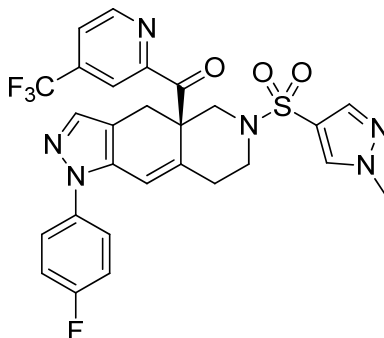


SUMMARY

[0010a] In an aspect of the present disclosure, there is provided a use of the heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM)

(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 (relacorilant) having the structure:



in the manufacture of a medicament for treating a neuroendocrine tumor in a patient hosting a neuroendocrine tumor without increasing cortisol levels or risk of hypokalemia in said patient, the tumor having a baseline level of somatostatin receptor expression, wherein:

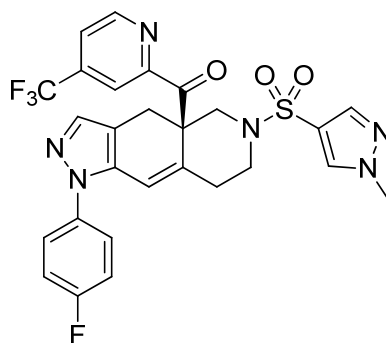
- a) at least one dose of a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) is to be administered, effective to stimulate the expression of somatostatin receptors (SRs) in said neuroendocrine tumor; and

- b) at least one dose of somatostatin or a somatostatin analog is to be administered;

whereby the neuroendocrine tumor is treated, without significant increases in cortisol and without increase in the risk of hypokalemia in the patient.

[0010b] In another aspect of the present disclosure, there is provided a use of the heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM)

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 (relacorilant) having the structure:



in the manufacture of a medicament for localizing a neuroendocrine tumor in a patient hosting a neuroendocrine tumor without increasing cortisol levels or risk of hypokalemia in said patient, the tumor having a baseline level of somatostatin receptor expression, wherein:

a) at least one dose of a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) is to be administered, effective to stimulate the expression of somatostatin receptors (SRs) in said neuroendocrine tumor;

b) at least one dose of somatostatin or a somatostatin analog is to be administered; and

c) the patient is to be imaged, effective to provide an image of the tumor within the patient,

whereby the neuroendocrine tumor is localized, without leading to significant increases in cortisol, and without increasing the risk of hypokalemia in the patient.

[0011] Applicant has surprisingly discovered that the heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) termed “relacorilant” is an effective glucocorticoid receptor antagonist (GRA) that can inhibit glucocorticoid receptor (GR) activation without raising cortisol levels, and thus without increasing the risk of hypokalemia in patients. Administration of heteroaryl-ketone fused azadecalin GRMs effective to block GR activation

also stimulates somatostatin receptor (SR) expression. Provided herein are methods for treating, identifying and localizing tumors expressing SR, including methods of enhancing the efficacy of imaging techniques by increasing SR expression in tumors. In preferred methods, the heteroaryl-ketone fused azadecalin GRM is relacorilant. In examples, the methods include selecting patients who may derive benefit from the treatment methods disclosed herein. Patients who may derive benefit from the treatment methods disclosed herein include those suspected of hosting a tumor, where the suspected tumor expresses low levels of somatostatin receptors, or where the suspected tumor is not visible, or is poorly visible, with imaging techniques such as techniques used to image somatostatin receptors, or where increasing said somatostatin receptor expression in the tumor would improve imaging, identification, or localization of the tumor, and combinations thereof.

[0012] Applicant discloses herein methods of treating a tumor in a patient hosting a tumor without increasing cortisol levels or risk of hypokalemia in the patient, the tumor having a baseline level of somatostatin receptor expression, the method comprising: a) Administering to the patient at least one dose of a heteroaryl-ketone fused azadecalin GRM, effective stimulate the expression of SRs in said tumor; and b) administering to the patient at least one dose of somatostatin or a somatostatin analog; whereby the tumor is treated without increasing cortisol levels or risk of hypokalemia in the patient. In examples, administration of a heteroaryl-ketone fused azadecalin GRM compound is effective to enhance SR expression and improve treatment, identification, and localization of a tumor while not leading to significant increases in cortisol, and while not increasing the risk of, or causing, hypokalemia. The tumors may be, e.g., neuroendocrine tumors. In examples, the tumor is a neuroendocrine tumor, and the methods include methods of treating a neuroendocrine tumor in a patient hosting a neuroendocrine tumor without increasing cortisol levels or risk of hypokalemia in the patient, the tumor having a baseline level of somatostatin receptor expression, the method comprising: a) Administering to the patient at least one dose of a heteroaryl-ketone fused azadecalin GRM, effective stimulate the expression of

1. Use of the heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM)

Cc1cc(S(=O)(=O)N2CC[C@]3(C2)C(=O)c4cc(F)cnc4C5=CC=CC=C5N3)cnc1

a) at least one dose of a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) is to be administered, effective to stimulate the expression of somatostatin receptors (SRs) in said neuroendocrine tumor; and

2. The use of claim 1, wherein somatostatin is to be administered.

4. The use of claim 1, wherein said baseline level of somatostatin receptor expression is undetectable, or only poorly detectable, with imaging.

5. The use of claim 1, wherein the somatostatin or somatostatin analog is a labeled somatostatin or somatostatin analog, and the labeled somatostatin or somatostatin analogs in the patient is to be imaged, effective to localize the tumor within the patient.

6. The use of claim 5, wherein labeled somatostatin or somatostatin analogs in the patient is to be imaged following said administration of said heteroaryl-ketone fused azadecalin GRM, effective to localize the tumor within the patient.

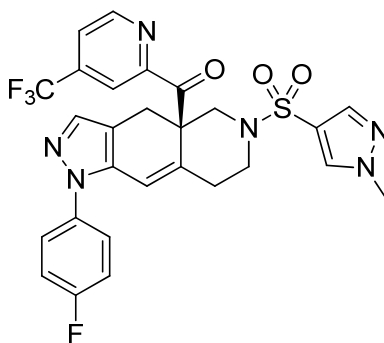
7. The use of claim 1, wherein said at least one dose of somatostatin or a somatostatin analog is to be administered to the patient, effective to increase the tumor's expression of somatostatin receptors above the baseline amount of somatostatin receptor expression in the tumor.

8. The use of claim 1, wherein said patient suffers from Cushing's syndrome, and said use is effective to treat said Cushing's syndrome.

9. The use of claim 8, wherein said patient suffers from Cushing's Disease, and said use is effective to treat said Cushing's Disease.

10. Use of the heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM)

(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 (relacorilant) having the structure:



a) at least one dose of a heteroaryl-ketone fused azadecalin glucocorticoid receptor modulator (GRM) is to be administered, effective to stimulate the expression of somatostatin receptors (SRs) in said neuroendocrine tumor;

b) at least one dose of somatostatin or a somatostatin analog is to be administered; and

c) the patient is to be imaged, effective to provide an image of the tumor within the patient,

whereby the neuroendocrine tumor is localized, without leading to significant increases in cortisol, and without increasing the risk of hypokalemia in the patient.

11. The use of claim 10, wherein somatostatin is to be administered.

12. The use of claim 10, wherein a somatostatin analog (SSA) selected from the group consisting of octreotide, radiolabeled octreotide, octreotate, pasireotide, lanreotide, pentetreotide, vapreotide, seglitide, cortistatin, and radiolabeled derivatives thereof selected from the group consisting of ^{123}I -Tyr³-octreotide, ^{111}In -DTPA-*D*-Phe¹-octreotide, [^{111}In -DTPA⁰]octreotide, [^{90}Y -DOTA, Tyr³]octreotide, ^{111}In -octreotide, ^{111}In -pentetreotide, and [^{177}Lu -DOTA, Tyr³]octreotate is to be administered.

13. The use of claim 10, wherein said baseline level of somatostatin receptor expression is undetectable, or only poorly detectable, with imaging.

14. The use of claim 10, wherein the somatostatin or somatostatin analog is a labeled somatostatin or somatostatin analog, and the labeled somatostatin or somatostatin analogs in the patient is to be imaged, effective to localize the tumor within the patient.

15. The use of claim 14, wherein labeled somatostatin or somatostatin analogs in the patient is to be imaged following said administration of said heteroaryl-ketone fused azadecalin GRM, effective to localize the tumor within the patient.

16. The use of claim 10, wherein said at least one dose of somatostatin or a somatostatin analog is to be administered to the patient, effective to increase the tumor's expression of somatostatin receptors above the baseline amount of somatostatin receptor expression in the tumor.

17. The use of claim 10, wherein said patient suffers from Cushing's syndrome, and said use is effective to treat said Cushing's syndrome.

18. The use of claim 17, wherein said patient suffers from Cushing's Disease, and said use is effective to treat said Cushing's Disease.