃)₂, -CH(OH)(CH₃) oder Phenyl ist, wobei die durch R³ dargestellte Phenylgruppe gegebenenfalls mit einer oder mehreren Gruppen substituiert ist, die aus Alkyl, Halogen, Halogenalkyl, Alkoxy, Halogenalkoxy, Nitro und -CN ausgewählt sind; und R^c, sofern vorhanden, H ist.

- 25 6. Verbindung nach einem der vorhergehenden Ansprüche, wobei:

R¹ Methyl ist,

R² -CH₂OH ist,

R³ Isopropyl ist, und

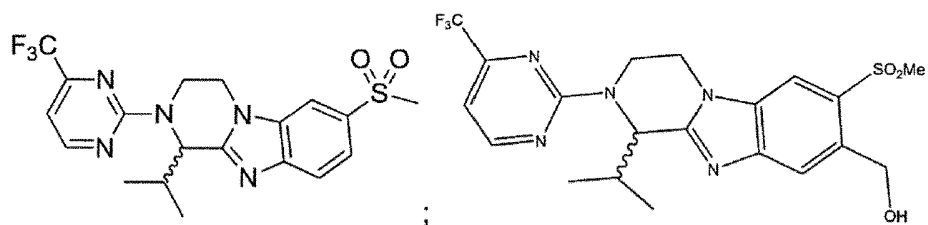
R⁴ Halogen, Hydroxy, Alkyl, Cycloalkyl, Cycloalkoxy, Alkoxy, Halogenalkoxy, Halogenalkyl, -N(R)₂, -C(O)OH, -C(O)O(Alkyl), -C(O)O(Halogenalkyl), -C(O)(Alkyl), -C(O)N(R)₂, -NRC(O)R, -SO₂N(R)₂, -OC(O)N(R)₂, -CN, Hydroxyalkyl oder Dihydroxyalkyl ist.

- 35 7. Verbindung nach einem der vorhergehenden Ansprüche, wobei R⁴ Methyl, Ethyl, Hydroxy, CF₃, Isopropyl, Cyclopropyl, CH₂OH, -CH(OH)(CH₂)(OH), -C(OH)(CH₃)₂, -CH(OH)(CH₃), -CH(OH)(CH₂)(CH₃), -CH(OH)(CH₂)₂(CH₃), -C(O)NH₂, C(O)N(CH₃)₂, -C(O)OH, -C(O)NH(CH₃), C(O)CH₃, C(O)CH₂CH₃, C(O)O(CH₂)(CH₃), -C(O)O(*tert*-Butyl), -C(O)O(C)(CH₃)₂(CF₃), -NHC(O)CH₃, -OCHF₂, -OCF₃, -OCH₂CH₃, -OCH(CH₃)₂ oder -OCH₃ ist.

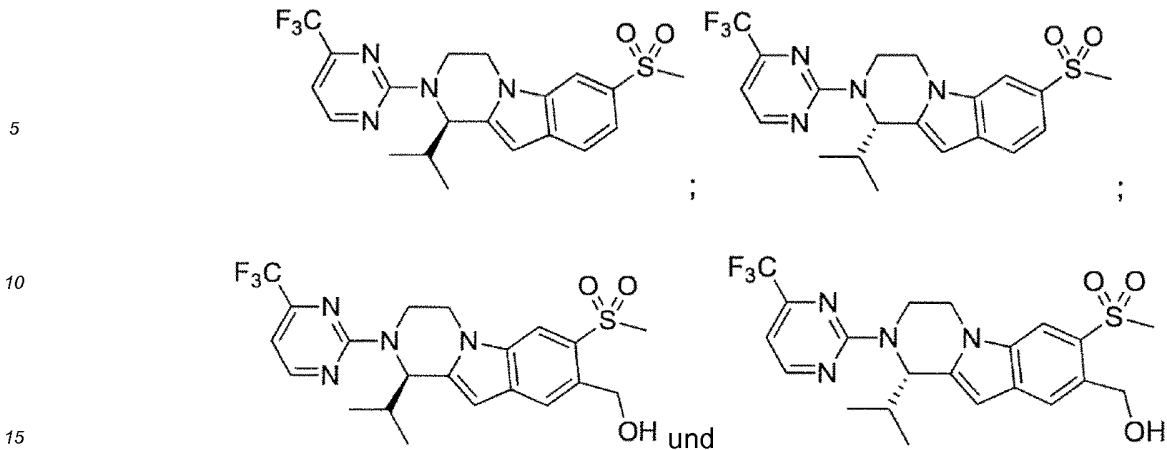
- 40 8. Verbindung nach einem der vorhergehenden Ansprüche, wobei R⁴ Methyl, CF₃, Cyclopropyl, -OCHF₂ oder -OCH₃ ist.

9. Verbindung nach einem der vorhergehenden Ansprüche, wobei R⁴ CF₃ ist.

- 45 10. Verbindung nach Anspruch 1, wobei die Verbindung durch eine Strukturformel dargestellt ist, die ausgewählt ist aus:



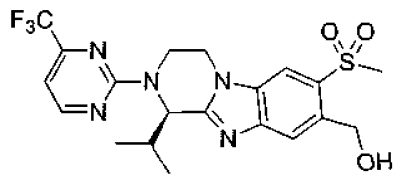
55



oder ein pharmazeutisch unbedenkliches Salz von jeglicher der vorstehenden Verbindungen.

11. Verbindung nach Anspruch 10, wobei die Verbindung durch die folgende Strukturformel dargestellt ist:

20



oder ein pharmazeutisch unbedenkliches Salz davon.

30

12. Pharmazeutische Zusammensetzung, umfassend einen pharmazeutischen Träger oder ein pharmazeutisches Verdünnungsmittel sowie die Verbindung nach einem der Ansprüche 1 bis 11.

13. Verbindung nach einem der Ansprüche 1 bis 11 zur Verwendung bei der Behandlung eines Subjekts mit einer Erkrankung oder Störung, die durch eine Hochregulierung der LXR-Aktivität behandelbar ist.

35

14. Verbindung zur Verwendung nach Anspruch 13, wobei die Krankheit oder Störung Hyperlipidämie, Hypercholesterinämie, Hyperlipoproteinämie, Hypertriglyceridämie, Lipodystrophie, Fettleber, nichtalkoholische Steatohepatitis (NASH), nichtalkoholische Fettleber (NAFLD), Hyperglykämie, Insulinresistenz, Diabetes mellitus, Dyslipidämie, Atherosklerose, Gallenstein, Acne vulgaris, Dermatitis, Psoriasis, Kontaktdermatitis, atopische Dermatitis, Ekzem, Hautwunden, Hautalterung, Photoalterung, Faltenbildung, Diabetes, Niemann-Pick-Krankheit Typ C, Morbus Parkinson, Morbus Alzheimer, Entzündung, Xanthom, Adipositas, metabolisches Syndrom, Syndrom X, Hirnschlag, periphere Verschlusskrankheit, Gedächtnisverlust, diabetische Neuropathien, Proteinurie, Glomerulopathien, diabetische Nephropathie, hypertensive Nephropathie, IgA-Nephritis, fokale segmentale Glomerulosklerose, Hyperphosphatämie, kardiovaskuläre Komplikationen einer Hyperphosphatämie, Krebs oder multiple Sklerose ist.

45

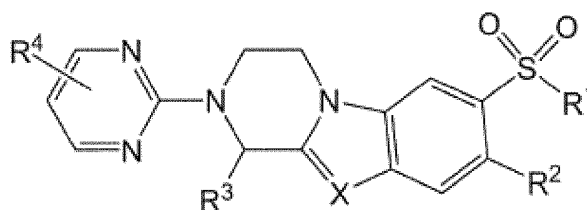
15. Verbindung zur Verwendung nach Anspruch 14 wobei die Erkrankung oder Störung Atherosklerose, Morbus Alzheimer, Ekzem, Psoriasis oder Dermatitis, wie etwa eine atopische Dermatitis oder eine Kontaktdermatitis ist.

50

Revendications

1. Composé représenté par la formule structurale suivante :

55



ou sel pharmaceutiquement acceptable de celui-ci, dans lequel :

X est N ou CR^c ;

R¹ est l'alkyle ou -NR^aR^b ;

R² est H ; l'halogène ; -CN ; -NRC(O)R ; -C(O)OR ; -C(O)NR^aR^b ; un hétéroaromate monocyclique facultativement substitué par un ou plusieurs groupes choisis parmi l'alkyle, -CN, -NRC(O)R, -C(O)OR, -C(O)NR^aR^b et l'halogène ; l'hétérocycle monocyclique non aromatique facultativement substitué par un ou plusieurs groupes choisis parmi l'alkyle, l'halogène, -CN et =O ; ou l'alkyle facultativement substitué par un ou plusieurs groupes choisis parmi l'halogène, l'hydroxy, l'alcoxy, NR^aR^b, -NRC(O)R, -NRC(O)O(alkyle), -NRC(O)N(R)₂, -C(O)OR, le thiol, l'alkylthiol, le nitro, -CN, =O, -OC(O)H, -OC(O)(alkyle), -OC(O)O(alkyle), -OC(O)N(R)₂ et -C(O)NR^aR^b ; R³ est l'alkyle, l'haloalkyle, l'hydroxyalkyle, l'alcoxyalkyle, le cycloalkyle, l'hétérocycle monocyclique non aromatique, l'hétéroaromate monocyclique ou le phényle, où les groupes phényle, hétérocycle monocyclique non aromatique et hétérocycle monocyclique aromatique représentés par R³ sont facultativement substitués par un ou plusieurs groupes choisis parmi l'alkyle, l'halogène, l'haloalkyle, l'alcoxy, l'haloalcoxy, le nitro et -CN ; R⁴ est l'halogène, -CN, -OR, -SR, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)O(alkyle), -C(O)O(haloalkyle), -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(alkyle), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂, -NRSO₂N(R)₂, l'haloalkyle, l'haloalcoxy, le cycloalcoxy, le cycloalkyle, l'hétérocycle monocyclique non aromatique, l'hétéroaromate monocyclique ou l'alkyle, où les groupes hétérocycle monocyclique non aromatique, hétéroaromate monocyclique et alkyle représentés par R⁴ sont facultativement substitués par un ou plusieurs groupes choisis parmi -CN, -OR, -SR, -N(R)₂, =O, -C(O)R, -C(O)OR, -C(O)O(haloalkyle), -OC(O)R, -OC(O)O(alkyle), -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(alkyle), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂ et -NRSO₂N(R)₂ ;

chaque R est indépendamment H ou l'alkyle ;

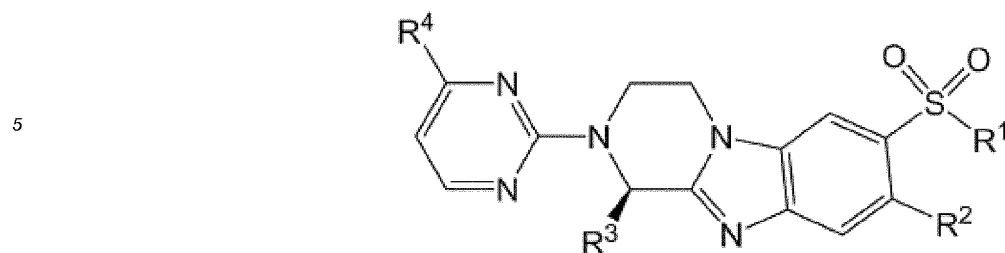
R^a et R^b sont indépendamment H, l'alkyle, ou R^a et R^b peuvent être pris conjointement avec l'atome d'azote auquel ils sont fixés pour former un hétérocycle monocyclique non aromatique ; et R^c est H, l'alkyle ou l'halogène.

2. Composé selon la revendication 1, dans lequel :

R³ est l'alkyle, l'haloalkyle, l'hydroxyalkyle, l'alcoxyalkyle, le cycloalkyle ou le phényle, où le phényle représenté par R³ est facultativement substitué par un ou plusieurs groupes choisis parmi l'alkyle, l'halogène, l'haloalkyle, l'alcoxy, l'haloalcoxy, le nitro et -CN ;

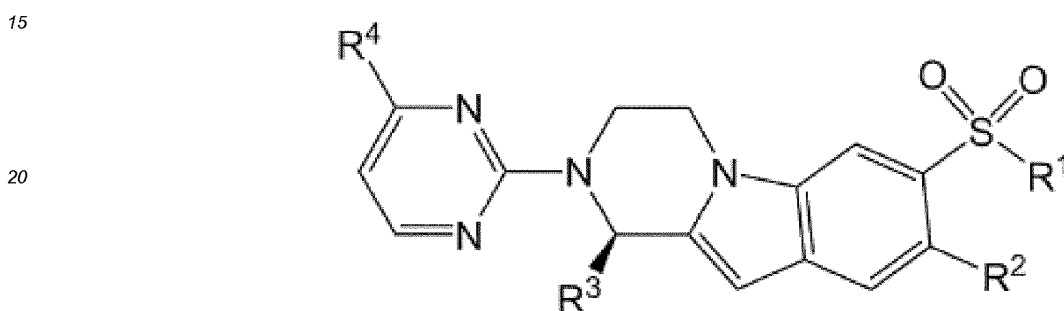
R⁴ est l'halogène, -CN, -OR, -SR, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)O(alkyle), -C(O)O(haloalkyle), -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(alkyle), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂, -NRSO₂N(R)₂, l'haloalkyle, l'haloalcoxy, le cycloalcoxy, le cycloalkyle ou l'alkyle, où le groupe alkyle représenté par R⁴ est facultativement substitué par un ou plusieurs groupes choisis parmi -CN, -OR, -SR, -N(R)₂, =O, -C(O)R, -C(O)OR, -C(O)O(haloalkyle), -OC(O)R, -OC(O)O(alkyle), -C(O)N(R)₂, -OC(O)N(R)₂, -NRC(O)R, -NRC(O)O(alkyle), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NRC(O)N(R)₂ et -NRSO₂N(R)₂.

3. Composé selon la revendication 1 ou 2, lequel composé est représenté par la formule structurale suivante :



ou sel pharmaceutiquement acceptable de celui-ci.

4. Composé selon la revendication 1 ou 2, lequel composé est représenté par la formule structurale suivante :



ou sel pharmaceutiquement acceptable de celui-ci.

5. Composé selon l'une quelconque des revendications précédentes, dans lequel :

30 R¹ est le méthyle ou -NH₂ ;

R² est H ou le méthyle, où le groupe méthyle représenté par R² est facultativement substitué par un ou plusieurs groupes choisis parmi l'halogène, l'hydroxy, l'alcoxy, NR^aR^b, -NRC(O)R, -NRC(O)O(alkyle), -NRC(O)N(R)₂, -C(O)OR, le thiol, l'alkylthiol, le nitro, -CN, =O, -OC(O)H, -OC(O)(alkyle), -OC(O)O(alkyle), -C(O)NR^aR^b et -OC(O)N(R)₂ ;

35 R³ est le méthyle, l'éthyle, le propyle, l'isopropyle, le tert-butyle, le sec-butyle, l'isobutyle, -CH₂CF₃, -CH(CH₂F)₂, -CH(CHF₂)₂, -CH(CF₃)₂, -CF(CH₃)₂, -CF₃, le cyclopropyle, le cyclobutyle, le cyclopentyle, le cyclohexyle, -C(OH)(CH₃)₂, -CH(OH)(CH₃) ou le phényle, où le groupe phényle représenté par R³ est facultativement substitué par un ou plusieurs groupes choisis parmi l'alkyle, l'halogène, l'haloalkyle, l'alcoxy, l'haloalcoxy, le nitro et -CN ;

40 et R^c, lorsqu'il est présent, est H.

6. Composé selon l'une quelconque des revendications précédentes, dans lequel :

45 R¹ est le méthyle ;

R² est -CH₂OH ;

R³ est l'isopropyle ; et

R⁴ est l'halogène, l'hydroxy, l'alkyle, le cycloalkyle, le cycloalcoxy, l'akcoxy, l'haloalcoxy, l'haloalkyle, -N(R)₂, -C(O)OH, -C(O)O(alkyle), -C(O)O(haloalkyle), -C(O)(alkyle), -C(O)N(R)₂, -NRC(O)R, -SO₂N(R)₂, -OC(O)N(R)₂, -CN, l'hydroxyalkyle ou le dihydroxyalkyle.

50

7. Composé selon l'une quelconque des revendications précédentes, dans lequel R⁴ est le méthyle, l'éthyle, l'hydroxy, CF₃, l'isopropyle, le cyclopropyle, -CH₂OH, -CH(OH)(CH₂)(OH), -C(OH)(CH₃)₂, -CH(OH)(CH₃), -CH(OH)(CH₂)(CH₃), -CH(OH)(CH₂)₂(CH₃), -C(O)NH₂, -C(O)N(CH₃)₂, -C(O)OH, -C(O)NH(CH₃), C(O)CH₃, C(O)CH₂CH₃, C(O)O(CH₂)(CH₃), -C(O)O(tert-butyle), -C(O)O(C)(CH₃)₂(CF₃), -NHC(O)CH₃, -OCHF₂, -OCF₃, -OCH₂CH₃, -OCH(CH₃)₂ ou -OCH₃.

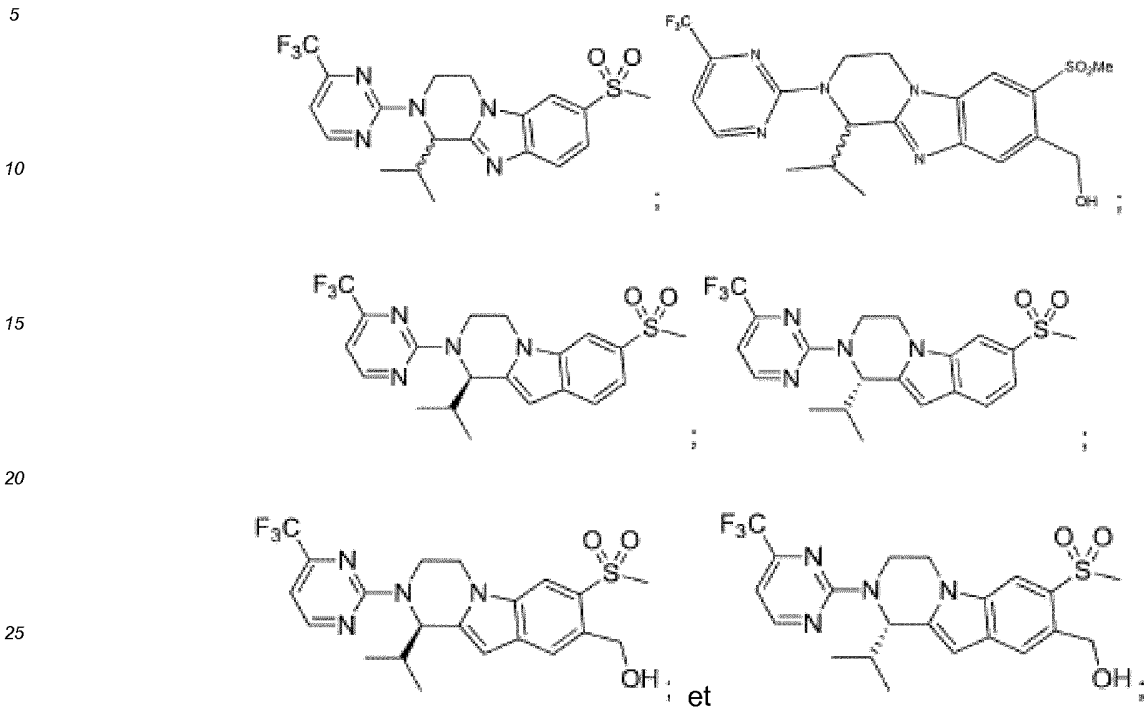
55

8. Composé selon l'une quelconque des revendications précédentes, dans lequel R⁴ est le méthyle, CF₃, le cyclopropyle, -OCHF₂ ou -OCH₃.

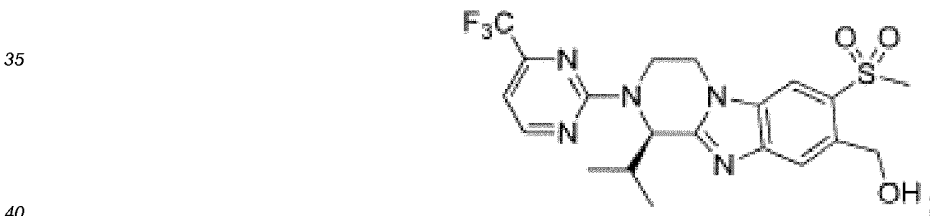
EP 2 825 541 B1

9. Composé selon l'une quelconque des revendications précédentes, dans lequel R⁴ est CF₃.

10. Composé selon la revendication 1, lequel composé est représenté par une formule structurale choisie parmi :



11. Composé selon la revendication 10, lequel composé est représenté par la formule structurale suivante :



12. Composition pharmaceutique comprenant un vecteur ou diluant pharmaceutique et le composé selon l'une quelconque des revendications 1 à 11.

13. Composé selon l'une quelconque des revendications 1 à 11 pour une utilisation dans le traitement d'un patient atteint d'une maladie ou d'un trouble traitable par une régulation à la hausse de l'activité LXR.

14. Composé pour une utilisation selon la revendication 13, dans lequel la maladie ou le trouble est l'hyperlipidémie, l'hypercholestérolémie, l'hyperlipoprotéïnémie, l'hypertriglycéridémie, la lipodystrophie, la stéatose hépatique, la stéatohépatite non alcoolique (NASH), l'hépatite graisseuse non alcoolique (NAFLD), l'hyperglycémie, l'insulinorésistance, le diabète sucré, la dyslipidémie, l'athérosclérose, le calcul biliaire, l'acné juvénile, la dermatite, le psoriasis, la dermatite de contact, la dermatite atopique, l'eczéma, les lésions cutanées, le vieillissement cutané, le photovieillissement, les rides, le diabète, la maladie de Niemann-Pick de type C, la maladie de Parkinson, la maladie d'Alzheimer, l'inflammation, le xanthome, l'obésité, le syndrome métabolique, le syndrome X, l'accident vasculaire cérébral, l'occlusion périphérique, la perte de mémoire, les neuropathies diabétiques, la protéinurie, les glomérulopathies, la néphropathie diabétique, la néphropathie hypertensive, la néphropathie à IgA, la glomérulosclérose segmentaire

EP 2 825 541 B1

focale, l'hyperphosphatémie, les complications cardiovasculaires de l'hyperphosphatémie, le cancer ou la sclérose en plaques.

- 5 **15.** Composé pour une utilisation selon la revendication 14, dans lequel la maladie ou le trouble est l'athérosclérose, la maladie d'Alzheimer, l'eczéma, le psoriasis ou la dermatite, notamment la dermatite atopique ou la dermatite de contact.

10

15

20

25

30

35

40

45

50

55

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 61612051 A [0001]
- WO 2009086129 A [0011]

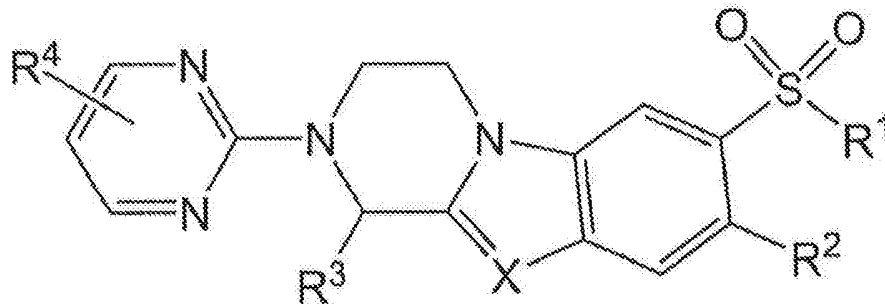
Non-patent literature cited in the description

- **VIENNOIS et al.** *Expert Opin. Ther. Targets*, 2011, vol. 15 (2), 219-232 [0004]
- **CALDAS et al.** *Kidney International*, 2011, vol. 80, 535-544 [0004]
- **KLEYER et al.** *J. Bone Miner. Res.*, 2012, vol. 27 (12), 2442-51 [0004]
- **JIANG et al.** *Neuron*, 2008, vol. 58, 681-693 [0006]
- Remington's Pharmaceutical Sciences. Mack Publishing Company, 1990, 1445 [0036]
- Goodman & Gilman's The Pharmacological Basis Of Basis Of Therapeutics. Mc-Graw-Hill, 1996 [0040]
- Physician's Desk Reference. Medical Economics Co., Inc, 2003 [0040]
- **FREIREICH et al.** *Cancer Chemother. Rep*, 1966, vol. 50, 219 [0051]
- Scientific Tables. Geigy Pharmaceuticals, 1970, 537 [0051]
- Remington: The Science and Practice of Pharmacy. Lippincott, Williams & Wilkins, 2005 [0052]
- the Handbook of Pharmaceutical Excipients. Pharmaceutical Press, 2005 [0055]
- Remington's Pharmaceutical Sciences. 2003 [0055]
- The United States Pharmacopeia: The National Formulary. USP, 1999 [0055]
- **MARCH.** Advanced Organic Chemistry. John Wiley & Sons, 1985 [0081]
- **GREENE ; WUTS.** Protective Groups in Organic Synthesis. John Wiley & Sons, 1991 [0081]
- **RICHARD LAROCK.** Comprehensive Organic Transformations. VCH publishers Inc, 1989 [0081]

Máj X receptor modulátorok

Szabadalmi igénypontok

1.



képletű vegyületek vagy valamely gyógyászatilag elfogadható sóik, ahol:

X jelentése N vagy CR^c;

R¹ alkil vagy -NR^aR^b csoport;

R² jelentése H; halogénatom; -CN; -NR^c(O)R; -C(O)OR; -C(O)NR^aR^b;

monociklusos heteroaromás csoport, mely adott esetben egy vagy több, alkil, -CN, -NR^c(O)R, -C(O)OR, -C(O)NR^aR^b csoport és halogénatom közül választott szubsztituenst tartalmaz; monociklusos nem-aromás heterociklusos csoport, mely adott esetben egy vagy több, alkil, halogénatom, -CN és =O közül választott szubsztituenst tartalmaz; vagy alkilcsoport, mely adott esetben egy vagy több, halogénatom, hidroxí, alkoxí, -NR^aR^b, -NR^c(O)R, -NR^c(O)O(alkil), -NR^c(O)N(R)₂, -C(O)OR, tiol, alkiltiol, nitro, -CN, =O, -OC(O)H, -OC(O)(alkil), -OC(O)O(alkil), -OC(O)N(R)₂ és -C(O)NR^aR^b közül választott szubsztituenst tartalmaz;

R³ alkil, halogénalkil, hidroxialkil, alkoxialkil, cikloalkil, monociklusos nem-aromás heterociklusos, monociklusos heteroaromás vagy fenilcsoport, ahol az R³ fenil, monociklusos nem-aromás heterociklusos, és monociklusos heteroaromás csoportok adott esetben egy vagy több, alkil, halogénatom, halogénalkil, alkoxí, halogénalkoxi, nitro és -CN közül választott szubsztituenst tartalmaznak;

R⁴ halogénatom, -CN, -OR, -SR, -N(R)₂, -C(O)R, -C(O)OR, -OC(O)O(alkil), -C(O)O(halogénalkil), -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -NR^c(O)R, -NR^c(O)O(alkil), -S(O)R, -SO₂R, -SO₂N(R)₂, -NRS(O)R, -NRSO₂R, -NR^c(O)N(R)₂, -NRSO₂N(R)₂, halogénalkil, halogénalkoxi, cikloalkoxi, cikloalkil, monociklusos

nem-aromás heterociklusos, monociklusos heteroaromás vagy alkilcsoport, ahol az R^4 monociklusos nem-aromás heterociklusos, monociklusos heteroaromás és alkilcsoportok adott esetben egy vagy több, $-CN$, $-OR$, $-SR$, $-N(R)_2$, $=O$, $-C(O)R$, $-C(O)OR$, $-C(O)O(\text{halogénalkil})$, $-OC(O)R$, $-OC(O)O(\text{alkil})$, $-C(O)N(R)_2$, $-OC(O)N(R)_2$, $-NR^c(O)R$, $-NR^c(O)O(\text{alkil})$, $-S(O)R$, $-SO_2R$, $-SO_2N(R)_2$, $-NRS(O)R$, $-NRSO_2R$, $-NR^c(O)N(R)_2$ és $-NRSO_2N(R)_2$ közül választott szubsztituenst tartalmaznak;

valamennyi R egymástól függetlenül H vagy alkilcsoport;

R^a és R^b egymástól függetlenül H , alkilcsoport, vagy R^a és R^b a hozzájuk kapcsolódó nitrogénatommal együtt egy monociklusos nem-aromás heterociklusos csoportot alkothat; és

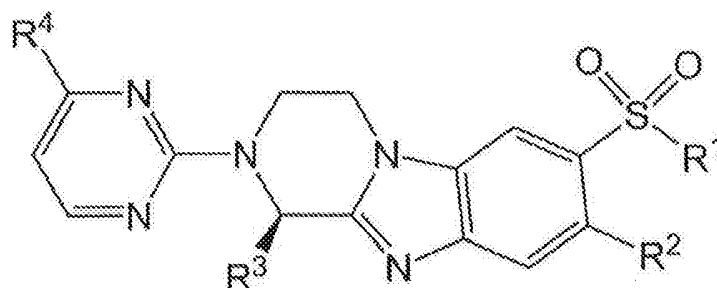
R^c jelentése H , alkilcsoport, vagy halogénatom.

2. Az 1. igénypont szerinti vegyület, ahol:

R^3 alkil, halogénalkil, hidroxialkil, alkoxilalkil, cikloalkil vagy fenilcsoport, ahol az R^3 fenilcsoport adott esetben egy vagy több, alkilcsoport, halogénatom, halogénalkil, alkoxi, halogénalkoxi, nitro és $-CN$ közül választott szubsztituenst tartalmaz;

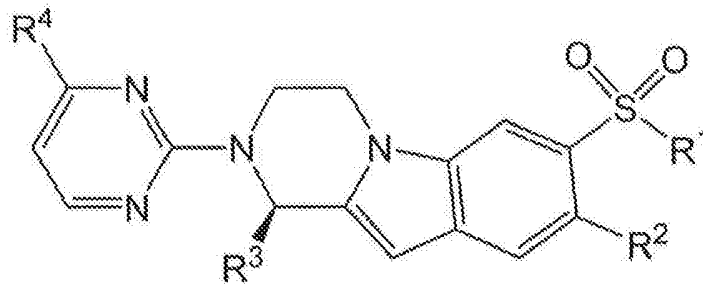
R^4 halogénatom, $-CN$, $-OR$, $-SR$, $-N(R)_2$, $-C(O)R$, $-C(O)OR$, $-OC(O)O(\text{alkil})$, $-C(O)O(\text{halogénalkil})$, $-OC(O)R$, $-C(O)N(R)_2$, $-OC(O)N(R)_2$, $-NR^c(O)R$, $-NR^c(O)O(\text{alkil})$, $-S(O)R$, $-SO_2R$, $-SO_2N(R)_2$, $-NRS(O)R$, $-NRSO_2R$, $-NR^c(O)N(R)_2$, $-NRSO_2N(R)_2$, halogénalkil, halogénalkoxi, cikloalkoxi, cikloalkil vagy alkilcsoport, ahol az R^4 alkilcsoport adott esetben egy vagy több, $-CN$, $-OR$, $-SR$, $-N(R)_2$, $=O$, $-C(O)R$, $-C(O)OR$, $-C(O)O(\text{halogénalkil})$, $-OC(O)R$, $-OC(O)O(\text{alkil})$, $-C(O)N(R)_2$, $-OC(O)N(R)_2$, $-NR^c(O)R$, $-NR^c(O)O(\text{alkil})$, $-S(O)R$, $-SO_2R$, $-SO_2N(R)_2$, $-NRS(O)R$, $-NRSO_2R$, $-NR^c(O)N(R)_2$ és $-NRSO_2N(R)_2$ közül választott szubsztituenst tartalmaz.

3. Az 1. vagy 2. igénypont szerinti vegyület, ahol a vegyület a



képletű, vagy gyógyászatiilag elfogadható sója.

4. Az 1. vagy 2. igénypont szerinti vegyület, ahol a vegyület a



képletű, vagy gyógyászatilag elfogadható sója.

5. Az előző igénypontok bármelyike szerinti vegyület, ahol:

R^1 metil vagy $-NH_2$ csoport;

R^2 jelentése H vagy metilcsoport, ahol az R^2 metilcsoport adott esetben egy vagy több, groups halogénatom, hidroxil, alkoxil, $-NR^aR^b$, $-NR^c(O)R$, $-NR^c(O)O(\text{alkil})$, $-NR^c(O)N(R)_2$, $-C(O)OR$, tiol, alkiltiol, nitro, $-CN$, $=O$, $-OC(O)H$ $-OC(O)(\text{alkil})$, $-OC(O)O(\text{alkil})$, $-C(O)NR^aR^b$ és $-OC(O)N(R)_2$ közül választott szubsztituenst tartalmaz;

R^3 jelentése metil, etil, propil, izopropil, terc-butil, szek-butil, izo-butil, $-CH_2CF_3$, $-CH(CH_2F)_2$, $-CH(CHF_2)_2$, $-CH(CF_3)_2$, $-CF(CH_3)_2$, $-CF_3$, ciklopropil, ciklobutil, ciklopentil, ciklohexil, $-C(OH)(CH_3)_2$, $-CH(OH)(CH_3)$, vagy fenilcsoport, ahol az R^3 fenilcsoport adott esetben egy vagy több, alkil, halogénatom, halogénalkil, alkoxil, halogénalkoxil, nitro és $-CN$ közül választott szubsztituenst tartalmaz; és R^c , ha jelen van, H.

6. Az előző igénypontok bármelyike szerinti vegyület, ahol:

R^1 metilcsoport;

R^2 $-CH_2OH$ csoport;

R^3 izopropilcsoport; és

R^4 halogénatom, hidroxil, alkil, cikloalkil, cikloalkoxil, alkoxil, halogénalkoxil, halogénalkil, $-N(R)_2$, $-C(O)OH$, $-C(O)O(\text{alkil})$, $-C(O)O(\text{halogénalkil})$, $-C(O)(\text{alkil})$, $-C(O)N(R)_2$, $-NR^c(O)R$, $-SO_2N(R)_2$, $-OC(O)N(R)_2$, $-CN$, hidroxialkil vagy dihidroxialkilcsoport.

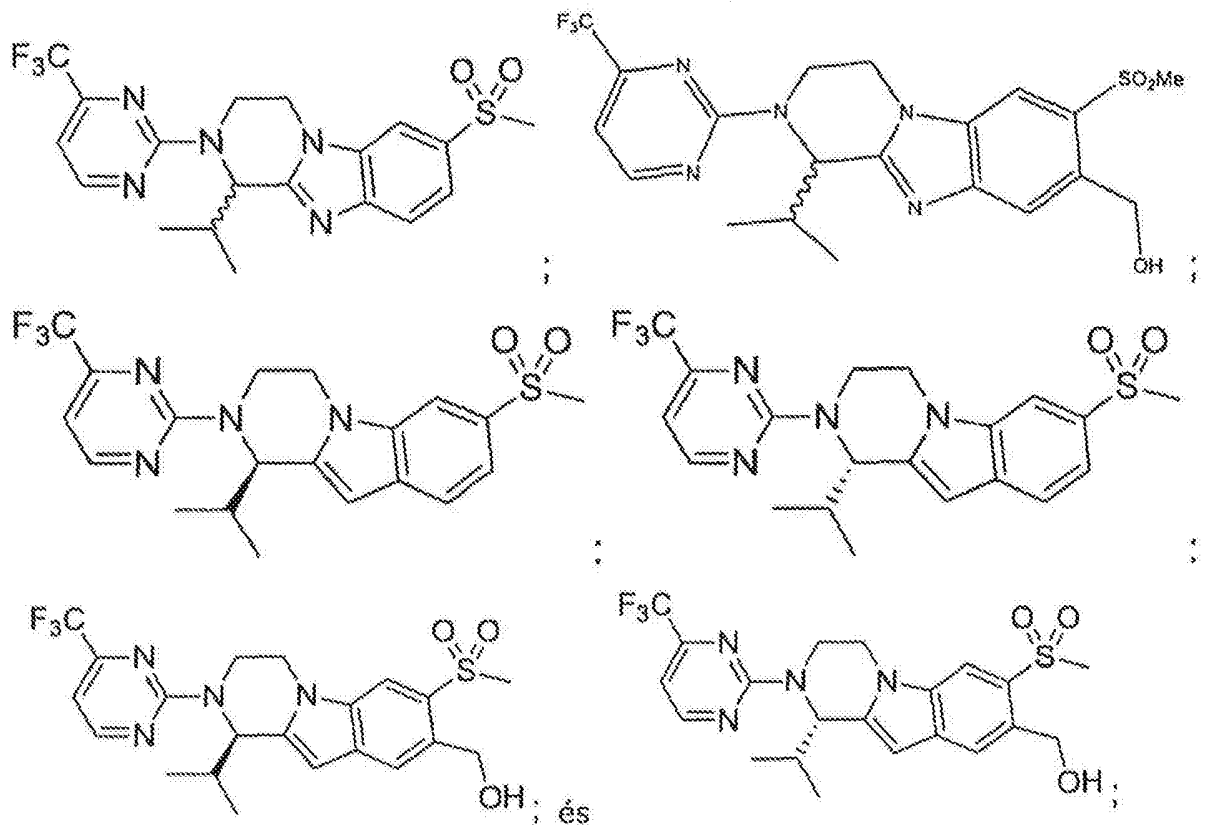
7. Az előző igénypontok bármelyike szerinti vegyület, ahol R^4 metil, etil, hidroxil, CF_3 , izopropil, ciklopropil, CH_2OH , $-CH(OH)(CH_2)(OH)$, $-C(OH)(CH_3)_2$,

-CH(OH)(CH₃), -CH(OH)(CH₂)(CH₃), -CH(OH)(CH₂)₂(CH₃), -C(O)NH₂,
 C(O)N(CH₃)₂, -C(O)OH, -C(O)NH(CH₃), C(O)CH₃, C(O)CH₂CH₃, C(O)O(CH₂)(CH₃),
 -C(O)O (terc-butil), -C(O)O(C)(CH₃)₂(CF₃), -NHC(O)CH₃, -OCHF₂, -OCF₃, -
 OCH₂CH₃, -OCH(CH₃)₂ vagy -OCH₃ csoport.

8. Az előző igénypontok bármelyike szerinti vegyület, ahol R⁴ metil, CF₃,
 ciklopropil, -OCHF₂ vagy -OCH₃ csoport.

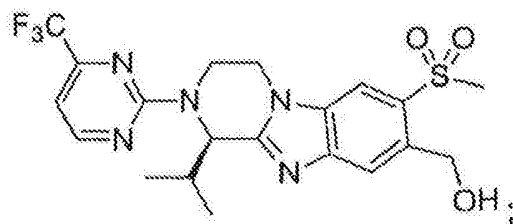
9. Az előző igénypontok bármelyike szerinti vegyület, ahol R⁴ CF₃ csoport.

10. Az 1. igénypont szerinti vegyület, ahol a vegyület a



szerkezetű, vagy azok bármelyikének gyógyászatiilag elfogadható sója.

11. Az 10. igénypont szerinti vegyület, ahol a vegyület a



szerkezetű, vagy annak gyógyászatilag elfogadható sója.

12. Gyógyászati készítmény, mely egy gyógyszerészetiileg elfogadható hordozót vagy hígítószeret és az 1-11. igénypontok bármelyike szerinti vegyületet tartalmaz.

13. Az 1-11. igénypontok bármelyike szerinti vegyület anyagnak az LXR aktivitás túlszabályozásával kezelhető betegsége vagy rendellenessége kezelésében történő alkalmazására.

14. Vegyület a 13. igénypont szerinti alkalmazásra, ahol a betegség vagy rendellenesség hyperlipidemia, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophia, májsajt steatosis, nem-alkoholos steatohepatitis (NASH), májszír-betegség (NAFLD), hyperglycemia, inzulin rezisztencia, diabetes mellitus, dyslipidemia, atherosclerosis, epekő, acne vulgaris, dermatitis, psoriasis, kontakt dermatitis, atopiás dermatitis, ekcéma, bőrspek, bőr öregedés, fénytől okozott öregedés, ráncosodás, diabetes, C típusú Niemann-Pick betegség, Parkinson-kór, Alzheimer-kór, gyulladás, xanthoma, elhízás, metabolikus szindróma, X szindróma, stroke, perifériális elzáródásos betegség, memóriavesztés, diabeteszes neuropatia, proteinuria, glomerulopathiák, diabeteszes nephropathia, hipertenzív nephropathia, IGA nephropathia, foális segmentális glomerulosclerosis, hyperphosphatemia, hyperphosphatemia cardiovascularis komplikációi, rák vagy sclerosis multiplex.

15. Vegyület a 13. igénypont szerinti alkalmazásra, ahol a betegség vagy rendellenesség atherosclerosis, Alzheimer-kór, ekcéma, psoriasis, vagy dermatitis, például atopiás dermatitis vagy kontakt dermatitis.