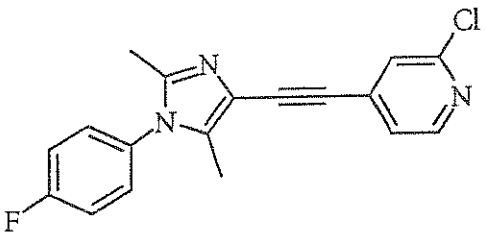
POLYMORPHS OF A MGLUR5 RECEPTOR ANTAGONIST

The present invention relates to mono-sulfate and hemi-sulfate salts of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine, to crystalline and amorphous forms thereof and to their use in pharmaceutical formulations.

2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine has been already described in published PCT patent application No. WO 2004/108701.

2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine has been described as active on the mGluR5 receptor for the treatment of diseases, related to this receptor, such acute and/or chronic neurological disorders, in particular anxiety, or for the treatment of chronic and acute pain, protection against liver damage, failure whether drug or disease induced, urinary incontinence, obesity, Fragile-X or Autism.

The present disclosure relates to mono-sulfate salt and hemi-sulfate salts of the following compound:



2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

The present disclosure relates to two distinct crystalline forms A and B of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

The present disclosure relates to the amorphous form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

The present disclosure relates to crystalline form A of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

The aforementioned salts and their crystalline and amorphous forms can be distinguished by physical and chemical properties that can be characterized by infrared spectra, X-ray powder diffraction patterns, melting behavior or glass transition temperatures.

In one aspect, there is provided a mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

In a second aspect, there is provided a hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

In a third aspect, there is provided a crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by at least three peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1 and 29.9 (± 0.2° 2Theta).

In a fourth aspect, there is provided a crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1 and 29.9 (± 0.2° 2Theta).

In a fifth aspect, there is provided a crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by the X-ray powder diffraction pattern shown on figure 1.

In a sixth aspect, there is provided a crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine according to any one of the first or third to fifth aspects

characterized by an infrared spectrum having sharp bands at 3068, 2730, 2618, 2236, 2213, 1628, 1587, 1569, 1518, 1384, 1374, 1295, 1236, 1168, 1157, 1116, 1064, 1019, 902, 855, 786 and 674 cm^{-1} ($\pm$ 3 cm^{-1})

In a seventh aspect, there is provided a crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine according to any one of first or third to sixth aspects characterized by the infrared spectrum shown on figure 2.

In an eighth aspect, there is provided a crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by at least three peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 8.9, 10.2, 14.3, 14.7, 15.4, 17.1, 18.8, 19.5, 20.9, 22.5 and 23.8 ($\pm$ 0.2° Theta).

In a ninth aspect, there is provided a crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 8.9, 10.2, 14.3, 14.7, 15.4, 17.1, 18.8, 19.5, 20.9, 22.5 and 23.8 ($\pm$ 0.2° 2Theta).

In a tenth aspect, there is provided a crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by the X-ray powder diffraction pattern shown on figure 4.

In an eleventh aspect, there is provided a crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine according to any one of the first or eighth to tenth aspects characterized by an infrared spectrum having sharp bands at 3122, 3039, 3003, 2923, 2853, 2719, 2608, 2231, 1622, 1585, 1565, 1515, 1439, 1373, 1346, 1224,1158, 1116, 1082, 1047, 1015, 987, 901, 787, and 673 ($\pm$ 3 cm^{-1})

In a twelfth aspect, there is provided a crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine according to any one of the first or eighth to eleventh aspects characterized by the infrared spectrum shown on figure 5.

In a thirteenth aspect, there is provided a crystalline form of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by at least three peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 7.4, 8.9, 11.0, 11.8, 12.8, 15.8, 17.3, 18.1, 19.8, 25.0 and 26.2 (± 0.2° 2Theta).

In a fourteenth aspect, there is provided a crystalline form of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 7.4, 8.9, 11.0, 11.8, 12.8, 15.8, 17.3, 18.1, 19.8, 25.0 and 26.2 (± 0.2° 2Theta).

In a fifteenth aspect, there is provided a crystalline form of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by the X-ray powder diffraction pattern shown on figure 7.

In a sixteenth aspect, there is provided a crystalline form of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine according to any one of the second or thirteenth to fifteenth aspects characterized by an infrared spectrum having sharp bands at 3364, 3075, 2717, 2577, 2234, 2208, 1568, 1632, 1585, 1567, 1514, 1468, 1413, 1372, 1222, 1159, 1084, 1038, 986, 902, 846, 788 712, 668 and 620 (± 3 cm^{-1})

In a seventeenth aspect, there is provided a crystalline form of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine according to any one of the second or thirteenth to sixteenth aspects characterized by the infrared spectrum shown on figure 8.

In an eighteenth aspect, there is provided an amorphous form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by an absence of sharp X-ray peaks in its XRPD pattern and/ or an infrared spectrum having sharp bands at 2730, 2592, 2219, 1633, 1586, 1570, 1513, 1375, 1226, 1157, 1130, 1115, 1084, 1040, 986, 903, 848, 788, 712 and 670 cm^{-1} ($\pm$ 3 cm^{-1}).

In a nineteenth aspect, there is provided an amorphous form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by the infrared spectrum shown on figure 11.

In a twentieth aspect, there is provided a compound according to the first aspect, wherein at least 70% are a crystalline polymorph according to any one of the first to twelfth aspects

In a twenty-first aspect, there is provided a compound according to the second aspect, wherein at least 70% are a crystalline polymorph according to any one of the thirteenth to seventeenth aspects.

In a twenty-second aspect, there is provided a compound according to the first aspect, wherein at least 70% are amorphous according to the eighteenth or nineteenth aspect.

In a twenty-third aspect, there is provided a process for the preparation of a compound of any one of the third to seventh aspects, comprising the steps of

(a) salt formation of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine with sulfuric acid in 2-propanol with subsequent spontaneous precipitation, or

(b) re-crystallization of the product of step (a) in ACN, ACN/water, methanol, ethanol, IPA, acetic acid, 1-octanol, or IPA/49% sulfuric acid (10:1, v/v).

In a twenty-fourth aspect, there is provided a process for the preparation of a compound of any one of the eighth to twelfth aspects, comprising

(a) solvent equilibration of the compound of any one of the third to seventh aspects in IPA/water (3:1 v/v), or

(b) re-crystallizing the compound of any one of the third to seventh aspects in IPA/water (e.g. 3:1 v/v), or

(c) digestion of the compound of any one of the third to seventh aspects in aqueous sulfuric acid.

In a twenty-fifth aspect, there is provided a process for the preparation of a compound of any one of the thirteenth to seventeenth aspects, comprising

(a) solvent equilibration of the compound of any one of the third to seventh aspects in water, or

(b) re-crystallizing or digesting of the compound of any one of the third to seventh aspects in water, water/methanol (e.g. 4:1, v/v), water/ethanol (e.g. 4:1, v/v), or water/2-propanol (e.g. 3:1, v/v).

In a twenty-sixth aspect, there is provided a process for the preparation of a compound of any one of the eighteenth or nineteenth aspects, comprising dissolving the compound of the first aspect in methanol and fast evaporation of the solvent at about 65°C under vacuum.

In a twenty-seventh aspect, there is provided a compound according to any one of the first to twenty-second aspects, for the use as therapeutically active substance.

In a twenty-eighth aspect, there is provided a salt according to the first or second aspect or a crystalline form according to any one of the third to seventeenth aspects or an amorphous form according to the eighteenth or nineteenth aspect for use in the prevention and/or the treatment of disorders selected from the group consisting of acute and/or chronic neurological disorders, in particular anxiety, or for the treatment of chronic and acute pain, protection against liver damage, failure whether drug or disease induced, urinary incontinence, obesity, Fragile-X or Autism.

In a twenty-ninth aspect, there is provided the use of a compound according to any one of the first to twenty-second aspects, for the preparation of a medicament for the treatment and/or prevention of disorders selected from the group consisting of acute and/or chronic neurological disorders, in particular anxiety, or for the treatment of chronic and acute pain, protection against liver damage, failure whether drug or disease induced, urinary incontinence, obesity, Fragile-X or Autism.

The present disclosure also provides pharmaceutical compositions containing the abovementioned salts, crystalline or amorphous forms, and a pharmaceutically acceptable carrier. In one aspect, there is provided a pharmaceutical composition comprising a salt according to the first or second aspect or a crystalline form according to any one of the third to seventeenth aspects or an amorphous form according to the eighteenth or nineteenth aspect, and one or more pharmaceutically acceptable carrier(s).

In accordance with the disclosure the abovementioned salts, crystalline or amorphous forms can be used for the preparation of medicaments useful in the control or prevention of illnesses based on the mGluR5 receptor. Such illnesses include acute and/or chronic neurological disorders, in particular anxiety, or for the treatment of chronic and acute pain, protection against liver damage, failure whether drug or disease induced, urinary incontinence, obesity, Fragile-X or Autism.

Figure 1: shows an XRPD (X-Ray Powder Diffraction, STOE diffractometer) pattern of a typical lot of form A of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

Figure 2: shows an IR (InfraRed spectroscopy, Nicolet spectrometer) spectrum of a typical lot of form A of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

Figure 3: shows a TGA (Thermo Gravimetric Analysis, Mettler-Toledo system) curve of a typical lot of form A of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

Figure 4: shows an XRPD (X-Ray Powder Diffraction, Scintag diffractometer) pattern of a typical lot of form B of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

Figure 5: shows an IR (Infra Red spectroscopy, Mattson spectrometer) spectrum of a typical lot of form B of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

Figure 6: shows a TGA (Thermo Gravimetric Analysis, TA Instruments system) curve of a typical lot of form B of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine

Figure 7: shows an XRPD (X-Ray Powder Diffraction, Scintag diffractometer) pattern of a typical lot of form A of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

Figure 8: shows an IR (Infra Red spectroscopy, Mattson spectrometer) spectrum of a typical lot of form A of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

Figure 9: shows a TGA (Thermo Gravimetric Analysis, TA Instruments system) curve of a typical lot of form A of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

Figure 10: shows an XRPD (X-Ray Powder Diffraction, STOE diffractometer) pattern of a typical lot of the amorphous form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

Figure 11: shows an IR (Infra Red spectroscopy, Nicolet spectrometer) spectrum of a typical lot of the amorphous form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

As used herein, "amorphous forms" or "amorphous" denote a material that lacks long range order and as such does not show sharp X-ray peaks, i.e. a Bragg diffraction peak. The XRPD pattern of an amorphous material is characterized by one or more amorphous halos.

Bragg's law describes the diffraction of crystalline material with the equation:

2d sin theta = n lambda

wherein d = perpendicular distance between pairs of adjacent planes in a crystal (d-spacing), theta = Bragg angle, lambda = wavelength and n = integer.

When Bragg's law is fulfilled, the reflected beams are in phase and interfere constructively so that *Bragg diffraction peaks* are observed in the X-ray diffraction pattern. At angles of incidence other than the Bragg angle, reflected beams are out of phase and destructive interference or cancellation occurs. Amorphous material does not satisfy Bragg's law and no *Bragg diffraction peaks* are observed in the X-ray diffraction pattern.

"An amorphous halo" is an approximately bell-shaped diffraction maximum in the X-ray powder diffraction pattern of an amorphous substance. The FWHM of an amorphous halo is bigger than two degrees in 2-theta.

"FWHM" means full width at half maximum, which is a width of a peak appearing in an XRPD pattern at its half height.

"Amorphous form of the mono-sulfate salt" is used herein as abbreviation of the amorphous form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

"API" is used herein as an acronym of active pharmaceutical ingredient.

"Form A of the mono-sulfate salt" is used herein as abbreviation for the crystalline form A of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

"Form A of the hemi-sulfate salt" is used herein as abbreviation for the crystalline form A of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

"Form B of the mono-sulfate salt" is used herein as abbreviation for the crystalline form B of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

"Free base" is used herein as the abbreviation of the free base of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

"IPA" is used herein as an acronym of 2-propanol.

'ACN' is used herein as an acronym of acetonitrile.

"IR" is used herein as an acronym of Infra Red, hence "IR spectrum" means Infra Red spectrum. IR spectra were recorded as film of a Nujol suspension of approximately 5 mg of sample and few Nujol between two sodium chloride plates, with an FTIR spectrometer in transmittance. The Spectrometer is a Nicolet™ 20SXB or equivalent (resolution 2 cm^{-1}, 32 or more coadded scans, MCT detector).

Alternatively, IR spectra were recorded as KBr disc with approximately 0.6 mg of sample and 160mg of KBr. In this case, the Spectrometer is a Mattson Galaxy 5000 FTIR system (resolution 2 cm^{-1}, 32 or more coadded scans).

"Pharmaceutically acceptable" such as pharmaceutically acceptable carriers, excipients, adjuvants, preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavoring agents, salts for varying the osmotic pressure, buffers, masking agents or antioxidants, etc., means pharmacologically acceptable and substantially non-toxic to the subject to which the particular compound is administered.

„Pharmaceutically acceptable" hence means substantially non-toxic to the subject to which the pharmaceutically acceptable material is administered.

"XRPD" is used herein as an acronym of X-Ray Powder Diffraction. X-ray diffraction patterns were recorded at ambient conditions in transmission geometry with a STOE STADI P diffractometer (Cu Kα radiation, primary monochromator, position sensitive detector, angular range 3 to 42 2Theta (deg), approximately 60 minutes total measurement time). The samples were prepared and analyzed without further processing (e.g. grinding or sieving) of the substance.

Alternatively, X-ray diffraction patterns were measured on a Scintag X1 powder X-ray diffractometer equipped with a sealed copper Kα1 radiation source. The samples were scanned from 2° to 36° 2θ (2 to 36 2Theta (deg)) at a rate of 1° per minute with incident beam slit widths of 2 and 4 mm and diffracted beam slit widths of 0.3 and 0.2 mm.

For single crystal structure analysis a single crystal was mounted in a loop on a goniometer and measured at ambient conditions. Alternatively, the crystal was cooled in a nitrogen stream during measurement. Data were collected on a STOE Imaging Plate Diffraction System (IPDS) from STOE (Darmstadt). In this case Mo-radiation of 0.71 Å wavelength was used for data collection. Data was processed with STOE IPDS-software. The crystal structure was solved and refined with standard crystallographic software. In this case the program ShelXTL from Bruker AXS (Karlsruhe) was used.

Alternatively, single crystal X-ray diffraction intensity data were measured at ambient conditions on a Bruker SMART APEX™ diffractometer (Mo Kα radiation, $\lambda = 0.71$ Å). Raw area detector data frame integration was performed with the following softwares: SMART™ Version 5.630, SAINT™+ Version 6.45 and SADABS™ Version 2.10. Bruker Analytical X-ray Systems, Inc., Madison, Wisconsin, USA, 2003. Direct methods structure solution, difference Fourier calculations and full-matrix least-squares refinement against F^2 were performed according to Sheldrick, G. M. SHELXTL™ Version 6.14; Bruker Analytical X-ray Systems, Inc., Madison, Wisconsin, USA, 2000.

"TGA" is used herein as an acronym of ThermoGravimetric Analysis. TGA curves were measured on a Mettler-Toledo™ thermogravimetric analyzer (TGA850/SDTA). System suitability tests and calibrations were carried out according to the internal standard operation procedure.

For the thermogravimetric analyses, approx. 5 -10 mg of sample were placed in aluminum pans, accurately weighed and hermetically closed with perforation lids. Prior to measurement, the lids were automatically pierced resulting in approx. 1.5 mm pin holes. The samples were then heated under a flow of nitrogen of about 50 mL/min using a heating rate of 5 K/min up to 280 °C.

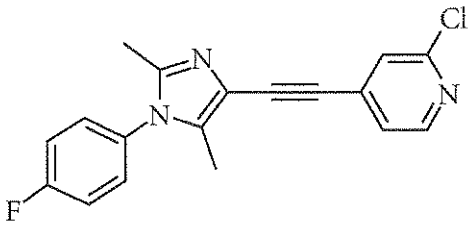
Alternatively, thermogravimetric analysis was conducted using a Hi-Res 2950 TGA from TA Instruments. The heating rate was 10°C/min with a nitrogen purge maintained throughout the run.

"Therapeutically effective amount" means an amount that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

Pharmaceutical compositions of the invention, in addition to one of the salts, crystalline or amorphous forms according to the invention mentioned hereinabove, can contain a pharmaceutically acceptable carrier or more pharmaceutically acceptable carriers. Suitable pharmaceutically acceptable carriers include pharmaceutically inert, inorganic and organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the solutions include, for example, water, polyols, sucrose, invert sugar, glucose, and the like.

The preparation of the free base 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine has been already described in published PCT patent applications Nos. WO 2004/108701, the content of which is incorporated by reference herein.

As already mentioned hereinabove, the present invention relates to novel salts and to crystalline and an amorphous form of these salts of the following compound:



2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

It has been found that 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine can be isolated, depending upon the method of preparation, as a mono-sulfate or as a hemi-sulfate salt.

Form A and form B of the mono-sulfate salt as well as an amorphous form can be isolated from the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

Form A of the hemi-sulfate salt can be obtained for the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

The mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine can be prepared by salt formation of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine with sulfuric acid in 2-propanol with subsequent spontaneous precipitation.

Form A of the mono-sulfate salt of the 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine is a solvent-free, crystalline form.

Form A of the mono-sulfate salt can be obtained by salt formation of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine with sulfuric acid in 2-propanol with subsequent spontaneous precipitation or by re-crystallization of form A of the mono-sulfate salt in solvents comprising but not limited to ACN, ACN/water, methanol, ethanol, IPA, acetic acid, 1-octanol, IPA/49% sulfuric acid (10:1, v/v).

Form A of the mono-sulfate salt can be characterized by at least three peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1 and 29.9 (± 0.2° 2Theta).

Form A of the mono-sulfate salt can be characterized by at least five peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1 and 29.9 (± 0.2° 2Theta).

Form A of the mono-sulfate salt can be characterized by at least seven peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1 and 29.9 (± 0.2° 2Theta).

Form A of the mono-sulfate salt can also be characterized by the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1 and 29.9 (± 0.2° 2Theta).

Form A of the mono-sulfate salt can also be characterized by the X-ray powder diffraction pattern shown on figure 1.

Form A of the mono-sulfate salt can also be characterized by an infrared spectrum having sharp bands at 3068, 2730, 2618, 2236, 2213, 1628, 1587, 1569, 1518, 1384, 1374, 1295, 1236, 1168, 1157, 1116, 1064, 1019, 902, 855, 786 and 674 cm^{-1} (± 3 cm^{-1}).

Form A of the mono-sulfate salt can also be characterized by the infrared spectrum shown on figure 2.

Form A of the mono-sulfate salt is a solvent-free form as no significant weight loss is observed in the TGA curve prior to decomposition as shown on figure 3.

As already mentioned hereinabove, all these characteristics are shown on figures 1 to 3 hereinafter.

A single crystal X-ray analysis of form A of the mono-sulfate salt was conducted. Table 1 lists as an example some crystal structure data. Crystal form A of the mono-sulfate salt was found to be an anhydrate form of mono-sulfate salt as determined by single crystal analysis. The experimental XRPD pattern collected with the form A of the mono-sulfate salt obtained is in excellent agreement with the simulated pattern calculated with atomic coordinates from single crystalline structure analysis, indicating that form A of the mono-sulfate salt was a pure crystalline phase. In the structure of form A of the mono-sulfate salt, the fluoro-benzene ring is almost perpendicular to the imidazole ring as indicated by a dihedral angle of 90.7°. A hydroxyl group of a bisulfate anion forms an intermolecular

hydrogen bond with an oxygen atom of a neighboring bisulfate anion. This bisulfate anion also serves as a hydrogen bond acceptor from a protonated imidazole nitrogen atom.

Table 1: crystal structure data of form A of the mono-sulfate salt

Name	Form A of the mono-sulfate salt
Temperature	293(2) K
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 9.996(2) Å α = 98.60(3)° b = 9.996(2) Å β = 98.97(3)° c = 11.287(2) Å γ = 112.49(3)°
Cell volume	1001.9(3)Å^3
Molecules in unit cell	2
Density (calculated)	1.398 g/cm^3

Form B of the mono-sulfate salt is a mono-hydrate crystalline form.

Form B of the mono-sulfate salt can be obtained by solvent equilibration of form A of the mono-sulfate salt in IPA/water (e.g. 3:1 v/v). Form B of the mono-sulfate salt can also be prepared by re-crystallization of form A of the mono-sulfate salt in IPA/water (e.g. 3:1 v/v). Form B of the mono-sulfate salt can further be obtained upon digestion of form A of the mono-sulfate salt in e.g. aqueous sulfuric acid.

Form B of the mono-sulfate salt can be characterized by at least three peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 8.9, 10.2, 14.3, 14.7, 15.4, 17.1, 18.8, 19.5, 20.9, 22.5 and 23.8 (± 0.2° 2Theta).

Form B of the mono-sulfate salt can be characterized by at least five peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 8.9, 10.2, 14.3, 14.7, 15.4, 17.1, 18.8, 19.5, 20.9, 22.5 and 23.8 (± 0.2° 2Theta).

Form B of the mono-sulfate salt can be characterized by at least seven peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 8.9, 10.2, 14.3, 14.7, 15.4, 17.1, 18.8, 19.5, 20.9, 22.5 and 23.8 (± 0.2° 2Theta).

Form B of the mono-sulfate salt can also be characterized by the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 8.9, 10.2, 14.3, 14.7, 15.4, 17.1, 18.8, 19.5, 20.9, 22.5 and 23.8 (± 0.2° 2Theta).

Form B of the mono-sulfate salt can also be characterized by the X-ray powder diffraction pattern shown on figure 4.

Form B of the mono-sulfate salt can also be characterized by an infrared spectrum having sharp bands at 3122, 3039, 3003, 2923, 2853, 2719, 2608, 2231, 1622, 1585, 1565, 1515, 1439, 1373, 1346, 1224,1158, 1116, 1082, 1047, 1015, 987, 901, 787, and 673 (± 3 cm^{-1}).

Form B of the mono-sulfate salt can also be characterized by the infrared spectrum shown on figure 5.

Form B of the mono-sulfate salt is a monohydrate with a corresponding weight loss in the TGA curve as shown on figure 6.

As mentioned hereinabove, all these characteristics are shown on figures 4 to 6 hereinafter.

A room temperature single crystal X-ray analysis of form B of the mono-sulfate salt was conducted. As an example table 2 lists some crystal structure data.

Form B of the mono-sulfate salt was found to be a mono-hydrate of the mono-sulfate salt as determined by single crystal analysis. The experimental XRPD pattern collected with the form B of the mono-sulfate salt obtained is in excellent agreement with the simulated pattern calculated with atomic coordinates from single crystal structure analysis, indicating

that form B of the mono-sulfate salt was a pure crystalline phase. In the structure of form B of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine, the dihedral angle between the fluoro-benzene ring and the imidazole ring was found to be approximately 77. 3°. The protonated imidazole nitrogen atom forms an intermolecular hydrogen bond with a bisulfate anion. At the same time, the bisulfate anion is also involved in hydrogen bonding networks with a chloro-pyridine nitrogen atom and a water molecule.

Table 2: Crystal structure data and structure refinement for form B of the mono-sulfate salt

Name	Form B of the mono-sulfate salt
Temperature	294(2) K
Crystal system, Space group	Triclinic, P-1
Unit cell dimensions	a = 8.9686(5) Å α = 107.0630(10) ° b = 10.6790(6) Å β = 100.1590(10)°. c = 10.9563(6) Å γ = 96.6930(10) °
Cell volume	971.51(9)Å^3
molecules in unit cell	2
Density (calculated)	1.510 g/cm^3

The amorphous form of mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine can be obtained from a methanol solution upon fast evaporation at about 65 °C under vacuum.

The amorphous form of mono-sulfate salt can be characterized by the lack of sharp X-ray diffraction peaks in its XRPD pattern; and/or an infrared spectrum having sharp bands at 2730, 2592, 2219, 1633, 1586, 1570, 1513, 1375, 1343, 1293, 1226, 1157, 1130, 1084, 1040, 986, 903, 848, 788, 712 and 670 cm^{-1} (± 3 cm^{-1}).

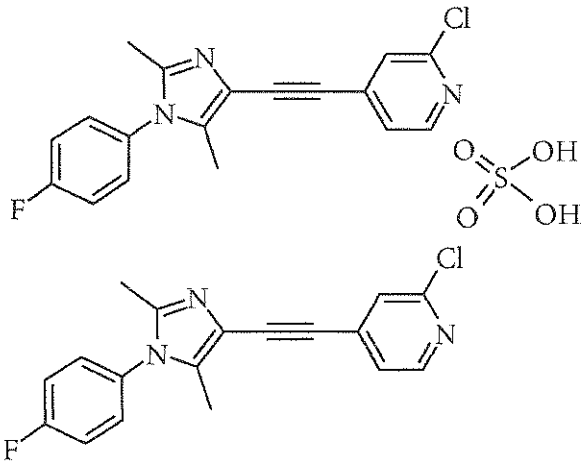
The amorphous form of mono-sulfate salt can also be characterized by the infrared spectrum shown on figure 11.

As mentioned hereinabove, all these characteristics are shown on figures 10 to 11 hereinafter.

The hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine can be prepared by solvent equilibration of form A of the mono-sulfate salt in water.

Form A of the hemi-sulfate salt can be obtained by solvent equilibration of form A of the mono-sulfate salt in water. It can also be prepared by re-crystallization or digestion of form A of the mono-sulfate salt in solvent systems comprising but not limited to water, water/methanol (e.g. 4:1, v/v), water/ethanol (e.g. 4:1, v/v), water/2-propanol (e.g. 3:1, v/v).

Form A of the hemi-sulfate salt is a crystalline hemi-hydrate form of the following salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine with sulfuric acid (2:1) (hemi sulfate salt of the 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine free base):



Form A of the hemi-sulfate salt can be characterized by at least three peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 7.4, 8.9, 11.0, 11.8, 12.8, 15.8, 17.3, 18.1, 19.8, 25.0 and 26.2 (± 0.2° 2Theta).

Form A of the hemi-sulfate salt can be characterized by at least five peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 7.4, 8.9, 11.0, 11.8, 12.8, 15.8, 17.3, 18.1, 19.8, 25.0 and 26.2 (± 0.2° 2Theta).

Form A of the hemi-sulfate salt can be characterized by at least seven peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 7.4, 8.9, 11.0, 11.8, 12.8, 15.8, 17.3, 18.1, 19.8, 25.0 and 26.2 (± 0.2° 2Theta).

Form A of the hemi-sulfate salt can also be characterized by the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 7.4, 8.9, 11.0, 11.8, 12.8, 15.8, 17.3, 18.1, 19.8, 25.0 and 26.2 (± 0.2° 2Theta).

Form A of the hemi-sulfate salt can also be characterized by the X-ray powder diffraction pattern shown on figure 7.

Form A of the hemi-sulfate salt can also be characterized by an infrared spectrum having sharp bands at 3364, 3075, 3004, 2922, 2851, 2717, 2208, 1658, 1632, 1585, 1567, 1514,1413, 1372, 1159, 1122, 1038, 986, 902, 846, 821, 788, 721, 712, and 668 (± 3 cm^{-1}).

Form A of the hemi-sulfate salt can also be characterized by the infrared spectrum shown on figure 8.

Form A of the hemi-sulfate salt is a hemi-hydrate with a corresponding weight loss in the TGA curve as shown on figure 9.

As already mentioned hereinabove, all these characteristics are shown on figures 7 to 9 hereinafter.

A low and room temperature single crystal X-ray analysis of form A of the hemi-sulfate salt was conducted. Table 3 lists as an example some crystal structure data.

Form A of the hemi-sulfate salt was found to be a hemi-hydrate of the hemisulfate as determined by single crystal structure analysis. In the structure of form A of the hemi-sulfate salt, there are two API molecules in the asymmetric unit. The experimental XRPD

pattern collected was consistent with the simulated pattern calculated with atomic coordinates from single crystal structure analysis, indicating a pure crystalline phase. The conformations of these two API molecules are slightly different as indicated by the dihedral angle differences between the fluoro-benzene ring and the imidazole ring (approximately 70° *vs* approximately 61°); however, in both molecules, the chloro-pyridine rings are almost co-planer to the imidazole ring as demonstrated by very small dihedral angles (approximately 5° *vs* approximately 6°). The protonated imidazole nitrogen atoms form intermolecular hydrogen bonds with a sulfate anion and a water molecule. At the same time, the water molecule is also involved in hydrogen bonding with two sulfate anions.

Table 3: Crystal structure data and structure refinement for form A of the hemi-sulfate salt

Name	Form A of the hemi-sulfate salt
Temperature	294(2) K
Crystal system, Space group	Monoclinic, C2/c
Unit cell dimensions	a = 18.3260(13) Å α = 90 ° b = 17.0770(12) Å β = 109.002(1)° c = 25.1530(18) Å γ = 90 °
Cell volume	7442.8(9)Å^3
molecules in unit cell	8
Density (calculated)	1.370 Mg/m^3

The salt can be formulated at low or high concentrations in a composition further comprising usual pharmaceutically acceptable adjuvants known in the art.

The present invention also provides pharmaceutical compositions containing one or more of the following species:

- a mono- or hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;
- form A or B of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;
- form A of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine;

- the amorphous form of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

and a pharmaceutically acceptable carrier.

Further, the pharmaceutical compositions may comprise more pharmaceutically acceptable carriers and/or one or more adjuvant(s).

These pharmaceutical compositions can be in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The invention also provides a process for the production of such compositions, which comprises bringing the aforementioned modifications and forms into a galenical administration form together with one or more therapeutically inert carriers.

In addition, the pharmaceutical compositions can contain pharmaceutically acceptable preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavoring agents, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

In one embodiment of the invention, the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine comprises at least 70% of a crystalline polymorph of form A or B as described above, preferably at least 90%, more preferably at least 95%, and most preferably at least 99%.

In one embodiment of the invention, the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine comprises at least 70% of an amorphous form as described above, preferably at least 90%, more preferably at least 95%, and most preferably at least 99%.

In one embodiment of the invention, the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine comprises at least 70% of a crystalline polymorph of form A as described above, preferably at least 90%, more preferably at least 95%, and most preferably at least 99%.

In accordance with the invention, the salts, crystalline or amorphous forms according to the invention mentioned hereinabove can be used for the preparation of medicaments useful in the treatment or prevention of illnesses in which the mGluR5 receptors play a role. Such illnesses include acute and/or chronic neurological disorders, in particular

anxiety, or for the treatment of chronic and acute pain, protection against liver damage, failure whether drug or disease induced, urinary incontinence, obesity, Fragile-X or Autism.

The salts and crystalline and amorphous forms of the compounds of the invention can be used in method of treating an illness selected from the group consisting of acute and/or chronic neurological disorders, in particular anxiety, or for the treatment of chronic and acute pain, protection against liver damage, failure whether drug or disease induced, urinary incontinence, obesity, Fragile-X or Autism, which method comprises administering to an individual an effective amount of one species selected from the group consisting of the salts, crystalline or amorphous forms according to the invention mentioned hereinabove.

The dosage at which the salts, crystalline or amorphous forms according to the invention are administered can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg, preferably from about 0.05 mg to about 20 mg, and still more preferably from about 0.5 mg to about 5 mg per day. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.
In a further embodiment, the dosage at which the salts, crystalline or amorphous forms according to the invention are administered ranges from about 0.001 mg to about 5 mg, preferably from about 0.001 mg to about 3 mg, from about 0.001 to about 2 mg, or from about 0.001 to about 1 mg.

Example 1

Preparation of form A of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine

General

Form A of the mono-sulfate salt of 2-chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine can be formed upon salt formation with or without seeding with form A of the mono-sulfate salt in an appropriate solvent system as e.g. 2-propanol/water, or by re-crystallization of form A of the mono-sulfate salt in solvents

comprising but not limited to acetonitrile, acetonitrile /water, methanol, ethanol, 2-propanol, acetic acid, 1-octanol, 2-propanol /49% sulfuric acid (10:1, v/v).

Preparation procedure

61.0 g of 2-chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine was dissolved in 610 mL of 2-propanol. The solution was filtered and the filter rinsed with 31 mL of 2-propanol. To the combined solutions a mixture of 30 mL of water and 18.91 g of sulfuric acid (97 %) was added drop-wise. The solution was cooled to 0-5 °C. Seeding was performed at 58 °C as needed. The solid residues were filtered, washed with 2-propanol (0-5 °C) and dried at 50 °C / <1 mbar for 18 h. Yield: 69.1 g (87.1 %).

Form A seeding crystals can be prepared upon cooling crystallization of a hot solution of 250 mg of the mono-sulfate salt of 2-chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine in 10 ml of 2-propanol. After cooling to 0 °C the solid residues can be filtered and dried at 50 °C under vacuum.

Solid state properties of form A of the mono-sulfate salt

XRPD-pattern, IR-spectrum and TGA-curve of a typical lot of form A of the mono-sulfate salt are listed in Figures 1 to 3.

Example 2

Preparation of form B of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine

General

Form B of the mono-sulfate salt of 2-chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine can be produced by solvent equilibration of form A of the mono-sulfate salt in solvent systems as e.g. 2-propanol/water or 1 N sulfuric acid, or upon seeded cooling crystallization of the mono-sulfate salt of 2-chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine in solvent systems as e.g. 2-propanol/water.

Preparation procedure

300 mg of form A of the mono-sulfate salt of 2-chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine was dissolved in 3 ml 2-propanol and 1 ml water at 60°C to produce a clear solution. The clear solution was seeded with form B of the mono-sulfate salt and sealed at room temperature. Single crystals were formed after 3 days.

Seeding crystals can be prepared by formation of a saturated slurry of form A of the mono-sulfate salt of 2-chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine in 2-propanol and water (3 : 1 v/v) at room temperature. The slurry was stirred at room temperature for approximately 3 weeks. The solids were filtered via a glass filter to afford crystalline form B of the mono-sulfate salt as a wet cake.

Solid state properties of form B of the mono-sulfate salt

XRPD-pattern, IR-spectrum and TGA-curve of a typical lot of form B of the mono-sulfate salt are listed in Figures 4 to 6.

Example 3

Preparation of form A of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine

General

Form A of the hemi-sulfate salt of 2-chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine can be produced by solvent equilibration of form A of the mono-sulfate salt in solvents as e.g. water. It can also be prepared by re-crystallization or digestion of form A of the mono-sulfate salt in solvent systems comprising but not limited to water, water/methanol (e.g. 4:1, v/v), water/ethanol (e.g. 4:1, v/v), water/2-propanol (e.g. 3:1, v/v).

Preparation procedure

41 g of form A of the mono-sulfate of 2-chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine was mixed with 128 g of water. The slurry was stirred at room temperature for 2-16h. After all the form A of the mono-sulfate salt had been converted to the hemi sulfate salt the crystals were collected by filtration and rinsed with water. The wet cake was dried at 40 °C in a vacuum oven for 48 hrs. The yield was ~93%.

Solid state properties of form A of the hemi-sulfate salt

XRPD-pattern, IR-spectrum and TGA-curve of a typical lot of form A of the hemi-sulfate salt are listed in Figures 7 to 9.

Example 4

Preparation of the amorphous form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine

Formation of the amorphous form

Amorphous mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine is accessible upon fast evaporation of a solution in an a appropriate solvent, preferably methanol.

Fast Evaporation

0.53 g of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine was dissolved in 10 mL of methanol at approximately 65 °C. After complete evaporation of the solvent under vacuum, the solid (foam) was further dried at ca. 50 °C / 5-20 mbar for 18 h. Analysis revealed amorphous 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

Solid state properties of the amorphous form

XRPD-pattern and IR-spectrum of the amorphous form are listed in Figures 10 to 11.

Formulation

Capsule Formulation (Wet granulation)

Item	Ingredients	mg/capsule			
		0.05 mg	0.5 mg	2.0 mg	20.0 mg
1.	Form A of monosulfate salt	0.065	0.650	2.602	26.02
2.	Lactose Monohydrate	108.934	109.349	107.398	83.98
3.	Starch Maize Partially Pregelatinized (type 1500)	60.00	60.00	60.00	60.00
4.	Croscarmellose Sodium	8.00	8.00	8.00	8.00
5.	Povidone 30	15.00	15.00	15.00	15.00
6.	Sodium lauryl sulfate	1.00	---	---	---
7.	Talc	6.00	6.00	6.00	6.00
8.	Magnesium Stearate	1.00	1.00	1.00	1.00
	Total	200.00	200.00	200.00	200.00

Manufacturing Procedure

1. Mix items 1, 2, 3, 4, 5 and 6 in a suitable mixer for 30 minutes.
2. Add items 7 and 8 and mix for 3 minutes.
3. Fill into a suitable capsule.

Claims

1. A mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

2. A hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine.

3. A crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by at least three peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1 and 29.9 (± 0.2° 2Theta).

4. A crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 9.8, 13.4, 14.2, 18.1, 18.9, 19.6, 22.6, 22.9, 25.7, 27.1 and 29.9 (± 0.2° 2Theta).

5. A crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by the X-ray powder diffraction pattern shown on figure 1.

6. A crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine according to any one of claim 1 or 3 to 5 characterized by an infrared spectrum having sharp bands at 3068, 2730, 2618, 2236, 2213, 1628, 1587, 1569, 1518, 1384, 1374, 1295, 1236, 1168, 1157, 1116, 1064, 1019, 902, 855, 786 and 674 cm^{-1} (± 3 cm^{-1})

7. A crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine according to any one of claim 1 or 3 to 6 characterized by the infrared spectrum shown on figure 2.

8. A crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by at least three peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 8.9, 10.2, 14.3, 14.7, 15.4, 17.1, 18.8, 19.5, 20.9, 22.5 and 23.8 (± 0.2° Theta).

9. A crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 8.9, 10.2, 14.3, 14.7, 15.4, 17.1, 18.8, 19.5, 20.9, 22.5 and 23.8 (± 0.2° 2Theta).

10. A crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by the X-ray powder diffraction pattern shown on figure 4.

11. A crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine according to any one of claims 1 or 8 to 10 characterized by an infrared spectrum having sharp bands at 3122, 3039, 3003, 2923, 2853, 2719, 2608, 2231, 1622, 1585, 1565, 1515, 1439, 1373, 1346, 1224,1158, 1116, 1082, 1047, 1015, 987, 901, 787, and 673 (± 3 cm^{-1})

12. A crystalline form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine according to any one of claim 1 or 8 to 11 characterized by the infrared spectrum shown on figure 5.

13. A crystalline form of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by at least three peaks selected from the following X-ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 7.4, 8.9, 11.0, 11.8, 12.8, 15.8, 17.3, 18.1, 19.8, 25.0 and 26.2 (± 0.2° 2Theta).

14. A crystalline form of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by the following X-

ray diffraction peaks obtained with a $Cu_{K\alpha}$ radiation at 2θ (2Theta (deg)) = 7.4, 8.9, 11.0, 11.8, 12.8, 15.8, 17.3, 18.1, 19.8, 25.0 and 26.2 (± 0.2° 2Theta).

15. A crystalline form of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by the X-ray powder diffraction pattern shown on figure 7.

16. A crystalline form of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine according to any one of claims 2 or 13 to 15 characterized by an infrared spectrum having sharp bands at 3364, 3075, 2717, 2577, 2234, 2208, 1568, 1632, 1585, 1567, 1514, 1468, 1413, 1372, 1222, 1159, 1084, 1038, 986, 902, 846, 788 712, 668 and 620 (± 3 cm^{-1})

17. A crystalline form of the hemi-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine according to any one of claim 1 or 13 to 16 characterized by the infrared spectrum shown on figure 8.

18. An amorphous form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by an absence of sharp X-ray peaks in its XRPD pattern and/ or an infrared spectrum having sharp bands at 2730, 2592, 2219, 1633, 1586, 1570, 1513, 1375, 1226, 1157, 1130, 1115, 1084, 1040, 986, 903, 848, 788, 712 and 670 cm^{-1} (± 3 cm^{-1}).

19. An amorphous form of the mono-sulfate salt of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine characterized by the infrared spectrum shown on figure 11.

20. A compound according to claim 1, wherein at least 70% are a crystalline polymorph according to any one of claims 1 to 12.

21. A compound according to claim 2, wherein at least 70% are a crystalline polymorph according to any one of claims 13 to 17.

22. A compound according to claim 1, wherein at least 70% are amorphous according to claim 18 or 19.

23. A pharmaceutical composition comprising a salt according to claim 1 or 2 or a crystalline form according to any one of claim 3 to 17 or an amorphous form according to claim 18 or 19 and one or more pharmaceutically acceptable carriers.

24. A process for the preparation of a compound of any one of claims 3 to 7, comprising the steps of

(a) salt formation of 2-Chloro-4-[1-(4-fluoro-phenyl)-2,5-dimethyl-1H-imidazol-4-ylethynyl]-pyridine with sulfuric acid in 2-propanol with subsequent spontaneous precipitation, or

(b) re-crystallization of the product of step (a) in ACN, ACN/water, methanol, ethanol, IPA, acetic acid, 1-octanol, or IPA/49% sulfuric acid (10:1, v/v).

25. A process for the preparation of a compound of any one of claims 8 to 12, comprising

(a) solvent equilibration of the compound of any one of claims 3 to 7 in IPA/water (3:1 v/v), or

(b) re-crystallizing the compound of any one of claims 3 to 7 in IPA/water (e.g. 3:1 v/v), or

(c) digestion of the compound of any one of claims 3 to 7 in aqueous sulfuric acid.

26. A process for the preparation of a compound of any one of claims 13 to 17, comprising

(a) solvent equilibration of the compound of any one of claims 3 to 7 in water, or

(b) re-crystallizing or digesting of the compound of any one of claims 3 to 7 in water, water/methanol (e.g. 4:1, v/v), water/ethanol (e.g. 4:1, v/v), or water/2-propanol (e.g. 3:1, v/v).

27. A process for the preparation of a compound of any one of claims 18 or 19, comprising dissolving the compound of claim 1 in methanol and fast evaporation of the solvent at about 65°C under vacuum.

28. A compound according to any one of claims 1 to 22, for the use as therapeutically active substance.

29. A salt according to claim 1 or 2 or a crystalline form according to any one of claim 3 to 17 or an amorphous form according to claim 18 or 19 for use in the prevention and/or the treatment of disorders selected from the group consisting of acute and/or chronic neurological disorders, in particular anxiety, or for the treatment of chronic and acute pain, protection against liver damage, failure whether drug or disease induced, urinary incontinence, obesity, Fragile-X or Autism.

30. Use of a compound according to any one of claims 1 to 22, for the preparation of a medicament for the treatment and/or prevention of disorders selected from the group consisting of acute and/or chronic neurological disorders, in particular anxiety, or for the treatment of chronic and acute pain, protection against liver damage, failure whether drug or disease induced, urinary incontinence, obesity, Fragile-X or Autism.