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Señor

SUPERINTENDENTE DE INDUSTRIA

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 12-004250- -00007-0000

Fecha: 2013-10-22 17:00:28

Tra. 11 PATENTEIYII

Act. 523 RESPUESTA

Dep. 2020 DIR.NUEVASCR

Eve: 379 FASENACIONALII

Folios: 15

Re: PI.-F. HOFFMANN-LA ROCHE AG.-Solicitud de Patente de Invención en Fase Nacional PCT para "5-(3,4-DICLORO-FENIL)-N-(2-HIDROXI-CICLOHEXIL)-6-(2,2,2-TRIFLUORO-ETOXI)-NICOTINAMIDA Y SALES DE LA MISMA, COMO AGENTES QUE ELEVAN EL COLESTEROL HDL". - Clase C07D 213/82.-Expediente número 12-004.250.-

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista de 30 de Julio de 2013.

2. Con el fin de responder a las objeciones expuestas por el Señor Examinador bajo los acápites de excepciones a la patentabilidad, reivindicaciones relativas a un uso o a un segundo uso y nivel inventivo, me permito presentar los siguientes argumentos técnicos y las siguientes modificaciones en el capítulo reivindicatorio de la solicitud de patente en cuestión, por medio de lo cual se superan completamente dichas objeciones.

3. **Excepciones de patentabilidad**

De acuerdo con el señor Examinador el objeto de las reivindicaciones 5 a 10 no es patentable de conformidad con el Artículo 20-d de la Decisión Andina 486 de 2000.

Atendiendo a lo anterior me permito señalar que el solicitante ha decidido eliminar dichas reivindicaciones 5 a 10 actualmente presentadas, con lo cual se supera completamente la objeción realizada por ese Despacho a éste respecto.

4. **Reivindicaciones relativas a un uso o a un segundo uso**

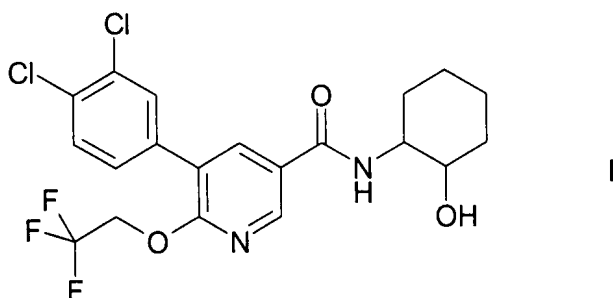
De acuerdo con el señor Examinador las reivindicaciones 11 a 13 no son patentables de conformidad con los Artículos 14 y 21 de la Decisión Andina 486 de 2000.

Atendiendo a lo anterior me permito señalar que el solicitante ha decidido eliminar dichas reivindicaciones 11 a 13 actualmente presentadas, con lo cual se supera completamente la objeción realizada por ese Despacho a éste respecto.

5. **Análisis del nivel inventivo de la solicitud**

Finalmente, de acuerdo con el señor Examinador la presente invención no es inventiva frente a las enseñanzas del documento WO 2006/106054 (**D1**). En vista de lo anterior, y con el ánimo de demostrar que el nuevo capítulo reivindicatorio de la solicitud en cuestión es inventivo frente a las enseñanzas de dicha anterioridad, atentamente me permito presentar ante ese Despacho las siguientes consideraciones técnicas:

- La solicitud de patente en cuestión se encuentra dirigida a proteger el siguiente compuesto químico específico:



incluyendo las formas isómeras y las sales farmacéuticamente aceptables del mismo.

- Ahora bien, de acuerdo con lo mencionado en la página 3 de la descripción, el objetivo técnico del solicitante fue proporcionar un compuesto que, en las concentraciones terapéuticamente activas que elevan el nivel de HDL, no interactuara con el receptor CB1, toda vez que los ligandos de dicho receptor CB1 ponen en entre dicho la utilidad terapéutica de los agentes que elevan el colesterol HDL debido a que los agonistas y los antagonistas del receptor CB1 tienen el potencial de producir marcados efectos secundarios.

Y es que en efecto, estudios científicos han demostrado de manera contundente que si bien los compuestos químicos que actúan como antagonistas del receptor CB1 son útiles en el tratamiento de la obesidad, éstos causan fuertes desórdenes psicológicos que incluyen depresión, ansiedad y el riesgo de suicidio de pacientes vulnerables. Debido a esto, por ejemplo, el producto químico comercialmente conocido como ACOMPLIA® (Rimonabant) de Sanofi Aventis, es un fármaco que actúa como antagonista del receptor CB1 que originalmente fue comercializado para tratar la obesidad pero que rápidamente debió ser retirado del mercado debido precisamente a los efectos colaterales severos que generaba (ver Anexo II del presente memorial).

- Ahora bien, tal y como el mismo solicitante lo afirma en la página 3 de la descripción, los compuestos divulgados en el documento D1 señalado por ese Despacho se caracterizan precisamente porque son útiles en el tratamiento y/o profilaxis de

enfermedades asociadas con la modulación del receptor CB1, supuestamente logrando de esta manera el tratamiento de enfermedades como obesidad, diabetes y trastornos psicológicos entre los que se incluyen la depresión y el abuso y/o dependencia a sustancias que incluyen el alcohol y la nicotina (página 25, líneas 25 y subsiguientes del documento D1).

Incluso, en la página 36 del mismo documento D1 se señala explícitamente que los compuestos químicos allí divulgados son antagonistas selectivos del receptor CB1 que muestran afinidades IC_{50} cercanas a 0,5 mM, preferiblemente por debajo de 200 nM y más preferiblemente entre 1 nM y 100 nM.

- Debido a lo anterior, resulta completamente sorprendente e inesperado que el compuesto químico revelado en la presente invención, esto es, un compuesto que simplemente se diferencia de aquel divulgado en el ejemplo 67 del documento D1 por la presencia adicional de un átomo de cloro en la posición 3 del anillo fenilo, se caracterice porque prácticamente no actúa como antagonista del receptor CB1, pero mantiene un fuerte efecto como compuesto que eleva el colesterol HDL.

Y es que en efecto, de acuerdo con lo revelado por el solicitante en la Tabla 2 (página 17) de la descripción, los compuestos "1R,2R" y "1S,2R" de la presente invención (correspondientes a los dos primeros compuestos de dicha Tabla) son alrededor de 50 y 350 veces menos potentes, respectivamente, que el compuesto del ejemplo 67 del documento D1 (tercer compuesto divulgado en la Tabla) como antagonistas del receptor CB1, lo anterior sin que se vea afectada su actividad como agentes que aumentan el colesterol HDL, tal y como se desprende de los resultados comparativos divulgados por el solicitante en la Tabla 1 (página 16) de la descripción.

- Teniendo presente los datos experimentales previamente mencionados y las características farmacológicas de los compuestos conocidos en el estado de la técnica anterior, es claro entonces que la persona medianamente versada en la materia no habría podido sugerir de manera alguna que un compuesto estructuralmente similar a aquel enseñado en el ejemplo 67 de D1 preserve la eficacia para aumentar el colesterol HDL pero no actúe como antagonista del receptor CB1 y por lo tanto no genere los efectos colaterales indeseados, en particular, aquellos relacionados con desórdenes psicológicos.

Con base en lo anteriormente planteado, me permito manifestar ante ese Despacho que la materia revelada en el capítulo reivindicatorio de la solicitud de patente en cuestión presenta un inequívoco carácter inventivo frente a las enseñanzas del documento D1, cumpliendo por lo tanto a cabalidad con las disposiciones de patentabilidad establecidas en el artículo 18 de la Decisión 486 de 2000.

6. Concesión de la patente en Europa

Finalmente y aparte de lo arriba mencionado, me permito señalar que la solicitud de patente en cuestión ha sido aceptada por la Oficina Europea de Patentes, razón por la cual el 3 de Julio de 2013 se concedió la patente EP 2 475 645 B1.

Ante todo, es preciso señalar que con la información mencionada anteriormente de ninguna manera pretendo desconocer la independencia de la que goza la Superintendencia de Industria y Comercio al momento de analizar los méritos de patentabilidad de una solicitud, de acuerdo con las disposiciones del Convenio de París para la protección de la propiedad industrial.

Sin embargo, sí considero de gran importancia resaltar el hecho de que la materia técnica revelada en la solicitud de patente en cuestión ha sido catalogada como novedosa, inventiva e industrialmente aplicable por los Examinadores de la Oficina Europea de Patentes, incluso luego de tener en cuenta el mismo documento D1 señalado por el señor Examinador para la solicitud de patente colombiana, esto es, el documento WO 2006/106054, hecho que evidentemente representa un claro indicio de que la solicitud de patente en cuestión cumple a cabalidad con los requisitos de patentabilidad establecidos en la Decisión 486 de 2000.

7. Conclusión

De conformidad con los argumentos presentados para demostrar la claridad y el nivel inventivo del capítulo reivindicatorio de la presente invención frente a las enseñanzas del documento D1, resulta completamente claro que se han superado las objeciones expuestas por el señor Examinador en su Concepto Técnico, y por lo tanto, dicha invención es merecedora del privilegio de patente solicitado.

8. Anexo me permito presentar:

- (i) Copia de las páginas **23** y **24**, que corresponde al nuevo capítulo reivindicatorio, el cual está compuesto por cinco (**5**) reivindicaciones y reemplaza al documento actualmente presentado;
- (ii) Copia del artículo publicado en la siguiente página de internet:
<http://es.wikipedia.org/wiki/Rimonabant>; y,
- (iii) Copia de la carátula y el capítulo reivindicatorio de la patente EP 2 475 645 B1.

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9. En vista de lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las modificaciones y los argumentos presentados y conceder el privilegio de patente solicitado.

Señor Superintendente,



Alicia Lloreda Ricaurte

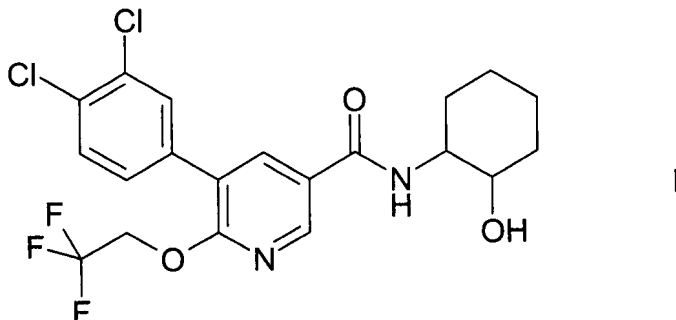
T. P. 53.215

Dirección para Notificaciones: notificacionespatentes@lloredacamacho.com

REIVINDICACIONES

5

1. Un compuesto de la fórmula



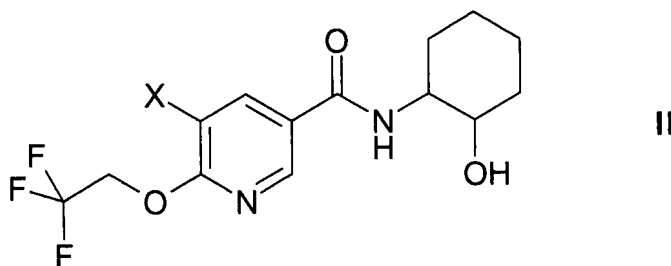
las formas isómeras y las sales farmacéuticamente aceptables del mismo.

2. Un compuesto de la fórmula I según la reivindicación 1, dicho compuesto es la 5-(3,4-dicloro-fenil)-N-((1R,2R)-2-hidroxi-ciclohexil)-6-(2,2,2-trifluoro-etoxi)-
10 nicotinamida.

3. Un compuesto de la fórmula I según la reivindicación 1, dicho compuesto es la 5-(3,4-dicloro-fenil)-N-((1S,2R)-2-hidroxi-ciclohexil)-6-(2,2,2-trifluoro-etoxi)-
nicotinamida.

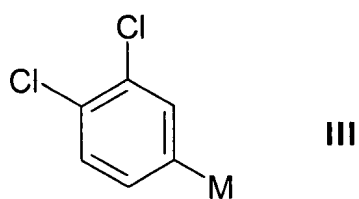
4. Una composición farmacéutica que contiene un compuesto de la fórmula I
15 según una cualquiera de las reivindicaciones de 1 a 3 y un vehículo y/o adyuvante farmacéuticamente aceptable.

5. Un proceso para la obtención de un compuesto de la fórmula I definida en una cualquiera de las reivindicaciones 1 a 3, dicho proceso consiste en condensar un compuesto de la fórmula



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en la que X es halógeno, con un compuesto aril-metal de la fórmula



- en la que M significa ácido borónico o un éster de ácido borónico, en presencia de un catalizador de Pd en medio básico,
- y opcionalmente separar los isómeros en una columna quiral de HPLC,
- 5 y, si se desea, convertir el compuesto resultante de la fórmula I en una sal farmacéuticamente aceptable del mismo.

Rimonabant

De Wikipedia, la enciclopedia libre

Rimonabant (conocido también como **SR141716**; y con nombres comerciales como **Acomplia**, **Bethin**, **Monaslim**, **Remonabent**, **Riobant**, **Slimona**, **Rimoslim**, **Zimulti**,^{n 1} y **Riomont**) es un inhibidor del apetito que actualmente se encuentra fuera del mercado en gran parte del mundo. Este es un antagonista selectivo del receptor cannabinoide CB1.² Su principal efecto es la reducción del apetito.

Rimonabant fue el primer bloqueador del receptor selectivo CB1 en ser aprobado en el mundo. En Europa, su uso principalmente era indicado en conjunto con dieta y ejercicio para pacientes con un índice de masa corporal superior a 30 kg/m², o pacientes con un índice de masa corporal superior a 27 kg/m² y que presentaban factores de riesgo asociados, tales como diabetes mellitus tipo 2 o dislipidemia. En el Reino Unido, esta droga estuvo disponible desde principios del mes de julio de 2006, mientras que ya en 2008, se encontraba disponible en al menos 56 países.

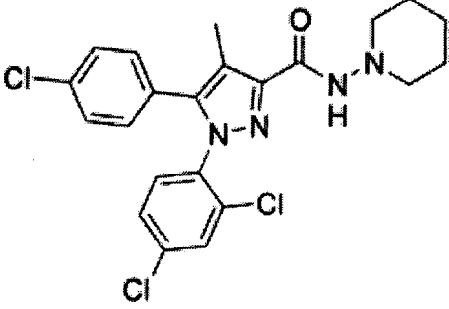
Sin embargo, el 23 de octubre de 2008, la Agencia Europea de Medicamentos (EMA) sugiere la suspensión de la comercialización de Acomplia (rimonabant), luego que su Comité para Productos Médicos de Uso Humano (CHMP) haya concluido que los riesgos de su consumo han superado a sus beneficios potenciales, principalmente después de haber detectado un aumento significativo de casos notificados de trastornos psiquiátricos severos, depresión, e incremento en casos de pensamientos suicidas y suicidio consumados.^{3 4} Su aprobación oficial para comercialización finalmente fue cancelada por EMA el 16 de enero de 2009,⁵ mientras que en Estados Unidos, el Comité Consultivo de Fármacos Endocrinológicos y Metabólicos de la FDA recomendó su no aprobación debido a los altos riesgos neurológicos y psiquiátricos para quienes la consuman.⁶

Notas

1. ↑ Rimonabant ha sido vendido en el Reino Unido por Sanofi-Aventis y en Dinamarca por Sanofi-Synthelabo bajo el nombre comercial de Acomplia, nombre que ha sido utilizado en 18 países a 2007. Bethin, Monaslim, Remonabent, Riobant, Slimona y Rimoslim son genéricos comercializados primordialmente en India. Para Estados Unidos, el

Rimonabant

 Aviso médico



Nombre (IUPAC) sistemático

5-(4- Clorofenil)-1-(2,4-dicloro-fenil)-
4-metil-*N*-(piperidin-1-yl)-
1*H*-pirazol-3-carboxamida

General

Fórmula	C ₂₂ H ₂₁ Cl ₃ N ₄ O ₁
semidesarrollada	
	Identificadores
Número CAS	158681-13-1 ¹
ChemSpider	94641
DrugBank	DB06155
PubChem	104850
UNII	RML78EN3XE
	Propiedades farmacológicas
Metabolismo	Hepático, involucra al CYP3A4
Excreción	Fecal (86%) y renal (3%)
Semivida	Variable: 6 a 9 días con IMC normal 16 días con IMC >30
Categoría embarazo	Uso no recomendado

nombre que se utilizaría sería Zimulti, aunque su permiso fue rechazado por la FDA.

Referencias

1. ↑ Número CAS (http://nlm.nih.gov/cgi/mesh/2006/MB_cgi?rn=1&term=158681-13-1)
2. ↑ Fong TM, Heymsfield SB (September 2009). «Cannabinoid-1 receptor inverse agonists: current understanding of mechanism of action and unanswered questions». *Int J Obes (Lond)* **33** (9): pp. 947–55. doi:10.1038/ijo.2009.132 (<http://dx.doi.org/10.1038/ijo.2009.132>). PMID 19597516 (<http://www.ncbi.nlm.nih.gov/pubmed/19597516>).
3. ↑ «European Medicines Agency (<http://www.emea.europa.eu/>)». Emea.europa.eu (15-02-2010). Consultado el 19-03-2010.
4. ↑ «Sanofi-aventis - A diversified healthcare company, focused on patients' needs (<http://en.sanofi-aventis.com/>)». En.sanofi-aventis.com. Consultado el 19-03-2010.
5. ↑ «Microsoft Word - Zimulti _Rimonabant_ Public Statement (<http://www.emea.europa.eu/humandocs/PDFs/EPAR/zimulti/3956009en.pdf>)» (PDF). Consultado el 11-08-2011.
6. ↑ «Warning Letter (<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm191168.htm>)» (16-11-2009). Consultado el 19-03-2010.

Obtenido de «<http://es.wikipedia.org/w/index.php?title=Rimonabant&oldid=67798099>»

Categorías: Anorexígenos | Obesidad | Organoclorados | Código ATC A

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(11) EP 2 475 645 B1

(12) EUROPEAN PATENT SPECIFICATION

- | | | |
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| (45) Date of publication and mention of the grant of the patent:
03.07.2013 Bulletin 2013/27 | (51) Int Cl.:
C07D 213/82 (2006.01)
A61K 31/465 (2006.01) | A61P 3/06 (2006.01) |
| (21) Application number: 10749873.5 | (86) International application number:
PCT/EP2010/063136 | |
| (22) Date of filing: 08.09.2010 | (87) International publication number:
WO 2011/029827 (17.03.2011 Gazette 2011/11) | |

(54) 5-(3,4-DICHLORO-PHENYL)-N-(2-HYDROXY-CYCLOHEXYL)-6-(2,2,2-TRIFLUORO-ETHOXY)-NICOTINAMIDE AND SALTS THEREOF AS HDL CHOLESTEROL RAISING AGENTS
5-(3,4-DICHLORO-PHENYL)-N-(2-HYDROXY-CYCLOHEXYL)-6-(2,2,2-TRIFLUORO-ETHOXY)-NICOTINAMIDE UND DEREN SALZE ALS HDL-CHOLERSTERINERHÖHENDE MITTEL
5-(3,4-DICHLORO-PHENYL)-N-(2-HYDROXY-CYCLOHEXYL)-6-(2,2,2-TRIFLUORO-ETHOXY)-NICOTINAMIDE ET SELS CORRESPONDANTS EN TANT QU'AGENTS AUGMENTATEURS DU CHOLESTÉROL HDL

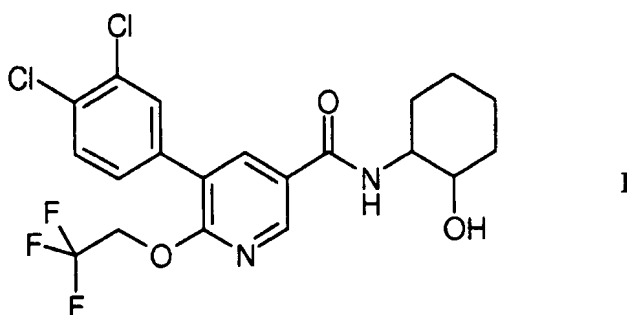
(84) Designated Contracting States: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR Designated Extension States: RS (30) Priority: 11.09.2009 EP 09170097 (43) Date of publication of application: 18.07.2012 Bulletin 2012/29 (73) Proprietor: F.Hoffmann-La Roche AG 4070 Basel (CH)	(72) Inventors: • ROEVER, Stephan 79594 Inzlingen (DE) • WRIGHT, Matthew CH-4053 Basel (CH) (74) Representative: Klostermeyer-Rauber, Dörte F. Hoffmann-La Roche AG Corporate Law Patents (CLP) Grenzacherstrasse 124 4070 Basel (CH) (56) References cited: WO-A1-2006/106054
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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

[0001] The present invention relates to a compound of formula I



and its isomeric forms and pharmaceutically acceptable salts thereof, their manufacture, pharmaceutical compositions containing them and their use as medicaments. The compound of formula I, its isomeric forms and pharmaceutically acceptable salts are especially useful as HDL-cholesterol raising agents.

[0002] Atherosclerosis and its associated coronary heart disease is the leading cause of death in the industrialized world. Risk for development of coronary heart disease has been shown to be strongly correlated with certain plasma lipid levels. Lipids are transported in the blood by lipoproteins. The general structure of lipoproteins is a core of neutral lipids (triglyceride and cholesterol ester) and an envelope of polar lipids (phospholipids and non esterified cholesterol). There are 3 different classes of plasma lipoproteins with different core lipid content: the low density lipoprotein (LDL) which is cholesteryl ester (CE) rich; high density lipoprotein (HDL) which is also cholesteryl ester (CE) rich; and the very low density lipoprotein (VLDL) which is triglyceride (TG) rich. The different lipoproteins can be separated based on their different flotation density or size.

[0003] High LDL-cholesterol (LDL-C) and triglyceride levels are positively correlated, while high levels of HDL-cholesterol (HDL-C) are negatively correlated with the risk for developing cardiovascular diseases.

[0004] No wholly satisfactory HDL-elevating therapies exist. Niacin can significantly increase HDL, but has serious toleration issues which reduce compliance. Fibrates and the HMG CoA reductase inhibitors raise HDL-cholesterol only modestly (~10-12%). As a result, there is a significant unmet medical need for a well tolerated agent which can significantly elevate plasma HDL levels.

[0005] Thus, HDL-cholesterol raising agents can be useful as medicaments for the treatment and/or prophylaxis of atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, and vascular complications of diabetes, obesity or endotoxemia.

[0006] In addition, HDL-cholesterol raising agents may be used in combination with another compound, said compound being an HMG-CoA reductase inhibitor, an microsomal triglyceride transfer protein (MTP)/ApoB secretion inhibitor, a PPAR activator, a bile acid reuptake inhibitor, a cholesteryl ester transfer protein (CETP) inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, preparations containing niacin or other HM74a agonists, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant.

[0007] Object of the present invention is therefore to provide a compound which is a potent HDL-cholesterol raising agent. It has been found that the compound of formula I of the present invention is very useful for the treatment and/or prophylaxis of diseases which can be treated with HDL-cholesterol raising agents, i.e. the compound of formula I is especially useful for the treatment and/or prevention of dyslipidemia, atherosclerosis and cardiovascular diseases. Object of the present invention is also to provide a compound which is, at therapeutically active concentrations that increase HDL-concentrations, not interacting with the CB1 receptor. This is because CB 1 receptor ligands may compromise the therapeutic utility of HDL-cholesterol raising agents, as both agonists and antagonists of the CB 1 receptor have the potential to lead to side effects.

[0008] Compounds with common structural elements have been disclosed as CB1 receptor antagonists (WO 2006/106054) and mixed CB1 receptor antagonists/HDL cholesterol raising agents (WO 2008/040651).

[0009] Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

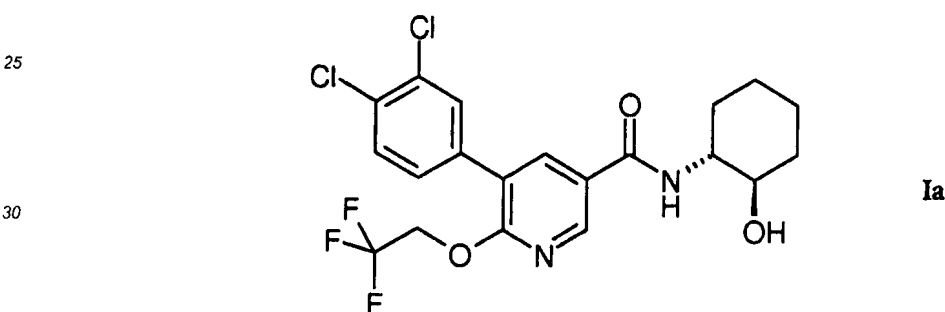
[0010] "Isomeric forms" are all forms of a compound characterized by having an identical molecular formula but that differ in the nature or the sequence of bonding of their atoms or in the arrangement of their atoms in space. Preferably, the isomeric forms differ in the arrangement of their atoms in space and can also be termed "stereoisomers". Stereo-

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somers that are not mirror images of one another are termed "diastereoisomers", and stereoisomers that are non-superimposable mirror images are termed "enantiomers", or sometimes optical isomers. A carbon atom bonded to four non-identical substituents is termed a "chiral center".

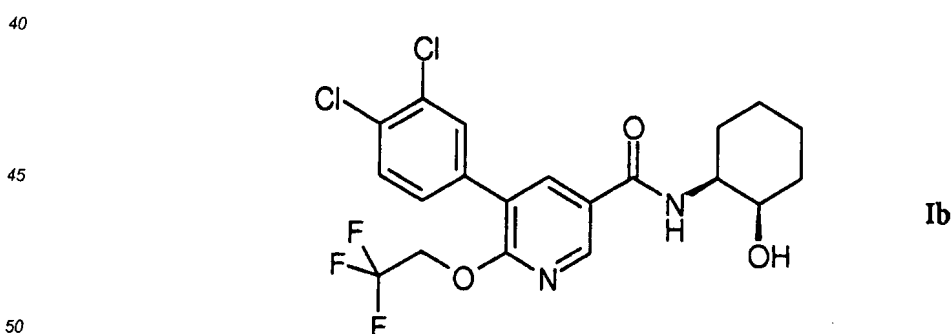
[0011] The term "pharmaceutically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, preferably hydrochloric acid, and organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, salicylic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, *N*-acetylcysteine and the like. Thus, preferred "pharmaceutically acceptable salts" include the acetate, bromide, chloride, formate, fumarate, maleate, mesylate, nitrate, oxalate, phosphate, sulfate, tartrate and tosylate salt of compounds of formula I. In addition, pharmaceutically acceptable salts may be prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethylamine, lysine, arginine, *N*-ethylpiperidine, piperidine, piperazine and the like. The compound of formula I can also be present in the form of zwitterions or in the form of hydrates. Particularly preferred pharmaceutically acceptable salts of compounds of formula I are the hydrochloride salts.

[0012] In a preferred aspect, the present invention relates to 5-(3,4-dichloro-phenyl)- *N*-((1*R*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide, i.e. a compound of formula I of the isomeric form Ia.



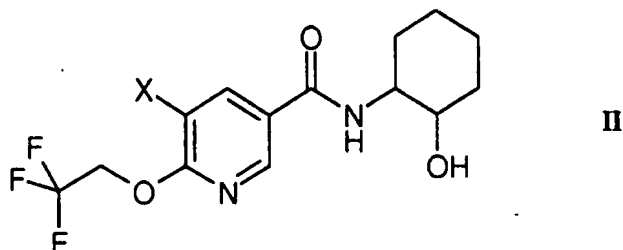
[0013] The invention also refers to 5-(3,4-dichloro-phenyl)- *N*-((1*R*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide and pharmaceutically acceptable salts thereof.

[0014] In another preferred aspect, the present invention refers to 5-(3,4-Dichloro-phenyl)- *N*-((1*S*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide, i.e. a compound of formula I of the isomeric form Ib.

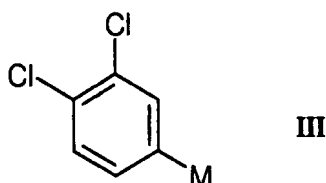


[0015] The invention also relates to 5-(3,4-dichloro-phenyl)- *N*-((1*S*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide and pharmaceutically acceptable salts thereof.

[0016] The compound of formula I can be prepared by a process, which process comprises coupling a compound of formula



wherein X is halogen, with an aryl metal species of the formula



wherein M means boronic acid or a boronic acid ester, in the presence of a Pd catalyst under basic conditions, and optionally separating the isomers on a chiral HPLC column, and, if desired, converting the resulting compound of formula I into a pharmaceutically acceptable salt thereof.

[0017] The aryl metal species is preferably an aryl boronic acid or arylboronic acid ester. The palladium catalyst is preferably a palladium(II)acetate/triphenylphosphine mixture or a palladium(II)chloride-dppf complex which is used in the presence of a base, preferably triethylamine or sodium carbonate. X is halogen, more preferably X is bromo or iodo.

[0018] The synthesis of the compounds with the general structure I can be accomplished according to the following schemes 1 to 2.

[0019] Following the procedure according to scheme 1, compound AA (5-bromo-6-chloro-3-pyridinecarboxylic acid, CAS RN 29241-62-1) can be used as starting material. AA is commercially available or can alternatively be prepared by a multi step sequence from 6-hydroxy-3-pyridinecarboxylic acid following literature procedures.

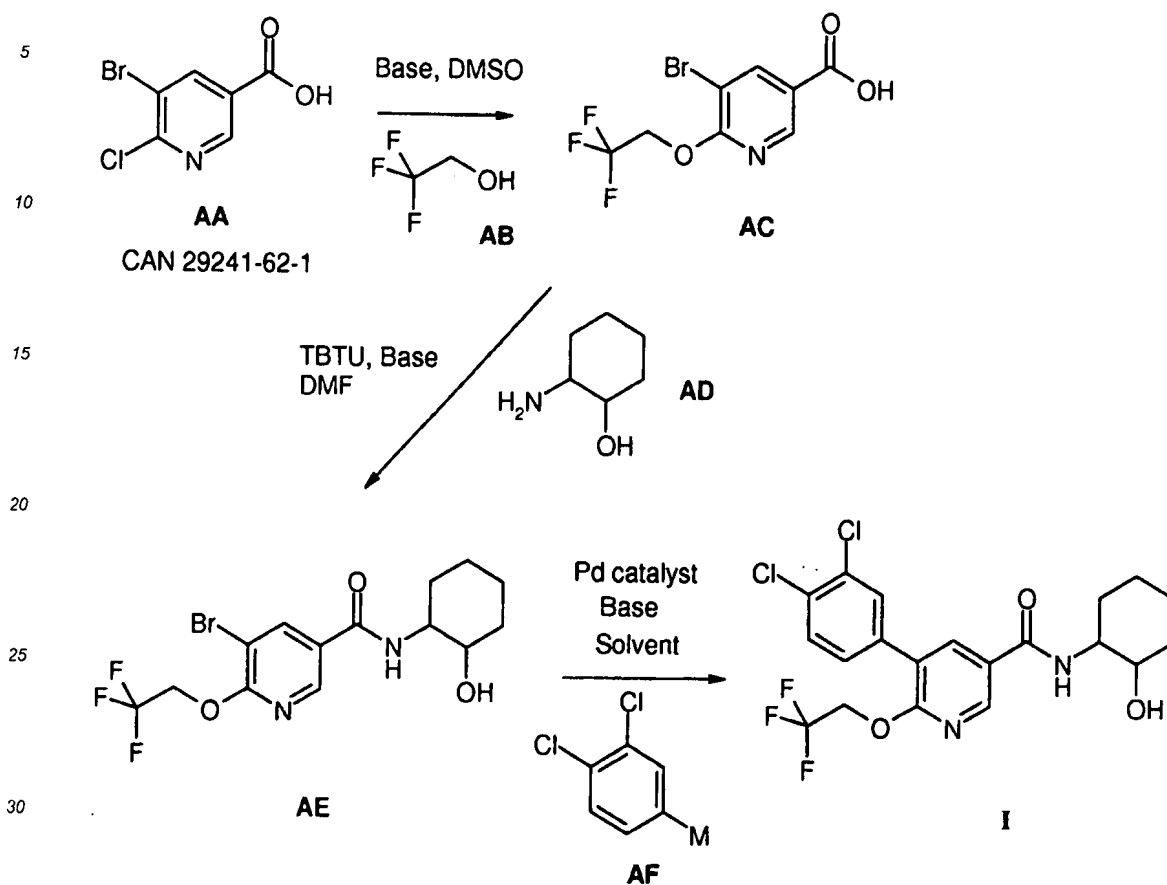
[0020] Compound AC can be prepared from AA by reaction with a suitably substituted primary or secondary alcohol of formula AB in the presence of a base, for example potassium hydroxide, in a inert solvent, for example dimethylsulfoxide, at temperatures from room temperature to reflux temperature of the solvent, preferably at room temperature.

[0021] Compound AE can be prepared by coupling AC and the corresponding amine of formula AD by suitable amide bond forming reactions. These reactions are known in the art. For example coupling reagents like N,N'-carbonyl-diimidazole (CDI), N,N'-dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (ED-Cl), 1-[bis(dimethylamino)-methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU), 1-hydroxy-1,2,3-benzotriazole (HOBt), and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) can be employed to affect such transformation. A convenient method is to use for example TBTU and a base, for example Hünig's base (N-ethyl-diisopropylamine) in an inert solvent such as for example dimethylformamide at room temperature.

[0022] In the following step compounds of formula I are obtained by coupling a suitably substituted aryl metal species of formula AF, preferably a arylboronic acid or arylboronic acid ester, with AE in the presence of a suitable catalyst, preferably a palladium catalyst and more preferably palladium(II)acetate/triphenylphosphine mixtures or palladium(II)chloride-dppf (1,1'-bis(diphenylphosphino)ferrocene) complexes and a base, preferably triethylamine or sodium carbonate in an inert solvent such as dimethylformamide or toluene.

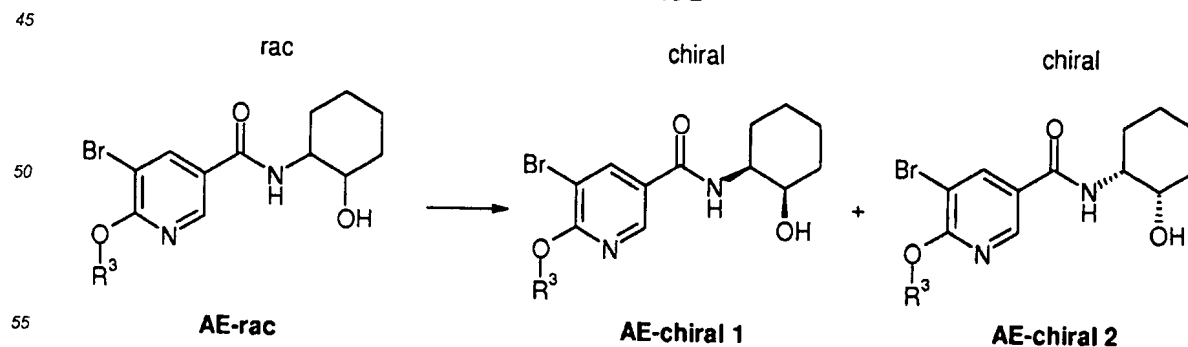
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Scheme 1



[0023] Compounds of formula AE or compounds I that are prepared according to scheme 1 may contain one or more chiral centers depending on the exact nature of the amine AD. Chiral compounds AE-chiral or I-chiral may be obtained by a variety of methods known in the art, like synthesis from chiral precursors or chiral separation methods. Chiral separation on chiral HPLC columns is advantageously performed for the compound that provides the higher solubility in the mobile phase. Compounds of formula AE are in general more soluble in heptane/alcohol mixtures than compounds of formula I. The separation of AE-chiral 1 and AE-chiral 2 from AE-rac can be performed according to scheme 2 using a suitable chiral HPLC column such as ChiralPak AD® or similar stationary phases either in batch or as moving bed process with suitable mobile phases such as heptane/isopropanol mixtures.

Scheme 2



[0024] As described above, the compounds of formula I of the present invention can be used as medicaments for the treatment and/or prophylaxis of diseases which can be treated with HDL-cholesterol raising agents. Examples of such

diseases are atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, cardiovascular diseases such as angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, and vascular complications of diabetes, obesity or endotoxemia. The use as medicament for the treatment and/or

prevention of dyslipidemia atherosclerosis and cardiovascular diseases is preferred.

[0025] The invention therefore also relates to a pharmaceutical composition comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant which are useful for the treatment and/or prophylaxis of diseases which can be treated with HDL-cholesterol raising agents.

[0026] Thus, the invention relates to a pharmaceutical composition as defined above for the treatment and/or prophylaxis of atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, cardiovascular diseases such as angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, and vascular complications of diabetes, obesity or endotoxemia.

[0027] In another embodiment, the invention relates to a compound of formula (I) for use in a method for the treatment and/or prophylaxis of diseases which can be treated with HDL-cholesterol raising agents. Examples of such diseases are atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, cardiovascular diseases such as angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, and vascular complications of diabetes, obesity or endotoxemia. A method for the treatment and/or prophylaxis of dyslipidemia atherosclerosis and cardiovascular diseases is preferred.

[0028] In addition, the invention relates to the use of compounds of formula I as defined above for the preparation of a medicament for the treatment and/or prophylaxis of diseases can be treated with HDL raising agents. Examples of such diseases are atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, cardiovascular diseases such as angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, and vascular complications of diabetes, obesity or endotoxemia. The use of compounds of formula I as defined above for the preparation of medicaments for the treatment and/or prophylaxis of dyslipidemia atherosclerosis and cardiovascular diseases is preferred.

[0029] In addition, HDL raising agents of formula I are useful in combination or association with another compound, said compound being selected from the group consisting of an HMG-CoA reductase inhibitor, an microsomal triglyceride transfer protein (MTP)/ApoB secretion inhibitor, a PPAR activator, a cholesteryl ester transfer protein (CETP) inhibitor, a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, a preparation containing niacin or other HM74a agonists, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant.

[0030] The invention therefore also relates to a pharmaceutical composition comprising a compound of formula I as defined above in combination or association with a compound selected from the group consisting of an HMG-CoA reductase inhibitor, an microsomal triglyceride transfer protein (MTP)/ApoB secretion inhibitor, a PPAR activator, a cholesteryl ester transfer protein (CETP) inhibitor, a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, a preparation containing niacin or other HM74a agonists, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant, as well as a pharmaceutically acceptable carrier and/or adjuvant.

[0031] The invention further relates to the use of compounds of formula I as defined above in combination or association with a compound selected from the group consisting of an HMG-CoA reductase inhibitor, an microsomal triglyceride transfer protein (MTP)/ApoB secretion inhibitor, a PPAR activator, a cholesteryl ester transfer protein (CETP) inhibitor, a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, a preparation containing niacin or other HM74a agonists, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant for the preparation of a medicament for the treatment and/or prophylaxis of diseases such as atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, and vascular complications of diabetes, obesity or endotoxemia.

[0032] The invention also relates a compound according to formula I in combination or association with a therapeutically effective amount of a compound selected from the group consisting of an HMG-CoA reductase inhibitor, an microsomal triglyceride transfer protein (MTP)/ApoB secretion inhibitor, a PPAR activator, a cholesteryl ester transfer protein (CETP) inhibitor, a bile acid reuptake inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, a preparation containing niacin or other HM74a agonists, an ion-exchange resin, an antioxidant, an ACAT inhibitor or a bile acid sequestrant for use in to a method for the treatment and/or prophylaxis of diseases which can be treated with HDL-cholesterol raising agents.

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[0033] The compounds of formula I and/or their pharmaceutically acceptable salts can be used in the form of pharmaceutical compositions for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, orally, e.g. in the form of buccal cavities, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions for intramuscular, intravenous or subcutaneous injection, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

[0034] The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

[0035] Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

[0036] Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavor-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

[0037] The therapeutically effective amount or dosage of the compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 100 mg, especially about 1 to 50 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the compound could be administered with one or several daily dosage units, e.g. in 1 to 3 dosage units.

[0038] The pharmaceutical compositions conveniently contain about 1-100 mg, preferably 5-50 mg, of a compound of formula I.

[0039] In the following examples the tests that were carried out in order to determine the activity of the compounds of formula I and especially their valuable pharmacological properties are described.

Examples

[0040] MS = mass spectrometry; EI = electron impact; ISP = ion spray, corresponds to ESI (electrospray); NMR data are reported in parts per million (δ) relative to internal tetramethylsilane and are referenced to the deuterium lock signal from the sample solvent (d_6 -DMSO unless otherwise stated); coupling constants (J) are in Hertz, mp = melting point; bp = boiling point; HPLC = LC = high performance liquid chromatography, Rt = retention time, TLC = thin layer chromatography, RT = room temperature, TBTU = O-(Benzotriazol-1-yl)-N,N'-tetramethyl-uronium-tetrafluoroborate; DMF = dimethylformamide, DMSO = dimethylsulfoxide, THF = tetrahydrofuran, CAN = CAS Registry Number.

Example 1

Effects on plasma lipid levels in hamsters

[0041] Efficacy of compounds in modulating plasma lipid levels was determined in hamsters after 5 days of daily administration of compounds. Male hamsters of 6-8 weeks of age were used in the studies. After one week of acclimation, blood samples were collected from 4 hour-fasted animals for plasma lipid determination. Animals were then assigned to treatment groups based on HDL-cholesterol levels. Compounds were administered by gavage, once daily for five days. Control animals received vehicle alone. Blood was collected on day five from 4 hour-fasted hamsters, 2 hours after a final treatment, for plasma lipid analysis. Total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were determined using colorimetric enzymatic assays (Roche Diagnostic GmbH, Mannheim, Germany). HDL-cholesterol was also determined after selective precipitation of HDL from plasma by standard procedures.

Table 1: Effects on HDL cholesterol levels in hamsters

Compound	HDL Cholesterol levels [as % compared to control] @ 30 mg/kg p.o. of compound
5-(3,4-Dichloro-phenyl)- N-((1R,2R)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide	+77.9 ± 11.1 %
5-(3,4-Dichloro-phenyl)-N-((1S,2R)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide	+121.9 ± 21.0%
5-(4-Chloro-phenyl)-N-((1R,2R)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide	+103.8 ± 14.7 %

Example 2

CB1 and CB2 receptor affinity

[0042] The affinity of the compounds of the invention for cannabinoid receptors was determined using membrane preparations of human embryonic kidney (HEK) cells in which the human cannabis CB1 receptor is transiently transfected using the Semliki Forest Virus system in conjunction with [3H]-CP-55,940 as radioligand. After incubation of freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glass fiber filters. Radioactivity on the filter was measured by scintillation counting.

[0043] The affinity of the compounds of the invention for cannabinoid CB2 receptors was determined using membrane preparations of human embryonic kidney (HEK) cells in which the human cannabis CB2 receptor is transiently transfected using the Semliki Forest Virus system in conjunction with [3H]-CP-55,940 as radioligand. After incubation of freshly prepared cell membrane preparation with the [3H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glass fiber filters. Radioactivity on the filter was measured by scintillation counting.

[0044] K_i values were calculated from the IC₅₀ using the Cheng-Prusoff equation.

Table 2: CB1 and CB2-receptor affinity

Compound	CB1 receptor affinity [K _i in μM]	CB2 receptor affinity [K _i in μM]
5-(3,4-Dichloro-phenyl)- N-((1R,2R)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide	1.3	>10
5-(3,4-Dichloro-phenyl)-N-((1S,2R)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide	>10	>10
5-(4-Chloro-phenyl)-N-((1R,2R)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide	0.028	>10

Example 3

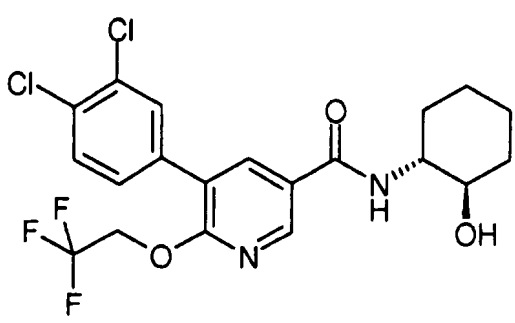
Preparation of 5-(3,4-dichloro-phenyl)-N-((1R,2R)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide

[0045]

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a) 5-Bromo-6-(2,2,2-trifluoro-ethoxy)-nicotinic acid

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[0046] 5-Bromo-6-chloro-3-pyridinecarboxylic acid (68.0 g, 0.288 mol, CAN 29241-62-1) was dissolved in DMSO (1000 mL). To this solution was added with stirring potassium hydroxide (48.25 g, 0.86 mol) and after 10 minutes of stirring at room temperature 2,2,2-trifluoroethanol (26.9 mL, 0.374 mol) was added. The mixture was stirred at room temperature for 24 h. Water (1000 mL) and concentrated hydrochloric acid (107 mL, 1280 mmol, 37%) was added and the suspension was stirred vigorously for 4 hours. The precipitate was filtered, washed with water (4x 100 mL) and vacuum dried over night to give the title compound (80.4 g) as an off white solid; MS (EI) 299, 301 (M)⁺.

b) 5-Bromo-N-((1R,2R)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide

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[0047] 5-Bromo-6-(2,2,2-trifluoro-ethoxy)-nicotinic acid (50.0 g, 0.166 mol) was dissolved in DMF (600 mL). To the solution was added TBTU (58.9 g, 0.183 mol), *N,N*-diisopropylethyl amine (142.6 mL, 0.83 mol) and (1*R*,2*R*)-2-amino-cyclohexanol (21.1 g, 0.183 mol). The reaction mixture was stirred for 3 h at room temperature. The solvent was evaporated *in vacuo*, the residue was dissolved in a mixture of ethyl acetate (1200 mL) and THF (300 mL). The solution was washed twice with water (700 mL) and the water phases were extracted with ethyl acetate (600 mL). Organic phases were pooled, dried with MgSO₄ and concentrated to about 900 mL. The product precipitated upon stirring and cooling to 0°C. Filtration, washing with ethyl acetate/*n*-heptane (1:1) and drying *in vacuo* gave the title compound (53.1 g) as a white solid; MS (ISP) 397, 399 (M)⁺.

c) 5-(3,4-dichloro-phenyl)-N-((1*R*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide

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[0048] 5-Bromo-N-((1*R*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide (59.8 g, 151 mmol) was dissolved in toluene (2500 mL) and DMF (200 mL). To this solution was added with stirring [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) CH₂Cl₂ (6.15 g, 7.5 mmol), 3,4-dichlorophenylboronic acid (30.2 g, 158 mmol) and sodium carbonate solution (2M, 150 mL). This mixture was heated to 90°C for 2 h, cooled to room temperature and filtered through diatomaceous earth. The filter cake was thoroughly washed with ethyl acetate (3000 mL). The filtrates were combined, washed twice with water (2x2000 mL), and the water phases were extracted with ethyl acetate (2x1500 mL). Organic phases were pooled, dried with MgSO₄ and the volatiles removed *in vacuo*. The residue was purified by filtration through silica (500g) with ethyl acetate. The solvent was removed and the residue was triturated with diethyl ether to give after drying *in vacuo* the title compound (45.6 g) as a grayish solid; MS 463.079, 465.077 (M+H)⁺.

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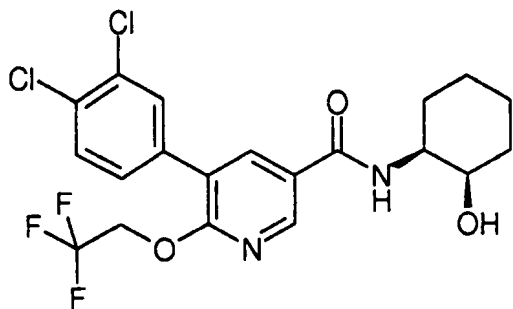
Example 4

Preparation of 5-(3,4-Dichloro-phenyl)-N-((1*S*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide

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[0049]

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a) 5-Bromo-*N*-((1*S*,2*RS*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide

[0050] 5-Bromo-6-(2,2,2-trifluoro-ethoxy)-nicotinic acid (75.0 g, 0.25 mol) was dissolved in DMF (850 mL). To the solution was added TBTU (91.0 g, 0.275 mol), *N,N*-diisopropylethyl amine (214 mL, 1.25 mol) and (1*S*,2*RS*)-2-amino-cyclohexanol hydrochloride (41.7 g, 0.275 mol). The reaction mixture was stirred for 1.5 h at room temperature. The solvent was evaporated *in vacuo*, the residue was partitioned between ethyl acetate (2500 mL) and 1 N sodium hydroxide solution (2000 mL), the water phase was separated, extracted once more with ethyl acetate (1000 mL) and the organic phases were washed 2 times with water (2x1500 mL). Organic phases were pooled, dried with MgSO₄ and concentrated to about 900 mL. The product precipitated upon stirring and cooling to 0°C. Filtration, washing with ethyl acetate/*n*-heptane (1:1) and drying *in vacuo* gave the title compound (81.1 g) as a white solid; MS (ISP) 397, 399 (M)⁺.

b) 5-Bromo-*N*-((1*S*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide

[0051] 5-Bromo-*N*-((1*S*,2*RS*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide (91.3 g, 0.23 mol) was submitted to preparative HPLC on ChiralPak AD® (250x110 mm column) using *n*-heptane/isopropanol 85/15 as mobile phase. Baseline separation was achieved and the title compound (43.6 g) was isolated as colorless solid from the first peak; MS (ISP) 395.2, 397.2 (M-H); ORD (589 nM, 20°C, CHCl₃) -21.6°.

c) 5-(3,4-Dichloro-phenyl)- *N*-((1*S*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide

[0052] 5-Bromo-*N*-((1*S*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide (42.0 g, 106 mmol) was dissolved in toluene (1900 mL) and DMF (100 mL). To this solution was added with stirring [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) CH₂Cl₂ (0.9 g, 1.06 mmol), 3,4-dichlorophenylboronic acid (20.2 g, 106 mmol) and sodium carbonate solution (2M, 106 mL). This mixture was heated to 90°C for 2 h, cooled to room temperature and partitioned between ethyl acetate (1000 mL) and water (2000 mL), the water phase was separated, extracted twice more with ethyl acetate (2x 1000 mL) and the organic phases were washed once with water and once with brine (1000 mL each). Organic phases were pooled, dried with MgSO₄ and the volatiles removed *in vacuo*. The residue was dissolved in diethyl ether (500 mL) and filtered through diatomaceous earth. The title compound precipitated when *n*-heptane (500 mL) was added drop wise to the diethyl ether solution, was filtered off and dried *in vacuo* to give 33.3 g the title compound as an off-white solid; MS 463.079 (M+H)⁺.

Example 5

[0053] Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg

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(continued)

	<u>Ingredients</u>	<u>Per tablet</u>	
5	Kernel:		
	Magnesium stearate	1.5 mg	4.5 mg
	(Kernel Weight)	120.0 mg	350.0 mg
10	Film Coat:		
	Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
	Polyethylene glycol 6000	0.8 mg	1.6 mg
	Talc	1.3 mg	2.6 mg
15	Iron oxide (yellow)	0.8 mg	1.6 mg
	Titan dioxide	0.8 mg	1.6 mg

[0054] The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is then mixed with sodium starch glycolate and magnesium stearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aq. solution / suspension of the above mentioned film coat.

Example 6

[0055] Capsules containing the following ingredients can be manufactured in a conventional manner:

	<u>Ingredients</u>	<u>Per capsule</u>
30	Compound of formula (I)	25.0 mg
	Lactose	150.0 mg
	Maize starch	20.0 mg
	Talc	5.0 mg

[0056] The components are sieved and mixed and filled into capsules of size 2.

Example 7

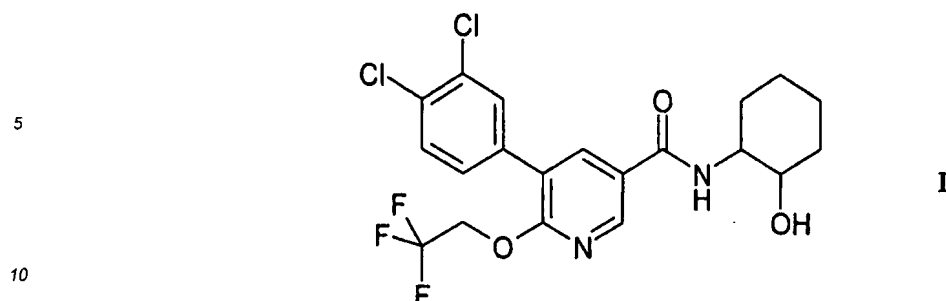
[0057] Injection solutions can have the following composition:

	Compound of formula (I)	3.0 mg
45	Polyethylene glycol 400	150.0 mg
	Acetic acid	q.s. ad pH 5.0
	Water for injection solutions	ad 1.0 ml

[0058] The active ingredient is dissolved in a mixture of Polyethylene glycol 400 and water for injection (part). The pH is adjusted to 5.0 by addition of acetic acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

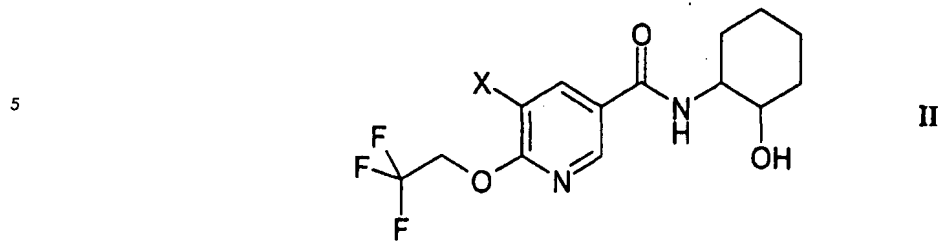
Claims

1. A compound of the formula



- and stereoisomers and pharmaceutically acceptable salts thereof.
- 15 2. A compound of formula I according to claim 1, wherein the compound is 5-(3,4-dichloro-phenyl)-N-((1*R*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide.
3. A compound of formula I according to claim 1, wherein the compound is 5-(3,4-dichloro-phenyl)-N-((1*S*,2*R*)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluoro-ethoxy)-nicotinamide.
- 20 4. A pharmaceutical composition comprising a compound of formula I according to any one of claims 1 to 3 and a pharmaceutically acceptable carrier and/or adjuvant.
5. The pharmaceutical composition according to claim 4 for the treatment and/or prophylaxis of diseases which can be treated with HDL-cholesterol raising agents.
- 25 6. A compound of formula I according to any one of claims 1 to 3 for use as medicament.
7. The compound of formula I according to claim 6 for use as medicament for the treatment and/or prophylaxis of atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, cardiovascular diseases such as angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, and vascular complications of diabetes, obesity or endotoxemia.
- 30 8. The compound of formula I according to claim 6 for use as medicament for the treatment and/or prophylaxis of dyslipidemia.
9. The compound of formula I according to claim 6 for use as medicament for the treatment and/or prophylaxis of atherosclerosis.
- 40 10. The compound of formula I according to claim 6 for use as medicament for the treatment and/or prophylaxis of cardiovascular diseases.
11. The use of a compound of formula I according to any one of claims 1 to 3 for the preparation of medicaments for the treatment and/or prophylaxis of diseases which can be treated with HDL-cholesterol raising agents.
- 45 12. The use according to claim 11 for the preparation of medicaments for the treatment and/or prophylaxis of atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial hypercholesterolemia, cardiovascular diseases such as angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, and vascular complications of diabetes, obesity or endotoxemia.
- 50 13. The use according to claim 11 for the preparation of medicaments for the treatment and/or prophylaxis of dyslipidemia, atherosclerosis and cardiovascular diseases.
- 55 14. A process for the manufacture of a compounds of formula I as defined in any one of claims 1 to 3, which process comprises coupling a compound of formula

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wherein X is halogen, with an aryl metal species of the formula

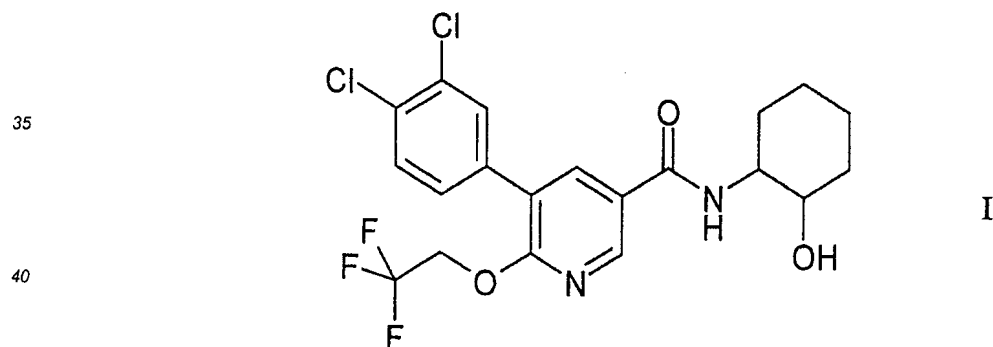


wherein M means boronic acid or a boronic acid ester, in the presence of a Pd catalyst under basic conditions, and optionally separating the isomers on a chiral HPLC column, and, if desired, converting the resulting compound of formula I into a pharmaceutically acceptable salt thereof.

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Patentansprüche

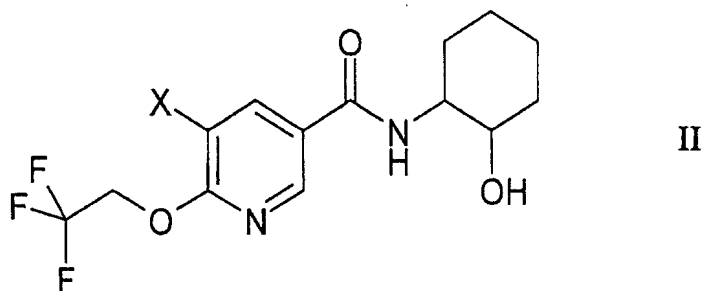
- 30 1. Eine Verbindung der Formel



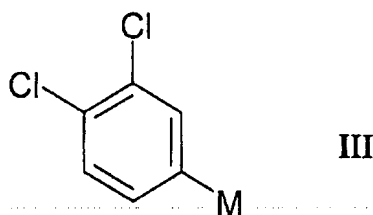
45 und Stereoisomere sowie pharmazeutisch verträgliche Salze davon.

2. Eine Verbindung der Formel I nach Anspruch 1, wobei die Verbindung 5-(3,4-Dichlorphenyl)-N-((1R,2R)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluor-ethoxy)-nicotinamid ist.
- 50 3. Eine Verbindung der Formel I nach Anspruch 1, wobei die Verbindung 5-(3,4-Dichlorphenyl)-N-((1S,2R)-2-hydroxy-cyclohexyl)-6-(2,2,2-trifluor-ethoxy)-nicotinamid ist.
4. Ein Arzneimittel, umfassend eine Verbindung der Formel I nach einem der Ansprüche 1 bis 3 und einen pharmazeutisch verträglichen Träger und/oder Hilfsstoff.
- 55 5. Das Arzneimittel nach Anspruch 4 zur Behandlung und/oder Vorbeugung von Erkrankungen, die mit Mitteln, die das HDL-Cholesterin erhöhen, behandelt werden können.
6. Eine Verbindung der Formel I nach einem der Ansprüche 1 bis 3 zur Verwendung als Medikament.

7. Die Verbindung der Formel I nach Anspruch 6 zur Verwendung als Medikament zur Behandlung und/oder Vorbeu-
gung von Atherosklerose, peripherer vaskulärer Erkrankung, Dyslipidämie, Hyperbetalipoproteinämie, Hypoalphi-
lipoproteinämie, Hypercholesterinämie, Hypertriglyceridämie, familiärer Hypercholesterinämie, kardiovaskulären
Erkrankungen, wie zum Beispiel Angina, Ischämie, kardiale Ischämie, Schlaganfall, Myokardinfarkt, Reperfusionss-
schaden, angioplastische Restenose, Hypertonie und vaskulären Komplikationen aufgrund von Diabetes, Fettlei-
bigkeit oder Endotoxämie.
8. Die Verbindung der Formel I nach Anspruch 6 zur Verwendung als Medikament zur Behandlung und/oder Vorbeu-
gung von Dyslipidämie.
9. Die Verbindung der Formel I nach Anspruch 6 zur Verwendung als Medikament zur Behandlung und/oder Vorbeu-
gung von Atherosklerose.
10. Die Verbindung der Formel I nach Anspruch 6 zur Verwendung als Medikament zur Behandlung und/oder Vorbeu-
gung von kardiovaskulären Erkrankungen.
11. Die Verwendung einer Verbindung der Formel I nach einem der Ansprüche 1 bis 3 zur Herstellung von Medikamenten
zur Behandlung und/oder Vorbeugung von Erkrankungen, die mit Mitteln, die das HDL-Cholesterin erhöhen, be-
handelt werden können.
12. Die Verwendung nach Anspruch 11 zur Herstellung von Medikamenten zur Behandlung und/oder Vorbeugung von
Atherosklerose, peripherer vaskulärer Erkrankung, Dyslipidämie, Hyperbetalipoproteinämie, Hypoalphilipoprotein-
ämie, Hypercholesterinämie, Hypertriglyceridämie, familiärer Hypercholesterinämie, kardiovaskulären Erkrankun-
gen, wie zum Beispiel Angina, Ischämie, kardiale Ischämie, Schlaganfall, Myokardinfarkt, Reperfusionsschaden,
angioplastische Restenose, Hypertonie und vaskulären Komplikationen aufgrund von Diabetes, Fettleibigkeit oder
Endotoxämie.
13. Die Verwendung nach Anspruch 11 zur Herstellung von Medikamenten zur Behandlung und/oder Vorbeugung von
Dyslipidämie, Atherosklerose und kardiovaskulären Erkrankungen.
14. Ein Verfahren zur Herstellung einer Verbindung der Formel I, wie in einem der Ansprüche 1 bis 3 definiert, wobei
das Verfahren Kuppeln einer Verbindung der Formel



wobei X Halogen ist, mit einer Aryl-Metall-Spezies der Formel



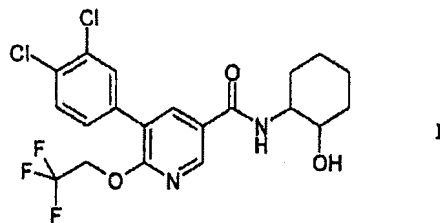
wobei M Borsäure oder ein Borsäureester bedeutet, in der Gegenwart eines Pd-Katalysators unter basischen Be-
dingungen,

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und gegebenenfalls Trennen der Isomere auf einer chiralen HPLC-Säule,
und, falls gewünscht, Umwandeln der resultierenden Verbindung der Formel I in ein pharmazeutisch verträgliches Salz davon umfasst.

Revendications

1. Composé de formule



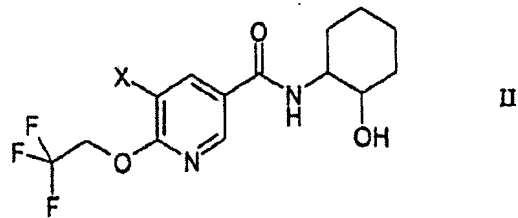
et ses stéréoisomères et sels pharmaceutiquement acceptables.

2. Composé de formule I suivant la revendication 1, le composé étant le 5-(3,4-dichlorophényl)-N-((1R,2R)-2-hydroxycyclohexyl)-6-(2,2,2-trifluoro-éthoxy)-nicotinamide.
3. Composé de formule I suivant la revendication 1, le composé étant le 5-(3,4-dichlorophényl)-N-((1S,2R)-2-hydroxycyclohexyl)-6-(2,2,2-trifluoro-éthoxy)nicotinamide.
4. Composition pharmaceutique comprenant un composé de formule I suivant l'une quelconque des revendications 1 à 3 et un support et/ou adjuvant pharmaceutiquement acceptable.
5. Composition pharmaceutique suivant la revendication 4 pour le traitement et/ou la prophylaxie de maladies qui peuvent être traitées avec des agents élevant le taux de cholestérol-HDL.
6. Composé de formule I suivant l'une quelconque des revendications 1 à 3, pour une utilisation comme médicament.
7. Composé de formule I suivant la revendication 6, pour une utilisation comme médicament pour le traitement et/ou la prophylaxie de l'athérosclérose, d'une maladie vasculaire périphérique, de la dyslipidémie, de l'hyper-bétalipoprotéïnémie, de l'hypoalphalipoprotéïnémie, de l'hypercholestérolémie, de l'hypertriglycéridémie, de l'hypercholestérolémie familiale, de maladies cardiovasculaires telles que l'angine de poitrine, une ischémie, une ischémie cardiaque, un ictus, un infarctus du myocarde, une lésion de reperfusion, une resténose angioplastique, l'hypertension, et des complications vasculaires du diabète, de l'obésité ou d'une endotoxémie.
8. Composé de formule I suivant la revendication 6, pour une utilisation comme médicament pour le traitement et/ou la prophylaxie de la dyslipidémie.
9. Composé de formule I suivant la revendication 6, pour une utilisation comme médicament pour le traitement et/ou la prophylaxie de l'athérosclérose.
10. Composé de formule I suivant la revendication 6, pour une utilisation comme médicament pour le traitement et/ou la prophylaxie de maladies cardiovasculaires.
11. Utilisation d'un composé de formule I suivant l'une quelconque des revendications 1 à 3 pour la préparation de médicaments pour le traitement et/ou la prophylaxie de maladies qui peuvent être traitées avec des agents élevant le taux de cholestérol-HDL.
12. Utilisation suivant la revendication 11 pour la préparation de médicaments pour le traitement et/ou la prophylaxie de l'athérosclérose, d'une maladie vasculaire périphérique, de la dyslipidémie, de l'hyperbêta-lipoprotéïnémie, de l'hypoalphalipoprotéïnémie, de l'hypercholestérolémie, de l'hypertriglycéridémie, de l'hypercholestérolémie familiale, de maladies cardiovasculaires telles que l'angine de poitrine, une ischémie, une ischémie cardiaque, un ictus,

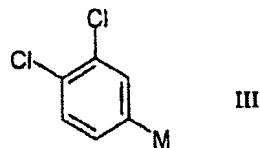
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un infarctus du myocarde, une lésion de reperfusion, une resténose angioplastique, l'hypertension, et des complications vasculaires du diabète, de l'obésité ou d'une endotoxémie.

13. Utilisation suivant la revendication 11 pour la préparation de médicaments pour le traitement et/ou la prophylaxie de la dyslipidémie, de l'athérosclérose et de maladies cardiovasculaires.
14. Procédé pour la production d'un composé de formule I répondant à la définition dans l'une quelconque des revendications 1 à 3, procédé qui comprend le couplage d'un composé de formule



dans laquelle X représente un atome d'halogène, avec une entité arylmétallique de formule



dans laquelle M représente l'acide boronique ou un ester d'acide boronique, en présence d'un catalyseur au Pd dans des conditions basiques, et, facultativement, la séparation des isomères sur une colonne de HPLC chirale, et, si cela est désiré, la conversion du composé résultant de formule I en un de ses sels pharmaceutiquement acceptables.

EP 2 475 645 B1**REFERENCES CITED IN THE DESCRIPTION**

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