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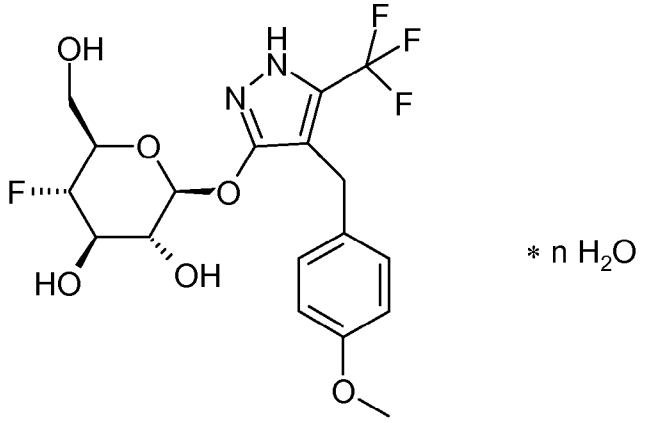
[Continued on next page]

(54) Title: A CRYSTALLINE HETEROAROMATIC FLUOROGLYCOSIDE HYDRATE, PROCESSES FOR MAKING, METHODS OF USE AND PHARMACEUTICAL COMPOSITIONS THEREOF



(I)

(57) Abstract: A novel crystalline heteroaromatic fluoroglycoside hydrate, processes for making, methods of use and pharmaceutical compositions thereof. The invention relates to a crystalline hydrate of the formula (I) in which n has a value of from 0.9 to 1.1. The compound is suitable, for example, as an antidiabetic.

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A CRYSTALLINE HETEROAROMATIC FLUOROGLYCOSIDE HYDRATE, PROCESSES FOR MAKING, METHODS OF USE AND PHARMACEUTICAL COMPOSITIONS THEREOF

Field of the Invention

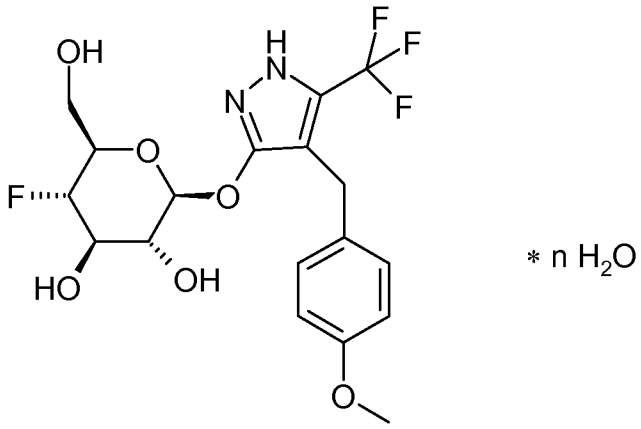
The invention relates to a crystalline hydrate of a heteroaromatic fluoroglycoside known as 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranoside.

Background of the Invention

Heteroaromatic fluoroglycosides have been described in EP1572708 B1 and Published United States Patent Application US 2004/0259819. The aforementioned patent and/or application makes no mention as to the particular physical form of 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranoside provided from the procedure disclosed therein or the hydration state or physical purity of the compound provided from the procedure. Furthermore, there is no physical chemical data reported for 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranoside in said published patent/application that suggests the physical form of the product obtained. It is an object of the invention to provide a stable hydrate of said compound.

It is an object of the invention to provide a heteroaromatic fluoroglycoside which, compared to that described in EP1572708 B1 and Published United States Patent Application US 2004/0259819, has improved properties. Another object is to increase the storage stability of the amorphous heteroaromatic fluoroglycoside from EP1572708 B1 which is a crucial parameter for formulating pharmaceuticals. Another object is to provide processes for the preparation of a stable monohydrate form of 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranoside or a tautomer thereof (henceforth referred to as “Form A”).

The object is achieved by providing a stable crystalline hydrate of the formula I



$* n H_2O$

in which n has a value of from 0.9 to 1.1 or a tautomer thereof.

Although widespread, not all pharmaceutically active compounds form hydrates or solvates. The existence of hydrates, their crystal structure and properties are unpredictable.

Preference is given to the crystalline hydrate of the compound of the formula I or a tautomer thereof in which n has a value of 1.

Detailed Description of the Drawings

Figure 1: Form A exhibits the XRPD shown. The XRPD was measured in transmission with Cu-K α1 radiation at room temperature.

Figure 2 shows the Raman spectrum of Form A.

Figure 3 shows the DSC thermogram of Form A.

Figure 4 shows the TG analysis of Form A.

Detailed Description of the Invention

By providing a crystalline hydrate of formula I (or more specifically, Form A) according to the invention, the active ingredient

- is easier to purify (for example by recrystallization)
- can have a defined purity required for the approval of a pharmaceutical
- is readily detectable and identifiable by customary methods such as XRPD (X-ray powder diffraction), melting point, IR (infrared spectrum), and it has
- has a reproducible and stable physical quality.

Crystalline active ingredients are generally more stable than amorphous active ingredients. Problems with the degradation of the active ingredients and the degradation products formed are thus avoided. The amorphous form of an active ingredient may also comprise an unwanted content of solvents. These are generally difficult to remove, since recrystallization is not possible.

The amorphous form is a more energetic state than a crystalline form and, as such, is more difficult to stabilize. Molecules of an amorphous material may spontaneously rearrange to a lower energy crystalline one leading to a change in activity of the active ingredient. As a consequence there may be significant effect on the reliability of the active ingredient and thus a risk for the patient. It is also difficult to prove that different batches of amorphous active ingredient are identical.

A further embodiment of the invention comprises Form A wherein the XRPD, measured with CuKα radiation, has a main peak of 20.27 degrees 2 theta ± 0.2 degrees 2 theta.

A further embodiment of the invention comprises Form A wherein the XRPD, measured with CuKα radiation, has at least peaks of the following 2 theta values: 14.88, 20.27, 22.98 ± 0.2 degrees 2 theta.

A further embodiment of the invention comprises Form A wherein the XRPD, measured with CuKα radiation, has at least peaks of the following 2 theta values:

5.98, 14.88, 20.27, 22.98, 26.52 ± 0.2 degrees 2 theta.

A further embodiment of the invention comprises Form A wherein the XRPD, measured with CuKα radiation, has at least peaks of the following 2 theta values: 5.98, 7.48, 12.09, 14.88, 14.99, 20.27, 20.75, 22.81, 22.98, 26.52, 27.60, 31.01 ± 0.2 degrees 2 theta.

Formulations

The amount of a compound of formula I necessary to achieve the desired biological effect depends on a number of factors, for example the specific compound chosen, the intended use, the mode of administration and the clinical condition of the patient. The daily dose is generally in the range from 0.01 mg to 100 mg (typically from 0.05 mg and 50 mg) per day and per kilogram of body weight, for example 0.05-10 mg/kg/day.

Single-dose formulations which can be administered orally, such as, for example, tablets or capsules may contain, for example, from 1.0 to 1000 mg, typically from 5 from 600 mg. For the therapy of the abovementioned conditions, the compounds of formula I may be used as the compound itself, but they are preferably in the form of a pharmaceutical composition with an acceptable carrier. The carrier must, of course, be acceptable in the sense that it is compatible with the other ingredients of the composition and is not harmful for the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as a single dose, for example as a tablet, which may contain from 0.05% to 95% by weight of the active ingredient. Other pharmaceutically active substances may likewise be present, including further compounds of the formula I. The pharmaceutical compositions of the invention can be produced by one of the known pharmaceutical methods, which essentially consist of mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Pharmaceutical compositions of the invention are those suitable for oral and peroral (for example sublingual) administration, although the most suitable mode of administration depends in each individual case on the nature and severity of the

condition to be treated and on the nature of the compound of formula I used in each case. Coated formulations and coated slow-release formulations also belong within the framework of the invention. Acid- and gastric juice-resistant formulations are possible. Suitable coatings resistant to gastric juice comprise cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical compounds for oral administration may be in the form of separate units such as, for example, capsules, cachets, suckable tablets or tablets, each of which contains a defined amount of the compound of formula I; as powders or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions may, as already mentioned, be prepared by any suitable pharmaceutical method which includes a step in which the active ingredient and the carrier (which may consist of one or more additional ingredients) are brought into contact. The compositions are generally produced by uniform and homogeneous mixing of the active ingredient with a liquid and/or finely divided solid carrier, after which the product is shaped if necessary. Thus, for example, a tablet can be produced by compressing or molding a powder or granules of the compound, where appropriate with one or more additional ingredients. Compressed tablets can be produced by tableting the compound in free-flowing form such as, for example, a powder or granules, where appropriate mixed with a binder, glidant, inert diluent and/or one (or more) surface-active/dispersing agent(s) in a suitable machine. Molded tablets can be produced by molding the compound, which is in powder form and is moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration comprise suckable tablets which contain a compound of formula I with a flavoring, normally sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Combination with other active ingredients

The compound(s) of the invention (I) can also be administered in combination with further active ingredients.

Further active ingredients suitable for combination products are:
All antidiabetics which are mentioned in the Rote Liste 2007, chapter 12; all weight-reducing agents/appetite suppressants which are mentioned in the Rote Liste 2005, chapter 1; all lipid-lowering agents which are mentioned in the Rote Liste 2007, chapter 58. They may be combined with the compound of the invention of the formula I in particular for a synergistic improvement in the effect. The active ingredient combination can be administered either by separate administration of the active ingredients to the patient or in the form of combination products in which a plurality of active ingredients is present in a pharmaceutical preparation. Most of the active ingredients mentioned hereinafter are disclosed in the USP Dictionary of USAN and International Drug Names, US Pharmacopeia, Rockville 2001.

Antidiabetics include insulin and insulin derivatives such as, for example, Lantus® (see www.lantus.com) or HMR 1964 or Levemir® (insulin detemir) or those described in WO2005005477 (Novo Nordisk), fast-acting insulins (see US 6,221,633), inhalable insulins such as, for example, Exubera ® or oral insulins such as, for example, IN-105 (Nobex) or Oral-lyn™ (Generex Biotechnology), GLP-1 derivatives and GLP-1 agonists such as, for example, exenatide, liraglutide or those which have been disclosed in WO98/08871 or WO2005027978, WO2006037811, WO2006037810 of Novo Nordisk A/S, in WO01/04156 of Zealand or in WO00/34331 of Beaufour-Ipsen, pramlintide acetate (Symlin; Amylin Pharmaceuticals), BIM-51077, PC-DAC:exendin-4 (an exendin-4 analog covalently bonded to recombinant human albumin), agonists like those described for example in D. Chen et al., Proc. Natl. Acad. Sci. USA 104 (2007) 943, those described in WO2006124529, and orally effective hypoglycemic active ingredients.

Antidiabetics also include agonists of the glucose-dependent insulinotropic polypeptide (GIP) receptor as described for example in WO2006121860.

The orally effective hypoglycemic active ingredients include preferably
sulfonylureas,
biguanidines,
meglitinides,
oxadiazolidinediones,
thiazolidinediones,
glucosidase inhibitors,
inhibitors of glycogen phosphorylase,
glucagon antagonists,
glucokinase activators,
inhibitors of fructose-1,6-bisphosphatase,
modulators of glucose transporter 4 (GLUT4),
inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT),
GLP-1 agonists,
potassium channel openers such as, for example, pinacidil, cromakalim, diazoxide or those described in R.D. Carr et al., Diabetes 52, 2003, 2513-2518, in J. B. Hansen et al., Current Medicinal Chemistry 11, 2004, 1595-1615, in T.M. Tagmose et al., J. Med. Chem. 47, 2004, 3202-3211 or in M. J. Coghlan et al., J. Med. Chem. 44, 2001, 1627-1653, or those which have been disclosed in WO 97/26265 and WO 99/03861 of Novo Nordisk A/S,
inhibitors of dipeptidylpeptidase IV (DPP-IV),
insulin sensitizers,
inhibitors of liver enzymes involved in stimulating gluconeogenesis and/or glycogenolysis,
modulators of glucose uptake, of glucose transport and of glucose reabsorption,
inhibitors of 11ß-HSD1,
inhibitors of protein tyrosine phosphatase 1B (PTP1B),
modulators of the sodium-dependent glucose transporter 1 or 2 (SGLT1, SGLT2),
compounds which alter lipid metabolism such as antihyperlipidemic active ingredients and antilipidemic active ingredients,
compounds which reduce food intake,
compounds which increase thermogenesis,

PPAR and RXR modulators and
active ingredients which act on the ATP-dependent potassium channel of the beta cells.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with an HMGCoA reductase inhibitor such as simvastatin, fluvastatin, pravastatin, lovastatin, atorvastatin, cerivastatin, rosuvastatin, L-659699.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a cholesterol absorption inhibitor such as, for example, ezetimibe, tiqueside, pamaqueside, FM-VP4 (sitostanol/campesterol ascorbyl phosphate; Forbes Medi-Tech, WO2005042692, WO2005005453), MD-0727 (Microbia Inc., WO2005021497, WO2005021495) or with compounds as described in WO2002066464, WO2005000353 (Kotobuki Pharmaceutical Co. Ltd.), or WO2005044256 or WO2005062824 (Merck & Co.) or WO2005061451 and WO2005061452 (AstraZeneca AB), and WO2006017257 (Phenomix) or WO2005033100 (Lipideon Biotechnology AG) or as described in WO2004097655, WO2004000805, WO2004000804, WO2004000803, WO2002050068, WO2002050060, WO2005047248, WO2006086562, WO2006102674, WO2006116499, WO2006121861, WO2006122186, WO2006122216, WO2006127893, WO2006137794, WO2006137796, WO2006137782, WO2006137793, WO2006137797, WO2006137795, WO2006137792, WO2006138163.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with Vytorin™, a fixed combination of ezetimibe with simvastatin.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a fixed combination of ezetimibe with atorvastatin.

In one embodiment of the invention, the compound of the formula I or Form A is

administered in combination with a fixed combination of ezetimibe with fenofibrate.

In a further embodiment of the invention, the compound of the formula I or Form A is administered in combination with a fixed combination of fenofibrate with rosuvastatin.

In a further embodiment of the invention, the compound of the formula I or Form A is administered in combination with synordia (R), a fixed combination of fenofibrate with metformin.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with ISIS-301012, an antisense oligonucleotide able to regulate the apolipoprotein B gene.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a PPAR gamma agonist such as, for example, rosiglitazone, pioglitazone, JTT-501, G1 262570, R-483 or CS-011 (rivoglitazone).

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with Competact™, a fixed combination of pioglitazone hydrochloride with metformin hydrochloride.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with Tandemact™, a fixed combination of pioglitazone with glimepride.

In a further embodiment of the invention, the compound of the formula I or Form A is administered in combination with a fixed combination of pioglitazone hydrochloride with an angiotensin II agonist such as, for example, TAK-536.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a PPAR alpha agonist such as, for example, GW9578, GW-590735, K-111, LY-674, KRP-101, DRF-10945, LY-518674 or those described in WO2001040207, WO2002096894, WO2005097076.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a mixed PPAR alpha/gamma agonist such as, for example, naveglitazar, LY-510929, ONO-5129, E-3030, AVE 8042, AVE 8134, AVE 0847, CKD-501 (lobeglitazone sulfate) or as described in WO 00/64888, WO 00/64876, WO 03/020269 or in J.P. Berger et al., TRENDS in Pharmacological Sciences 28(5), 244-251, 2005.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a PPAR delta agonist such as, for example, GW-501516 or as described in WO2006059744, WO2006084176, WO2006029699, WO2007039172, WO2007039178.

In one embodiment, the compound of the formula I or Form A is administered in combination with metaglidasen or with MBX-2044 or other partial PPAR gamma agonists/antagonists.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a fibrate such as, for example, fenofibrate, clofibrate or bezafibrate.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with an MTP inhibitor such as, for example, implitapide, BMS-201038, R-103757, AS-1552133 or those described in WO2005085226, WO2005121091, WO2006010423.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a CETP inhibitor such as, for example, torcetrapib or JTT-705 or those described in WO2006002342, WO2006010422, WO2006012093, WO2006073973, WO2006072362, WO2006097169, WO2007041494.

In one embodiment of the invention, the compound of the formula I or Form A is

administered in combination with a bile acid absorption inhibitor (see, for example, US 6,245,744, US 6,221,897 or WO00/61568), such as, for example, HMR 1741 or those as described in DE 10 2005 033099.1 and DE 10 2005 033100.9, WO2007009655-56.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a polymeric bile acid adsorbent such as, for example, cholestyramine or colesevelam.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with an LDL receptor inducer (see US 6,342,512), such as, for example, HMR1171, HMR1586 or those as described in WO2005097738.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with an ABCA1 expression enhancer as described for example in WO2006072393.

In a further embodiment of the invention, the compound of the formula I or Form A is administered in combination with an RNAi therapeutic directed against PCSK9 (proprotein convertase subtilisin/kexin type 9).

In one embodiment, the compound of the formula I or Form A is administered in combination with Omacor® (omega-3 fatty acids; highly concentrated ethyl esters of eicosapentaenoic acid and of docosahexaenoic acid).

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with an ACAT inhibitor such as, for example, avasimibe or SMP-797.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with an antioxidant such as, for example, OPC-14117, probucol, tocopherol, ascorbic acid, β-carotene or selenium.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a vitamin such as, for example, vitamin B6 or vitamin B12.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a lipoprotein lipase modulator such as, for example, ibrolipim (NO-1886).

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with an ATP citrate lyase inhibitor such as, for example, SB-204990.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a squalene synthetase inhibitor such as, for example, BMS-188494, TAK-475 or as described in WO2005077907, JP2007022943.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a lipoprotein(a) antagonist such as, for example, gemcabene (CI-1027).

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with an agonist of GPR109A (HM74A receptor agonist; NAR agonist (nicotinic acid receptor agonist) such as, for example, nicotinic acid or extended release niacin in conjunction with MK-0524A or the compounds described in WO2006045565, WO2006045564, WO2006069242, WO2006124490, WO2006113150, WO2007017261, WO2007017262, WO2007017265, WO2007015744, WO2007027532.

In another embodiment of the invention, the compound of the formula I or Form A is administered in combination with an agonist of GPR116 as described for example in WO2006067531, WO2006067532.

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with a lipase inhibitor such as, for example, orlistat or cetilistat (ATL-962).

In one embodiment of the invention, the compound of the formula I or Form A is administered in combination with insulin.

In one embodiment, the compound of the formula I or Form A is administered in combination with a sulfonylurea such as, for example, tolbutamide, glibenclamide, glipizide or glimepiride.

In one embodiment, the compound of the formula I or Form A is administered in combination with a substance which enhances insulin secretion, such as, for example, KCP-265 (WO2003097064) or those described in WO2007026761.

In one embodiment, the compound of the formula I or Form A is administered in combination with agonists of the glucose-dependent insulinotropic receptor (GDIR), such as, for example, APD-668.

In one embodiment, the compound of the formula I or Form A is administered in combination with a biguanide such as, for example, metformin.

In another embodiment, the compound of the formula I or Form A is administered in combination with a meglitinide such as, for example, repaglinide, nateglinide or mitiglinide.

In a further embodiment, the compound of the formula I or Form A is administered with a combination of mitiglinide with a glitazone, e.g. pioglitazone hydrochloride.

In a further embodiment, the compound of the formula I or Form A is administered with a combination of mitiglinide with an alpha-glucosidase inhibitor.

In one embodiment, the compound of the formula I or Form A is administered in

combination with a thiazolidinedione such as, for example, troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 of Dr. Reddy's Research Foundation, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy]phenyl]methyl]-2,4-thiazolidinedione.

In one embodiment, the compound of the formula I or Form A is administered in combination with an α-glucosidase inhibitor such as, for example, miglitol or acarbose.

In one embodiment, the compound of the formula I or Form A is administered in combination with an active ingredient which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide, glibenclamide, glipizide, glimepiride or repaglinide.

In one embodiment, the compound of the formula I or Form A is administered in combination with more than one of the aforementioned compounds, e.g. in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

In one embodiment, the compound of the formula I or Form A is administered in combination with an inhibitor of glycogen phosphorylase, such as, for example, PSN-357 or FR-258900 or those as described in WO2003084922, WO2004007455, WO2005073229-31 or WO2005067932.

In one embodiment, the compound of the formula I or Form A is administered in combination with glucagon receptor antagonists such as, for example, A-770077, NNC-25-2504 or as described in WO2004100875 or WO2005065680.

In one embodiment, the compound of the formula I or Form A is administered in combination with activators of glucokinase, such as, for example, LY-2121260 (WO2004063179), PSN-105, PSN-110, GKA-50 or those as are described for example in WO2004072031, WO2004072066, WO2005080360, WO2005044801, WO2006016194, WO2006058923, WO2006112549, WO2006125972,

WO2007017549, WO2007017649, WO2007007910, WO2007007040-42, WO2007006760-61, WO2007006814, WO2007007886, WO2007028135, WO2007031739, WO2007041365, WO2007041366, WO2007037534, WO2007043638, WO2007053345, WO2007051846, WO2007051845, WO2007053765, WO2007051847.

In one embodiment, the compound of the formula I or Form A is administered in combination with an inhibitor of gluconeogenesis, such as, for example, FR-225654.

In one embodiment, the compound of the formula I or Form A is administered in combination with inhibitors of fructose-1,6-bisphosphatase (FBPase), such as, for example, CS-917 (MB-06322) or MB-07803 or those described in WO2006023515, WO2006104030, WO2007014619.

In one embodiment, the compound of the formula I or Form A is administered in combination with modulators of glucose transporter 4 (GLUT4), such as, for example, KST-48 (D.-O. Lee et al.: Arzneim.-Forsch. Drug Res. 54 (12), 835 (2004)).

In one embodiment, the compound of the formula I or Form A is administered in combination with inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT), as are described for example in WO2004101528.

In one embodiment, the compound of the formula I or Form A is administered in combination with inhibitors of dipeptidylpeptidase IV (DPP-IV), such as, for example, vildagliptin (LAF-237), sitagliptin (MK-0431), sitagliptin phosphate, saxagliptin (BMS-477118), GSK-823093, PSN-9301, SYR-322, SYR-619, TA-6666, TS-021, GRC-8200, GW-825964X, KRP-104, DP-893, ABT-341, ABT-279 or another salt thereof, or the compounds described in WO2003074500, WO2003106456, WO2004037169, WO200450658, WO2005058901, WO2005012312, WO2005/012308, WO2006039325, WO2006058064, WO2006015691, WO2006015701, WO2006015699, WO2006015700, WO2006018117, WO2006099943, WO2006099941, JP2006160733, WO2006071752, WO2006065826, WO2006078676, WO2006073167, WO2006068163, WO2006090915,

WO2006104356, WO2006127530, WO2006111261, WO2007015767, WO2007024993, WO2007029086.

In one embodiment, the compound of the formula I or Form A is administered in combination with Janumet™, a fixed combination of sitagliptin phosphate with metformin hydrochloride.

In one embodiment, the compound of the formula I or Form A is administered in combination with inhibitors of 11-beta-hydroxysteroid dehydrogenase 1 (11ß-HSD1), such as, for example, BVT-2733, JNJ-25918646, INCB-13739 or those as are described for example in WO200190090-94, WO200343999, WO2004112782, WO200344000, WO200344009, WO2004112779, WO2004113310, WO2004103980, WO2004112784, WO2003065983, WO2003104207, WO2003104208, WO2004106294, WO2004011410, WO2004033427, WO2004041264, WO2004037251, WO2004056744, WO2004058730, WO2004065351, WO2004089367, WO2004089380, WO2004089470-71, WO2004089896, WO2005016877, WO2005097759, WO2006010546, WO2006012227, WO2006012173, WO2006017542, WO2006034804, WO2006040329, WO2006051662, WO2006048750, WO2006049952, WO2006048331, WO2006050908, WO2006024627, WO2006040329, WO2006066109, WO2006074244, WO2006078006, WO2006106423, WO2006132436, WO2006134481, WO2006134467, WO2006135795, WO2006136502, WO2006138695, WO2006133926, WO2007003521, WO2007007688, US2007066584, WO2007047625, WO2007051811, WO2007051810.

In one embodiment, the compound of the formula I or Form A is administered in combination with inhibitors of protein tyrosine phosphatase 1B (PTP1B), as are described for example in WO200119830-31, WO200117516, WO2004506446, WO2005012295, WO2005116003, WO2005116003, WO2006007959, DE 10 2004 060542.4, WO2007009911, WO2007028145, WO2007081755.

In one embodiment, the compound of the formula I or Form A is administered in combination with modulators of the sodium-dependent glucose transporter 1 or 2

(SGLT1, SGLT2), such as, for example, KGA-2727, T-1095, SGL-0010, AVE 2268, SAR 7226 and sergliflozin or as are described for example in WO2004007517, WO200452903, WO200452902, PCT/EP2005/005959, WO2005085237, JP2004359630, WO2005121161, WO2006018150, WO2006035796, WO2006062224, WO2006058597, WO2006073197, WO2006080577, WO2006087997, WO2006108842, WO2007000445, WO2007014895, WO2007080170 or by A. L. Handlon in Expert Opin. Ther. Patents (2005) 15(11), 1531-1540.

In one embodiment, the compound of the formula I or Form A is administered in combination with modulators of GPR40 as described for example in WO2007013689, WO2007033002.

In one embodiment, the compound of the formula I or Form A is administered in combination with modulators of GPR119b as described for example in WO2004041274.

In one embodiment, the compound of the formula I or Form A is administered in combination with modulators of GPR119 as described for example in WO2005061489 (PSN-632408), WO2004065380, WO2007003960-62 and WO2007003964.

In a further embodiment, the compound of the formula I or Form A is administered in combination with modulators of GPR120.

In one embodiment, the compound of the formula I or Form A is administered in combination with inhibitors of hormone-sensitive lipase (HSL) and/or phospholipases as described for example in WO2005073199, WO2006074957, WO2006087309, WO2006111321, WO2007042178.

In one embodiment, the compound of the formula I or Form A is administered in combination with inhibitors of acetyl-CoA carboxylase (ACC), such as, for example, those as described in WO199946262, WO200372197, WO2003072197,

WO2005044814, WO2005108370, JP2006131559, WO2007011809, WO2007011811, WO2007013691.

In a further embodiment, the compound of the formula I or Form A is administered in combination with modulators of xanthine oxidoreductase (XOR).

In one embodiment, the compound of the formula I or Form A is administered in combination with an inhibitor of phosphoenolpyruvate carboxykinase (PEPCK), such as, for example, those as described in WO2004074288.

In one embodiment, the compound of the formula I or Form A is administered in combination with an inhibitor of glycogen synthase kinase 3 beta (GSK-3 beta), as described for example in US2005222220, WO2005085230, WO2005111018, WO2003078403, WO2004022544, WO2003106410, WO2005058908, US2005038023, WO2005009997, US2005026984, WO2005000836, WO2004106343, EP1460075, WO2004014910, WO2003076442, WO2005087727 or WO2004046117.

In one embodiment, the compound of the formula I or Form A is administered in combination with an inhibitor of the serum/glucocorticoid-regulated kinase (SGK) as described for example in WO2006072354.

In one embodiment, the compound of the formula I or Form A is administered in combination with an agonist of the RUP3 receptor as described for example in WO2007035355.

In one embodiment, the compound of the formula I or Form A is administered in combination with an inhibitor of protein kinase C beta (PKC beta), such as, for example, ruboxistaurin.

In another embodiment, the compound of the formula I or Form A is administered in combination with an activator of the gene which codes for the ataxia telangiectasia mutated (ATM) protein kinase, such as, for example, chloroquine.

In one embodiment, the compound of the formula I or Form A is administered in combination with an endothelin A receptor antagonist such as, for example, avosentan (SPP-301).

In one embodiment, the compound of the formula I or Form A is administered in combination with inhibitors of "I-kappaB kinase" (IKK inhibitors), as are described for example in WO2001000610, WO2001030774, WO2004022553 or WO2005097129.

In one embodiment, the compound of the formula I or Form A is administered in combination with modulators of the glucocorticoid receptor (GR), like those described for example in WO2005090336, WO2006071609, WO2006135826.

In a further embodiment, the compound of the formula I or Form A is administered in combination with CART modulators (see "Cocaine-amphetamine-regulated transcript influences energy metabolism, anxiety and gastric emptying in mice" Asakawa, A. et al.: Hormone and Metabolic Research (2001), 33(9), 554-558);
NPY antagonists such as, for example, naphthalene-1-sulfonic acid {4-[(4-aminoquinazolin-2-ylamino)methyl]cyclohexylmethyl}amide hydrochloride (CGP 71683A);
NPY-5 receptor antagonists such as L-152804 or such as described, for example, in WO2006001318;
NPY-4 receptor antagonists such as described, for example, in WO2007038942;
NPY-2 receptor antagonists such as described, for example, in WO2007038943;
peptide YY 3-36 (PYY3-36) or analogous compounds, such as, for example, CJC-1682 (PYY3-36 conjugated with human serum albumin via Cys34), CJC-1643 (derivative of PYY3-36 which conjugates in vivo to serum albumin) or those as are described in WO2005080424, WO2006095166;
derivatives of the peptide obestatin such as those described in WO2006096847;
CB1R (cannabinoid receptor 1) antagonists (such as, for example, rimonabant, SR147778, SLV-319, AVE-1625, MK-0364 or salts thereof or compounds such as those described for example in EP 0656354, WO 00/15609, WO2001/64632-64634, WO 02/076949, WO2005080345, WO2005080328, WO2005080343,

WO2005075450, WO2005080357, WO200170700, WO2003026647-48, WO200302776, WO2003040107, WO2003007887, WO2003027069, US6,509,367, WO200132663, WO2003086288, WO2003087037, WO2004048317, WO2004058145, WO2003084930, WO2003084943, WO2004058744, WO2004013120, WO2004029204, WO2004035566, WO2004058249, WO2004058255, WO2004058727, WO2004069838, US20040214837, US20040214855, US20040214856, WO2004096209, WO2004096763, WO2004096794, WO2005000809, WO2004099157, US20040266845, WO2004110453, WO2004108728, WO2004000817, WO2005000820, US20050009870, WO200500974, WO2004111033-34, WO200411038-39, WO2005016286, WO2005007111, WO2005007628, US20050054679, WO2005027837, WO2005028456, WO2005063761-62, WO2005061509, WO2005077897, WO2006047516, WO2006060461, WO2006067428, WO2006067443, WO2006087480, WO2006087476, WO2006100208, WO2006106054, WO2006111849, WO2006113704, WO2007009705, WO2007017124, WO2007017126, WO2007018459, WO2007016460, WO2007020502, WO2007026215, WO2007028849, WO2007031720, WO2007031721, WO2007036945, WO2007038045, WO2007039740, US20070015810, WO2007046548, WO2007047737, WO2007084319, WO2007084450);

cannabinoid receptor 1/cannabinoid receptor 2 (CB1/CB2) modulating compounds as described for example in WO2007001939, WO2007044215, WO2007047737;

MC4 agonists (e.g. 1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid [2-(3a-benzyl-2-methyl-3-oxo-2,3,3a,4,6,7-hexahydropyrazolo[4,3-c]pyridin-5-yl)-1-(4-chlorophenyl)-2-oxoethyl]amide; (WO 01/91752)) or LB53280, LB53279, LB53278 or THIQ, MB243, RY764, CHIR-785, PT-141 or those that are described in WO2005060985, WO2005009950, WO2004087159, WO2004078717, WO2004078716, WO2004024720, US20050124652, WO2005051391, WO2004112793, WOUS20050222014, US20050176728, US20050164914, US20050124636, US20050130988, US20040167201, WO2004005324, WO2004037797, WO2005042516, WO2005040109, WO2005030797, US20040224901, WO200501921, WO200509184, WO2005000339, EP1460069, WO2005047253, WO2005047251, WO2005118573, EP1538159, WO2004072076,

WO2004072077, WO2006021655-57, WO2007009894, WO2007015162, WO2007041061, WO2007041052;

orexin receptor antagonists (e.g. 1-(2-methylbenzoxazol-6-yl)-3-[1,5]naphthyridin-4-ylurea hydrochloride (SB-334867-A) or those as are described for example in WO200196302, WO200185693, WO2004085403, WO2005075458, WO2006067224);

histamine H3 receptor agonists (e.g. 3-cyclohexyl-1-(4,4-dimethyl-1,4,6,7-tetrahydroimidazo[4,5-c]pyridin-5-yl)propan-1-one oxalic acid salt (WO 00/63208) or those as are described in WO200064884, WO2005082893, WO2006107661, WO2007003804, WO2007016496, WO2007020213);

histamine H1/histamine H3 modulators such as, for example, betahistine or its dihydrochloride;

CRF antagonists (e.g. [2-methyl-9-(2,4,6-trimethylphenyl)-9H-1,3,9-triazafluoren-4-yl]dipropylamine (WO 00/66585));

CRF BP antagonists (e.g. urocortin);

urocortin agonists;

agonists of the beta-3 adrenoceptor such as, for example, 1-(4-chloro-3-methanesulfonylmethylphenyl)-2-[2-(2,3-dimethyl-1H-indol-6-yloxy)ethylamino]ethanol hydrochloride (WO 01/83451) or solabegron (GW-427353) or N-5984 (KRP-204), or those as are described in JP2006111553, WO2002038543, WO2007048840-843;

MSH (melanocyte-stimulating hormone) agonists;

MCH (melanin-concentrating hormone) receptor antagonists (such as, for example, NBI-845, A-761, A-665798, A-798, ATC-0175, T-226296, T-71, GW-803430 or compounds such as are described in WO2005085200, WO2005019240, WO2004011438, WO2004012648, WO2003015769, WO2004072025, WO2005070898, WO2005070925, WO2004039780, WO2004092181, WO2003033476, WO2002006245, WO2002089729, WO2002002744, WO2003004027, FR2868780, WO2006010446, WO2006038680, WO2006044293, WO2006044174, JP2006176443, WO2006018280, WO2006018279, WO2006118320, WO2006130075, WO2007018248, WO2007012661, WO2007029847, WO2007024004, WO2007039462, WO2007042660,

WO2007042668, WO2007042669, US2007093508, US2007093509, WO2007048802, JP2007091649);

CCK-A agonists (such as, for example, {2-[4-(4-chloro-2,5-dimethoxyphenyl)-5-(2-cyclohexylethyl)thiazol-2-ylcarbamoyl]-5,7-dimethylindol-1-yl}acetic acid trifluoroacetic acid salt (WO 99/15525) or SR-146131 (WO 0244150) or SSR-125180) or those as are described in WO2005116034;

serotonin reuptake inhibitors (e.g. dexfenfluramine);

mixed serotonin/dopamine reuptake inhibitors (e.g. bupropion) or fixed combinations of bupropion with naltrexone;

mixed serotoninergic and noradrenergic compounds (e.g. WO 00/71549);

5-HT receptor agonists, e.g. 1-(3-ethylbenzofuran-7-yl)piperazine oxalic acid salt (WO 01/09111);

mixed dopamine/norepinephrine/acetylcholine reuptake inhibitors (e.g. tesofensine);

5-HT2C receptor agonists (such as, for example, lorcaserin hydrochloride (APD-356) or BVT-933 or those as are described in WO200077010, WO200077001-02, WO2005019180, WO2003064423, WO200242304, WO2005035533, WO2005082859, WO2006077025, WO2006103511);

5-HT6 receptor modulators such as, for example E-6837 or BVT-74316 or those as are described in WO2005058858, WO2007054257;

bombesin receptor agonists (BRS-3 agonists);

galanin receptor antagonists;

growth hormone (e.g. human growth hormone or AOD-9604);

growth hormone-releasing compounds (tertiary butyl 6-benzyloxy-1-(2-diisopropyl-aminoethylcarbamoyl)-3,4-dihydro-1H-isoquinoline-2-carboxylate (WO 01/85695));

growth hormone secretagogue receptor antagonists (ghrelin antagonists) such as, for example, A-778193 or those as are described in WO2005030734;

TRH agonists (see, for example, EP 0 462 884);

uncoupling protein 2 or 3 modulators;

leptin agonists (see, for example, Lee, Daniel W.; Leinung, Matthew C.; Rozhavskaya-Arena, Marina; Grasso, Patricia. Leptin agonists as a potential approach to the treatment of obesity. Drugs of the Future (2001), 26(9), 873-881);

DA agonists (bromocriptine or Doprexin);

lipase/amylase inhibitors (for example WO 00/40569);
inhibitors of diacylglycerol O-acyltransferases (DGATs) such as for example BAY-74-4113 or as described for example in US2004/0224997, WO2004094618, WO200058491, WO2005044250, WO2005072740, JP2005206492, WO2005013907, WO2006004200, WO2006019020, WO2006064189, WO2006082952, WO2006120125, WO2006113919, WO2006134317, WO2007016538;
inhibitors of fatty acid synthase (FAS) such as, for example, C75 or those as described in WO2004005277;
inhibitors of stearoyl-CoA delta9 desaturase (SCD1) as described for example in WO2007009236, WO2007044085, WO2007046867, WO2007046868, WO20070501124;
oxyntomodulin;
oleoyl-estrone

or thyroid hormone receptor agonists or partial agonists such as, for example: KB-2115 or those as described in WO20058279, WO200172692, WO200194293, WO2003084915, WO2004018421, WO2005092316, WO2007003419, WO2007009913, WO2007039125.

In one embodiment, the further active ingredient is varenicline tartrate, a partial agonist of the alpha 4-beta 2 nicotinic acetylcholine receptor.

In one embodiment, the further active ingredient is trodusquemine.

In one embodiment, the further active ingredient is a modulator of the SIRT1 enzyme.

In one embodiment of the invention, the further active ingredient is leptin;
see, for example, “Perspectives in the therapeutic use of leptin”, Salvador, Javier; Gomez-Ambrosi, Javier; Fruhbeck, Gema, Expert Opinion on Pharmacotherapy (2001), 2(10), 1615-1622.

In one embodiment, the further active ingredient is dexamphetamine or amphetamine.

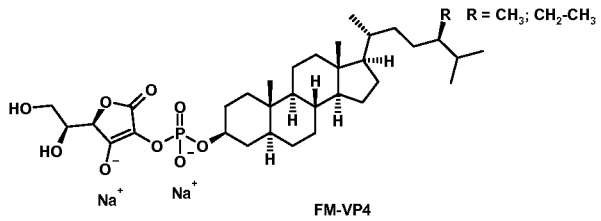
In one embodiment, the further active ingredient is fenfluramine or dexfenfluramine.

In another embodiment, the further active ingredient is sibutramine.

In one embodiment, the further active ingredient is mazindole or phentermine.

In one embodiment, the compound of the formula I or Form A is administered in combination with bulking agents, preferably insoluble bulking agents (see, for example, Carob/Caromax® (Zunft H J; et al., Carob pulp preparation for treatment of hypercholesterolemia, ADVANCES IN THERAPY (2001 Sep-Oct), 18(5), 230-6). Caromax is a carob-containing product from Nutrinova, Nutrition Specialties & Food Ingredients GmbH, Industriepark Höchst, 65926 Frankfurt/Main)). Combination with Caromax® is possible in one preparation or by separate administration of compounds of the formula I and Caromax®. Caromax® can in this connection also be administered in the form of food products such as, for example, in bakery products or muesli bars.

It will be understood that every suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more further pharmacologically active substances will be regarded as falling within the protection conferred by the present invention.



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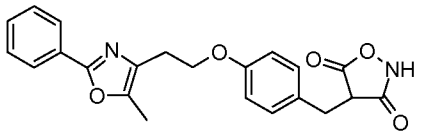

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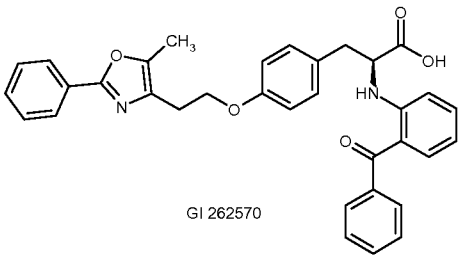

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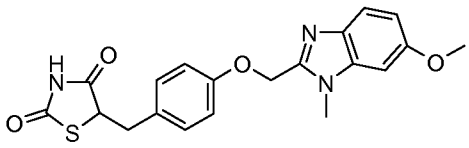

CS-011

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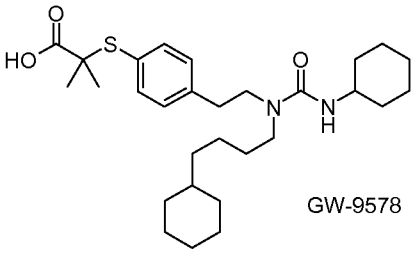

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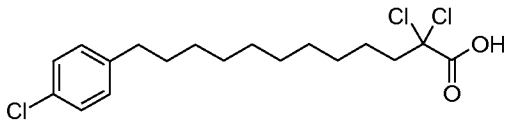

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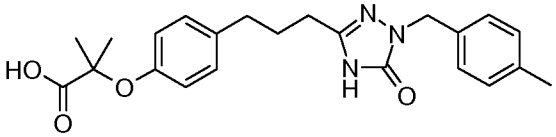

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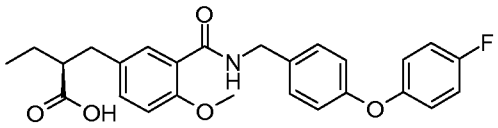

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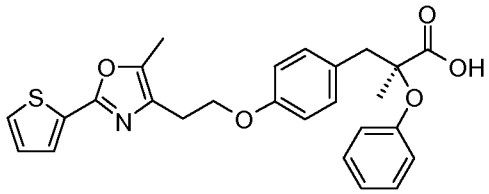

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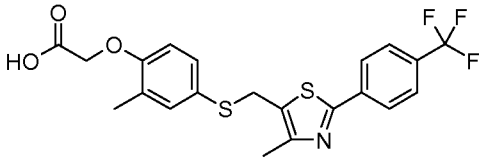

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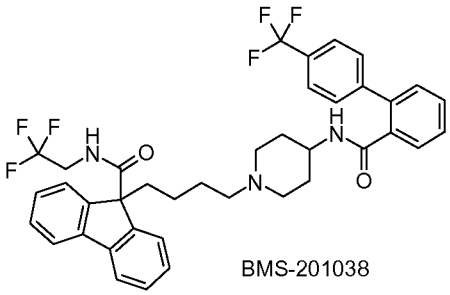

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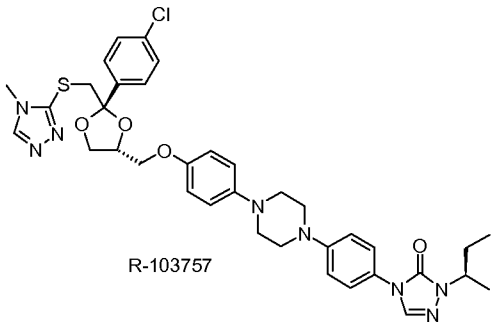

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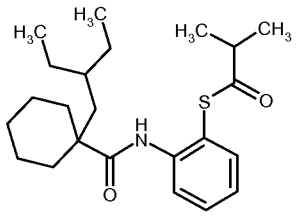
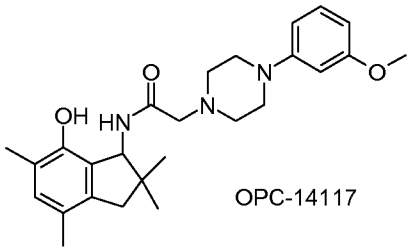


JTT-705



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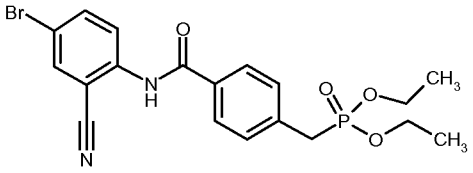
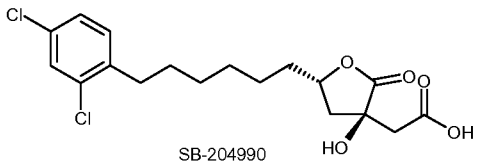


NO-1886



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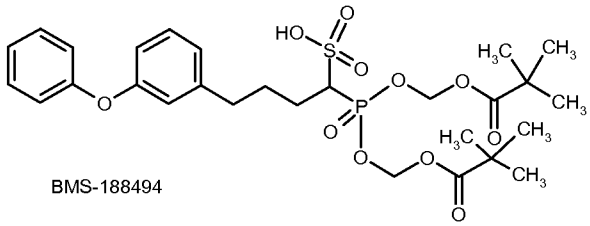

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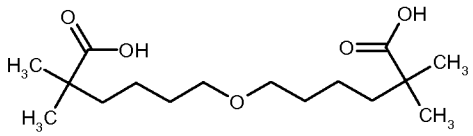

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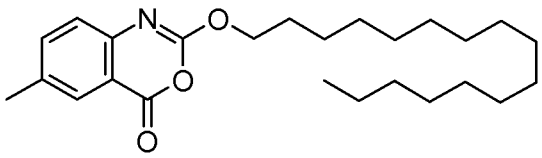

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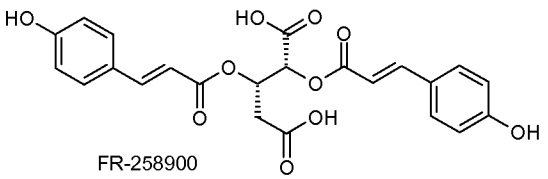

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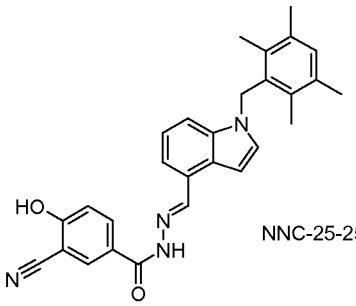

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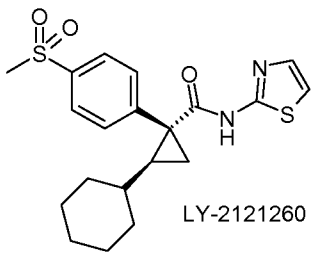

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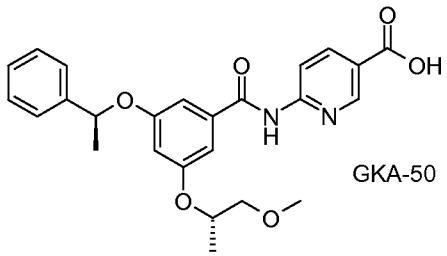
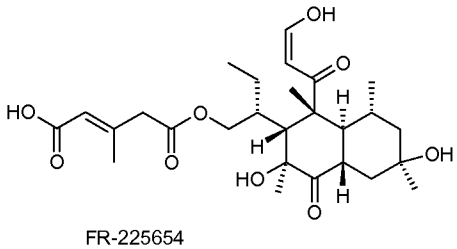


GKA-50



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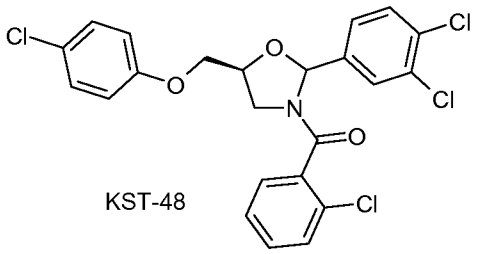

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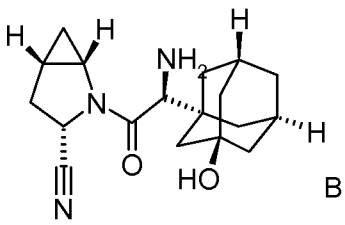

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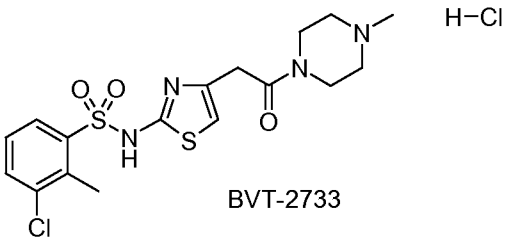

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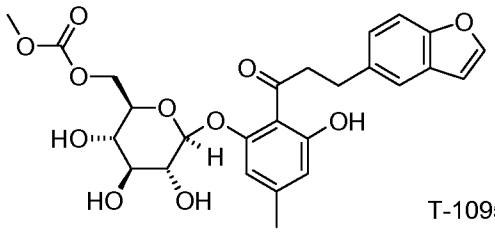

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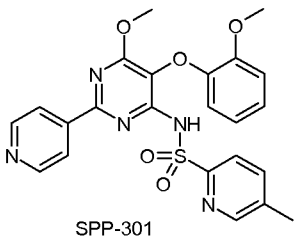

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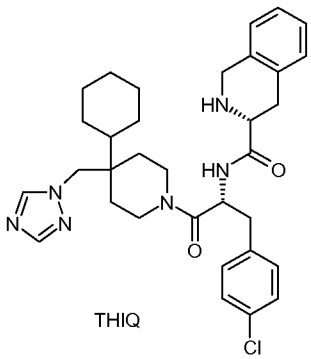

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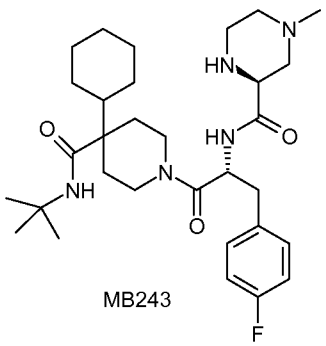

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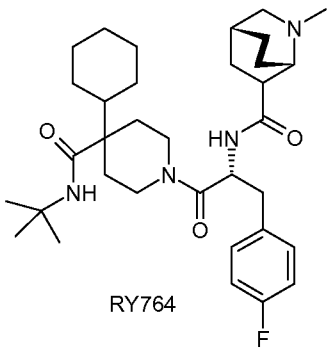

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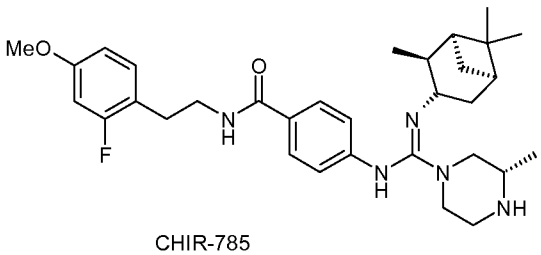

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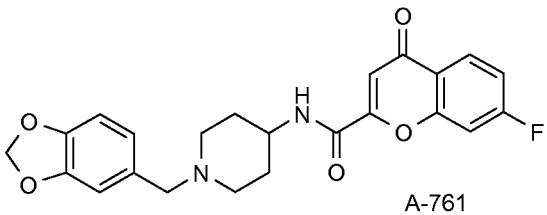

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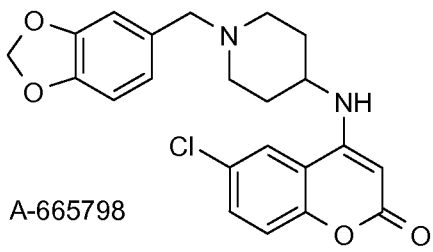

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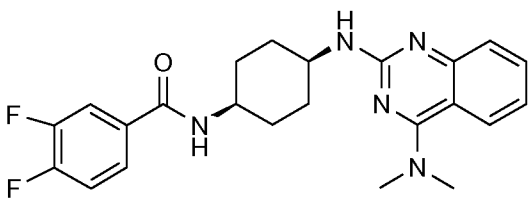

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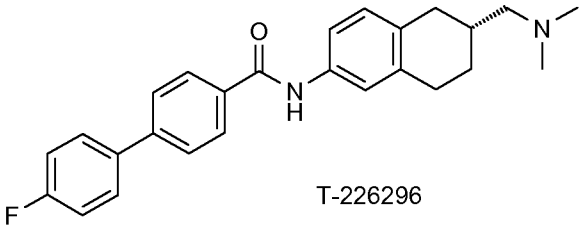

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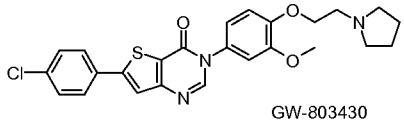

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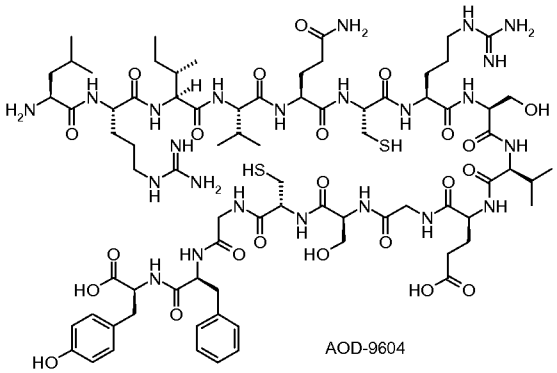

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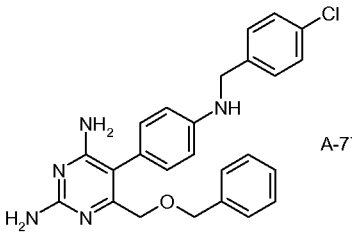

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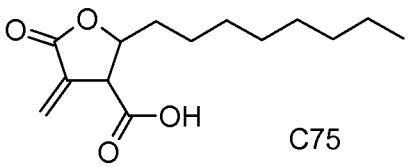

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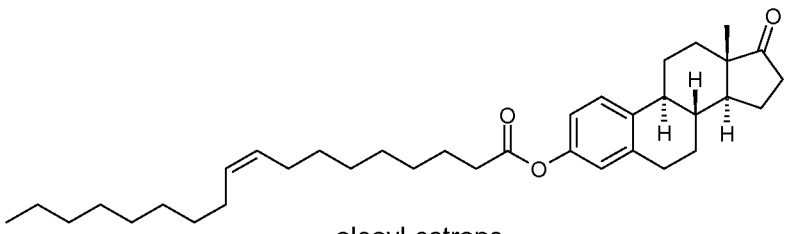

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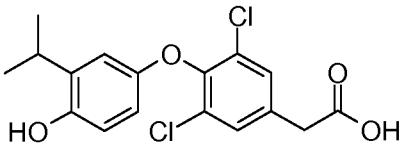

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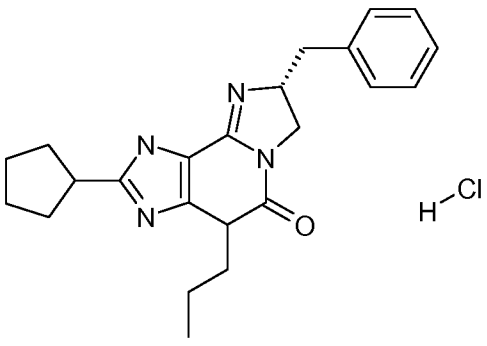

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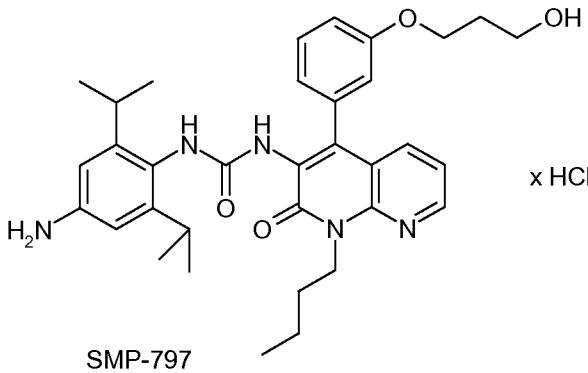
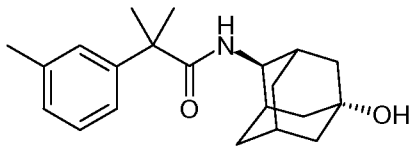


x HCl

SMP-797



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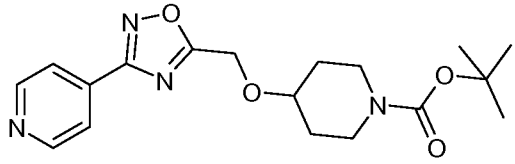

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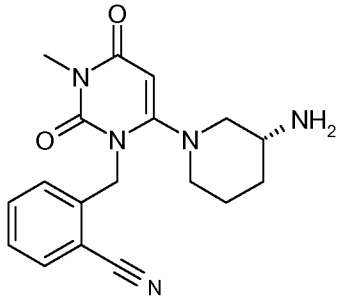

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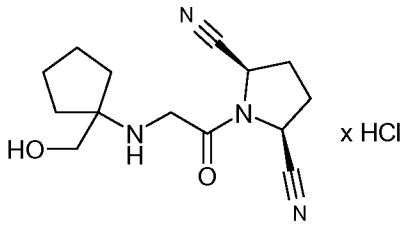
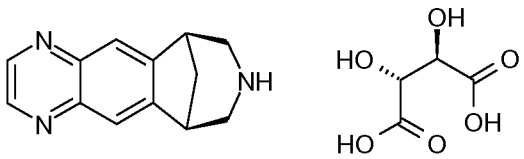
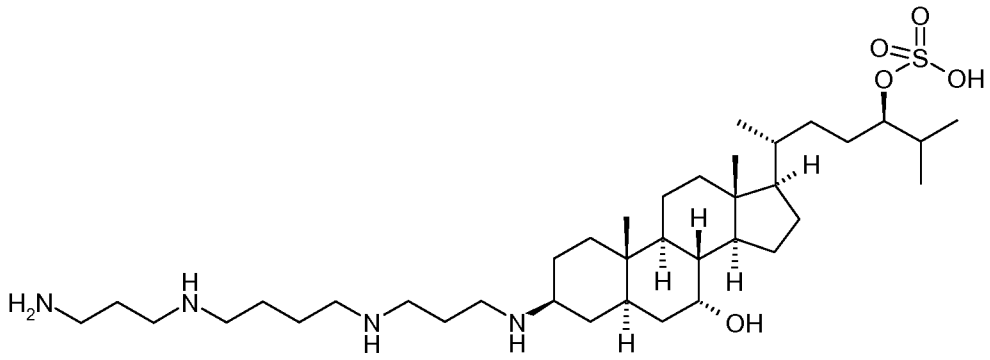


x HCl

DP-893



varenicline tartrate



trodusquemine

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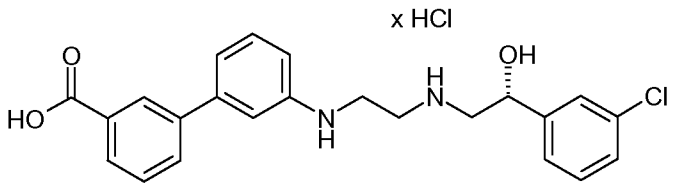
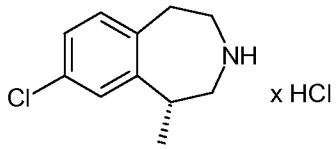


Solabegron



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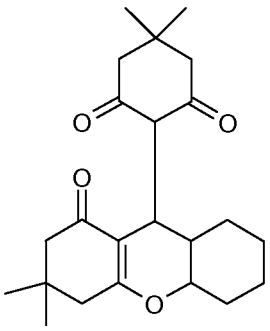

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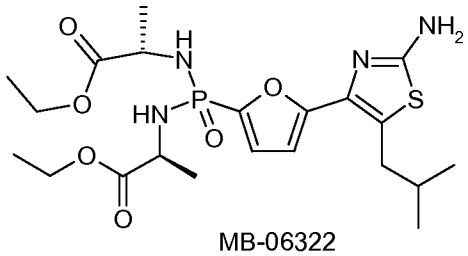

MB-06322
CS-917

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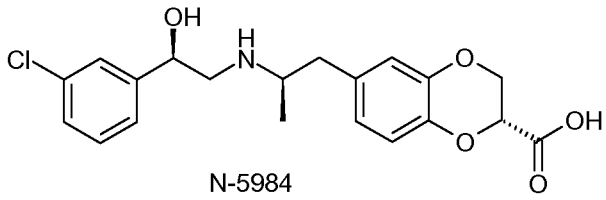

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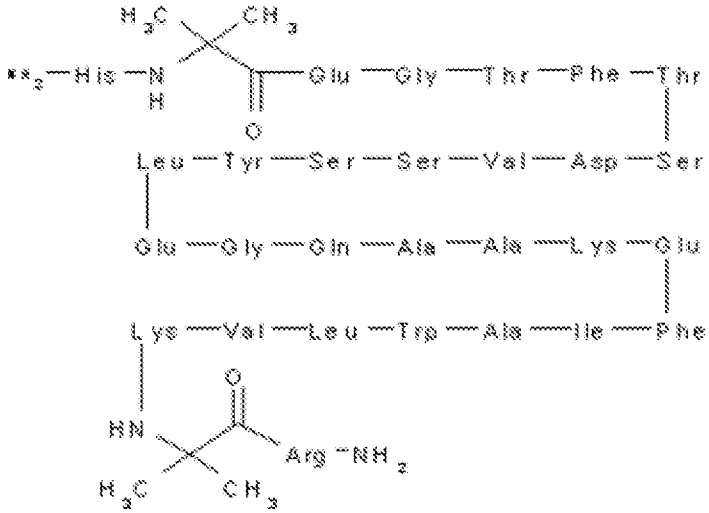

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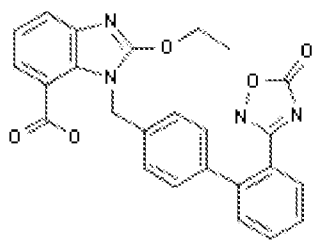

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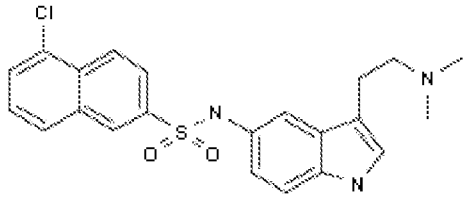
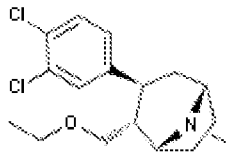
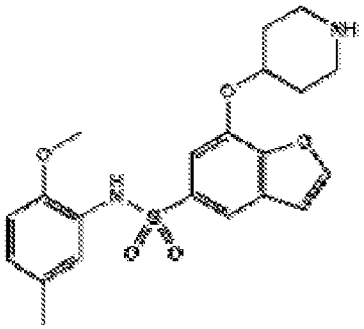


E-6837



tesofensine



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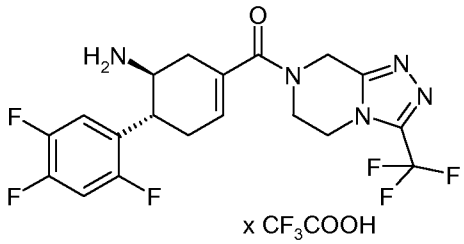

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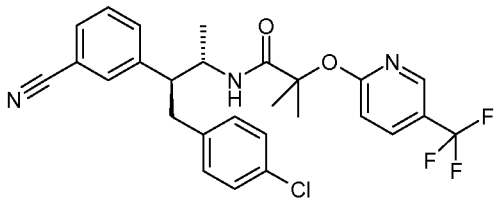

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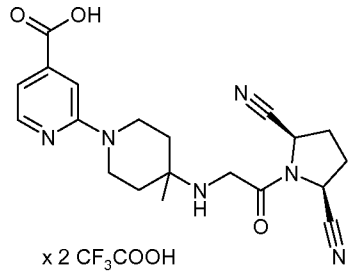

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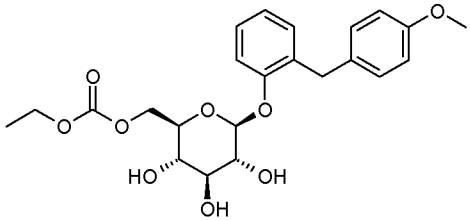
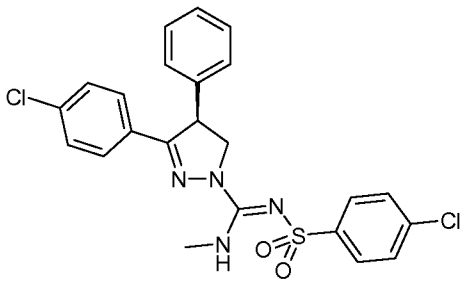
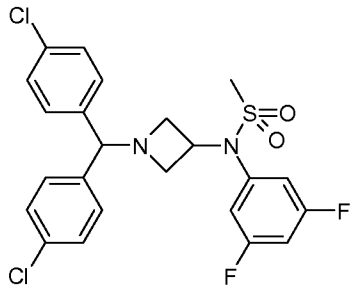


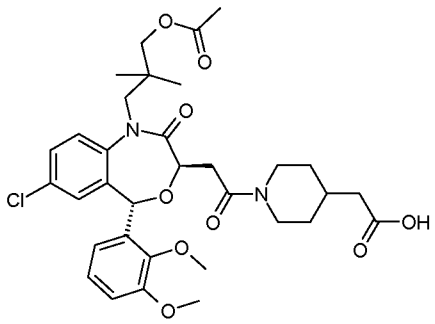
sergliflozin



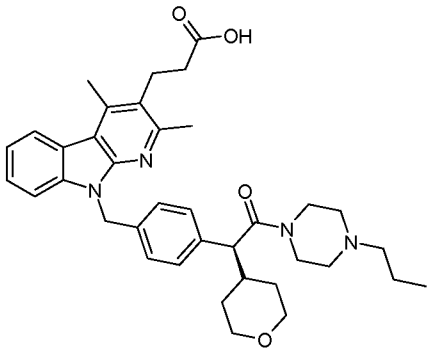
SLV-319



AVE 1625



TAK-475



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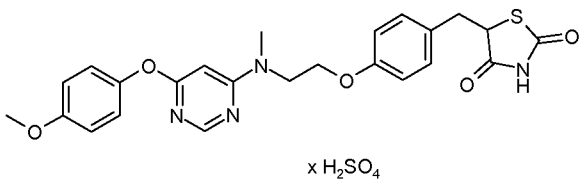


x H_2SO_4

CKD-501 (lobeglitazone sulphate)

The invention furthermore relates to processes for preparing the crystalline compound of the formula I or a tautomer thereof. In another embodiment, the invention provides Form A. Unless otherwise specified, the starting material (i.e. the compound of Formula I) employed for the processes and procedures described herein should be essentially pure. "Essentially pure" means the starting material has an HPLC purity grade of at least 98%. The HPLC purity grade for the starting material is preferably at least 99.8%.

The experiments described herein comprise thermodynamically controlled crystallization of essentially pure 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranoside by varying solvent and cooling rate and also by adding anti-solvents. The particular forms may also be produced through maturation procedures and/or dehydration of hydrates followed by rehydration.

Crystallization from a solution of essentially pure 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranoside(anhydrate or hydrate) in isopropanol/water mixture containing about 1.9 equivalents of KOAc/HOAc (pH about 6) produces Form A.

Form A is isolated by dissolving an essentially pure hydrate of 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranoside in isopropyl acetate and adding an anti solvent such as *n*-heptane. Alternative antisolvents such as methylcyclohexane may also be used.

Form A may be isolated from an aqueous solution of a salt of 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]4-deoxy-4-fluoro-beta-D-glucopranoside. For example, a sodium salt of the pyrazole functionality, or other suitable salt of the pyrazole may be used to prepare the aqueous solution. The pH is adjusted and the free acid is extracted into an organic solvent, preferably isopropyl acetate. Addition of an antisolvent such as, for example, n-heptane

crystallizes 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranosidehydrate i.e. Form A. Alternative antisolvents such as methylcyclohexane may also be used.

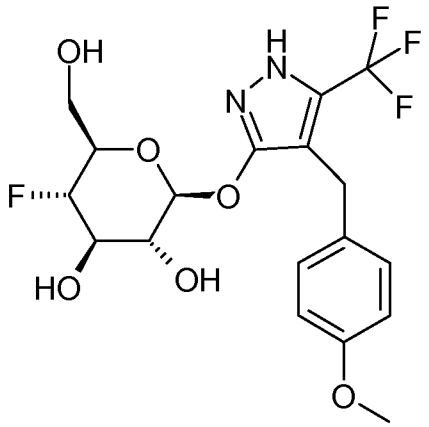
In addition, Form A can be obtained after completely or substantially dehydrating solid essentially pure 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]i4-deoxy-4-fluoro-beta-D-glucopyranoside hydrate by drying by heating followed by a rehydration process of the resultant solid in a humid environment (relative humidity: 20-90%).

Form A may be maintained during drying of wet 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranosidemonohydrate by avoiding dehydration, for example by drying under a humid environment (relative humidity 20-90%).

The following examples detailed below are provided to more specifically describe and to better teach how to make and practice the claimed compounds of the present invention and methods for their preparation. The examples are provided for illustrative purposes only and it is to be recognized that not all embodiments of the invention can be disclosed in this manner. Therefore, the examples are to be construed in this way and should not be interpreted as limiting the spirit and scope of the invention as later recited by the claims that follow.

EXAMPLES

Unless otherwise specified, the experiments specifically disclosed herein were carried out using a hydrated compound of the formula II



n H_2O
where n =1, 2

II

wherein the HPLC purity grade of the compound is at least 99.8 %.

Crystallisation by adding antisolvent at room temperature

Form A was precipitated from different solvents at room temperature by adding n-heptane or diisopropylether as antisolvent.

Example 1a: 0.209 g of compound of the formula II was dissolved in 12.45 mL of ethanol. The slightly turbid solution was stirred overnight. 75mL of diisopropylether were added to the stirred solution. Since no precipitation appeared, the sample was evaporated at room temperature.

Crystallisation by evaporation of the solvent at elevated temperatures

The compound of the formula II was dissolved at elevated temperatures in several solvents and the solvents were then allowed to evaporate from the stirred solutions.

Example 1b: 0.212 g of compound of the formula II was dissolved in 2.50 mL of water/methanol 1:1 (vol/vol) at about 65°C. The solvent was allowed to evaporate from the stirred solution at the same temperature overnight.

Other crystallisation methods

Samples of the compound of formula II were dissolved at 65°C in several solvents

and transferred to 0°C environment in which they were stirred for 0.5, 19 or 24 hours before vacuum filtration.

Example 1c: Rapid cooling of a stirred solution (slightly turbid) of 0.220 g of compound of formula II in 8.0 mL butyl acetate from 65°C to 0°C. Since no precipitation occurred the sample was evaporated at room temperature.

Example 1d: Rapid cooling of a stirred solution (slightly turbid)) of 0.224 g of compound of formula II in 13.0 mL ethanol from 65°C to 0°C. Since no precipitation occurred the sample was evaporated at room temperature.

Example 1e: Rapid cooling of a stirred solution (slightly turbid)) of 0.210 g of compound of formula II in 1.0 mL methyl ethyl ketone from 65°C to 0°C. Since no precipitation occurred, the sample was evaporated at room temperature.

Example 1f: Preparation of Form A

4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranosidemonohydrate (25.50kg) and potassium acetate (10.40kg) were charged to a reactor and a nitrogen atmosphere was established. n-Propanol (61kg) and demineralized water (74kg) were added and the temperature adjusted to 22±3°C. Acetic acid (3.30kg) was then added maintaining the batch temperature at 22±3°C and was followed by a rinse of the charging line with demineralized water (2.6kg). The mixture was stirred at 22±3°C for not less than 15 minutes and visually checked for complete dissolution. The batch was then transferred to a second reactor through a polishing filter fitted with a 0.45µm cartridge and the first reactor was rinsed with n-propanol (20kg) and demineralized water (25.5kg). The rinses were charged to this second reactor and the mixture was heated to 45±3°C. Demineralized water (281kg) was added at a controlled rate maintaining the batch temperature at 42±5°C. The resultant solution was cooled to 29±1°C and then gradually to 22±1°C using a jacket cooling profile (4.5°C/hr). The resulting slurry was heated to 36±2°C and maintained at 36±2°C for not less than 80

minutes. The batch was then cooled to 1±3°C using a jacket cooling profile (3°C/hr) and held for not less than 1 hour at 1±3°C. The batch was filtered, washed twice with demineralized water (2 X 160kg), dried under reduced pressure (<100mm Hg) at 60±5°C such that water content was less than 3.0% by KF titration and then allowed to rehydrate to give the product 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranosideas the monohydrate form A (22.95kg; molar yield 90.0%).

Example 1g: Preparation of Form A

4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranosidemonohydrate (11.70kg) and isopropyl acetate (68.0kg) were charged to a reactor. The mixture was stirred at 45±3°C until all the solids dissolved. The solution was cooled down to 22±3°C and transferred to a second reactor through a polishing filter fitted with a 0.8µm cartridge. The temperature of the batch was adjusted to 55±3°C and n-heptane (54.0kg) were added maintaining a batch temperature of 55±3°C. The solution was cooled to 0±2°C over a period of 3.5 hours, filtered, washed with n-heptane (27.0kg) and dried under reduced pressure (<100mm Hg) at a temperature of not more than 50°C such that residual solvent levels for isopropyl acetate and n-heptane were less than 5000 ppm each. The solids were then allowed to rehydrate under humid conditions to give the product 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranosideas the monohydrate form A (10.90kg; molar yield 93.2%).

Example 1h: Preparation of Form A through solid state dehydration/rehydration

A 24.8439g sample of 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranoside(a mixture of crystalline hydrates) was transferred into an open crystallization dish to form an 3 cm thick layer. The dish was placed in an open aluminum dessicator and transferred to a vacuum oven. The sample was dried at 60°C under vacuum for 24 hours. The sample was

then placed on an analytical balance in the presence of an open vessel containing water and allowed to rehydrate. The weight stabilized at 1 molar equivalent of water and analytical studies confirmed the sample as form A.

Form A was characterized by the following methods:

X-ray powder diffraction experiments (XRPD) were performed with a STOE Stadi-P transmission diffractometer using Cu-Kα_1 radiation. For room temperature powder diffraction, linear position sensitive detectors were used. Dry samples were investigated in a flat preparation. The measured data was evaluated and plotted with the software WinXPOW v2.12.

All DSC measurements were performed with a METTLER DSC822e (module DSC822e/700/109/414935/0025). If not indicated differently, 40µL Al-crucibles with sealed lid and hole were used. All measurements were carried out in a nitrogen gas flow of 50 mL/min and typical heating rates range from 1 to 50°/min. The measured data was evaluated via the software provided with said instrument.

The thermogravimetric analyses were performed with a METTLER TGA85 1e (module TGAISDTA85 1 elSF 1 1001042). Open 100µL Al-crucibles were used and the measurements were performed in a nitrogen gas flow of 50 mL/min. The measured data was evaluated via the software STARe V8.10.

Infra-red absorption spectra were recorded on a FT-IR Spectrometer (Nexus 470, NICOLET). The spectra are evaluated and plotted by the software Omnic V. 6.1A.

Raman spectra were recorded with an FT-Raman spectrometer (RFS-1 OOIS, BRUKER) equipped with a 1.5 W NIR-Laser (Nd:YAG; h=1064 nm) and a nitrogen-cooled D4 1 8-T NIR-Detector. The spectra are evaluated and plotted by the software OPUS V. 4.2.

Form A exhibits the XRPD shown in Figure 1. The XRPD was measured in transmission with Cu-Kalpha1 radiation at room temperature. The most important 2 theta values are summarized in table 1.

Table 1:

2 theta (+/- 0.2 degrees 2 theta)
5.98
7.48
12.09
14.88
14.99
20.27
20.75
22.81
22.98
26.52
27.60
31.01

Owing to natural deviations in the samples or in the measuring method, the 2 theta values of the peaks can be stated with an accuracy of +/- 0.2 degrees theta.

Long term stability

The following tables 2 to 5 show data for the storage stability of Form A. Samples of Form A were packed into LDPE (low density polyethylene) flat bags which are used as primary packaging material. Physical and chemical stability was monitored over a period up to 12 month under different conditions as indicated at each table.

Table 2

Storage condition:

Container LDPE flat bags

Temperature: +5°+/-3° C

Test item & Acceptance criteria	**Initial results**	**1 month**	**6 month**	**12 month**
Visual appearance: White to light yellow powder	Nearly white powder	Nearly white powder	Nearly white powder	Nearly white powder
Identification (XRPD)	Form A	Form A	Form A	Form A
Assay Form A (HPLC) [%] 95.0% - 102.0% as is (corr. To 91.3-98.0% active moiety)	99.6 (95.7)	99.7 (95.8)	100.3 (96.4)	100.1 (96.1)
Water content (K.F.) [%]	4.1	4.1	3.9	4.3
Specific surface area (BET) [m^2/g]	2.8	3.0	2.7	2.5

Table 3

Storage condition:

Container LDPE flat bags

Temperature: +25°+/-2° C/60+/-5° RH (relative humidity)

Test item & Acceptance criteria	**Initial results**	**3 month**	**6 month**	**9 month**	**12 month**
Visual appearance: White to light yellow powder	Nearly white powder	Yellowish white powder	Nearly white powder	Nearly white powder	Nearly white powder
Identification (XRPD)	Form A	Form A	Form A	Form A	Form A
Assay Form A (HPLC) [%] 95.0% - 102.0% as is (corr. To 91.3-98.0% active moiety)	99.6 (95.7)	100.2 (99.5)	101.1 (97.1)	101.8 (97.8)	99.9 (95.9)
Water content (K.F.) [%]	4.1	4.2	4.0	4.3	4.2
Specific surface area (BET) [m^2/g]	2.8	2.6	2.5	2.4	2.5

Table 4

Storage condition:

Container LDPE flat bags

Temperature: +30°+/-2° C / 66+/-5° RH

Test item & Acceptance criteria	**Initial results**	**1 month**	**3 month**	**6 month**	**9 month**	**12 month**
Visual appearance: White to light yellow powder	Nearly white powder	Nearly white powder	Yellowish white powder	Nearly white powder	Nearly white powder	Nearly white powder
Identification (XRPD)	Form A	Form A	Form A	Form A	Form A	Form A
Assay Form A (HPLC) [%] 95.0% - 102.0% as is (corr. To 91.3-98.0% active moiety)	99.6 (95.7)	99.5 (95.6)	101.1 (97.1)	99.8 (95.9)	100.8 (96.8)	99.7 (95.8)
Water content (K.F.) [%]	4.1	4.3	4.4	3.9	4.3	4.2
Specific surface area (BET) [m^2/g]	2.8	2.5	2.6	2.4	2.4	2.4

Table 5

Storage condition:

Container LDPE flat bags

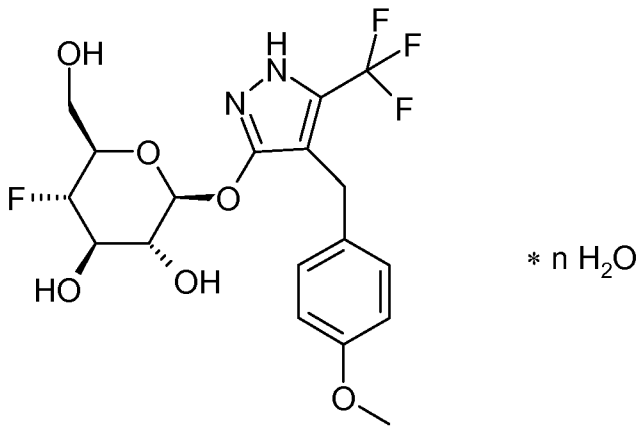
Temperature: +40°+/-3° C / 75+/-5% RH

Test item & Acceptance criteria	**Initial results**	**1 month**	**3 month**	**6 month**
Visual appearance: White to light yellow powder	Nearly white powder	Nearly white powder	Nearly white powder	Nearly white powder
Identification (XRPD)	Form A	Form A	Form A	Form A
Assay Form A (HPLC) [%] 95.0% - 102.0% as is (corr. To 91.3-98.0% active moiety)	99.6 (95.7)	99.4 (95.5)	100.5 (99.5)	100.5 (96.5)
Water content (K.F.) [%]	4.1	4.4	4.2	4.1
Specific surface area (BET) [m^2/g]	2.8	2.2	2.2	2.2

5

CLAIMS

1. A crystalline hydrate of the formula I,



$* n H_2O$

I

in which n has a value of from 0.9 to 1.1 or a tautomer thereof.

2. The crystalline hydrate of the formula I as claimed in claim 1 wherein n has a value of 1.

3. The crystalline hydrate of the formula I as claimed in one or more of claims 1 to 2 comprising a measured XRPD reflection at 20.27 degrees 2 theta ± 0.2 degrees 2 theta as measured using copper K-alpha radiation.

4. The crystalline hydrate of the formula I as claimed in claims 1 to 3 comprising a measured XRPD reflection at 20.27 ± 0.2 degrees 2 theta and 22.98 ± 0.2 degrees 2 theta as measured using copper K-alpha radiation.

5. The crystalline hydrate of the formula I as claimed in one or more of claims 1 to 4 comprising a measured XRPD reflection at 14.88, 20.27 and 22.98 ± 0.2 degrees 2 theta as measured using copper K-alpha radiation.

6. The crystalline hydrate of the formula I as claimed in claims 1 to 5 comprising a measured XRPD reflection at 5.98, 14.88, 20.27, 22.98 and 26.52 ± 0.2 degrees 2 theta as measured using copper K-alpha radiation.

7. The crystalline hydrate of the formula I as claimed in claims 1 to 5 comprising a measured XRPD reflection at 5.98, 7.48, 12.09, 14.88, 14.99, 20.27, 20.75, 22.81, 22.98, 26.52, 27.60 and 31.01 ± 0.2 degrees 2 theta as measured

using copper K-alpha radiation.

8. A medicament comprising the compound as claimed in one or more of claims 1 to 7.

9. A medicament comprising the compound as claimed in one or more of claims 1 to 7 and one or more blood glucose-lowering active ingredients.

10. The use of the compound as claimed in one or more of claims 1 to 7 for producing a medicament for the treatment of type 1 and type 2 diabetes.

11. The use of the compound as claimed in one or more of claims 1 to 7 for producing a medicament for lowering blood glucose.

12. The use of the compound as claimed in one or more of claims 1 to 7 in combination with at least one other blood glucose-lowering active ingredient for producing a medicament for the treatment of type 1 and type 2 diabetes.

13. The use of the compound as claimed in one or more of claims 1 to 7 in combination with at least one other blood glucose-lowering active ingredient for producing a medicament for lowering blood glucose.

14. A process for producing a medicament comprising the compound as claimed in one or more of claims 1 to 7, which comprises mixing the active ingredient with a pharmaceutically suitable carrier and converting this mixture into a form suitable for administration.

15. The use of the compound as claimed in one or more of claims 1 to 7 as a pharmaceutical.

16. The method for the treatment of a diabetic patient in need thereof consisting of the administration of an efficacious amount of the compound as claimed in claims 1 to 7.

17. The crystalline hydrate of formula I as claimed in claims 1 and 2 having a significant peak at 800 cm^{-1} as measured by Raman spectroscopy.

18. A method of preparing a the crystalline monohydrate of claims 3 to 7 comprising the step of stirring an essentially pure suspension of 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranoside(anhydrate or hydrate) in a ethanol/water mixture (water activity below 0.7) at a temperature of about 20°C.

19. A method of preparing the crystalline monohydrate of claims 3 to 7 comprising the step of adding diisopropylether to a solution essentially pure

monohydrate of 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranoside in ethanol and evaporating the resultant solution to yield a solid.

20. A method of preparing the crystalline monohydrate of claims 3 to 7 comprising the step of crystallizing said monohydrate from a solution of essentially pure 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranoside(anhydrate or hydrate) in n-propanol/water mixture containing about 1.9 equivalents of KOAc/HOAc wherein the pH is about 6.

21. A method of preparing the crystalline monohydrate of claims 3 to 7 comprising the steps of:

1) dissolving an essentially pure hydrate of 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranosidein isopropyl acetate; and
2) adding an anti solvent.

22. The method of claim 21 wherein the antisolvent is n-heptane.

23. A method of preparing the crystalline monohydrate of claims 3 to 7 comprising the steps of:

a. preparing an aqueous solution of a salt of essentially pure 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]4-deoxy-4-fluoro-beta-D-glucopranoside;
b. adjusting the pH of said aqueous solution so that the free acid is generated;
c. extracting said free acid into an organic solvent; and
d. adding an antisolvent.

24. The method of claim 23 where the salt is a potassium or sodium salt.

25. The method of claim 23 wherein the organic solvent is isopropyl acetate.

26. The method of claim 25 wherein the antisolvent is n-heptane.

27. A method of preparing the crystalline monohydrate of claims 3 to 7 comprising the steps of:

1) completely or substantially dehydrating solid essentially pure 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-

beta-D-glucopyranosidehydrate by drying by heating; and

2) rehydrating the resultant solid in an environment with a relative humidity of 20-90%.

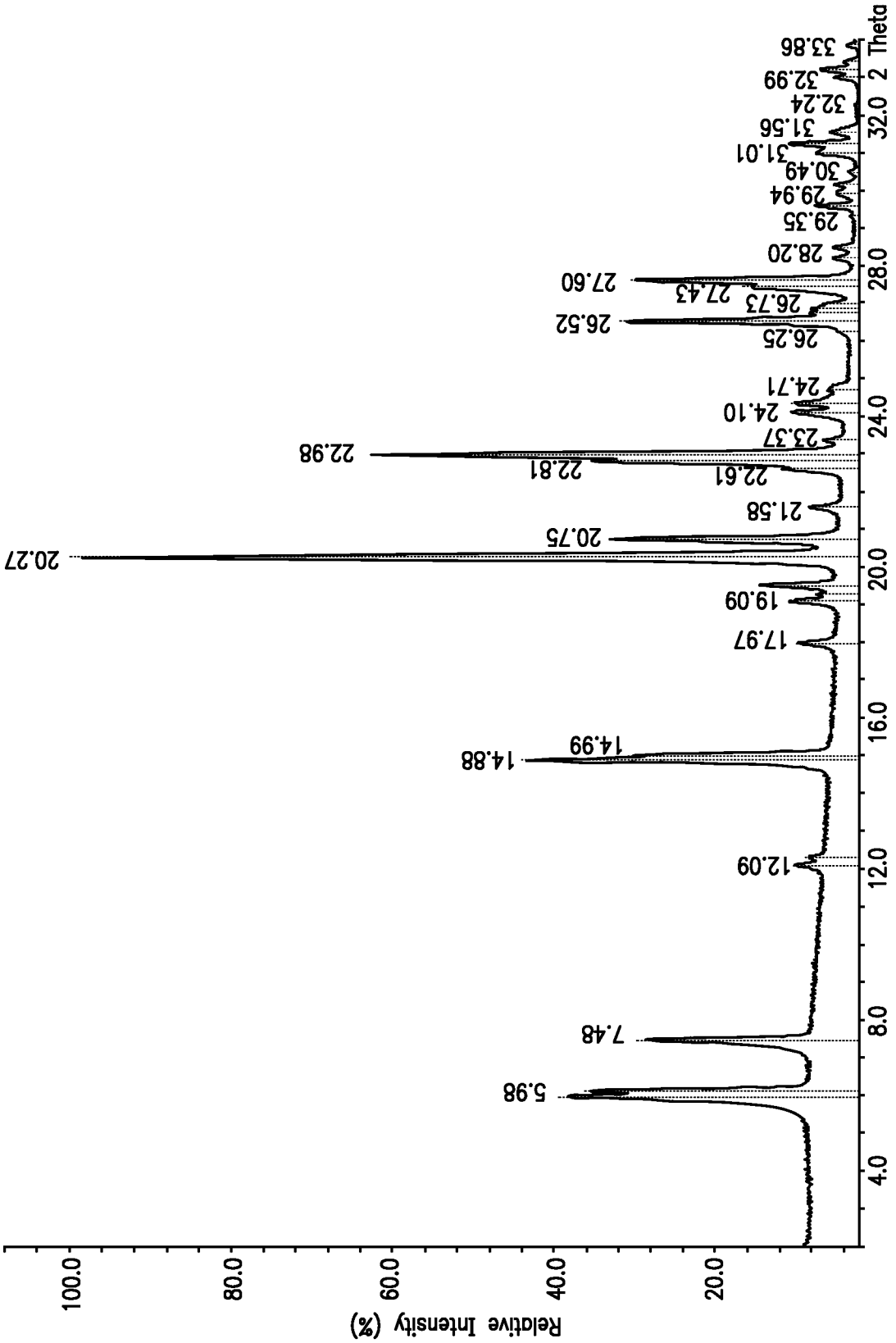
28. A method of preparing the crystalline monohydrate of claims 3 to 7 comprising the steps of:

1) dissolving an essentially pure hydrate of 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]-4-deoxy-4-fluoro-beta-D-glucopyranoside in a solvent selected from the group consisting of butyl acetate, ethanol and methyl ethyl ketone at an elevated temperature sufficient to dissolve the amorphous compound; and

2) evaporating the solvent to induce crystallization.

29. The method of claim 28 wherein the elevated temperature is about 65°C.

30. A monohydrate of 4-[(4-methoxyphenyl)methyl]-5-(trifluoromethyl)-1H-pyrazole-3-yl]4-deoxy-4-fluoro-beta-D-glucopranoside.


Relative Intensity (%)
100.0
80.0
60.0
40.0
20.0
4.0
8.0
12.0
16.0
20.0
24.0
28.0
32.0
2 Theta
5.98
7.48
12.09
14.88
14.99
17.97
19.09
20.27
20.75
21.58
22.61
22.81
22.98
23.37
24.10
24.71
26.25
26.52
26.73
27.43
27.60
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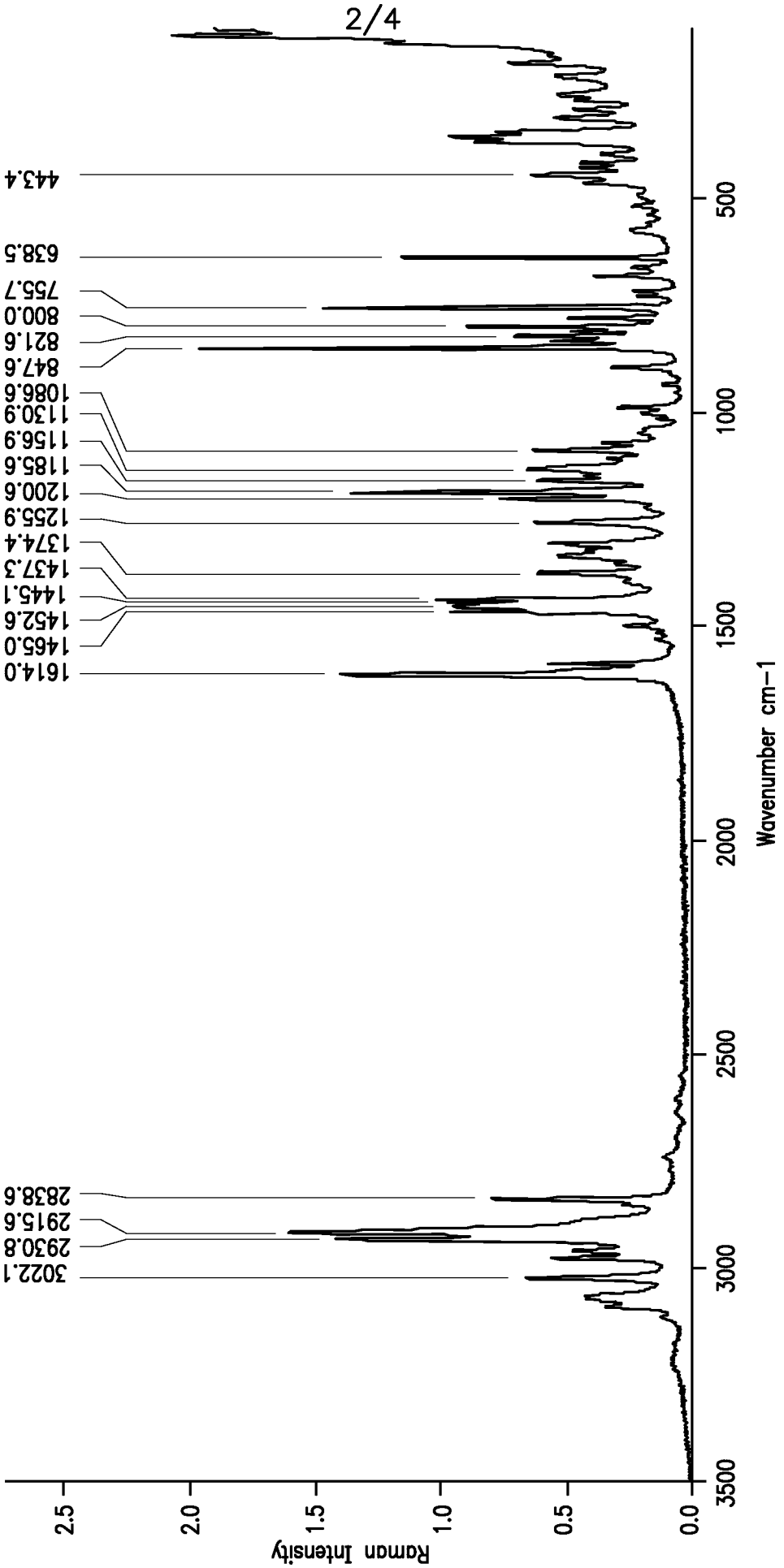
29.35
29.94
30.49
31.01
31.56
32.24
32.99
33.86

FIG. 1


2/4
Raman Intensity
2.5
2.0
1.5
1.0
0.5
0.0
Wavenumber cm−1
3500
3000
2500
2000
1500
1000
500
3022.1
2930.8
2915.6
2838.6
1614.0
1465.0
1452.6
1445.1
1437.3
1374.4
1255.9
1200.6
1185.6
1156.9
1130.9
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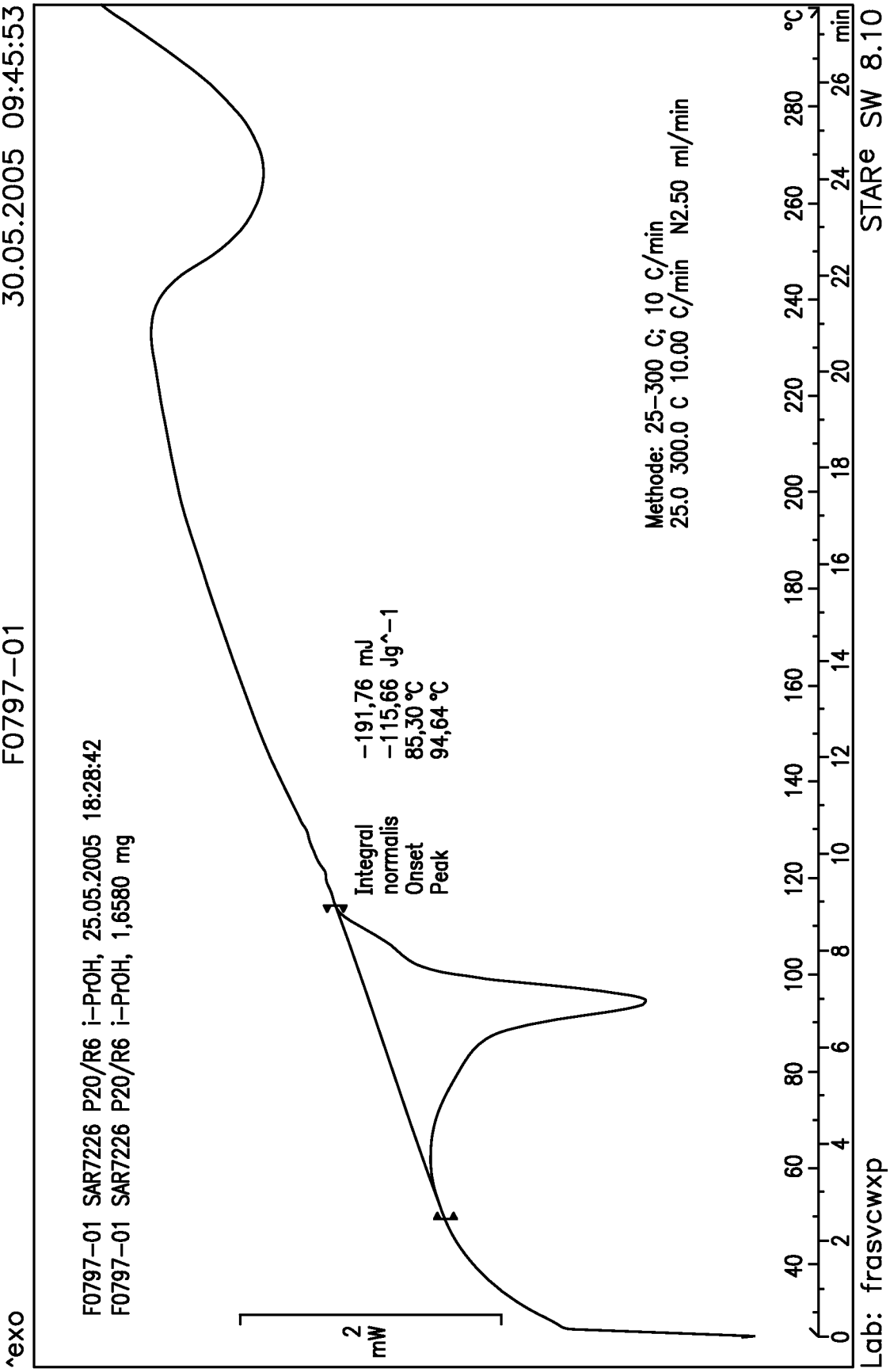
800.0
755.7
638.5
443.4

FIG. 2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2 mW
Integral -191,76 mJ
normalis -115,66 Jg^-1
Onset 85,30 °C
Peak 94,64 °C
Methode: 25-300 C; 10 C/min
25.0 300.0 C 10.00 C/min N2.50 ml/min
STARe SW 8.10
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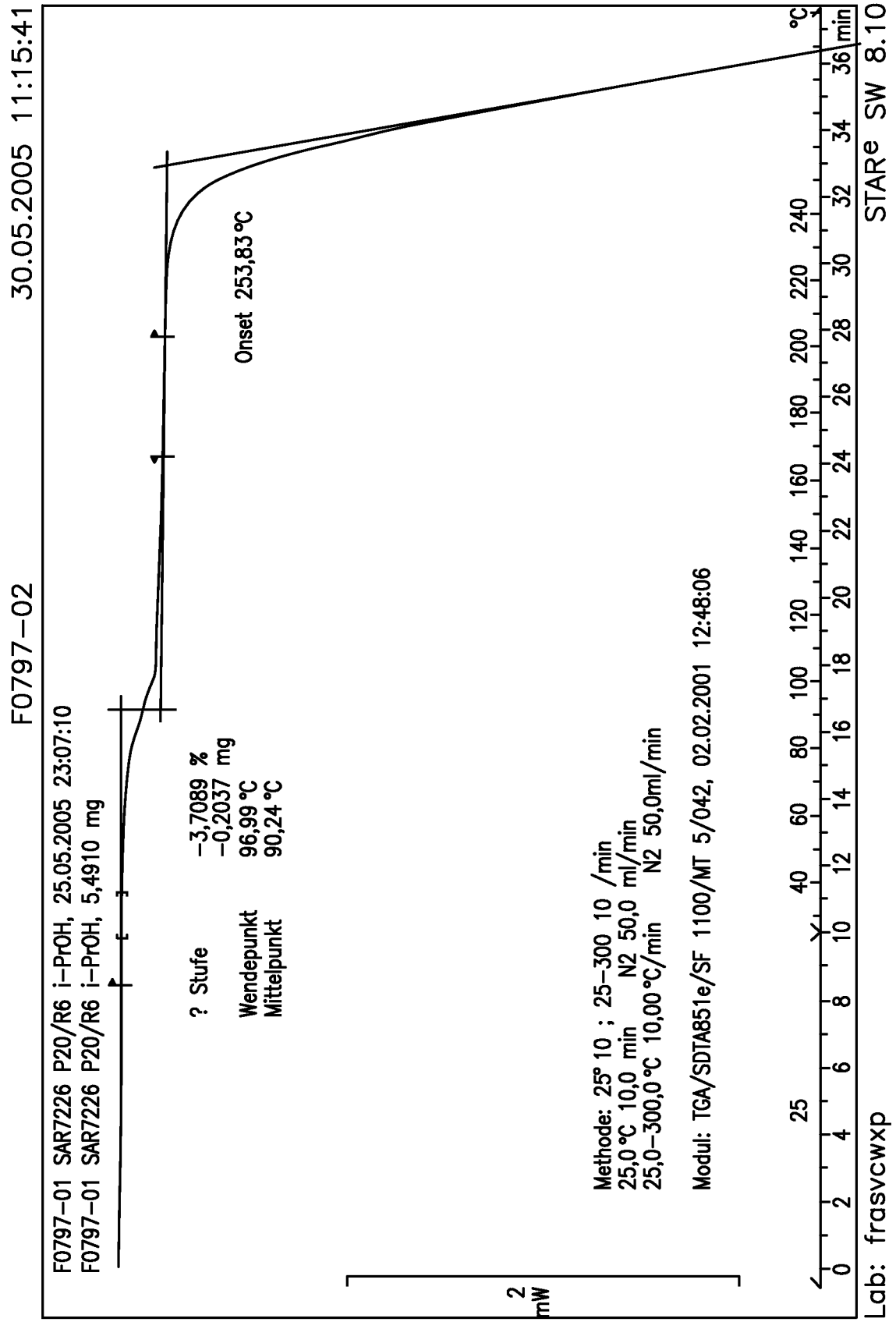
°C
min

FIG. 3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? Stufe -3,7089 %
-0,2037 mg
Wendepunkt 96,99 °C
Mittelpunkt 90,24 °C
Onset 253,83 °C
Methode: 25° 10 ; 25-300 10 /min
25,0 °C 10,0 min N2 50,0 ml/min
25,0-300,0 °C 10,00 °C/min N2 50,0ml/min
Modul: TGA/SDTA851e/SF 1100/MT 5/042, 02.02.2001 12:48:06
2 mW
°C
min
STARe SW 8.10
Lab: frasvcwxp

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/067046

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07H17/00 C07H17/02 A61K31/70

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)
C07H 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, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 572 708 A1 (AVENTIS PHARMA GMBH [DE] SANOFI AVENTIS DEUTSCHLAND [DE]) 14 September 2005 (2005-09-14) cited in the application	8-9
A	example 5	1-7, 10-30

☐ 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
8 February 2010	15/02/2010

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	Nikolai, Joachim

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/067046

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1572708 A1	14-09-2005	AT 323713 T	15-05-2006
		AU 2003289911 A1	30-06-2004
		BR 0317283 A	08-11-2005
		CA 2508226 A1	24-06-2004
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