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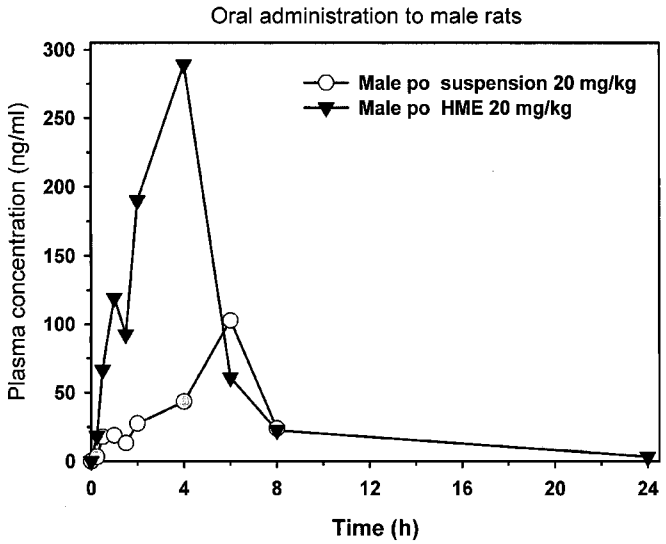
(54) **Title**: PHARMACEUTICAL FORMULATION COMPRISING A CB1-RECEPTOR COMPOUND IN A SOLID SOLUTION AND/OR SOLID DISPERSION

Figure 10)



(57) **Abstract**: The present invention relates to a pharmaceutical formulation comprising 5-(4-chlorophenyl)- 1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1 H-pyrazole-3- carboxamide as racemate or (S)-enantiomer or mixtures thereof in a solid solution and/or solid dispersion.

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Pharmaceutical formulation comprising a CB1-Receptor compound in a solid solution and/or solid dispersion

The present invention relates to a pharmaceutical formulation comprising 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide as racemate or (S)-enantiomer or mixtures thereof in a solid solution and/or solid dispersion.

Cannabinoids are compounds, which are derived from the cannabis sativa plant which is commonly known as marijuana. The most active chemical compound of the naturally occurring cannabinoids is tetrahydrocannabinol (THC), particularly Δ^9-THC.

These naturally occuring cannabinoids as well as their synthetic analogues promote their physiological effects via binding to specific G-coupled receptors, the so-called cannabinoid-receptors.

At present, two distinct types of receptors that bind both the naturally occurring and synthetic cannabinoids have been identified and cloned. These receptors, which are designated CB_1 and CB_2 are involved in a variety of physiological or pathophysiological processes in humans and animals, e.g. processes related to the central nervous system, immune system, cardiovascular system, endocrinous system, respiratory system, the gastrointestinal tract or to reproduction, as described for example, in Hollister, Pharm. Rev. 38, 1986, 1-20; Reny and Singha, Prog. Drug. Res., 36, 71-114, 1991; Consroe and Sandyk, in Marijuana/Cannabinoids, Neurobiology and Neurophysiology, 459, Murphy L. and Barthe A. Eds., CRC Press, 1992.

Therefore, compounds, which have a high binding affinity for these cannabinoid receptors and which are suitable for modulating these receptors are useful in the prevention and/or treatment of cannabinoid-receptor related disorders.

In particular, the CB_1-Receptor is involved in many different food-intake related disorders such as bulimia or obesity, including obesity associated with type II diabetes (non-insulin-dependent diabetes) and thus, compounds suitable for regulating this receptor may be used in the prophylaxis and/or treatment of these disorders.

Also dyslipidaemia, metabolic syndrome (both in its weight dependent or weight independent aspects) and diabetes type II have over the last decades risen in importance for the public health, especially for the developed or developing countries, likely due to a demoscopically marked increase in the proportion of obese or overweight members of the population or in average age.

The racemic compound denominated cis-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide (the compound according to formula I below) is disclosed in WO07/09689 (see compound nr 103 on page 229); the content of this publication being included here by reference. For the synthesis of the compounds according to formulas (Ia) and (Ib) see below the experimental part. All of these compounds were shown to be CB1-binders and/or compounds with antiobesity activity and/or compounds having a reducing effect on triglyceride levels in blood in in-vivo models. Thus, these compounds according to formulas (I), (Ia) and (Ib) did show clear effects especially hinting at a great potential for the treatment or prevention of obesity, dyslipidaemia, metabolic syndrome (both in its weight dependent or weight independent aspects) and/or diabetes type II.

Thus, it was an object of the present invention to provide suitable pharmaceutical compositions for these compounds. As these compounds do have a tendency to be not highly soluble, this aspect - important when dealing with pharmaceutical compositions, especially those suitable to enhance the absorption of the active principle through a mucosa, especially for pharmaceutical compositions for oral administration - under certain therapeutical circumstances needs improvement.

Accordingly it would be desirable to find a formulation or a way to achieve a formulation in which the active principle would be realeased into an aqueous medium - simulating oral application – with a higher dissolution rate than is seen with the active principle alone. Especially it would be desirable to have a high dissolution rate in an aqueous medium like a 0.1 N hydrochloric acid – simulating the gastric acid - in the first 10 to 30 minutes like more than double of that seen in the active principle to be dissolved. Most preferably even much higher rates of dissolution in the first 10 to 30 minutes are desirable.

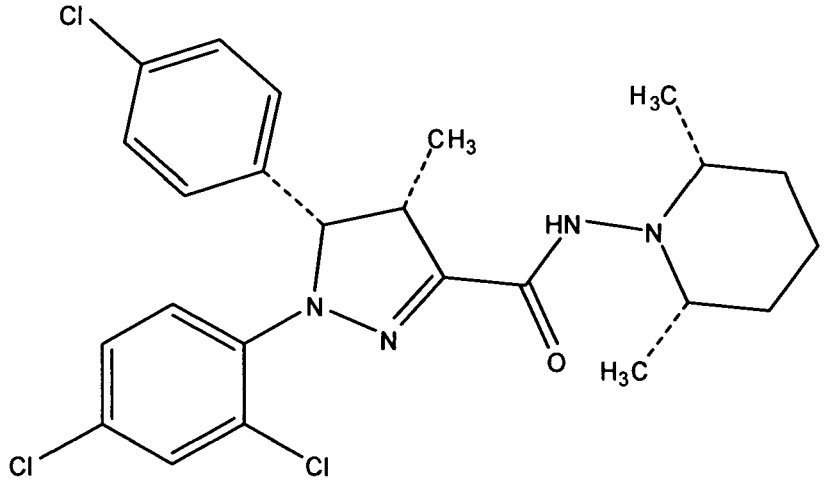
Also it would be desirable to find a formulation or a way to achieve a formulation in which the after oral administration in an in-vivo model the active principle would be found in blood plasma with a much higher concentration (measured as AUC_{o-t}) and/or reaching T_{max} much faster compared to the active principle alone.

It would be even more desirable to find a formulation or a way to achieve a formulation

- in which the active principle would be realeased into an aqueous medium - simulating oral application – with a higher dissolution rate than is seen with the active principle alone
- and in which the after oral administration in an in-vivo model the active principle would be found in blood plasma with a much higher concentration (measured as AUC_{o-t}) and/or reaching T_{max} much faster compared to the active principle alone.

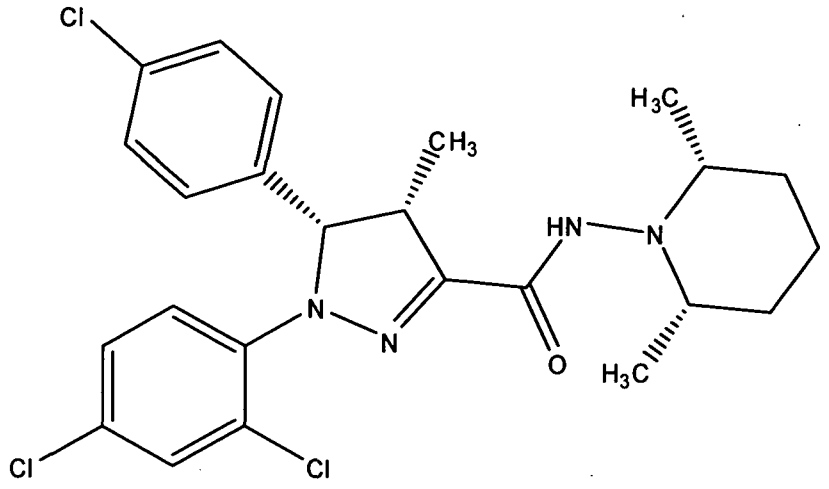
Said object was achieved by providing a pharmaceutical composition comprising a solid dispersion and/or solid solution according to the invention and optionally further pharmaceutical acceptable ingredients.

Thus in another related aspect the invention further provides a solid dispersion and/or solid solution of one or more active principles selected from compounds of formula (I), (Ia) or (Ib) or mixtures thereof



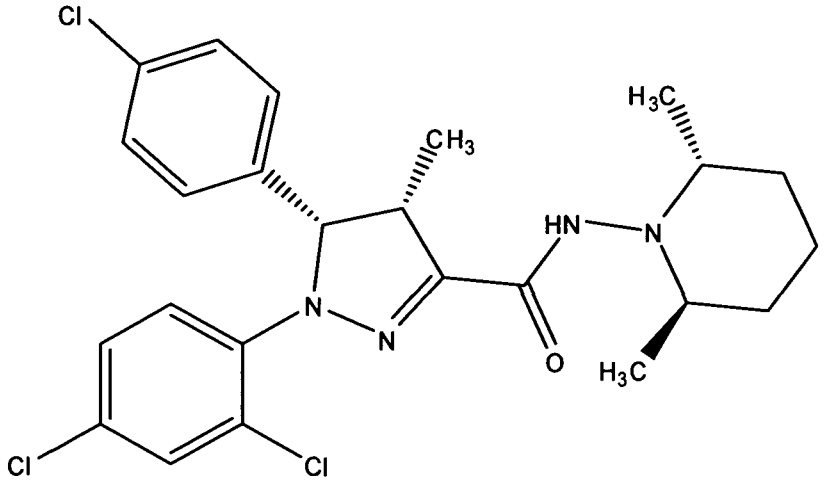
cis-rac-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide

(I)



(4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide

(Ia)



(4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide

(Ib)

, optionally in form of one or more of the appropriate polymorphs, in amorphous form and/or corresponding salts and/or corresponding solvates thereof,

obtainable by a process in which

a) the active principle/s is/are mixed with an at least equimolar amount or at least an equal weight of at least one carrier,
b) thereafter or during step a) the mixture is heated until the carrier in the mixture is melted and

c) subsequently the – preferably eutectic - mixture is cooled below the melting point of the carrier in the mixture.

It is found that the release and uptake of the active principle may be greatly enhanced and improved by the pharmaceutical compositions according to the invention. Especially these compositions do show an improved dissolution or dissolution profile, mostly expressed as a higher dissolution rate of the active principle (e.g. expressed as mg/hr). As this is positively influencing also the uptake of the active principle into the body, as a consequence the pharmaceutical composition is allowing for a lowered effective dose to be used, which thus clearly also acts positively on any unwanted side effect. On the other hand the composition according to the invention by its improved dissolution rate results also in a higher ratio of the active principle, creating faster the - in some cases - necessary concentrations of the active principle in the peripherical system, while at the same time allowing thus for an even further reduction of the amount of active principle having to be applied to the patient. In addition the formulations according to the invention are also thus especially useful for the treatment of acute abuse e.g. as an emergency treatment after abuse of a medicament/drug.

"Solid dispersion and/or solid solution" is defined according to the invention as a dispersion or solution of the active principle in an inert carrier or matrix at solid state prepared through melting with a carrier or coprecipitation/coevaporation from a solution with a carrier and a solvent. Preferably the active principle/s is/are finely dispersed/dissolved up to and including single molecules being dispersed/dissolved in the carrier. During the preparation by melting a physical mixture of at least one active principle is mixed with at least one carrier, melted (at least the carrier in the mixture) and the melt rapidly solidified by lowering the temperature. During the preparation by coprecipitation/coevaporation from a solution carrier and active principle are dissolved in a solvent, mixed and the solvent removed (usually evaporated or maybe freezedried or spraydried). Most preferably according to the invention "solid dispersion and/or solid solution" is defined as a dispersion of the active principle in an inert carrier or matrix at solid state prepared through melting.

"Carrier" in the sense of this application is a substance in which one or more active principles may be dispersed/dissolved, preferably finely dispersed/dissolved up to and including single molecules being dispersed in the carrier. Preferably a carrier is defined by one or more, preferably most, more preferably all – where applicable - of the following criteria:

- be freely water-soluble with intrinsic rapid dissolution properties;
- be nontoxic and pharmacologically inert;

- be heat stable with low/med melting point (if melting is used for the preparation of the solid dispersion);
- be soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation (if solvent evaporation is used for the preparation of the solid dispersion);
- be able to increase the aqueous solubility of at least on of the active principles;
- be chemically compatible with the drug and not form a strongly bonded complex with any of the active principles dispersed therein.

Further examples of carriers may be found in Ford, J.L.; Acta Helv. 1986, 61, 69-88, enclosed here by reference.

"Hot melt extrusion" (HME from now on) is defined as an extrusion of the active principle/s together with the carrier/s in an extruder, where the carrier/s and active principle/s are mixed and melted or softened by melting the carrier before or during extrusion thus creating upon extrusion a solid dispersion and/or solid solution (see above). Hot-melt extrusion is described e.g. by Koleng at al. "Hot-Melt Extrusion Technology", Encyclopedia of Pharmaceutical Technology (2002), Macel Dekker, Inc.

The active principle according to the invention may be subject to any particle size reduction like milling, grinding, nanosizing or micronisations, or to complexation like e.g. complexation with Ciclodextrines, or PEG.

In a preferred embodiment of the solid dispersion and/or solid solution according to the invention the carrier is either hydrophilic or hygroscopic and has a melting point between +40°C and the melting point of the active principle or mixture of active principles +20 °C.

Preferably "hydrophilic" means in the context of this application that the carrier shows an HLB (hydrophilic-lipophilic balance) determined according to the method of W. C. Griffin (1954) of 12 to 20, more preferably 15 to 20.

In another preferred embodiment of the solid dispersion and/or solid solution according to the invention the carrier is selected from

- sugars, like dextrose, sucrose, galactose, sorbitol, maltose, xylitol, manitol, lactose;
- acids, like citric acid, succinic acid, ascorbic acid;
- polymeric materials, like povidone (PVP), polyethylene oxide (PEO), polyethylene glycol (PEG), hydroxpropylmethylcellulose (HPMC),

methylcellulose (MC), ethylcellulose (EC), hydroxyethylcelllose (HEC), cylodextrin, hydroxypropylcellulose (HPC), pectin, galactomannan, chitosan, carrageenan

- insoluble or enteric polymers, like hydroxypropylmethylcellulose phthalate, polymethacrylates (e.g. Eudragit L-100, Eudragit S-100, Eudragit RL, Eudragit RS, Eudragit EPO);
- surfactants, like polyoxyethylene stearate, renex, poloxamer 188, texafor, AIP, deoxycholic acid, polyoxy-ethylene-sorbitan higher fatty acid esters (e.g. Tween, like Tween 80), spans;
- others, consisting of: carnuba wax, pentaerythritol, pentaerythrityltetraacetate, urea, urethane, hydroxyalkylxanthins;
- excipients derived from fatty acids, monoglycerides and polyoxiglycerides

preferably the carriers are selected from
PVP, PEG, Kollidon VA 64, EUDRAGIT, MYRJ 52, VITE-TPGS, GELUCIRE 50/13, HPMC-PHTALATE, HPMC, HEC, HPC-SL, PEO and/or POLOXAMER;

In a very preferred embodiment of the solid dispersion and/or solid solution according to the invention the carrier is an Eudragit, like Eudragit EPO, Eudragit L-100, Eudragit S-100, Eudragit RL, or Eudragit RS.

In another preferred embodiment of the solid dispersion and/or solid solution according to the invention

- the melting temperature in step (b) is in the range between +40°C and the melting point of the active principle or mixture of active principles +20 °C; and/or
- the cooling step (c) is done by lowering the temperature by more than 10°C/sec, preferably 20°C/sec, down to temperatures below 25 °C, preferably below 0 °C; and/or is done by contacting the melt of step (b) with an environment having a temperature of 25°C or lower, preferably 0°C or lower.

In another preferred embodiment of the solid dispersion and/or solid solution according to the invention the weight or molecular ratio between active principle and carrier is between 1:1 and 1: 20, preferably is between 1:1 and 1:10, more preferably is between 1:2 and 1:5.

In another aspect the invention is referring to a pharmaceutical composition comprising the solid solution and/or solid dispersion according to the invention and optionally further pharmaceutical acceptable ingredients.

In a preferred embodiment of the pharmaceutical composition according to the invention

- the active principle is present in an amount of 10 to 60, preferably 20 to 40 % by weight based on the total weight of the composition;

and/or

- the active principle is present in an amount of 1 to 250 mg, preferably 10 to 200 mg, more preferably 15 to 150 mg in the composition.

In another preferred embodiment of the pharmaceutical composition according to the invention it is suitable to enhance the absorption of the active principle through a mucosa. Thereby it is preferred if the mucosa is selected from the

- nasal or olfactory mucosa,
- buccal or oral mucosa,
- gastric mucosa,
- intestinal mucosa
- vaginal mucosa, or
- rectal mucosa,

preferably selected from

- gastric mucosa, or
- intestinal mucosa.

In another preferred embodiment of the pharmaceutical composition according to the invention the pharmaceutical composition is selected from

- a pharmaceutical composition for oral application,
- a pharmaceutical composition for nasal application,
- a pharmaceutical composition for buccal application,
- a pharmaceutical composition for rectal application, or
- a pharmaceutical composition for vaginal application;

or

- a pharmaceutical composition for transdermal application;
- a pharmaceutical composition for systemic application;

preferably selected from

- a pharmaceutical composition for oral application.

In another preferred embodiment of the pharmaceutical composition according to the invention the pharmaceutical composition is selected from

- a tablet,
- a capsule,
- a sachet,
- a powder,
- a caplet,
- a gel,
- a film,
- a pellet,
- a granule,
- an implant,
- a multiparticulate with granules compressed into a tablet,
- a multiparticulate with granules filled into a capsule,
- a multiparticulate with pelets compressed into a tablet,
- a multiparticulate with pelets filled into a capsule, or
- a suppository,

or

- an injectable solution/dispersion
- a transdermal system like a patch;

preferably selected from

- a tablet,
- a capsule,
- a pellet,
- a granule,
- a multiparticulate with granules compressed into a tablet,

- a multiparticulate with granules filled into a capsule,
- a multiparticulate with pelets compressed into a tablet, or
- a multiparticulate with pelets filled into a capsule.

In another preferred embodiment of the pharmaceutical composition according to the invention

- the further pharmaceutical acceptable ingredients are present in a total amount of 5 to 95 %, preferably 50 to 90 % by weight based on the total weight of the composition;

and/or

- the further pharmaceutical acceptable ingredients are present in a total amount of 0 to 300 mg, preferably 0 to 250 mg, more preferably 20 to 250 mg.

In another preferred embodiment of the pharmaceutical composition according to the invention the further pharmaceutical acceptable ingredient/s is/are selected from a diluent, a binder and/or a lubricant, and/or optionally a flowing agent, an antiadhesive, a preservative, and/or, optionally, a taste masking agent, a coloring agent and/or a flavoring agent and/or a permeation enhancer.

In another preferred embodiment of the pharmaceutical composition according to the invention the pharmaceutical composition is prepared using hot-melt extrusion.

Another preferred aspect of the invention is a pharmaceutical composition comprising as active principle at least one of

- (cis-rac)- 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide;
- (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide , or
- (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide ,
- or mixtures thereof;

optionally in form of one or more of the appropriate polymorphs, in amorphous form and/or corresponding salts and/or corresponding solvates thereof,
in a solid dispersion and/or solid solution in a carrier, the carrier having a melting point between +40°C and the melting point of the active principle +20 °C and being hydrophilic or hygroscopic;

and optionally further pharmaceutical acceptable ingredients

Preferred concentration/weight/percentage ranges, forms of the compositions, as well as appropriate lists of preferred excipients or carriers have already been described above.

In a preferred embodiment of any of the pharmaceutical compositions or the solid dispersion according to the invention described above the active principle is selected from

a) (cis-rac)- 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide;
preferably in
- crystalline form;
- amorphous form;
- form of a solvate, preferably a hydrate, more preferably a monohydrate;
- the free base; or
- a salt with an acid with a $pk_a \leq 3.0$,especially the acid being selected from 2,5-dihydroxybenzenesulfonic acid, 2-naphthalenesulfonic acid, aspartic acid, benzenesulfonic acid, amphor-10-sulfonic acid, cyclohexylsulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, fumaric acid, glutamic acid, hydrobromic acid, hydrochloric acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, nitric acid, phosophoric acid, *p*-toluenesulfonic acid, sulfuric acid and/or thiocyanic acid; more preferably the salt being a hydrochloride;

b) (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide, preferably
preferably in
- crystalline form;

- amorphous form;
- form of a solvate, preferably a hydrate,
- the free base;
- a salt with an acid with a $pk_a \leq 3.0$,especially the acid being selected from 2,5-dihydroxybenzenesulfonic acid, 2-naphthalenesulfonic acid, aspartic acid, benzenesulfonic acid, amphor-10-sulfonic acid, cyclohexylsulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, fumaric acid, glutamic acid, hydrobromic acid, hydrochloric acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, nitric acid, phosophoric acid, *p*-toluenesulfonic acid, sulfuric acid and/or thiocyanic acid; more preferably the salt being a hydrochloride;

c) (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide,

preferably in

- crystalline form;
- amorphous form;
- form of a solvate, preferably a hydrate,
- the free base;
- a salt with an acid with a $pk_a \leq 3.0$,especially the acid being selected from 2,5-dihydroxybenzenesulfonic acid, 2-naphthalenesulfonic acid, aspartic acid, benzenesulfonic acid, amphor-10-sulfonic acid, cyclohexylsulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, fumaric acid, glutamic acid, hydrobromic acid, hydrochloric acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, nitric acid, phosophoric acid, *p*-toluenesulfonic acid, sulfuric acid and/or thiocyanic acid; more preferably the salt being a hydrochloride;

or

d) a nonracemic mixtures of (b) and (c).

The crystalline form of (cis-rac)- 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide; especially (4S,5S)-

5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide and (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is described below. The amorphous form of (cis-rac)- 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide; especially (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide and (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is described below.

Solid solutions and dispersions of salts with an acid with a $pk_a \leq 3.0$ of (cis-rac)- 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide; especially (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide and (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide are also included in the scope of this invention. Specifically included are salts of the the acid being selected from 2,5-dihydroxybenzenesulfonic acid, 2-naphthalenesulfonic acid, aspartic acid, benzenesulfonic acid, amphor-10-sulfonic acid, cyclohexylsulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, fumaric acid, glutamic acid, hydrobromic acid, hydrochloric acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, nitric acid, phosophoric acid, *p*-toluenesulfonic acid, sulfuric acid and/or thiocyanic acid.
Some salts like e.g. hydrochloride salts etc. of (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide have also been described below.

The daily dosage for humans and animals may vary depending on factors that have their basis in the respective species or other factors, such as age, sex, weight or degree of illness and so forth. The daily dosage for humans may preferably be in the range from10 to 400, preferably 15 to 300, more preferably 25 to 250 milligrams of active substance to be administered during one or several intakes per day. Most preferably is a dosage of 25 to 250 mg of active principle in one dosage unit.

The pharmaceutical acceptable ingredients excipients which optionally may be included in the composition according to the present invention include especially a diluent, a binder and/or a lubricant, wheras a flowing agent, a preservative, an antiadhesive and, optionally, a

taste masking agent and a coloring agent and/or a flavoring agent as well as one or more permeation enhancers can also be added.

The diluent – if used - in the composition of the present invention can be one or more compounds which are capable of densifying the active principle to give the desired mass. The preferred diluents are inorganic phosphates such as calcium phosphates; sugars such as hydrated or anhydrous lactose, or mannitol; and cellulose or cellulose derivatives such as, for example, microcrystalline cellulose, starch, corn starch or pregelatinized starch. Lactose monohydrate, mannitol, microcrystalline cellulose and corn starch, used by themselves or in a mixture, for example a mixture of lactose monohydrate and corn starch, are very particularly preferred. The diluent – if present at all - is present in a proportion of 5 % to 90 % by weight based on the total weight of the composition according to the invention

The binder – if employed - in the composition of the present invention can be one or more compounds which are capable of densifying the active principle within the overall e.g. granular formulation by converting it to larger and denser particles with improved solid characteristics. The preferred binders are alginic acid or sodium alginate; cellulose and cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose or methyl cellulose; gelatin; acrylic acid polymers; and povidone, for example povidone K 30, which is a very particularly preferred binder. The binder – if present at all - is present in a proportion of 1% to 30% by weight based on the total weight of the composition according to the invention.

The lubricant – if employed - in the composition of the present invention can be one or more compounds which are capable of preventing the problems associated with the preparation of the dosage form, such as the sticking and/or seizing problems which occur in the machines during compression or filling. The preferred lubricants are fatty acids or fatty acid derivatives such as calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, sodium laurylsulfate, sodium stearylfumarate, zinc stearate or stearic acid; hydrogenated vegetable oils, for example hydrogenated castor oil; polyalkylene glycols, especially polyethylene glycol; sodium benzoate; or talcum. Magnesium stearate is preferred according to the present invention. The lubricant – if present at all - is present in a proportion of 0.2% to 5% by weight based on the total weight of the composition according to the invention.

The antiadhesive which may be employed in the composition of the present invention can be one or more compounds which are capable of reducing the sticky character of the

formulation, for example of preventing adhesion to metal surfaces. The preferred antiadhesives are compounds containing silicon, for example silica or talcum. The antiadhesive – if present at all - can be present in a proportion of 0 to 5% by weight in the pharmaceutical composition according to the invention.

The flowing agent which may be employed in the composition of the present invention can be one or more compounds which are capable of facilitating the flow of the prepared formulation. The preferred flowing agents are compounds containing silicon, for example anhydrous colloidal silica or precipitated silica. The flowing agent – if present at all - can be present in a proportion of 0 to 15% by weight in the pharmaceutical composition according to the invention.

The permeation enhancer which may be employed in the composition of the present invention, especially if the composition is a transdermal formulation, can be one or more compounds which are capable of facilitating the permeation of the active principle from the composition trough a biological barrier like e.g. the skin. Preferred permeation enhancers are high-boiling alcohols, diols, fatty acid esters, oleic acid and glyceride-based solvents, like for example isobutyl or isopropyl alcohol. Other permeation enhancers include linoleic acid, oleic acid, dimethylacetamide, lauric acid, myristic acid, palmitic acid, dimethyl sulfoxide, glycofurol, thymol, pyrrolidone, macrogol 15 hydroxystearate; mineral oil, light; polyoxyethylene alkyl ethers, menthol, polycarbophil, isopropyl myristate, glyceryl monooleate, ethyl acetate, polyethylene glycol, carbomer. The permeation enhancer/s – if present at all - can be present in a proportion of 0 to 25% by weight in the pharmaceutical composition according to the invention.

According to the present invention, the pharmaceutical compositions may preferably be prepared by a direct compression process, a granulation, extrusion and further spheronization, or by a layering process into for example nonpareil seeds.

Thus, for the direct compression process the active principle in a solid solution and/or solid dispersion and the optional diluent, binder are combined by geometrical mixing and further mixed with other optional excipients such colorants or taste masking agents, afterwards the mixture can be either compressed, encapsulated or dosified into sachets or any other unidose system.

For the dry granulation process the internal phase, thus the active principle in a solid solution and/or solid dispersion, the optional diluent, the optional binder, and, optionally, the coloring

agent are mixed optionally at room temperature. The ingredient or ingredients of the optional external phase, namely the optional lubricant, possibly the antiadhesive, the flowing agent and, if appropriate, the coloring agent and/or the flavoring agent, are then added to the graded dry grains.

For the extrusion-espheronization process, a mass comprising the active principle in a solid solution and/or solid dispersion – for example the one obtained in the previous pharagraph - is passed through a pharmaceutical extruder and further spheronized until obtaining multiparticulates containing the active principle of a desired particle size. Later on these particles are dried and susceptible to either encapsulation or added into sachets (adding lubricants and other required processing agents), compressed (if mixed with the proper compression base) or coated for further manipulation, e.g. further layering (see below).

In one embodiment of the layering process to an inert sugar/starch/cellulose spherical core, a layer is applied containing a mixture of the active principle in a solid solution and/or solid dispersion, the optional diluent, the optional binder, and, optionally, the coloring agent, optionally followed by a another – e.g. isolation - layer formed by water soluble polymers and compatible excipients. Finally, optionally a layer consisting of a controlled release coating - like e.g. an enteric coating - is applied.

In another possibility of the layering process to a spherical core comprising already the active principle in a solid solution and/or solid dispersion produced by e.g. the extrusion-spheronization process described above, optionally one or more futher layers are applied containing a mixture of e.g. the optional diluent, the optional binder, and, optionally, the coloring agent, optionally water soluble polymers and compatible excipients. Finally, optionally a layer consisting of a controlled release coating - like e.g. an enteric coating - is applied.

The liquid oral forms for administration may also contain certain additives such as sweeteners, flavoring, preservatives, and emulsifying agents. Non-aqueous liquid compositions for oral administration may also be formulated, containing edible oils. Such liquid compositions may be conveniently encapsulated in e.g., gelatin capsules in a unit dosage amount.

In another preferable aspect of the invention the pharmaceutical composition according to the invention is suitable for the modulation (regulation) of cannabinoid-receptors, preferably cannabinoid 1 (CB_1) receptors, for the prophylaxis and/or treatment of disorders of the

central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.

Particularly preferably said pharmaceutical composition is suitable for the prophylaxis and/or treatment of psychosis and also depression as well as memory disorders.

Also particularly preferably said pharmaceutical composition is suitable for the prophylaxis and/or treatment of neuropathic pain, hyperalgesia or allodynia.

Also particularly preferably said pharmaceutical composition is suitable for the prophylaxis and/or treatment of food intake disorders, preferably bulimia, anorexia, cachexia, obesity and/or type II diabetus mellitus (non-insuline dependent diabetes mellitus), more preferably obesity and/or type II diabetus mellitus (non-insuline dependent diabetes mellitus). The inventive medicament also seems to be active in the prophylaxis and/or treatment of appetency disorders, e.g. the pyrazoline compounds of general formula I also reduce the desire for sweets and other macronutrients. In addition said pharmaceutical composition is also suitable for the prophylaxis and/or treatment of metabolic syndrome (both in its weight dependent or weight independent aspects) and dyslipidaemia.

Also particularly preferably said pharmaceutical composition is suitable for the prophylaxis and/or treatment of cancer, preferably for the prophylaxis and/or treatment of one or more types of cancer selected from the group consisting of brain cancer, bone cancer, lip cancer, mouth cancer, esophageal cancer, stomach cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, skin cancer, colon cancer, bowel cancer and prostate cancer, more preferably for the prophylaxis and/or treatment of one or more types of cancer selected from the group consisting of colon cancer, bowel cancer and prostate cancer.

Particularly preferably said pharmaceutical composition is suitable for the prophylaxis and/or treatment of alcohol abuse and/or alcohol addiction, nicotine abuse and/or nicotine addiction, drug abuse and/or drug addiction and/or medicament abuse and/or medicament addiction, preferably drug abuse and/or drug addiction and/or nicotine abuse and/or nicotine addiction.

Medicaments and/or drugs, which are frequently the subject of misuse include opioids, barbiturates, cannabis, cocaine, amphetamines, phencyclidine, hallucinogens and benzodiazepines. The formulations according to the invention are especially useful for the

treatment of acute abuse e.g. as an emergency treatment after abuse of any of the medicaments/drugs mentioned above.

The pharmaceutical composition according to the invention is also suitable for the prophylaxis and/or treatment of one or more disorders selected from the group consisting of bone disorders, preferably osteoporosis (e.g. osteoporosis associated with a genetic predisposition, sex hormone deficiency, or ageing), cancer-associated bone disease or Paget's disease of bone; schizophrenia, anxiety, depression, epilepsy, neurodegenerative disorders, cerebellar disorders, spinocerebellar disorders, cognitive disorders, cranial trauma, head trauma, stroke, panic attacks, peripheric neuropathy, inflammation, glaucoma, migraine, Morbus Parkinson, Morbus Huntington, Morbus Alzheimer, Raynaud's disease, tremblement disorders, compulsive disorders, senile dementia, thymic disorders, tardive dyskinesia, bipolar disorders, medicament-induced movement disorders, dystonia, endotoxemic shock, hemorragic shock, hypotension, insomnia, immunologic disorders, sclerotic plaques, vomiting, diarrhea, asthma, memory disorders, pruritus, pain, or for potentiation of the analgesic effect of narcotic and non-narcotic analgesics, or for influencing intestinal transit.

In an embodiment of the pharmaceutical composition according to the invention the medicament is for the regulation of triglyceride levels in the blood plasma and for the prophylaxis and/or treatment of disorders of the central nervous system, especially stroke, of disorders of the cardiovascular system and of of food intake disorders, preferably bulimia, anorexia, cachexia, obesity, type II diabetus mellitus (non-insuline dependent diabetes mellitus), preferably obesity and diabetis.

In an embodiment of the pharmaceutical composition according to the invention the composition is for the prophylaxis and/or treatment of disorders of the central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.

In an embodiment of the pharmaceutical composition according to the invention the composition is for the modulation of cannabinoid-receptors, preferably cannabinoid 1 (CB_1) receptors, for the prophylaxis and/or treatment of disorders of the central nervous system, disorders of the immune system, disorders of the cardiovascular system, disorders of the endocrinous system, disorders of the respiratory system, disorders of the gastrointestinal tract or reproductive disorders.

Brief description of the figures

Figure 1 shows improved dissolutions of HME powders in pH 1.2 HCL 0.1 N. Apparatus II paddles 50 rpm, in Non SINK CONDITIONS (oversaturation)

Figure 2 shows improved dissolutions of HME powders in pH 1.2 HCL 0.1 N 0.1% SLS. Apparatus II paddles 50 rpm, in SINK CONDITIONS

Figure 3 shows a DSC Thermogram of the (4S,5S)-cis enantiomer taken alone. The fusion temperature of said compound is 144,70 °C

Figure 4 shows a DSC Thermogram of the (4S,5S)-cis enantiomer in the HME formulation together with Eudragit EPO and trieltylcitrate. The peak at 144,70 °C corresponding to the fusion temperature of the (4S,5S)-cis enantiomer has disapeared.

Figure 5 shows a DSC Thermogram of the (4S,5S)-cis enantiomer in the HME formulation together with PEG8000 and Sucrose ester.

Figure 6 shows a DSC Thermogram of the (4S,5S)-cis enantiomer in the HME formulation together with Eudragit EPO and stearic acid.

Figure 7 shows a DSC Thermogram of the (4S,5S)-cis enantiomer in the HME formulation together with Eudragit EPO.

Figure 8 shows a DSC Thermogram of the (4S,5S)-cis enantiomer in the HME formulation together with PEG8000.

Figure 9 shows a DSC Thermogram of the (4S,5S)-cis enantiomer in the HME formulation together with Kollidon VA64.

Figure 10 shows a graph that compares the plasma concentration of the (4S, 5S) cis enantiomer after an oral administration to male rats of the (4S, 5S)-cis enantiomer in suspension or as HME from example 15.

The following part of the description is exemplifying the invention and is not meant to limit it.

Examples:

Example 1: Blend 1 (solid solution)

10 weight % of the final solid solution of active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 90 weight % of the final solid solution of Eudragit EPO in an apparatus suitable for hot-Melt Extrusion. The mixture is extruded with an extrusion temperature of 150°C and instantly cooled. The solid solution can then be formulated with excipient by granulation into pellets or compressed into tablets.

Example 2: Blend 2 (solid solution)

30 weight % of the final solid solution of active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 70 weight % of the final solid solution of Eudragit EPO in an apparatus suitable for hot-Melt Extrusion. The mixture is extruded with an extrusion temperature of 187°C and instantly cooled. The solid solution can then be formulated with excipient by granulation into pellets or compressed into tablets.

Example 3: Blend 2 (solid dispersion)

30 weight % of the final solid dispersion of active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 70 weight % of the final solid dispersion of Eudragit EPO in an apparatus suitable for hot-Melt Extrusion. The mixture is extruded with an extrusion temperature of 150°C and instantly cooled. The solid dispersion can then be formulated with excipient by granulation into pellets or compressed into tablets.

Example 4: Blend 3 (solid solution)

50 weight % of the final solid solution of active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 50 weight % of the final solid solution of Eudragit EPO in an apparatus suitable for hot-Melt Extrusion. The mixture is extruded with an extrusion temperature of 187°C and instantly cooled. The solid solution can then be formulated with excipient by granulation into pellets or compressed into tablets.

Example 5: Blend 3 (solid dispersion)

50 weight % of the final solid dispersion of active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 50 weight % of the final solid dispersion of Eudragit EPO in an apparatus suitable for hot-Melt Extrusion. The mixture is extruded with an extrusion temperature of 150°C and instantly cooled. The solid dispersion can then be formulated with excipient by granulation into pellets or compressed into tablets.

Example 6: Overview of Examples 1 to 5

Formulations: 3 different blends of the active principle, ((4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide, and Eudragit EPO are formed as shown in Table I.

Component	Blend 1	Blend 2	Blend 3

Active Principle	10%	30%	50%
Eudragit EPO	90%	70%	50%

Table I. Formulation composition

Hot Melt Extrusion: Haake Minilab equipped with two co-rotatory screws is used to obtain extrudate strands. Extrusion temperature applied to the three blends is shown in Table II. Obtention of solid solutions or solid dispersions depends on extrusion temperarure.

Temperature	Blend 1	Blend 2	Blend 3
150 °C	Solid solution (Ex. 1)	Solid dispersion (Ex. 3)	Solid dispersion (Ex. 5)
187°C	---	Solid solution (Ex. 2)	Solid solution (Ex. 4)

Table II. Extrusion temperature and solid state of extrudate strands.

Example 7: (solid solution)

90 mg of the active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 210 mg Eudragit EPO. The mixture is melted and after melting instantly cooled in an ice bath. The solid solution/dispersion can then be formulated with excipient by granulation into pellets or compressed into tablets.

FINAL COMPOSITION	**mg**	**%**
(4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide (Pellets)	90	30
Eudragit EPO	210	70

Example 8: (hot melt extrusion)

90 mg of the active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 180 mg Eudragit EPO and 30 mg of Vitamin E and subsequently melted and extruded in a holt-melt extruder. The solid solution/dispersion can then be formulated with excipient by granulation into pellets or compressed into tablets.

FINAL COMPOSITION	mg	%
(4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide (Pellets)	90	30
Eudragit EPO	180	60
Vitamin E	30	10

Example 9 (Comparative example-Tablet):

1) Granulation step: In a wet low-shear granulator the following excipients are mixed :

- The active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide,
- Lactose
- Maize starch-part

The blend is mixed for 2 minutes and then, while under chopper and mixer action a solution containing PVP K 30 is incorporated. The mixture is granulated and the granulator unloaded.

2) Sieving (1): The final product is sieved to avoid agglomerates.

3) Drying: The final product from step 3 is dried using a fluid bed at 50°C until relative humidity is below 2%.

4) Blending: External phase excipients are added to the dry granule (Maize starch-part; SLS, CMC and Mg Stearate)

5) Sieving (2): The final product is sieved to avoid agglomerates.

6) Compression step:

FINAL COMPOSITION	%
(4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide	28,4
Maize Starch	22,7
Lactose Monohydrate	42,6
PVP K30	2,8
SLS	0,1
CMC	2,6
Mg Stearate	0,9

Compressed as tablets.

Example 10 (Comparative example-Non-excipients):

90 mg of the active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide was placed into #1 hard gelatin capsules.

Example 11: (solid solution, trans-2,6-enantiomer)

90 mg of the active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 210 mg Eudragit EPO. The mixture is melted and after melting instantly cooled in an ice bath. The solid solution/dispersion can then be formulated with excipient by granulation into pellets or compressed into tablets.

FINAL COMPOSITION	**mg**	**%**
(4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide (Pellets)	90	30
Eudragit EPO	210	70

Example 12: (hot melt extrusion, trans 2,6-enantiomer)

90 mg of the active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(trans-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 180 mg Eudragit EPO and 30 mg of Vitamin E and subsequently melted and extruded in a holt-melt extruder. The solid solution/dispersion can then be formulated with excipient by granulation into pellets or compressed into tablets.

FINAL COMPOSITION	**mg**	**%**
(4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide (Pellets)	90	30
Eudragit EPO	180	60
Vitamin E	30	10

Example 13: (solid solution, racemic)

90 mg of the active principle (rac)- 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 210 mg Eudragit EPO. The mixture is melted and after melting instantly cooled in an ice bath. The solid solution/dispersion can then be formulated with excipient by granulation into pellets or compressed into tablets.

FINAL COMPOSITION	mg	%
(rac)- 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N -(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro- 1H-pyrazole-3-carboxamide (Pellets)	90	30
Eudragit EPO	210	70

Example 14: (hot melt extrusion, racemic)

90 mg of the active principle (rac)- 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 180 mg Eudragit EPO and 30 mg of Vitamin E and subsequently melted and extruded in a holt-melt extruder. The solid solution/dispersion can then be formulated with excipient by granulation into pellets or compressed into tablets.

FINAL COMPOSITION	mg	%
(rac)- 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)- N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro- 1H-pyrazole-3-carboxamide (Pellets)	90	30
Eudragit EPO	180	60
Vitamin E	30	10

Example 15:

10 weight % of the final solid solution of active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 90 weight % of the final solid solution of Eudragit EPO in an apparatus suitable for hot-Melt Extrusion. The mixture is extruded with an extrusion temperature of 150°C and instantly cooled. The solid solution can then be formulated with excipient by granulation into pellets or compressed into tablets.

Example 16:

9 weight % of the final solid solution of active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 81 weight % of the final solid solution of Eudragit EPO and with 10 weight % of triethylcitrate in an apparatus suitable for hot-Melt Extrusion. The mixture is extruded with an extrusion temperature of 140°C and instantly cooled. The solid solution can then be formulated with excipient by granulation into pellets or compressed into tablets.

Example 17:

9 weight % of the final solid solution of active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 81 weight % of the final solid solution of Eudragit EPO and with 10 weight % of stearic acid in an apparatus suitable for hot-Melt Extrusion. The mixture is extruded with an extrusion temperature of 120°C and instantly cooled. The solid solution can then be formulated with excipient by granulation into pellets or compressed into tablets.

Example 18:

10 weight % of the final solid solution of active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 90 weight % of the final solid solution of Kollidon VA 64 in an apparatus suitable for hot-Melt Extrusion. The mixture is extruded with an extrusion temperature of 170°C and instantly cooled. The solid solution can then be formulated with excipient by granulation into pellets or compressed into tablets.

Example 19:

10 weight % of the final solid solution of active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 90 weight % of the final solid solution of PEG 8000 in an apparatus suitable for hot-Melt Extrusion. The mixture is extruded with an extrusion temperature of 58°C and instantly cooled. The solid solution can then be formulated with excipient by granulation into pellets or compressed into tablets.

Example 20:

10 weight % of the final solid solution of active principle (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is mixed with 20 weight % of the final solid solution of sucrose ester and 70% weight PEG 8000 in an apparatus suitable for hot-Melt Extrusion. The mixture is extruded with an extrusion temperature of 58°C and instantly cooled. The solid solution can then be formulated with excipient by granulation into pellets or compressed into tablets.

PHARMACOLOGICAL EXAMPLES:

For a better understanding, the compound (4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(cis-2,6-dimethyl piperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide is called

from now on the (4S,5S) cis enantiomer or compound (Ia) as described in the chemical example 4.

IN-VITRO TESTS:

Example 21: Preparation of the HME formulations for in-vitro tests:

A mixture has been prepared during two minutes in proportion as described in Table 4. The "Hot Melt Extrusion" formulations, in percentage, have been developed for each series.

The mixture has been loaded in an extruder and the temperature has been adjusted according to the type of polymer used, as described below:

Process temperatures °C	
Eudragit EPO	150
Eudragit EPO - TEC	140
Eudragit EPO-stearic acid	120
Kollidon VA 64	170
PEG 8000	58
PEG 8000+ Sucrose ester	58

The obtained extrudates have been cooled at room temperature and milled. The particle size has then been homogenized. A powder has been obtained which has then been dosified in capsules for administration

The DSC thermogram of the (4S,5S)-cis enantiomer taken alone and the ones of the studied HME formulations are shown in Figures 3 to 9.

Dissolution profiles of the Hot Melt Extrusion Formulations

The dissolution apparatus used was HANSON RESEARCH. SR8 PLUS, the UV spectrophotometer HEWLET PACKARD 8452.

The Table 1 underneath shows the percentage of dissolved fraction vs time (min) for each of the developed hot melt extrusion formulations of Table 4, in Non-Sink conditions

In the NON-SINK conditions, the active ingredient concentration in the dissolution medium is above the saturation concentration, i.e. the active ingredient is in a medium in which it is not soluble.

The conditions used for the Non-Sink assays were:
Apparatus II Paddles
Speed 50 rpm
Dissolution medium: HCL 0.1N, pH 1.2
Volume 1000 ml
Vessel temperature 37°C

Table 1:

Formulations of Table 4	TIME (minutes) % dissolved (pH 1.2)							
	0	5	10	15	20	30	45	60
(4S,5S) cis enantiomer Active substance alone	0,0	2,2	1,9	1,4	1,5	1,6	2,7	2,9
Kollidone VA 64	0,0	67,2	92,5	101,2	103,7	104,8	104,0	104,7
Eudragit EPO	0,0	70,9	87,1	90,3	90,8	89,7	89,1	88,9
PEG8000	0,0	35,8	39,9	42,1	42,8	44,1	43,7	43,4
Eudragit EPO + Triethylcitrate	0,0	71,5	85,3	88,1	89,1	88,1	87,8	87,1
PEG8000 + Sucrose ester	0,0	23,7	33,5	36,8	39,3	45,7	46,3	44,5
Eudragit EPO +stearic acid	0,0	81,1	91,2	93,8	94,4	94,7	95,6	95,1

The results are shown in Figure 1.

The Table 2 underneath shows the percentage of dissolved fraction vs time (min) for each of the developed hot melt extrusion formulations of Table 4, in Sink conditions

In the SINK conditions, the active ingredient concentration in the dissolution medium is below 20% of the saturation concentration, i.e. the active ingredient will dissolve easily in the medium.

The conditions used for the Sink assays were:
Apparatus II Paddles
Speed 50 rpm
Dissolution medium: HCL 0.1N, pH 1.2 + Sodium Lauryl Sulfate 0.1%

Volume 1000 ml
Vessel temperature 37°C

Table 2:

Formulations of Table 4	TIME (minutes) % dissolved (pH 1.2 SLS 0.1%)							
	0	5	10	15	20	30	45	60
(4S,5S) cis enantiomer Active substance alone	0,0	4,1	6,5	11,8	16,0	24,3	37,8	53,0
Kollidone VA 64	0,0	41,0	51,2	56,3	60,1	67,8	75,6	87,4
Eudragit EPO	0,0	87,7	94,2	94,3	94,7	94,5	94,7	94,3
PEG8000	0,0	58,1	66,8	72,8	74,7	77,5	82,3	86,8
Eudragit EPO + Triethylcitrate	0,0	85,0	86,6	88,4	89,4	89,7	90,2	90,0
PEG8000 + Sucrose ester	0,0	42,0	62,0	69,2	75,8	83,6	88,0	91,0
Eudragit EPO + stearic acid	0,0	85,9	87,0	89,0	89,4	90,0	89,6	89,9

The results are shown in Figure 2.

The Table 3 underneath shows the solubility Increase (Δ) at 60 min for each of the developed hot melt extrusion formulations, in Sink and Non-Sink conditions

Table 3:

Excipient	Increase (Δ) 60 min. Non Sink Conditions	Increase (Δ) 60 min. Sink Conditions
(4S,5S) cis enantiomer	0,00	0,00
Kollidone VA 64	35,51	1,65
Eudragit EPO	30,13	1,78
PEG8000	14,73	1,64
Eudragit EPO + TEC	29,55	1,70
PEG8000 + Sucrose	15,10	1,72
Eudragit EPO +stearic acid	32,25	1,70

Solubility increase (Δ) = FD60min formulation / FD % 60 min (drug)

FD=dissolved drug fraction

CONCLUSIONS

- Data from thermogram DSC study showed that all the HME prototypes developed with three different polymers Eudragit EPO, PEG 8000 and Kollidon VA 64 and combinations with plasticizers are solid solutions.

- Data from dissolution study (sink conditions) under conditions paddle 50 rpm, medium pH 1.2 with 0.1% SLS showed that the prototypes developed from each series improved 1.7-1.8 folds drug solubility at 60 minutes.

- Data from dissolution study (non sink conditions) under conditions paddle 50 rpm, medium pH 1.2 showed that the prototypes developed composed by Kollidon VA64

improved 35 folds drug solubility at 60 minutes, Eudragit EPO series improved 29-32 folds drug solubility at 60 minutes

EUDRAGIT EPO Series	
Product	**%**
CB1 (drug)	10,0
Eugradit EPO	90,0
Total	**100,0**
CB1 (drug)	9,0
Triethyl citrate	10,0
Eugradit EPO	81,0
Total	**100,0**
CB1 (drug)	9,0
stearic acid	10,0
Eugradit EPO	81,0
Total	**100,0**

Table 4:

Developed Hot Melt Extrusion formulations for each series expressed in percentages

PEG8000 Series	
Product	**%**
CB1 (drug)	10,0
PEG 8000	90,0
Total	**100,0**
CB1 (drug)	10,0
Sucrose ester	20,0
PEG 8000	70,0
Total	**100,0**

Series Kollidon VA64	
Product	**%**
CB1 (drug)	10,0
Kollidon VA 64	90,0
Total	**100,0**

IN-VIVO TESTS:

Pharmacokinetics

A pharmacokinetic study in rats is performed with the formulations according to Examples 15 to 20 (formulations from Table 4) compared to the active principle alone. The formulation according to Examples 15 to 20 as well as the active principle alone are given orally at a concentration 20 mg/kg (of active principle) to male Wistar Hannover rats. Plasma samples are centrifugated and after protein precipitation are analyzed by HPLC/MS/MS using an enantioselective method.

The aim of this study is to quantify the (4S,5S) cis enantiomer in male rats after single oral administration of the (4S,5S) cis enantiomer (as HME formulation and as active ingredient) using a chiral HPLC method with tandem mass spectrometric detection. Plasma levels of the (4S,5S) cis enantiomer and the enantiomer (4R,5R) are determined in rat after oral administration by a chiral LC-MS/MS method previously validated.

The method is selective too for the stereoisomers (4S,5R) and (4R,5S), Anyway the absence of in vivo interconversion was demonstrated in a previous study.

Male Wistar Hannover rats (HSDHan:WIST), weighing 175 g – 200 g were supplied by Harlan Italia. The quarantine of the animals was at least 5 days. At the end of quarantine, the animals were transferred to the treatment room for at least 1 day to acclimatise where they were in 50 x 25 x 15 cm Makrolon cages with a grating floor to prevent coprophagy and with a maximum of 5 rats per cage. The room was air-conditioned, with the temperature controlled to 22 ± 2ºC and a relative humidity of 50 ± 20% (Trend 963 Secure Supervisor©, Trend Control Systems Ltd., UK). There was a cycle of 12 h of light and 12 h of darkness.

The products were singly administered in fasting conditions at a dose of 20 mg/kg to animals by means of a gavage and the administration volume was 10 ml/kg. The suspension to be administered was prepared for each group of five rats to ensure an equivalent state of it in 5% arabic gum.

Blood samples (around 700 µl) were extracted from the retro-ocular puncture at the following times: Predose, 15min, 30min, 1h, 1.5h, 2h, 4h, 6h, 8h y 24h.

The blood was transferred into plastic tubes containing 18% EDTA-K3. The resulting plasma samples were frozen and kept at least at -65ºC ± 5ºC until analysis

The following protein precipitation extraction method was used for the extraction of parent compounds: 600 µl of acetonitrile containing internal standard (15 ng/ml) were added to the samples (100 µl) in order to precipitate proteins. The suspensions were mixed thoroughly and centrifugated at 4ºC and aprox. 100000 x g. 250 µl of the supernatant were diluted with 250 µl of 0.1% formic acid in water to be analyzed.

A Chiralcel OJRH 4.6 x 150 mm column was used for chromatographic separation. The mobile phase was 0.05% acetic acid in water adjusted to pH 3.5 with diluted ammonium/ Acetonitrile (40/60 v/v) at a flow rate of 0.8 ml/min. The injection volume was 40 µl.

The MS/MS ionization mode was Turbo spray – positive ion mode in MRM scan type. The transition Q1 to Q3 used for quantification was 493.20 (amu) to 365.00 (amu).

Pharmacokinetic parameter estimation were performed on mean plasma concentration vs time data (from 5 animals per timepoint) by means of non-compartmental pharmacokinetic analysis.

Pharmacokinetic parameters of the (4S, 5S) cis enantiomer in plasma after administration of the (4S, 5S) cis enantiomer to rat

The formulation used for the in-vivo adminsitration was the one from example 15

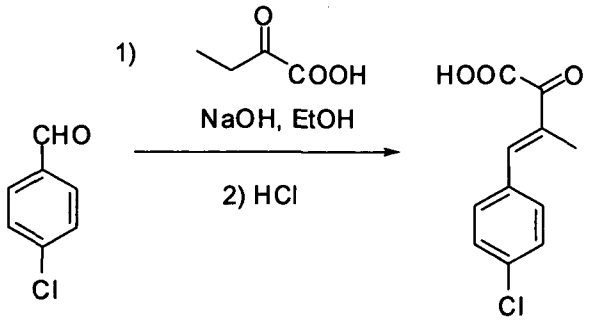
Route	Sex	Dose (mg/kg)	Formulation	Pharmacokinetic parameters								
				$t_{1/2}$	tmax	Cmax[a]	AUC_{0-t}	$AUC_{0-\infty}$	Vd[b]	Vss	Cl[c]	F[d]
				(h)	(h)	(ng/ml)	(ng·h/ml)	(ng·h/ml)	(l/kg)	(l/kg)	(l/hr/kg)	(%)
po	male	20	suspension	NC	6.0	102.8	374.2	NC	NC	-	NC	3.5
po	male	20	HME	4.8	4.0	289.2	1301.7	1324.3	103.6	-	15.1	12.2
iv	male	1	solution	8.2	-	828.5	533.6	558.7	21.1	8.7	1.8	-

a: C0 for intravenous
b: Vd/F for oral
c: Cl/F for oral
d: Absolute bioavailability estimated from AUC0-t
NC: Not calculated

The p.o. results of the in-vivo test on which the above table is based are shown in Figure 10.

CHEMICAL EXAMPLES:

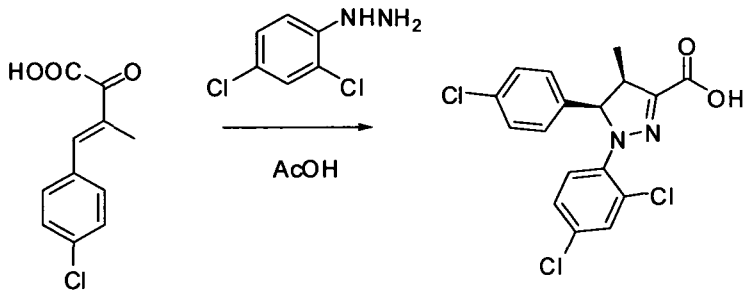
Chemical -Example 1: Preparation of (E)-4-(4-Chlorophenyl)-3-methyl-2-oxo-but-3-enoic acid



To a solution of aqueous 0.5 M NaOH (85.2 g, 2.13 mol 1.5 eq) in water (4.26 L), under N_2 at room temperature, 2-oxobutyric acid (159.7 g, 1.56 mol, 1.1 eq) was added in portions (60 mL of EtOH were used to wash the product container). The reaction was then left stirring for 5 min and a solution of 4-chlorobenzaldehyde (200.0 g, 1.42 mol, 1 eq) in abs. EtOH (710 mL) was then slowly added (approx. rate of addition: 2 h at 150 mL/h and 7h at 50 mL /h). The reaction was left to stir at 25 °C overnight. Water was added (800 mL) and the solution evaporated under reduced pressure to eliminate the excess of EtOH. The solution was then washed with toluene and evaporated (3 x 500 mL) to eliminate traces of this solvent. The aqueous solution was then cooled down in an ice bath and conc. HCl (240 mL) was slowly added under magnetically stirring. A white solid precipitated from the solution which was kept at 0 °C for another hour. The solid was filtered under vacuum through a sintered funnel (porosity 3) and dried at 40 °C under vacuum (287.8 g, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17 (3H, s, CH_3), 7.44 (4H, ap d, *J* 3.28 Hz, ArH), 8.41 (1H, s, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2 (CH_3), 129.2 (CH), 129.6 (C), 131.9 (CH), 133.4 (C), 136.4 (C), 147.6 (CH), 164.4 (CO), 187.1 (CO).

Chemical-Example 2: Preparation of racemate *cis*-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxylic acid



To a suspension of 2,4-dichlorophenylhydrazine hydrochloride (277.5 g, 1.27 mol, 1 eq) in acetic acid (2.0 L) at 80 °C, a solution of crude (E)-4-(4-chlorophenyl-3-methyl-2-oxo-3-butenoic acid (286.2 g, 1.27 mol) in glacial acetic acid (1.27 L) was slowly added and the reaction was maintained at 80 °C for 2 h. The reaction mixture was then allowed to cool down to 50 °C and concentrated under reduced pressure to approximately 2/3 of its initial volume. The solution was mechanically stirred at room temperature overnight and a yellow precipitated was formed. The solid was then filtered under vacuum through a sintered funnel (porosity 3) to obtain a mixture of racemates *cis* and *trans* 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1*H*-pyrazol-3-carboxylic acid (430 g, 88.4 % yield) as a yellow solid, which was suspended in water (1.0 L), stirred for 30 min and filtered. This operation was repeated four times (until the pH of the filtered water was between 5 and 6). The solid was then left to dry under vacuum at 40 °C for 48 h (249 g, 51.2 % yield). The solid

was suspended in toluene (1125 mL) and heated to 80 °C. The suspension was transformed into a solution, which was left at this temperature for 10 min and then at room temperature overnight. The following morning a yellow precipitated had formed. Filtration through a Buchner funnel under vacuum provided a whitish powdery solid of pure racemate *cis*-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1*H*-pyrazol-3-carboxylic acid (189.7 g, 39 % yield, 76 % yield of crystallization).

IR (NaCl film, cm^{-1}) of the racemate *cis*-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1*H*-pyrazol-3-carboxylic acid, measured with FT-IR Nexus by Thermo Nicolet: 2976, 1682, 1566, 1542, 1490, 1270, 1242, 1117.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.96 (d, *J*=7.42 Hz, 3 H) 3.82 (td, *J*=11.72, 7.42 Hz, 1 H) 5.91 (d, *J*=11.72 Hz, 1 H) 7.04 (d, *J*=8.60 Hz, 2 H) 7.11 (dd, *J*=8.60, 2.34 Hz, 1 H) 7.21 - 7.30 (m, 4 H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 43.5 (CH), 72.0 (CH), 124.9 (CH), 127.6 (CH), 129.1 (CH), 129.6 (CH), 130.9 (CH), 131.3 (C), 132.7 (C), 134.5 (C), 138.7 (C), 144.6 (C), 165.9 (CO).

Chemical-Example 3: Separation of *(4R, 5R)* and *(4S, 5S)*-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxylic acid from racemate *cis*-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxylic acid

a) Separation by chiral HPLC.

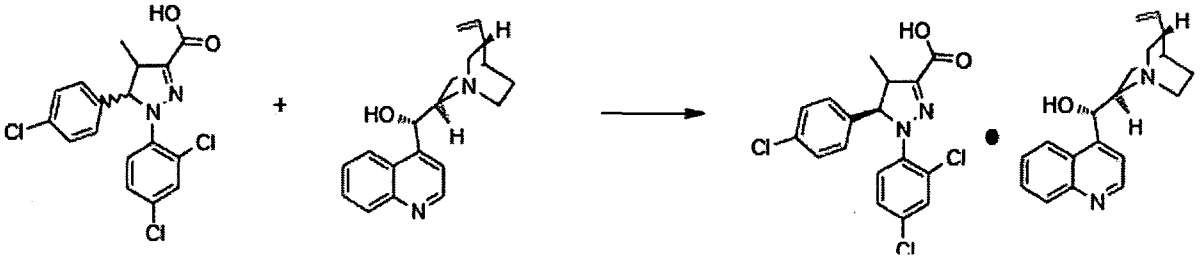
Conditions for the isolation of each enantiomer of racemate *cis*-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxylic acid by preparative chiral HPLC were the following:

- Column: 250 x 20 mm CHIRALPAK® AD-H 5 µm
- Mobile Phase: 80/20 CO_2 / Methanol
- Flow rate: 60 mL/min
- Detection: UV 230 nm
- Outlet Pressure: 150 bar
- Temperature: 25 ° C

First eluting enantiomer, with a retention time of 5.56 min, was obtained with an enantiomeric excess higher than 99 %, and was identified as *(4S, 5S)*-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxylic acid (6.70 g, 47.8 % yield, $[\alpha]_D$= +130.9 °). Second eluting enantiomer, with a retention time of 8.51 min, was also obtained with an enantiomeric excess higher than 99 %, and was identified as *(4R, 5R)*-5-(4-

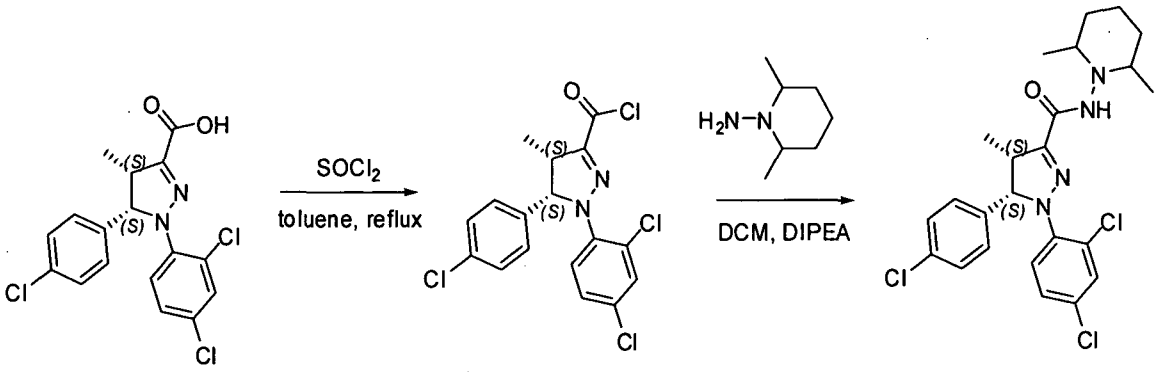
chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxylic acid (6.55 g, 46.8 % yield, $[\alpha]_D$= -128.5 °).

b) Diastereomeric resolution with chiral amines



To a suspension of (+)-cinchonine in refluxing MeCN (2 mL), a solution of the racemate *cis*-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxylic acid (2.0 g, 5.2 mmol) in MeCN (2 ml) was added. To this mixture MeCN was added in small portions until all solids were dissolved. The solution was allowed to cool to r.t. overnight. White crystals were formed, collected by filtration and washed with MeCN. The crystals were dried under vacuum to obtain mainly *(4R, 5R)*-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxylic acid (1.7 g, 2.51 mmol, 48% (50% max), ee= 88.3 %). The acid was liberated by extraction of the white solid in toluene and 6 N HCl. The organic layer was dried over Na_2SO_4 and concentrated to give a light yellow foam (0.95 g, 2.47 mmol, 48 % yield, ee= 91.7%). To a solution of this foam in refluxing MeCN (2 ml), (+)-cinchonine (765 mg, 2.60 mmol) was added in a second crystallization process. To this mixture MeCN was added in small portions until all solids were dissolved. The solution was allowed to cool to r.t. overnight. White crystals were formed, collected by filtration and washed with MeCN. The crystals were dried under vacuum. The acid was liberated by extraction in toluene and 6 N HCl to give a white solid identified as pure *(4R, 5R)*-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxylic acid (860 mg, 42% yield, ee= 99.5%, $[\alpha]_D$= -128.5 °). Recrystallization of mother liquors led to the (4*S*, 5*S*) enantiomer.

Chemical-Example 4: Preparation of (4*S*,5*S*)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide



(4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxylic acid (20.0 g, 52.13 mmol) obtained according to the step above was dissolved in dry toluene (120 mL) and thionyl chloride (4.5 mL, 62.56 mmols) was added. The mixture was heated to 80 ºC for 2.5 hours. The solvent was removed under reduced pressure and the resulting crude residue was used without any further purification.

(4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carbonyl chloride was obtained as an oil.

IR (NaCl film, cm^{-1}) : 1732, 1700, 1533, 1478, 1212, 826.

Under nitrogen atmosphere *cis*-2,6-dimethylaminopiperidine (8.01 g, 62.56 mmoles) and diisopropylethylamine (DIPEA) (2.695 g, 208.5 mmol, 35.7 mL) were dissolved in methylene chloride (DCM) (100 mL). The resulting mixture was ice-cooled down to 0°C and a solution of *(4S,5S)*-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carbonyl chloride (20.96 g, 52.13 mmol), obtained in the former step, in methylene chloride (50 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature (approximately 25 °C) overnight. Afterwards, the reaction mixture was washed with water, followed by a saturated aqueous solution of sodium bicarbonate, then again with water, dried over sodium sulfate, filtered and evaporated to dryness in a rotavapor. The resulting crude was purified by silicagel chromatography using a CombiFlash Companion apparatus, using a gradient of cyclohexane and ethyl acetate to obtain a white solid (18.3 g, 71 % yield).

1H NMR (300 MHz, DMSO-d6) δ ppm 0.73 (d, J=7.18 Hz, 3 H) 0.95 (d, J=6.01 Hz, 6 H) 1.23 (br. s., 3 H) 1.63 (m, 3 H) 2.55 (br. s., 2 H) 3.83 (dd, J=11.13, 7.18 Hz, 1 H) 5.88 (d, J=11.13 Hz, 1 H) 7.12 (d, J=8.35 Hz, 2 H) 7.30 (m, 3 H) 7.45 (d, J=2.20 Hz, 1 H) 7.67 (d, J=8.79 Hz, 1 H) 8.64 (br. s., 1 H). MS (M+H)+: 493. [α]D= +57.19 º.

Alternatively, a solution of 2 N HCl in diethyl ether were added over the solid dissolved in diethyl ether to form the hydrochloride, which was collected by filtration.

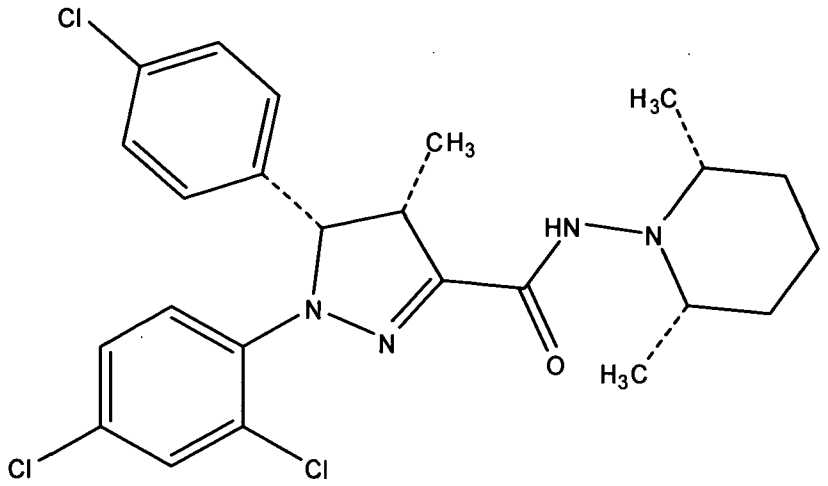
1H NMR (300 MHz, DMSO-d6) δ ppm 0.75 (d, J=7.32 Hz, 3 H) 1.05 (d, J=6.01 Hz, 6 H) 1.33 (m, 1 H) 1.47 (m, 2 H) 1.61 (d, J=9.96 Hz, 1 H) 1.72 (m, 2 H) 2.96 (br. s., 2 H) 3.87 (m, 1 H)) 5.92 (d, J=11.28 Hz, 1 H) 7.14 (d, J=8.35 Hz, 2 H) 7.32 (m, 3 H) 7.48 (d, J=2.20 Hz, 1 H) 7.65 (d, J=8.64 Hz, 1 H) 9.80 (br. s., 1 H). MS (M+H)+: 493.

Chemical-Example 5: Preparation of (4*S*,5*S*)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide

The preparation of (4*S*,5*S*)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide was done in an analoguous way to the preparation of (4*S*,5*S*)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide according to Chemical-Example 4.

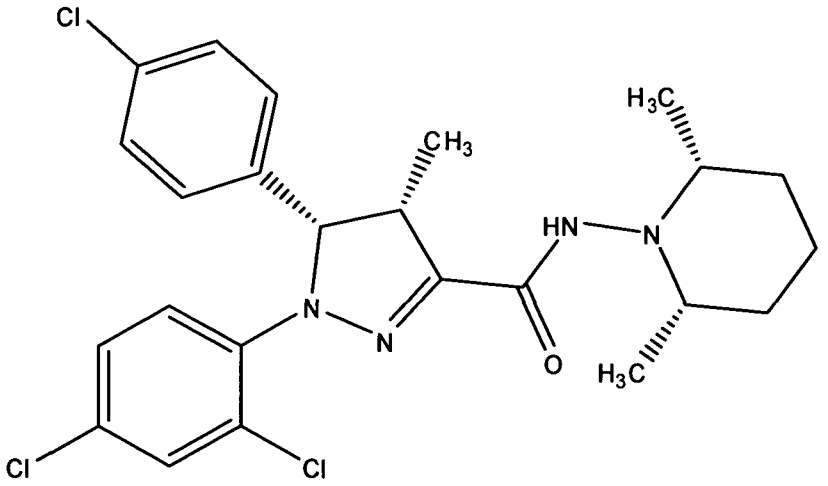
Claims:

1. Solid dispersion and/or solid solution of one or more active principles selected from compounds of formula (I), (Ia) or (Ib) or mixtures thereof



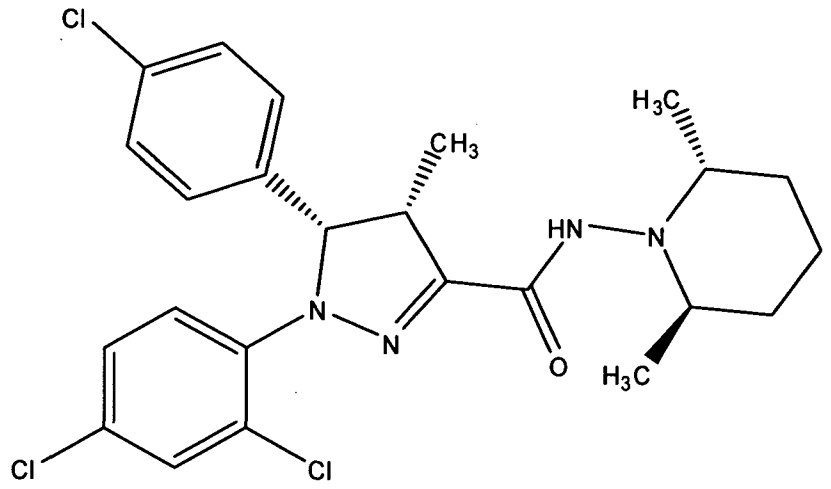
cis-rac-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide

(I)



(4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide

(Ia)



(4S,5S)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide

(Ib)

, optionally in form of one or more of the appropriate polymorphs, in amorphous form and/or corresponding salts and/or corresponding solvates thereof,

obtainable by a process in which

a) the active principle/s is/are mixed with an at least equimolar amount or at least equal weight of at least one carrier,
b) thereafter or during step a) the mixture is heated until the carrier in the mixture is melted and
c) subsequently the mixture is cooled below the melting point of the carrier in the mixture.

2. Solid dispersion and/or solid solution according to claim 1, characterized in that the carrier is either hydrophilic or hygroscopic and has a melting point between +40°C and the melting point of the active principle or mixture of active principles +20 °C.

3. Solid dispersion and/or solid solution according to claim 1, characterized in that the carrier is selected from

- sugars, like dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mamitol, lactose;
- acids, like citric acid, succinic acid;
- polymeric materials, like povidone (PVP), polyethylene oxide, polyethylene glycol (PEG), hydroxpropylmethylcellulose,

methylcellulose, ethylcellulose hydroxyethylcelllose, cylodextrin, hydroxypropylcellulose, pectin, galactomannan, chitosan, carrageenan;

- insoluble or enteric polymers, like hydroxypropylmethylcellulose phthalate, polymethacrylates (e.g. Eudragit L-100, Eudragit S-100, Eudragit RL, Eudragit RS, Eudragit EPO);
- surfactants, like polyoxyethylene stearate, renex, poloxamer 188, texafor, AIP, deoxycholic acid, polyoxy-ethylene-sorbitan higher fatty acid esters (e.g. Tween, like Tween 80), spans;
- others, consisting of: carnuba wax, pentaerythritol, pentaerythrityltetraacetate, urea, urethane, hydroxyalkylxanthins;
- excipients derived from fatty acids, monoglycerides and polyoxyglycerides

preferably the carriers are selected from
PVP, PEG, Kollidon VA 64, EUDRAGIT, MYRJ 52, VITE-TPGS, GELUCIRE 50/13, HPMC-PHTALATE, HPMC, HEC, HPC-SL, PEO and/or POLOXAMER.

4. Solid dispersion and/or solid solution according to any of claims 1 to 3, characterized in that
   - the melting temperature in step (b) is in the range between +40°C and the melting point of the active principle or mixture of active principles +20 °C; and/or
   - the cooling step (c) is done by lowering the temperature by more than 10°C/sec, preferably 20°C/sec, down to temperatures below 25 °C, preferably below 0 °C; and/or is done by contacting the melt of step (b) with an environment having a temperature of 25°C or lower, preferably 0°C or lower.

5. Solid dispersion and/or solid solution according to claim 1, characterized in that the weight or molecular ratio between active principle and carrier is between 1:1 and 1: 20, preferably is between 1:1 and 1:10, more preferably is between 1:2 and 1:5.

6. A pharmaceutical composition comprising the solid solution and/or solid dispersion according to any of claims 1 to 5 and optionally further pharmaceutical acceptable ingredients.

7. A pharmaceutical composition according to claim 6, characterized in that

- the active principle is present in an amount of 10 to 60, preferably 20 to 40 % by weight based on the total weight of the composition;

and/or

- the active principle is present in an amount of 1 to 250 mg, preferably 10 to 200 mg, more preferably 15 to 150 mg in the composition.

8. A pharmaceutical composition comprising the solid solution according to any of claims 6 or 7, characterized in that it is suitable to enhance the absorption of the active principle through a mucosa or a physiological membrane.

9. A pharmaceutical composition according to claim 8, characterized in that the mucosa is selected from the

- nasal or olfactory mucosa,
- buccal or oral mucosa,
- gastric mucosa,
- intestinal mucosa
- vaginal mucosa, or
- rectal mucosa,

preferably selected from

- gastric mucosa, or
- intestinal mucosa.

10. A pharmaceutical composition according to any of claims 6 to 9, characterized in that the pharmaceutical composition is selected from

- a pharmaceutical composition for oral application,
- a pharmaceutical composition for nasal application,
- a pharmaceutical composition for buccal application,
- a pharmaceutical composition for rectal application, or
- a pharmaceutical composition for vaginal application;

or

- a pharmaceutical composition for transdermal application;

- a pharmaceutical composition for systemic application;

preferably selected from

- a pharmaceutical composition for oral application.

11. A pharmaceutical composition according to any of claims 6 to 10, characterized in that the pharmaceutical composition is selected from

- a tablet,
- a capsule,
- a sachet,
- a powder,
- a caplet,
- a gel,
- a film,
- a pellet,
- a granule,
- an implant,
- a multiparticulate with granules compressed into a tablet,
- a multiparticulate with granules filled into a capsule,
- a multiparticulate with pelets compressed into a tablet,
- a multiparticulate with pelets filled into a capsule, or
- a suppository,

or

- an injectable solution/dispersion
- a transdermal system like a patch;

preferably selected from

- a tablet,
- a capsule,
- a pellet,
- a granule,
- a multiparticulate with granules compressed into a tablet,
- a multiparticulate with granules filled into a capsule,
- a multiparticulate with pelets compressed into a tablet, or

- a multiparticulate with pelets filled into a capsule.

12. A pharmaceutical composition according to any of claims 6 to 11, characterized in that

- the further pharmaceutical acceptable ingredients are present in a total amount of 5 to 95 %, preferably 50 to 90 % by weight based on the total weight of the composition;

and/or

- the further pharmaceutical acceptable ingredients are present in a total amount of 0 to 300 mg, preferably 0 to 250 mg, more preferably 20 to 250 mg.

13. A pharmaceutical composition according to any of claims 6 to 12, characterized in that the further pharmaceutical acceptable ingredient/s is/are selected from
a diluent, a binder and/or a lubricant, and/or optionally a flowing agent, an antiadhesive, a preservative, and/or, optionally, a taste masking agent, a coloring agent and/or a flavoring agent and/or a permeation enhancer.

14. A pharmaceutical composition according to any of claims 6 to 13, characterized in that the pharmaceutical composition is prepared using hot-melt extrusion.

15. A pharmaceutical composition for oral administration comprising the solid solution and/or solid dispersion according to any of claims 1 to 5 and optionally further pharmaceutical acceptable ingredients.

16. A solid dispersion and/or solid solution according to any of claims 1 to 5 or a pharmaceutical composition according to any of claims 6 to 14 and 15, characterized in that the active principle is selected from

a) (rac)- 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide;
preferably in
- cystalline form;
- amorphous form;

- form of a solvate, preferably a hydrate, more preferably a monohydrate;
- the free base; or
- a salt with an acid with a $pk_a \leq 3.0$,especially the acid being selected from 2,5-dihydroxybenzenesulfonic acid, 2-naphthalenesulfonic acid, aspartic acid, benzenesulfonic acid, amphor-10-sulfonic acid, cyclohexylsulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, fumaric acid, glutamic acid, hydrobromic acid, hydrochloric acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, nitric acid, phosophoric acid, *p*-toluenesulfonic acid, sulfuric acid and/or thiocyanic acid; more preferably the salt being a hydrochloride;

b) (4s,5s)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide, preferably

preferably in

- cystalline form;
- amorphous form;
- form of a solvate, preferably a hydrate,
- the free base;
- a salt with an acid with a $pk_a \leq 3.0$,especially the acid being selected from 2,5-dihydroxybenzenesulfonic acid, 2-naphthalenesulfonic acid, aspartic acid, benzenesulfonic acid, amphor-10-sulfonic acid, cyclohexylsulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, fumaric acid, glutamic acid, hydrobromic acid, hydrochloric acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, nitric acid, phosophoric acid, *p*-toluenesulfonic acid, sulfuric acid and/or thiocyanic acid; more preferably the salt being a hydrochloride;

c) (4s,5s)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(*trans*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide,

preferably in

- crystalline form;
- form of a solvate, preferably a hydrate,

- the free base;
- a salt with an acid with a $pk_a \leq 3.0$,especially the acid being selected from 2,5-dihydroxybenzenesulfonic acid, 2-naphthalenesulfonic acid, aspartic acid, benzenesulfonic acid, amphor-10-sulfonic acid, cyclohexylsulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, fumaric acid, glutamic acid, hydrobromic acid, hydrochloric acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, nitric acid, phosophoric acid, *p*-toluenesulfonic acid, sulfuric acid and/or thiocyanic acid; more preferably the salt being a hydrochloride;

or

d) *a nonracemic mixtures of* (b) *and* (c).

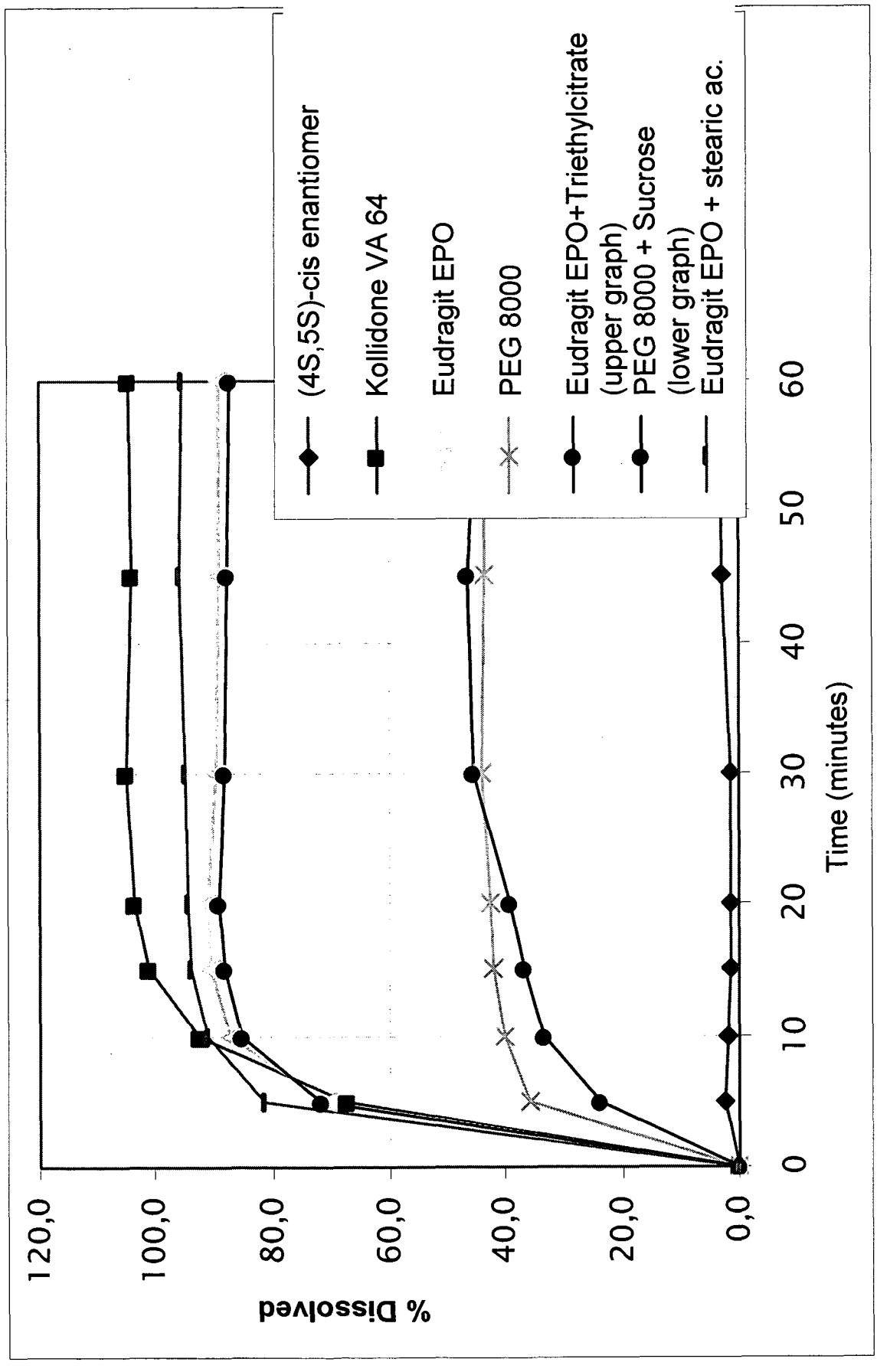

(4S,5S)-cis enantiomer
Kollidone VA 64
Eudragit EPO
PEG 8000
Eudragit EPO+Triethylcitrate (upper graph)
PEG 8000 + Sucrose (lower graph)
Eudragit EPO + stearic ac.
% Dissolved
120,0
100,0
80,0
60,0
40,0
20,0
0,0
0
10
20
30
40
50
60
Time (minutes)

Figure 1)

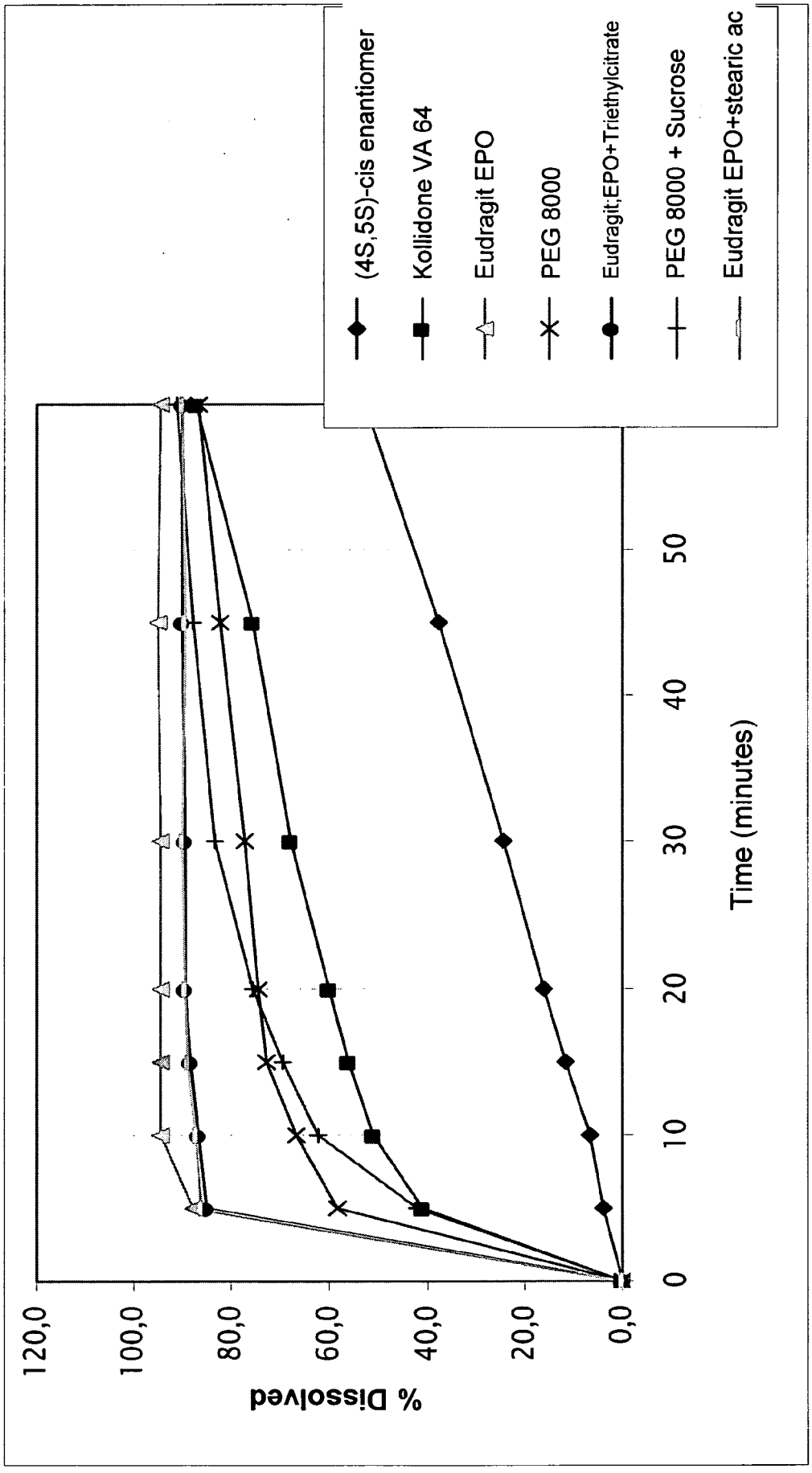
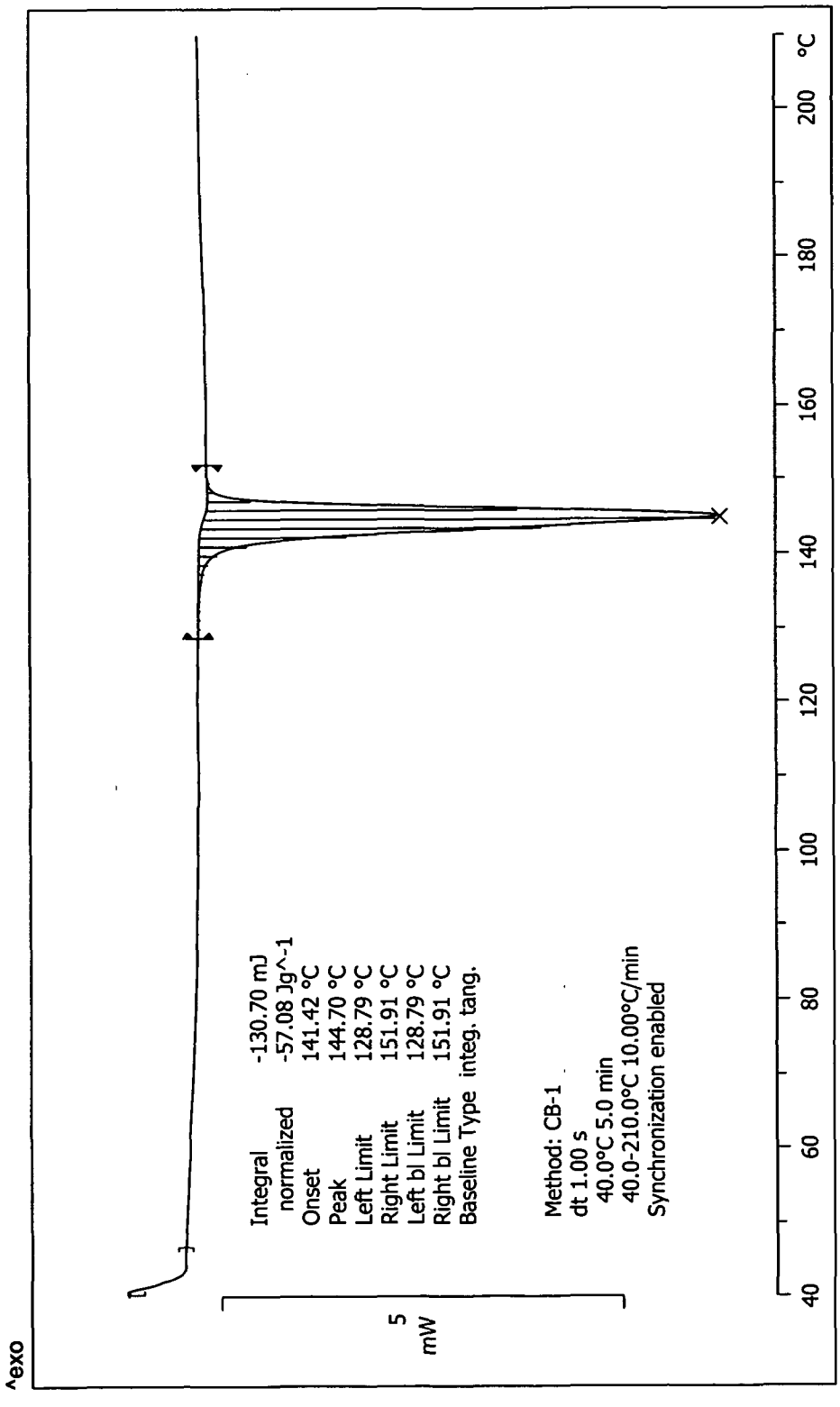

(4S,5S)-cis enantiomer
Kollidone VA 64
Eudragit EPO
PEG 8000
Eudragit;EPO+Triethylcitrate
PEG 8000 + Sucrose
Eudragit EPO+stearic ac
% Dissolved
120,0
100,0
80,0
60,0
40,0
20,0
0,0
0
10
20
30
40
50
Time (minutes)

Figure 2)

Figure 3)


^exo
5
mW
Integral -130.70 mJ
normalized -57.08 Jg^-1
Onset 141.42 °C
Peak 144.70 °C
Left Limit 128.79 °C
Right Limit 151.91 °C
Left bl Limit 128.79 °C
Right bl Limit 151.91 °C
Baseline Type integ. tang.
Method: CB-1
dt 1.00 s
40.0°C 5.0 min
40.0-210.0°C 10.00°C/min
Synchronization enabled
40
60
80
100
120
140
160
180
200
°C

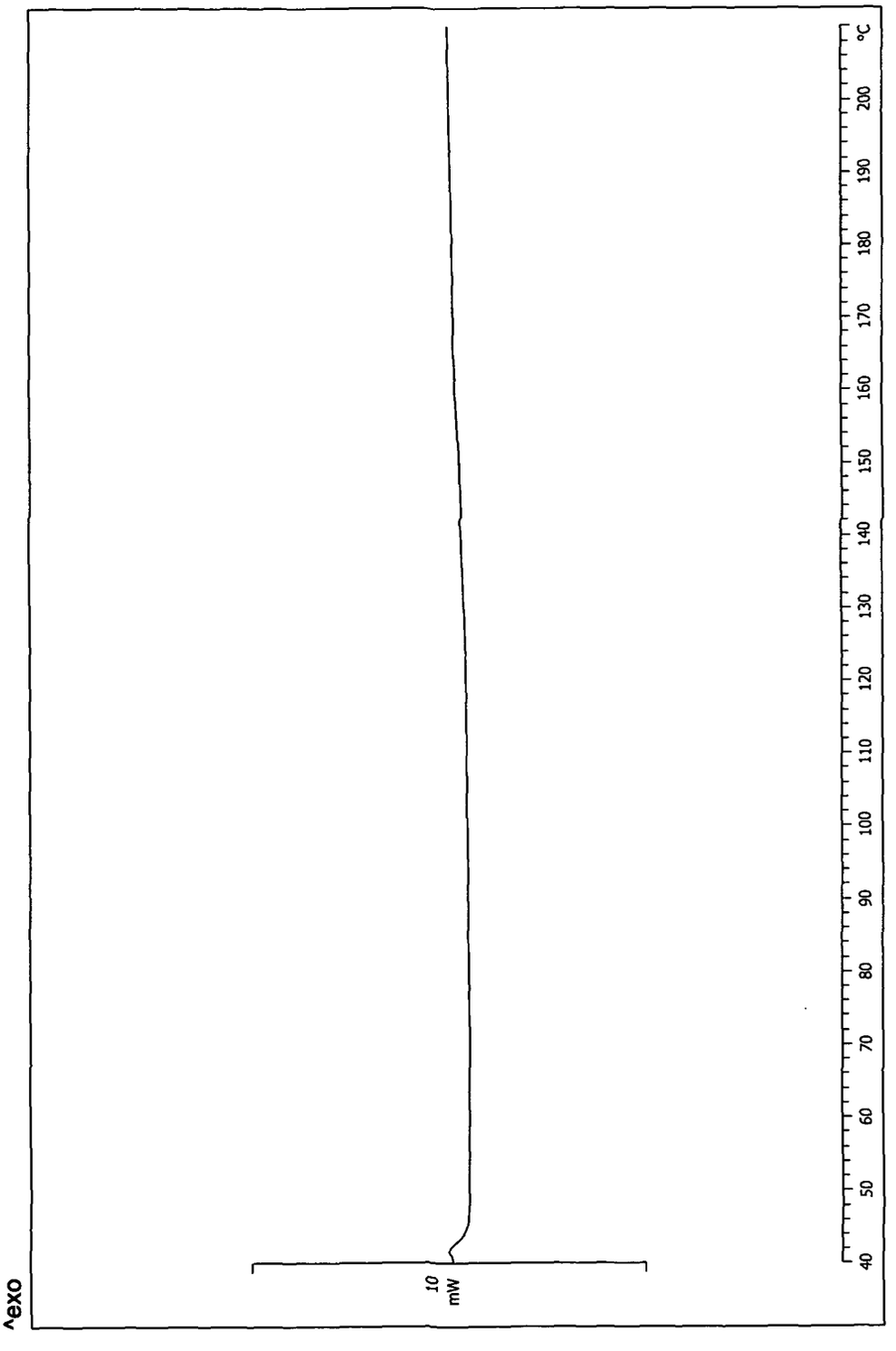
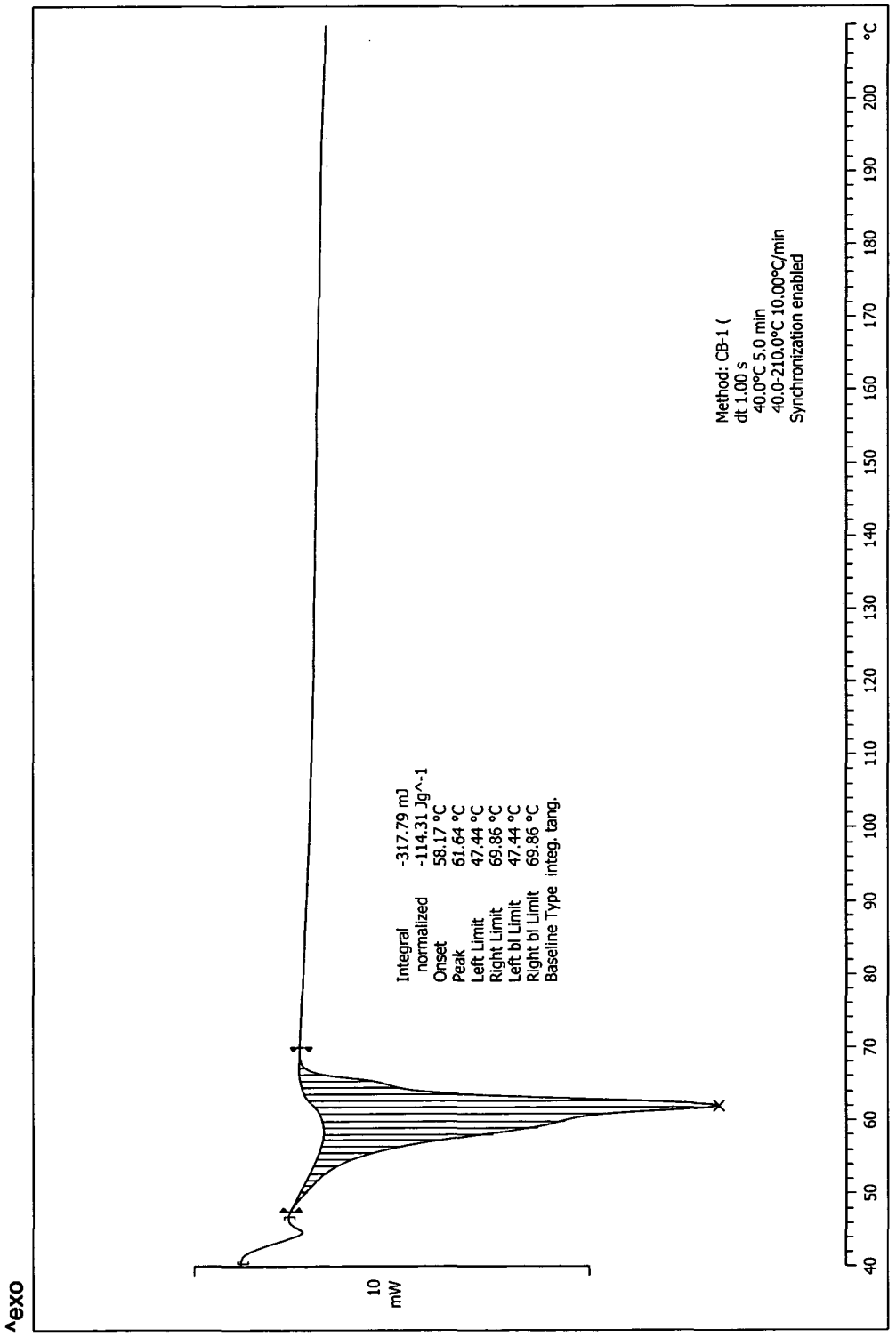

^exo
10
mW
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
°C

Figure 4)

Figure 5)


^exo
10
mW
Integral -317.79 mJ
normalized -114.31 Jg^-1
Onset 58.17 °C
Peak 61.64 °C
Left Limit 47.44 °C
Right Limit 69.86 °C
Left bl Limit 47.44 °C
Right bl Limit 69.86 °C
Baseline Type integ. tang.
Method: CB-1 (
dt 1.00 s
40.0°C 5.0 min
40.0-210.0°C 10.00°C/min
Synchronization enabled
40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 °C

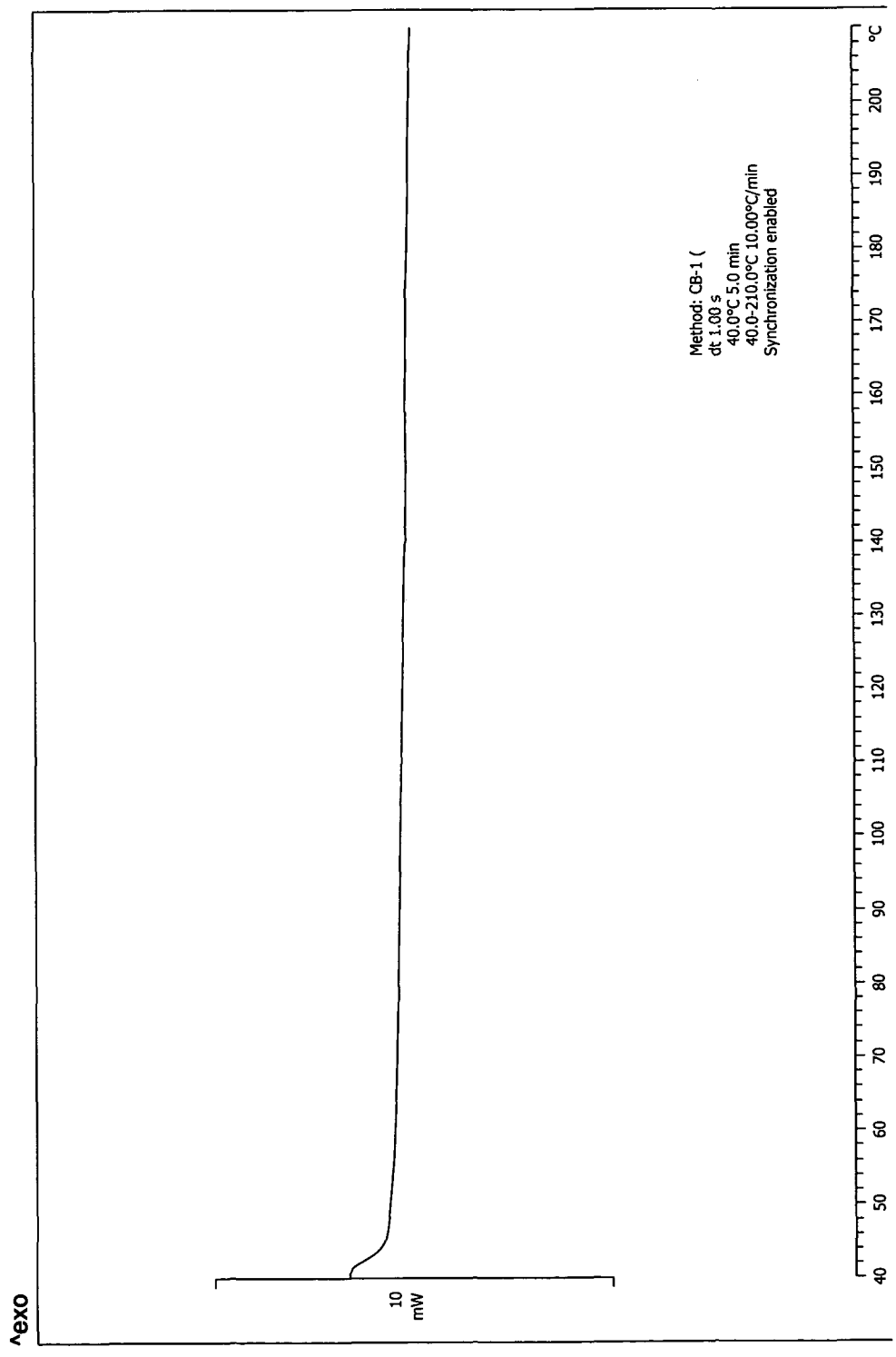

^exo
10
mW
Method: CB-1 (
dt 1.00 s
40.0°C 5.0 min
40.0-210.0°C 10.00°C/min
Synchronization enabled
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
°C

Figure 6)

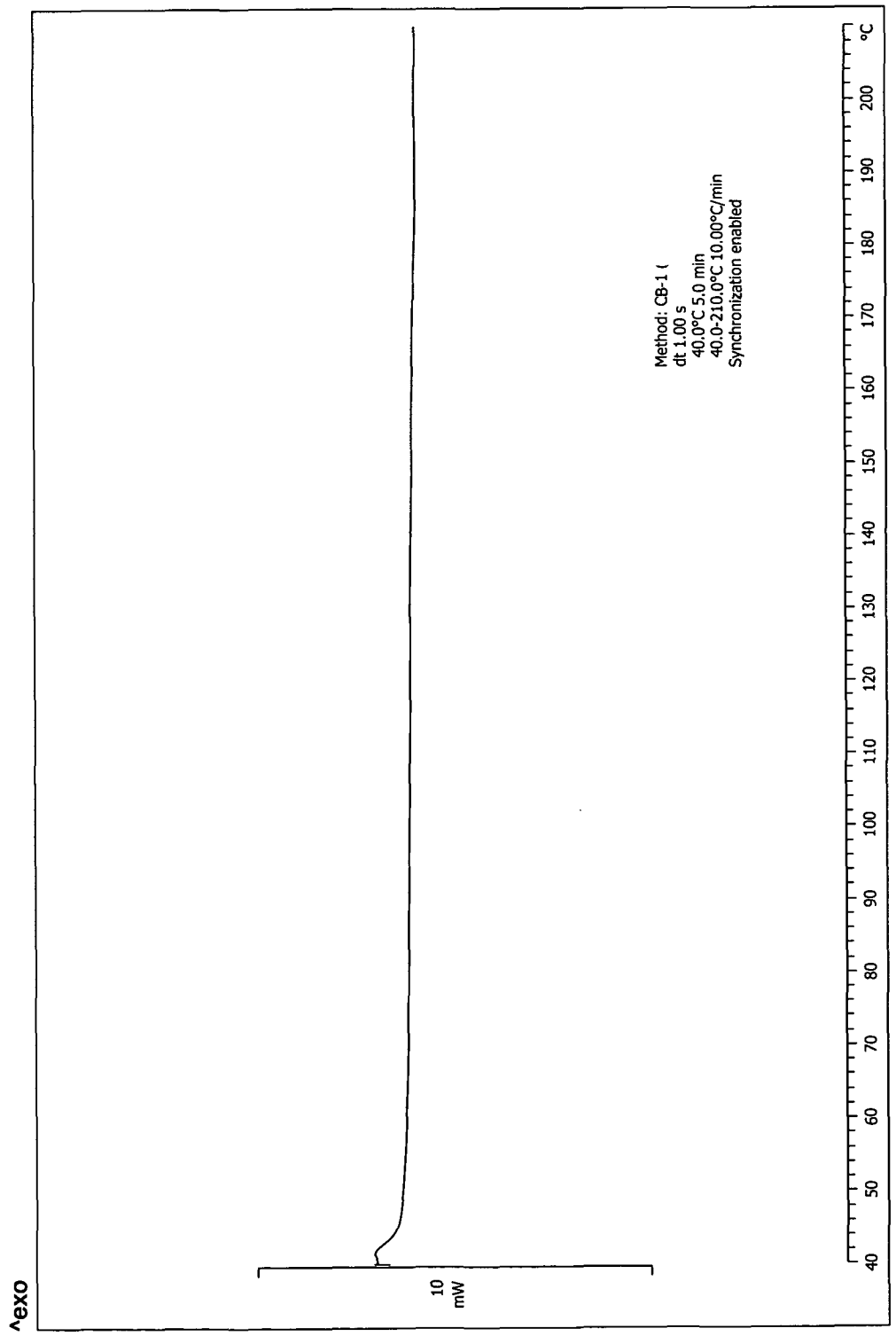
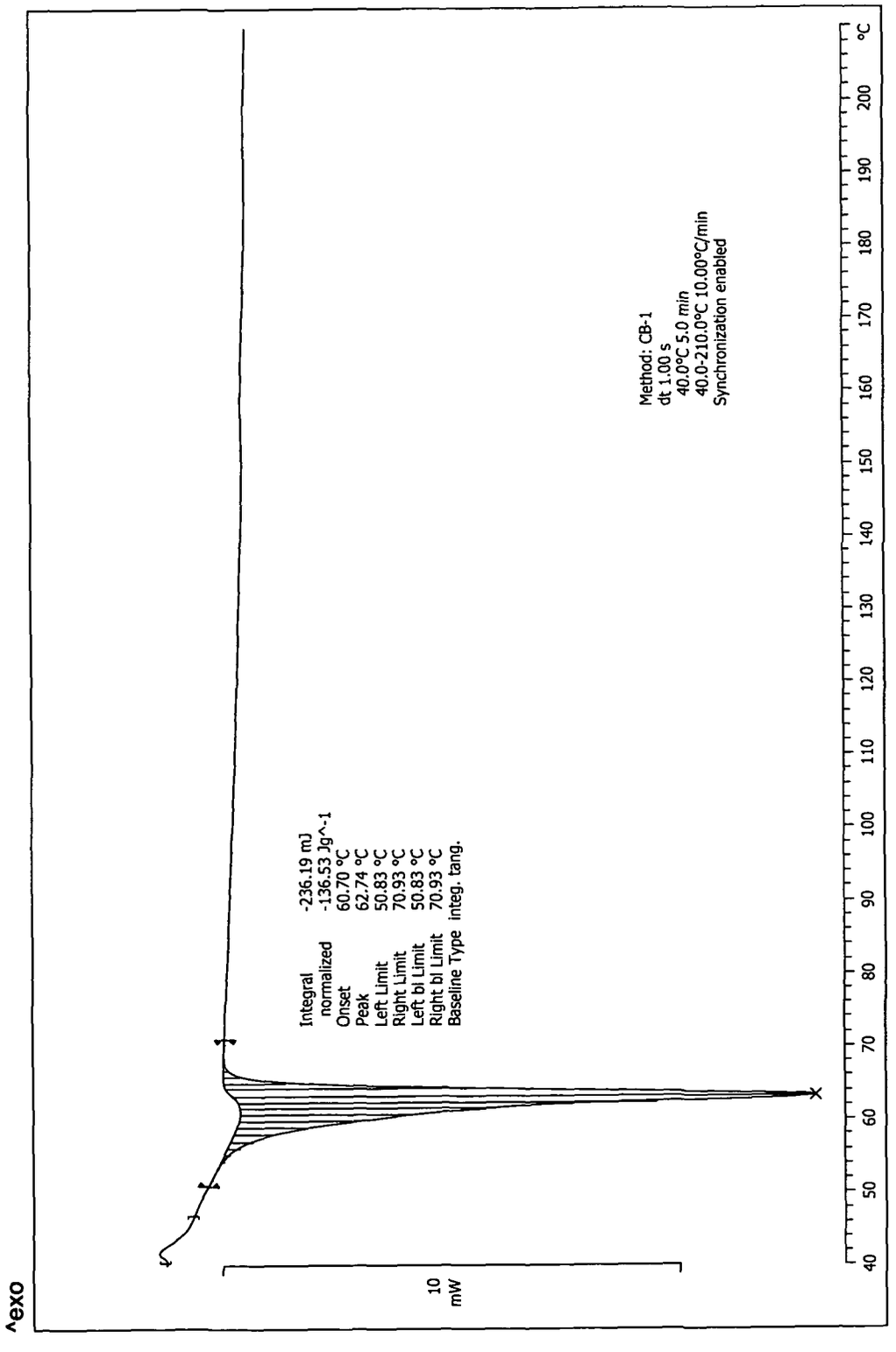

^exo
10
mW
Method: CB-1 (
dt 1.00 s
40.0°C 5.0 min
40.0-210.0°C 10.00°C/min
Synchronization enabled
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
°C

Figure 7)

Figure 8)


^exo
10
mW
Integral -236.19 mJ
normalized -136.53 Jg^-1
Onset 60.70 °C
Peak 62.74 °C
Left Limit 50.83 °C
Right Limit 70.93 °C
Left bl Limit 50.83 °C
Right bl Limit 70.93 °C
Baseline Type integ. tang.
Method: CB-1
dt 1.00 s
40.0°C 5.0 min
40.0-210.0°C 10.00°C/min
Synchronization enabled
40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 °C

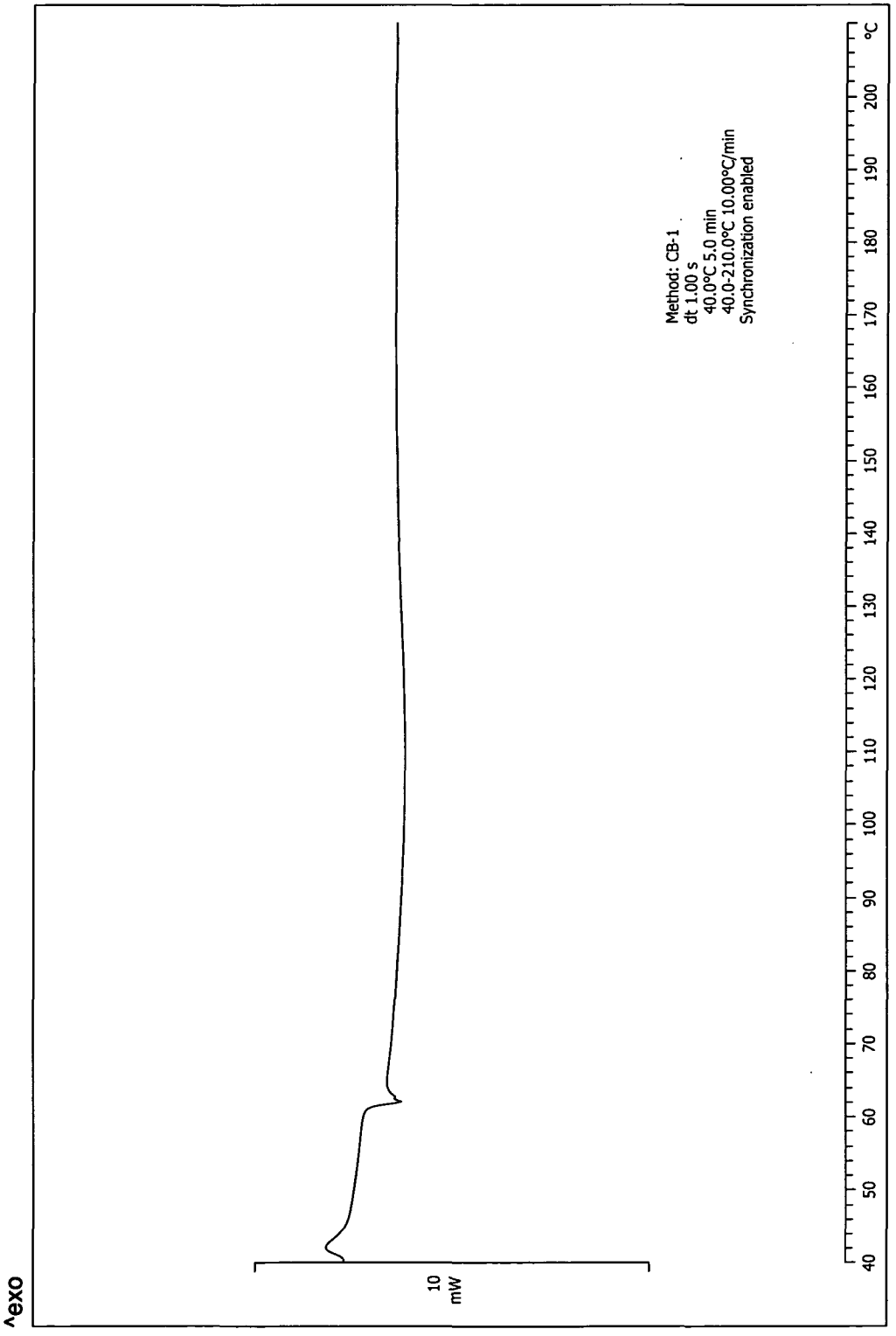

^exo
10
mW
Method: CB-1
dt 1.00 s
40.0°C 5.0 min
40.0-210.0°C 10.00°C/min
Synchronization enabled
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
°C

Figure 9)

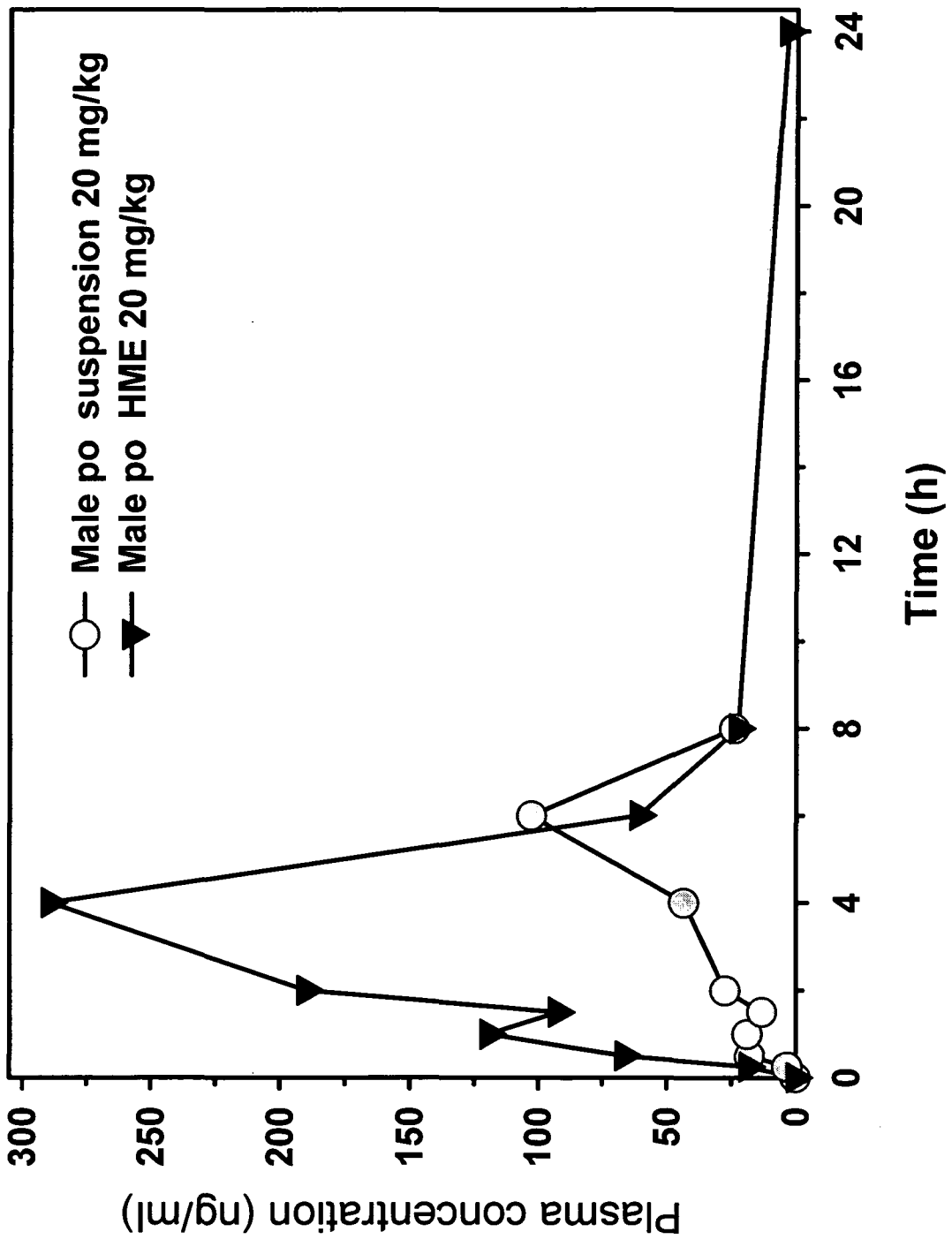

Oral administration to male rats
Male po suspension 20 mg/kg
Male po HME 20 mg/kg
Plasma concentration (ng/ml)
300
250
200
150
100
50
0
0
4
8
12
16
20
24
Time (h)

Figure 10)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/005425

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 743 890 A (ESTEVE LABOR DR [ES]) 17 January 2007 (2007-01-17) page 52, paragraph 151 -----	1-16
A	EP 1 946 777 A (ESTEVE LABOR DR [ES]) 23 July 2008 (2008-07-23) page 90 - page 91 -----	1-16

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

☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier document 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
7 September 2009	11/09/2009

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	Boulois, Denis

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/005425

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1743890 A	17-01-2007	AU 2006271994 A1	25-01-2007
		CA 2611364 A1	25-01-2007
		CA 2611366 A1	25-01-2007
		CA 2612468 A1	25-01-2007
		CN 101248063 A	20-08-2008
		CN 101238117 A	06-08-2008
		CN 101263120 A	10-09-2008
		EP 1910344 A2	16-04-2008
		EP 1937668 A1	02-07-2008
		EP 1910339 A2	16-04-2008
		EP 1910301 A2	16-04-2008
		EP 1917247 A1	07-05-2008
		WO 2007009689 A1	25-01-2007
		WO 2007009721 A2	25-01-2007
		WO 2007009722 A1	25-01-2007
		WO 2007009723 A2	25-01-2007
		WO 2007009724 A2	25-01-2007
		JP 2009501181 T	15-01-2009
		JP 2009501182 T	15-01-2009
		JP 2009501183 T	15-01-2009
		KR 20080032157 A	14-04-2008
		US 2007073056 A1	29-03-2007
		US 2008269201 A1	30-10-2008
		US 2009054509 A1	26-02-2009
		US 2009131497 A1	21-05-2009
		US 2008293797 A1	27-11-2008
EP 1946777 A	23-07-2008	NONE	