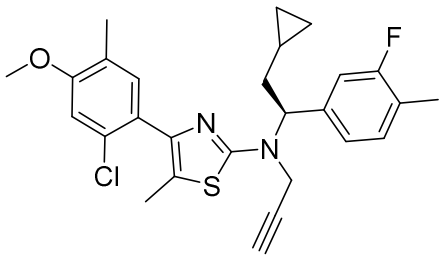
Accordingly, a significant need exists for efficient methods for the preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**) to support further clinical trials and commercial efforts.

SUMMARY

The present disclosure provides, *inter alia*, processes for the preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine (Compound 1) and intermediates related thereto.

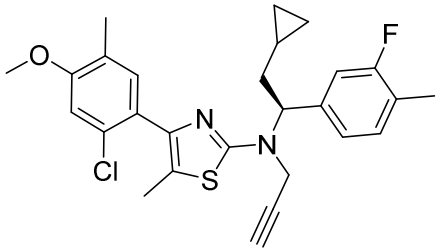
In one aspect, the present disclosure refers to a compound that is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**):



Compound 1 ;

wherein the enantiomeric excess (e.e.%) of the compound is at least 99.7%.

In one aspect the present disclosure refers to a pharmaceutically acceptable salt of 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**):

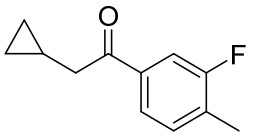


Compound 1 ;

wherein the enantiomeric excess (e.e.%) of **Compound 1** is at least 99.7%.

The processes and intermediates of the present disclosure are useful in preparing 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**), pharmaceutical salts, crystalline forms, and pharmaceutical compositions that are useful in the treatment of corticotropin releasing factor 1 (CRF_1) receptor-mediated disorders.

One example of the present disclosure pertains to processes for preparing 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-

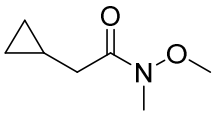


3A

,

comprising:

reacting 2-cyclopropyl-*N*-methoxy-*N*-methylacetamide (**Compound 2A**):



2A

,

with an organomagnesium reagent of 4-bromo-2-fluoro-1-methylbenzene in the presence of a reacting-step solvent to form 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (**Compound 3A**).

One example of the present disclosure pertains an anhydrous crystalline form of 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**, free base).

One example of the present disclosure pertains to an anhydrous crystalline form of 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**, tosylate salt).

One example of the present disclosure pertains to pharmaceutical compositions comprising a crystalline form (**Compound 1**, free base) as described herein, and a pharmaceutically acceptable carrier.

One example of the present disclosure pertains to pharmaceutical products selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising a crystalline form (**Compound 1**, free base) as described herein.

One example of the present disclosure pertains to pharmaceutical compositions comprising a crystalline form (**Compound 1**, tosylate salt) as described herein, and a pharmaceutically acceptable carrier.

One example of the present disclosure pertains to pharmaceutical products selected from: a pharmaceutical composition, a formulation, a unit dosage form, and a kit; each comprising a crystalline form (**Compound 1**, tosylate salt) as described herein.

One example of the present disclosure pertains to compositions comprising:

a. 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**), or a pharmaceutically acceptable salt thereof; and

b. at least one compound selected from:

(*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methylthiazol-2-amine (**Compound 9A**);

(*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyl-1-(*p*-tolyl)ethyl)-5-methyl-*N*-(prop-2-yn-1-yl)thiazol-2-amine (**Compound IIa**);

(*S*)-4-(2-chloro-5-methyl-4-(prop-2-yn-1-yloxy)phenyl)-*N*-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-*N*-(prop-2-yn-1-yl)thiazol-2-amine (**Compound IIb**);

4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*R*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-(2-propyn-1-yl)-2-thiazolamine (**Compound IIc**);

ethanol; and

propargyl bromide.

One example of the present disclosure pertains to methods of treating a disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form (**Compound 1**, free base) as described herein; a crystalline form (**Compound 1**, tosylate salt) as described herein; **Compound 1** (with high e.e.%), or a pharmaceutically acceptable salt thereof as described herein; a pharmaceutical composition as described herein; a pharmaceutical product as described herein; or a composition as described herein; wherein the subject has abnormal levels of CRF_1.

One example of the present disclosure pertains to methods of treating a Corticotropin Releasing Factor 1 (CRF_1) disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form (**Compound 1**, free base) as described herein; a crystalline form (**Compound 1**, tosylate salt) as described herein; **Compound 1** (with high e.e.%), or a pharmaceutically acceptable salt thereof as described herein; a pharmaceutical composition as described herein; a pharmaceutical product as described herein; or a composition as described herein.

One example of the present disclosure pertains to methods of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a crystalline form (**Compound 1**, free base) as described herein; a crystalline form (**Compound 1**, tosylate salt) as described herein; **Compound 1** (with high e.e.%), or a pharmaceutically acceptable salt thereof as described herein; a pharmaceutical composition as described herein; a pharmaceutical product as described herein; or a composition as described herein. In some examples, the congenital adrenal hyperplasia is classic congenital adrenal hyperplasia. In some examples, the method further comprises administering to the subject a glucocorticoid. In some examples, the glucocorticoid is hydrocortisone.

One example of the present disclosure pertains to uses of an anhydrous crystalline form (**Compound 1**, free base) as described herein; the crystalline form (**Compound 1**, tosylate salt) as described herein; or **Compound 1** (with high e.e.%), or a pharmaceutically acceptable salt thereof as described herein; for the manufacture of a medicament for the treatment of a subject wherein the subject has abnormal levels of CRF_1.

One example of the present disclosure pertains to uses of an anhydrous crystalline form (**Compound 1**, free base) as described herein; the crystalline form (**Compound 1**, tosylate salt) as described herein; or **Compound 1** (with high e.e.%), or a pharmaceutically acceptable salt thereof as described herein; for the manufacture of a medicament for the treatment of a Corticotropin Releasing Factor 1 (CRF_1) disorder.

One example of the present disclosure pertains to uses of an anhydrous crystalline form (**Compound 1**, free base) as described herein; the crystalline form (**Compound 1**, tosylate salt) as described herein; or **Compound 1** (with high e.e.%), or a pharmaceutically acceptable salt thereof as described herein; for the manufacture of a medicament for the treatment of congenital adrenal hyperplasia (CAH). In some examples, the congenital adrenal hyperplasia is classic congenital adrenal hyperplasia. In some examples, the treatment of congenital adrenal hyperplasia comprises administering a glucocorticoid. In some examples, the medicament is formulated for administration with a glucocorticoid. In some examples, the glucocorticoid is hydrocortisone.

In one aspect, the present disclosure refers to use of a compound as described herein, in the manufacture of a medicament for treating congenital adrenal hyperplasia (CAH) in a subject in need thereof.

In one aspect, the disclosure refers to use of a pharmaceutically acceptable salt of **Compound 1** as described herein, in the manufacture of a medicament for treating congenital adrenal hyperplasia (CAH), in a subject in need thereof.

One example of the present disclosure pertains to an anhydrous crystalline form (**Compound 1**, free base) as described herein; a crystalline form (**Compound 1**, tosylate salt) as described herein; **Compound 1** (with high e.e.%), or a pharmaceutically acceptable salt thereof as described herein; a pharmaceutical composition as described herein; a pharmaceutical product as described herein; or a composition as described herein; for use in a method of treatment of the human or animal body by therapy.

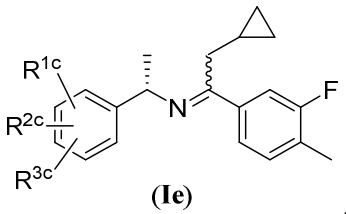
One example of the present disclosure pertains to an anhydrous crystalline form (**Compound 1**, free base) as described herein; a crystalline form (**Compound 1**, tosylate salt) as described herein; **Compound 1** (with high e.e.%), or a pharmaceutically acceptable salt thereof as described herein; a pharmaceutical composition as described herein; a pharmaceutical product as described herein; or a composition as described herein; for use in a method of treatment of a disorder in a subject wherein the subject has abnormal levels of CRF_1.

One example of the present disclosure pertains to an anhydrous crystalline form (**Compound 1**, free base) as described herein; a crystalline form (**Compound 1**, tosylate salt) as described herein; **Compound 1** (with high e.e.%), or a pharmaceutically acceptable salt thereof as described herein; a

pharmaceutical composition as described herein; a pharmaceutical product as described herein; or a composition as described herein; for use in a method of treatment of a Corticotropin Releasing Factor 1 (CRF_1) disorder.

One example of the present disclosure pertains to an anhydrous crystalline form (**Compound 1**, free base) as described herein; a crystalline form (**Compound 1**, tosylate salt) as described herein; **Compound 1** (with high e.e.%), or a pharmaceutically acceptable salt thereof as described herein; a pharmaceutical composition as described herein; a pharmaceutical product as described herein; or a composition as described herein; for use in a method of treating congenital adrenal hyperplasia (CAH). In some examples, the congenital adrenal hyperplasia is classic congenital adrenal hyperplasia. In some examples, the method of treating congenital adrenal hyperplasia comprises administering a glucocorticoid. In some examples, the glucocorticoid is hydrocortisone.

One example of the present disclosure pertains to Compounds of Formula (**Ie**):

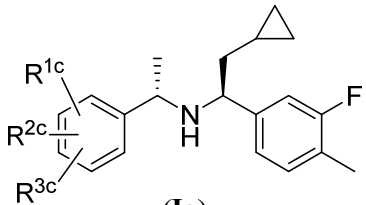


(**Ie**),

wherein:

R^{1c}, R^{2c}, and R^{3c} are each independently selected from: H, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and halogen.

One example of the present disclosure pertains to Compounds of Formula (**Ig**) or a salt thereof:



(**Ig**),

wherein:

R^{1c}, R^{2c}, and R^{3c} are each independently selected from: H, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and halogen.

One example of the present disclosure pertains to processes for preparing a pharmaceutical composition comprising admixing a crystalline form (**Compound 1**, free base) as described herein; a

crystalline form (**Compound 1**, tosylate salt) as described herein; or a composition according as described herein; and a pharmaceutically acceptable carrier.

These and other examples of the disclosure disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows an exemplary X-ray powder diffraction (XRPD) pattern for a sample of crystalline Form I of 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**) prepared according to **Example 3**.

FIG. 2 shows an exemplary Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) thermograms for a sample of crystalline Form I of 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**) prepared according to **Example 3**.

FIG. 3 shows an exemplary Gravimetric Vapor Sorption (GVS) for a sample of crystalline Form I of 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**) as described in **Example 4**.

FIG. 4 shows general synthetic schemes for the preparation of 1-(2-chloro-4-methoxy-5-methylphenyl)-2-thiocyanatopropan-1-one (**Compound 8A**), 4-chloro-2-(methoxy-^{13}C-d_3)-1-methylbenzene (**Compound 7A'**), and 1-(2-chloro-4-(methoxy-^{13}C-d_3)-5-methylphenyl)-2-thiocyanatopropan-1-one (**Compound 8A'**). The synthesis of 1-(2-chloro-4-methoxy-5-methylphenyl)-2-thiocyanatopropan-1-one (**Compound 8A**) has previously been described in International Publication Number WO2010/125414 by Sanofi-Aventis.

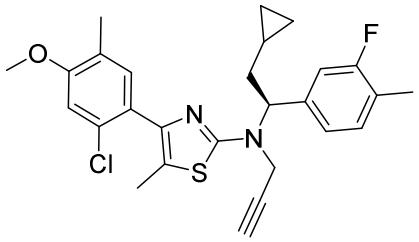
FIG. 5 shows a general scheme for the preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**).

FIG. 6 shows a general scheme for the preparation of (*S*)-4-(2-chloro-4-(methoxy-^{13}C-d_3)-5-methylphenyl)-*N*-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methyl-*N*-(prop-2-yn-1-yl)thiazol-2-amine (**Compound 3**).

FIG. 7 shows an exemplary X-ray powder diffraction (XRPD) pattern for a sample of crystalline Form I of 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**).

CLAIMS

1. A compound that is 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**):



Compound 1 ;

wherein the enantiomeric excess (e.e.%) of the compound is at least 99.7%.

2. The compound according to claim 1, wherein the enantiomeric excess (e.e.%) of **Compound 1** is at least 99.8%.

3. The compound according to claim 1, wherein the enantiomeric excess (e.e.%) of **Compound 1** is at least 99.9%.

4. Use of a compound according to claim 1, in the manufacture of a medicament for treating congenital adrenal hyperplasia (CAH) in a subject in need thereof.

5. The use according to claim 4, wherein the enantiomeric excess (e.e.%) of **Compound 1** is at least 99.8%.

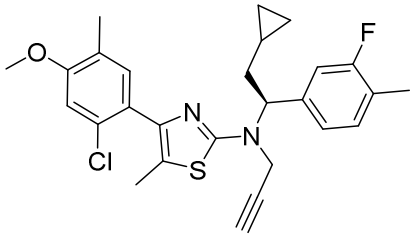
6. The use according to claim 4, wherein the enantiomeric excess (e.e.%) of **Compound 1** is at least 99.9%.

7. The use according to claim 4, wherein the congenital adrenal hyperplasia is classic congenital adrenal hyperplasia.

8. The use according to claim 4, wherein the medicament is to be administered with a glucocorticoid.

9. The use according to claim 7, wherein the medicament is to be administered with a glucocorticoid.

10. A pharmaceutically acceptable salt of 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**):



Compound 1 ;

wherein the enantiomeric excess (e.e.%) of **Compound 1** is at least 99.7%.

11. The salt according to claim 10, wherein the enantiomeric excess (e.e.%) of **Compound 1** is at least 99.8%.

12. The salt according to claim 10, wherein the enantiomeric excess (e.e.%) of **Compound 1** is at least 99.9%.

13. Use of a pharmaceutically acceptable salt of **Compound 1** according to claim 10, in the manufacture of a medicament for treating congenital adrenal hyperplasia (CAH), in a subject in need thereof.

14. The use according to claim 13, wherein the enantiomeric excess (e.e.%) of **Compound 1** is at least 99.8%.

15. The use according to claim 13, wherein the enantiomeric excess (e.e.%) of **Compound 1** is at least 99.9%.

16. The use according to claim 13, wherein the congenital adrenal hyperplasia is classic congenital adrenal hyperplasia.

17. The use according to claim 13, wherein the medicament is to be administered with a glucocorticoid.

18. The use according to claim 16, wherein the medicament is to be administered with a glucocorticoid.