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(54) **Title**: AMINE SALTS OF PITAVASTATIN AND ROSUVASTATIN

(57) **Abstract**: The present invention relates to oxygen-comprising amine salts of HMG-CoA reductase inhibitors, to a method of producing said amine salts and to the use of said amine salts in the production of pharmaceutically acceptable salts of HMG-CoA reductase inhibitors.

AMINE SALTS OF PITAVASTATIN AND ROSUVASTATIN

Field of the invention

The present invention relates to oxygen-comprising amine salts of HMG-CoA reductase inhibitors, to a method of producing said amine salts and to the use of said amine salts in the production of pharmaceutically acceptable salts of HMG-CoA reductase inhibitors.

Background of the invention

HMG-CoA reductase inhibitors, also known as statins, are widely used drugs prescribed to treat hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis. Examples of HMG-CoA reductase inhibitors are atorvastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

Production of HMG-CoA reductase inhibitors is known and includes (bio)-chemical conversion, chromatography, crystallization extraction, fermentation and the like. Some HMG-CoA reductase inhibitors, like lovastatin, are produced by fermentation using microorganisms of different species identified as species belonging to Aspergillus, Monascus, Nocardia, Amycolatopsis, Mucor or Penicillium genus. Some, like mevastatin, pravastatin and simvastatin, are obtained by treating the fermentation products using the methods of chemical or enzymatic synthesis. Others, like atorvastatin, fluvastatin, pitavastatin and rosuvastatin, are the products of total chemical synthesis.

In several cases, production of HMG-CoA reductase inhibitors includes isolation and purification through salt formation. For example, in US 4,319,039 and US 4,342,767, the ammonium salt of lovastatin is isolated from the organic phase which has been extracted from the fermentation medium. In the same documents the ethylene diamine, tetramethyl ammonium, potassium and *N*-methylglucamine salts as well as salts of different amino acids such as L-arginine, L-lysine and L-ornithine is described. EP 65,835 discloses the preparation of the *tert*-octyl amine and L-ornithine salts of certain modified HMG-CoA reductase inhibitors, whereby also other salts with

amines such as ammonia, amino acids or organic amines like benzyl amine, cycloheptyl amine, cyclohexyl amine, cyclopentyl amine, dibenzyl amine, dicyclohexyl amine, *N*,*N*-diethylbenzyl amine, *N*,*N*-diethylcycloheptyl amine, *N*,*N*-dimethylbenzyl amine, *N*,*N*-dimethylcyclohexyl amine, *N*,*N*-dimethylcyclopentyl amine, *N*-ethylcycloheptyl amine, *N*-ethylcyclohexyl amine, 2-ethylhexyl amine, *N*-ethyl-*N*-methylbenzyl amine, *N*-methylbenzyl amine, 2-methylbenzyl amine, *N*-methylcyclopentyl amine, *N*-methylpiperidine, *N*-methylpyrrolidine, morpholine, octyl amine, phenethyl amine, piperidine, pyrrolidine and tribenzyl amine are mentioned. US 5,763,646 and US 5,763,653 disclose the preparation of the cyclopropyl amine and *n*-butyl amine salts of lovastatin and their use in a process of chemical semi synthesis of simvastatin. US 5,403,860 discloses amine salts of octahydronaphthalene oxime derivatives of HMG-CoA reductase inhibitors ML-236A, ML-236B, MB-530A and MB-530B. As final amine salts, dibenzyl amine, dicyclohexyl amine, D-glucosamine, morpholine, *tert*-octyl amine and D-phenylglycine alkyl ester salts are mentioned. WO 00/17150 describes amine salts of HMG-CoA reductase inhibitors in the process for semi synthetic preparation of HMG-CoA reductase inhibitors and the conversion of the amine salts of HMG-CoA reductase inhibitors into the pharmaceutically acceptable salts of the HMG-CoA reductase inhibitors. WO 00/17150 mentions atorvastatin, fluvastatin, lovastatin, mevastatin, pravastatin and simvastatin as HMG-CoA reductase inhibitors on the one hand and a wide range of alkyl amines on the other hand, preferred examples of which are straight, branched or cyclic alkyl amines such as *tert*-amyl amine, *n*-butyl amine, *sec*-butyl amine, *tert*-butyl amine, cyclohexyl amine, dibutyl amine, dicyclohexyl amine, *N*,*N'*-diisopropylethylene diamine and *N*-methyl-cyclohexyl amine.

The first reports of amine salts of rosuvastatin are of a more recent date. For example, WO 2010/081861 describes the preparation of amine salts of rosuvastatin and their use in the preparation of the calcium salt of rosuvastatin. Amines disclosed by WO 2010/081861 include *sec*-butyl amine, *tert*-butyl amine, cycloheptyl amine and cyclopentyl amine. Other amine salts of rosuvastatin are disclosed in WO 2012/073256 (rosuvastatin salts of lysine, arginine, triethanol amine, ethanol amine, choline, epolamine, meglumine and ethylene diamine), WO 2012/063115 (rosuvastatin salts of thioureas, heterocyclic amines such as tetrahydrofurfuryl amine, azoles, amino acids, triazoles and pyridines); WO 2012/046193 (rosuvastatin salts of histidine and lysine); WO 2010/035284 (rosuvastatin salts of (S)-2-amino-3,3-dimethyl butane and (S)-(-)-α-

methylbenzyl amine), WO 2001/60804 (rosuvastatin salts of ammonium, methyl ammonium, ethyl ammonium, diethanol ammonium, tri(hydroxymethyl)-methyl ammonium, benzyl ammonium, and 4-methoxybenzyl ammonium) and WO 2005/077916 (rosuvastatin salts of cyclohexyl ammonium, diisopropyl ammonium, isopropyl ammonium, dicyclohexyl ammonium, and (S)-(+)-α-methylbenzyl ammonium).

For pitavastatin, the number of disclosures of amine salts is more limited. In EP 742209 short chain (1-3) alkyl amine salts of pitavastatin are disclosed, in WO 2007/132482 the arginine salt is disclosed while WO 2012/106584 discloses diethanol amine and meglumine salts of pitavastatin.

Driven by the pressure to avail medication such as HMG-CoA reductase inhibitors at affordable prices, industry is in constant need for process rationalization and optimization. There is thus a need for starting substances and intermediates that are of high purity that can be prepared using simple and low cost techniques. From this perspective, it is an aim of the invention to provide alternative amine salts of HMG-CoA reductase inhibitors that can be used in the production of HMG-CoA reductase inhibitors.

Detailed description of the invention

In a first aspect the invention provides an amine salt of HMG-CoA reductase inhibitors wherein said amine comprises an oxygen atom. It was surprisingly found that HMG-CoA reductase inhibitors readily form salts with said amines and crystallize once they are formed. It has been found that crystals of the amine salt of the desired HMG-CoA reductase inhibitor of high purity may be obtained from solutions comprising a large number of impurities and undesired HMG-CoA reductase inhibitor analogs.

In a first embodiment the amine comprises an oxygen atom and preferably the amine comprises an ether bond. The amine comprising an oxygen atom may be straight, branched or cyclic. Preferred examples are choline, ethyldiethanol amine, 2-furfuryl amine, 3-furfuryl amine, glucosamine, meglumine, *N*-methylglucamine 2-tetrahydrofurfuryl amine, 3-tetrahydrofurfuryl amine, tetramethyl ammonium hydroxide and tromethamine.

In a second embodiment the oxygen-comprising amine is unsaturated. In this respect, the term unsaturated refers to at least one double bond or at least one triple bond between two carbon atoms. The unsaturated amine may be straight, branched or

cyclic. A preferred example is 2-furfuryl amine. Furfurylamine is present as a key structural element in Furosemide (a diuretic used for hypertension and edema), and it is used in skin care cosmetics for anti-aging.

Furfural and derivatives have favorable toxicological properties, see for example "Furfural and Derivatives", H.E. Hoydonkx et al., pp. 285-313, in: Ullmann's Encyclopedia of Industrial Chemistry, 2012, Wiley-VHC Verlag, Weinheim, Germany.

It has advantageously been found that formation of the amine salts of pitavastatin and rosuvastatin can be combined in a single process step with the deprotection sequence that is usually required in the synthesis of HMG-CoA reductase inhibitors that are made through total synthesis. During production carboxyl and hydroxyl functions of these molecules need to be protected and protective groups are removed at the final stage of the synthesis. Removal of protective groups usually includes an acidic treatment. It was found that the amines of the present invention not only are suitable for formation of stable and pure salts but simultaneously can function to neutralize acidic conditions, thereby preventing the formation of additional foreign salts.

In a second aspect, the present invention provides a process for the preparation of salts of HMG-CoA reductase inhibitors pitavastatin and rosuvastatin with amines as specified in the first aspect of the invention.

In one embodiment, the process may be performed as follows. A protected derivative of pitavastatin or rosuvastatin, for example the methyl ester of pitavastatin acetonide or rosuvastatin acetonide, is dissolved or suspended in a suitable solvent, for example acetonitrile. Removal of protecting groups may be carried out by treatment with acid followed by treatment with base, or vice versa. Optionally the organic solvent may be changed by distillation followed by addition of a second solvent, for example ethyl acetate. Preferably the aqueous phase is removed after which the amine of choice is added to the organic phase. Preferably the amount of amine added is from 1.0 to 2.0 mole-equivalents compared to the HMG-CoA reductase inhibitor. The resulting mixture can optionally be concentrated in order to reduce mother liquor losses, if any. The desired amine salt of the HMG-CoA reductase inhibitor precipitates or crystallizes and can be isolated following simple techniques known to the skilled artisan, such as centrifugation, decantation, filtration and the like. Preferably the salt

thus obtained is washed with the same solvent as used for the crystallization/precipitation process. Optionally the amine salt of the HMG-CoA reductase inhibitor may be re-crystallized, for instance from an alternate solvent such as acetonitrile.

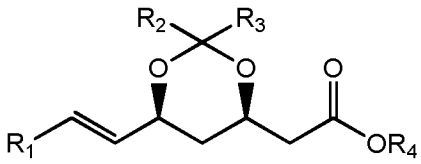
It was found that furfurylamine, having a boiling point of 145°C, can be advantageously removed via distillation instead of extraction. In general, not many high-boiling amines can be removed in this way, as they require more lengthy and less economical extraction procedures.

In a third aspect, the present invention provides a process for the preparation of metal salts of pitavastatin or rosuvastatin. Preferably said metal salts are pharmaceutically acceptable, examples of which are calcium and magnesium. Contrary to the teaching of US 5,403,860 that lower yields are obtained when using the salts of HMG-CoA reductase inhibitors as starting or intermediate substances, we have found that, when using the amine salts of HMG-CoA reductase inhibitors according to the present invention, the yields and the purity of the prepared HMG-CoA reductase inhibitors are equal to or greater than when using the HMG-CoA reductase inhibitors in the lactone form. Thus, it was found that in processes for the synthetic construction of HMG-CoA reductase inhibitors the formation of amine salts of HMG-CoA reductase inhibitors in the synthetic medium, in comparison with the mere metal salts as described in publicly accessible literature, represents an efficient means for the isolation and/or purification of HMG-CoA reductase inhibitors by simple crystallization. The amines which are described in the present invention and which readily form salts with HMG-CoA reductase inhibitors are thus particularly suitable as auxiliary materials or processing aids for the isolation and/or purification of HMG-CoA reductase inhibitors. Accordingly, the novel amine salts of HMG-CoA reductase inhibitors of the present invention are also highly valuable as such.

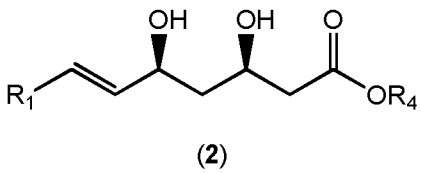
EXAMPLES

Example 1

Preparation of amine salts of pitavastatin and rosuvastatin

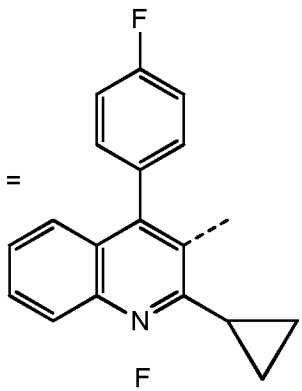


(**1**)

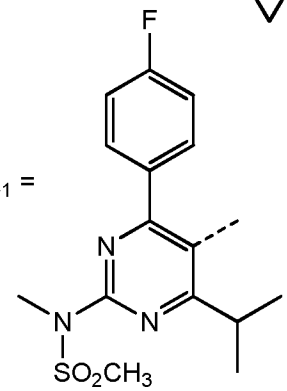


(**2**)

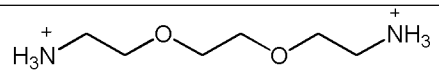
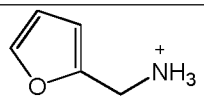
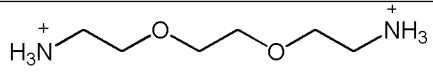
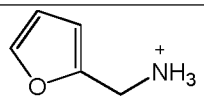
(**1a, 2a**): R_1 =



(**1b, 2b**): R_1 =



The methyl ester of pitavastatin acetonide (**1a**, $R_2 = R_3 = R_4 = CH_3$; 5.6 mmol) or rosuvastatin acetonide (**1b**, $R_2 = R_3 = R_4 = CH_3$; 5.6 mmol) was added to acetonitrile (21 mL). The mixture was heated to 35°C until complete dissolution was obtained. To the solution 0.02 N aqueous HCl (9 mL) was added over a period of 1 h. The mixture was stirred for 12 h, followed by addition of 1 N aqueous NaOH in 15 min until pH = 12. After stirring for 1 h, the mixture was concentrated under vacuum to remove acetonitrile. Next, ethyl acetate (30 mL) was added followed by addition of 1 N aqueous HCl until pH = 4. The ethyl acetate phase was separated. To the ethyl acetate phase was added over a period of 30 min, 1 equiv. (5.6 mmol) of amine (see Table below) dissolved in ethyl acetate (10 mL). Upon addition, a white precipitate was formed. The resulting slurry was stirred for 1h, followed by filtration of the amine salt of the HMG-CoA reductase inhibitor pitavastatin or rosuvastatin. The amine salt was washed with ethyl acetate (2 x 5 mL), dried and re-crystallized from acetonitrile.

HMG-CoA Reductase Inhibitor	Amine	Product Formula	
			R_4
Pitavastatin	Ethyldiethanol amine	**2a**	
Pitavastatin	2-Furfuryl amine	**2a**	
Rosuvastatin	Ethyldiethanol amine	**2b**	
Rosuvastatin	2-Furfuryl amine	**2b**	

Example 2

Preparation of the calcium salts of pitavastatin and rosuvastatin

The amine salt of the HMG-CoA reductase inhibitor pitavastatin or rosuvastatin obtained in Example 1 was added to water (20 mL) and the pH was adjusted to 12 with 1 N aqueous NaOH. The reaction mixture was extracted with ethyl acetate (20 mL). The organic phase was separated and the aqueous phase was concentrated to 15 mL. To the obtained clear aqueous solution was added in portions over a period of 1 h, 7 mL of a solution of 4.5 w/w% $Ca(OAc)_2 \cdot H_2O$ in water. Upon addition white precipitate was formed. After 1 h the precipitate was filtered and dried to give the calcium salt of pitavastatin or rosuvastatin as a white solid.

Example 3

Preparation of rosuvastatin-Ca ((2b), $R_4 = Ca^{2+}$) from ((4*R*,6*S*)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester ((1b), $R_2 = R_3 = R_4 = CH_3$)

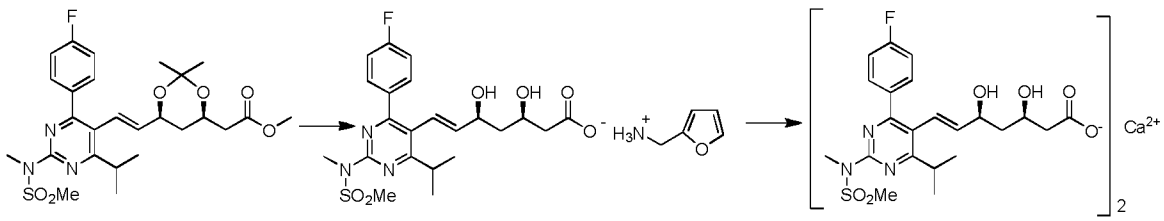
2-((4*R*,6*S*)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester (3.0 g, 5.6 mmol) was added to acetonitrile (21 mL). The mixture was heated to 35°C until complete dissolution was obtained. To the solution, 0.02 N aqueous HCl (9 mL) was added over a period of 1 h. The mixture was stirred for 12 h, followed by addition of 1 N aqueous

NaOH in 15 min until pH = 12. After stirring for 1 h, the mixture was concentrated under vacuum to remove the acetonitrile. Next ethyl acetate (30 mL) was added followed by addition of 1 N aqueous HCl until pH = 4. The ethyl acetate phase was separated. To the ethyl acetate phase was added over a period of 30 min, 1 equiv. of the amine dissolved in ethyl acetate (10 mL). Upon addition, a white precipitate was formed. The resulting slurry was stirred for 1 h, followed by filtration of the rosuvastatin-amine salt. The salt was washed with ethyl acetate (2 x 5 mL) and dried. The salt was re-crystallized from acetonitrile.

The salt was added to water (20 mL) and the pH was adjusted to 12 with 1 N aqueous NaOH. The reaction mixture was extracted with ethyl acetate (20 mL) and the organic phase was separated. The aqueous phase was concentrated to 15 mL. To the obtained clear aqueous solution was added in portions over a period of 1 h, 7 mL of a solution of 4.5 w/w% $Ca(OAc)_2 \cdot H_2O$ in water. Upon addition white precipitate was formed. After 1 h the precipitate was filtered and dried to give 2.1 g of the calcium salt of rosuvastatin as a white solid (yield 72%). ^{1}H NMR (300 MHz, DMSO): δ 7.72 (dd, 2H), 7.29 (t, 2H), 6.51 (d, 1H), 5.54 (dd, 1H), 4.21 (dd, 1H), 3.71 (m, 1H), 3.55 (s, 3H), 3.51-3.41 (m, 4H), 2.09 (dd, 1H), 1.92 (dd, 1H), 1.57-1.42 (m, 1H), 1.36-1.25 (m, 1H), 1.22 (dd, 6H).

Example 4

Preparation of rosuvastatin-Ca ((2b), $R_4 = Ca^{2+}$) from 2-((4*R*,6*S*)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester ((1b), $R_2 = R_3 = R_4 = CH_3$) via furfuryl amine salt



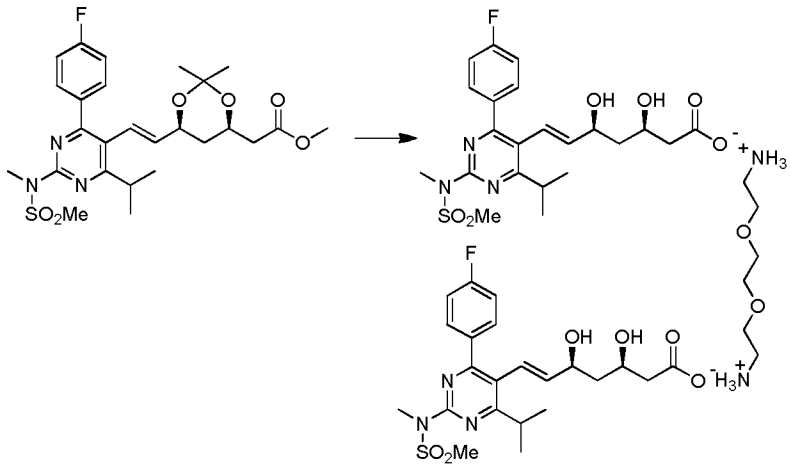
2-((4*R*,6*S*)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester (3.0 g, 5.6 mmol) was added to acetonitrile (21 mL). The mixture was heated to 35°C until complete dissolution was obtained. To the solution, 0.02 N aqueous HCl (9 mL) was added over a period of 1 h. The mixture was stirred for 12 h, followed by addition of 1 N aqueous

NaOH in 15 min until pH = 12. After stirring for 1 h, the mixture was concentrated under vacuum to remove the acetonitrile. Next ethyl acetate (30 mL) was added followed by addition of 1 N aqueous HCl until pH = 4. The ethyl acetate phase was separated. The ethyl acetate phase was heated to 50°C. Then furfurylamine (0.82 g, 8.4 mmol, 1.5 equiv.) dissolved in ethyl acetate (10 mL) was added in 10 min. Upon addition, a white precipitate was formed. The reaction mixture was cooled to 20-25°C and stirred for 2 h, followed by filtration of the rosuvastatin furfuryl amine salt. The salt was washed with ethyl acetate (2 x 5 mL) and dried. The salt was added to acetonitrile (20 mL) and heated to 60°C until complete dissolution. The solution was cooled to 20-25°C and the resulting slurry was stirred for 2 h. The rosuvastatin furfuryl amine salt was isolated by filtration, washed with acetonitrile (2 x 5 mL) and dried.

The salt was added to water (20 mL) and the pH adjusted to 3 with 1N aqueous HCl. The reaction mixture was extracted with MTBE (20 mL). The organic phase was separated and extracted with 1N aqueous NaOH. The aqueous phase was separated and concentrated to 15 mL. To the obtained clear aqueous solution was added in portions over a period of 1 h, 7 mL of a solution of 4.5 w/w% $Ca(OAc)_2 \cdot H_2O$ in water. Upon addition white precipitate was formed. After 1 h the precipitate was filtered and dried to give the calcium salt of rosuvastatin as a white solid (2.1 g, yield 72%). From the filtrate, the Rosuvastatin can be recovered in order to increase the overall yield. For example, this can be done, after acidification to pH = 4 and extraction with methyl tert butylether by formation of the amine salt as described in this example. In another embodiment, this filtrate can be combined with the extraction procedure as described in the example leading to a single step.

Example 5

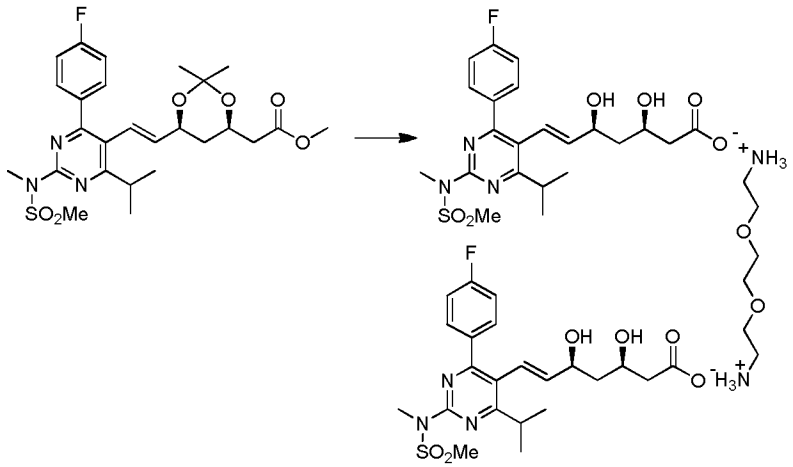
Preparation of rosuvastatin-2,2'-(ethylenedioxy)diethyl amine salt ((2b), $R_4 = H_2NO(CH_2)_2O(CH_2)_2NH_3^+$) from 2-((4*R*,6*S*)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethyl- sulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester ((1b), $R_2 = R_3 = R_4 = CH_3$)



2-((4*R*,6*S*)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester (5.4 g, 10.0 mmol) was added to acetonitrile (35 mL) and 0.02 N aqueous HCl (17 mL) was added. The reaction mixture was stirred for 18 h at 25°C. Then 1 N aqueous NaOH was added in 15 min until pH = 12. After stirring for 1 h, the mixture was concentrated under vacuum to remove the acetonitrile. Then ethyl acetate (50 mL) was added followed by addition of 1 N aqueous HCl until pH = 4. The ethyl acetate phase was separated. To the ethyl acetate phase was added 2,2'-(ethylenedioxy)diethyl amine (0.75 g, 5.1 mmol, 0.5 equiv.). The ethyl acetate phase was concentrated and a thick oil was obtained. The residue was taken up in acetonitrile (60 mL) and water (2.6 mL) and heated to 50°C. The reaction mixture was cooled to 20-25°C and stirred for 2 h. The precipitated solid was filtered and washed with acetonitrile/water (10/1 v/v, 10 mL). The product was dried to give the 2,2'-(ethylenedioxy)diethyl amine di-salt of rosuvastatin (4.5 g, 81% yield).

Example 6

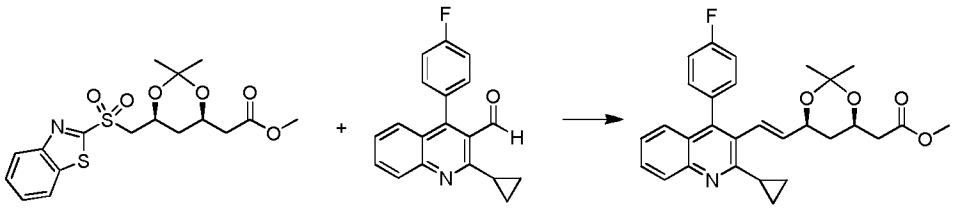
Preparation of rosuvastatin-2,2'-(ethylenedioxy)diethyl amine salt ((2b), $R_4 = H_2NO(CH_2)_2O(CH_2)_2NH_3^+$) from 2-((4*R*,6*S*)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethyl- sulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester ((1b), $R_2 = R_3 = R_4 = CH_3$)



2-((4*R*,6*S*)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester (5.4 g, 10.0 mmol) was added to acetonitrile (35 mL) and 0.02 N aqueous HCl (17 mL) was added. The reaction mixture was stirred for 18 h at 25°C. Then 1 N aqueous NaOH was added in 15 min until pH = 12. After stirring for 1 h, saturated NaCl solution (15 mL) was added, followed by 1 N aqueous HCl until pH = 4. The acetonitrile phase was separated and concentrated to 20 mL. Next acetonitrile (30 mL) and water (1 mL) were added. The acetonitrile was heated to 50°C and a solution of 2,2'-(ethylenedioxy)diethyl amine (0.75 g, 5.1 mmol, 0.5 equiv.) in acetonitrile (10 mL) was added. The reaction mixture was cooled to 20-25°C and stirred for 3 h. The precipitated solid was filtered and washed with acetonitrile/water (10/1 v/v, 10 mL). The product was dried to give the 2,2'-(ethylenedioxy)diethyl amine di-salt of rosuvastatin (4.7 g, 84% yield).

Example 7

Preparation of 2-((4*R*,6*S*)-6-((E)-2-(2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate, methyl ester from 2-cyclopropyl-4-(4--fluorophenyl)quinolin-3-carbaldehyde and 2-((4*R*,6*S*)-6-((benzo[d]thiazol-2-ylsulfonyl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester

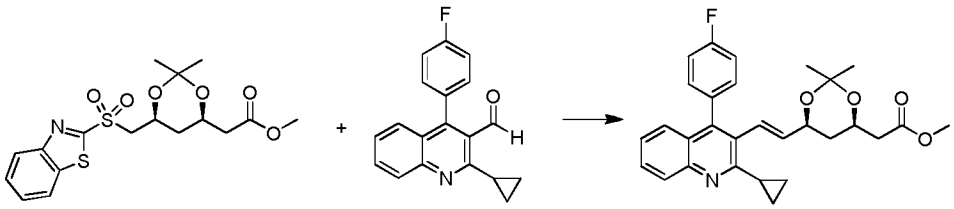


2-((4*R*,6*S*)-6-((Benzo[d]thiazol-2-ylsulfonyl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester (35.0 g, 87 mmol) and 2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-carbaldehyde (23.9 g, 82 mmol) were added to 78 mL of N-methyl-2-pyrrolidone and 280 mL of 2-methyltetrahydrofuran. The mixture was heated until 50°C and filtered. The solution was cooled to - 62°C, followed by addition of 54 mL of 2M NaO-*t*Bu in tetrahydrofuran (108 mmol) in 2.5 h keeping the temperature between -55 and -60°C. The temperature was allowed to increase to -20°C and quenched with 200 mL of water. The mixture was transferred to another reactor using 30 mL of 2-methyltetrahydrofuran and the reaction mixture heated to 50°C. The pH was adjusted to 12 with 29 mL of 4N aqueous NaOH. The layers were separated. The organic phase was washed 2 times with 200 mL of a 5 w/w % aqueous NaCl solution, whereby the pH was adjusted to 12 using 4N aqueous NaOH, followed by 1 time with 100 mL of a 5 w/w% aqueous NaCl solution, whereby the pH was adjusted to 12 with 4N aqueous NaOH. Finally, the organic phase was washed with 100 mL of 5 w/w% aqueous $NaHCO_3$. The organic layer was evaporated to give a thick oil. The solid was re-crystallized from 200 mL of isopropanol to give 2-((4*R*,6*S*)-6-((E)-2-(2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate, methyl ester as a white solid (32.1 g, yield 77.6%) with an HPLC purity of 99.7%.

The ^{1}H NMR data of this compound were in agreement with the literature data, see Hiyama T.; Minami T.; Yanagawa Y.; Ohara Y. WO 95/11898, 1995 to Nissan Chemical Industries, example 4 of this publication).

Example 8

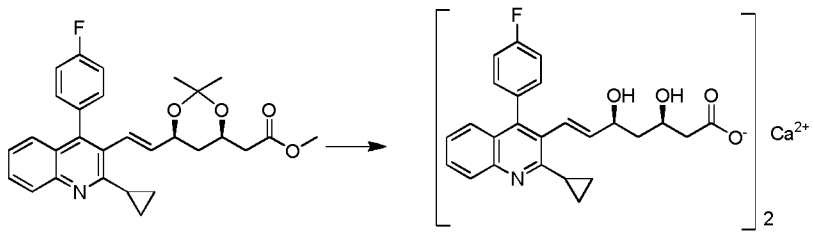
Preparation of 2-((4*R*,6*S*)-6-((E)-2-(2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate, methyl ester from 2-cyclopropyl-4-(4--fluorophenyl)quinolin-3-carbaldehyde and 2-((4*R*,6*S*)-6-((benzo[d]thiazol-2-ylsulfonyl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester



2-((4*R*,6*S*)-6-((Benzo[d]thiazol-2-ylsulfonyl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester (30.0 g, 75 mmol) and 2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-carbaldehyde (20.3 g, 70 mmol) were added to 35 mL of N-methyl-2-pyrrolidone and 200 mL of 2-methyltetrahydrofuran at 22°C. The reaction mixture was cooled to - 60°C. Then 42 mL of 2M NaO-*t*Bu in tetrahydrofuran (84 mmol) was added in 2.5 h keeping the temperature between -55 and -60°C. The temperature was allowed to increase to -50°C and quenched with 100 mL of water. The mixture was transferred to another reactor using 30 mL of 2-methyltetrahydrofuran, heated to 50°C and the pH adjusted to 12.6 with 31 mL of 4N aqueous NaOH. The layers were separated. The organic phase was washed 2 times with 100 mL of a 5 w/w % aqueous NaCl solution, whereby the pH was adjusted each time to 12 using 4N aqueous NaOH. Next, the organic phase was washed with 100 mL of 5 w/w% aqueous $NaHCO_3$. The organic layer was evaporated to give a thick oil. The solid was re-crystallized from 200 mL of isopropanol to give 2-((4*R*,6*S*)-6-((E)-2-(2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate, methyl ester as a white solid (29.0 g, yield 81.3%) with an HPLC purity of 99.5%.

Example 9

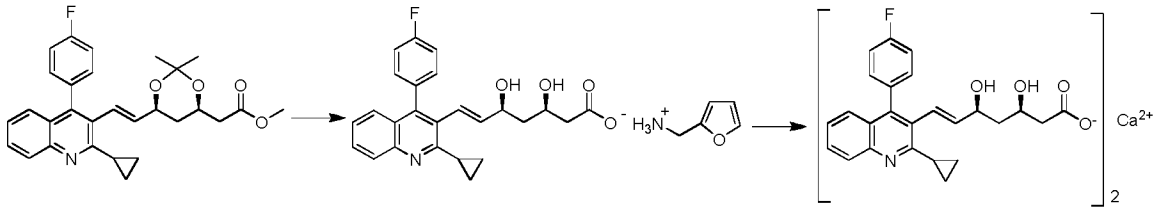
Preparation of Pitavastatin-Ca ((2a), $R_4 = Ca^{2+}$) from 2-((4*R*,6*S*)-6-((E)-2-(2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester ((1a), $R_2 = R_3 = R_4 = CH_3$)



2-((4*R*,6*S*)-6-((E)-2-(2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester (10.0 g, 21.0 mmol) was added to acetonitrile (50 mL). The mixture was heated to 45°C, followed by addition of 4N aqueous HCl (5.3 mL, 21 mmol). The reaction mixture was stirred for 1.5 h and cooled to 22°C. Then in total 12 mL of 4N aqueous NaOH was added until pH 12.7. After stirring for 30 minutes, the pH was reduced to 9 by addition of acetic acid. The acetonitrile was removed via distillation under vacuum, followed by addition of 30 mL of water. To the clear solution was added over a period of 30 min, 47.3 mL of a solution of 4.5 w/w% $Ca(OAc)_2 \cdot H_2O$ in water. Upon addition white precipitate was formed. After 1 h the precipitate was filtered, washed with water (2 x 15 mL) and dried to give 9.0 g of the calcium salt of Pitavastatin as a solid. HPLC purity 98.8%, KF 2.1% water.

Example 10

Preparation of Pitavastatin-Ca ((2a), $R_4 = Ca^{2+}$) from 2-((4*R*,6*S*)-6-((E)-2-(2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester ((1a), $R_2 = R_3 = R_4 = CH_3$) via furfuryl amine salt



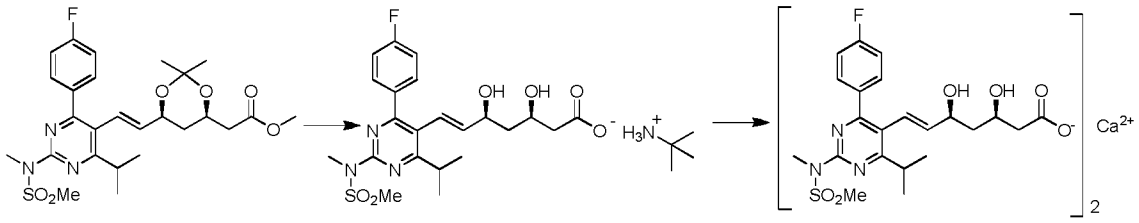
2-((4*R*,6*S*)-6-((E)-2-(2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester (10.0 g, 21.0 mmol) was added to acetonitrile (50 mL). The mixture was heated to 45°C and 4N aqueous HCl (5 mL, 20 mmol) was added. The reaction was stirred for 2.5 h. After cooling to 22°C, 4M aqueous NaOH is added over a period of 1.5 h. The pH is reduced to 6.5 by addition of 1N aqueous HCl, and then concentrated under vacuum to remove the acetonitrile. Next methyl *tert*-butylether (20 mL) was added followed by addition of 1 N aqueous HCl until pH = 4. The organic layer was separated and concentrated under vacuum. To the residue was added acetonitrile (68 mL) and water (3.9 mL). The reaction mixture was cooled to 10°C; Then Then furfurylamine (2.04 g, 21.0 mmol) dissolved in acetonitrile (13.5 mL) was added in 1.5 h. Upon addition, a white precipitate was formed. The reaction mixture was stirred for 30 min, followed by filtration of the Pitavastatin-furfuryl amine salt. The salt was washed with ethyl acetate (2 x 10 mL) and dried to give 8.3 g of a white solid. .

The salt was added to water (100 mL) and the pH adjusted to 12.3 using 3.4 mL aqueous 4N NaOH. The reaction mixture is heated and 3 x 40 mL of water was removed via distillation under vacuum. After each distillation, the volume distilled water was replaced by adding the same volume of fresh water. After cooling to 22°C, 1 g of active carbon was added. The mixture was stirred for 1 h and the carbon removed by filtration. The pH of the solution was lowered by addition of acetic acid to 9.7 and 20 mL of water was added. Then over a period of 45 min, 33 mL of a solution of 4.5 w/w% $Ca(OAc)_2 \cdot H_2O$ in water was added. Upon addition white precipitate was formed. After 30 minutes stirring, the solid was filtered and dried to give the calcium salt of

Pitavastatin as a white solid (7.5 g, KF 2.8%). From the filtrate, the Pitavastatin can be recovered in order to increase the overall yield. For example, this can be done, after acidification to pH = 4 and extraction with methyl *tert* butylether by formation of the amine salt as described in this example. In another embodiment, this filtrate can be combined with the extraction procedure as described in the example leading to a single step

Comparative Example 1

Preparation of rosuvastatin-Ca ((2b), $R_4 = Ca^{2+}$) from 2-((4*R*,6*S*)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester ((1b), $R_2 = R_3 = R_4 = CH_3$) via *tert*-butyl amine salt



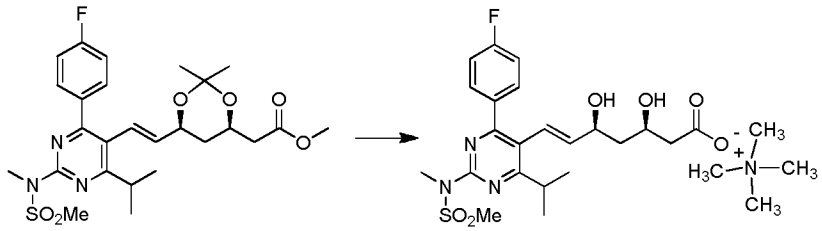
2-((4*R*,6*S*)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester (3.9 g, 7.2 mmol) was added to acetonitrile (23 mL). To the mixture was added 0.02 N aqueous HCl (7.7 mL) and stirred for 18 h at 20°C. Then 1N aqueous NaOH was added in 15 min until pH = 12. After stirring for 1 h, the mixture was concentrated under vacuum to remove the acetonitrile. Next ethyl acetate (30 mL) was added followed by addition of 1N aqueous HCl until pH = 4. The ethyl acetate phase was separated. The ethyl acetate phase was heated to 60°C and *tert*-butyl amine (0.8 g, 11.0 mmol, 1.5 equiv.) dissolved in ethyl acetate (10 mL) was added. The reaction mixture was cooled to 40°C, when precipitation occurred. The slurry was further cooled to 20°C and stirred for 2 h at this temperature. The solid was isolated by filtration and washed with ethyl acetate (2 x 3 mL) and dried. The salt was added to acetonitrile (19 mL) and water (1 mL) and heated to reflux. The reaction mixture was cooled to 20°C and stirred for 1.5 h. The

rosuvastatin *tert*-butyl amine salt was isolated by filtration, washed with acetonitrile (2 x 5 mL) and dried.

The salt was added to water (30 mL) and the pH was adjusted to 12 with 1N aqueous NaOH. The solution was concentrated to 20 mL. The pH was adjusted to 8.5-9 with acetic acid. Then 8 mL of a solution of 4.5 w/w% $Ca(OAc)_2 \cdot H_2O$ in water was added in 1 h. The reaction mixture was stirred for 3 h and the solid isolated by filtration and washed with water (2 x 5 mL). The solid was dried to give the calcium salt of rosuvastatin as a white solid (2.9 g, yield 80%).

Comparative Example 2

Preparation of rosuvastatin tetramethyl ammonium salt ((2b), $R_4 = (CH_3)_4N^+$) from 2-((4*R*,6*S*)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester ((1b), $R_2 = R_3 = R_4 = CH_3$)



2-((4*R*,6*S*)-6-((E)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate methyl ester (12.1 g, 22.5 mmol) was added to acetonitrile (80 mL), followed by addition of 0.02 N aqueous HCl (35 mL). The reaction mixture was stirred for 18 h at 25°C. Then 1N aqueous NaOH was added in 15 min until pH = 12. After stirring for 1 h, the mixture was concentrated under vacuum to remove the acetonitrile. Next ethyl acetate (100 mL) was added followed by addition of 1N aqueous HCl until pH = 4. The ethyl acetate phase was separated. To the ethyl acetate layer was added tetramethyl ammoniumhydroxide pentahydrate (4.1 g, 22.5 mmol, 1 equiv.). The ethyl acetate phase was concentrated and a thick oil was obtained. The residue was taken up in THF (75 mL) and heated to 50°C. The reaction mixture was cooled to 20-25°C and stirred for 4 h. The precipitated solid was filtered

and washed with 15 mL of THF. The product was dried to give the tetramethyl ammonium salt of rosuvastatin (8.4 g, 67% yield).

CLAIMS

1. An amine salt of pitavastatin or rosuvastatin, characterized in that said amine comprises at least one oxygen atom.
2. The amine salt of claim 1 wherein the amine comprises a compound selected from the group consisting of ethyldiethanol amine, 2-furfuryl amine and 3-furfuryl amine.
3. The amine salt of claim 2 which is the 2-furfuryl amine salt of rosuvastatin.
4. A method for the preparation of the amine salt of any one of claims 1-3 comprising the steps of:
    a) Contacting a protected derivative of pitavastatin or rosuvastatin with acid followed by base or with base followed by acid;
    b) Treating the mixture obtained in step a) with an amine;
    c) Isolating the amine salt obtained in step b),

    characterized in that said amine comprises at least one oxygen atom.
5. Use of an amine salt of any one of claims 1-3 in the preparation of amorphous or crystalline pitavastatin calcium salt or amorphous or crystalline rosuvastatin calcium salt.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2014/056268

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 2, 4, 5(all partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/056268

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/14 C07D239/42
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/106584 A2 (REDDYS LAB LTD DR [IN]; REDDYS LAB INC DR [US]; KVS RAMA RAO [IN]; KAT) 9 August 2012 (2012-08-09) cited in the application claims 1,10-11, 22-28 page 22, line 20 - page 23, line 4 examples 5-6 -----	1,2,4,5
X	EP 0 520 406 A1 (NISSAN CHEMICAL IND LTD [JP]) 30 December 1992 (1992-12-30) reference example 2 -----	1
X	WO 2005/077916 A1 (RANBAXY LAB LTD [IN]; KUMAR YATENDRA [IN]; RAFEEQ MOHAMMAD [IN]; DE SH) 25 August 2005 (2005-08-25) cited in the application claims 1-13 the whole document -----	1,2,4,5
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 April 2014	01/07/2014

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/056268

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/073256 A1 (CADILA HEALTHCARE LTD [IN]; DWIVEDI SHRIPRAKASH DHAR [IN]; PATEL DHIMA) 7 June 2012 (2012-06-07) cited in the application examples 1-4 claims 1-39, 45-47	1,2,4,5
X	WO 2004/014872 A1 (ASTRAZENECA UK LTD [GB]; HORBURY JOHN [GB]; TAYLOR NIGEL PHILIP [GB]) 19 February 2004 (2004-02-19) example 4 claims 1-14,17	1,2,4,5
X	WO 2006/136407 A1 (LEK PHARMACEUTICALS [SI]; ZLICAR MARKO [SI]) 28 December 2006 (2006-12-28) page 19, line 12 - line 18 claims 1 -4,14-28, 31 examples	1,2,4,5
X	WO 2012/063115 A2 (JUBILANT LIFE SCIENCES LTD [IN]; SINGH KHUSHWANT [IN]; SINGH ANAND KUM) 18 May 2012 (2012-05-18) cited in the application claims 1-2, 7-10 examples 5-7	1,2,4,5
X	WO 2010/027060 A1 (NISSAN CHEMICAL IND LTD [JP]; TAKADA YASUTAKA [JP]) 11 March 2010 (2010-03-11) page 32, paragraph 11 - page 33, paragraph 13 abstract	1,2,4,5

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/056268

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/056268

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 2010027060 A1	11-03-2010	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 2, 4, 5(all partially)

   An amine salt of pitavastatin or rosuvastatin, characterized that said amine is a saturated amine, i.e. ethyldiethanolamine

   ---

2. claims: 3(completely); 1, 2, 4, 5(partially)

   An amine salt of pitavastatin or rosuvastatin, characterized that said amine is a unsaturated amine, i.e. a furfuryl amine

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