and that samples are only taken from the patients after the metyrapone administration. Although metyrapone-IPSS improves the CRH-IPSS – since it dispenses with the need for sampling before the administration of metyrapone, and thus reduces the duration of catheterization and likelihood of infection, thrombis, or bleeding associated therewith – it also has serious limitations. First, metyrapone acts to block the conversion of 11-deoxycortisol to cortisol by 11β-hydroxylase, causing a decrease in cortisol level, which in turn stimulates ACTH production and release. Since its effect on the ACTH secretion is indirect, the test result may be skewed by other factors affecting the cortisol synthesis. Second, as a cortisol synthesis blocker, treatment of metyrapone – especially at a high dose – may result in adrenal insufficiency or have deleterious effects on various normal bodily functions that require cortisol – for example, the anti-stress and anti-inflammation functions. Third, metyrapone is currently not available in the United States, consequently this diagnosis method is out of reach for many patients in this country.

SUMMARY

[0006a] In one aspect of the present disclosure, there is provided a method of differentially diagnosing adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome in a patient where the differential diagnosis is between ectopic ACTH syndrome and Cushing's Disease, the method comprising the steps of:

(i) obtaining from a patient an ACTH concentration in a fluid sample obtained from either the left or right inferior petrosal venous sinus and an ACTH concentration from fluid obtained from a periphery venous sample, and

(ii) obtaining an ACTH concentration from the ACTH concentrations, wherein the patient is a patient with Cushing's syndrome and also elevated ACTH levels to whoma dose of glucocorticoid receptor antagonist (GRA) sufficient to increase ACTH from the pituitary gland by at least two fold in persons with normal Hypothalamus Pituitary Adrenal (HPA) function had been administered;

wherein the samples were obtained at least two hours after administration of GRA;

wherein an ACTH concentration ratio of greater than 3 for the ACTH concentration from the inferior venous sinus sample over the periphery venous sinus sample is diagnostic of Cushing's disease.

[0006b] In another aspect of the present disclosure, there is provided a method of obtaining a measurement indicative of differential diagnosis of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome in a patient where the differential diagnosis is between ectopic ACTH syndrome and Cushing's disease, the method comprising the steps of:

(i) obtaining from a patient an ACTH concentration in a fluid sample obtained from either the left or right inferior petrosal venous sinus and an ACTH concentration from fluid obtained from a periphery venous sample, and

(ii) obtaining an ACTH concentration ratio from the ACTH concentrations, wherein the patient is a patient with Cushing's syndrome and an elevated ACTH level to whom a dose of glucocorticoid receptor antagonist sufficient to increase ACTH from the pituitary gland by at least two fold in persons with normal Hypothalamus Pituitary Adrenal (HPA) function had been administered;

wherein the samples were obtained at least two hours after administration of GRA; and

wherein an ACTH concentration ratio of greater than 3 for the ACTH concentration from the inferior venous sinus sample over the periphery venous sinus sample is indicative of Cushing's disease.

[0007] The present disclosure also relates to a method of differentially diagnosing adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome in a patient with hypercortisolemia where the differential diagnosis is between ectopic ACTH syndrome and Cushing Disease. The method comprises: (i) selecting a patient with Cushing's syndrome and elevated ACTH levels; (ii) administering a dose of glucocorticoid receptor antagonist (GRA) sufficient to increase ACTH from the pituitary gland by at least two fold in persons with normal HPA function; (iii) waiting for at least two hours; and (iv) obtaining from the patient an ACTH concentration ratio, which is derived both from the ACTH concentrations in

fluid obtained from either the left or right inferior petrosal venous sinus and from fluid obtained from a periphery vein, e.g., a jugular vein. The patient is diagnosed with Cushing Disease if the ACTH concentration ratio is greater than 3.

[0008] In some embodiments, the periphery venous sample is a jugular venous sample. In some embodiments, the ratio is derived from the ACTH concentration in fluid obtained from the left and right inferior petrosal venous sinuses. In some embodiments, the GRA is a selective inhibitor of the glucocorticoid receptor. In some cases, the first and second

WHAT IS CLAIMED IS:

1. A method of differentially diagnosing adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome in a patient where the differential diagnosis is between ectopic ACTH syndrome and Cushing's Disease, the method comprising the steps of:

(i) obtaining from a patient an ACTH concentration in a fluid sample obtained from either the left or right inferior petrosal venous sinus and an ACTH concentration from fluid obtained from a periphery venous sample, and

(ii) obtaining an ACTH concentration from the ACTH concentrations, wherein the patient is a patient with Cushing's syndrome and also elevated ACTH levels to whom a dose of glucocorticoid receptor antagonist (GRA) sufficient to increase ACTH from the pituitary gland by at least two fold in persons with normal Hypothalamus Pituitary Adrenal (HPA) function had been administered;

wherein the samples were obtained at least two hours after administration of GRA;

wherein an ACTH concentration ratio of greater than 3 for the ACTH concentration from the inferior venous sinus sample over the periphery venous sinus sample is diagnostic of Cushing's disease.

2. The method of claim 1 wherein the periphery venous sample is a jugular venous sample.

3. The method of claim 1 wherein the glucocorticoid receptor antagonist is a selective inhibitor of the glucocorticoid receptor.

4. The method of claim 1 wherein a first and second sampling of the ACTH concentrations in the are taken 5-10 minutes apart from both the inferior petrosal venous sinus and a periphery venous sample.

5. The method of claim 1, wherein the glucocorticoid receptor antagonist comprises a steroidal backbone with at least one phenyl-containing moiety in the 11-β position of the steroidal backbone.

6. The method of claim 5 wherein the phenyl-containing moiety in the 11-β position of the steroidal backbone is a dimethylaminophenyl moiety.

7. The method of claim 5, wherein the glucocorticoid receptor antagonist is mifepristone.

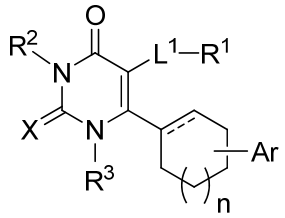
8. The method of claim 1, wherein the glucocorticoid receptor antagonist is selected from the group consisting of 11β-(4-dimethylaminoethoxyphenyl)-17α-propynyl-17β-hydroxy-4,9 estradien-3-one and (17α)-17-hydroxy-19-(4-methylphenyl)androsta-4,9(11)-dien-3-one.

9. The method of claim 1, wherein the glucocorticoid receptor antagonist is (11β,17β)-11-(1,3-benzodioxol-5-yl)-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one.

10. The method of claim 1, wherein the glucocorticoid receptor antagonist has a non-steroidal backbone.

11. The method of claim 10, wherein the glucocorticoid receptor antagonist backbone is a cyclohexyl pyrimidine.

12. The method of claim 11, wherein the cyclohexyl pyrimidine has the following formula:



wherein

the dashed line is absent or a bond;

X is selected from the group consisting of O and S;

R^1 is selected from the group consisting of cycloalkyl, heterocycloalkyl, aryl and heteroaryl, optionally substituted with from 1 to 3 R^{1a} groups;

each R^{1a} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkyl OR^{1b}, halogen, C_{1-6} haloalkyl, C_{1-6} haloaloxy, OR^{1b}, $NR^{1b}R^{1c}$, $C(O)R^{1b}$, $C(O)OR^{1b}$, $OC(O)R^{1b}$, $C(O)NR^{1b}R^{1c}$, $NR^{1b}C(O)R^{1c}$, SO_2R^{1b}, $SO_2NR^{1b}R^{1c}$, cycloalkyl, heterocycloalkyl, aryl and heteroaryl;

R^{1b} and R^{1c} are each independently selected from the group consisting of H and C_{1-6} alkyl;

R^2 is selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkyl-OR^{1b}, C_{1-6} alkyl $NR^{1b}R^{1c}$ and C_{1-6} alkylene heterocycloalkyl;

R^3 is selected from the group consisting of H and C_{1-6} alkyl;

Ar is aryl, optionally substituted with 1-4 R^4 groups;

each R^4 is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} alkoxy, halogen, C_{1-6} haloalkyl and C_{1-6} haloalkoxy;

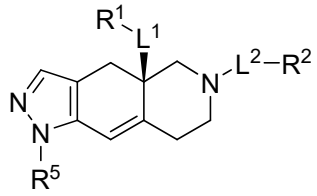
L^1 is a bond or C_{1-6} alkylene; and

subscript n is an integer from 0 to 3,

or salts thereof.

13. The method of claim 10, wherein the glucocorticoid receptor antagonist backbone is a fused azadecalin.

14. The method of claim 13, wherein the fused azadecalin is a compound having the following formula:



wherein

L^1 and L^2 are members independently selected from a bond and unsubstituted alkylene;

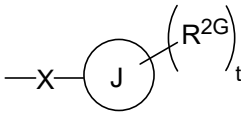
R^1 is a member selected from unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted heterocycloalkyl, $-OR^{1A}$, $NR^{1C}R^{1D}$, $-C(O)NR^{1C}R^{1D}$, and $-C(O)OR^{1A}$, wherein

R^{1A} is a member selected from hydrogen, unsubstituted alkyl and unsubstituted heteroalkyl,

R^{1C} and R^{1D} are members independently selected from unsubstituted alkyl and unsubstituted heteroalkyl,

wherein R^{1C} and R^{1D} are optionally joined to form an unsubstituted ring with the nitrogen to which they are attached, wherein said ring optionally comprises an additional ring nitrogen;

R^2 has the formula:



wherein

R^{2G} is a member selected from hydrogen, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, -CN, and $-CF_3$;

J is phenyl;

t is an integer from 0 to 5;

X is $-S(O_2)-$; and

R^5 is phenyl optionally substituted with 1-5 R^{5A} groups, wherein

R^{5A} is a member selected from hydrogen, halogen, $-OR^{5A1}$, $S(O_2)NR^{5A2}R^{5A3}$, -CN, and unsubstituted alkyl, wherein

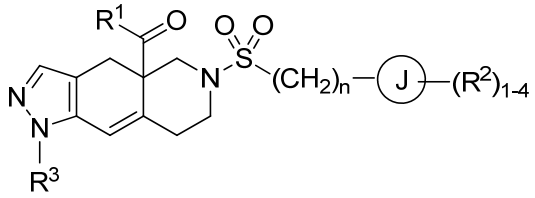
R^{5A1} is a member selected from hydrogen and unsubstituted alkyl, and

R^{5A2} and R^{5A3} are members independently selected from hydrogen and unsubstituted alkyl,

or salts thereof.

15. The method of claim 10, wherein the glucocorticoid receptor antagonist backbone is a heteroaryl ketone fused azadecalin or an octahydro fused azadecalin.

16. The method of claim 15, wherein the heteroaryl ketone fused azadecalin has the formula:



wherein

R^1 is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from R^{1a};

each R^{1a} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, CN, N-oxide, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl;

ring J is selected from the group consisting of a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring and a heteroaryl ring, wherein the heterocycloalkyl and heteroaryl rings have from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S;

each R^2 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, $C_{1\ 6}$ haloalkyl, $C_{1\ 6}$ alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl-C_{1-6} alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, SR^{2a}, $S(O)R^{2a}$, $S(O)_2R^{2a}$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl, wherein the heterocycloalkyl groups are optionally substituted with 1-4 R^{2c} groups;

alternatively, two R^2 groups linked to the same carbon are combined to form an oxo group (=O);

alternatively, two R^2 groups are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 R^{2d} groups;

R^{2a} and R^{2b} are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

each R^{2c} is independently selected from the group consisting of hydrogen, halogen, hydroxy, C_{1-6} alkoxy, C_{1-6} haloalkoxy, CN, and $NR^{2a}R^{2b}$;

each R^{2d} is independently selected from the group consisting of hydrogen and C_{1-6} alkyl, or two R^{2d} groups attached to the same ring atom are combined to form (=O);

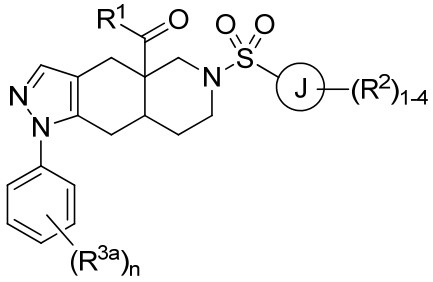
R^3 is selected from the group consisting of phenyl and pyridyl, each optionally substituted with 1-4 R^{3a} groups;

each R^{3a} is independently selected from the group consisting of hydrogen, halogen, and C_{1-6} haloalkyl; and

subscript n is an integer from 0 to 3;

or salts thereof.

17. The method of claim 15, wherein the octahydro fused azadecalin has the formula:



wherein

R^1 is a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S, optionally substituted with 1-4 groups each independently selected from R^{1a};

each R^{1a} is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, N-oxide, and C_{3-8} cycloalkyl;

ring J is selected from the group consisting of an aryl ring and a heteroaryl ring having from 5 to 6 ring members and from 1 to 4 heteroatoms each independently selected from the group consisting of N, O and S;

each R^2 is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} alkyl-C_{1-6} alkoxy, CN, OH, $NR^{2a}R^{2b}$, $C(O)R^{2a}$, $C(O)OR^{2a}$, $C(O)NR^{2a}R^{2b}$, SR^{2a}, $S(O)R^{2a}$, $S(O)_2R^{2a}$, C_{3-8} cycloalkyl, and C_{3-8} heterocycloalkyl having from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S;

alternatively, two R^2 groups on adjacent ring atoms are combined to form a heterocycloalkyl ring having from 5 to 6 ring members and from 1 to 3 heteroatoms each independently selected from the group consisting of N, O and S, wherein the heterocycloalkyl ring is optionally substituted with from 1 to 3 R^{2c} groups;

R^{2a}, R^{2b} and R^{2c} are each independently selected from the group consisting of hydrogen and C_{1-6} alkyl;

each R^{3a} is independently halogen; and

subscript n is an integer from 0 to 3,

or salts thereof.

18. A method of obtaining a measurement indicative of differential diagnosis of adrenocorticotropic hormone (ACTH)-dependent Cushing's syndrome in a patient where the differential diagnosis is between ectopic ACTH syndrome and Cushing's disease, the method comprising the steps of:

(i) obtaining from a patient an ACTH concentration in a fluid sample obtained from either the left or right inferior petrosal venous sinus and an ACTH concentration from fluid obtained from a periphery venous sample, and

(ii) obtaining an ACTH concentration ratio from the ACTH concentrations, wherein the patient is a patient with Cushing’s syndrome and an elevated ACTH level to whom a dose of glucocorticoid receptor antagonist (GRA) sufficient to increase ACTH from the pituitary gland by at least two fold in persons with normal Hypothalamus Pituitary Adrenal (HPA) function had been administered;

wherein the samples were obtained at least two hours after administration of GRA; and

wherein an ACTH concentration ratio of greater than 3 for the ACTH concentration from the inferior venous sinus sample over the periphery venous sinus sample is indicative of Cushing's disease.