[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 the following disorders:

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;

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 the following disorders:

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~~disorder 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 disorder ~~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 disorder ~~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 disorder~~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.

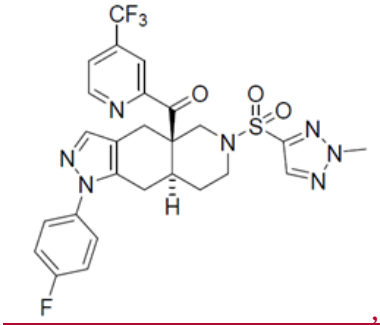
6. The use of claim 1, wherein said disorder ~~symptom or comorbidity thereof~~ is an abnormal heartbeat interval or median heart rate, wherein said medicament is for treatment to significantly improve an abnormal patient heartbeat QT interval or ECG median heart rate as compared to the patient's baseline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

7. The use of claim 1, wherein said disorder ~~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.

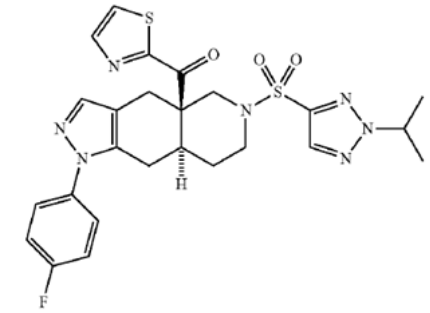
8. The use of claim 1, wherein said disorder ~~symptom or comorbidity thereof~~ is an abnormal fructosamine level, wherein said medicament is for treatment to significantly improve an abnormal patient fructosamine level as compared to the patient's baseline fructosamine level measured prior to treatment.

9. The use of claim 1, wherein said disorder ~~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 disorder ~~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, wherein said selective GRM is an octahdryo fused azadecalin compound selected from CORT125281 ((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), which has the structure:

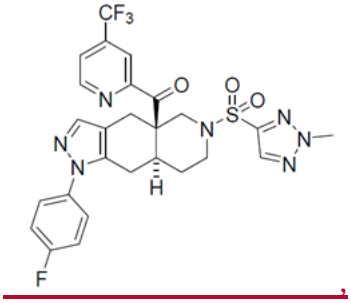


, and CORT125329, ((4aR,8aS)-1-(4-fluorophenyl)-6-((2-isopropyl-2H-1,2,3-triazol-4-yl)sulfonyl)-4,4a,5,6,7,8,8a,9-octahydro-1H-pyrazolo[3,4-g]isoquinolin-4a-yl)(thiazol-2-yl)methanone), which has the structure:

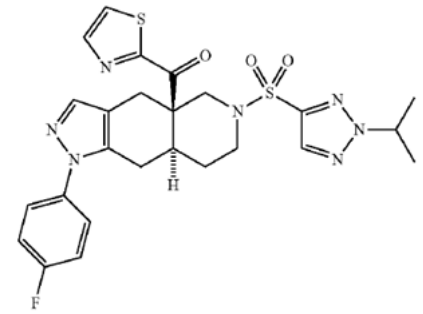


.

11. The use of claim 1, wherein said disorder ~~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 , wherein said selective GRM is an octahdryo fused azadecalin compound selected from CORT125281 ((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), which has the structure:



, and CORT125329, ((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), which has the structure:



.

12. The use of claim 1, wherein said disorder ~~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 disorder ~~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 disorder ~~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.

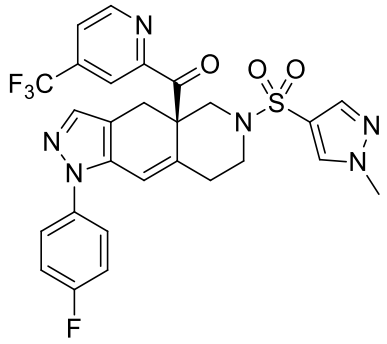
15. The use of claim 1, wherein said disorder ~~symptom or comorbidity thereof~~ is impaired cognition in a Cushing's patient, wherein said medicament is for treatment to significantly improve patient cognition as measured by a cognitive test, as compared to the patient's baseline cognition as measured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

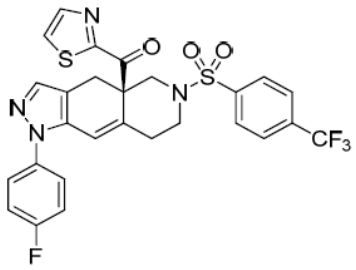
for treatment to significantly reduce patient depression as indicated by the Beck Depression Scale as compared to the patient's baseline depression as so measured prior to treatment.

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



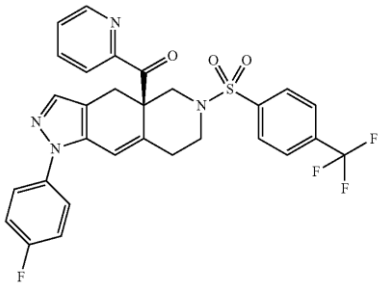
,

(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



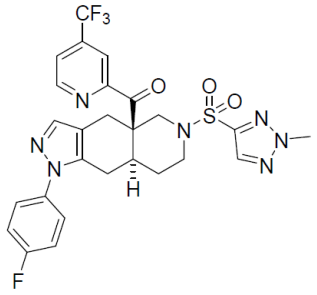
,

(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



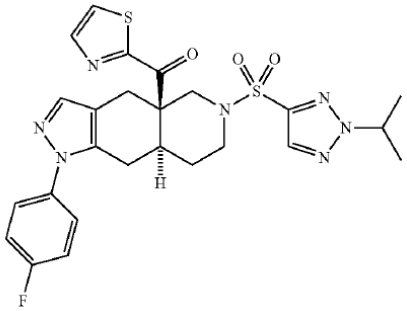
,

((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:



.

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.