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(54) Title: SALT FORMS OF AN OXAZINE DERIVATIVE BACE INHIBITOR

(57) Abstract: The present invention relates to salt forms of an oxazine derivative BACE-1 inhibitor for use in the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy and the advantageous properties associated with said salt forms.

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Salt Forms of an Oxazine Derivative BACE Inhibitor

Field of the Invention

The present invention relates to salt forms, specifically the fumarate, succinate and tartrate salt forms, of the BACE inhibitor *N*-(6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide, and the advantageous properties associated therewith.

Background of the Invention

Alzheimer's disease (AD) is one of the most prevalent neurological disorders worldwide and the most common and debilitating age-related condition, causing progressive amnesia, dementia, and ultimately global cognitive failure and death. Currently, the only pharmacological therapies available are symptomatic drugs such as cholinesterase inhibitors or other drugs used to control the secondary behavioral symptoms of AD. Investigational treatments targeting the AD pathogenic cascade include those intended to interfere with the production, accumulation, or toxic sequelae of amyloid-β (Aβ) species (Kramp VP, Herrling P, 2011).

Cerebral amyloid angiopathy (CAA) is a common age related cerebral small vessel disease, characterised by progressive deposition of Aβ, in particular Aβ40, in the wall of small to medium sized arteries, arterioles and capillaries of the cerebral cortex and overlying leptomeninges (Charidimou A *et al.*, 2011). CAA often coexists with AD. Mild forms of CAA often appear asymptomatic; however, CAA may also lead to severe vascular pathologies and is a risk factor for cerebral hemorrhages ranging from silent microbleeds to spontaneous intracerebral haemorrhage, a devastating form of stroke.

ApoE4 is a strong genetic risk factor for both AD and CAA (Shinohara M *et al.,* 2016). Human *APOE* is located on chromosome 19 (gene *APOE*, Uniprot P02649). Three major isoforms (ApoE2, -3 and -4) are known in humans. ApoE4 (with Arg at positions 112 and 158) has an allele frequency of 5-35% in humans (Verghese PB *et al.*, 2011) and *ApoE4* homozygotes are estimated to represent about 2 to 3% of the general population (Quintino-Santos SR *et al.*, 2012).

Strategies that target decreasing Aβ by: (1) enhancing the amyloid clearance with an active or passive immunotherapy against Aβ; or (2) decreasing production through inhibition of Beta-site-APP cleaving enzyme-1 (BACE-1, an enzyme involved in the processing of the amyloid precursor protein [APP]), are of potential therapeutic value in the treatment or

prevention of AD and CAA, particularly in patients carrying one or two copies of the *ApoE4* allele.

N-(6-((3*R*,6*R*)-5-Amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide, referred to herein as "Compound 1", is an orally active BACE inhibitor, previously described in WO 2012/095469 A1.

During formulation of Compound 1 into a pharmaceutical composition, drug substance is micronized in order to increase its surface area and thereby improve its dissolution rate and bioavailability. However, micronization of Compound 1 is extremely challenging at relevant operational conditions due to poor flow and the tendency of the drug substance to adhere to the mill. These characteristics make the manufacture of a pharmaceutical composition comprising Compound 1 problematic. It is therefore an objective of the present invention to provide a solution to the problems observed when milling Compound 1.

Summary of the Invention

It has surprisingly been found that the poor milling properties of Compound 1 are overcome by use of its fumarate, succinate and tartrate salt forms.

In a first aspect of the invention, there is therefore provided the fumarate, succinate and tartrate salt forms of Compound 1.

It has further been found that the fumarate, succinate and tartrate salt forms of Compound 1 are more stable than the free form, and other tested salt forms, when in physical mixture with pharmaceutical excipients.

In a second aspect of the invention, there is therefore provided a pharmaceutical composition comprising the fumarate, succinate and tartrate salt forms of Compound 1.

In a third aspect of the invention, there is provided Compound 1 in fumarate, succinate or tartrate salt form for use as a medicament.

In a fourth aspect of the invention, there is provided Compound 1 in fumarate, succinate or tartrate salt form for use in the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy.

In a fifth aspect of the invention, there is provided a method for the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy which method comprises administering to a patient in need thereof a therapeutically effective amount of Compound 1 in fumarate, succinate or tartrate salt form.

In a sixth aspect of the invention, there is provided the use of Compound 1 in fumarate, succinate or tartrate salt form for the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy.

In a seventh aspect of the invention, there is provided the use of Compound 1 in fumarate, succinate or tartrate salt form, for the manufacture of a medicament for the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy.

Description of the Invention

List of Figures

Figure 1 shows shows the X-ray powder diffraction pattern for crystalline free base Compound 1 Form A when measured using CuK_α radiation.

Figure 2 shows the X-ray powder diffraction pattern for micronized crystalline free base Compound 1 Form A when measured using CuK_α radiation.

Figure 3 shows the DSC thermogram for crystalline free base Compound 1 Form A.

Figure 4 shows the X-ray powder diffraction pattern for crystalline Compound 1 in hemifumarate hemihydrate salt form when measured using CuK_α radiation.

Figure 5 shows the X-ray powder diffraction pattern for micronized crystalline Compound 1 in hemifumarate hemihydrate salt form when measured using CuK_α radiation.

Figure 6 shows the DSC thermogram for crystalline Compound 1 in hemifumarate hemihydrate salt form.

Figure 7 shows the X-ray powder diffraction pattern for crystalline Compound 1 in hemisuccinate hemihydrate salt form when measured using CuK_α radiation.

Figure 8 shows the X-ray powder diffraction pattern for micronized crystalline Compound 1 in hemisuccinate hemihydrate salt form when measured using CuK_α radiation.

Figure 9 shows the DSC thermogram for crystalline Compound 1 in hemisuccinate hemihydrate salt form.

Figure 10 shows the X-ray powder diffraction pattern for crystalline Compound 1 in hemi-L-tartrate hemihydrate salt form when measured using CuK_α radiation.

Figure 11 shows the X-ray powder diffraction pattern for micronized crystalline Compound 1 in hemi-L-tartrate hemihydrate salt form when measured using CuK_α radiation.

Figure 12 shows the DSC thermogram for crystalline Compound 1 in hemi-L-tartrate hemihydrate salt form.

Figure 13 shows the design of a two part, open-label, two-period, fixed-sequence study in healthy subjects to evaluate the PK of Compound 1 when given alone and in combination with the strong CYP3A4 inhibitor itraconazole or the strong CYP3A4 inducer rifampicin.

Embodiments of the First Aspect of the Invention

Embodiment A1: Compound 1 in fumarate, succinate or tartrate salt form.

Embodiment A2: Compound 1 in fumarate salt form.

Embodiment A3: Compound 1 according to Embodiment A2 in hemifumarate salt form.

Embodiment A4: Compound 1 in succinate salt form.

Embodiment A5: Compound 1 according to Embodiment A4 in hemisuccinate salt form.

Embodiment A6: Compound 1 in tartrate salt form.

Embodiment A7: Compound 1 according to Embodiment A6 in L-tartrate salt form.

Embodiment A8: Compound 1 according to Embodiment A6 in hemitartrate salt form or A7 in hemi-L-tartrate salt form.

Embodiment A9: Compound 1 according to any one of Embodiments A1 to A8 in hydrated salt form.

Embodiment A10: Compound 1 according to Embodiment A9 in hemihydrate or monohydrate salt form.

Embodiment A11: Compound 1 according to Embodiment A10 in hemihydrate salt form.

Embodiment A12: Compound 1 in hemifumarate hemihydrate salt form.

Embodiment A13: Compound 1 in hemisuccinate hemihydrate salt form.

Embodiment A14: Compound 1 in hemitartrate hemihydrate salt form.

Embodiment A15: Compound 1 in hemi-L-tartrate hemihydrate salt form.

Embodiment A16: Compound 1 according to any one of Embodiments A1 to A15 in crystalline form.

Embodiment A17: Compound 1 according to Embodiment A16 in substantially pure form.

Detailed Compound 1 fumarate salt embodiments

Embodiment A18: Compound 1 according to Embodiment A2 in crystalline fumarate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 11.9, 13.9 and 19.9º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A19: Compound 1 according to Embodiment A2 in crystalline fumarate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 23.0, 27.9 and 30.8º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A20: Compound 1 according to Embodiment A2 in crystalline fumarate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 11.9, 13.9, 16.2, 17.3 and 19.9º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A21: Compound 1 according to Embodiment A2 in crystalline fumarate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 11.9, 19.9, 23.0, 27.9 and 30.8º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A22: Compound 1 according to Embodiment A2 in crystalline fumarate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 4.0, 11.9, 13.9, 15.6, 16.2, 17.3, 19.9, 23.0, 27.9 and 30.8º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A23: Compound 1 according to Embodiment A2 in crystalline fumarate salt form and having an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 4 when measured using CuKα radiation.

Embodiment A24: Compound 1 according to Embodiment A2 in micronized fumarate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 14.0, 16.1 and 19.0º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A25: Compound 1 according to Embodiment A2 in micronized fumarate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 9.1, 11.8, 14.0, 16.1 and 19.0º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A26: Compound 1 according to Embodiment A2 in micronized fumarate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 3.9, 7.3, 9.1, 11.8, 14.0, 16.1, 17.1, 19.0, 19.7 and 22.3º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A27: Compound 1 according to Embodiment A2 in micronized fumarate salt form and having an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 5 when measured using CuKα radiation.

Embodiment A28: Compound 1 according to Embodiment A2 in crystalline fumarate salt form and having an endotherm at about 239 ºC when analysed by DSC at a heating rate of 10 ºC per minute.

Embodiment A29: Compound 1 according to Embodiment A2 in crystalline fumarate salt form and having a DSC thermogram substantially the same as that shown in Figure 6.

Embodiment A30: Compound 1 according to any one of Embodiments A18 to A29 wherein Compound 1 is in hemifumarate salt form.

Embodiment A31: Compound 1 according to any one of Embodiments A18 to A30 wherein Compound 1 is in hydrated salt form.

Embodiment A32: Compound 1 according to any one of Embodiments A18 to A31 wherein Compound 1 is in hemihydrate salt form.

Detailed Compound 1 succinate salt embodiments

Embodiment A33: Compound 1 according to Embodiment A4 in crystalline succinate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 12.0, 14.0 and 20.1º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A34: Compound 1 according to Embodiment A4 in crystalline succinate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 12.0, 14.0, 17.3, 17.6 and 20.1º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A35: Compound 1 according to Embodiment A4 in crystalline succinate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 4.0, 12.0, 14.0, 15.7, 16.2, 17.3, 17.6, 20.1, 23.3 and 31.2º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A36: Compound 1 according to Embodiment A4 in crystalline succinate salt form and having an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 7 when measured using CuKα radiation.

Embodiment A37: Compound 1 according to Embodiment A4 in micronized succinate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 10.1, 15.5 and 19.8º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A38: Compound 1 according to Embodiment A4 in micronized succinate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 10.1, 14.5, 15.5, 19.8 and 23.3º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A39: Compound 1 according to Embodiment A4 in micronized succinate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 9.2, 10.1, 11.9, 12.7, 14.5, 15.5, 19.8, 22.0, 23.3 and 24.5º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A40: Compound 1 according to Embodiment A4 in micronized succinate salt form and having an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 8 when measured using CuKα radiation.

Embodiment A41: Compound 1 according to Embodiment A4 in crystalline succinate salt form and having an endotherm at about 217 ºC when analysed by DSC at a heating rate of 10 ºC per minute.

Embodiment A42: Compound 1 according to Embodiment A4 in crystalline succinate salt form and having a DSC thermogram substantially the same as that shown in Figure 9.

Embodiment A43: Compound 1 according to any one of Embodiments A33 to A42 wherein Compound 1 is in hemisuccinate salt form.

Embodiment A44: Compound 1 according to any one of Embodiments A33 to A43 wherein Compound 1 is in hydrated salt form.

Embodiment A45: Compound 1 according to any one of Embodiments A33 to A44 wherein Compound 1 is in hemihydrate salt form.

Detailed Compound 1 tartrate salt embodiments

Embodiment A46: Compound 1 according to Embodiment A6 in crystalline tartrate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 14.0, 17.7 and 19.8º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A47: Compound 1 according to Embodiment A6 in crystalline tartrate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 12.2, 14.0, 17.7, 19.8 and 20.4º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A48: Compound 1 according to Embodiment A6 in crystalline tartrate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 12.2, 14.0, 16.0, 17.1, 17.3, 17.7, 19.8, 20.4, 23.5 and 31.5º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A49: Compound 1 according to Embodiment A6 in crystalline tartrate salt form and having an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 10 when measured using CuKα radiation.

Embodiment A50: Compound 1 according to Embodiment A6 in micronized tartrate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 13.0, 17.1 and 20.3º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A51: Compound 1 according to Embodiment A6 in micronized tartrate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 7.1, 13.0, 17.1, 19.8 and 20.3º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A52: Compound 1 according to Embodiment A6 in micronized tartrate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 7.1, 13.0, 13.7, 13.9, 15.9, 17.1, 19.8, 20.3, 22.4 and 24.7º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

Embodiment A53: Compound 1 according to Embodiment A6 in micronized tartrate salt form and having an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 11 when measured using CuKα radiation.

Embodiment A54: Compound 1 according to Embodiment A6 in crystalline tartrate salt form and having an endotherm at about 253 ºC when analysed by DSC at a heating rate of 10 ºC per minute.

Embodiment A55: Compound 1 according to Embodiment A6 in crystalline tartrate salt form and having a DSC thermogram substantially the same as that shown in Figure 12.

Embodiment A56: Compound 1 according to any one of Embodiments A46 to A55 wherein Compound 1 is in hemitartrate salt form.

Embodiment A57: Compound 1 according to any one of Embodiments A46 to A56 wherein Compound 1 is in hemi-L-tartrate salt form.

Embodiment A58: Compound 1 according to any one of Embodiments A46 to A57 wherein Compound 1 is in hydrated salt form.

Embodiment A59: Compound 1 according to any one of Embodiments A46 to A58 wherein Compound 1 is in hemihydrate salt form.

Embodiments of the Second Aspect of the Invention

Embodiment B1: A pharmaceutical composition comprising Compound 1 according to any one of Embodiments A1 to A59.

Embodiment B2: The pharmaceutical composition according to Embodiment B1 wherein the pharmaceutical composition comprises 1 to 100 mg of the base of Compound 1.

Embodiment B3: The pharmaceutical composition according to Embodiment B1 wherein the pharmaceutical composition comprises 1 to 75 mg of the base of Compound 1.

Embodiment B4: The pharmaceutical composition according to Embodiment B1 wherein the pharmaceutical composition comprises 1, 10, 15, 25, 50 or 75 mg of the base of Compound 1.

Embodiment B5: The pharmaceutical composition according to Embodiment B1 wherein the pharmaceutical composition comprises 15 mg of the base of Compound 1.

Embodiment B6: The pharmaceutical composition according to Embodiment B1 wherein the pharmaceutical composition comprises 50 mg of the base of Compound 1.

Embodiment B7: The pharmaceutical composition according to any one of Embodiments B1 to B6 wherein the pharmaceutical composition comprises a gelatin capsule.

Embodiment B8: The pharmaceutical composition according to any one of Embodiments B1 to B7 wherein the pharmaceutical composition comprises magnesium stearate, sodium stearyl fumarate, or Aerosil 200 PH.

Embodiment B9: The pharmaceutical composition according to any one of Embodiments B1 to B7 wherein the pharmaceutical composition comprises magnesium stearate.

Embodiment B10: The pharmaceutical composition according to any one of Embodiments B1 to B7 wherein the pharmaceutical composition comprises sodium stearyl fumarate.

Embodiment B11: The pharmaceutical composition according to any one of Embodiments B1 to B7 wherein the pharmaceutical composition comprises Aerosil 200 PH.

Embodiments of the Third and Fourth Aspects of the Invention

Embodiment C1: Compound 1 according to any one of Embodiments A1 to A59 for use as a medicament.

Embodiment C2: Compound 1 according to any one of Embodiments A1 to A59 for use in the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy.

Embodiment C3: Compound 1 according to any one of Embodiments A1 to A59 for use in the prevention of Alzheimer's disease and/or cerebral amyloid angiopathy.

Embodiment C4: Compound 1 for the use according to Embodiment C2 or C3 in a patient carrying one or two copies of the *ApoE4* allele.

Embodiment C5: Compound 1 for the use according to any one of Embodiments C1 to C4 wherein Compound 1 is used at a dose of between 10 and 30 mg of the base of Compound 1 per day.

Embodiment C6: Compound 1 for the use according to any one of Embodiments C1 to C4 wherein Compound 1 is used at a dose of between 30 and 100 mg of the base of Compound 1 per day.

Embodiment C7: Compound 1 for the use according to any one of Embodiments C1 to C4 wherein Compound 1 is used at a dose of between 30 and 50 mg of the base of Compound 1 per day.

Embodiment C8: Compound 1 for the use according to any one of Embodiments C1 to C4 wherein Compound 1 is used at a dose of 15 mg of the base of Compound 1 per day.

Embodiment C9: Compound 1 for the use according to any one of Embodiments C1 to C4 wherein Compound 1 is used at a dose of 50 mg of the base of Compound 1 per day.

Embodiments of the Fifth Aspect of the Invention

Embodiment D1: A method for the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy which method comprises administering to a patient in need thereof a therapeutically effective amount of Compound 1 according to any one of Embodiments A1 to A59.

Embodiment D2: A method for the prevention of Alzheimer's disease and/or cerebral amyloid angiopathy which method comprises administering to a patient in need thereof a therapeutically effective amount of Compound 1 according to any one of Embodiments A1 to A59.

Embodiment D3: The method according to Embodiment D1 or D2 in a patient carrying one or two copies of the *ApoE4* allele.

Embodiment D4: The method according to any one of Embodiments D1 to D3, wherein the base of Compound 1 is used at a dose of between 10 and 30 mg per day.

Embodiment D5: The method according to any one of Embodiments D1 to D3, wherein the base of Compound 1 is used at a dose of between 30 and 100 mg per day.

Embodiment D6: The method according to any one of Embodiments D1 to D3, wherein the base of Compound 1 is used at a dose of between 30 and 50 mg per day.

Embodiment D7: The method according to any one of Embodiments D1 to D3, wherein the base of Compound 1 is used at a dose of 15 mg per day.

Embodiment D8: The method according to any one of Embodiments D1 to D3, wherein the base of Compound 1 is used at a dose of 50 mg per day.

Embodiments of the Sixth Aspect of the Invention

Embodiment E1: Use of Compound 1 according to any one of Embodiments A1 to A59 for the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy.

Embodiment E2: The use of Compound 1 according to Embodiment E1 for the prevention of Alzheimer's disease and/or cerebral amyloid angiopathy.

Embodiment E3: The use of Compound 1 according to Embodiment E1 or E2 in a patient carrying one or two copies of the *ApoE4* allele.

Embodiment E4: The use of Compound 1 according to any one of Embodiments E1 to E3, wherein the drug substance is used at a dose of between 10 and 30 mg of the base of Compound 1 per day.

Embodiment E5: The use of Compound 1 according to any one of Embodiments E1 to E3, wherein the drug substance is used at a dose of between 30 and 100 mg of the base of Compound 1 per day.

Embodiment E6: The use of Compound 1 according to any one of Embodiments E1 to E3, wherein the drug substance is used at a dose of between 30 and 50 mg of the base of Compound 1 per day.

Embodiment E7: The use of Compound 1 according to any one of Embodiments E1 to E3, wherein the drug substance is used at a dose of 15 mg of the base of Compound 1 per day.

Embodiment E8: The use of Compound 1 according to any one of Embodiments E1 to E3, wherein the drug substance is used at a dose of 50 mg of the base of Compound 1 per day.

Embodiments of the Seventh Aspect of the Invention

Embodiment F1: Use of Compound 1 according to any one of Embodiments A1 to A59, for the manufacture of a medicament for the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy.

Embodiment F2: The use of Compound 1 according to Embodiment F1 for the manufacture of a medicament for the prevention of Alzheimer's disease and/or cerebral amyloid angiopathy.

Embodiment F3: The use of Compound 1 according to Embodiment F1 or F2 for the manufacture of a medicament for the prevention of Alzheimer's disease and/or cerebral amyloid angiopathy in a patient carrying one or two copies of the *ApoE4* allele.

Embodiment F4: The use of Compound 1 according to any one of Embodiments F1 to F3, wherein the drug substance is used for the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy at a dose of between 10 and 30 mg of the base of Compound 1 per day.

Embodiment F5: The use of Compound 1 according to any one of Embodiments F1 to F3, wherein the drug substance is used for the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy at a dose of between 30 and 100 mg of the base of Compound 1 per day.

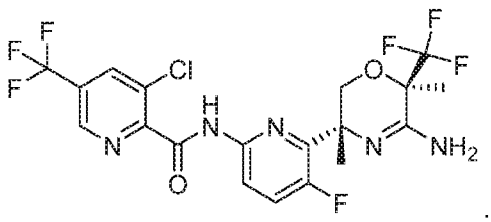
Embodiment F6: The use of Compound 1 according to any one of Embodiments F1 to F3, wherein the drug substance is used for the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy at a dose of between 30 and 50 mg of the base of Compound 1 per day.

Embodiment F7: The use of Compound 1 according to any one of Embodiments F1 to F3, wherein the drug substance is used for the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy at a dose of 15 mg of the base of Compound 1 per day.

Embodiment F8: The use of Compound 1 according to any one of Embodiments F1 to F3, wherein the drug substance is used for the treatment or prevention of Alzheimer's disease and/or cerebral amyloid angiopathy at a dose of 50 mg of the base of Compound 1 per day.

Definitions

As used herein, the terms "Compound 1", "Cmpd 1", "the base of Compound 1", "the free base of Compound 1" or "the free form of Compound 1" refer to *N*-(6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide and having the following structural formula:



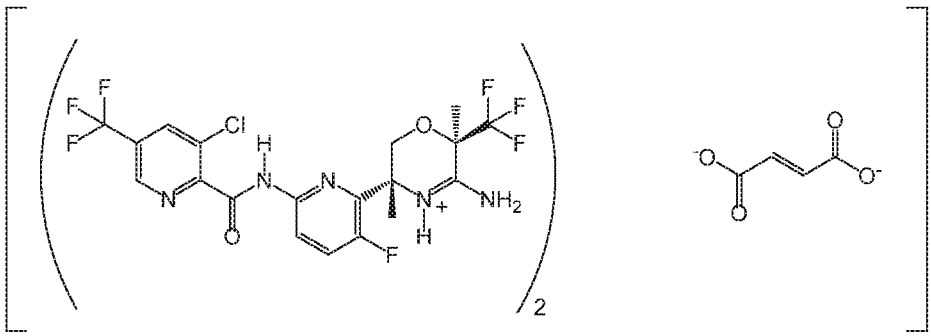
In Example 1, using an alternative chemical naming format, "Compound 1" is also referred to as 3-chloro-5-trifluoromethyl-pyridine-2-carboxylic acid [6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-trifluoromethyl-3,6-dihydro-2H-[1,4]oxazin-3-yl)-5-fluoro-pyridin-2-yl]-amide.

The terms "Compound 1", "Cmpd 1", "the base of Compound 1", "the free base of Compound 1", "the free form of Compound 1" and its corresponding full chemical name are used interchangeably throughout the description of the invention. Compound 1 is described in WO 2012/095469 A1, Example 34. WO 2012/095469 A1 is incorporated herewith by reference in its entirety, in particular the disclosure related to the synthesis of Example 34.

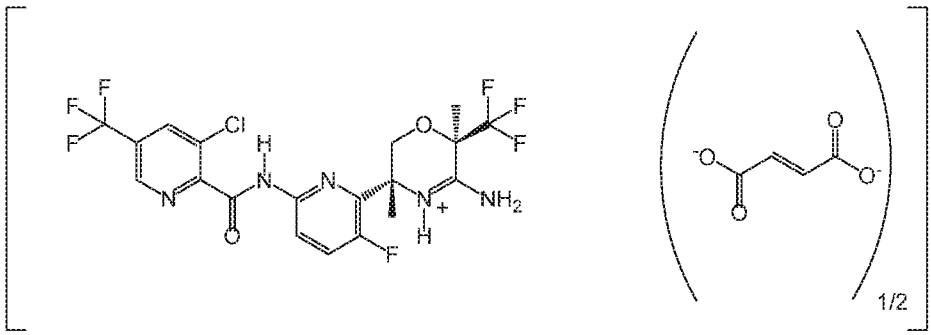
As used herein, the term "salt" includes both hydrated and anhydrous salt forms and all stoichiometric ratios of the base of Compound 1 to its salt counterion or to molecules of water if a hydrated salt form.

As used herein, the terms “hemifumarate”, “hemisuccinate”, or “hemitartrate” salt of Compound 1 refers to a salt having a stoichiometric ratio of two molecules of Compound 1 to one molecule of fumarate, succinate, or tartrate counterion, respectively. The terms “hemifumarate”, “hemisuccinate”, or “hemitartrate” salt of Compound 1 include hydrated salt forms, for example, hemifumarate hemihydrate, hemisuccinate hemihydrate and hemitartrate hemihydrate salt forms. The term “hemihydrate” refers to a hydrated form of a Compound 1 salt having a stoichiometric ratio of two molecules of Compound 1 to one molecule of water. The hemifumarate, hemisuccinate and hemitartrate salts of Compound 1 may be represented as shown below.

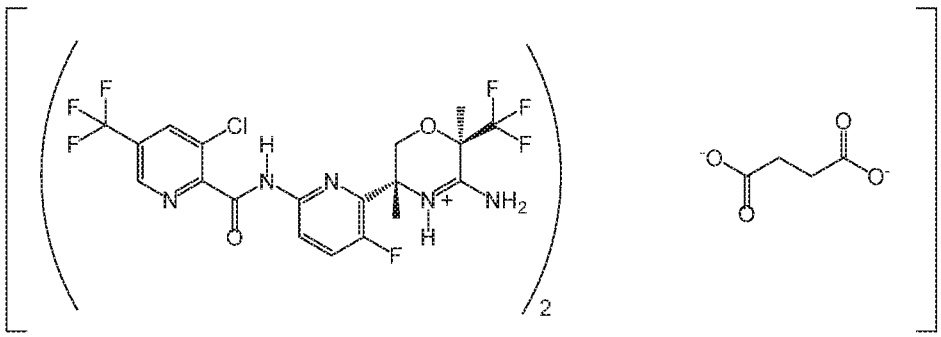
Compound 1 hemifumarate



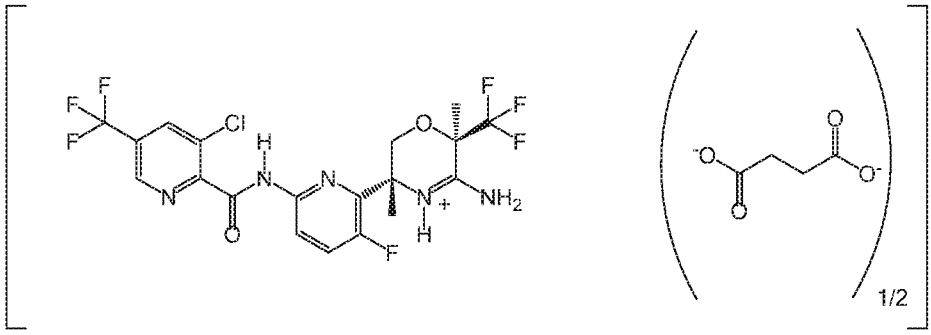
or



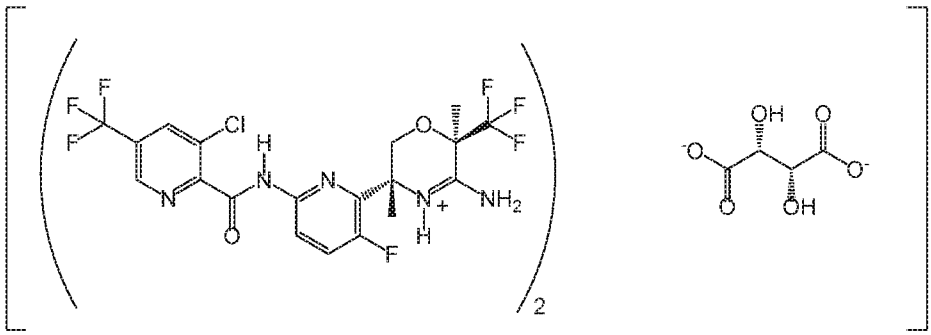
Compound 1 hemisuccinate



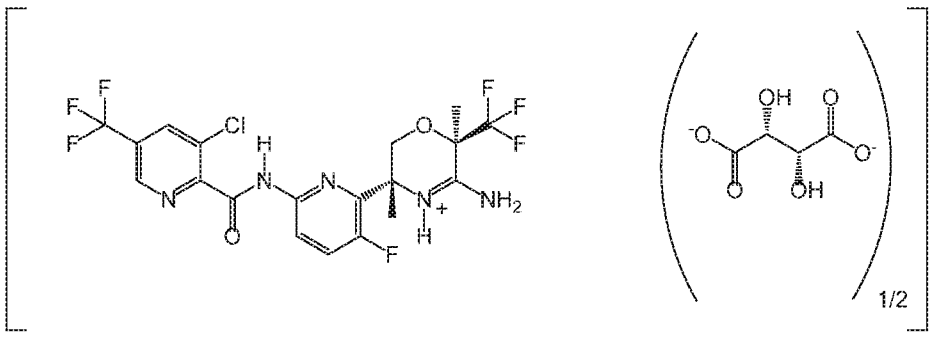
or



Compound 1 hemi-L-tartrate

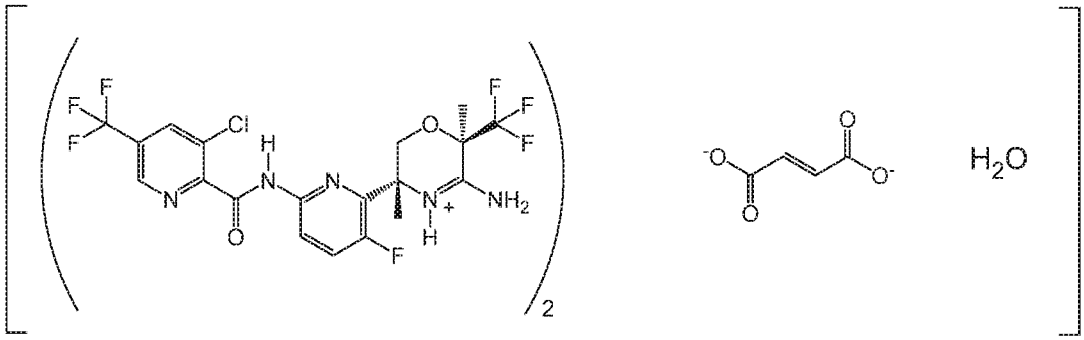


or

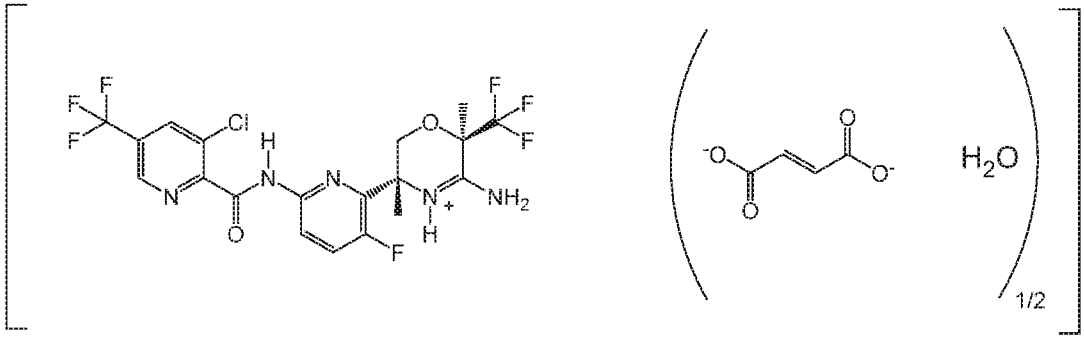


The hemifumarate hemihydrate, hemisuccinate hemihydrate and hemitartrate hemihydrate salts of Compound 1 may be represented as shown below.

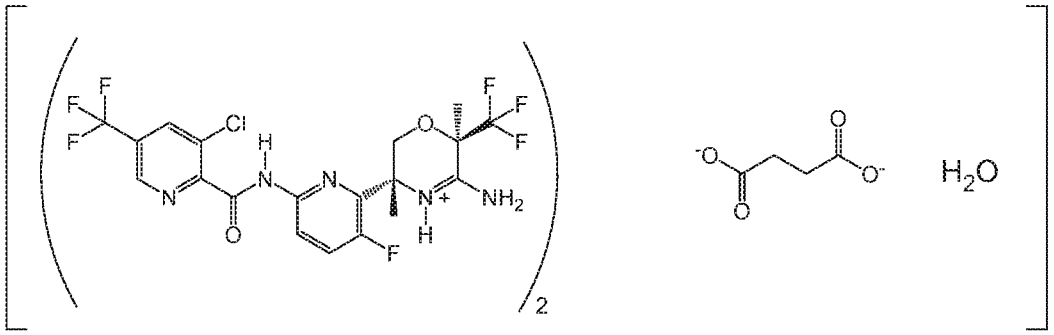
Compound 1 hemifumarate hemihydrate



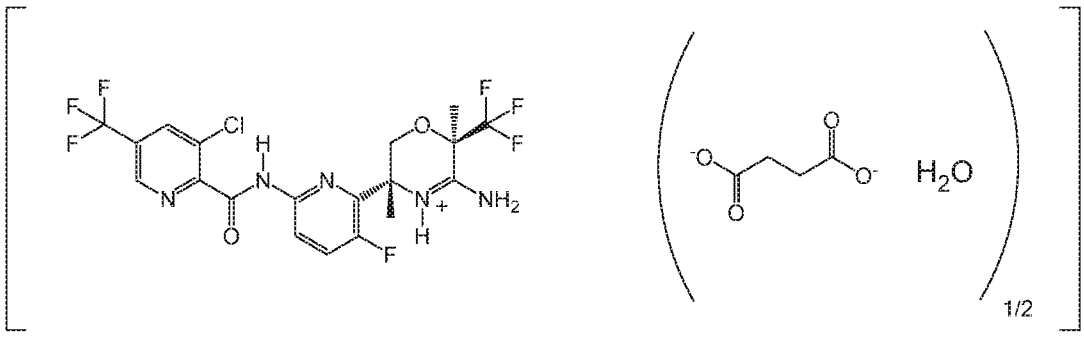
or



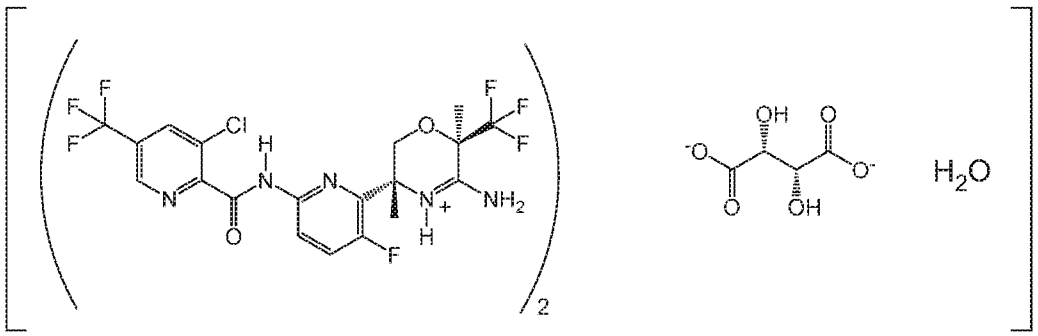
Compound 1 hemisuccinate hemihydrate



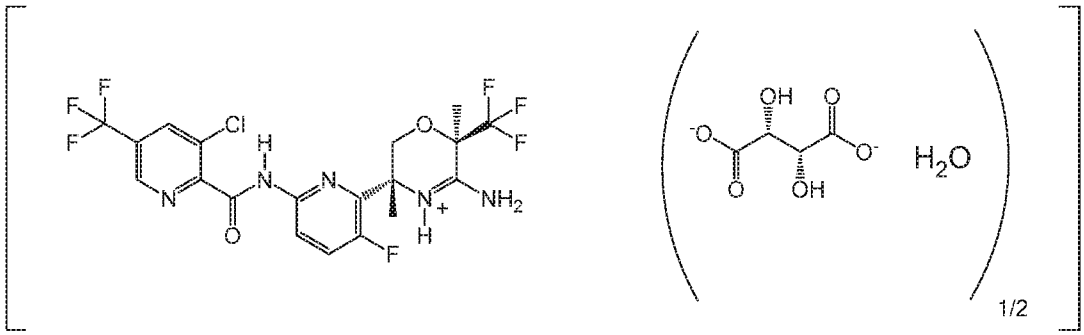
or



Compound 1 hemi-L-tartrate hemihydrate



or



The hemifumarate hemihydrate, hemisuccinate hemihydrate, and hemi-L-tartrate hemihydrate salts of Compound 1 are referred to herein as:

N-(6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide hemifumarate hemihydrate;

N-(6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide hemisuccinate hemihydrate; and

N-(6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide hemi-L-tartrate hemihydrate;

respectively. In accordance with IUPAC recommendations, the foregoing salts may also be referred to as:

(2*E*)-But-2-enedioic acid—*N*-{6-[(3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl]-5-fluoropyridin-2-yl}-3-chloro-5-(trifluoromethyl)pyridine-2-carboxamide—water (1/2/1);

Butanedioic acid—*N*-{6-[(3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl]-5-fluoropyridin-2-yl}-3-chloro-5-(trifluoromethyl)pyridine-2-carboxamide—water (1/2/1); and

(2*R*,3*R*)-2,3-Dihydroxybutanedioic acid—*N*-{6-[(3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl]-5-fluoropyridin-2-yl}-3-chloro-5-(trifluoromethyl)pyridine-2-carboxamide—water (1/2/1);

respectively, and the different naming formats of the Compound 1 salts may be used interchangeably.

As used herein, the term "tartrate salt" includes salts of Compound 1 derived from all possible stereoisomers of tartaric acid, and encompasses: 2*S*,3*S*-tartaric acid (D-tartaric acid); 2*R*,3*R*-tartaric acid (L-tartaric acid); 2*S*,3*R*-tartaric acid tartaric acid (Meso-tartaric acid); racemic mixtures of 2*S*,3*S*-tartaric acid and 2*R*,3*R*-tartaric acid; and mixtures of 2*S*,3*S*-tartaric acid, 2*R*,3*R*-tartaric acid and 2*S*,3*R*-tartaric acid. In one embodiment, the tartrate salt of Compound 1 is 2*S*,3*S*-tartaric acid. In another embodiment, the tartrate salt of Compound 1 is 2*R*,3*R*-tartaric acid.

The term "substantially pure," when used in reference to crystalline fumarate, succinate and tartrate salt forms of *N*-(6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide, means having a purity greater than 90 weight %, including greater than 90, 91, 92, 93, 94, 95, 96, 97, 98, and 99 weight %, and also including equal to about 100 weight % of *N*-(6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide, based on the weight of the compound in its salt form.

As used herein, the term "Aerosil 200 PH" refers to AEROSIL® 200 Pharma grade, a high purity amorphous anhydrous colloidal silicon dioxide used as a pharmaceutical excipient.

The term "substantially the same" with reference to X-ray diffraction patterns and peak positions means that typical peak position and intensity variability are taken into account. For example, one skilled in the art will appreciate that the peak positions (2Θ) will show some inter-apparatus variability, typically as much as 0.2°. X-ray powder diffraction analysis is typically carried out at room temperature, i.e. between 20 and 30 ºC. Further, one skilled in the art will appreciate that relative peak intensities will show inter-apparatus variability as well as variability due to degree of crystallinity, preferred orientation, prepared sample surface, and other factors known to those skilled in the art, and should be taken as a qualitative measure only. One of ordinary skill in the art will also appreciate that an X-ray

diffraction pattern may be obtained with a measurement error that is dependent upon the measurement conditions employed. In particular, it is generally known that intensities in an X-ray diffraction pattern may fluctuate depending upon measurement conditions employed. It should be further understood that relative intensities may also vary depending upon experimental conditions and, accordingly, the exact order of intensity should not be taken into account. Additionally, a measurement error of diffraction angle for a conventional X-ray diffraction pattern is typically about 5% or less, and such degree of measurement error should be taken into account as pertaining to the aforementioned diffraction angles. Consequently, it is to be understood that the crystal form of the instant invention is not limited to the crystal form that provides an X-ray diffraction pattern completely identical to the X-ray diffraction patterns depicted in the accompanying Figures 4, 5, 7, 8, 10 and 11 disclosed herein. Any crystal forms that provide X- ray diffraction patterns substantially identical to that disclosed in the accompanying Figures 4, 5, 7, 8, 10 and 11 fall within the scope of the present invention. The ability to ascertain substantial identities of X-ray diffraction patterns is within the purview of one of ordinary skill in the art. An expression referring to a crystalline form of Compound 1 having "an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure X" may be interchanged with an expression referring to a crystalline form of Compound 1 having "an X-ray powder diffraction pattern characterised by the representative X-ray powder diffraction pattern shown in Figure X".

As used herein, the term "about X ºC", in the context of the endotherm temperature as measured by DSC analysis, means within a range of +/- 5 ºC of temperature X, more particularly within a range of +/- 2.5 ºC of temperature X.

As used herein, the term "Alzheimer's disease" or "AD" encompasses both preclinical and clinical Alzheimer's disease unless the context makes clear that either only preclinical Alzheimer's disease or only clinical Alzheimer's disease is intended.

As used herein, the term "treatment of Alzheimer's disease" refers to the administration of Compound 1 of the present invention to a patient in order to ameliorate at least one of the symptoms of Alzheimer's disease.

As used herein, the term "prevention of Alzheimer's disease" refers to the prophylactic treatment of AD; or delaying the onset or progression of AD. For example, the onset or progression of AD is delayed for at least 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 years. In one embodiment, "prevention of Alzheimer's disease" refers to the prophylactic treatment of preclinical AD; or delaying the onset or progression of preclinical AD. In a further embodiment, the onset or progression of preclinical AD is delayed for at least 0.5, 1, 2, 3, 4,

5, 6, 7, 8, 9, or 10 years. In another embodiment, "prevention of Alzheimer's disease" refers to the prophylactic treatment of clinical AD; or delaying the onset or progression of clinical AD. In a further embodiment, the onset or progression of clinical AD is delayed for at least 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 years.

As used herein, the term "clinical Alzheimer's disease" or "clinical AD" encompasses both Mild Cognitive Impairment (MCI) due to AD and dementia due to AD, unless the context makes clear that either only MCI due to AD or dementia due to AD is intended. The European Medicines Agency (EMA) in its 'Draft guidelines on the clinical investigation of medicines for the treatment of AD and other dementias' (EMA/Committee for Medicinal Products for Human Use (CHMP)/539931/2014) summarises the National Institute on Aging criteria for the diagnosis of MCI due to AD and AD dementia as set out below.

Diagnosis of MCI due to AD requires evidence of intra-individual decline, manifested by:

a) A change in cognition from previously attained levels, as noted by self- or informant report and/or the judgment of a clinician.
b) Impaired cognition in at least one domain (but not necessarily episodic memory) relative to age-and education-matched normative values; impairment in more than one cognitive domain is permissible.
c) Preserved independence in functional abilities, although the criteria also accept 'mild problems' in performing instrumental activities of daily living (IADL) even when this is only with assistance (i.e. rather than insisting on independence, the criteria allow for mild dependence due to functional loss).
d) No dementia, which nominally is a function of c (above).
e) A clinical presentation consistent with the phenotype of AD in the absence of other potentially dementing disorders. Increased diagnostic confidence may be suggested by
    1) Optimal: A positive Aβ biomarker and a positive degeneration biomarker
    2) Less optimal:
        i. A positive Aβ biomarker without a degeneration biomarker
        ii. A positive degeneration biomarker without testing for Aβ biomarkers

Diagnosis of AD dementia requires:

a) The presence of dementia, as determined by intra-individual decline in cognition and function.
b) Insidious onset and progressive cognitive decline.
c) Impairment in two or more cognitive domains; although an amnestic presentation is most common, the criteria allow for diagnosis based on nonamnestic presentations (e.g. impairment in executive function and visuospatial abilities).

d) Absence of prominent features associated with other dementing disorders.

Increased diagnostic confidence may be suggested by the biomarker algorithm discussed in the MCI due to AD section above.

As used herein, the term "preclinical Alzheimer's disease" or "preclinical AD" refers to the presence of *in vivo* molecular biomarkers of AD in the absence of clinical symptoms. The National Institute on Aging and Alzheimer's Association provide a scheme, shown in Table A below, which sets out the different stages of preclinical AD (Sperling et al., 2011).

Table A: Preclinical AD staging categories

Stage	**Description**	**Aβ (PET or CSF)**	**Markers of neuronal injury (tau, FDG, sMRI)**	**Evidence of subtle cognitive change**
Stage 1	Asymptomatic cerebral amyloidosis	Positive	Negative	Negative
Stage 2	Asymptomatic amyloidosis + "downstream" neurodegeneration	Positive	Positive	Negative
Stage 3	Amyloidosis + neuronal injury + subtle cognitive/behavioral decline	Positive	Positive	Positive

sMRI = structural magnetic resonance imaging

As used herein, the term "Cerebral Amyloid Angiopathy" or "CAA" refers to a disease characterised by the accumulation of β-amyloid (Aβ) proteins in the walls of cortical and leptomeningeal blood vessels. CAA is a common cause of vessel wall breakdown and vascular dysfunction in older adults, making it a major contributor to fatal or disabling intracerebral hemorrhages (ICH) as well as ischemic injury and dementia (Gurol ME *et al.*, 2016). As used herein, the term "Cerebral Amyloid Angiopathy" or "CAA" encompasses both CAA-Type 1 and CAA-Type 2 unless the context makes clear that only CAA-Type 1 or CAA-Type 2 is intended.

As used herein, the term "CAA-Type 1" refers to capillary CAA (capCAA) characterised by Aβ protein depositions in the walls of cortical capillaries (Thal *et al.*, 2002).

As used herein, the term "CAA-Type 2" refers to CAA characterised by Aβ protein depositions in the walls of leptomeningeal and cortical vessels, with the exception of cortical capillaries (Thal *et al.*, 2002).

As used herein, the term "treatment of CAA" refers to the administration of Compound 1 of the present invention to a patient in order to slow or arrest the development of CAA or at least one of the clinical symptoms of CAA, for example ICH, ischemic injury, or dementia. The development of CAA may be assessed by measuring the accumulation of Aβ in the

walls of cortical (for example occipital cortex) and leptomeningeal blood vessels using a Positron Emission Tomography (PET) tracer, for example ^{18}F-florbetapir (Gurol ME *et al.*, 2016). Alternatively, the development of CAA may be assessed by monitoring cerebral microbleeds (CMB) as a haemorrhagic marker of CAA (Greenberg SM *et al.*, 2014). Suitable techniques for the monitoring of CMB include, for example, magnetic resonance imaging (MRI) susceptibility-weighted imaging (SWI) and MRI T2*-weighted gradient-recalled echo imaging (GRE), and are described in Cheng AL *et al.*, 2013. In addition, white matter hyperintensities (WMH) occur at much greater volume in patients diagnosed with CAA than in healthy aged individuals or in patients suffering from AD or mild cognitive impairment (MCI) (Greenberg SM *et al.*, 2014). Therefore, CAA development may be monitored by the measurement of WMH volume using MRI (Chen YW *et al.*, 2006). It is expected that the "treatment of CAA" will have the resultant benefit of reducing the likelihood of a cerebral ischemic event in the patient undergoing treatment for CAA. Therefore, in one embodiment of the invention, the term "treatment of CAA" is equivalent to the term "treatment of intracerebral haemorrhage". In another embodiment of the invention, the term "treatment of CAA" is equivalent to the term "treatment of CAA and/or intracerebral haemorrhage". In a further embodiment of the invention, the term "treatment of CAA" is equivalent to the term "treatment of CAA and intracerebral haemorrhage associated therewith".

As used herein, the term "prevention of CAA" refers to the prophylactic treatment of CAA; delaying the onset or progression of CAA; or delaying the onset or progression of at least one of the clinical symptoms of CAA. For example, the onset or progression of CAA is delayed for at least 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 years. In one embodiment of the invention, the term "prevention of CAA" is equivalent to the term "prevention of intracerebral haemorrhage". In another embodiment of the invention, the term "prevention of CAA" is equivalent to the term "prevention of CAA and/or intracerebral haemorrhage". In a further embodiment of the invention, the term "prevention of CAA" is equivalent to the term "prevention of CAA and intracerebral haemorrhage associated therewith".

As used herein, the term "a genetic predisposition for the development of CAA" includes, but is not limited to situations where the genetic predisposition is due to: Down's syndrome; a mutation in the gene for amyloid precursor protein or presenilin-1; or the presence of one or two copies of the *ApoE4* allele.

As used herein, the term "patient" refers to a human subject.

As used herein, a "pharmaceutical composition" comprises Compound 1 of the present invention and at least one pharmaceutically acceptable carrier or excipient, in a unit dose solid form suitable for oral administration (typically a capsule, more particularly a hard gelatin

capsule). A list of pharmaceutically acceptable carriers and excipients can be found in Remington's Pharmaceutical Sciences.

The term "a therapeutically effective amount" refers to an amount of Compound 1 of the present invention that will elicit inhibition of BACE-1 in a patient as evidenced by a reduction in CSF or plasma Aβ 1-40 levels relative to an initial baseline value. Aβ 1-40 levels may be measured using standard immunoassay techniques, for example Meso Scale Discovery (MSD) 96-well MULTI-ARRAY human/rodent (4G8) Aβ40 Ultrasensitive Assay (#K110FTE-3, Meso Scale Discovery, Gaithersburg, USA).

List of abbreviations

Abbreviation	Description
ACN	acetonitrile
APP	amyloid precursor protein
Aβ	beta-amyloid peptide
aq.	aqueous
AUClast	The area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated using the linear trapezoidal rule [mass × time/volume]
AUCinf	The area under the plasma concentration-time curve from time zero to infinity, calculated using the linear trapezoidal rule calculated as AUCinf = AUClast + Clast/Lambda_z, where Clast is the last measurable oncentration and Lambda_z is the elimination rate constant [mass × time/volume]
Aβ40	beta-amyloid peptide 40
BACE-1	beta site APP cleaving enzyme-1
BACE-2	beta site APP cleaving enzyme -2
BACE	beta site APP cleaving enzyme
Boc_2O	di-*tert*-butyl dicarbonate
BuLi or nBuLi	n-butyllithium
C	concentration
CI	confidence interval
conc.	concentrated
Cpd	compound
CSF	cerebrospinal fluid
d	day
DCM	dichloromethane
DDI	drug-drug interaction
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide

Abbreviation	Description
DSC	differential scanning calorimetry
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
eq	equivalent (Molar)
EtOAc	ethyl acetate
g	gram/gravitational acceleration
h, hr	hour(s)
HOAt	1-hydroxy-7-azabenzotriazole
HPLC, LC	high-performance liquid chromatography, liquid chromatography
IPAc	isopropyl acetate
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
LC-MS/MS	tandem mass spectrometry
MeOH	methanol
m	meter
min	minute(s)
ml	milliliter
µl	microliter
µM	micromolar
µmol	micromoles
min	minute
MS	mass spectrometry
MSD	MesoScale Discovery (supplier of immunoassay kits)
MTBE	tert- butyl methyl ether
nM	nanoMolar
nmol	nanomoles
NMR	nuclear magnetic resonance spectrometry
PET	positron emission tomography
pg	picogram
PK	pharmacokinetic
pmol	picomoles
q.d. or QD	quaque die
Rf	retention factor
RH	relative humidity
rpm	revolutions per minute
RT, rt	room temperature
SEM	standard error of the mean
SD	single dose
T	time
TFA	trifluoroacetic acid

Abbreviation	Description
THF	tetrahydrofuran
TLC	thin layer chromatography
Tris	tris-hydroxymethyl(aminomethane) buffer substance
UPLC	ultra performance liquid chromatography
vol	volume
vs	versus
WL	copper Kα radiation wavelength (λ_{Cu} = 1.5406 Å)
wt	weight ratio based on the quantity of starting material
XRPD	x-ray powder diffraction

Examples

The following Examples illustrate and provide comparisons for various aspects of the invention.

Example summary

Example 1 shows how Compound 1 may be prepared and crystallised.

Example 2 describes the XRPD analysis of Compound 1 free Form A.

Example 3 describes the XRPD analysis of micronized Compound 1 in free base form.

Example 4 describes the DSC analysis of Compound 1 free Form A.

Example 5 describes the preparation of Compound 1 in hemifumarate hemihydrate salt form.

Example 6 describes the XRPD analysis of crystalline Compound 1 in hemifumarate hemihydrate salt form.

Example 7 describes the XRPD analysis of micronized Compound 1 in hemifumarate hemihydrate salt form.

Example 8 describes the DSC analysis of Compound 1 in hemifumarate hemihydrate salt form.

Example 9 describes the preparation of Compound 1 in hemisuccinate hemihydrate salt form.

Example 10 describes the XRPD analysis of crystalline Compound 1 in hemisuccinate hemihydrate salt form.

Example 11 describes the XRPD analysis of micronized Compound 1 in hemisuccinate hemihydrate salt form.

Example 12 describes the DSC analysis of Compound 1 in hemisuccinate hemihydrate salt form.

Example 13 describes the preparation of Compound 1 in hemi-L-tartrate hemihydrate salt form.

Example 14 describes the XRPD analysis of crystalline Compound 1 in hemi-L-tartrate hemihydrate salt form.

Example 15 describes the XRPD analysis of micronized Compound 1 in hemi-L-tartrate hemihydrate salt form.

Example 16 describes the DSC analysis of Compound 1 in hemi-L-tartrate hemihydrate salt form.

Example 17 describes the stoichiometric analysis of Compound 1 in fumarate, succinate and tartrate salt form.

Example 18 compares the milling behavior of free base Compound 1 with the hemifumarate hemihydrate, hemisuccinate hemihydrate and hemi-L-tartrate hemihydrate salt forms.

Example 19 describes the preparation of further alternative salt forms of Compound 1.

Example 20 compares the bulk stability of Compound 1 in free form with alternative salt forms and in the presence of sodium stearyl fumarate.

Example 21 compares the bulk stability of Compound 1 in free form with the hemifumarate hemihydrate, hemisuccinate hemihydrate and hemi-L-tartrate hemihydrate salt forms in the presence of various pharmaceutical excipients.

Example 22 describes an in human study to assess free base Compound 1 PK when given administered in combination with a strong CYP3A4 inhibitor or inducer.

Detailed Examples

Example 1: Preparation of free base Compound 1

The preparation of Compound 1 is described in WO 2012/095469 A1 (Example 34). Compound 1 may also be prepared as described below.

NMR Methodology

Proton spectra are recorded on a Bruker 400 MHz ultrashield spectrometer unless otherwise noted. Chemical shifts are reported in ppm relative to methanol (δ 3.31), dimethyl sulfoxide (δ 2.50), or chloroform (δ 7.29). A small amount of the dry sample (2-5 mg) is dissolved in an appropriate deuterated solvent (0.7 mL). The shimming is automated and the spectra obtained in accordance with procedures well known to the person of ordinary skill in the art.

General chromatography information

HPLC method H1 (Rt_{H1}):

HPLC-column dimensions:	3.0 x 30 mm
HPLC-column type:	Zorbax SB-C18, 1.8 µm
HPLC-eluent:	A) water + 0.05 Vol.-% TFA; B) ACN + 0.05 Vol.-% TFA
HPLC-gradient:	30-100 % B in 3.25 min, flow = 0.7 ml / min

LCMS method H2 (Rt_{H2}):

HPLC-column dimensions:	3.0 x 30 mm
HPLC-column type:	Zorbax SB-C18, 1.8 µm
HPLC-eluent:	A) water + 0.05 Vol.-% TFA, B) ACN + 0.05 Vol.-% TFA
HPLC-gradient:	10-100 % B in 3.25 min, flow = 0.7 ml / min

UPLCMS method H3 (Rt_{H3}):

HPLC-column dimensions:	2.1 x 50 mm
HPLC-column type:	Acquity UPLC HSS T3, 1.8 µm
HPLC-eluent:	A) water + 0.05 Vol.-% formic acid + 3.75 mM ammonium acetate B) ACN + 0.04 Vol.-% formic acid
HPLC-gradient:	2-98 % B in 1.4 min, 98% B 0.75 min, flow = 1.2 ml / min
HPLC-column temperature:	50 °C

LCMS method H4 (Rt_{H4}):

HPLC-column dimensions:	3.0 x 30 mm
HPLC-column type:	Zorbax SB-C18, 1.8 µm
HPLC-eluent:	A) water + 0.05 Vol.-% TFA; B) ACN + 0.05 Vol.-% TFA
HPLC-gradient:	70 - 100 % B in 3.25 min, flow = 0.7 ml / min

LCMS method H5 (Rt_{H5}):

HPLC-column dimensions:	3.0 x 30 mm
HPLC-column type:	Zorbax SB-C18, 1.8 µm

HPLC-eluent:	A) water + 0.05 Vol.-% TFA; B) ACN + 0.05 Vol.-% TFA
HPLC-gradient:	80 - 100 % B in 3.25 min, flow = 0.7 ml / min

LCMS method H6 (Rt_{H6}):

HPLC-column dimensions:	3.0 x 30 mm
HPLC-column type:	Zorbax SB-C18, 1.8 µm
HPLC-eluent:	A) water + 0.05 Vol.-% TFA; B) ACN + 0.05 Vol.-% TFA
HPLC-gradient:	40 - 100 % B in 3.25 min, flow = 0.7 ml / min

a) 2-Bromo-5-fluoro-4-triethylsilanyl-pyridine

A solution of diisopropylamine (25.3 g, 250 mmol) in 370 ml THF was cooled with a dry-ice acetone bath at -75 °C. BuLi (100 ml, 250 mmol, 2.5 M in hexanes) was added dropwise while maintaining the temperature below -50 °C. After the temperature of the mixture had reached -75 °C again, a solution of 2-bromo-5-fluoropyridine (36.7 g, 208 mmol) in 45 ml THF was added dropwise. The mixture was stirred for 1 h at -75 °C. Triethylchlorosilane (39.2 g, 260 mmol) was added quickly. The temperature stayed below -50 °C. The cooling bath was removed and the reaction mixture was allowed to warm to -15 °C, poured onto aq. NH_4Cl (10%). TBME was added and the layers were separated. The organic layer was washed with brine, dried with $MgSO_4.H_2O$, filtered and evaporated to give a brown liquid which was distilled at 0.5 mm Hg to yield the title compound as a slightly yellow liquid (b.p. 105-111 °C). HPLC: Rt_{H4} = 2.284 min; ESIMS: 290, 292 [$(M+H)^+$, 1Br]; ^{1}H-NMR (400 MHz, $CDCl_3$): 8.14 (s, 1H), 7.40 (d, 1H), 1.00-0.82 (m, 15H).

b) 1-(6-Bromo-3-fluoro-4-triethylsilanyl-pyridin-2-yl)-ethanone

A solution of diisopropylamine (25.4 g, 250 mmol) in 500 ml THF was cooled to -75 °C. BuLi (100 ml, 250 mmol, 2.5 M in hexanes) was added dropwise while maintaining the temperature below -50 °C. After the reaction temperature had reached -75 °C again, a solution of 2-bromo-5-fluoro-4-triethylsilanyl-pyridine (56.04 g, 193 mmol) in 60 ml THF was added dropwise. The mixture was stirred in a dry ice bath for 70 minutes. N,N-dimethylacetamide (21.87 g, 250 mmol) was added quickly, the reaction temperature rose to -57 °C. The reaction mixture was stirred in a dry ice bath for 15 min and then allowed to warm to -40 °C. It was poured on a mixture of 2M aq. HCl (250 ml, 500 mmol), 250 ml water and 100 ml brine. The mixture was extracted with TBME, washed with brine, dried over $MgSO_4.H_2O$, filtered and evaporated to give a yellow oil which was purified on a silica gel column by eluting with hexane/0-5% TBME to yield 58.5 g of the title compound as a yellow liquid. TLC (Hex/TBME 99/1): R_f = 0.25; HPLC: Rt_{H4} = 1.921 min; ESIMS: 332, 334 [$(M+H)^+$, 1Br]; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.57 (d, 1H), 2.68 (s, 3H), 1.00-0.84 (m, 15H).

c) (*S*)-2-(6-Bromo-3-fluoro-4-triethylsilanyl-pyridin-2-yl)-2-trimethylsilanyloxy-propionitrile

At first, the catalyst solution was prepared by dissolving water (54 mg, 3.00 mmol) in 100 ml dry DCM (≦0.001% water). This wet DCM (44 ml, 1.32 mmol water content) was added to a well stirred solution of titanium(IV) butoxide (500 mg, 1.47 mmol) in 20 ml dry DCM. The resulting clear solution was refluxed for 1 h. This solution was then cooled to rt and 2,4-di-tert-butyl-6-{[(E)-(S)-1-hydroxymethyl-2-methyl-propylimino]-methyl}-phenol [CAS 155052-31-6] (469 mg, 1.47 mmol) was added. The resulting yellow solution was stirred at rt for 1 h. This catalyst solution (0.023 M, 46.6 ml, 1.07 mmol) was added to a solution of 1-(6-bromo-3-fluoro-4-triethylsilanyl-pyridin-2-yl)-ethanone (35.53 g, 107 mmol) and trimethylsilyl cyanide (12.73 g, 128 mmol) in 223 ml dry DCM. The mixture was stirred for 2 days and evaporated to give 47 g of the crude title compound as an orange oil. HPLC: Rt_{H5} = 2.773 min; ESIMS: 431, 433 [$(M+H)^+$, 1Br]; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.46 (d, 1H), 2.04 (s, 3H), 1.00 (t, 9H), 1.03-0.87 (m, 15H), 0.20 (s, 9H).

d) (*R*)-1-Amino-2-(6-bromo-3-fluoro-4-triethylsilanyl-pyridin-2-yl)-propan-2-ol hydrochloride

Borane dimethyl sulfide complex (16.55 g, 218 mmol) was added to a solution of crude (*S*)-2-(6-bromo-3-fluoro-4-triethylsilanyl-pyridin-2-yl)-2-trimethylsilanyloxy-propionitrile (47 g, 109 mmol) in 470 ml THF. The mixture was refluxed for 2 h. The heating bath was removed and the reaction mixture was quenched by careful and dropwise addition of MeOH. After the evolution of gas had ceased, aq. 6M HCl (23.6 ml, 142 mmol) was added slowly. The resulting solution was evaporated and the residue was dissolved in MeOH and evaporated (twice) to yield 44.5 g of a yellow foam, pure enough for further reactions. HPLC: Rt_{H1} = 2.617 min; ESIMS: 363, 365 [$(M+H)^+$, 1Br]; ^{1}H-NMR (400 MHz, $CDCl_3$): 7.93 (s, br, 3H), 7.53 (d, 1H), 6.11 (s, br, 1H), 3.36-3.27 (m, 1H), 3.18-3.09 (m, 1H), 1.53 (s, 3H), 0.99-0.81 (m, 15H).

e) (*R*)-N-(2-(6-bromo-3-fluoro-4-(triethylsilyl)pyridin-2-yl)-2-hydroxypropyl)-4-nitrobenzenesulfonamide

To a solution of crude (*R*)-1-amino-2-(6-bromo-3-fluoro-4-triethylsilanyl-pyridin-2-yl)-propan-2-ol hydrochloride (43.5 g, 109 mmol) in 335 ml THF was added a solution of $NaHCO_3$ (21.02 g, 250 mmol) in 500 ml water. The mixture was cooled to 0-5 °C and a solution of 4-nitrobenzenesulfonyl chloride (26.5 g, 120 mmol) in 100 ml THF was added in a dropwise. The resulting emulsion was stirred overnight while allowing the temperature to reach rt. The

mixture was extracted with TBME. The organic layer was dried with $MgSO_4.H_2O$, filtered and evaporated to give an orange resin which was purified on a silca gel column by eluting with Hexanes/10-20% EtOAc to yield 37.56 g of the title compound as a yellow resin. TLC (Hex/EtOAc 3/1): R_f = 0.34; HPLC: Rt_{H4} = 1.678 min; ESIMS: 548, 550 [$(M+H)^+$, 1Br]; ^{1}H-NMR (400 MHz, DMSO-d_6): 8.40 (d, 2H), 8.06 (t, 1H), 7.97 (d, 2H), 7.45 (d, 1H), 5.42 (s, 1H), 3.23 (d, 2H), 1.44 (s, 3H) 0.97-0.81 (m, 15H); Chiral HPLC (Chiralpak AD-H 1213, UV 210 nm): 90% ee.

f) 6-Bromo-3-fluoro-2-[(*S*)-2-methyl-1-(4-nitro-benzenesulfonyl)-aziridin-2-yl]-4-triethylsilanyl-pyridine

A solution of triphenylphosphine (21.55 g, 82 mmol) and (*R*)-N-(2-(6-bromo-3-fluoro-4-(triethylsilyl)pyridin-2-yl)-2-hydroxypropyl)-4-nitrobenzenesulfonamide (37.56 g, 69 mmol) in 510 ml THF was cooled to 4 °C. A solution of diethyl azodicarboxylate in toluene (40% by weight, 38.8 g, 89 mmol) was added in a dropwise while maintaining the temperature below 10 °C. The cooling bath was removed and the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with approx. 1000 ml toluene and THF was removed by evaporation at the rotavap. The resulting toluene solution of crude product was pre-purified on a silca gel column by eluting with hexanes/5-17% EtOAc. Purest fractions were combined, evaporated and crystallized from TBME/hexane to yield 29.2 g of the title compound as white crystals. HPLC: Rt_{H4} = 2.546 min; ESIMS: 530, 532 [$(M+H)^+$, 1Br]; ^{1}H-NMR (400 MHz, $CDCl_3$): 8.40 (d, 2H), 8.19 (d, 2H), 7.39 (d, 1H), 3.14 (s, 1H), 3.02 (s, 1H), 2.01 (s, 3H) 1.03 – 0.83 (m, 15H); α[D] -35.7° (c = 0.97, DCM).

g) 6-Bromo-3-fluoro-2-[(*S*)-2-methyl-1-(4-nitro-benzenesulfonyl)-aziridin-2-yl]-pyridine

Potassium fluoride (1.1 g, 18.85 mmol) was added to a solution of 6-bromo-3-fluoro-2-[(*S*)-2-methyl-1-(4-nitro-benzenesulfonyl)-aziridin-2-yl]-4-triethylsilanyl-pyridine (5 g, 9.43 mmol) and AcOH (1.13 g, 9.43 mmol) in 25 ml THF. DMF (35 ml) was added and the suspension was stirred for 1 h at rt. The reaction mixture was poured onto a mixture of sat. aq. $NaHCO_3$ and TBME. The layers were separated and washed with brine and TBME. The combined organic layers were dried over $MgSO_4.H_2O$, filtered and evaporated to give a yellow oil which was crystallized from TBME/hexane to yield 3.45 g of the title compound as white crystals. HPLC: Rt_{H6} = 2.612 min; ESIMS: 416, 418 [$(M+H)^+$, 1Br]; ^{1}H-NMR (400 MHz, $CDCl_3$): 8.41 (d, 2H), 8.19 (d, 2H), 7.48 (dd, 1H), 7.35 (t, 1H), 3.14 (s, 1H), 3.03 (s, 1H), 2.04 (s, 3H); α[D] -35.7° (c = 0.89, DCM).

h) (*R*)-2-[(*R*)-2-(6-Bromo-3-fluoro-pyridin-2-yl)-2-(4-nitro-benzenesulfonylamino)-propoxy]-3,3,3-trifluoro-2-methyl-propionic acid ethyl ester

A solution of (*R*)-3,3,3-trifluoro-2-hydroxy-2-methyl-propionic acid ethyl ester (11.93 g, 64.1 mmol) in DMF (158 ml) was evacuated/flushed with nitrogen twice. A solution of KOtBu (6.21 g, 55.5 mmol) in DMF (17 ml) was added dropwise while maintaining a reaction temperature of ca 25 °C using cooling with a water bath. After 15 min solid 6-bromo-3-fluoro-2-[(S)-2-methyl-1-(4-nitro-benzenesulfonyl)-aziridin-2-yl]-pyridine (17.78 g, 42.7 mmol) was added and stirring was continued for 3 h. The reaction mixture was poured onto a mixture of 1M HCl (56 ml), brine and TBME. The layers were separated, washed with brine and TBME. The combined organic layers were dried over $MgSO_4.H_2O$, filtered and evaporated. The crude reaction product was purified via chromatography on silica gel (hexanes/25-33% TBME) to yield 16.93 g of the title compound as a yellow resin that was contaminated with an isomeric side-product (ratio 70:30 by ^{1}H-NMR).

HPLC: Rt_{H6} = 2.380 min; ESIMS: 602, 604 [$(M+H)^+$, 1Br]; ^{1}H-NMR (400 MHz, $CDCl_3$): 8.32 (d, 2H), 8.07 (d, 2H), 7.46 – 7.41 (m, 1H), 7.30 – 7.23 (m, 1H), 6.92 (s, 1H), 3.39 – 4.30 (m, 2H), 3.95 (d, 1H), 3.84 (d, 1H), 1.68 (s, 3H), 1.56 (s, 3H), 1.40-1.34 (m, 3H) + isomeric side-product.

i) (*R*)-2-[(*R*)-2-(6-Bromo-3-fluoro-pyridin-2-yl)-2-(4-nitro-benzenesulfonylamino)-propoxy]-3,3,3-trifluoro-2-methyl-propionamide

A solution of (*R*)-2-[(*R*)-2-(6-bromo-3-fluoro-pyridin-2-yl)-2-(4-nitro-benzenesulfonylamino)-propoxy]-3,3,3-trifluoro-2-methyl-propionic acid ethyl ester (16.93 g, 28.1 mmol) in a NH_3/MeOH (7M, 482 ml) was stirred at 50 °C in a sealed vessel for 26 h. The reaction mixture was evaporated and the residue was crystallized from DCM to yield 9.11 g of the title compound as colorless crystals.

HPLC: Rt_{H6} = 2.422 min; ESIMS: 573, 575 [$(M+H)^+$, 1Br]; ^{1}H-NMR (400 MHz, $CDCl_3$): 8.33 (d, 2H), 8.06 (d, 2H), 7.42 (dd, 1H), 7.30 – 7.26 (m, 1H), 7.17 (s, br, 1H), 6.41 (s, 1H), 5.57 (s, br, 1H), 4.15 (m, 2H), 1.68 (s, 3H), 1.65 (s, 3H).

j) N-[(*R*)-1-(6-Bromo-3-fluoro-pyridin-2-yl)-2-((R)-1-cyano-2,2,2-trifluoro-1-methyl-ethoxy)-1-methyl-ethyl]-4-nitro-benzenesulfonamide

A suspension of (*R*)-2-[(*R*)-2-(6-bromo-3-fluoro-pyridin-2-yl)-2-(4-nitro-benzenesulfonylamino)-propoxy]-3,3,3-trifluoro-2-methyl-propionamide (8.43 g, 14.70 mmol) and triethylamine (5.12 ml, 36.8 mmol) in 85 ml DCM was cooled to 0-5 °C. Trifluoroacetic anhydride (2.49 ml, 17.64 mmol) was added dropwise over 30 min. Additional triethylamine (1.54 ml, 11.07 mmol) and trifluoroacetic anhydride (0.75 ml, 5.29 mmol) were added to complete the reaction. The reaction mixture was quenched by addition of 14 ml aqueous ammonia (25%) and 14 ml water. The emulsion was stirred for 15 min, more water and DCM were added and the layers were separated. The organic layer was dried with $MgSO_4$ H_2O,

filtered and evaporated. Purification by column chromatography on a silica gel (hexanes/10-25% EtOAc) gave 8.09 g of the title compound as a yellow resin.

HPLC: Rt_{H6} = 3.120 min; ESIMS: 555, 557 [$(M+H)^+$, 1Br]; ^{1}H-NMR (400 MHz, $CDCl_3$): 8.35 (d, 2H), 8.11 (d, 2H), 7.50 (dd, 1H), 7.32 (dd, 1H), 6.78 (s, 1H), 4.39 (d 1H), 4.22 (d, 1H), 1.68 (s, 6H).

k) (2*R*,5*R*)-5-(6-Bromo-3-fluoro-pyridin-2-yl)-2,5-dimethyl-2-trifluoromethyl-5,6-dihydro-2H-[1,4]oxazin-3-ylamine

A solution of N-[(*R*)-1-(6-bromo-3-fluoro-pyridin-2-yl)-2-((R)-1-cyano-2,2,2-trifluoro-1-methyl-ethoxy)-1-methyl-ethyl]-4-nitro-benzenesulfonamide (9.18 g, 16.53 mmol) and N-acetylcysteine (5.40 g, 33.10 mmol) in 92 ml ethanol was evacuated and flushed with nitrogen. K_2CO_3 (4.57 g, 33.1 mmol) was added and the mixture was stirred at 80 °C for 3 days. The reaction mixture was concentrated in vacuo to about 1/4 of the original volume and partitioned between water and TBME. The organic layer was washed with 10% aq. K_2CO_3 solution, dried over Na_2SO_4, filtered and evaporated to give a yellow oil. Column chromatography on silica (hexanes/14-50% (EtOAc:MeOH 95:5)) gave 4.55 g of the title compound as an off-white solid.

HPLC: Rt_{H2} = 2.741 min; ESIMS: 370, 372 [$(M+H)^+$, 1Br]; ^{1}H-NMR (400 MHz, DMSO-d_6): 7.71 – 7.62 (m, 2H), 5.97 (s, br, 2H), 4.02 (d 1H), 3.70 (d, 1H), 1.51 (s, 3H), 1.47 (s, 3H).

l) (2*R*, 5*R*)-5-(6-Amino-3-fluoro-pyridin-2-yl)-2,5-dimethyl-2-trifluoromethyl-5,6-dihydro-2H-[1,4]oxazin-3-yl amine

A glass/stainless steel autoclave was purged with nitrogen, Cu_2O (0.464 g, 3.24 mmol), ammonia (101 ml, 25%, aq., 648 mmol, 30 equivalents) and (2*R*,5*R*)-5-(6-Bromo-3-fluoro-pyridin-2-yl)-2,5-dimethyl-2-trifluoromethyl-5,6-dihydro-2H-[1,4]oxazin-3-ylamine (8 g, 21.6 mmol) in ethylene glycol (130 ml) was added. The autoclave was closed and the suspension heated up to 60 °C and the solution was stirred for about 48 hours (max. pressure 0.7 bar, inside temperature 59-60 °C). The reaction mixture was diluted with ethyl acetate and water. The organic phase was washed with water and 4 times with 12% aq. ammonia and finally with brine, dried over sodium sulfate, filtered and evaporated. The crude product (7 g, containing some ethylen glycol, quantitative yield) was used in the next step without further purification.

HPLC: Rt_{H3} = 0.60 min; ESIMS: 307 [$(M+H)^+$].

m) [(2*R*, 5*R*)-5-(6-Amino-3-fluoro-pyridin-2-yl)-2,5-dimethyl-2-trifluoromethyl-5,6-dihydro-2H-[1,4]oxazin-3-yl]-carbamic acid tert-butyl ester

A solution of (2*R*, 5*R*)-5-(6-amino-3-fluoro-pyridin-2-yl)-2,5-dimethyl-2-trifluoromethyl-5,6-dihydro-2H-[1,4]oxazin-3-yl amine (6.62 g, 21.6 mmol), Boc_2O (4.72 g, 21.6 mmol) and Hünig's base (5.66 ml, 32.4 mmol) in dichloromethane (185 ml) was stirred at rt for 18 hours. The reaction mixture was washed with sat. aq. $NaHCO_3$ and brine. The aqueous layers were back extracted with dichloromethane and the combined organic layers were dried over sodium sulfate, filtered and evaporated to give a light green solid (14 g). The crude product was chromatographed over silicagel (cyclohexane:ethyl acetate 95:5 to 60:40) to afford 7.68 g of the title compound.

TLC (cyclohexane:ethyl acetate 3:1): R_f = 0.21; HPLC: Rt_{H3} = 1.14 min; ESIMS: 408 [$(M+H)^+$]; ^{1}H-NMR (400 MHz, CDCl3): 11.47 (br. s, 1H), 7.23 (dd, *J*=10.42, 8.78 Hz, 1H), 6.45 (dd, *J*=8.78, 2.64 Hz, 1H), 4.50 (br. s, 2H), 4.32 (d, *J*=2.38 Hz, 1H), 4.10 (d, *J*=11.80 Hz, 1H), 1.69 (s, 3H, CH3), 1.65 (s, 3H, CH3), 1.55 (s, 9H).

n) ((2*R*, 5*R*)-5-{6-[(3-Chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-3-fluoro-pyridin-2-yl}-2,5-dimethyl-2-trifluoromethyl-5,6-dihydro-2H-[1,4]oxazin-3-yl)-carbamic acid tert-butyl ester

A mixture of [(2*R*, 5*R*)-5-(6-amino-3-fluoro-pyridin-2-yl)-2,5-dimethyl-2-trifluoromethyl-5,6-dihydro-2H-[1,4]oxazin-3-yl]-carbamic acid tert-butyl ester (3.3 g, 8.12 mmol), 3-chloro-5-trifluoromethylpicolinic acid (2.2 g, 9.74 mmol), HOAt (1.99 g, 14.62 mmol) and EDC hydrochloride (2.33 g, 12.18 mmol) was stirred in DMF (81 ml) at rt for 48 hours. The reaction mixture was diluted with ethyl acetate and washed with water and brine, dried over sodium sulfate, filtered and evaporated. The crude product (12 g) was chromatographed over silicagel (cyclohexane to cyclohexane:ethyl acetate 1:1) to yield 5.2 g of the title compound.

TLC (silica, cyclohexane:ethyl acetate 3:1): R_f=0.47; HPLC: Rt_{H3} = 1.40 min; ESIMS: 615, 616 [$(M+H)^+$, 1Cl]; ^{1}H-NMR (400 MHz, $CDCl_3$): 11.68 (s, 1H), 10.41 (s, 1H), 8.81 (dd, *J*=1.82, 0.69 Hz, 1 H), 8.45 (dd, *J*=8.91, 3.14 Hz, 1 H), 8.19 (dd, *J*=1.88, 0.63 Hz, 1 H), 7.59 (dd, *J*=9.79, 9.16
Hz, 1 H), 4.38 (d, *J*=2.13 Hz, 1 H), 4.18 (d, *J*=11.80 Hz, 1 H), 1.75 (s, 3H), 1.62 (s, 3H), 1.60 (s, 9H).

o) 3-Chloro-5-trifluoromethyl-pyridine-2-carboxylic acid [6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-trifluoromethyl-3,6-dihydro-2H-[1,4]oxazin-3-yl)-5-fluoro-pyridin-2-yl]-amide

A mixture of ((2*R*, 5*R*)-5-{6-[3-chloro-5-trifluoromethyl-pyridine-2-carbonyl)-amino]-3-fluoro-pyridin-2-yl}-2,5-dimethyl-2-trifluoromethyl-5,6-dihydro-2H-[1,4]oxazin-3-yl)-carbamic acid tert-butyl ester (4.99 g, 8.13 mmol) and TFA (6.26 ml, 81 mmol) in dichloromethane (81 ml)

was stirred at rt for 18 hours. The solvent was evaporated and the residue diluted with a suitabable organic solvent, such as ethyl acetate and aq. ammonia. Ice was added and the organic phase was washed with water and brine, dried over sodium sulfate, filtered and evaporated to yield 3.78 g of the title compound.

HPLC: Rt_{H3} = 0.87 min; ESIMS: 514, 516 [$(M+H)^+$, 1Cl]; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.11 (s, 1H), 9.06 (s, 1H), 8.69 (s, 1H), 8.13 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.80 – 7.68 (m, 1H), 5.88 (br. s, 2H), 4.12 (d, *J* = 11.5 Hz, 1H), 3.72 (d, *J* = 11.4 Hz, 1H), 1.51 (s, 3H), 1.49 (s, 3H).

p) Crystallisation procedure for free base Compound 1 (Form A)

1 wt of Compound 1 was dissolved in 5.11 wt of IPAc at 70-80 ºC. The solution was filtered (filter <2µm) and then 1.52 wt of n-heptane added. The solution was cooled to 55 ºC, and seeded with 0.5% w/w of Compound 1. The suspension was held at 55 ºC for 30-60 mins and then cooled to 35 ºC over 2 hours. The suspension was aged for 1 hour and then 8.2 wt of n-heptane were added over 3 hours. The suspension was aged for 1 hour and then cooled to 0-5 ºC over 2 hours and aged for at least 2 hours. The suspension was filtered under vacuum, and the cake washed with 10/90 w/w isopropyl acetate/n-heptane. The cake was dried under vacuum at 40-45 ºC until dry, to produce Form A.

Example 2: XRPD analysis of free base Compound 1 Form A

Crystalline free base Compound 1 Form A was analysed by XRPD and the ten most characteristic peaks are shown in Table 1 (see also Figure 1).

Table 1

2-theta in degrees	relative intensity in %
10.7	67.4
14.8	100.0
18.7	23.5
19.5	46.6
21.4	71.4
21.7	19.9
25.5	5.4
29.9	6.8
35	6.0
37.8	4.5

The five most characteristic peaks of crystalline Compound 1 in free Form A are at: 10.7, 14.8, 18.7, 19.5 and 21.4° 2-theta.

The three most characterictic peaks of crystalline Compound 1 in free Form A are at: 10.7, 14.8 and 19.5° 2-theta.

X-ray powder diffraction (XRPD) analysis was performed using a Bruker D8 Advance x-ray diffractometer in reflection geometry. Measurements were taken at about 30 kV and 40 mA under the following conditions:

Table 2

Scan rate (continuous scan):	3 s/step
Step size:	0.017° (2-theta)
Soller slit:	2.5°
Slits (from left to right):	V12 (variable)

The X-ray diffraction pattern was recorded between 2° and 40° (2-theta) with CuK_α radiation for identification of the whole pattern.

Example 3: Micronization procedure and XRPD analysis for Compound 1 free Form A

Crystalline Compound 1 free Form A was micronized according to the following method:

A spiral jet-milling instrument was used with a ring of 50 mm diameter. The carrier gas was nitrogen and the energy was targeted at 1800kJ/kg (cumulative parameter considering injector and grinding nozzle number and diameter, injector and grinding nozzle pressure, and feed rate according to Midoux N *et al.*, 1999).

Micronized Crystalline Form A was analysed by XRPD and the ten most characteristic peaks are shown in Table 3 (see also Figure 2).

Table 3

2-theta in degrees	relative intensity in %
10.6	49.8
12.1	33.1
14.7	52.8
15.9	83.5
18.5	90.3
19.4	39.0
21.2	76.1
24.0	100.0
24.7	72.0
29.7	76.1

The five most characteristic peaks of micronized crystalline Compound 1 in free Form A are at: 12.1, 15.9, 18.5, 19.4, 24.0° 2-theta.

The three most characterictic peaks of micronized crystalline Compound 1 in free Form A are at: 12.1, 19.4, 24.0° 2-theta.

X-ray powder diffraction (XRPD) analysis was performed using a Bruker D8 Advance x-ray diffractometer in reflection geometry. Measurements were taken at about 30 kV and 40 mA under the conditions shown in Table 4.

Table 4

Scan rate (continuous scan):	3 s/step
Step size:	0.017° (2-theta)
Soller slit:	2.5°
Slits (from left to right):	V12 (variable)

The X-ray diffraction pattern was recorded between 2° and 40° (2-theta) with CuK_α radiation for identification of the whole pattern.

Example 4: DSC analysis of Compound 1 free Form A

Crystalline Compound 1 free Form A was analysed by differential scanning calorimetry (DSC) using a Q1000 Diffraction Scanning Calorimeter from TA Instruments and found to have an endotherm at about 171 ºC when analysed at a heating rate of 10 ºC per minute, see Figure 3.

Example 5: Preparation of Compound 1 hemifumarate hemihydrate salt

Small scale preparation

300 mg of free base Compound 1 was dissolved in 3mL acetonitrile and 33.9 mg fumaric acid (0.5 eq) was added to the solution at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

Large scale preparation

1 wt of free base Compound 1 was dissolved in 12 vol of acetone at 30ºC. 0.5 equivalent of fumaric acid was dissolved into 12 vol. of EtOH. 1 wt of the ethanol fumaric acid solution was added to the Compound 1 solution and seeded with 0.5% w/w of Compound 1 fumarate salt.

The suspension was aged for 1 hour and the remaining ethanol solution added over 6 hours. The suspension was aged at 30ºC until filtration. The solid was filtered and dried under full vacuum at 45ºC.

Example 6: XRPD analysis of Compound 1 hemifumarate hemihydrate salt

Crystalline Compound 1 in hemifumarate hemihydrate salt form, prepared using the large scale procedure described in Example 5, was analysed by XRPD and the ten most characteristic peaks are shown in Table 5 (see also Figure 4).

Table 5

2-theta in degrees	Relative intensity
4.0	13.1%
11.9	92.5%
13.9	64.7%
15.6	21.7%
16.2	28.1%
17.3	36.1%
19.9	100.0%
23.0	27.5%
27.9	18.5%
30.8	28.1%

The five most characteristic peaks of crystalline Compound 1 in hemifumarate hemihydrate salt form are at: 11.9, 13.9, 16.2, 17.3 and 19.9° 2-theta.

Alternatively, crystalline Compound 1 in hemifumarate hemihydrate salt form may be characterised by peaks at: 11.9, 19.9, 23.0, 27.9 and 30.8° 2-theta.

The three most characterictic peaks of crystalline Compound 1 in hemifumarate hemihydrate salt form are at: 11.9, 13.9 and 19.9° 2-theta.

Alternatively, crystalline Compound 1 in hemifumarate hemihydrate salt form may be characterised by peaks at: 23.0, 27.9 and 30.8° 2-theta.

X-ray powder diffraction (XRPD) analysis was performed using a Bruker D8 Advance x-ray diffractometer in reflection geometry. Measurements were taken at about 30 kV and 40 mA under the conditions shown in Table 6.

Table 6

Scan rate (continuous scan):	3 s/step
Step size:	0.017° (2-theta)
Soller slit:	2.5°
Slits (from left to right):	Primary: fixed illuminated sample size 10 mm, secondary slit: 2°

The X-ray diffraction pattern was recorded between 2° and 40° (2-theta) with CuK_α radiation for identification of the whole pattern.

Example 7: XRPD analysis of micronized Compound 1 hemifumarate hemihydrate salt form

Crystalline Compound 1 in hemifumarate hemihydrate salt form, prepared using the large scale procedure described in Example 5, was micronized as described in Example 3, analysed by XRPD using the methodology and equipment described in Example 3, and the ten most characteristic peaks are shown in Table 7 (see also Figure 5).

Table 7

2-theta in degrees	Relative intensity in %
3.9	20.3
7.3	18.1
9.1	12.0
11.8	31.7
14.0	32.8
16.1	74.6
17.1	86.9
19.0	44.7
19.7	100
22.3	98

The five most characteristic peaks of micronized Compound 1 in hemifumarate hemihydrate salt form are at: 9.1, 11.8, 14.0, 16.1 and 19.0° 2-theta.

The three most characterictic peaks of micronized Compound 1 in f hemifumarate hemihydrate salt form are at: 14.0, 16.1 and 19.0° 2-theta.

Example 8: DSC analysis of Compound 1 hemifumarate hemihydrate salt

Crystalline Compound 1 in hemifumarate hemihydrate salt form, prepared using the large scale procedure described in Example 5, was analysed by DSC using a Discovery(R)

instrument from TA Instruments and found to have an endotherm at about 239 ºC when analysed at a heating rate of 10 ºC per minute, see Figure 6.

Example 9: Preparation of Compound 1 hemisuccinate hemihydrate salt

Small scale preparation

300 mg of free base Compound 1 was dissolved in 3 mL ethanol and 69 mg succinic acid (1 equivalent) was added to the solution at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m. at 25°C and dried at 25°C for 6 hours.

Large scale preparation

1 wt of free base Compound 1 and 1 equivalent of succinic acid were dissolved in 12 vol of MeOH at 60ºC. The solution was cooled to 45ºC and seeded with 0.5% w/w of Compound 1 succinate salt. The suspension was aged for 1 hour and cooled to 25ºC over 2 hours. 13.3 vol of water was added over 2 hours. The solid was then filtered and dried under full vacuum at 45ºC.

Example 10: XRPD analysis of Compound 1 hemisuccinate hemihydrate salt

Crystalline Compound 1 in hemisuccinate hemihydrate salt form, prepared using the large scale procedure described in Example 9, was analysed by XRPD using the methodology and equipment described in Example 6 and the ten most characteristic peaks are shown in Table 8 (see also Figure 7).

Table 8

2-theta in degrees	Relative intensity
4.0	31.1%
12.0	100.0%
14.0	78.9%
15.7	22.2%
16.2	34.4%
17.3	41.1%
17.6	51.5%
20.1	70.6%
23.3	26.7%
31.2	25.2%

The five most characteristic peaks of crystalline Compound 1 in hemisuccinate hemihydrate salt form are at: 12.0, 14.0, 17.3, 17.6 and 20.1° 2-theta.

The three most characterictic peaks of crystalline Compound 1 in hemisuccinate hemihydrate salt form are at: 12.0, 14.0 and 20.1° 2-theta.

Example 11: XRPD analysis of micronized Compound 1 hemisuccinate hemihydrate salt

Crystalline Compound 1 in hemisuccinate hemihydrate salt form, prepared using the large scale procedure described in Example 9, was micronized as described in Example 3, analysed by XRPD using the methodology and equipment described in Example 3 and the ten most characteristic peaks are shown in Table 9 (see also Figure 8).

Table 9

2-theta in degrees	relative intensity in %
9.2	11.9
10.1	13.5
11.9	27.4
12.7	22.2
14.5	38.8
15.5	31.0
19.8	77.7
22.0	100
23.3	51.4
24.5	58.2

The five most characteristic peaks of micronized Compound 1 in hemisuccinate hemihydrate salt form are at: 10.1, 14.5, 15.5, 19.8 and 23.3° 2-theta.

The three most characterictic peaks of micronized Compound 1 in hemisuccinate hemihydrate salt form are at: 10.1, 15.5 and 19.8° 2-theta.

Example 12: DSC analysis of Compound 1 hemisuccinate hemihydrate salt

Crystalline Compound 1 in hemisuccinate hemihydrate salt form, prepared using the large scale procedure described in Example 9, was analysed by DSC using a Discovery(R) instrument from TA instruments and found to have an endotherm at about 217 ºC when analysed at a heating rate of 10 ºC per minute, see Figure 9.

Example 13: Preparation of Compound 1 hemi-L-tartrate hemihydrate salt

Small scale preparation

300mg free base Compound 1 was dissolved in 3 mL acetonitrile and 43.8 mg L-tartaric acid (0.5 equivalent) was added to the solution at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14

hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

Large scale preparation

1 wt of free base Compound 1 was dissolved in 12 vol of acetone at 30ºC. 0.5 equivalent of L-tartaric acid was dissolved in 12 vol of water. 5 g of the L-tartaric aqueous solution was added to the Compound 1 solution, which was then seeded with 0.5% w/w of Compound 1 L-tartrate salt. The suspension was aged for 1 hour, then the remainder of the aqueous solution added over 6 hours. The suspension was aged at 30ºC until filtration. The solid was dried under full vacuum at 45ºC.

Example 14: XRPD analysis of Compound 1 hemi-L-tartrate hemihydrate salt

Crystalline Compound 1 in hemi-L-tartrate hemihydrate salt form, prepared using the large scale procedure described in Example 13, was analysed by XRPD using the methodology and equipment described in Example 6 and the ten most characteristic peaks are shown in Table 10 (see also Figure 10).

Table 10

2-theta in degrees	relative intensity
12.2	59.9%
14.0	100.0%
16.0	44.7%
17.1	52.2%
17.3	23.2%
17.7	74.7%
19.8	95.2%
20.4	54.0%
23.5	27.1%
31.5	30.3%

The five most characteristic peaks of crystalline Compound 1 in hemi-L-tartrate hemihydrate salt form are at: 12.2, 14.0, 17.7, 19.8 and 20.4° 2-theta.

The three most characterictic peaks of crystalline Compound 1 in hemi-L-tartrate hemihydrate salt form are at: 14.0, 17.7 and 19.8° 2-theta.

Example 15: XRPD analysis of micronized Compound 1 hemi-L-tartrate hemihydrate salt

Crystalline Compound 1 in hemi-L-tartrate hemihydrate salt form, prepared using the large scale procedure described in Example 13, was micronized as described in Example 3,

analysed by XRPD using the methodology and equipment described in Example 3 and the ten most characteristic peaks are shown in Table 11 (see also Figure 11).

Table 11

2-theta in degrees	relative intensity in %
7.1	18.2
13.0	28.1
13.7	78.3
13.9	74.3
15.9	57.9
17.1	74.4
19.8	100
20.3	64.8
22.4	86.2
24.7	59.6

The five most characteristic peaks of micronized Compound 1 in hemi-L-tartrate hemihydrate salt form are at: 7.1, 13.0, 17.1, 19.8 and 20.3° 2-theta.

The three most characterictic peaks of micronized Compound 1 in hemi-L-tartrate hemihydrate salt form are at: 13.0, 17.1 and 20.3° 2-theta.

Example 16: DSC analysis of Compound 1 hemi-L-tartrate hemihydrate salt

Crystalline Compound 1 in hemi-L-tartrate hemihydrate salt form, prepared using the large scale procedure described in Example 13, was analysed by DSC using Discovery(R) instrument from TA instruments and found to have an endotherm at about 253 ºC when analysed at a heating rate of 10 ºC per minute, see Figure 12.

Example 17: Stoichiometric analysis of Compound 1 fumarate, succinate and tartrate salt forms

The stoichiometric composition of the Compound 1 salt forms was examined by proton NMR spectroscopy which confirmed that the stoichiometry of the ratio between Compound 1 and the salt forming agent was 2:1 for the succinate, fumarate and tartrate salts.

The solvated/hydrated nature of the different salts was examined experimentally by analysis of residual organic solvent, thermogravimetric analysis of loss on drying, and storage behaviour at different relative humidities in combination with dynamic vapour sorption. In addition, for the succinate and fumarate salts, the natures of the solvents/hydrates were also supported by structural investigation based on single crystal X-ray data analysis. The results of these orthogonal techniques provide evidence that the fumarate, succinate and tartrate

salt forms of Compound 1 obtained as described above contain water in their crystal structures consistent with a composition ratio of 2:1:1 (Compound 1: salt coformer: water).

Example 18: Milling properties of Compound 1 free base form and hemifumarate hemihydrate, hemisuccinate hemihydrate and hemi-L-tartrate hemihydrate salt forms

The behaviour of the free base and hemifumarate hemihydrate, hemisuccinate hemihydrate and hemi-L-tartrate hemihydrate salt forms were evaluated during jet milling. A spiral jet-milling instrument was used with a ring of 50mm diameter. The carrier gas was nitrogen and the energy was targeted at 1800kJ/kg (cumulative parameter considering injector and grinding nozzle number and diameter, injector and grinding nozzle pressure, and feed rate according to Midoux N *et al.*, 1999). The percentage yields upon micronization are shown in Table 12 below.

Table 12

Solid form	Free base	Hemifumarate hemihydrate	Hemisuccinate hemihydrate	Hemi-L-tartrate hemihydrate
Batch size (g)	53	40	46	47
Yield upon micronization	<75%*	93%	91%	96%

* Process stopped after delivery of 40g free base Compound 1 into mill due to clogging of grinding chamber.

In terms of micronization capacity, the free form was not processable and blocked the mill. However, yields higher than 90% were achieved for the three salts. The yield and processability upon micronization at small scale indicates unambiguously the improved properties of the three salts compared to the free form of Compound 1.

Example 19: Preparation of further alternative salt forms of Compound 1

HCl: 300mg free base Compound 1 was added to 3mL MTBE and 1 eq HCl (6.0N) was added to the suspension at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

HCl, hydrate: 300mg free base Compound 1 was dissolved in 3mL ethanol and 1 eq HCl (6.0N) was added to the solution at 50°C. The mixture was stirred at 50°C for 4 hours and

cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

H_2SO_4: 300mg free base Compound 1 was dissolved in 3mL IPAc and 1 eq H2SO4 (98%) was added to the solution at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

H_3PO_4: 300mg free base Compound 1 was added to 3mL MTBE and 1 eq H3PO4 (85%) was added to the suspension at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

Acetate: 300mg free base Compound 1 was dissolved in 3mL ethanol and 35.3mg acetic acid (1 eq) was added to the solution at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

Citrate: 300mg free base Compound 1 was dissolved in 3mL IPAc and 56.1mg citric acid (0.5 eq) was added to the solution at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

Butyrate: 300mg free base Compound 1 was dissolved in 3mL IPAc and 51.5mg butyric acid (1 eq) was added to the solution at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

D-glucuronate: 300mg free base Compound 1 was dissolved in 3mL acetonitrile and 113.4mg D-glucuronic acid (1 eq) was added to the solution at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

Galactarate: 300mg free base Compound 1 was dissolved in 3mL ethanol and 61.3mg galactaric acid (0.5 eq) was added to the solution at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

Glutarate: 300mg free base Compound 1 was added to 3mL MTBE and 77.1mg glutaric acid (1 eq) was added to the suspension at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

L-aspartate: 300mg free base Compound 1 was dissolved in 3mL ethanol and 77.7mg L-aspartic acid (1 eq) was added to the solution at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

Pyruvate: 300mg free base Compound 1 was added to 3mL MTBE and 51.4mg pyruvic acid (1 eq) was added to the suspension at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

Maleate: 300mg free base Compound 1 was added to 3mL MTBE and 67.8mg maleic acid (1 eq) was added to the suspension at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

Glycolate: 300mg free base Compound 1 was added to 3mL MTBE and 44.4mg glycolic acid (1 eq) was added to the suspension at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

N-acetylglicine: 300mg free base Compound 1 was added to 3mL MTBE and 68.4mg N-acetylglycine (1 eq) was added to the suspension at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

Propionate: 300mg free base Compound 1 was added to 3mL MTBE and 43.3mg propionic acid (1 eq) was added to the suspension at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

D-quinate: 300mg free base Compound 1 was dissolved in 3mL IPAc and 112.2mg D-quinic acid (1 eq) was added to the suspension at 50°C. The mixture was stirred at 50°C for 4 hours and cooled to 25°C within a 4 hour period. The mixture was kept stirring at 25°C for 14 hours. The solids were separated by centrifuge at 4000 r.p.m.at 25°C and dried at 25°C for 6 hours.

Example 20: Bulk stability of Compound 1 salts in comparison to the free form after three weeks stress exposure at 80°C/75% relative humidity and in the presence of 90% sodium stearyl fumarate

In order to assess the potential of the salts to provide improved properties over the free form, the discrimination parameters were set as follow: bulk stability (3 weeks 80°C/75%RH open dish) and physical mixture 1:9 (w/w) with sodium stearyl fumarate (Table 13).

Table 13

Compound 1	**Initial material**	**80°C/75%RH for 3 weeks**	**80°C/75%RH with 90% sodium stearyl fumarate for 3 weeks**
	Initial %	DP %	DP %
Free form (Form A)	100	<0.05	5.37
HCl	100	0.06	99.81
HCl, hydrate	100	0.24	99.82
H2SO4	99.33	0.81	75.68
H3PO4	100	1.05	99.89
Acetate	100	<0.05	6.49
Hemi-L-tartrate Hh	100	<0.05	1.22
Hemifumarate Hh	99.60	0.40	0.98
Maleate	99.50	0.55	99.86
Pyruvate	99.94	88.90	99.84
Galactarate	100	2.85	56.44
Citrate	100	0.07	99.89
Hemisuccinate Hh	100	<0.05	0.80
D-glucuronate	100	8.96	99.92
L-aspartate	100	<0.05	99.84
Glycolate	100	0.05	99.83
Glutarate	100	81.13	99.84
Butyrate	100	<0.05	*5.73*
N-acetylglycine	100	6.59	99.84
Propionate	100	0.10	*5.69*
D-quinate	100	81.07	99.13

DP: degradation product (DPs are analysed by HPLC. They are calculated as area-% products or against external standard 1%) Hh: hemihydrate

As pure bulk, some salts, namely, pyruvate, galactarate, glucoronate, glutarate N-acetylgycinate and quinate are chemically unstable when exposed for 3 weeks at 80ºC/75%RH. No degradation was observed for the free form.

As physical mixture with sodium stearyl fumarate (90% w/w), the discrimination power of this stress experiment was more pronounced. Almost all salts are more sensitive than the free form. The main degradation product was characterized by LC-MS.

A similar sensitivity compared to the free form was observed for the butarate and propionate, and enhanced stability was observed for the hemifumarate hemihydrate, hemisuccinate hemihydrate and hemi-L-tartrate hemihydrate salts.

Example 21: Bulk stability of Compound 1 hemifumarate hemihydrate, hemisuccinate hemihydrate and hemi-L-tartrate hemihydrate salts in comparison to the free form after three weeks stress exposure at 80°C/75% relative humidity and in the presence of pharmaceutical excipients

In order to assess the potential of the salts to provide improved properties over the free form in the presence of pharmaceutical excipients, the stability of Compound 1 in hemifumarate hemihydrate, hemisuccinate hemihydrate and hemi-L-tartrate hemihydrate salt form was tested relative to the free base form in an open dish for 3 weeks 80°C/75%RH (Table 14).

Table 14

Test Conditions	Physical Form			
	Free base Mod A	Hemisuccinate hemihydrate salt	Hemifumarate hemihydrate salt	Hemi-L-tartrate hemihydrate salt
	DP [%]	DP [%]	DP [%]	DP [%]
Initial purity	**99.98**	**99.93**	**99.98**	**99.98**
4 weeks 50°C, 75%RH, open dish				
5% in Na stearyl fumarate	0.17	0.11	0.06	0.05
5% in Mg stearate	0.12	0.17	0.04	0.11
5% in Aerosil 200 PH	0.98	0.51	0.13	0.08
5% in lactose (fast flow 316 grade)	0.11	0.12	0.06	0.07
5% in mannitol PH	0.16	0.11	0.05	0.06
5% in Avicel PH 101	0.21	0.15	0.05	0.06
5% HP-C low subst	0.14	0.15	0.06	0.05
5% croscarmellose sodium	0.13	0.13	0.08	0.06
3 weeks 80°C, 75%RH, open dish (UPLC)				
5% in Na stearyl fumarate	4.41	0.42	0.37	0.47
5% in Mg stearate	43.94	1.80	0.61	2.00
5% in Aerosil 200PH	9.54	6.54	5.07	3.67
5% in lactose (fast flow 316 grade	0.97	0.67	0.36	0.36
5% in mannitol PH	0.55	0.56	0.28	0.23
5% in Avicel PH 101	2.40	2.01	0.87	0.37
5% HP-C low	1.50	1.46	0.59	0.30
5% croscarmellose sodium	1.52	0.58	0.34	0.25

DP: degradation product (DPs are analysed by HPLC. They are calculated as area-% products or against external standard 1%); PH: Pharma grade material; HP-C low subst: Low-Substituted Hydroxypropyl Cellulose

Under the test conditions, the free form is significantly more sensitive to degradation than the salts. Its chemical degradation is very significant, particularly in the presence of magnesium stearate and sodium stearyl fumarate. Such chemical sensitivity is somewhat limited in milder stress conditions (4 weeks, 50 degrees Celsius, 75% RH). Some incompatibility with the free form is also clearly identified with Aerosil 200 PH.

Example 22: In human study of pharmacokinetics of free base Compound 1 when given alone and in combination with the strong CYP3A4 inhibitor itraconazole or the strong CYP3A4 inducer rifampicin

In a drug-drug interaction (DDI) study in healthy volunteers, the effect of a strong CYP3A4 inhibitor (itraconazole) and a strong CYP3A4 inducer (rifampicin) on the PK of Compound 1 was evaluated. The DDI study design is outlined in Figure 13. Itraconazole, at a dose of 200 mg q.d., increased mean AUC of Compound 1 2-3-fold and mean Cmax of Compound 1 by 25%, when given together with Compound 1 as compared to when Compound 1 was given alone (Table 15). Rifampicin, at a dose of 600 mg q.d., decreased mean AUC of Compound 1 5-6-fold and mean Cmax of Compound 1 2.5-fold, when given together with Compound 1 as compared to when Compound 1 was given alone (Table 16). In conclusion, the effect of a strong CYP3A4 inducer and a strong CYP3A4 inhibitor on Compound 1 exposure in a Phase 1 study has shown that CYP3A4 is of major importance for the elimination of Compound 1 and that the effects of co-treatment with a strong CYP3A4 inhibitor or inducer need to be taken into account when administering Compound 1.

Table 15: Pharmacokinetic results – Statistical analysis of the effect of itraconazole on the plasma PK parameters of Compound 1: Compound 1 30 mg SD + itraconazole 200 mg QD vs Compound 1 30 mg SD

Parameter [Unit]	Treatment	n*	Adjusted geometric mean	Geometric mean ratio (Test/Reference)	90% CI for ratio
AUCinf (ng*hr/mL)	Cmpd 1 30 mg SD	17	3560	3.05	[2.91 , 3.20]
	Cmpd 1 30 mg SD + Itraconazole 200 mg QD	17	10900		
AUClast (ng*hr/mL)	Cmpd 1 30 mg SD	17	3150	2.20	[2.11 , 2.30]
	Cmpd 1 30 mg SD + Itraconazole 200 mg QD	17	6930		
Cmax (ng/mL)	Cmpd 1 30 mg SD	17	74.1	1.23	[1.18 , 1.29]
	Cmpd 1 30 mg SD + Itraconazole 200 mg QD	17	91.3		

n* = number of subjects with non-missing values.

An ANOVA model with fixed effects for treatment and subject was fitted to each log-transformed PK parameter. Results were back transformed to obtain 'Adjusted geo-mean', 'Geo-mean ratio' and '90% CI'.

Table 16: Pharmacokinetic results – statistical analysis of the effect of rifampicin on the plasma PK parameters of Compound 1: Compound 1 100 mg SD + rifampicin 600 mg QD vs Compound 1 100 mg SD

Parameter [Unit]	Treatment	n*	Adjusted geometric mean	Geometric mean ratio (Test/Reference)	90% CI for ratio
AUCinf (ng*hr/mL)	Cmpd 1 100 mg SD	13	10200	0.172	[0.152, 0.194]
	Cmpd 1 100 mg SD + Rifampicin 600 mg QD	13	1750		
AUClast (ng*hr/mL)	Cmpd 1 100 mg SD	13	8560	0.196	[0.176 , 0.219]
	Cmpd 1 100 mg SD + Rifampicin 600 mg QD	13	1680		
Cmax (ng/mL)	Cmpd 1 100 mg SD	13	222	0.414	[0.365 , 0.470]
	Cmpd 1 100 mg SD + Rifampicin 600 mg QD	13	92.2		

n* = number of subjects with non-missing values.

An ANOVA model with fixed effects for treatment and subject was fitted to each log-transformed PK parameter. Results were back transformed to obtain 'Adjusted geo-mean', 'Geo-mean ratio' and '90% CI'.

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All references, e.g., a scientific publication or patent application publication, cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each reference was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

Claims

1. The compound *N*-(6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide in fumarate, succinate or tartrate salt form.

2. The compound according to Claim 1 in fumarate salt form.

3. The compound according to Claim 1 in succinate salt form.

4. The compound according to Claim 1 in tartrate salt form.

5. The compound according to any one of Claims 1 to 4 in hemi salt form.

6. The compound according to any one of Claims 1 to 5 in hydrated salt form.

7. The compound according to any one of Claims 1 to 6 in hemihydrate salt form.

8. The compound according to Claim 1 which is *N*-(6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide hemifumarate hemihydrate.

9. The compound according to Claim 1 which is *N*-(6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide hemisuccinate hemihydrate.

10. The compound according to Claim 1 which is *N*-(6-((3*R*,6*R*)-5-amino-3,6-dimethyl-6-(trifluoromethyl)-3,6-dihydro-2*H*-1,4-oxazin-3-yl)-5-fluoropyridin-2-yl)-3-chloro-5-(trifluoromethyl)picolinamide hemi-L-tartrate hemihydrate.

11. The compound according to any one of Claims 1 to 10 in crystalline salt form.

12. The compound according to Claim 11 in substantially pure form.

13. The compound according to Claim 1 in crystalline fumarate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 11.9, 13.9 and 19.9º when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

14. The compound according to Claim 1 in crystalline succinate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 12.0, 14.0 and 20.1° when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

15. The compound according to Claim 1 in crystalline tartrate salt form and having an X-ray powder diffraction pattern with angle of refraction 2 theta (θ) peak values of 14.0, 17.7 and 19.8° when measured using CuKα radiation, wherein said values are plus or minus 0.2° 2θ.

16. The compound according to Claim 1 in crystalline fumarate salt form and having an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 4 when measured using CuKα radiation.

17. The compound according to Claim 1 in crystalline succinate salt form and having an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 7 when measured using CuKα radiation.

18. The compound according to Claim 1 in crystalline tartrate salt form and having an X-ray powder diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in Figure 10 when measured using CuKα radiation.

19. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 18.

20. A compound according to any one of Claims 1 to 18 for use as a medicament.

21. A compound according to any one of Claims 1 to 18 for use in the treatment or prevention of Alzheimer's disease.

Figure 1: X-ray powder diffraction pattern for crystalline free base Compound 1 Form A when measured using CuK_{α} radiation

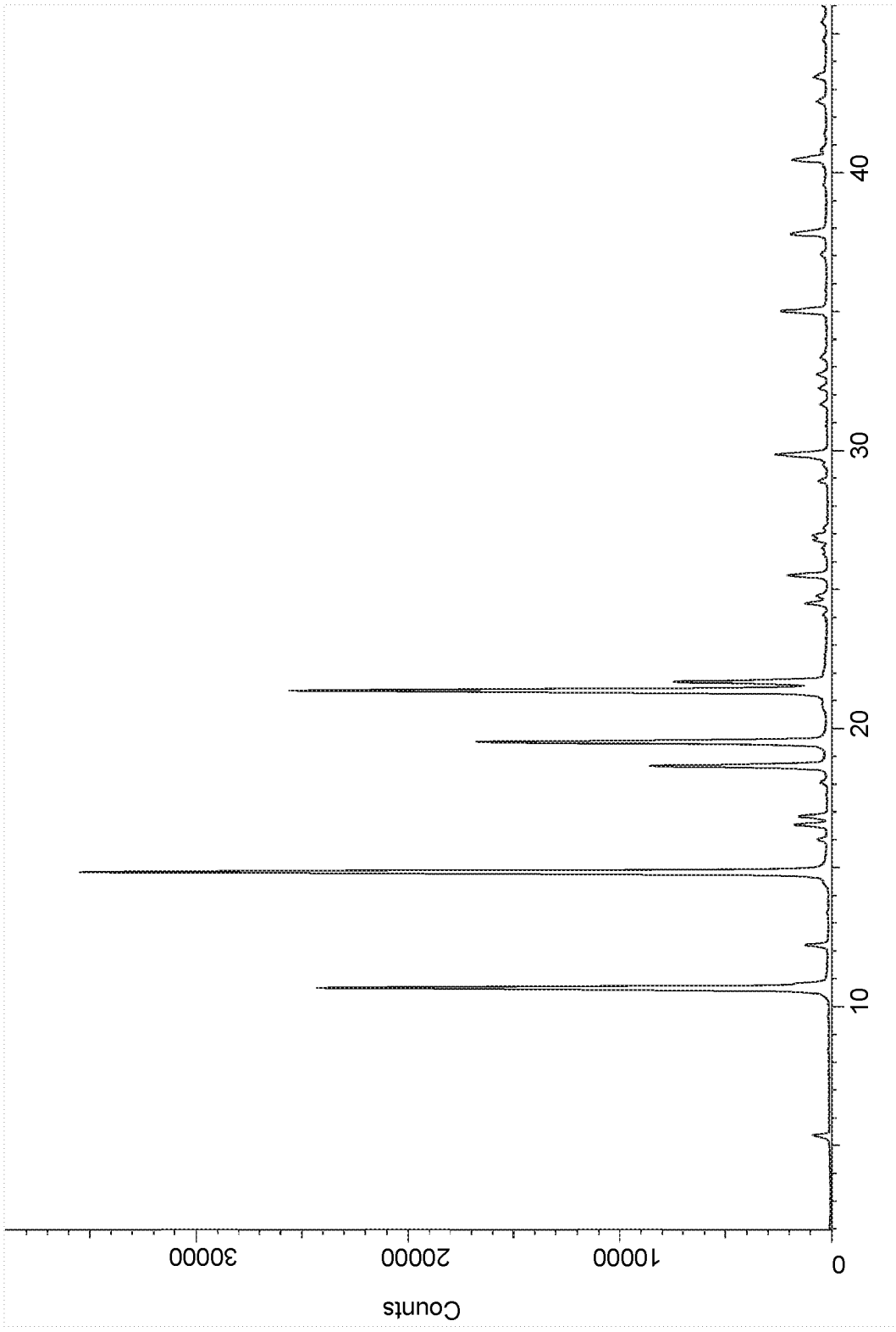


Figure 2: X-ray powder diffraction pattern for micronized crystalline free base Compound 1 Form A when measured using CuK_α radiation

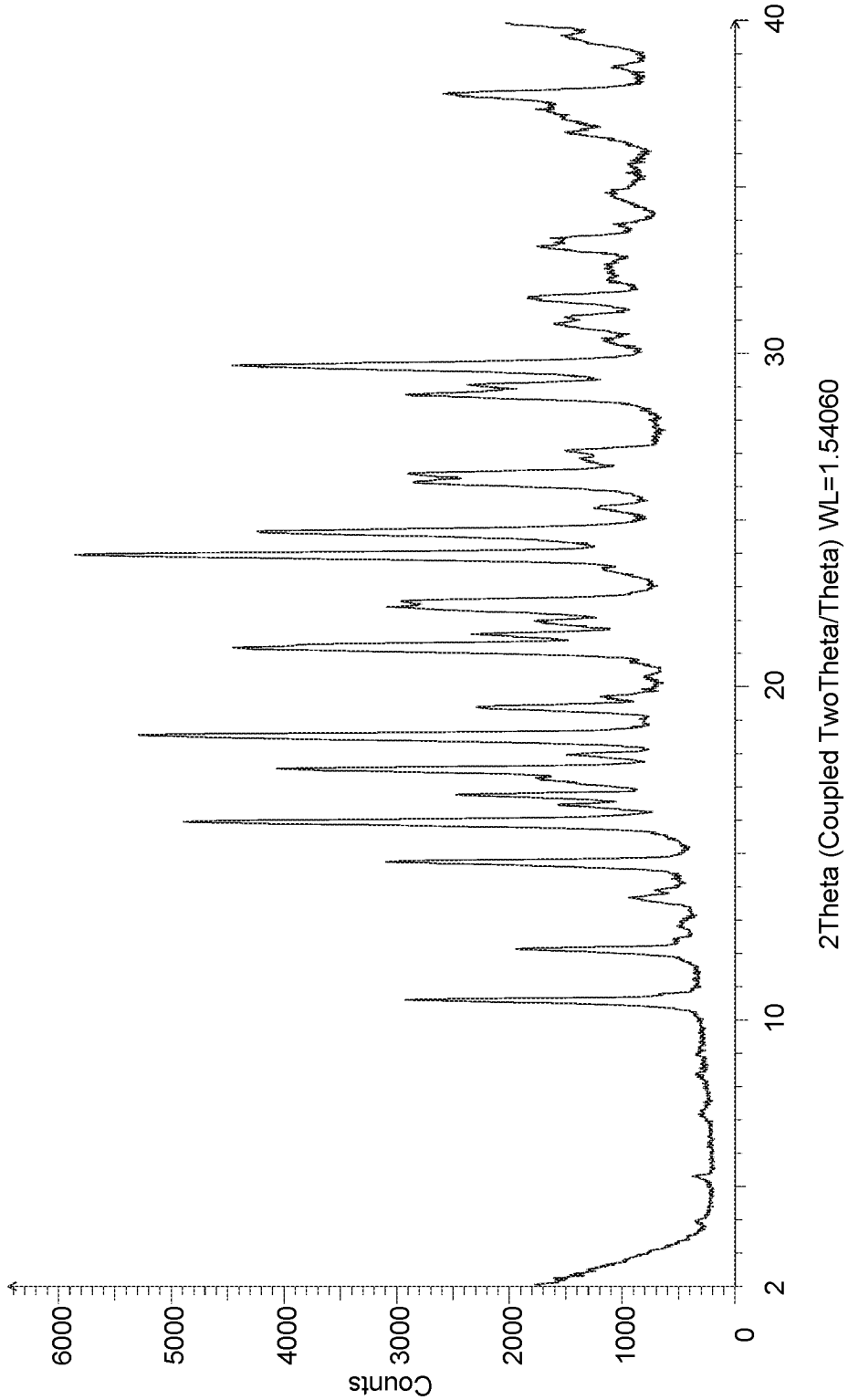


Figure 3: DSC thermogram for crystalline free base Compound 1 Form A

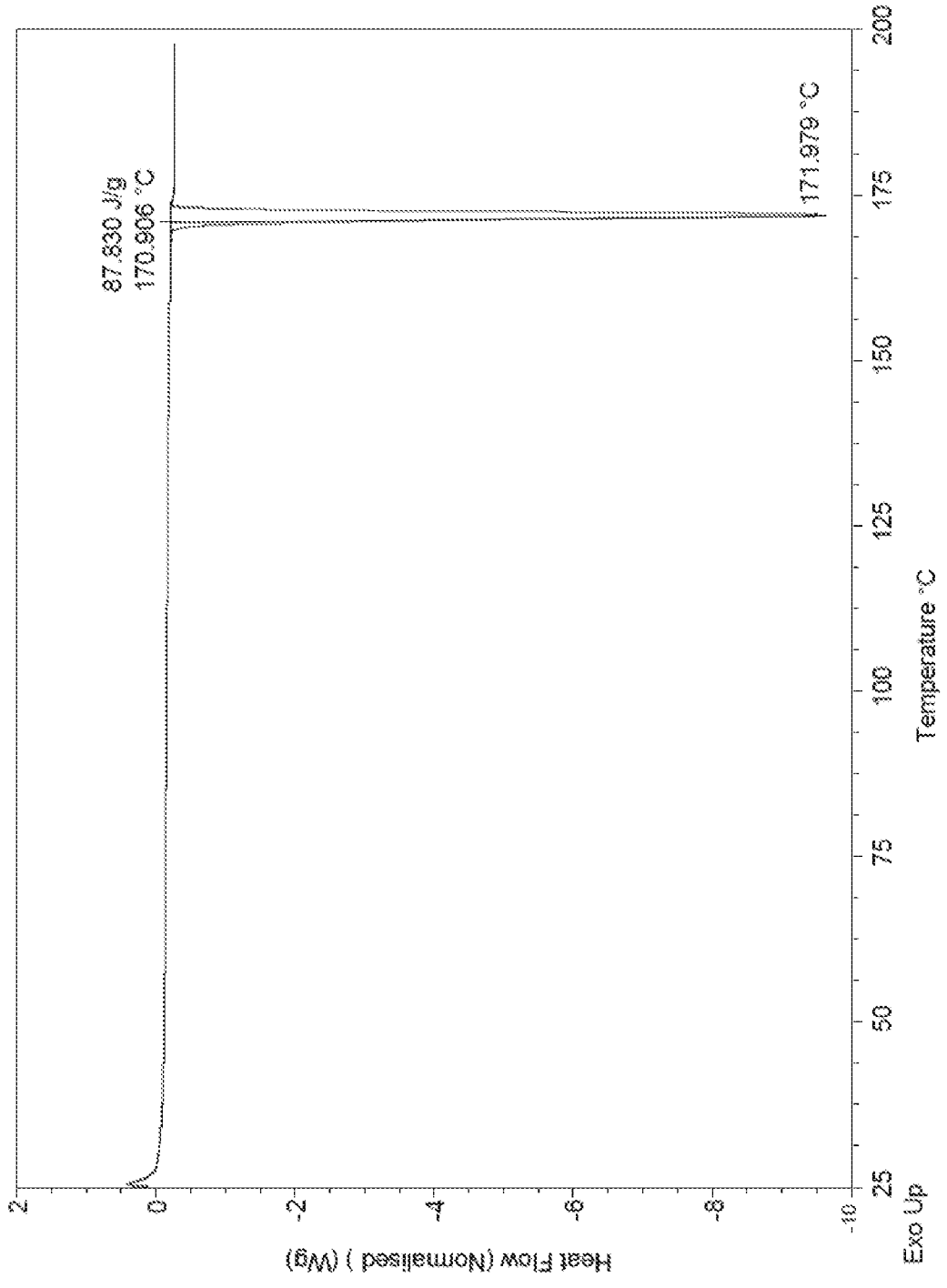


Figure 4: X-ray powder diffraction pattern for crystalline Compound 1 in hemifumarate hemihydrate salt form when measured using CuK_{α} radiation

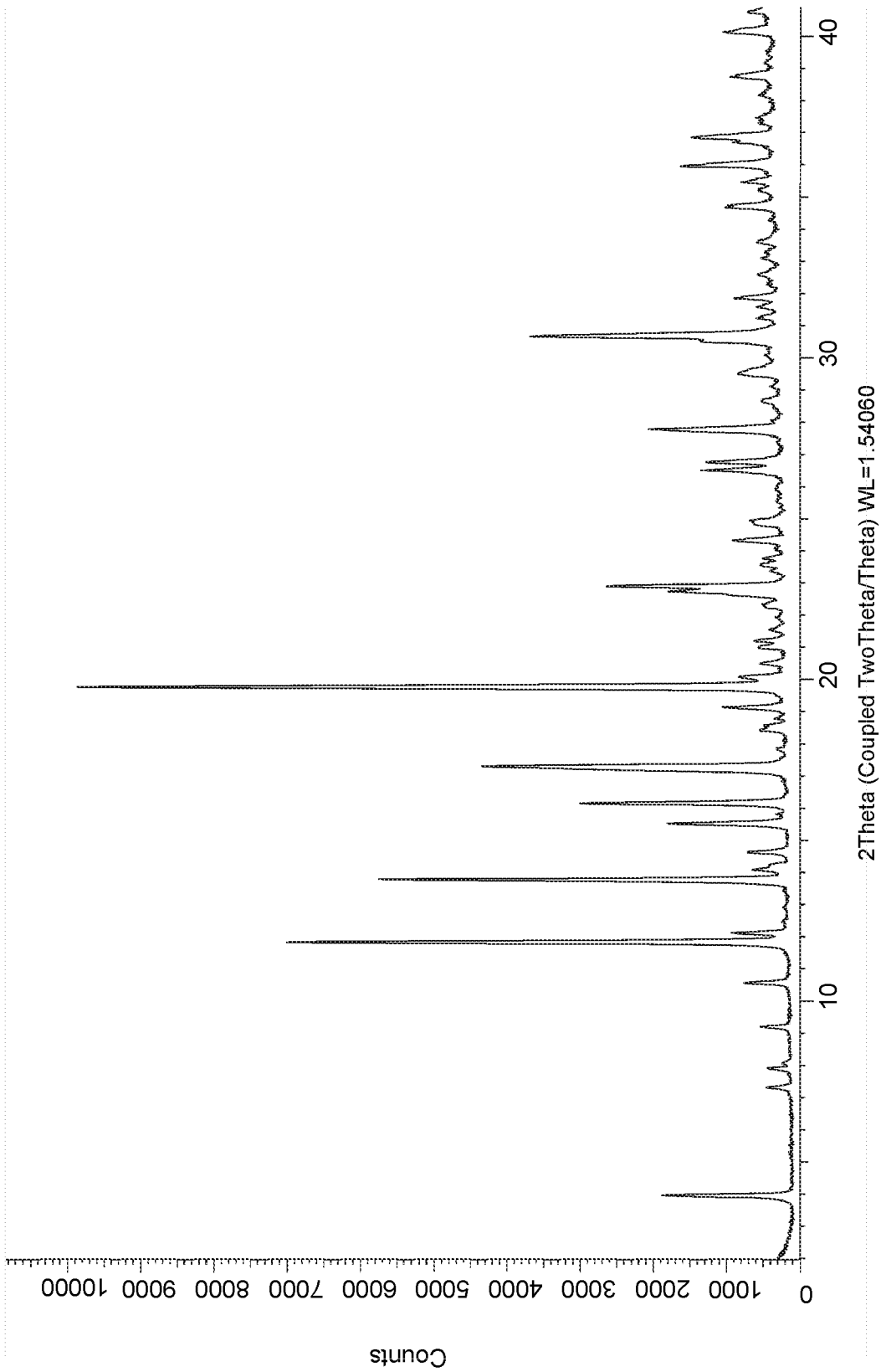


Figure 5: X-ray powder diffraction pattern for micronized crystalline Compound 1 in hemifumarate hemihydrate salt form when measured using CuK_{α} radiation

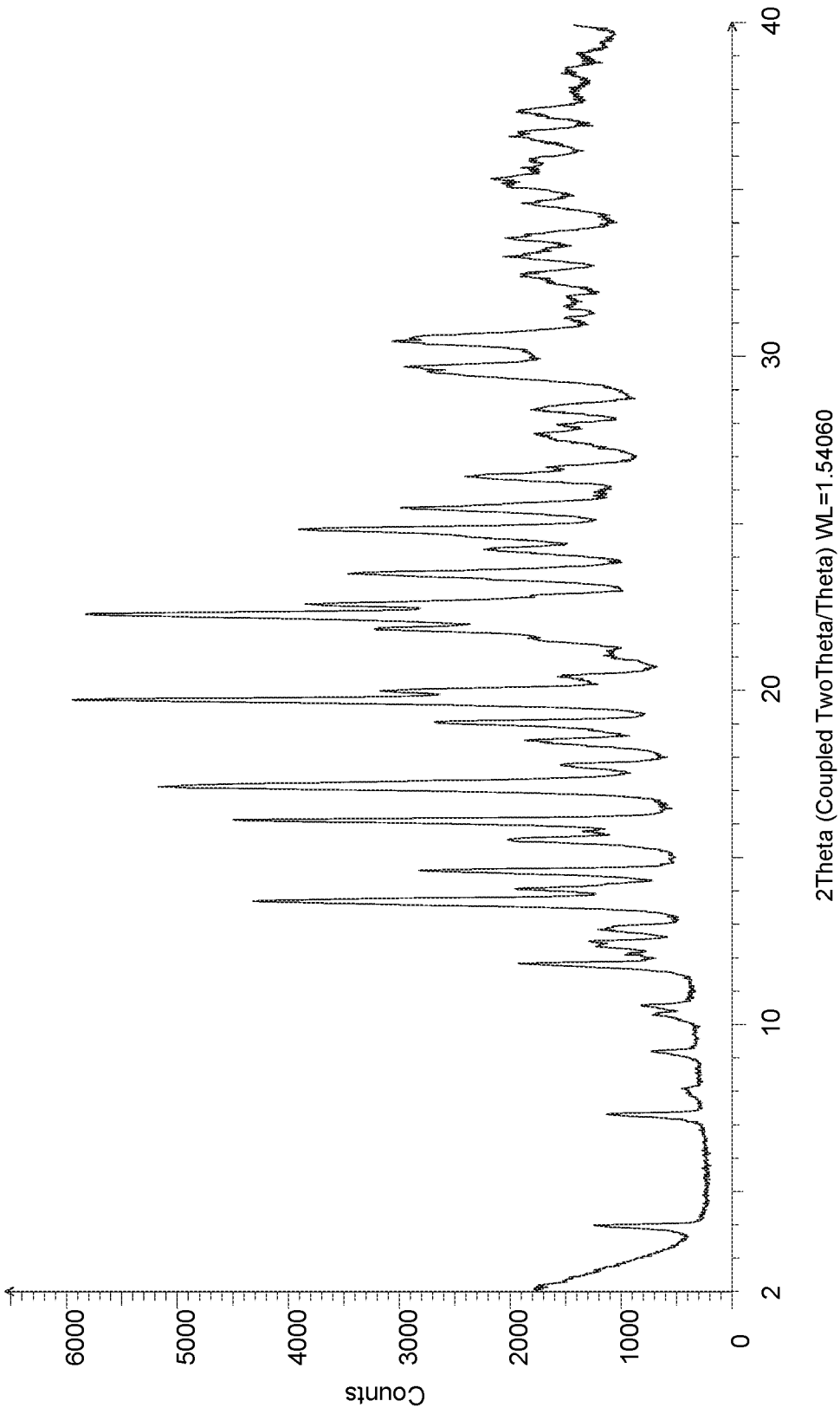


Figure 6: DSC thermogram for crystalline Compound 1 in hemifumarate hemihydrate salt form

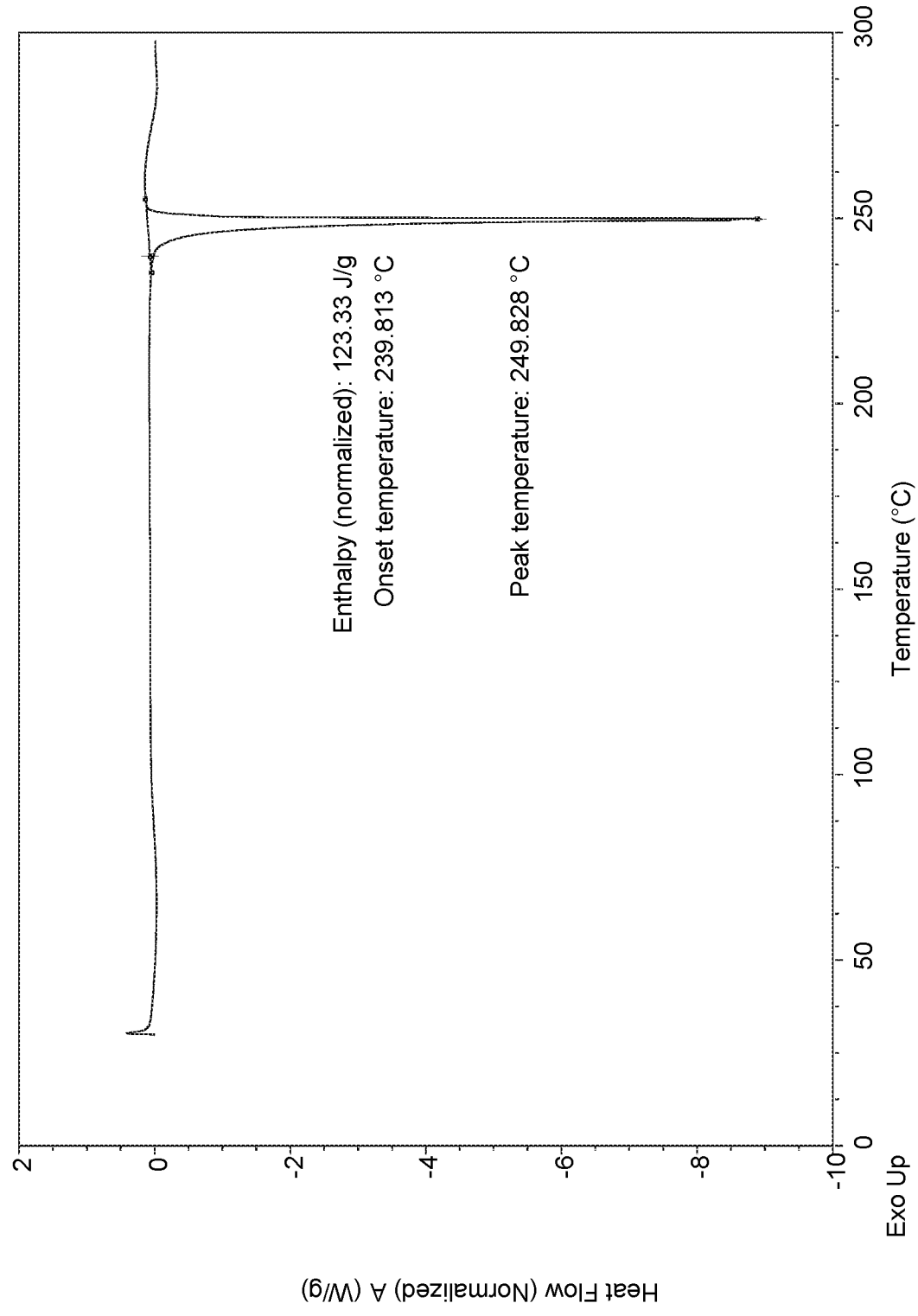


Figure 7: X-ray powder diffraction pattern for crystalline Compound 1 in hemisuccinate hemihydrate salt form when measured using CuK_{α} radiation

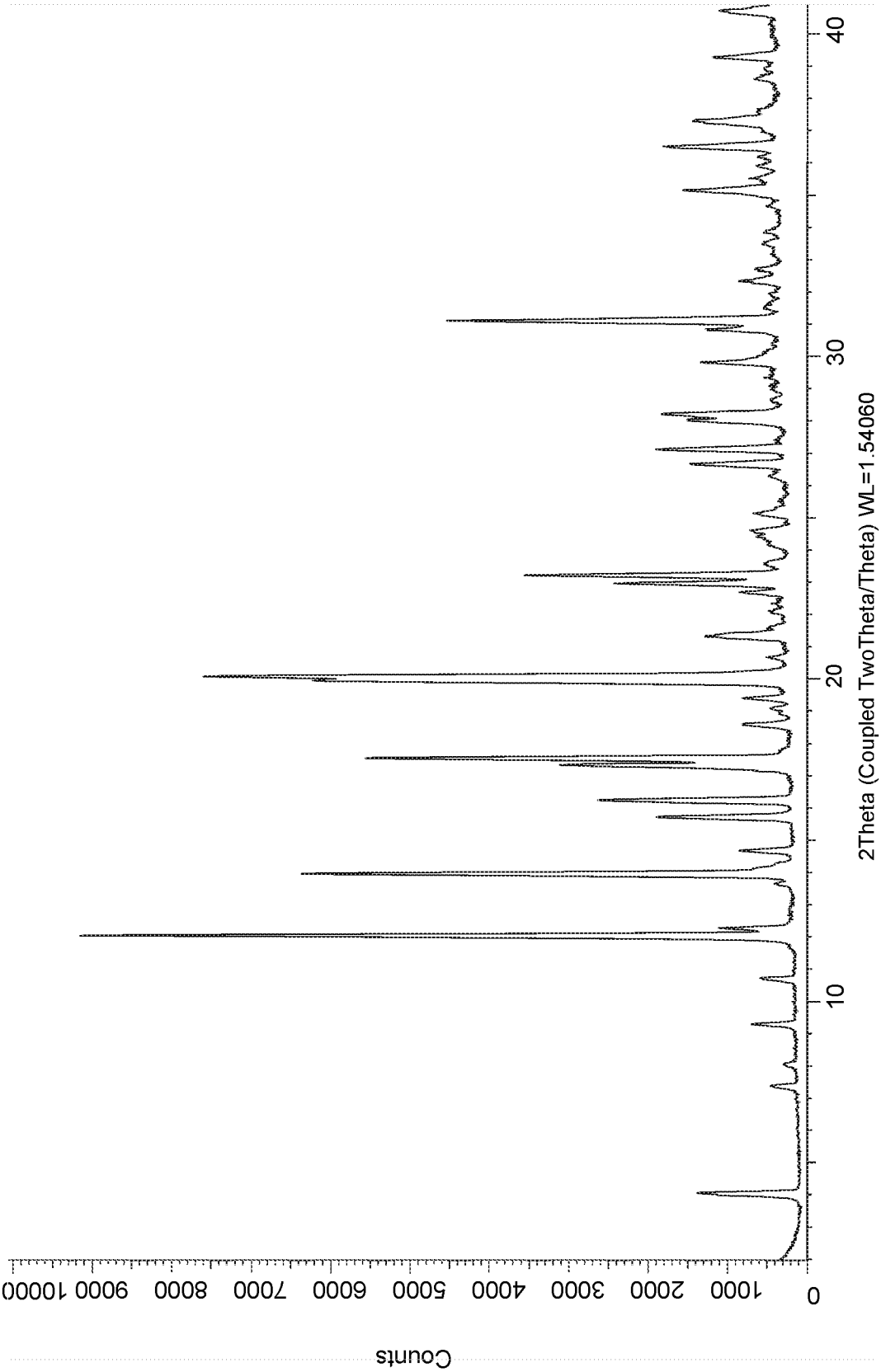


Figure 8: X-ray powder diffraction pattern for micronized crystalline Compound 1 in hemisuccinate hemihydrate salt form when measured using CuK_{α} radiation

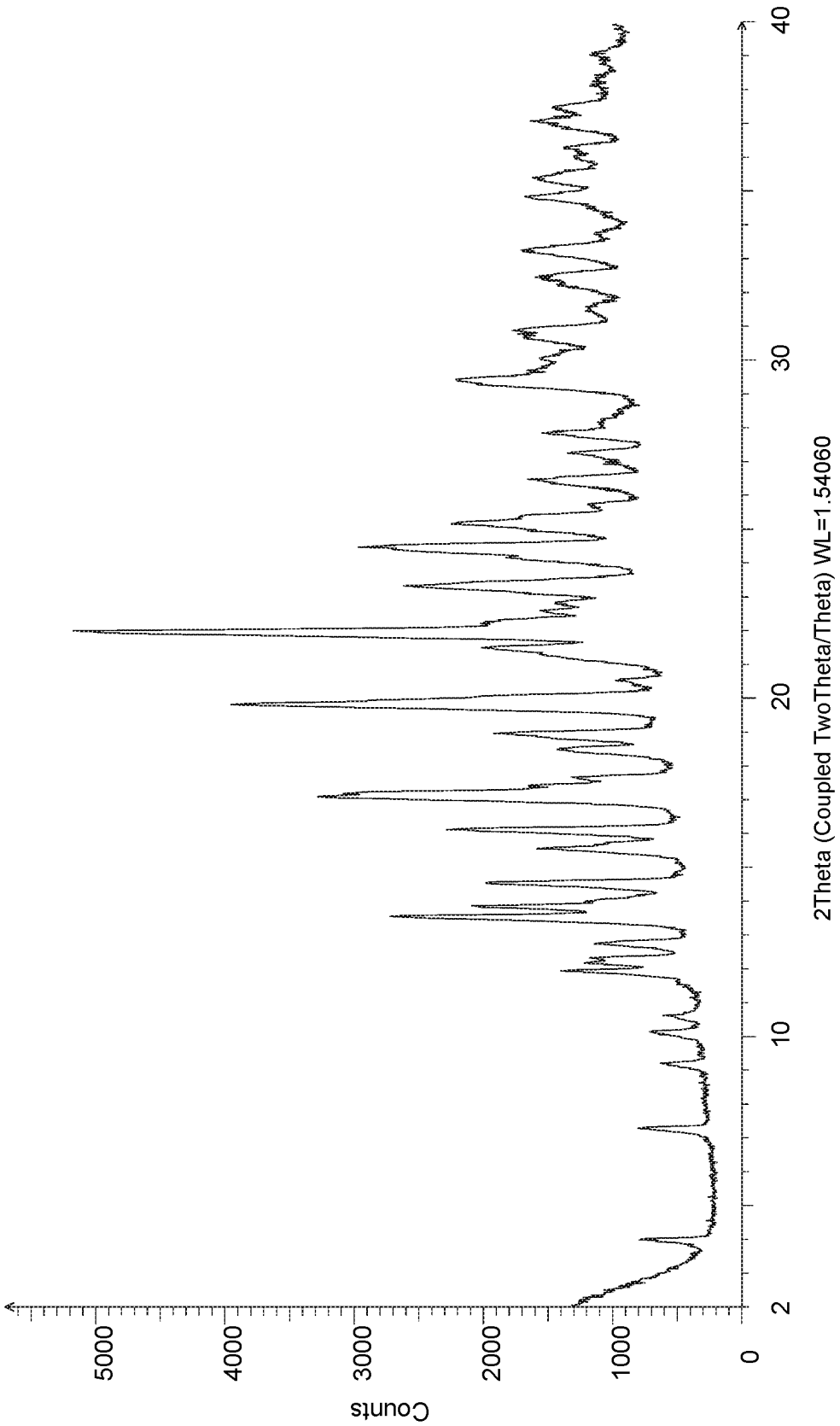


Figure 9: DSC thermogram for crystalline Compound 1 in hemisuccinate hemihydrate salt form

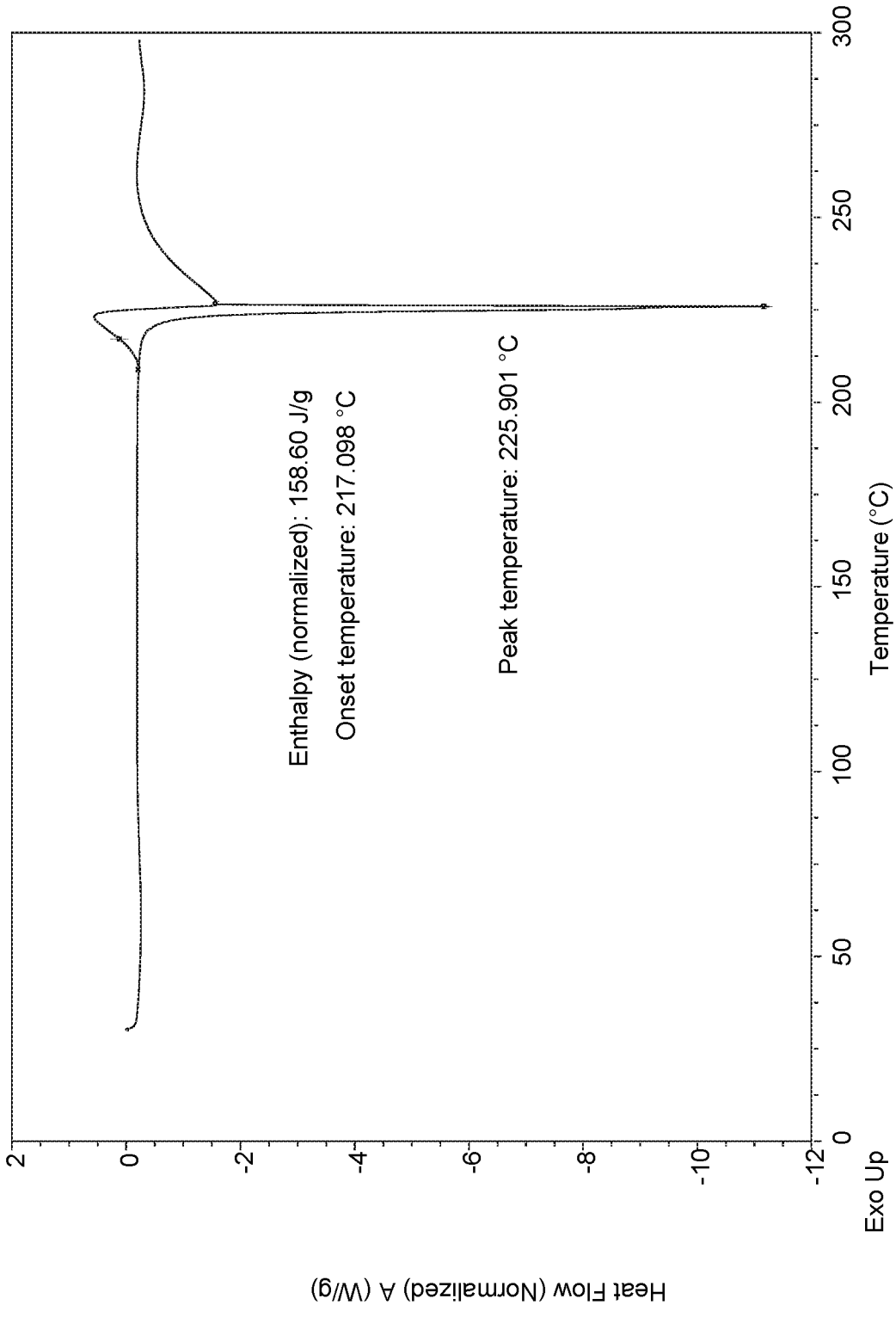


Figure 10: X-ray powder diffraction pattern for crystalline Compound 1 in hemi-L-tartrate hemihydrate salt form when measured using CuK_{α} radiation

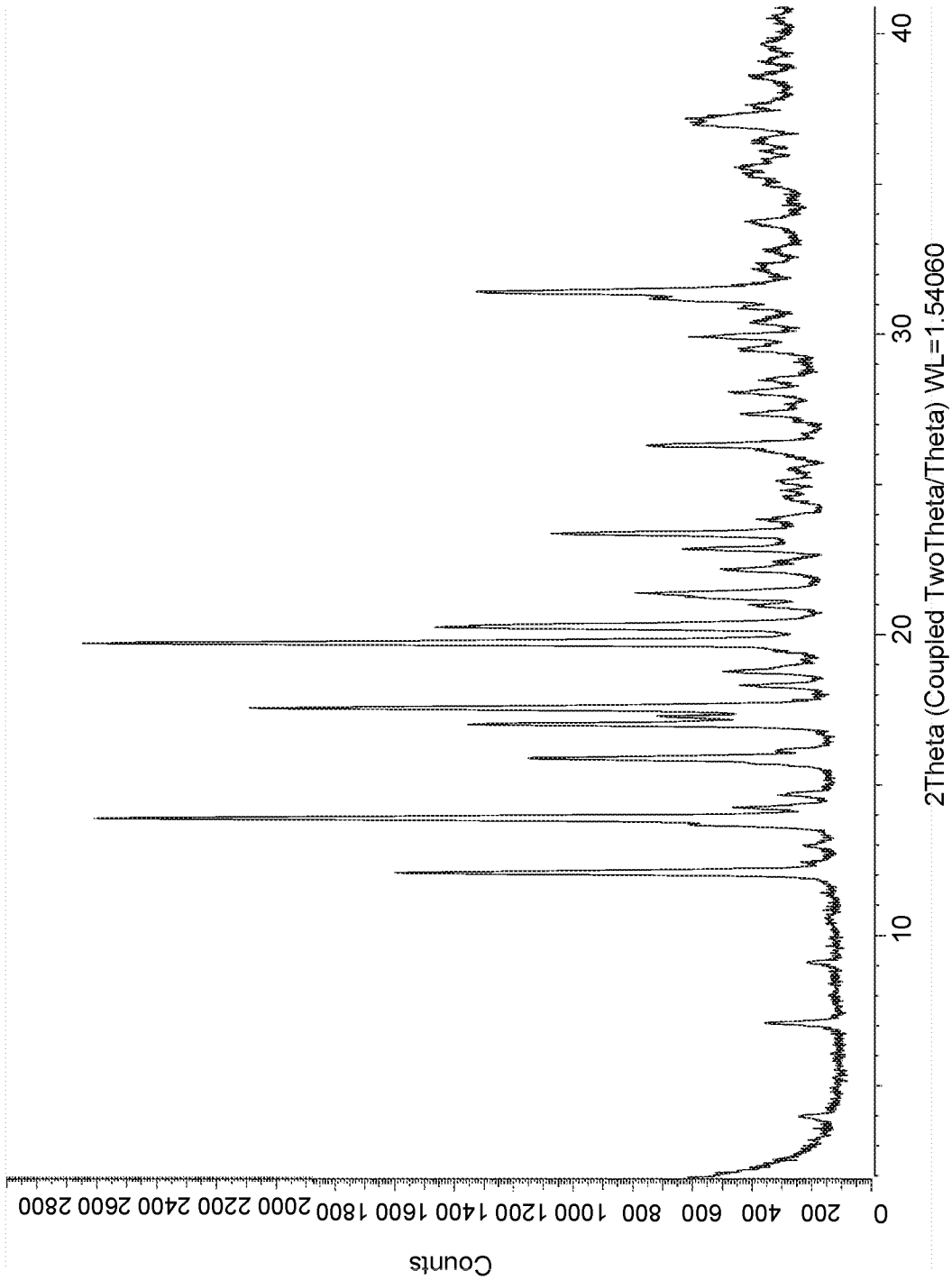
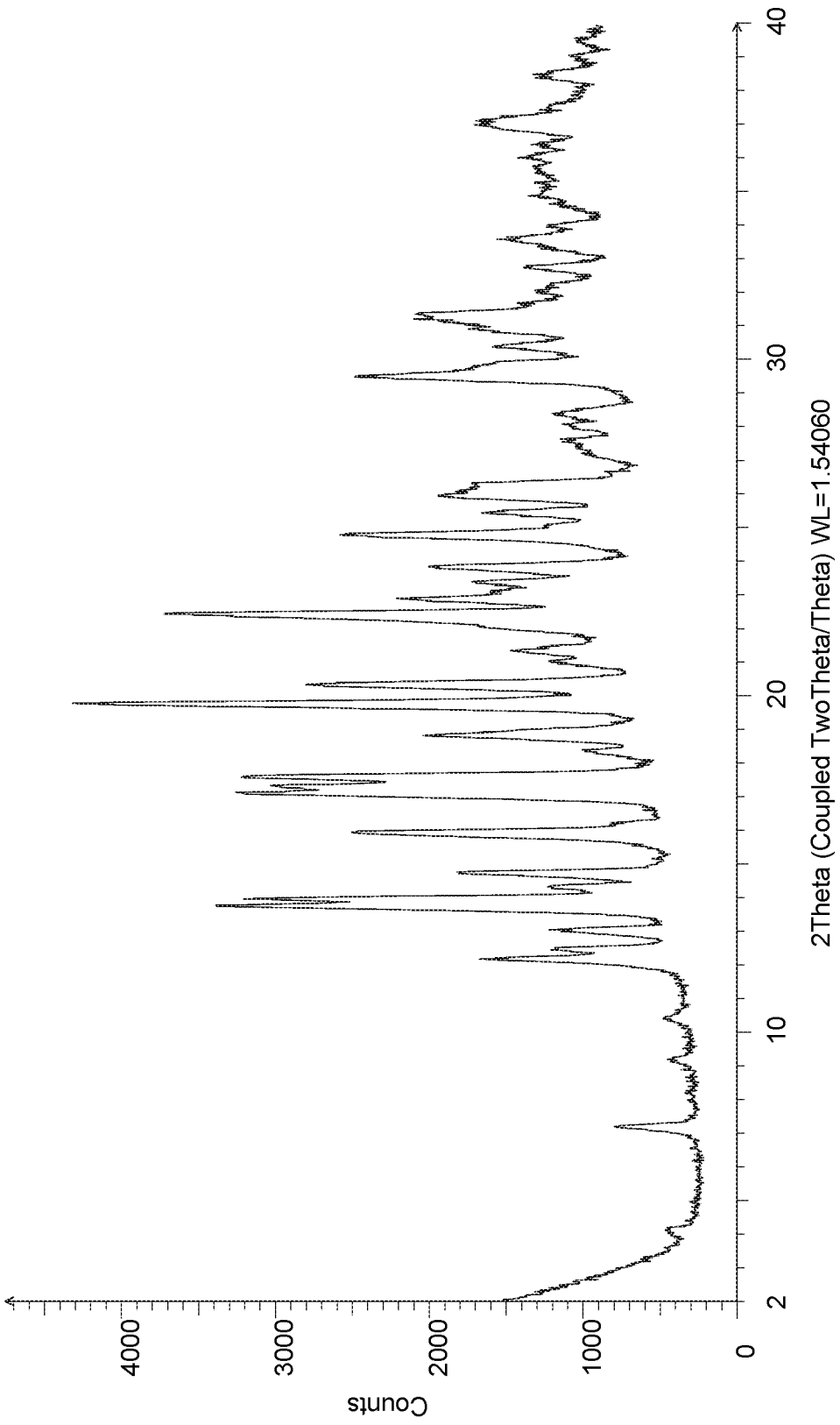


Figure 11: X-ray powder diffraction pattern for micronized crystalline Compound 1 in hemi-L-tartrate hemihydrate salt form when measured using CuK_{α} radiation



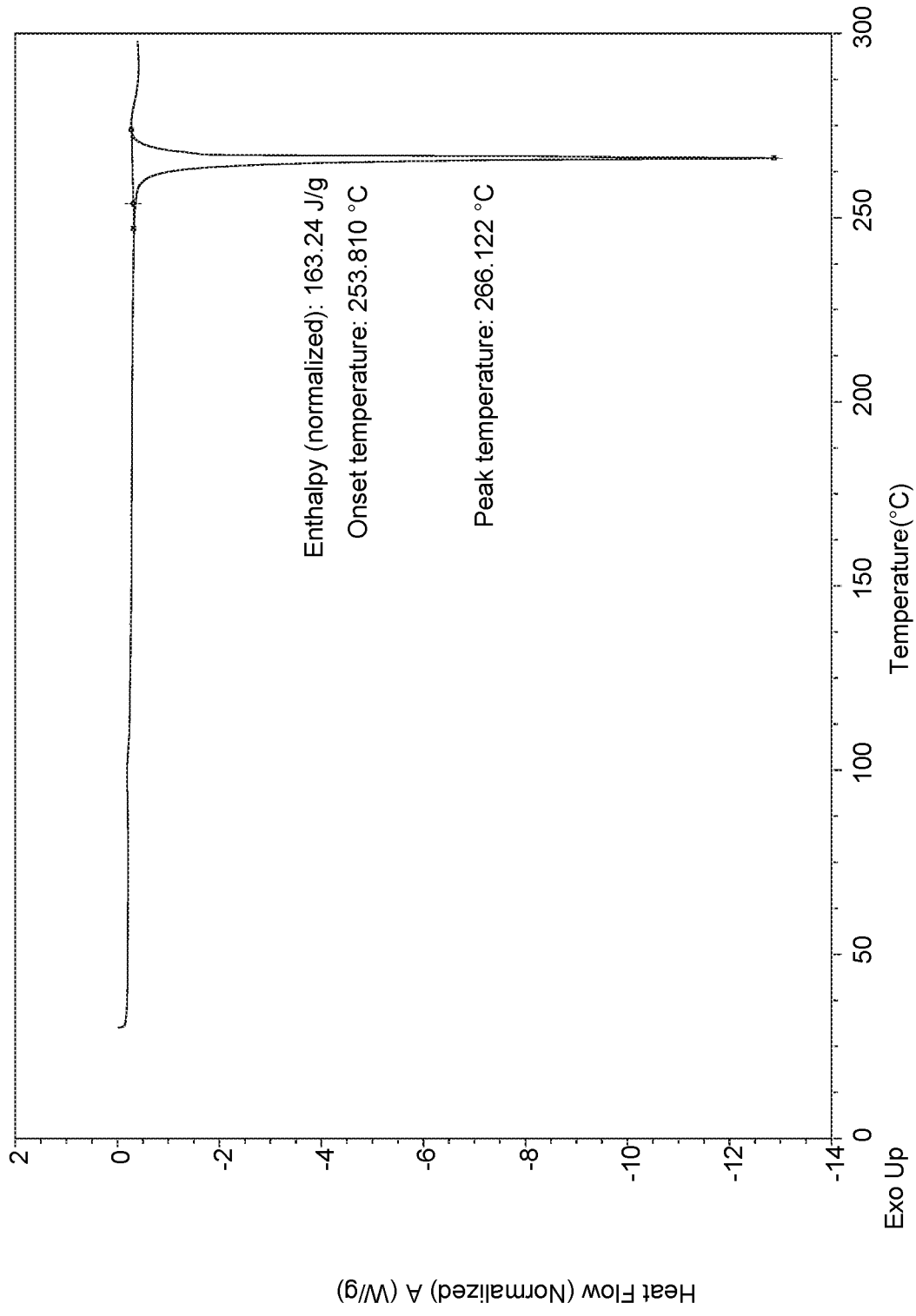
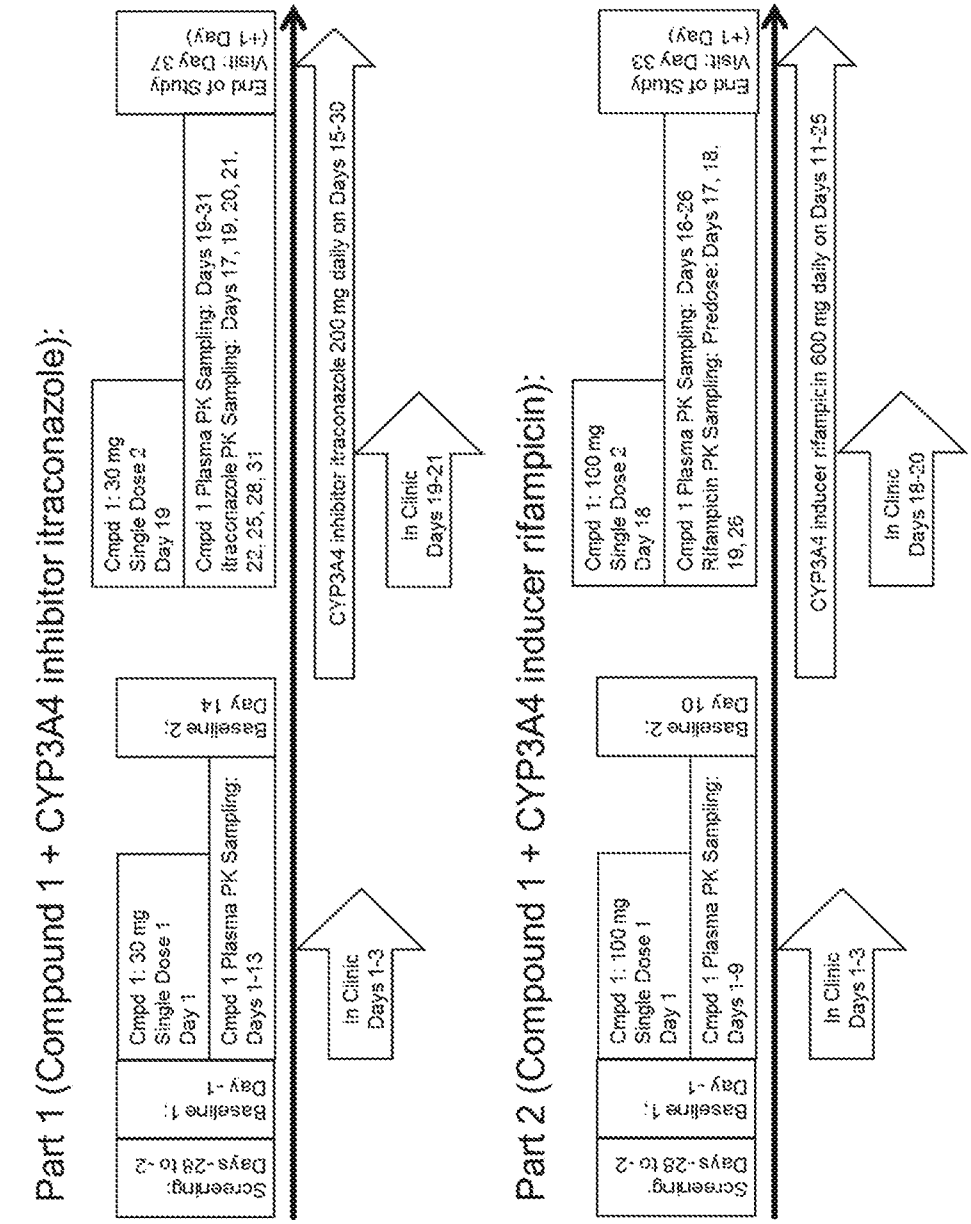


Figure 12: DSC thermogram for crystalline Compound 1 in hemi-L-tartrate hemihydrate salt form

Figure 13: Design of a two part, open-label, two-period, fixed-sequence study in healthy subjects to evaluate the PK of Compound 1 when given alone and in combination with the strong CYP3A4 inhibitor itraconazole or the strong CYP3A4 inducer rifampicin



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/050339

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14 A61P25/28 A61K31/5377
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, 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.
A	WO 2012/095469 A1 (NOVARTIS AG [CH]; BADIGER SANGAMESH [IN]; CHEBROLU MURALI [IN]; HURTH) 19 July 2012 (2012-07-19) cited in the application example 34 -----	1-21
A	RICHARD J BASTIN ET AL: "Salt Selection and Optimisation Procedures for Pharmaceutical New Chemical Entities", ORGANIC PROCESS RESEARCH AND DEVELOP, AMERICAN CHEMICAL SOCIETY, US, vol. 4, no. 5, 19 July 2000 (2000-07-19), pages 427-435, XP008154792, ISSN: 1083-6160, DOI: 10.1021/OP000018U [retrieved on 2000-07-19] abstract ----- -/--	1-18

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

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2019	01/04/2019

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	Schuemacher, Anne

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2019/050339

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2018/134761 A1 (NOVARTIS AG [CH]) 26 July 2018 (2018-07-26) claim 1 -----	1-21

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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