(19) DANMARK

(10) DK/EP 3514157 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 D 453/02 (2006.01)* *A 61 P 3/00 (2006.01)* *A 61 P 35/00 (2006.01)* *A 61 P 43/00 (2006.01)* *C 07 D 277/30 (2006.01)* *C 07 D 417/06 (2006.01)* *C 07 D 417/12 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2023-11-27**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2023-09-06**

(86) Europæisk ansøgning nr.: **19153389.2**

(86) Europæisk indleveringsdag: **2014-03-13**

(87) Den europæiske ansøgnings publiceringsdag: **2019-07-24**

(30) Prioritet: **2013-03-15 US 201361791913 P**

(62) Stamansøgningsnr: **14718835.3**

(84) Designerede stater: **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**

(73) Patenthaver: **Genzyme Corporation, 450 Water Street, Cambridge, MA 02141, USA**

(72) Opfinder: **SIEGEL, Craig, c/o Sanofi U.S., 55 Corporate Drive, Bridgewater, New Jersey 08807, USA**
GIMI, Rayomand, c/o Sanofi U.S., 55 Corporate Drive, Bridgewater, New Jersey 08807, USA
REARDON, Michael, c/o Sanofi U.S., 55 Corporate Drive, Bridgewater, New Jersey 08807, USA
ZHAO, Jin, c/o Sanofi U.S., 55 Corporate Drive, Bridgewater, New Jersey 08807, USA

(74) Fuldmægtig i Danmark: **RWS Group, Europa House, Chiltern Park, Chiltern Hill, Chalfont St Peter, Bucks SL9 9FG, Storbritannien**

(54) Benævnelse: **FREMGANGSMÅDE TIL FREMSTILLING AF GLUCOSYLCERAMIDSYNTHASE-HÆMMERE**

(56) Fremdragne publikationer:
EP-A1- 0 747 355
WO-A1-97/30998
WO-A1-2012/063933
WO-A1-2012/175119
WO-A1-2014/043068
WO-A2-2012/129084
DE-A1- 1 768 808
DE-A1- 4 326 510
GB-A- 725 228
WILLIAM J. MIDDLETON: "1,3,4-Dioxazol-2-ones: a potentially hazardous class of compounds", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 48, no. 21, 1 October 1983 (1983-10-01), pages 3845-3847, XP055117449, ISSN: 0022-3263, DOI: 10.1021/jo00169a059
MAZUROV A ET AL: "2-(Arylmethyl)-3-substituted quinuclidines as selective alpha7 nicotinic receptor ligands", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 15, no. 8, 15 April 2005 (2005-04-15) , pages 2073-2077, XP027801786, ISSN: 0960-894X [retrieved on 2005-04-15]

Fortsættes ...

D GEFFKEN: "3-(1-Hydroxyalkyl)-1,4,2-dioxazol-5-one und 3-Hydroxyoxazolidin-2,4-dione aus 2-Hydroxycarbohydroxamsauren und 1,1'-Carbonyldiimidazol", LIEBIGS ANN. CHEM., 1 January 1982 (1982-01-01), pages 211-218, XP055117457,

DESCRIPTION

Background

[0001] The disclosure relates to a method of preparing inhibitors of glucosylceramide synthase (GCS) useful for the treatment metabolic diseases, such as lysosomal storage diseases, either alone or in combination with enzyme replacement therapy, and for the treatment of cancer.

[0002] Glucosylceramide synthase (GCS) is a pivotal enzyme which catalyzes the initial glycosylation step in the biosynthesis of glucosylceramide-base glycosphingolipids (GSLs) namely via the pivotal transfer of glucose from UDP-glucose (UDP-Glc) to ceramide to form glucosylceramide. GCS is a transmembrane, type III integral protein localized in the cis/medial Golgi. Glycosphingolipids (GSLs) are believed to be integral for the dynamics of many cell membrane events, including cellular interactions, signaling and trafficking. Synthesis of GSL structures has been shown (see, Yamashita et al., Proc. Natl. Acad. Sci. USA 1999, 96(16), 9142-9147) to be essential for embryonic development and for the differentiation of some tissues. Ceramide plays a central role in sphingolipid metabolism and downregulation of GCS activity has been shown to have marked effects on the sphingolipid pattern with diminished expression of glycosphingolipids. Sphingolipids (SLs) have a biomodulatory role in physiological as well as pathological cardiovascular conditions. In particular, sphingolipids and their regulating enzymes appear to play a role in adaptive responses to chronic hypoxia in the neonatal rat heart (see, El Alwanit et al., Prostaglandins & Other Lipid Mediators 2005, 78(1-4), 249-263).

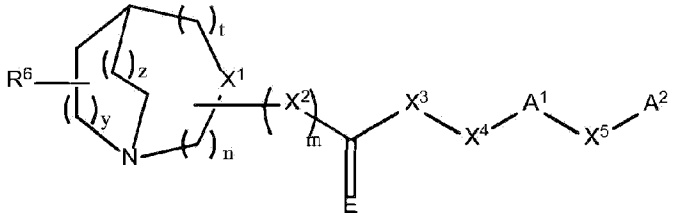
[0003] GCS inhibitors have been proposed for the treatment of a variety of diseases (see for example, WO 2005/068426). Such treatments include treatment of glycolipid storage diseases (e.g., Tay Sachs, Sandhoffs, GM2 Activator deficiency, GM 1 gangliosidosis and Fabry diseases), diseases associated with glycolipid accumulation (e.g., Gaucher disease; Miglustat (Zavesca), a GCS inhibitor, has been approved for therapy in type 1 Gaucher disease patients, see, Treiber et al., Xenobiotica 2007, 37(3), 298-314), diseases that cause renal hypertrophy or hyperplasia such as diabetic nephropathy; diseases that cause hyperglycemia or hyperinsulemia; cancers in which glycolipid synthesis is abnormal, infectious diseases caused by organisms which use cell surface glycolipids as receptors, infectious diseases in which synthesis of glucosylceramide is essential or important, diseases in which synthesis of glucosylceramide is essential or important, diseases in which excessive glycolipid synthesis occurs (e.g., atherosclerosis, polycystic kidney disease, and renal hypertrophy), neuronal disorders, neuronal injury, inflammatory diseases or disorders associated with macrophage recruitment and activation (e.g., rheumatoid arthritis, Crohn's disease, asthma and sepsis) and diabetes mellitus and obesity (see, WO 2006/053043).

[0004] In particular, it has been shown that overexpression of GCS is implicated in multidrug resistance and disrupts ceramide-induced apoptosis. For example, Turzanski et al.,

(Experimental Hematology 2005, 33 (1), 62-72) have shown that ceramide induces apoptosis in acute myeloid leukemia (AML) cells and that P-glycoprotein (p-gp) confers resistance to ceramide-induced apoptosis, with modulation of the ceramide-glucosylceramide pathway making a marked contribution to this resistance in TF-1 cells. Thus, GCS inhibitors can be useful for treatment of proliferative disorders by inducing apoptosis in diseased cells. Synthesis methods for the preparation of carbamates are known in organic chemistry. WO 2012/175119 A1 discloses a process for obtaining (S)-((R)-quinuclidin-3-yl) 1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (solifenacin) from (R)-quinuclidin-3-yl phenethylcarbamate. This starting material may be obtained by a reaction which involves 2-phenethylamine and an acyl compound comprising imidazole-1-yl as the leaving group. WO 2012/129084 A2 discloses GCS inhibitors of structural formula I, and processes for the preparation of the same. Example 75 discloses the synthesis of (S)-quinuclidin-3-yl 2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-ylcarbamate, although not via an imidazole-1-carboxamide intermediate.

Summary of the Invention

[0005] The present invention relates to a method of preparing a compound of the formula,



I

wherein:

n is 1, 2 or 3;

m is 1;

t is 0, 1 or 2;

y is 1 or 2;

z is 0, 1 or 2;

E is O;

$X^1$is CR^1;

X^2 is O;

X^3 is -NH;

X^4 is CR^4R^5, CH_2 CR^4R^5 or CH_2 -(C_1-C_6) alkyl-CR^4R^5;

X^5 is a direct bond;

R^1 is H;

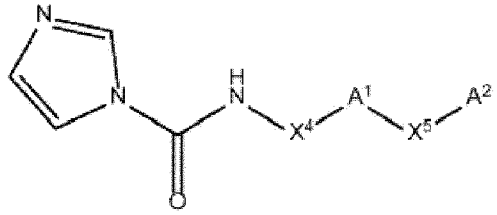
R^4 and R^5 are independently selected from H and $(C_1\text{-}C_6)$alkyl; or are taken together with the carbon to which they are attached to form a spiro $(C_3\text{-}C_{10})$cycloalkyl ring or spiro $(C_3\text{-}C_{10}$)cycloalkoxy ring;

R_6 is H;

A1 is $(C_2\text{-}C_9)$heteroaryl optionally substituted with one or more substituents selected from the group consisting of hale, $(C_1\text{-}C_6)$alkyl optionally substituted by one to three halo; $(C_1\text{-}C_6)$alkenyl, amino, $(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$dialkylamino, $(C_1\text{-}C_6)$alkoxy, nitro, CN, -OH, $(C_1\text{-}C_6)$alkyloxy optionally substituted by one to alkylcarbonyl; three halo; $(C_1\text{-}C_6)$alkoxycarbonyl, and $(C_1\text{-}C_6)$

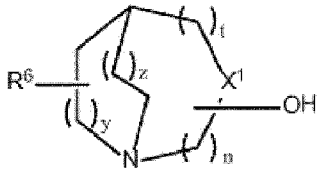
A_2 is $(C_6\text{-}C_{12})$aryl optionally substituted with one or more substituents selected from the group consisting of hale, $(C_1\text{-}C_6)$alkyl optionally substituted by one to three halo; $(C_1\text{-}C_6)$alkylenyl, amino, $(C_1\text{-}C_6)$ alkylamino, $(C_1\text{-}C_6)$dialkylamino, $(C_1$ -$C_6)$alkoxy, O($C_3\text{-}C_6$ cycloalkyl), $(C_3\text{-}C_6)$ cycloalkoxy, nitro, CN, OH, $(C_1\text{-}C_6$)alkylexy optionally substituted by one to three hale; $(C_3\text{-}C_6)$ cycloalky 1, $(C_1\text{-}C_6)$ alkoxycarbonyl, $(C_1\text{-}C_6)$ alkylcarbonyl, $(C_1\text{-}C_6)$ haloalkyl;

with the proviso that the sum of n + t + y + z is not greater than 6; comprising reacting the compound of Formula II



II

with the compound of Formula III



III

wherein n, t, y, z, R^6, X^4, A^1, X^5 and A^2 are as defined above.

[0006] In embodiments, n is 1; t is 0; y is 1 and z is 1.

[0007] In embodiments, X^4 is CR^4R^5.

[0008] In embodiments, R^4 and R^5 are each methyl.

[0009] In embodiments, A^1 is thiophene, thiazole, isothiazole, furane, oxazole, isoxazole, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrimidine, pyridazine, indole, benzothiazole, benzopyrazole, benzoimidazole, benzofuran, benzooxazole or benzoisoxazole.

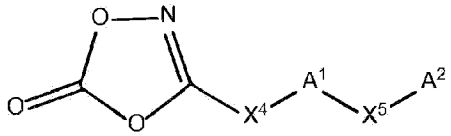
[0010] In embodiments, A^1 is thiazole.

[0011] In embodiments, A^2 is phenyl.

[0012] In embodiments, the phenyl group is substituted by halo.

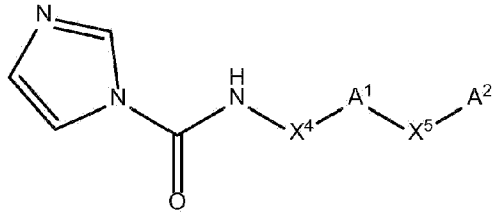
[0013] In embodiments, the halo group is fluoro.

[0014] In embodiments, the method further includes reacting the compound of Formula V



V

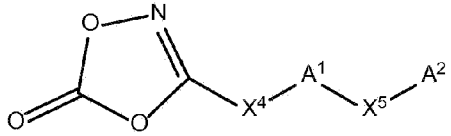
with imidazole to form the compound of Formula II



II

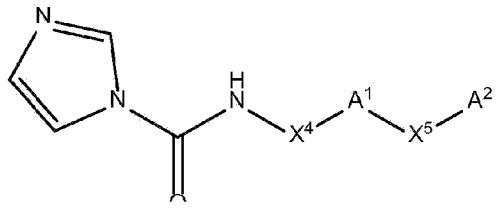
wherein X^4, A^1, X^5 and A^2 are as defined above.

[0015] In embodiments, the method further includes reacting, while heating to reflux, the compound of Formula V

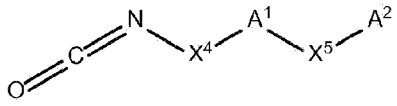


V

with imidazole to form the compounds of Formula II and Formula IV



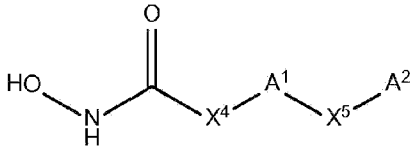
II ;



IV

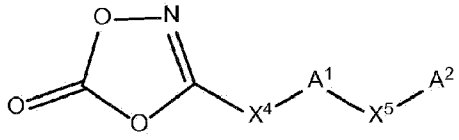
wherein X^4, A^1, X^5 and A^2 are as defined above.

[0016] In embodiments, the method further includes reacting the compound of Formula VI



VI

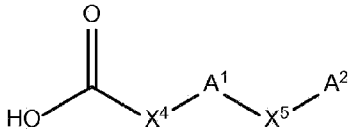
with N, N'- carbonyldiimidazole to form the compound of Formula V



V

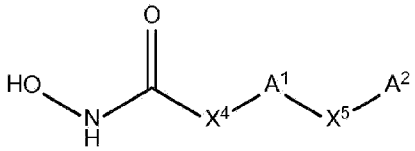
wherein X^4, A^1, X^5 and A^2 are as defined above.

[0017] In embodiments, the method further includes reacting the compound of Formula VII



VII

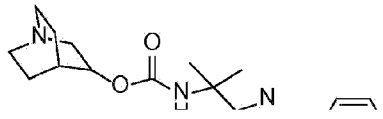
with N, N'- carbonyldiimidazole and hydroxylamine to form the compound of Formula VI

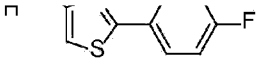


VI

wherein X^4, A^1, X^5 and A^2 are as defined above.

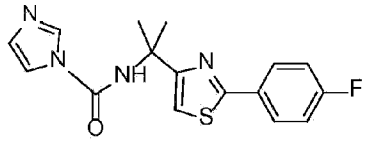
[0018] The present invention also relates to a method of preparing the compound of Formula VIII (which is a compound of Formula I)





VIII

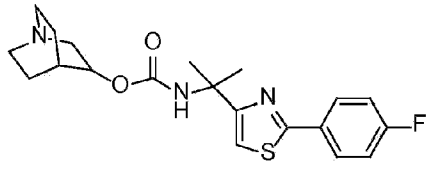
comprising reacting a compound of Formula IX (which is a compound of Formula II)



IX

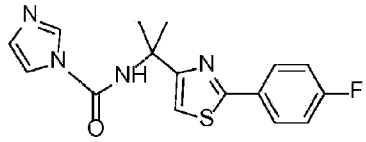
with quinuclidinol (which is a compound of Formula III).

[0019] In embodiments, the method of preparing the compound of Formula VIII

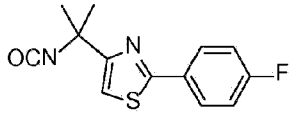


VIII

comprises reacting compounds of Formula IX and Formula X



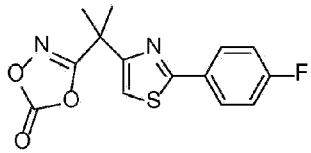
IX ;



X

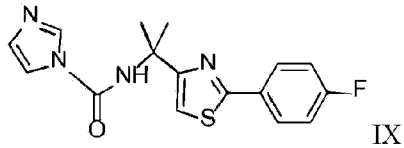
with quinuclidinol.

[0020] In embodiments, the method further includes reacting the compound of Formula XI



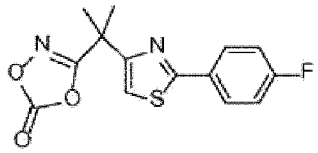
XI

with imidazole to form the compound of Formula IX



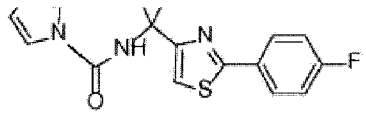
IX

[0021] In embodiments, the method further includes reacting, while heating to reflux, the compound of Formula XI

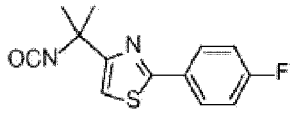


XI

with imidazole to form the compounds of Formula IX and Formula X

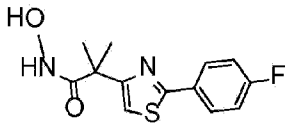


IX ;



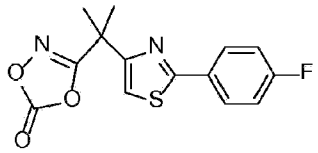
X .

[0022] In embodiments, the method further includes reacting the compound of Formula XII



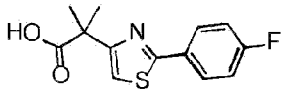
XII

with N,N'- carbonyldiimidazole to form the compound of Formula XI



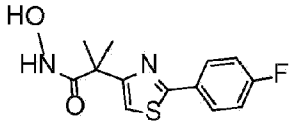
XI

[0023] In embodiments, the method further includes reacting the compound of Formula XIII



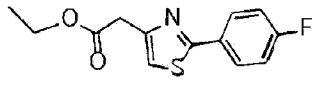
XIII

with N, N'- carbonyldiimidazole and hydroxylamine to form the compound of Formula XII



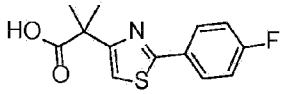
XII

[0024] In embodiments, the method still further includes reacting the compound of Formula XIV



XIV

with potassium tert-butoxide and methyl iodine followed by reacting the ethyl ester so formed with lithium hydroxide to form the compound of Formula XIII

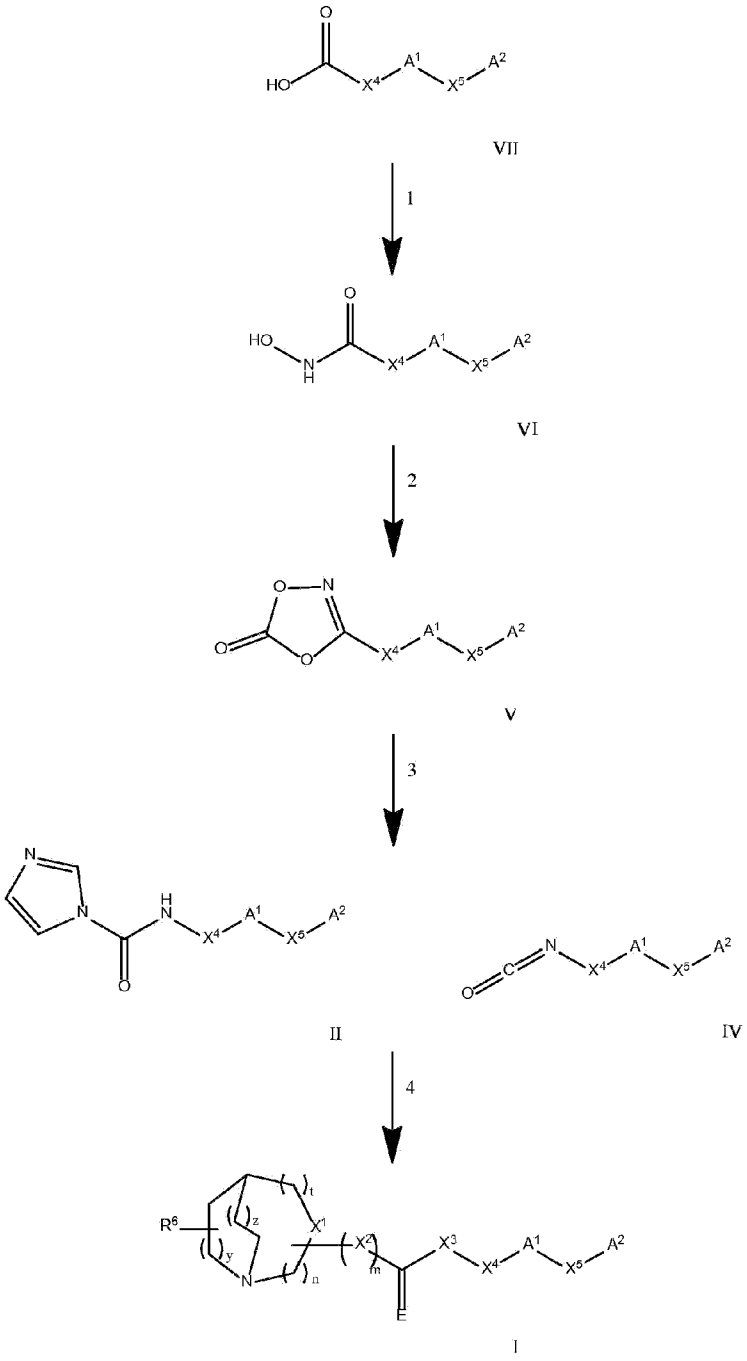


XIII

Detailed Description of the Invention

[0025]

Scheme 1



[0026] In reaction 1 of Scheme 1, the carboxylic acid compound of Formula **VII** is converted to the corresponding hydroxamic acid compound of Formula **VI** by reacting **VII** with N, N'-carbonyldiimidazole (i.e. CDI) in a polar aprotic solvent, such as tetrahydrofuran (THF). The solution is stirred at a temperature between about -5°C to about 25°C, preferable about 20°C, for a time period between about 5 minutes to about 30 minutes, preferably about 10 to 15 minutes. The resulting solution mixture is allowed to warm to room temperature and stirred for an additional time period between about 30 minutes to about 2 hours, preferably about 1 hour. Hydroxylamine is then added to the solution mixture at a temperature between about -5°C to about 10°C, preferably about 3°C. The resulting reaction mixture is stirred under inert

atmosphere (i.e., nitrogen) for a time period between about 5 min to about 8 hours, preferably about 10 min.

[0027] In reaction 2 of Scheme 1, the hydroxamic acid compound of Formula **VI** is converted to the corresponding compound of Formula **V** by the addition of N, N'-carbonyldiimidazole to a solution of **VI** in toluene under inert atmosphere (i.e., nitrogen) and stirred for a time period between about 30 minutes to about 4 hours, preferably about 2.5 hours.

[0028] In reaction 3 of Scheme 1, the compound of Formula **V** is converted to the corresponding compounds of Formula **II** and Formula **IV** by reacting **V** with imidazole in the presence of an aprotic solvent, such as toluene. The reaction mixture is heated to reflux for a time period between about 4 hours to about 28 hours, preferably about 6 hours.

[0029] In reaction 4 of Scheme 1, a mixture of the compounds of Formula **II** and Formula **IV** (or each intermediate separately) is converted to the corresponding compound of Formula **I** by reacting **II** and **IV** with (S)-(+)-quinuclidinol in the presence of an aprotic solvent, such as toluene. The reaction mixture is heated to reflux for a time period between about 12 hours to about 24 hours, preferably about 18 hours.

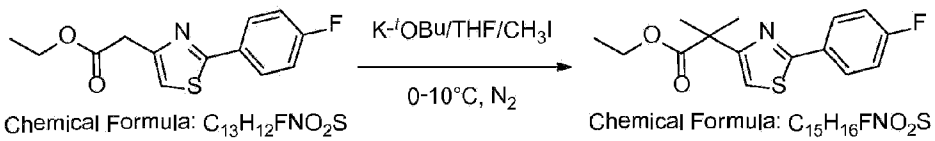
Preparation A

[0030] To 4-Fluorophenylthioamide (50.35g, 1 eq.) was added 8.6 weight volumes of 200 proof ethanol (based on thioamide) (430mL) and ethyl 4-chloroacetoacetate (68.2g, 1.1 eq.). The mixture was place under a nitrogen atmosphere. It was heated under reflux for 5h and allowed to cool to room temperature. The solution was concentrated to an oil and TBME (10 volumes, 500mL) and 6 volumes of saturated $NaHCO_3$ (300mL) added. The aqueous layer was back extracted with 5 volumes (250mL) of TBME. The combined organic layer was washed with water and then concentrated to an oil and then dried to a solid. The product was crystallized from 3 weight volumes of hot hexanes.Yield 89 % Product 98.7% pure by HPLC (area %).

Example 1

(S)-Ouinuclidin-3-vl (2-(2-(4-fluorophenvi)thiazol-4-yl)propan-2-yl)carbamate Step 1: Dimethylation with methyl iodide

[0031]



Chemical Formula: $C_{13}H_{12}FNO_2S$ Chemical Formula: $C_{15}H_{16}FNO_2S$

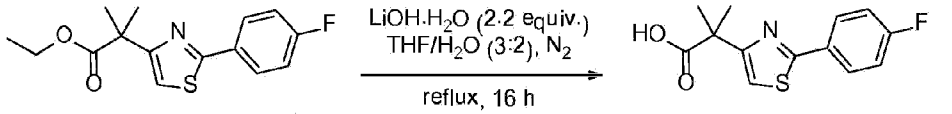
Exact Mass: 265.06
Molecular Weight: 265.30

Exact Mass: 293.09
Molecular Weight: 293.36

[0032] Procedure: In a 100 L reactor was added tetrahydrofuran (THF, 28.4 Kg) and potassium tert-butoxide (MW 112.21, 2.28 Kg g, 4.0 equiv.). This mixture was cooled to 0-2°C (internal temperature). The starting ester (MW 265.3, 2.0 Kg, 1.0 equiv.) was dissolved in THF (4 L) and transferred to the reactor over a period of 10-60 min, keeping the internal temperature below 10°C during the addition. The reaction mixture was stirred at 3-9 °C for 15-60 min. A solution of methyl iodide (MW 141.94, 1.88 L, 4.0 equiv.) in THF (4.8 L) was added to the reactor over 30-120 min keeping the internal temperature below 10°C. A solution of NaCl (2.0 Kg) in water (14L) was added over 10 min and the mixture was stirred for at least 10 min more. The reaction was made acidic by the addition of 1 M HCl (~ 1.44L). The layers were separated and the aqueous layer was back extracted with THF (6.2 kg). The combined organic layers were vacuum distilled to - 16 L. This THF solution of the Step 1 product was used in the next reaction.

Step 2: Hydrolysis of the ethyl ester with LiOH monohydrate

[0033]



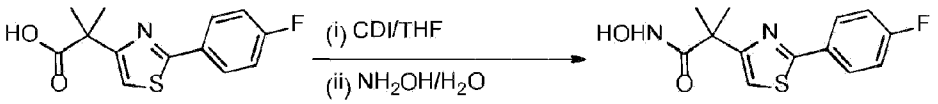
Chemical Formula: $C_{15}H_{16}FNO_2S$
Exact Mass: 293.09
Molecular Weight: 293.36

Chemical Formula: $C_{13}H_{12}FNO_2S$
Exact Mass: 265.06
Molecular Weight: 265.30

[0034] Procedure: To the ester in THF was added a solution of $LiOH.H_2O$ (MW 41.96, 0.695 Kg, 2.2 equiv.) in water (9.3 L). The mixture was heated at reflux for 8 -16 hours. After the reaction was judged complete by HPLC, water (12 L) was added and the mixture was vacuum distilled to ~ 16L. TBME (5.9 kg) was added and after stirring the layers were separated. The aqueous layer containing the product was washed a second time with TBME (5.9 Kg). TBME was added to the aqueous layer and the mixture was made acidic (pH ≤ 3) by the addition of 5 M HCl (~ 3.67 Kg). The layers were separated and the aqueous layer was extracted a second time with TBME (4.5 Kg). Heptane (15 Kg) was added to the combined organic layers and the mixture was vacuum distilled to ~ 16L. After heating and cooling to 5-25 °C and stirring for at least 3 h, the product was filtered, washed with heptane, and vacuum dried. Yield 85.8 % (2.15 Kg) HPLC purity (area %) 99.72%

Reaction 1 : Formation of hydroxamic acid with NH_2OH

[0035]



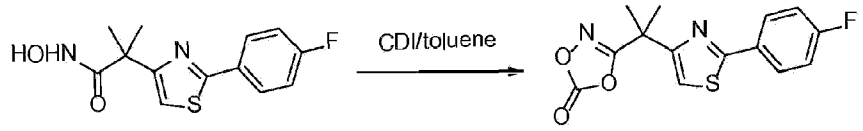
Chemical Formula: $C_{13}H_{12}FNO_2S$
Exact Mass: 265.0573
Molecular Weight: 265.3033

Chemical Formula: $C_{13}H_{13}FN_2O_2S$
Exact Mass: 280.07
Molecular Weight: 280.32

[0036] Procedure: To a 100 L reactor was added THF (14.2 Kg) and N, N'-carbonyldiimidazole (CDI; MW 162.15, 1.34 Kg, 1.1 equiv.). The acid from step 2 (2.0 Kg, 1.0 equiv) dissolved in THF (4L) was added over 15- 20 min. The mixture was stirred at room temperature for 2.5-3 h. The reaction was cooled to 0-3 °C. Aqueous hydroxylamine (50% aqueous; 1.7 L, 4.0 equiv.) was added over 5-15 min keeping the internal temperature less than 18 °C. After the addition was complete, the layers were separated and the organic layer was washed with water (12 Kg) and a solution of sodium chloride (2.0 Kg) in water (12L). The separated organic layer was vacuum distilled to ~ 16L. Toluene (13.8 Kg) was added and the mixture was again vacuum distilled to ~ 16L. Heptane (11 kg) was added and the mixture was stirred at room temperature for at least 16 h. The resulting solid was filtered , washed with heptane (11 Kg) and vacuum dried at room temperature. The yield was 1.58 Kg (74.8%).

Reaction 2 : Conversion of hydroxamic acid to a dioxazolone

[0037]



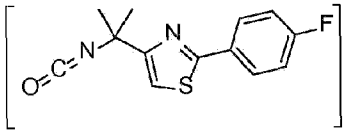
Chemical Formula: $C_{13}H_{13}FN_2O_2S$
Exact Mass: 280.0682
Molecular Weight: 280.3179

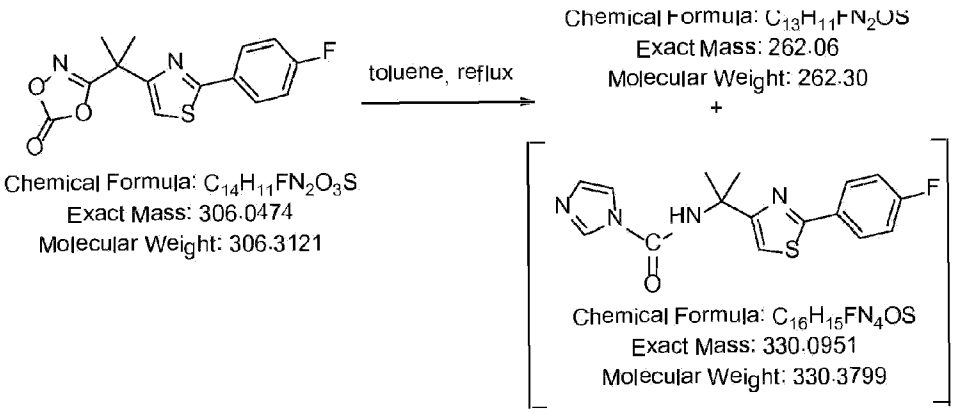
Chemical Formula: $C_{14}H_{11}FN_2O_3S$
Exact Mass: 306.05
Molecular Weight: 306.31

[0038] Procedure: Toluene (17.3 Kg) and the hydroxamic acid from, reaction 1 (MW 280.32, 2.0 Kg) was transferred to a 100 L reactor. After stirring at room temperature for at least 15 min carbonyl diimidazole CDI (MW 162.15, 1.27 Kg, 1.1 equiv.) was added. The mixture was stirred at room temperature for 1-4 h until the reaction was judged complete by HPLC.

Reaction 3: Conversion of the dioxazolone to a mixture of the imidazole urea and isocyanate

[0039]

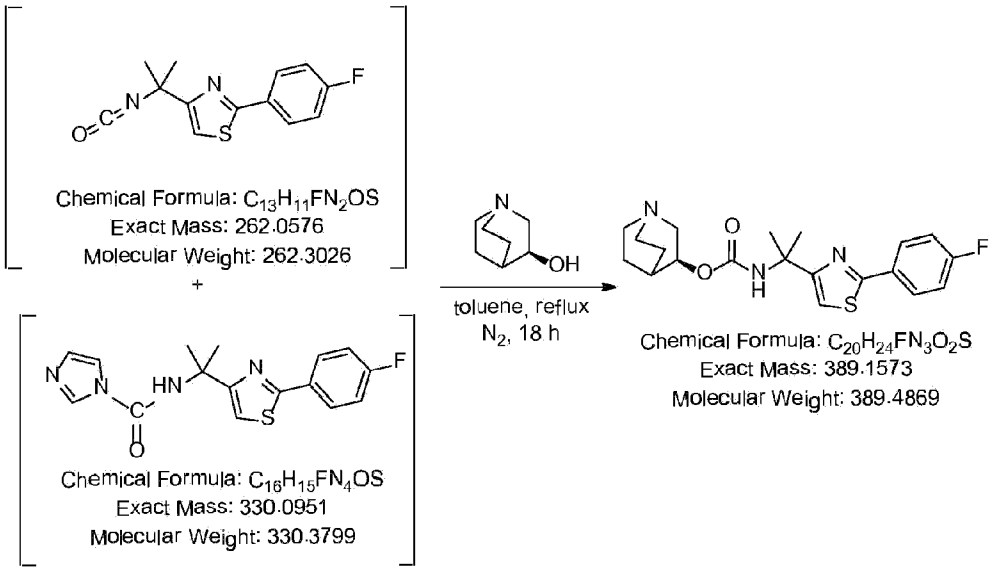




[0040] Procedure : The solution of the dioxazolone (reaction 2) was heated at 60 °C for 6-16 hours to complete the conversion to a mixture of the isocyanate and imidazole urea as judged by HPLC analysis.

Reaction 4 : Final conversion to the carbamate

[0041]



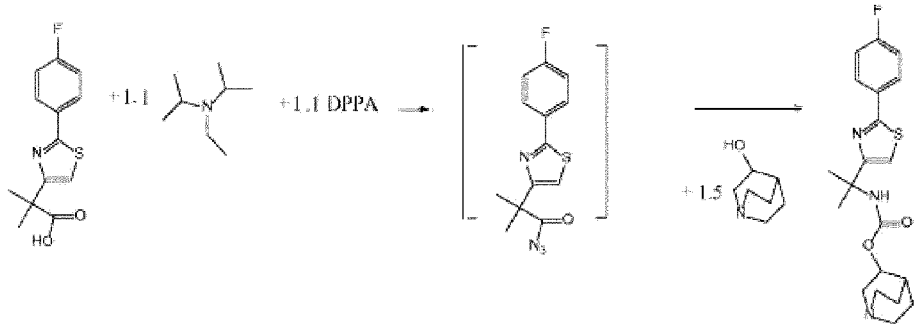
[0042] Procedure: (S)-(+)-3- quinuclidinol (1.14 Kg , 1.18 equiv.) was added to the mixture of the isocyanate and imidazole urea toluene solution (reaction 3) and the solution was heated at 100-110 °C for 18-28 h. Toluene (8.6 Kg) was added to the reaction and the mixture was washed twice with water (20 Kg). The product was removed from the organic layer with two extractions of aqueous 1M HCl (19.7 Kg). Isopropyl acetate (34.8 Kg) was added to the combined acidic aqueous layers. The mixture was cooled to 5-10 °C and 10M aqueous NaOH (5.3 Kg) was added. The layers were separated and the organic layer was vacuum distilled to ~ 16 L. Heptane (21.4 Kg) was added to the remaining isopropyl acetate solution and again the solution was distilled to ~ 16 L. the resulting suspension was stirred for at least 4 h. The

product was filtered, washed with heptane (13.7 Kg) and vacuum dried at room temperature. The yield was 2.3 Kg (82.8 % yield). HPLC purity (Area %) 99.7 % .

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 - 7.83 (m, 2H), 7.20 - 6.99 (m, 3H), 5.53 (s, 1H), 4.73 - 13 4.55 (m, 1H), 3.18 (dd, *J* = 14.5, 8.4 Hz, 1H), 3.05 - 2.19 (m, 5H), 2.0 - 1.76 (m, 11H). C NMR (100 MHz, $CDCl_3$) δ 166.38, 165.02, 162.54, 162.8-155.0 (d, C-F), 130.06, 128.43, 128.34, 116.01, 115.79, 112.46, 71.18, 55.70, 54.13, 47.42, 46.52, 27.94, 25.41, 24.67, 19.58.

Example 2 (Reference) (S)-Quinuclidin-3-yl(2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate

[0043]



[0044] 2-(2-(4-fluorophenyl)thiazol-4-yl)-2-methylpropanoic acid (1g) and diisopropylethyl amine (0.57 ml) were dissolved in toluene and stirred at 110°C under N_2. DPPA (0.9 ml) was added dropwise. The mixture was stirred for 3 hours at 110 ° C to complete the conversion of the acetyl azide and isocyanate. Quinuclidin-3-ol (0.72 g) was added and stirred for 18 hours. The resulting mixture was diluted with toluene (50 ml) and washed with saturated sodium bicarbonate solution. The organic layer was concentrated to oil. Product of quinuclidin-3-yl (2-(2-(4-fluorophenyl)thiazol-4-yl)propan-2-yl)carbamate was purified by crystallization from EtOAc (0.6 g).

REFERENCES CITED IN THE DESCRIPTION

Cited references

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

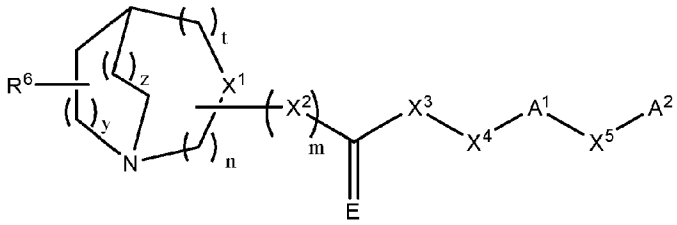
- WO2005068426A [0003]
- WO2006053043A [0003]
- WO2012175119A1 [0004]
- WO2012129084A2 [0004]

Non-patent literature cited in the description

- **YAMASHITA et al.**Proc. Natl. Acad. Sci. USA, 1999, vol. 96, 169142-9147 [0002]
- **EL ALWANIT et al.**Prostaglandins & Other Lipid Mediators, 2005, vol. 78, 1-4249-263 [0002]
- **TREIBER et al.**Xenobiotica, 2007, vol. 37, 3298-314 [0003]
- **TURZANSKI et al.**Experimental Hematology, 2005, vol. 33, 162-72 [0004]

Patentkrav

1. Fremgangsmåde til fremstilling af en forbindelse med formlen



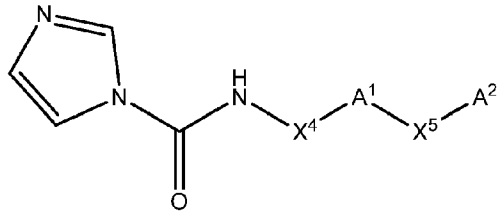
I

hvor:
n er 1, 2 eller 3;
m er 1;
t er 0, 1 eller 2;
y er 1 eller 2;
z er 0, 1 eller 2;
E er O;
X^1 er CR^1;
X^2 er O;
X^3 er -NH;
X^4 er CR^4R^5, $CH_2CR^4R^5$ eller CH_2-$(C_1$-$C_6)$alkyl-CR^4R^5;
X^5 er en direkte binding;
R^1 er H;
R^4 og R^5 er valgt uafhængigt blandt H og $(C_1$-$C_6)$alkyl; eller sammen med carbonatomet, hvortil de er bundet, danner en spiro$(C_3$-$C_{10})$cycloalkylring eller spiro$(C_3$-$C_{10})$cycloalkoxyring;
R^6 er H;
A^1 er $(C_2$-$C_9)$heteroaryl eventuelt substitueret med en eller flere substituenter valgt fra gruppen, der består af halogen, $(C_1$-$C_6)$alkyl eventuelt substitueret med en til tre halogen; $(C_1$-$C_6)$alkenyl, amino, $(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$dialkylamino, $(C_1$-$C_6)$alkoxy, nitro, CN, -OH, $(C_1$-$C_6)$alkyloxy eventuelt substitueret med en til tre halogen; $(C_1$-$C_6)$alkoxycarbonyl og $(C_1$-$C_6)$alkylcarbonyl; og
A^2 er $(C_6$-$C_{12})$aryl eventuelt substitueret med en eller flere substituenter valgt fra gruppen, der består af halogen, $(C_1$-$C_6)$alkyl eventuelt substitueret med en til tre halogen; $(C_1$-$C_6)$alkylenyl, amino, $(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$dialkylamino, $(C_1$-$C_6)$alkoxy, O$(C_3$-C_6cycloalkyl), $(C_3$-$C_6)$cycloalkoxy, nitro, CN, OH,

(C_1-C_6)alkyloxy eventuelt substitueret med en til tre halogen; (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylcarbonyl og (C_1-C_6)halogenalkyl;

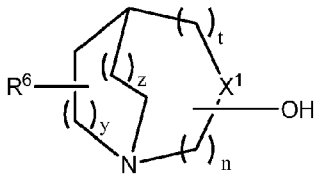
med det forbehold, at summen af n + t + y + z ikke er over 6;

hvilken fremgangsmåde omfatter reaktion af forbindelsen med formel II



II

med en forbindelse med formel III



III

hvor n, t, y, z, R^6, X^4, A^1, X^5 og A^2 er som defineret ovenfor.

2. Fremgangsmåde ifølge krav 1, hvor n er 1; t er 0; y er 1, og z er 1.

3. Fremgangsmåde ifølge krav 1 eller krav 2, hvor X^4 er CR^4R^5, eventuelt hvor R^4 og R^5 begge er methyl.

4. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 3, hvor A^1 er thiophen, thiazol, isothiazol, furan, oxazol, isoxazol, pyrrol, imidazol, pyrazol, triazol, pyridin, pyrimidin, pyridazin, indol, benzothiazol, benzopyrazol, benzoimidazol, benzofuran, benzooxazol eller benzoisoxazol.

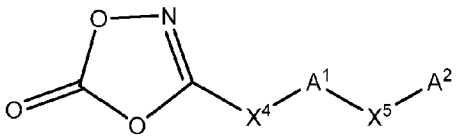
5. Fremgangsmåde ifølge krav 4, hvor A^1 er thiazol.

6. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 5, hvor A^2 er phenyl.

7. Fremgangsmåde ifølge krav 6, hvor phenylgruppen er substitueret med halogen, eventuelt hvor halogengruppen er

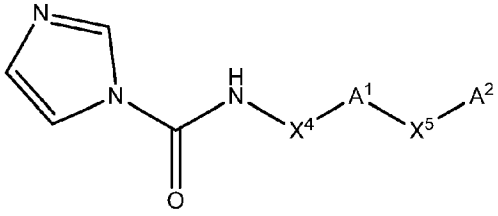
fluor.

8. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 7, som yderligere indbefatter reaktion af forbindelsen med formel V



V

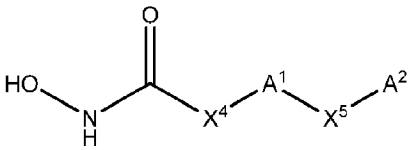
med imidazol til frembringelse af forbindelsen med formel II



II

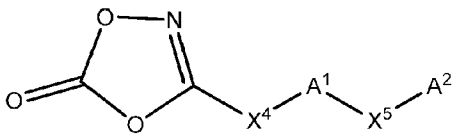
hvor X^4, A^1, X^5 og A^2 er som defineret i et hvilket som helst af kravene 1 til 7.

9. Fremgangsmåde ifølge krav 8, som yderligere indbefatter reaktion af forbindelsen med formel VI



VI

med N,N'-carbonyldiimidazol til frembringelse af forbindelsen med formel V

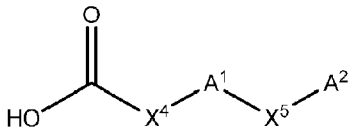


V

hvor X^4, A^1, X^5 og A^2 er som defineret i et hvilket som helst af kravene 1 til 7.

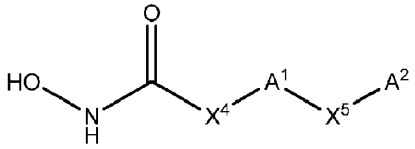
10. Fremgangsmåde ifølge krav 9, som yderligere indbefatter

reaktion af forbindelsen med formel VII



VII

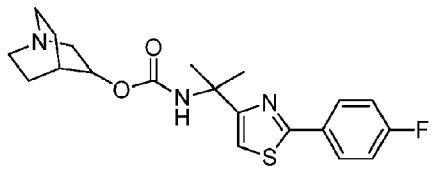
med N,N'-carbonyldiimidazol og hydroxylamin til frembringelse af forbindelsen med formel VI



VI

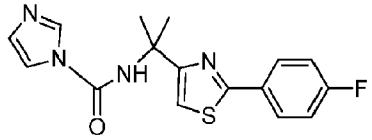
hvor X^4, A^1, X^5 og A^2 er som defineret i et hvilket som helst af kravene 1 til 7.

11. Fremgangsmåde ifølge krav 1, hvor forbindelsen med formel I er en forbindelse med formel VIII:



VIII,

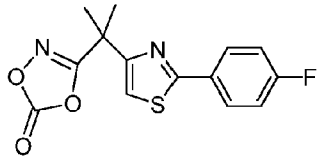
hvor forbindelsen med formel II er en forbindelse med formel IX:



IX, og

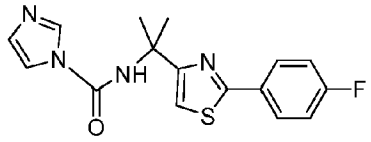
hvor forbindelsen med formel III er quinuclidinol.

12. Fremgangsmåde ifølge krav 11, som yderligere indbefatter reaktion af forbindelsen med formel XI



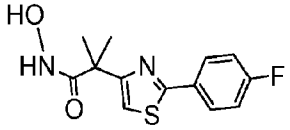
XI

med imidazol til frembringelse af forbindelsen med formel IX



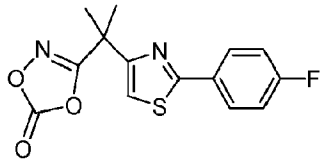
IX.

13. Fremgangsmåde ifølge krav 12, som yderligere indbefatter reaktion af forbindelsen med formel XII



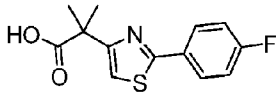
XII

med N,N'-carbonyldiimidazol til frembringelse af forbindelsen med formel XI



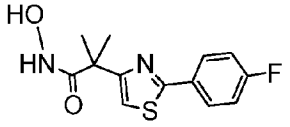
XI.

14. Fremgangsmåde ifølge krav 13, som yderligere indbefatter reaktion af forbindelsen med formel XIII



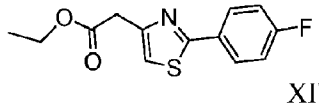
XIII

med N,N'-carbonyldiimidazol og hydroxylamin til frembringelse af forbindelsen med formel XII



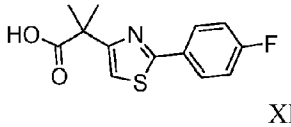
XII.

15. Fremgangsmåde ifølge krav 14, som yderligere indbefatter reaktion af forbindelsen med formel XIV



XIV

med kalium-tert-butoxid og methyliod efterfulgt af reaktion af ethylesteren, der dannes således, med lithiumhydroxid til frembringelse af forbindelsen med formel XIII



XIII.