between inclusion complex former and API). The formation of cyclodextrin inclusion complexes and their guest to host stoichiometries are highly dependent on the molecular structures and the geometrical sizes of the guest molecules [*T. Uyar et al., Cryst. Growth Des. (2006) 6:1113-1119*].

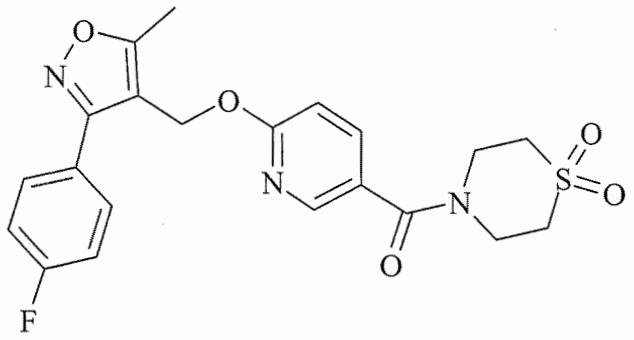
The compound of formula (I), its manufacture, its pharmacological activity as inverse agonists of the GABA A α5 receptor, and its use for the treatment, prevention and/or delay of progression of various central nervous system (CNS) conditions have been described in WO 2009/071476. Based on its physicochemical properties, the compound of formula (I), as described in WO 2009/071476, is a BCS 2 compound, exhibiting low aqueous solubility and high permeability, according to the biopharmaceutical classification system [*G.L. Amidon, H. Lennernas, V.P. Shah, J.R. Crison, Pharm. Res. (1995) 12:413-420*]. Hence the limited oral bioavailability is a major issue for oral formulation development.

If anhydrous solid forms of the compound of formula (I), as described in WO 2009/071476, are selected for clinical development, a physical instability in terms of hydrate formation during pharmaceutical processing and/or storage of the drug product is possible. Anhydrous solid form A of the compound of formula (I) as described in WO 2009/071476 and herein, has further been found to be only metastable and hence may convert into different solid forms. Hence there is a need to find new solid forms which feature enhanced physicochemical properties and improved bioavailability.

Further, the discovery of new solid forms of an API (polymorphs, solvates, salts, inclusion complexes) enlarges the repertoire of materials that a formulation scientist has available with which to design a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristics. Therefore, there is a need to find more solid forms of the compound of formula (I).

It has now been surprisingly found, that under certain conditions new solid forms, particularly crystalline or amorphous forms, most particularly crystalline forms, of the compound of formula (I) may be obtained, which are described hereinafter, which have advantageous utilities and properties. They exhibit substantially different and superior physical and physicochemical properties which may be beneficial in various aspects relevant in API and drug product development, e.g. for dissolution of API, stability and shelf live of API and drug product, and/or facilitated routes of manufacturing or purification. The instant ~~invention~~ disclosure provides novel solid forms of the compound of formula (I) with improved solubility, dissolution rate, oral bioavailability as well as increased stability of the API.

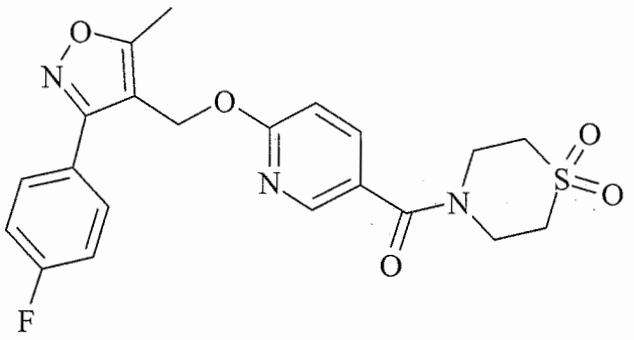
In a first aspect, there is provided a solid form of the compound of formula (I)



(I),

having an XRPD pattern comprising at least one XRPD peak in the range of angles of diffraction 2Theta of 10.3° to 13.3°, wherein the solid form is crystalline (1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone in anhydrous polymorphic form C.

In a second aspect, there is provided a high-shear process for preparing a solid form of a compound of formula (I)



(I),

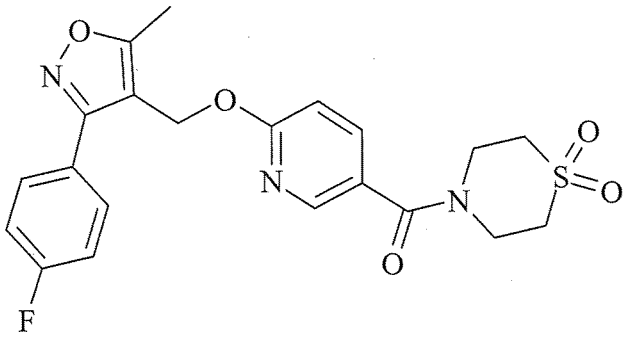
having an XRPD pattern comprising at least one XRPD peak in the range of angles of diffraction 2Theta of 10.3° to 13.3°, comprising:

a) injecting a solution of an educt solid form of compound (I) in a solvent into a high-shear mixer having a rotor-stator systemcomprising an antisolvent;

b) agitating the rotor-stator system of the high-shear mixer to form a suspension; and

c) physically separating the solid form from from the suspension.

In a third aspect, there is provided a pharmaceutical composition comprising a solid form of a compound of formula (I)



(I),

having an XRPD pattern comprising at least one XRPD peak in the range of angles of diffraction 2Theta of 10.3° to 13.3°,

and a pharmaceutically acceptable excipient,

wherein the solid form is crystalline (1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone in anhydrous polymorphic form C,

wherein the pharmaceutical composition is administered in an administrative form selected from tablets, powders, and capsules

In addition, the instant ~~invention~~ disclosure provides novel inclusion complexes of compounds of formula (I) with cyclodextrins. Such inclusion complexes further feature improved dissolution rate and bioavailability.

The new solid forms as described herein are distinguishable by X-ray powder diffraction, crystal structure analysis, vibrational spectroscopy, magnetic resonance and mass spectroscopy, calorimetry, thermogravimmetry, dynamic vapour sorption as well as by microscopy.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The nomenclature used in this Application is based on IUPAC systematic nomenclature, unless indicated otherwise.

Any open valency appearing on a carbon, oxygen, sulfur or nitrogen atom in the structures herein indicates the presence of a hydrogen, unless indicated otherwise.

The term "optional" or "optionally" denotes that a subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

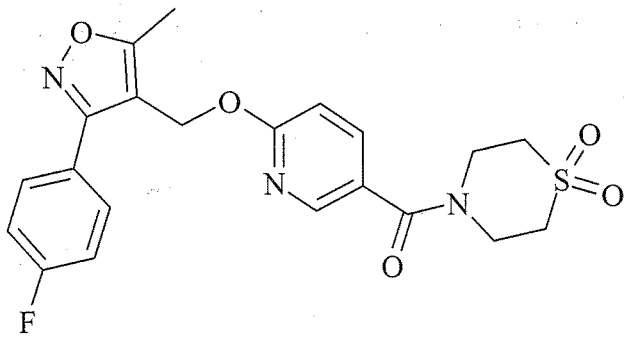
The term "substituent" denotes an atom or a group of atoms replacing a hydrogen atom on the parent molecule.

The term "substituted" denotes that a specified group bears one or more substituents. Where any group may carry multiple substituents and a variety of possible substituents is provided, the substituents are independently selected and need not to be the same. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents, independently chosen from the group of possible substituents. When indicating the number of substituents, the term "one or more" means from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

The term "halogen" denotes fluoro, chloro, bromo, or iodo. Particular halogen is fluoro.

Claims

1. A solid form of the compound of formula (I)



(I),

having an XRPD pattern comprising at least one XRPD peak in the range of angles of diffraction 2Theta of 10.3° to 13.3°, wherein the solid form is crystalline (1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone in anhydrous polymorphic form C.

2. The compound of claim 1, comprising crystalline 1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone in anhydrous polymorphic form C, having an XRPD diffraction pattern comprising XRPD peaks at angles of diffraction 2Theta of approximately 17.4°, 23.4°.

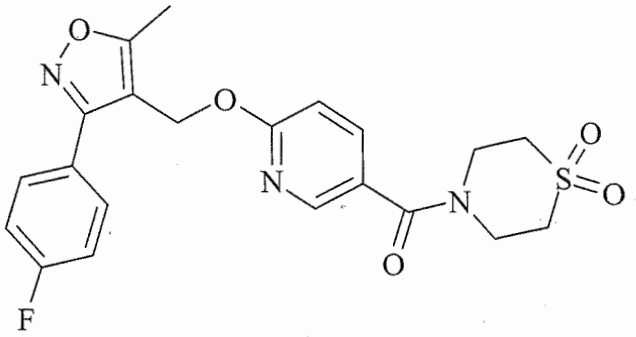
3. The compound of claim 1, having crystalline polymorphic form C, having the XRPD diffraction pattern of Fig. 3.

4. The compound of claim 1, comprising crystalline polymorphic form C, having the FTIR spectrum of Fig. 10.

5. The compound of claim 1, comprising crystalline polymorphic form C, having the Raman spectrum of Fig. 16.

6. The solid form of claim 1, having a purity of at least 90% (w/w).

7. A high-shear process for preparing a solid form of a compound of formula (I)



(I),

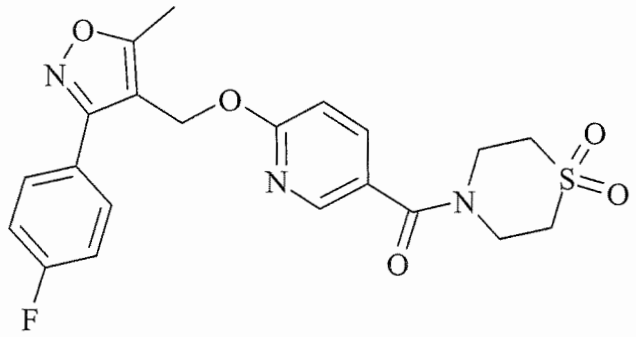
having an XRPD pattern comprising at least one XRPD peak in the range of angles of diffraction 2Theta of 10.3° to 13.3°, comprising:

a) injecting a solution of an educt solid form of compound (I) in a solvent into a high-shear mixer having a rotor-stator systemcomprising an antisolvent;

b) agitating the rotor-stator system of the high-shear mixer to form a suspension; and

c) physically separating the solid form from from the suspension.

8. A pharmaceutical composition comprising a solid form of a compound of formula (I)



(I),

having an XRPD pattern comprising at least one XRPD peak in the range of angles of diffraction 2Theta of 10.3° to 13.3°,

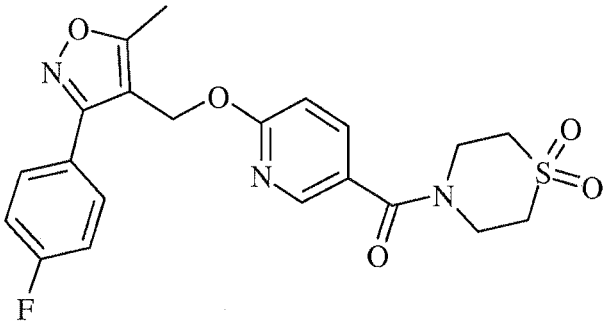
and a pharmaceutically acceptable excipient,

wherein the solid form is crystalline (1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone in anhydrous polymorphic form C,

wherein the pharmaceutical composition is administered in an administrative form selected from tablets, powders, and capsules.

Claims

1. A solid form of a compound of formula (I)



(I),

or a solvate thereof;
or an inclusion complex thereof with one or more inclusion complex forming agents;
or a solvate of an inclusion complex thereof with one or more inclusion complex forming agents;
characterized by an XRPD pattern comprising at least one XRPD peak in the range of angles of diffraction 2Theta of 10.3° to 13.3°.

2. Crystalline (1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone monohydrate in polymorphic form B according to claim 1, characterized by an XRPD diffraction pattern comprising XRPD peaks at angles of diffraction 2Theta of approximately 13.3°, 20.6°, 22.5°.

3. Crystalline polymorphic form B according to claim 2, characterized by the XRPD diffraction pattern of figure 2.

4. Crystalline polymorphic form B according to any of claims 2 or 3, characterized by the FTIR spectrum of figure 9.

5. Crystalline polymorphic form B according to any of claims 2 to 4, characterized by the Raman spectrum of figure 15.

6. Crystalline 1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone in anhydrous polymorphic form C according to claim 1, characterized by an XRPD diffraction pattern comprising XRPD peaks at angles of diffraction 2Theta of approximately 17.4°, 23.4°.

7. Crystalline polymorphic form C according to claim 6, characterized by the XRPD diffraction pattern of figure 3.

8. Crystalline polymorphic form C according to any of claims 6 or 7, characterized by the FTIR spectrum of figure 10.

9. Crystalline polymorphic form C according to any of claims 6 to 8, characterized by the Raman spectrum of figure 16.

10. Crystalline (1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone trifluoroethanol mono-solvate in polymorphic form D according to claim 1, characterized by an XRPD diffraction pattern comprising XRPD peaks at angles of diffraction 2Theta of approximately 6.1°, 16.8°, 22.6°.

11. Crystalline polymorphic form D according to claim 10, characterized by the XRPD diffraction pattern of figure 4.

12. Crystalline polymorphic form D according to any of claims 10 or 11, characterized by the FTIR spectrum of figure 11.

13. Crystalline (1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone in anhydrous polymorphic form E according to claim 1, characterized by an XRPD diffraction pattern comprising XRPD peaks at angles of diffraction 2Theta of approximately 16.5°, 20.8°.

14. Crystalline polymorphic form E according to claim 13, characterized by the XRPD diffraction pattern of figure 6.

15. Crystalline polymorphic form E according to any of claims 13 or 14, characterized by the Raman spectrum of figure 17.

16. A 1:1 inclusion complex of (1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone with γ-Cyclodextrin according to claim 1.

17. The inclusion complex according to claim 16, characterized by an XRPD diffraction pattern comprising XRPD peaks at angles of diffraction 2Theta of approximately 7.4°, 14.9°, 16.7°, 21.8°.

18. The inclusion complex according to any of claims 16 or 17, characterized by the XRPD diffraction pattern of figure 7.

19. The inclusion complex according to any of claims 16 to 18, characterized by the FTIR spectrum of figure 13.

20. The inclusion complex according to any of claims 16 to 19, characterized by the Raman spectrum of figure 19.

21. The inclusion complex according to any of claims 16 to 19, comprising a residual water content of 1% to 20%(w/w).

22. Amorphous (1,1-dioxo-1λ^6-thiomorpholin-4-yl)-{6-[3-(4-fluoro-phenyl)-5-methyl-isoxazol-4-ylmethoxy]-pyridin-3-yl}-methanone, characterized by at least one amorphous halo and a lack of a sharp Bragg diffraction peak in the XRPD diffraction pattern.

23. Amorphous Form according to claim 22, characterized by the XRPD diffraction pattern of figure 7.

24. Amorphous Form according to any of claims 22 or 23, characterized by the FTIR spectrum of figure 12.

25. Amorphous Form according to any of claims 22 to 24, characterized by the Raman spectrum of figure 18.

26. Amorphous Form according to any of claims 22 to 25, characterized a glass transition temperature Tg of 60°C to 70 °C

27. A solid form of a compound of formula (I) according to any of claims 1 to 26, wherein the solid form is present in the specified solid form in a purity of at least 90% (w/w).

28. A distillative solvent exchange process for the preparation of solid forms of compounds of formula (I) according to any of claims 1 to 15 comprising:

a) dissolution of the educt solid form in a solvent;

b) distillation of the solvent while keeping the reactor liquid level constant by replacing the distillate by an antisolvent;

c) physical separation of the desired solid form from the suspension.

29. A high-shear process for the preparation of solid forms of compounds of formula (I) according to any of claims 1 to 15 comprising:

d) injection of a solution of the educt solid form in a solvent into a high-shear mixer comprising an antisolvent;

e) agitation of the rotor-stator system of the high-shear mixer;

f) physical separation of the desired solid form from the suspension.

30. A solid form of a compound of formula (I) according to any of claims 1 to 15, obtainable by the process of any of claims 28 or 29.

31. Crystalline polymorphic form C according to any of claims 6 to 9, obtainable by the process of any of claims 28 or 29.

32. Pharmaceutical compositions comprising a solid form of a compound of formula (I) according to any of claims 1 to 27 and a pharmaceutically acceptable excipient.

33. Solid forms of a compound of formula (I) according to any of claims 1 to 27 for use as therapeutically active substances.

34. Solid forms of a compound of formula (I) according to any of claims 1 to 27 for the treatment or prevention of acute and/or chronic neurological disorders, cognitive disorders, Alzheimer's disease, memory deficits, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, bipolar disorders, autism, Down syndrome, neurofibromatosis type I, sleep disorders, disorders of circadian rhythms, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, psychotic disorders, substance-induced psychotic disorder, anxiety disorders, generalized anxiety disorder, panic disorder, delusional disorder, obsessive/compulsive disorders, acute stress disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, multi-infarct dementia, mood disorders, depression, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, neuropathic pain, stroke, Multiple Sclerosis (MS), acute Meningitis, Fetal Alcohol Syndrome, and attentional disorders, for stroke recovery therapy, or for use as cognitive enhancers.

35. A method for the treatment or prevention of acute and/or chronic neurological disorders, cognitive disorders, Alzheimer's disease, memory deficits, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, bipolar disorders, autism, Down syndrome, neurofibromatosis type I, sleep disorders, disorders of circadian rhythms, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, psychotic disorders, substance-induced psychotic disorder, anxiety disorders, generalized anxiety disorder, panic disorder, delusional disorder, obsessive/compulsive disorders, acute stress disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, multi-infarct dementia, mood disorders, depression, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, neuropathic pain, stroke, Multiple Sclerosis (MS), acute Meningitis, Fetal Alcohol Syndrome, and attentional disorders, for stroke recovery therapy, or for cognition enhancement, which method

comprises administering a solid form of a compound of formula (I) according to any of claims 1 to 27 to a human being or animal.

36. The use of solid forms of a compound of formula (I) according to any of claims 1 to 27 for the preparation of medicaments useful for the treatment or prevention of acute and/or chronic neurological disorders, cognitive disorders, Alzheimer's disease, memory deficits, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, bipolar disorders, autism, Down syndrome, neurofibromatosis type I, sleep disorders, disorders of circadian rhythms, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, psychotic disorders, substance-induced psychotic disorder, anxiety disorders, generalized anxiety disorder, panic disorder, delusional disorder, obsessive/compulsive disorders, acute stress disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, multi-infarct dementia, mood disorders, depression, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, neuropathic pain, stroke, Multiple Sclerosis (MS), acute Meningitis, Fetal Alcohol Syndrome, and attentional disorders or for cognition enhancement.

37. The use of solid forms of a compound of formula (I) according to any of claims 1 to 27 for the treatment or prevention of acute and/or chronic neurological disorders, cognitive disorders, Alzheimer's disease, memory deficits, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, bipolar disorders, autism, Down syndrome, neurofibromatosis type I, sleep disorders, disorders of circadian rhythms, amyotrophic lateral sclerosis (ALS), dementia caused by AIDS, psychotic disorders, substance-induced psychotic disorder, anxiety disorders, generalized anxiety disorder, panic disorder, delusional disorder, obsessive/compulsive disorders, acute stress disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, multi-infarct dementia, mood disorders, depression, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, neuropathic pain, stroke, Multiple Sclerosis (MS), acute Meningitis, Fetal Alcohol Syndrome, and attentional disorders or for cognition enhancement.

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