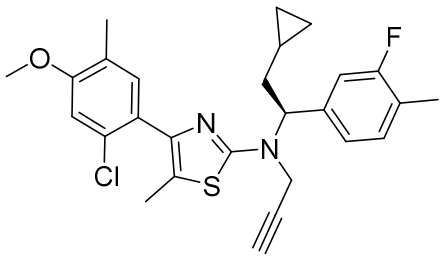
Accordingly, a significant need exists for efficient methods for the preparation of 4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-[(1*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**) to support further clinical trials and commercial efforts.

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.

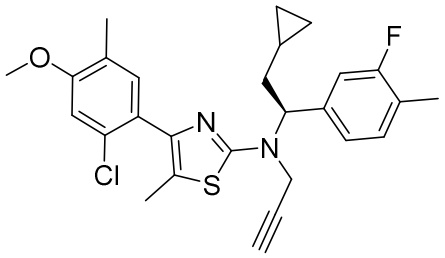
In one aspect, the present disclosure refers to a compound that is 4-(2-chloro-4-methoxy-5-methylphenyl)-N-[(1S)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl]-5-methyl-N-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**):



Compound 1 ;

or a pharmaceutically acceptable salt thereof, wherein the enantiomeric excess (e.e.%) of the compound is at least 99.4% as determined by chiral HPLC.

In one aspect, the present disclosure refers to 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**) as described herein:



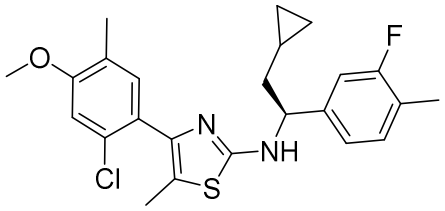
Compound 1

;

or a pharmaceutically acceptable salt thereof,

prepared by a process comprising:

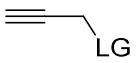
alkylating (*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methylthiazol-2-amine (**Compound 9A**) or a salt thereof:



9A

,

with a Compound of Formula (**Ii**):



(Ii)

,

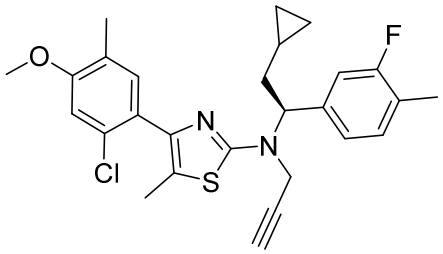
wherein: LG is a leaving group;

in the presence of an alkylating-step solvent, a phase-transfer catalyst, an alkylating-step base, and water to form 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.

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-

methyl-*N*-prop-2-ynyl-1,3-thiazol-2-amine (**Compound 1**) or a pharmaceutically acceptable salt thereof:

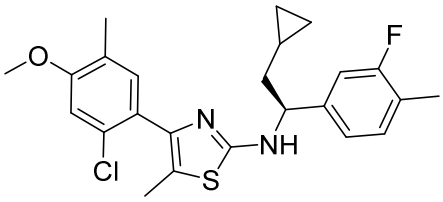


Compound 1

;

comprising:

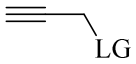
alkylating (*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methylthiazol-2-amine (**Compound 9A**) or a salt thereof:



9A

,

with a Compound of Formula (**Ii**):

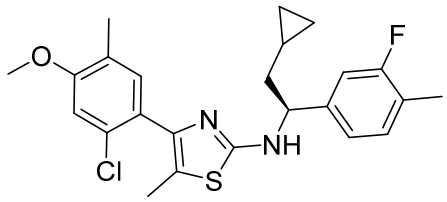


(Ii) ,

wherein: LG is a leaving group;

in the presence of an alkylating-step solvent, a phase-transfer catalyst, an alkylating-step base, and water to form 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.

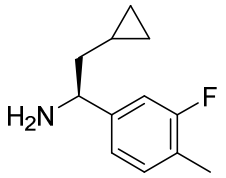
One example of the present disclosure pertains to processes for preparing (*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methylthiazol-2-amine (**Compound 9A**) or a salt thereof:



9A ,

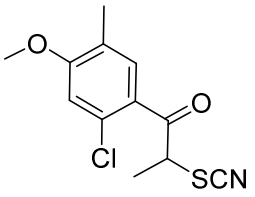
comprising:

cyclizing (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-amine (**Compound 6A**) or a salt thereof:



6A ,

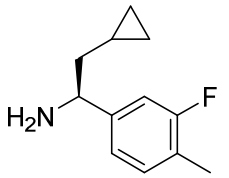
with 1-(2-chloro-4-methoxy-5-methylphenyl)-2-thiocyanatopropan-1-one (**Compound 8A**) or a tautomeric form thereof:



8A ;

in the presence of a cyclizing-step solvent to form (*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methylthiazol-2-amine (**Compound 9A**) or a salt thereof.

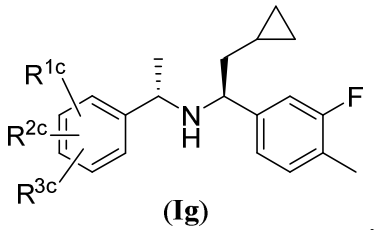
One example of the present disclosure pertains to processes for preparing (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-amine (**Compound 6A**) or a salt thereof:



6A,

comprising:

deprotecting a Compound of Formula (**Ig**), or a salt thereof,



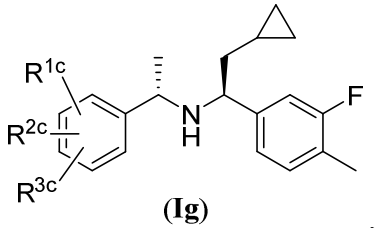
(**Ig**),

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;

in the presence of a deprotecting-catalyst, hydrogen, and a deprotecting-step solvent to form (*S*)-2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-amine (**Compound 6A**) or a salt thereof.

One example of the present disclosure pertains to processes for preparing a Compound of Formula (**Ig**), or a salt thereof,



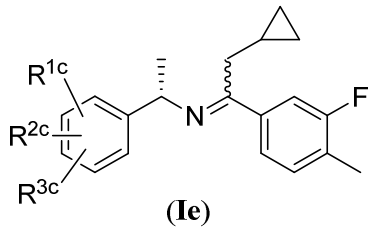
(**Ig**),

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;

comprising:

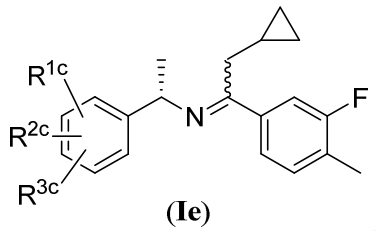
reducing a Compound of Formula (**Ie**):



(**Ie**),

in the presence of a reducing-catalyst, hydrogen, and a reducing-step solvent to form a Compound of Formula (**Ig**), or a salt thereof.

One example of the present disclosure pertains to processes for preparing a Compound of Formula (**Ie**):



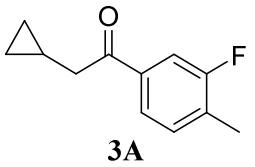
(**Ie**),

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;

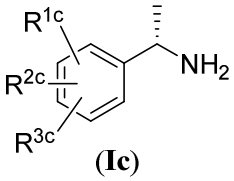
comprising:

condensing 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (**Compound 3A**):



3A,

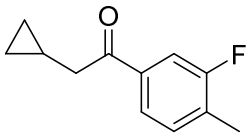
with a Compound of Formula (**Ic**), or a salt thereof:



(**Ic**),

in the presence of a condensing-step acid and a condensing-step solvent to a Compound of Formula (**Ie**).

One example of the present disclosure pertains to processes for preparing 2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethan-1-one (**Compound 3A**):

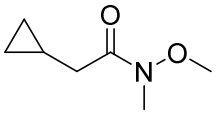


3A

,

comprising:

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



2A

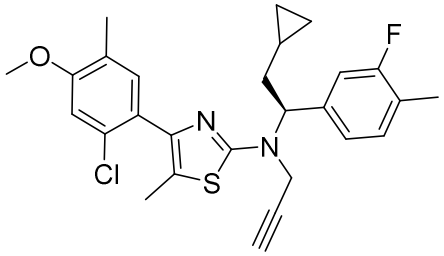
,

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).

In one aspect, the present disclosure refers to a composition comprising 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**) as described herein:

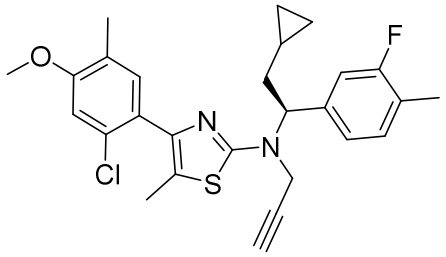


Compound 1

;

or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to a composition comprising the 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**) as described herein:

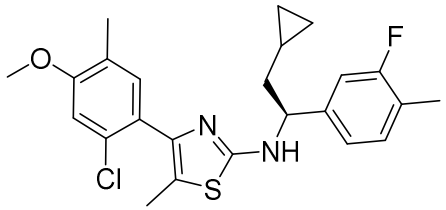


Compound 1 ;

or a pharmaceutically acceptable salt thereof,

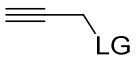
prepared by a process comprising:

alkylating (*S*)-4-(2-chloro-4-methoxy-5-methylphenyl)-*N*-(2-cyclopropyl-1-(3-fluoro-4-methylphenyl)ethyl)-5-methylthiazol-2-amine (**Compound 9A**) or a salt thereof:



9A ,

with a Compound of Formula (**Ii**):



(Ii) ,

wherein: LG is a leaving group;

in the presence of an alkylating-step solvent, a phase-transfer catalyst, an alkylating-step base, and water to form 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.

In one aspect, the present disclosure refers to a pharmaceutical product selected from:

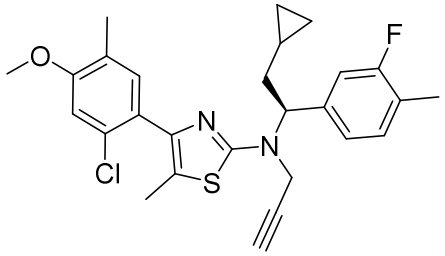
a pharmaceutical composition, a formulation, a unit dosage form, and a kit;

each comprising **Compound 1**, as described herein, or a pharmaceutically acceptable salt thereof.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising **Compound 1**, as described herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In one aspect, the present disclosure refers to a pharmaceutical composition comprising:

(a) 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**) as described herein:



Compound 1

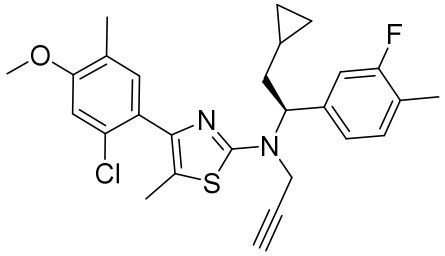
,

or a pharmaceutically acceptable salt thereof; and

(b) one or more of an oily phase vehicle, an emulsifying agent, a nonionic surfactant, and a solubilizing agent.

In one aspect, the present disclosure refers to a pharmaceutical composition in oral solution dosage form comprising:

(a) 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**) as described herein:



Compound 1

,

or a pharmaceutically acceptable salt thereof;

(b) one or more of a sweetener, an anti-oxidant, and a flavor; and

(c) a liquid vehicle, wherein the liquid vehicle is selected from medium-chain triglycerides, propylene glycol dicaprylate/dicaprate, glycerin, propylene glycol, polyethylene glycol, olive oil, soybean oil, corn oil, and transcutol.

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.

In one aspect, the present disclosure refers to a method of treating a disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

a compound as described herein, or a pharmaceutically acceptable salt thereof;

a composition as described herein;

a pharmaceutical product as described herein; or

a pharmaceutical 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.

In one aspect, the present disclosure refers to a method 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 compound as described herein, or a pharmaceutically acceptable salt thereof;

a composition as described herein;

a pharmaceutical product as described herein; or

a pharmaceutical 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.

In one aspect, the present disclosure refers to a method of treating congenital adrenal hyperplasia (CAH), in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

a compound as described herein, or a pharmaceutically acceptable salt thereof;

a composition as described herein;

a pharmaceutical product as described herein; or

a pharmaceutical composition as described herein.

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.

In one aspect, the present disclosure refers to use of a compound as described herein, or a pharmaceutically acceptable salt thereof, 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.

In one aspect, the present disclosure refers to use of a compound as described herein or a pharmaceutically acceptable salt thereof, 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 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of congenital adrenal hyperplasia (CAH).

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.

In one aspect, the present disclosure refers to a compound as described herein, or a pharmaceutically acceptable salt thereof;

a composition as described herein;

a pharmaceutical product as described herein; or

a pharmaceutical composition as described herein;

for use in a method of treatment or prophylaxis 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.

In one aspect, the present disclosure refers to a compound as described herein, or a pharmaceutically acceptable salt thereof;

a composition as described herein;

a pharmaceutical product as described herein; or

a pharmaceutical 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

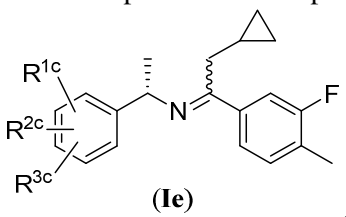
pharmaceutical composition as described herein; a pharmaceutical product as described herein; or a composition as described herein; for use in a method of treatment of a Corticotropin Releasing Factor 1 (CRF_1) disorder.

In one aspect, the present disclosure refers to a compound as described herein, or a pharmaceutically acceptable salt thereof;
a composition as described herein;
a pharmaceutical product as described herein; or
a pharmaceutical 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.

In one aspect, the present disclosure refers to a compound as described herein, or a pharmaceutically acceptable salt thereof;
a composition as described herein;
a pharmaceutical product as described herein; or
a pharmaceutical composition as described herein;
for use in a method of treating congenital adrenal hyperplasia (CAH).

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

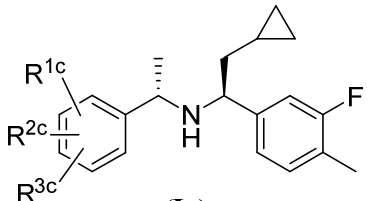


(**Ie**),

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.

In one aspect, the present disclosure refers to a method for preparing a pharmaceutical composition comprising the step of admixing a compound as described herein, or a pharmaceutically acceptable salt thereof, 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**).