[0004] When excess pituitary ACTH release causes the excess cortisol, the disorder is termed “Cushing’s Disease”. Such excess pituitary ACTH release is typically caused by a pituitary tumor. First-line treatment for Cushing’s Disease involves surgery to remove the pituitary tumor; however, in many cases not all of the tumor is able to be resected (e.g., if the tumor has invaded cranial regions outside the *sella turcica*, or has invaded bone, or for other reasons), or it may grow back, or may have metastasized (more often for non-pituitary (ectopic) tumors than for pituitary tumors). In some cases, radiation treatment is applied following surgery. Conventional chemotherapy treatment often used for other tumors may be inapplicable for pituitary tumors, or may not be suitable for patients suffering from pituitary tumors. Medical treatment to reduce cortisol production, or to block the effects of cortisol (e.g., mifepristone (prescribed as KORLYM®)) is often administered, particularly when symptoms persist following surgery. Radiation and standard chemotherapy may have severe side-effects, which may make them unsuitable for Cushing’s patients. Thus, medical (i.e., non-surgical) treatments for pituitary tumors which cause Cushing’s Disease are needed, and improved treatments would be helpful.

[0005] Patients suffering from other disorders may also exhibit excess cortisol, and excess cortisol may be a cause of such disorders. For example, patients suffering from psychotic major depression typically exhibit excess cortisol. However, methods and compositions effective for reducing the effects of cortisol, and particularly for reducing the effects of excess cortisol, remain lacking.

SUMMARY

[0005a] In one aspect, the present disclosure refers to a use of a nonsteroidal selective glucocorticoid receptor modulator (selective GRM) having a heteroaryl-ketone fused azadecalin structure, or a nonsteroidal selective GRM having an octahydro fused azadecalin structure, in the manufacture of a medicament for treating a patient suffering from hypercortisolemia, and a symptom or comorbidity thereof, wherein said symptom or comorbidity of hypercortisolemia is one or more of:

hyperglycemia, wherein said medicament is for treatment to significantly lower the patient’s $AUC_{glucose}$ as compared to the patient’s baseline $AUC_{glucose}$ measured prior to treatment;

hypertension, wherein said medicament is for treatment to significantly lower the patient’s blood pressure as compared to the patient’s baseline blood pressure measured prior to treatment;

an abnormal liver enzyme level, wherein said medicament is for treatment to significantly lower an abnormal patient liver enzyme level as compared to the patient's baseline liver enzyme level measured prior to treatment;

an abnormal fructosamine level, wherein said medicament is for treatment to significantly improve an abnormal patient fructosamine level as compared to the patient's baseline fructosamine level measured prior to treatment;

an abnormal serum osteocalcin level, wherein said medicament is for treatment to significantly improve an abnormal patient serum osteocalcin level as compared to the patient's baseline serum osteocalcin level measured prior to treatment;

an abnormal heartbeat interval or median heart rate, wherein said medicament is for treatment to significantly improve an abnormal patient heartbeat interval or median heart rate as compared to the patient's baseline heartbeat interval or median heart rate measured prior to treatment;

an abnormal blood coagulation measure, wherein said medicament is for treatment to significantly improve an abnormal patient blood coagulation measure as compared to the patient's baseline blood coagulation as measured prior to treatment;

an abnormal blood cell measure, wherein said medicament is for treatment to significantly improve an abnormal patient blood cell measure as compared to the patient's baseline blood cell measure as measured prior to treatment;

an abnormal adrenocorticotropic hormone (ACTH) or pro-opiomelanocortin (POMC) level, wherein said medicament is for treatment to significantly improve an abnormal patient ACTH or POMC level as compared to the patient's baseline ACTH or POMC level as measured prior to treatment;

improve quality of life in a Cushing's patient, wherein said medicament is for treatment to significantly improve patient quality of life as compared to the patient's baseline quality of life as measured prior to treatment;

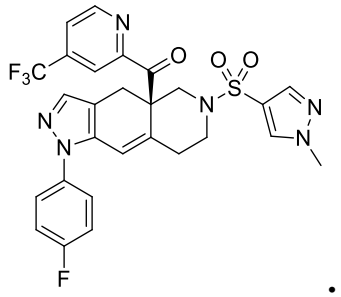
improve cognition in a Cushing's patient, wherein said medicament is for treatment to significantly improve patient cognition as compared to the patient's baseline cognition as measured prior to treatment;

lessen patient depression, as measured by a psychological measure of depression, wherein said medicament is for treatment to significantly reduce patient depression as compared to the patient's baseline depression as measured prior to treatment.

[0006] Disclosed herein are novel methods for treating a variety of disorders and diseases related to, or caused by, cortisol excess (hypercortisolemia or hypercortisolism), and for treating a variety of disorders and diseases which may be treated or symptoms ameliorated by reducing the effects or action of cortisol. Such diseases and disorders may include, without limitation, Cushing's syndrome, Cushing's Disease, hyperglycemia secondary to hypercortisolemia, liver diseases (e.g., fatty liver disease, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic liver diseases, liver fibrosis, and other liver disorders), cardiac disorders (including, e.g., prolonged Q-T interval or other disorder of the heart rhythm), high blood pressure, hypercoagulopathy, cancers, bone disorders, blood clotting disorders, psychological disorders, weight gain (including weight gain due to antipsychotic medication), metabolic syndrome, pre-diabetes or diabetes, osteoporosis, hypogonadism, pseudoacromegaly, pituitary tumors, functional

hypercortisolism, ACTH secreting tumors, peripheral neuropathy, dyslipidemia, and other diseases and disorders. Cortisol excess may also be found, for example, in patients with metabolic syndrome, pre-diabetes or diabetes; or may also be found, for example, in patients with liver disorders, such as, e.g., fatty liver disease, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), alcoholic liver diseases, liver fibrosis, and other liver disorders. The methods may include immunotherapy treatments. Reducing the effects of excess cortisol may improve the quality of life of a patient suffering from excess cortisol or its effects. Reducing the effects of excess cortisol may improve the psychological status of a patient suffering from excess cortisol or its effects.

[0007] The methods comprise administering to the subject an effective amount of a glucocorticoid receptor modulator (GRM) to reduce the effects of such cortisol excess, and, in examples, comprise administering to the subject an effective amount of a GRM along with another treatment (e.g., another pharmaceutical composition, or surgery, or radiation, or psychotherapy, or other treatment). In examples, the GRM is a nonsteroidal GRM. In examples, the GRM is a nonsteroidal selective GRM. In examples, the GRM is a nonsteroidal heteroaryl-ketone fused azadecalin selective GRM compound or a nonsteroidal octahydro fused azadecalin selective GRM compound. In preferred examples, the GRM is the nonsteroidal heteroaryl-ketone fused azadecalin selective GRM compound having the chemical name (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone, termed “relacorilant”, having the formula



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[0008] In examples, the methods disclosed herein include administration of a GRM, such as the heteroaryl-ketone fused azadecalin GRM relacorilant, to a patient in need of such treatment, to treat a disorder selected from Cushing’s syndrome; Cushing’s Disease; hyperglycemia secondary to hypercortisolemia; metabolic syndrome, pre-diabetes, or diabetes; a liver disease (e.g., fatty liver disease, non-alcoholic fatty liver disease (NAFLD),

non-alcoholic steatohepatitis (NASH), alcoholic liver diseases, liver fibrosis, and other liver disorders); a cardiac disorder (including, e.g., prolonged Q-T interval or other disorder of the heart rhythm, with or without Left Ventricular Hypertrophy (LVH)); high blood pressure; cancer; a psychological disorder (e.g., depression, such as psychotic major depression); weight gain (including weight gain due to antipsychotic medication), and other diseases and disorders. A GRM, such as relacorilant, may be administered to a patient as a monotherapy; and, in examples, a GRM, such as relacorilant, may be administered to a patient along with another treatment. The GRM may be administered before, or after, or along with, or any combination thereof, another treatment. In addition, the methods disclosed herein include administration of a GRM, such as relacorilant, to a patient in need of diagnosis, to diagnose a disorder such as, e.g., Cushing's Disease.

[0009] In some cases, the GRM (e.g., relacorilant) is orally administered. In examples, the GRM is administered with food. In examples, the GRM is administered to a patient who is fasting. In some cases, the GRM (e.g., a relacorilant) is administered with at least one pharmaceutical agent. In some cases, the GRM (e.g., a relacorilant) is administered after the subject or patient has been administered at least one other pharmaceutical agent. In some cases, the GRM (e.g., a relacorilant) is administered before the subject or patient is administered at least one other pharmaceutical agent. In some cases, the GRM (e.g., a relacorilant) is administered to a subject after the subject or patient has undergone surgery. In some cases, the GRM (e.g., a relacorilant) is administered to a subject before the subject or patient undergoes surgery.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] FIG. 1 Patients achieving clinically meaningful reductions in HbA1c, 2-hour oGTT or use of antidiabetic medications.

[0011] FIG. 2 Patients achieving clinically meaningful improvements in hypertension (high blood pressure).

[0012] FIG. 3 Relacorilant effects on Coagulation: There is a high risk of thrombotic events in patients with Cushing's syndrome; Cushing's syndrome patients treated with relacorilant showed improvement in coagulation factors. This result indicates that relacorilant may be useful to improve pre-operative coagulation control (before surgery for Cushing's syndrome) in Cushing's syndrome patients at high risk of thrombotic events.

WE CLAIM:

1. Use of a nonsteroidal selective glucocorticoid receptor modulator (selective GRM) having a heteroaryl-ketone fused azadecalin structure, or a nonsteroidal selective GRM having an octahydro fused azadecalin structure, in the manufacture of a medicament for treating a patient suffering from hypercortisolemia, and a symptom or comorbidity thereof, wherein said symptom or comorbidity of hypercortisolemia is one or more of:

hyperglycemia, wherein said medicament is for treatment to significantly lower the patient's $AUC_{glucose}$ as compared to the patient's baseline $AUC_{glucose}$ measured prior to treatment;

hypertension, wherein said medicament is for treatment to significantly lower the patient's blood pressure as compared to the patient's baseline blood pressure measured prior to treatment;

an abnormal liver enzyme level, wherein said medicament is for treatment to significantly lower an abnormal patient liver enzyme level as compared to the patient's baseline liver enzyme level measured prior to treatment;

an abnormal fructosamine level, wherein said medicament is for treatment to significantly improve an abnormal patient fructosamine level as compared to the patient's baseline fructosamine level measured prior to treatment;

an abnormal serum osteocalcin level, wherein said medicament is for treatment to significantly improve an abnormal patient serum osteocalcin level as compared to the patient's baseline serum osteocalcin level measured prior to treatment;

an abnormal heartbeat interval or median heart rate, wherein said medicament is for treatment to significantly improve an abnormal patient heartbeat interval or median heart rate as compared to the patient's baseline heartbeat interval or median heart rate measured prior to treatment;

an abnormal blood coagulation measure, wherein said medicament is for treatment to significantly improve an abnormal patient blood coagulation measure as compared to the patient's baseline blood coagulation as measured prior to treatment;

an abnormal blood cell measure, wherein said medicament is for treatment to significantly improve an abnormal patient blood cell measure as compared to the patient's baseline blood cell measure as measured prior to treatment;

an abnormal adrenocorticotropic hormone (ACTH) or pro-opiomelanocortin (POMC) level, wherein said medicament is for treatment to significantly improve an abnormal patient ACTH or POMC level as compared to the patient's baseline ACTH or POMC level as measured prior to treatment;

improve quality of life in a Cushing's patient, wherein said medicament is for treatment to significantly improve patient quality of life as compared to the patient's baseline quality of life as measured prior to treatment;

improve cognition in a Cushing's patient, wherein said medicament is for treatment to significantly improve patient cognition as compared to the patient's baseline cognition as measured prior to treatment;

lessen patient depression, as measured by a psychological measure of depression, wherein said medicament is for treatment to significantly reduce patient depression as compared to the patient's baseline depression as measured prior to treatment.

2. The use of claim 1, wherein said symptom or comorbidity thereof is hyperglycemia, wherein said treatment is effective to improve the patient's glucose control as compared to the patient's baseline glucose control measured prior to treatment.

3. The use of claim 1, wherein said symptom or comorbidity thereof is hyperglycemia, wherein said medicament is for treatment to lower the patient's hemoglobin A1c (HbA1c) by at least about 0.5% as compared to the patient's baseline HbA1c measured prior to treatment.

4. The use of claim 1, wherein said symptom or comorbidity thereof is hyperglycemia, wherein said medicament is for treatment to lower the patient's $AUC_{glucose}$ by at least about 15% as compared to the patient's baseline $AUC_{glucose}$ measured prior to treatment.

5. The use of claim 1, wherein said symptom or comorbidity thereof is hypertension, wherein said medicament is for treatment to lower the patient's 24-hour mean systolic or 24 hour mean diastolic blood pressure by at least about 5 millimeters of mercury (mmHg) as compared to the patient's baseline blood pressure measured prior to treatment.

6. The use of claim 1, wherein said symptom or comorbidity thereof is an abnormal heartbeat interval or median heart rate, wherein said medicament is for treatment to significantly improve an abnormal patient heartbeat QT interval or ECG median heart rate as compared to the patient's baseline heartbeat QT interval or ECG median heart rate measured prior to treatment.

7. The use of claim 1, wherein said symptom or comorbidity thereof is an abnormal liver enzyme level, wherein said medicament is for treatment to significantly lower patient alanine aminotransferase (ALT) or aspartate aminotransferase (AST) liver enzyme level, or both, as compared to the patient's baseline ALT or AST liver enzyme level measured prior to treatment.

8. The use of claim 1, wherein said symptom or comorbidity thereof is an abnormal fructosamine level, wherein said medicament is for treatment to significantly improve an abnormal patient fructosamine level as compared to the patient's baseline fructosamine level measured prior to treatment.

9. The use of claim 1, wherein said symptom or comorbidity thereof is an abnormal osteocalcin level, wherein said medicament is for treatment to significantly improve an abnormal patient osteocalcin level as compared to the patient's baseline osteocalcin level measured prior to treatment.

10. The use of claim 1, wherein said symptom or comorbidity thereof is an abnormal blood coagulation factor level, wherein said medicament is for treatment to significantly improve an abnormal Factor IX or an abnormal Factor X level as compared to the patient's baseline Factor IX or Factor X level as measured prior to treatment.

11. The use of claim 1, wherein said symptom or comorbidity thereof is an abnormal blood coagulation measure, wherein said medicament is for treatment to significantly improve an abnormal thrombin-antithrombin (ATT) or an abnormal activated partial thromboplastin time (aPTT) as compared to the patient's baseline ATT or aPTT as measured prior to treatment.

12. The use of claim 1, wherein said symptom or comorbidity thereof is an abnormal blood cell measure selected from an abnormal eosinophil measure or abnormal platelet count, wherein said medicament is for treatment to significantly improve an abnormal patient eosinophil measure or abnormal platelet count as compared to the patient's baseline eosinophil measure or abnormal platelet count as measured prior to treatment.

13. The use of claim 1, wherein said symptom or comorbidity thereof is an abnormal adrenocorticotropic hormone (ACTH) or pro-opiomelanocortin (POMC) level, wherein said medicament is for treatment to significantly improve an abnormal patient ACTH or POMC level as compared to the patient's baseline ACTH or POMC level as measured prior to treatment.

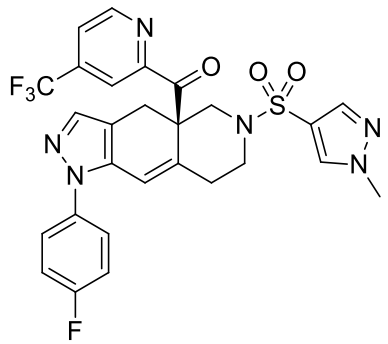
14. The use of claim 1, wherein said symptom or comorbidity thereof is impaired quality of life in a Cushing's patient, wherein said medicament is for treatment to significantly improve patient quality of life as measured by Cushing Quality of Life Score, as compared to the patient's baseline quality of life as so measured prior to treatment.

15. The use of claim 1, wherein said symptom or comorbidity thereof is impaired cognition in a Cushing's patient, wherein said medicament is for treatment to significantly improve patient cognition as measured by a cognitive test, as compared to the patient's baseline cognition as measured by said cognitive test prior to treatment.

16. The use of claim 15, wherein said cognitive test is a Trail Making Test.

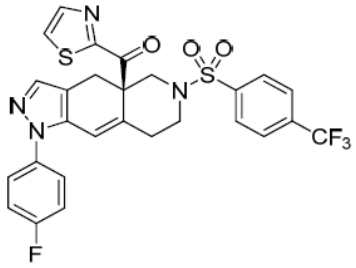
17. The use of claim 1, wherein said symptom or comorbidity thereof is depression, as measured by the Beck Depression Scale, wherein said medicament is for treatment to significantly reduce patient depression as indicated by the Beck Depression Scale as compared to the patient's baseline depression as so measured prior to treatment.

18. The use of claim 1, wherein said nonsteroidal selective glucocorticoid receptor modulator (selective GRM) is selected from the group consisting of relacorilant, (R)-(1-(4-fluorophenyl)-6-((1-methyl-1H-pyrazol-4-yl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone, which has the formula



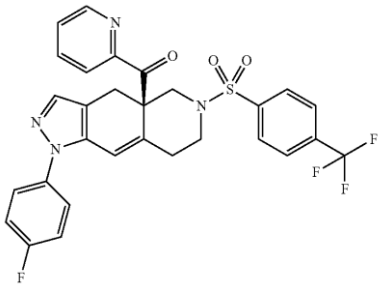
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(R)-(1-(4-flurophenyl)-6-((4-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(thiazol-2-yl)methanone, termed "CORT122928", having the formula



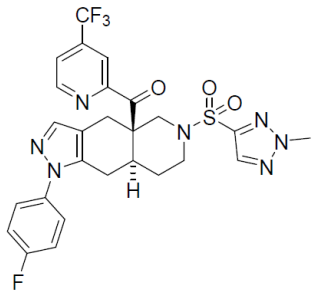
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(R)-(1-(4-fluorophenyl)-6-((4-(trifluoromethyl)phenyl)sulfonyl)-4,4a,5,6,7,8-hexahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(pyridin-2-yl)methanone, termed "CORT113176", having the formula



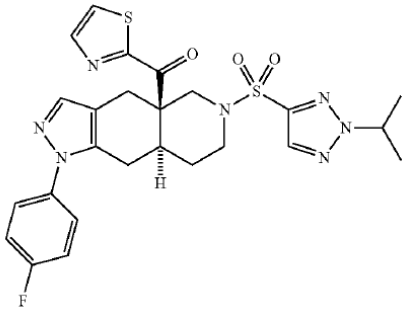
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((4aR,8aS)-1-(4-fluorophenyl)-6-((2-methyl-2H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(4-(trifluoromethyl)pyridin-2-yl)methanone ("CORT125281") which has the structure:



, and

((4aR,8aS)-1-(4-fluorophenyl)-6-((2-isopropyl-2H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(thiazol-2-yl)methanone, termed "CORT125329", having the formula:



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19. The use of claim 3, wherein said nonsteroidal selective glucocorticoid receptor modulator (selective GRM) is a heteroaryl-ketone fused azadecalin compound selected from relacorilant, CORT122928, and CORT113176.

20. The use of claim 3, wherein said nonsteroidal selective glucocorticoid receptor modulator (selective GRM) is an octahdryo fused azadecalin compound selected from CORT125281, and CORT125329.

21. The use of claim 5, wherein said nonsteroidal selective glucocorticoid receptor modulator (selective GRM) is a heteroaryl-ketone fused azadecalin compound selected from relacorilant, CORT122928, and CORT113176.

22. The use of claim 5, wherein said nonsteroidal selective glucocorticoid receptor modulator (selective GRM) is an octahdryo fused azadecalin compound selected from CORT125281, and CORT125329.

23. The use of claim 7, wherein said nonsteroidal selective glucocorticoid receptor modulator (selective GRM) is a heteroaryl-ketone fused azadecalin compound selected from relacorilant, CORT122928, and CORT113176.

24. The use of claim 7, wherein said nonsteroidal selective glucocorticoid receptor modulator (selective GRM) is an octahdryo fused azadecalin compound selected from CORT125281, and CORT125329.

25. The use of claim 9, wherein said nonsteroidal selective glucocorticoid receptor modulator (selective GRM) is a heteroaryl-ketone fused azadecalin compound selected from relacorilant, CORT122928, and CORT113176.

26. The use of claim 9, wherein said nonsteroidal selective glucocorticoid receptor modulator (selective GRM) is an octahdryo fused azadecalin compound selected from CORT125281, and CORT125329.