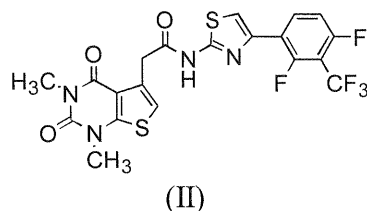


Further, development of a commercial drug candidate involves many steps, such as development of a cost effective synthetic method which is efficient in large scale manufacturing process.

### Summary of the Invention

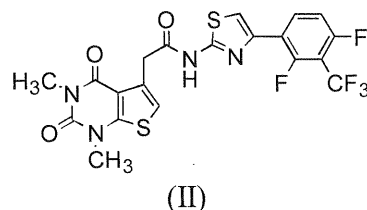
The present application relates to salts of *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide represented by formula (II)



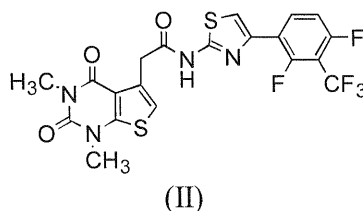
and process for preparation thereof.

*N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide, herein after designated as 'compound of formula (II)

In an ~~embodiment~~ one aspect, ~~the present invention relates to~~ there is provided a potassium salt of *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide represented by the formula (II)



In another ~~embodiment~~ aspect, ~~the present invention relates to~~ Potassium ~~there is~~ provided a potassium salt of *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide represented by the formula (II)



in crystalline form.

In yet another embodiment, potassium salt of a compound of formula (II) is provided in an amorphous form.

In yet another embodiment, the solid state forms of potassium salt of a compound of formula (II) exist in an anhydrous and/or solvent-free form or as a hydrate and/or a  
5 solvate form.

In another embodiment, there is provided a method for treating diseases, conditions and/or disorders modulated by TRPA1; comprising administering a solid state form of potassium salt of compound of formula (II), or a pharmaceutical composition that comprises the solid state form of potassium salt of compound of formula (II) along with  
10 pharmaceutically acceptable excipients.

In yet another embodiment, there is provided a method for treating diseases, conditions and/or disorders modulated by TRPA1; comprising administering crystalline

In yet another embodiment, there is provided the crystalline potassium salt of compound of formula (II) has about 10% of the particles ( $D_{10}$ ) having size in the range from about 0.5  $\mu\text{m}$  to about 8  $\mu\text{m}$ .

5 In yet another embodiment, there is provided the crystalline potassium salt of compound of formula (II) has about 10% of the particles ( $D_{10}$ ) having size in the range from about 0.5  $\mu\text{m}$  to about 5  $\mu\text{m}$ .

In another embodiment, there is provided the potassium salt of compound of formula (II) has about 90% of the particles ( $D_{90}$ ) having size in the range from about 4  $\mu\text{m}$  to about 300  $\mu\text{m}$ .

10 In yet another embodiment, there is provided the potassium salt of compound of formula (II) has about 90% of the particles ( $D_{90}$ ) having size in the range from about 5  $\mu\text{m}$  to about 250  $\mu\text{m}$ .

In yet another embodiment, there is provided the potassium salt of compound of formula (II) has about 90% of the particles ( $D_{90}$ ) having size in the range from about 5  $\mu\text{m}$  to about 200  $\mu\text{m}$ .

15 In yet another embodiment, there is provided the potassium salt of compound of formula (II) has about 90% of the particles ( $D_{90}$ ) having size in the range from about 5  $\mu\text{m}$  to about 150  $\mu\text{m}$ .

20 In another embodiment, there is provided the crystalline potassium salt of compound of formula (II) has about 90% of the particles ( $D_{90}$ ) having size in the range from about 4  $\mu\text{m}$  to about 300  $\mu\text{m}$ .

In yet another embodiment, there is provided the crystalline potassium salt of compound of formula (II) has about 90% of the particles ( $D_{90}$ ) having size in the range from about 5  $\mu\text{m}$  to about 250  $\mu\text{m}$ .

25 In yet another embodiment, there is provided the crystalline potassium salt of compound of formula (II) has about 90% of the particles ( $D_{90}$ ) having size in the range from about 5  $\mu\text{m}$  to about 200  $\mu\text{m}$ .

30 In yet another embodiment, there is provided the crystalline potassium salt of compound of formula (II) has about 90% of the particles ( $D_{90}$ ) having size in the range from about 5  $\mu\text{m}$  to about 150  $\mu\text{m}$ .

In another embodiment, the present ~~invention~~disclosure also relates to substantially pure potassium salt of compound of formula (II). For the purposes of this ~~invention~~disclosure, substantially pure is greater than about 90% pure.

In yet another embodiment, the present ~~invention~~disclosure relates to substantially pure potassium salt of compound of formula (II) having purity greater than about 95%.

In yet another embodiment, the present ~~invention~~disclosure relates to substantially pure potassium salt of compound of formula (II) having purity greater than about 98%.

In yet another embodiment, the present ~~invention~~disclosure relates to substantially pure potassium salt of compound of formula (II) having purity greater than about 99%.

In yet another embodiment, the present ~~invention~~disclosure also relates to substantially pure crystalline potassium salt of compound of formula (II). For the purposes of this ~~invention~~disclosure, substantially pure is greater than about 90% pure.

In yet another embodiment, the present ~~invention~~disclosure relates to substantially pure crystalline potassium salt of compound of formula (II) having purity greater than about 95%.

In yet another embodiment, the present ~~invention~~disclosure relates to substantially pure crystalline potassium salt of compound of formula (II) having purity greater than about 98%.

In yet another embodiment, the present ~~invention~~disclosure relates to substantially pure crystalline potassium salt of compound of formula (II) having purity greater than about 99%.

In another embodiment, the present ~~invention~~disclosure relates to crystalline potassium salt of compound of formula (II) and process for the preparation thereof.

In yet another embodiment, the present ~~invention~~disclosure relates to crystalline potassium salt of compound of formula (II).

In yet another embodiment, the present ~~invention~~disclosure relates to process to prepare crystalline form of potassium salt of compound of formula (II).

In another embodiment, the present ~~invention~~disclosure relates to crystalline form of potassium salt of compound of formula (II) which is designated as Form I.

In yet another ~~embodiment~~aspect, the present ~~invention~~disclosure relates to there is provided a process ~~to prepare for the preparation of~~ crystalline form of potassium salt of compound of formula (II) which is N-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide

designated as Form I, which process comprises the following steps:

- (a) taking *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide in a mixture of ethanol and *n*-pentane;
- (b) adding ethanolic solution of potassium tertiary butoxide or potassium ethoxide to the solution or suspension of step (a) or adding the solution or suspension of step (a) to ethanolic solution of potassium tertiary butoxide or potassium ethoxide; and
- (c) isolating the desired potassium salt.

In another embodiment the present invention-disclosure relates to crystalline form of potassium salt of compound of formula (II) which is designated as Form II.

~~In yet another embodiment aspect, the present invention relates to there is provided a process for the preparation of crystalline form of potassium salt of compound of formula (II) *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide designated as Form II, which process comprises the following steps:~~

- ~~(a) taking *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide in a mixture of tertiary butanol and *n*-pentane;~~
- ~~(b) adding potassium tertiary butoxide in tertiary butanol to the solution or suspension of step (a) or adding the solution or suspension of step (a) to potassium tertiary butoxide in tertiary butanol; and~~
- ~~(c) isolating the desired potassium salt.~~

~~In another aspect, there is provided crystalline *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide designated as Form Y characterised by the X-ray Powder Diffraction (XRPD) pattern as provided in Fig. 14.~~

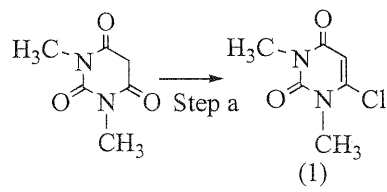
~~In another aspect, there is provided crystalline *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide designated as Form Y characterised by the Fourier Transform Infrared Spectroscopy (FT-IR) pattern wherein the ratio between the intensity of the absorption bands at wavelengths 1500 cm<sup>-1</sup> and 1480 cm<sup>-1</sup> is from 1:1.7 to 1:2.4.~~

In another aspect, there is provided crystalline *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide designated as Form Z characterised by the X-ray Powder Diffraction (XRPD) pattern as provided in Fig. 16.

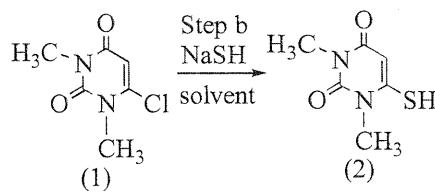
In another aspect, there is provided crystalline *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide designated as Form Z characterised by the Fourier Transform Infrared (FT-IR) Spectroscopy pattern wherein the ratio between the intensity of the absorption bands at wavelengths  $1500\text{ cm}^{-1}$  and  $1480\text{ cm}^{-1}$  is from 1:2.5 to 1:2.9.

In another aspect, there is provided a process for the preparation of *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide or pharmaceutically acceptable salt thereof, which process comprises the steps of

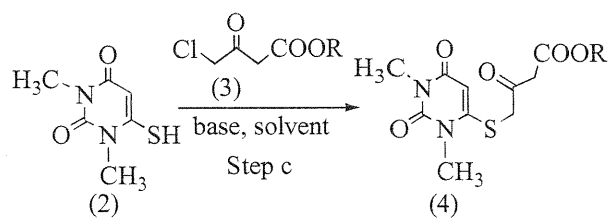
- (a) treating dimethylbarbituric acid with a suitable chlorinating agent to afford 6-chloro-1,3-dimethyluracil of formula (1);



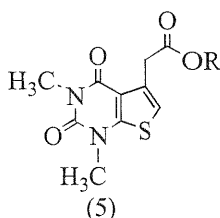
- (b) treating 6-chloro-1,3-dimethyluracil of formula (1) with sodium hydrosulphide hydrate to give 6-mercapto-1,3-dimethyluracil of the formula (2);



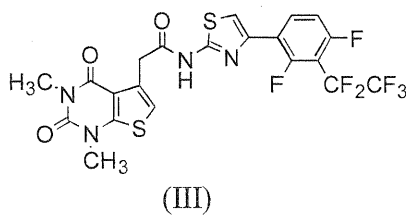
- (c) treating 6-mercapto-1,3-dimethyluracil of the formula (2) with the compound of formula (3) wherein R is (C<sub>1</sub>-C<sub>4</sub>)alkyl, to give ester compound of formula (4); and



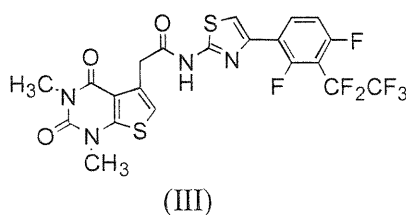
(d) cyclising keto ester of the formula (4) to obtain thieno-pyrimidinyl ester of the formula (5)



5      In another aspect, there is provided *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-5-yl)acetamide having less than about 0.1 % (by HPLC) of the compound of formula (III):



10      In another aspect, there is provided a compound of Formula (III)



or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a method for treating diseases, conditions and/or disorders modulated by TRPA1; comprising administering Form I of potassium salt of compound of formula (II), or a pharmaceutical composition that comprises Form I of potassium salt of compound of formula (II) along with  
5 pharmaceutically acceptable excipients.

In another embodiment, there is provided a method for treating diseases, conditions and/or disorders modulated by TRPA1; comprising administering Form II of potassium salt of compound of formula (II), or a pharmaceutical composition that comprises Form II of potassium salt of compound of formula (II) along with  
10 pharmaceutically acceptable excipients.

In another embodiment, the present ~~invention-disclosure~~ relates to amorphous potassium salt of compound of formula (II) and process for the preparation thereof.

In yet another embodiment, the present ~~invention-disclosure~~ relates to amorphous potassium salt of compound of formula (II).

15 In yet another embodiment the present ~~invention-disclosure~~ relates to process for the preparation of amorphous potassium salt of compound of formula (II).

In another embodiment, there is provided a method for treating diseases, conditions and/or disorders modulated by TRPA1; comprising administering amorphous form of potassium salt of compound of formula (II), or a pharmaceutical composition that  
20 comprises amorphous form of potassium salt of compound of formula (II) along with pharmaceutically acceptable excipients.

In another embodiment, the present ~~invention-disclosure~~ relates to crystalline sodium salt of compound of formula (II) which is designated as Form A and process for the preparation thereof.

25 In yet another embodiment, the present ~~invention-disclosure~~ relates to crystalline sodium salt of compound of formula (II) which is designated as Form A.

In yet another embodiment the present ~~invention-disclosure~~ relates to process for the preparation of crystalline sodium salt of compound of formula (II) which is designated as Form A.

30 In another embodiment, there is provided a method for treating diseases, conditions and/or disorders modulated by TRPA1; comprising administering crystalline Form A of sodium salt of compound of formula (II), or a pharmaceutical composition that comprises crystalline Form A of sodium salt of compound of formula (II) along with pharmaceutically acceptable excipients.

In another embodiment, the present ~~invention-disclosure~~ relates to amorphous sodium salt of compound of formula (II) and process for the preparation thereof.

In another embodiment, the present ~~invention-disclosure~~ relates to amorphous sodium salt of compound of formula (II).

5 | In yet another embodiment the present ~~invention-disclosure~~ relates to process for the preparation of amorphous sodium salt of compound of formula (II).

In another embodiment, there is provided a method for treating diseases, conditions and/or disorders modulated by TRPA1; comprising administering amorphous sodium salt of compound of formula (II), or a pharmaceutical composition that comprises  
10 | amorphous sodium salt of compound of formula (II) along with pharmaceutically acceptable excipients.

In another embodiment, the present ~~invention-disclosure~~ relates to lithium salt of compound of formula (II).

In yet another embodiment the present ~~invention-disclosure~~ relates to process for  
15 | the preparation of lithium salt of compound of formula (II).

In another embodiment, the present ~~invention-disclosure~~ relates to crystalline lithium salt of compound of formula (II) which may be designated as Form alpha and process for the preparation thereof.

In another embodiment, the present ~~invention-disclosure~~ relates to crystalline  
20 | lithium salt of compound of formula (II) which may be designated as Form alpha.

In yet another embodiment the present ~~invention-disclosure~~ relates to process for the preparation of crystalline lithium salt of compound of formula (II) which may be designated as Form alpha.

In another embodiment, there is provided a method for treating diseases,  
25 | conditions and/or disorders modulated by TRPA1; comprising administering lithium salt of compound of formula (II), or a pharmaceutical composition that comprises lithium salt of compound of formula (II) along with pharmaceutically acceptable excipients.

In another embodiment, there is provided a method for treating diseases, conditions and/or disorders modulated by TRPA1; comprising administering crystalline  
30 | lithium salt of compound of formula (II), or a pharmaceutical composition that comprises crystalline lithium salt of compound of formula (II) along with pharmaceutically acceptable excipients.

In yet another embodiment, there is provided crystalline compound of formula (II) having surface area of less than about 50 m<sup>2</sup>/gm, preferably less than 25 m<sup>2</sup>/gm or more preferably less than 10 m<sup>2</sup>/gm.

5 In yet another embodiment, there is provided crystalline compound of formula (II) having surface area of less than about 50 m<sup>2</sup>/gm.

In yet another embodiment, there is provided crystalline compound of formula (II) having surface area of less than about 25 m<sup>2</sup>/gm.

In yet another embodiment, there is provided crystalline compound of formula (II) having surface area of less than about 10 m<sup>2</sup>/gm.

10 The present ~~invention~~ disclosure also relates to the process for the preparation of thienopyrimidinedione compound of formula (II).

#### Brief description of the figures

FIG.1 is powder X-ray diffraction pattern of crystalline potassium salt of *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-5-yl)acetamide designated as Form I.

FIG.2 is Infra-Red (IR) spectra of crystalline potassium salt of *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-5-yl)acetamide designated as Form I.

FIG.3 is powder X-ray diffraction pattern of crystalline potassium salt of *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-5-yl)acetamide designated as Form II.

FIG.4 is Infra-Red (IR) spectra of crystalline potassium salt of *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-5-yl)acetamide designated as Form II.

FIG.5 is powder X-ray diffraction pattern of amorphous potassium salt of *N*-{4-[2,4-difluoro-3-(trifluoromethyl)phenyl]-1,3-thiazol-2-yl}-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidin-5-yl)acetamide.