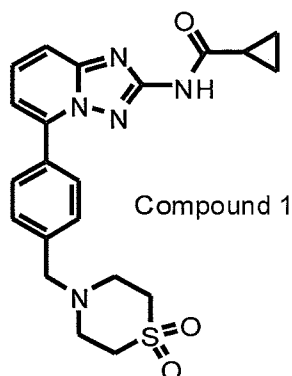


SUMMARY OF THE INVENTION

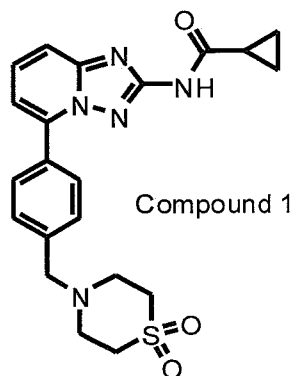
[0037] The present disclosure is based on the identification of novel salts and crystalline forms of Compound 1, useful in the treatment and/or prophylaxis of inflammatory conditions, autoimmune diseases, proliferative diseases, allergy, transplant rejection, diseases involving degradation and/or disruption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

[0038] 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 some examples, the salt of the disclosure 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 some examples, the salt of the disclosure 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 some examples, the salts of the disclosure 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 some examples, the present disclosure provides pharmaceutical compositions comprising a salt of the disclosure, and a pharmaceutical carrier, excipient or diluent. In some examples, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the salts of the disclosure. In 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 disclosure, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

[0045] 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 disclosure as described herein.

[0046] In another aspect, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable hydrate of a salt described herein, and a pharmaceutically acceptable carrier, excipient or diluent. In yet another aspect, the present invention provides a pharmaceutically acceptable salt described herein, or a pharmaceutical composition described herein for use in medicine. The present disclosure also provides pharmaceutical compositions comprising a salt of the disclosure, and a suitable pharmaceutical carrier, excipient or diluent for use in medicine. In a particular example, 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.

[0046a] In yet another aspect, the present invention provides a pharmaceutically acceptable salt described herein, or a pharmaceutical composition described herein 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.

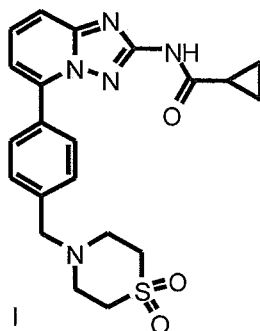
[0047] In additional aspects, this invention provides a method for preparing a [Compound according to Formula I:HCl:3H₂O] adduct in a solid crystalline form comprising the steps of:

- 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).

Also disclosed is 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. Also disclosed is 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. Also disclosed is 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 are methods for synthesizing the salts of the disclosure, 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, 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 any one of claim 1-2, wherein the salt is a pharmaceutically acceptable solvate of the salt.
- 5) A pharmaceutically acceptable salt according to any one of claim 1-2, wherein the salt is a hydrate of the salt.
- 6) A pharmaceutically acceptable salt according to claim 5, wherein the hydrate of the salt is a 1:1:3 Free Base/HCl/H₂O adduct.
- 7) A pharmaceutically acceptable salt or pharmaceutically acceptable hydrate of a salt according to claims 6, wherein the hydrate of the salt is in a crystalline form.
- 8) A pharmaceutically acceptable hydrate of a salt according to claim 7, 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.
- 9) A pharmaceutically acceptable hydrate of a salt according to claim 7, 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

- 10) A pharmaceutical composition comprising a pharmaceutically acceptable hydrate of a salt according to any one of claims 1-9, and a pharmaceutically acceptable carrier, excipient or diluent.
- 11) A pharmaceutical composition according to claim 10, comprising a further therapeutic agent.
- 12) A pharmaceutically acceptable salt according to any one of claims 1-9, or a pharmaceutical composition according to 10 or 11 for use in medicine.
- 13) A pharmaceutically acceptable salt according to any one of claims 1-9, or a pharmaceutical composition according to 10 or 11 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.
- 14) The use according to claim 12 or 13, wherein the pharmaceutically acceptable salt according to any one of claims 1-9, or the pharmaceutical composition according to 10 or 11 is to be administered in combination with another therapeutic agent.
- 15) The pharmaceutical composition according to claim 11, or the use according to claim 15, wherein the further therapeutic agent is an 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.
- 16) 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).
- 17) 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.
- 18) 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.
- 19) The method according to claim 17 or 18, 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.
- 20) The method according to claim 17 or 18, wherein the solvent is selected from acetonitrile, dioxane, THF, acetone, DCM, and MeOH.
- 21) A process for the preparation of the maleic acid salt of a compound according to Formula I according to claims 3 comprising the following steps:
- 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).