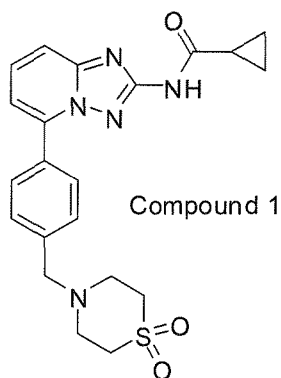


SUMMARY OF THE INVENTION

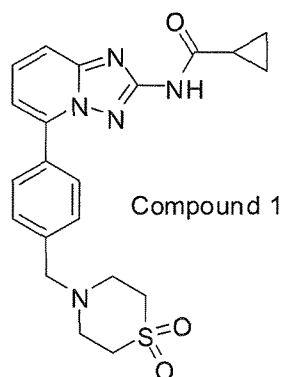
[0037] The present ~~invention-disclosure~~ is based on the identification of novel salts and crystalline forms of Compound 1, useful in the treatment and/or prophylaxis of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving degradation and/or disruption of cartilage homeostasis, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons. In particular, the salts of the ~~invention-disclosure~~ may act as inhibitors of JAK, and in more particularly of JAK1. The present ~~invention-disclosure~~ also provides methods for the production of these salts, pharmaceutical compositions comprising these salts and methods for the treatment and/or prophylaxis of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving degradation and/or disruption of cartilage homeostasis, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons by administering the salts of the invention.

[0038] ~~Accordingly, in one aspect the present invention provides~~ Also disclosed is a salt of a compound according to Formula (I) below (hereafter also named Compound 1):



wherein said salt is formed with hydrobromic acid, hydrochloric acid, sulfuric acid, toluenesulfonic acid, benzenesulfonic acid, oxalic acid, maleic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-2-ethane disulfonic acid, methanesulfonic acid, 2-hydroxy ethanesulfonic acid, phosphoric acid, ethane sulfonic acid, malonic acid, 2-5-dihydroxybenzoic acid, or L-Tartaric acid.

[0039] Accordingly, in one aspect the present invention provides a salt of a compound according to Formula (I) below (hereafter also named Compound 1):



wherein said salt is formed with hydrochloric acid, or a maleic acid salt.

[0040] In ~~another aspect of the invention~~some examples, the salt of the invention is a [Compound 1.HCl.3H₂O] adduct in a solid crystalline form, wherein the crystalline form is characterized at least by a powder X-ray diffraction peak at any one or more of the following positions: 7.3, 8.4, 8.8, 10.7, 12.0, 12.2, 13.2, 13.7, 14.5, 16.3, 16.7, 17.6, 19.3, 20.2, 20.6, 21.0, 21.4, 21.8, 22.8, 23.4, 23.9, 24.5, 25.2, 25.7, 25.9, 26.4, 27.2, 27.7, 28.3, 28.6, 28.9, 29.2, 29.6, 7 and 32.7° 2 θ $\pm$ 0.2° 2 θ .

[0041] In ~~a particular aspect of the invention~~some examples, the salt of the invention exhibits improved solubility and exposure over the free base, which may result in an improved efficacy and a drug's lower dosage being administered. In turn, lowering the drug dosage level may potentially lower toxicity that may occur via drug-drug interaction.

[0042] In ~~a particular aspect~~some examples, the salts of the invention are provided for use in the prophylaxis and / or treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving degradation and/or disruption of cartilage homeostasis, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons.

[0043] In ~~a further aspect~~some examples, the present ~~invention~~disclosure provides pharmaceutical compositions comprising a salt of the invention, and a pharmaceutical carrier, excipient or diluent. In ~~a particular aspect~~some examples, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the salts of the invention. In ~~a more particular aspect~~some examples, the further therapeutically active ingredient is an agent for the treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving degradation and/or disruption of cartilage homeostasis, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons.

[0044] Moreover, the salts of the invention, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

[0045] In ~~a further aspect of the invention, this invention provides~~Also disclosed is a method of treating a mammal, in particular humans, afflicted with a condition selected from among those listed herein, and particularly inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving degradation and/or disruption of cartilage homeostasis, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons, which method comprises administering an effective amount of the pharmaceutical composition or salts of the invention as described herein.

[0046] The present invention also provides pharmaceutical compositions comprising a salt of the invention, and a suitable pharmaceutical carrier, excipient or diluent for use in medicine. In a particular aspect, the pharmaceutical composition is for use in the prophylaxis and/or treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving degradation and/or disruption of cartilage homeostasis, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons.

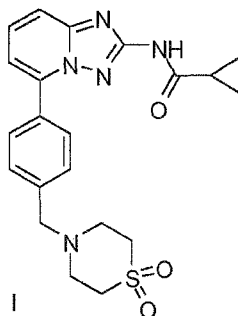
[0047] In additional aspects, this invention provides a method for preparing a [Compound according to Formula I:HCl:3H₂O] adduct in a solid crystalline form comprising the steps of:

- i) mixing the compound of Formula I suspended in DCM, with MeOH at 35°C,
- ii) adding water under stirring at 35°C, for at least 15 min,
- iii) separating the organic layer,
- iv) adding a 10% w/w solution of HCl in MeOH to the organic layer obtained in the previous step iii), v)
- v) separating the resulting solid by filtration obtained in the previous step iv),
- vi) drying said resulting solid obtained in the previous step v),
- vii) adding the solid obtained in the previous step vi) to a 1.6/0.4 formic acid/water solution, under stirring at 55°C,
- viii) adding water to the solution obtained in the previous step vii),
- ix) separating by filtration the resulting solid obtained in the previous step viii), and
- x) drying the resulting solid obtained in the previous step ix).

In another aspect, the invention provides a method for preparing a maleic acid salt of a compound according to Formula I as described herein by combining the compound according to Formula I with maleic acid, in an inert solvent and precipitating said salt from said solvent. In another aspect, the invention provides a method for preparing a maleic acid salt of a Compound according to Formula I as described herein by combining Compound 1 and a salt forming agent in a suitable solvent in order to achieve full dissolution, followed by a controlled solvent evaporation in order to achieve supersaturation, and thus crystallization of the corresponding salt. In another aspect, the invention provides the method which described herein, wherein the salt is obtained by mixing Compound 1, and the acid in a molar ratio of between 2:1 and 1:2 of Compound 1:acid. Also disclosed is methods for synthesizing the salts of the invention, with representative synthetic protocols and pathways disclosed later on herein.

CLAIMS

- 1) A pharmaceutically acceptable salt of a compound according to Formula (I):



wherein the salt is an hydrochloric acid salt.

- 2) A pharmaceutically acceptable salt according to claim 1, wherein the salt is a 1:1 free base/hydrochloric acid salt.
- 3) A pharmaceutically acceptable salt according to any one of claim 1-2, wherein the salt is a pharmaceutically acceptable solvate of the salt.
- 4) A pharmaceutically acceptable salt according to any one of claim 1-2, wherein the salt is a hydrate of the salt.
- 5) A pharmaceutically acceptable salt according to claim 4, wherein the hydrate of the salt is a 1:1:3 Free Base/HCl/H₂O adduct.
- 6) A pharmaceutically acceptable salt or pharmaceutically acceptable hydrate of a salt according to claims 5, wherein the hydrate of the salt is in a crystalline form.
- 7) A pharmaceutically acceptable hydrate of a salt according to claim 6, wherein the 1:1:3 Free Base/HCl/H₂O hydrate of the salt is characterized at least by a powder X-ray diffraction peak at any one or more of the following positions: 7.25, 8.31, 8.78, 10.69, 11.96, 12.25, 13.17, 13.74, 16.23, 16.71, 19.26, 19.64, 20.15, 20.57, 20.95, 21.38, 21.69, 22.77, 23.37, 25.14, 25.71, 25.89, 27.66, 28.57, 28.81, 29.17, 29.58, 30.63, 30.94, 32.06, 32.63, 34.14, 36.22, 36.67, and 37.12° 2θ ± 0.2° 2θ.
- 8) A pharmaceutically acceptable hydrate of a salt according to claim 6, wherein the 1:1:3 Free Base/HCl/H₂O hydrate of the salt characterized by the following diffraction parameters:

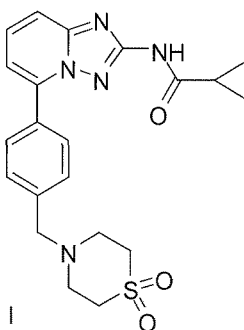
Molecular formula	C ₂₁ H ₂₄ N ₅ O ₃ S.Cl ₃ (H ₂ O)				
Molecular weight	516.02				
Crystal system	Monoclinic				
Space group	P2 _{1/n}	a	13.1388(4) Å	α	102.089(2)°
		b	8.9437(3) Å	β	
		c	21.6376(9) Å	γ	
V	2486.24(15) Å ³				
Z	4				
Dc	1.379 mg / m ³				
μ	0.284 mm ⁻¹				
Source	Mo-Kα, 0.71073 Å				
F(000)	1088				

T	120(2) K
Crystal	colourless prism, 0.39 x 0.16 x 0.12 mm
θ range for data collection	2.982 – 27.483°
Completeness	99.3%
Reflections	21028
Unique reflections	5649
R_{int}	0.0307

- 9) A pharmaceutical composition comprising a pharmaceutically acceptable hydrate of a salt according to any one of claims 1-8, and a pharmaceutically acceptable carrier, excipient or diluent.
- 10) A pharmaceutical composition according to claim 9, comprising a further therapeutic agent.
- 11) A pharmaceutically acceptable salt according to any one of claims 1-8, or a pharmaceutical composition according to 9 or 10 for use in medicine.
- 12) A pharmaceutically acceptable salt according to any one of claims 1-8, or a pharmaceutical composition according to 9 or 10 for use in the prophylaxis and/or treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving degradation and/or disruption of cartilage homeostasis, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons.
- 13) The use according to claim 11 or 12, wherein the pharmaceutically acceptable salt according to any one of claims 1-8, or the pharmaceutical composition according to 9 or 10 is administered in combination with another therapeutic agent.
- 14) The pharmaceutical composition according to claim 10, or the use according to claim 13, wherein the further therapeutic agent is and agent for the prophylaxis and/or treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving degradation and/or disruption of cartilage homeostasis, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons.
- 15) A method for preparing a [Compound according to Formula I:HCl:3H₂O] adduct in a solid crystalline form comprising the steps of:
 - i) mixing the compound of Formula I suspended in DCM, with MeOH at 35°C,
 - ii) adding water under stirring at 35°C for at least 15 min,
 - iii) separating the organic layer,
 - iv) adding a 10% w/w solution of HCl in MeOH to the organic layer obtained in the previous step iii),
 - v) separating the resulting solid by filtration obtained in the previous step iv),
 - vi) drying said resulting solid obtained in the previous step v),
 - vii) adding the solid obtained in the previous step vi) to a 1.6/0.4 formic acid/water solution, under stirring at 55°C
 - viii) adding water to the solution obtained in the previous step vii),
 - ix) separating by filtration the resulting solid obtained in the previous step viii), and
 - x) drying the resulting solid obtained in the previous step ix).

CLAIMS

- 1) A pharmaceutically acceptable salt of a compound according to Formula (I):



wherein the salt is an hydrochloric acid, or a maleic acid salt.

- 2) A pharmaceutically acceptable salt according to claim 1, wherein the salt is a 1:1 free base/hydrochloric acid salt.
- 3) A pharmaceutically acceptable salt according to claim 1, wherein the salt is a 1:1 free base/maleic acid salt.
- 4) A pharmaceutically acceptable salt according to claim 1, wherein the salt is in a crystalline form.
- 5) A pharmaceutically acceptable salt according to any one of claim 1-2, wherein the salt is a pharmaceutically acceptable solvate of the salt.
- 6) A pharmaceutically acceptable salt according to any one of claim 1-2, wherein the salt is a hydrate of the salt.
- 7) A pharmaceutically acceptable salt according to claim 6, wherein the hydrate of the salt is a 1:1:3 Free Base/HCl/H₂O adduct.
- 8) A pharmaceutically acceptable salt or pharmaceutically acceptable hydrate of a salt according to claims 7, wherein the hydrate of the salt is in a crystalline form.
- 9) A pharmaceutically acceptable hydrate of a salt according to claim 8, wherein the 1:1:3 Free Base/HCl/H₂O hydrate of the salt is characterized at least by a powder X-ray diffraction peak at any one or more of the following positions: 7.25, 8.31, 8.78, 10.69, 11.96, 12.25, 13.17, 13.74, 16.23, 16.71, 19.26, 19.64, 20.15, 20.57, 20.95, 21.38, 21.69, 22.77, 23.37, 25.14, 25.71, 25.89, 27.66, 28.57, 28.81, 29.17, 29.58, 30.63, 30.94, 32.06, 32.63, 34.14, 36.22, 36.67, and 37.12° 2θ ± 0.2° 2θ.
- 10) A pharmaceutically acceptable hydrate of a salt according to claim 8, wherein the 1:1:3 Free Base/HCl/H₂O hydrate of the salt characterized by the following diffraction parameters:

Molecular formula	C ₂₁ H ₂₄ N ₅ O ₃ S.Cl ₃ (H ₂ O)				
Molecular weight	516.02				
Crystal system	Monoclinic				
Space group	P2 _{1/n}	a	13.1388(4) Å	α	102.089(2)°
		b	8.9437(3) Å	β	
		c	21.6376(9) Å	γ	
V	2486.24(15) Å ³				
Z	4				

Dc	1.379 mg / m ³
μ	0.284 mm ⁻¹
Source	Mo-K α , 0.71073 Å
F(000)	1088
T	120(2) K
Crystal	colourless prism, 0.39 x 0.16 x 0.12 mm
θ range for data collection	2.982 – 27.483°
Completeness	99.3%
Reflections	21028
Unique reflections	5649
R _{int}	0.0307

- 11) A pharmaceutical composition comprising a pharmaceutically acceptable hydrate of a salt according to any one of claims 1-10, and a pharmaceutically acceptable carrier, excipient or diluent.
- 12) A pharmaceutical composition according to claim 11, comprising a further therapeutic agent.
- 13) A pharmaceutically acceptable salt according to any one of claims 1-10, or a pharmaceutical composition according to 11 or 12 for use in medicine.
- 14) A pharmaceutically acceptable salt according to any one of claims 1-10, or a pharmaceutical composition according to 11 or 12 for use in the prophylaxis and/or treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving degradation and/or disruption of cartilage homeostasis, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons.
- 15) The use according to claim 13 or 14, wherein the pharmaceutically acceptable salt according to any one of claims 1-10, or the pharmaceutical composition according to 11 or 12 is to be administered in combination with another therapeutic agent.
- 16) The pharmaceutical composition according to claim 12, or the use according to claim 15, wherein the further therapeutic agent is and agent for the prophylaxis and/or treatment of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving degradation and/or disruption of cartilage homeostasis, congenital cartilage malformations, and/or diseases associated with hypersecretion of IL6 or interferons.
- 17) A method for preparing a [Compound according to Formula I:HCl:3H₂O] adduct in a solid crystalline form comprising the steps of:
 - i) mixing the compound of Formula I suspended in DCM, with MeOH at 35°C,
 - ii) adding water under stirring at 35°C for at least 15 min,
 - iii) separating the organic layer,
 - iv) adding a 10% w/w solution of HCl in MeOH to the organic layer obtained in the previous step iii),
 - v) separating the resulting solid by filtration obtained in the previous step iv),
 - vi) drying said resulting solid obtained in the previous step v),
 - vii) adding the solid obtained in the previous step vi) to a 1.6/0.4 formic acid/water solution, under stirring at 55°C

- viii) adding water to the solution obtained in the previous step vii),
 - ix) separating by filtration the resulting solid obtained in the previous step viii), and
 - x) drying the resulting solid obtained in the previous step ix).
- 18) A method for preparing a maleic acid salt of a compound according to Formula I according to claims 1 by combining the compound according to Formula I with maleic acid, in an inert solvent and precipitating said salt from said solvent.
 - 19) A method for preparing a maleic acid salt of a Compound according to Formula I according to claims 1 by combining Compound 1 and a salt forming agent in a suitable solvent in order to achieve full dissolution, followed by a controlled solvent evaporation in order to achieve supersaturation, and thus crystallization of the corresponding salt.
 - 20) The method according to claim 18 or 19, wherein the salt is obtained by mixing Compound 1, and the acid in a molar ratio of between 2:1 and 1:2 of Compound 1:acid.
 - 21) The method according to claim 18 or 19, wherein the solvent is selected from acetonitrile, dioxane, THF, acetone, DCM, and MeOH.
 - 22) The maleic acid salt of a compound according to Formula I according to claims 1 obtainable by:
 - i) suspending 1 equivalent of the compound of Formula I in 20 volumes of 5 % water in acetone at 25°C,
 - ii) warming the suspension of step i) to 50°C,
 - iii) adding 2.1 equivalent of maleic acid (1 M solution in THF) to the stirred suspension at 50°C obtained in the previous step ii),
 - iv) cooling the mixture of step iii) to 25°C at 1°C/min and stirring at 25°C for 22 h,
 - v) separating by filtration the resulting solid obtained in the previous step iv),
 - vi) drying under suction said resulting solid obtained in the previous step v).