Methods for the diagnosis and/or treatment of neuroendocrine cancers

Field

[0001] The present invention relates to methods of radioimaging and/or radiotherapy, comprising the administration of a specific chemical compounds complexed with $^{64}Cu/^{67}Cu$ radioisotopes to deliver a targeted dose of radiation for the imaging and/or treatment of a neuroendocrine cancer, particularly neuroblastoma in children.

Background

[0002] The neuroendocrine system of the body is responsible for creating, storing and secreting peptides and hormones. Neuroendocrine cancers often present as tumours and are typically found in the gastrointestinal or respiratory system, however neuroendocrine cancers may also be found in other sites such as the adrenal glands, the nervous system and skin. Specific sites for neuroendocrine tumours include the large bowel and appendix, small intestine, pancreas, stomach and the lungs.

[0003] Neuroblastoma is a neuroendocrine cancer, where the cancer forms in early nerve tissue (i.e. neuroblasts) of the sympathetic nervous system and can be found anywhere in this system, including the adrenal glands, neck, chest and spinal cord. Neuroblastomas occur most often in infants and young children under the age of 5 and accounts for approximately 13% of pediatric cancer mortalities. Given the complexity and heterogeneity of neuroblastoma, many factors determine the outcome. For example, whether the cancer will spontaneously regress or metastasize and become refractory to therapy may relate to the age at diagnosis, stage of disease, and molecular, cellular and genetic features of the disease.

[0004] Diagnosis of the neuroendocrine cancer is typically achieved by a combination of techniques, including biopsies, blood tests, endoscopies, ultrasounds, x-rays, CT scans, MRI scans and nuclear medicine imaging, such as PET scans. While techniques such as biopsies can allow for definitive diagnosis, this requires that the cancer is first located. Other techniques, such as PET scans, allow for the whole subject to be assessed at once in order to determine the presence of cancer. The use of nuclear medicine imaging requires the administration of a suitable radioactive tracer that is capable of binding to the cancer site. In order for imaging to be successful, the agent that is administered must bind selectively to the cancer site, retain and deliver the radioisotope to the cancer site, persist for a sufficient time to allow for images of

sufficient quality to be obtained and also induce little or no side effects to the subject. Treatment of cancer is typically accompanied by various side effects and adverse events that are associated with the form of treatment. Often, adverse events that are experienced by the patient may be severe enough to limit or end the prescribed course of treatment early, or otherwise cause detrimental effects to the patient.

[0005] Patients are classified into low, intermediate, and high-risk categories. In general, those with low-risk disease have excellent event free survival and overall survival (OS) rates with observation only or minimal therapeutic interventions. The outcome of patients with intermediate-risk disease, who are treated primarily with surgery and chemotherapy, has improved to the point where many groups are focused on using biologic markers to help further decrease therapy in this group of children.

[0006] Patients with high-risk disease comprise approximately half of all new neuroblastoma cases each year. This group requires treatment with multimodal therapy, including induction chemotherapy, surgery, radiotherapy, high-dose chemotherapy with autologous stem cell rescue, and biologic and immunotherapeutic maintenance therapy in order to improve their survival odds. However, even with this aggressive therapeutic strategy, a significant number of patients will still relapse and eventually die of this disease.

[0007] Despite recent advances in understanding of the pathogenesis of neuroblastoma, patients suffering from high-risk refractory or relapsed disease have no established curative treatment options. Patients with relapsed disease often develop metastatic tumors resistant to standard therapies and treatment goals are often not curative but aimed at prolonging survival and symptom control. The 1- and 4-year OS rates remain at only 57% and 20%, respectively. To improve outcomes in these patients, novel treatment strategies are needed. The substitution of ^{123}I for ^{131}I in meta-iodobenzylguanidine (MIBG) enables a therapeutic radiopharmaceutical suitable for treatment of neuroblastoma and other neuroendocrine tumors. However, the use of ^{131}I-MIBG for neuroblastoma remains experimental and it is currently used only in a clinical trial setting. In addition, ^{131}I-MIBG therapy is an extremely involved and logistically difficult process due to the long half-life (8 days) of ^{131}I. Although single-agent molecular radiotherapy with ^{131}I-MIBG has shown to have some efficacy in the relapsed or refractory population, the overall response rate (ORR) is only 36%, with a median time to progression of approximately 5 months, and significant toxicities are seen in most patients.

Additionally, approximately 10% of patients have MIBG non-avid disease and are not suitable for treatment.

[0008] There remains a need to develop targeted diagnosis and/or therapies for neuroendocrine cancers that deliver the highest tolerated dose of radioactivity, while reducing unwanted off-target effects and sparing patients from adverse treatment-related effects, and in the sense of diagnosis, provides images that are of a sufficient quality for better diagnosis of the cancer.

Summary of the invention

[0009] The present invention provides a method for the diagnosis and/or treatment of a neuroendocrine cancer, particularly neuroblastoma by administration of a compound of Formula (I) complexed with either a $^{64}Cu/^{67}Cu$ radioisotope. The compound of Formula (I) is a somatostatin analogue containing an octreotate fragment and a sarcophagine fragment that is capable of being radiolabelled with a radioisotope of copper. The compound of Formula (I) coordinates and retains the copper radioisotope, and also shows high-affinity binding to somatostatin receptors, which allows for the targeted delivery of radiation to tumour sites that express the receptor. Since neuroblastoma has been shown to express somatostatin receptor 2 (SSTR2), the compound of Formula (I) is suited to use for specific targeting of neuroblastoma sites and other neuroendocrine cancers where the same receptor is expressed.

[0010] The methods for diagnosis of a neuroendocrine cancer or a neuroblastoma as disclosed herein are more effective when compared to the current standard of care model, i.e. with the administration of ^{123}I-MIBG and subsequent imaging. In accordance with current standard models, imaging after administration of ^{123}I-MIBG is by SPECT, however images obtained are typically of a low resolution and can limit the ability of the physician to make clinical diagnoses and decisions for treatment of the patient. In accordance with the methods disclosed herein, the present inventors believe that the administration of ^{64}Cu-Sartate with subsequent PET imaging provides for more efficient and accurate evaluation of patients and therefore diagnosis of neuroendocrine cancers and neuroblastomas in such patients. Since the resolution of the images obtained by PET after administration of ^{64}Cu-Sartate have a higher resolution (see Figure 1) and specificity, the nature and location of any tumours in the subject are more readily determined and can provide a more definite diagnosis for the subject.

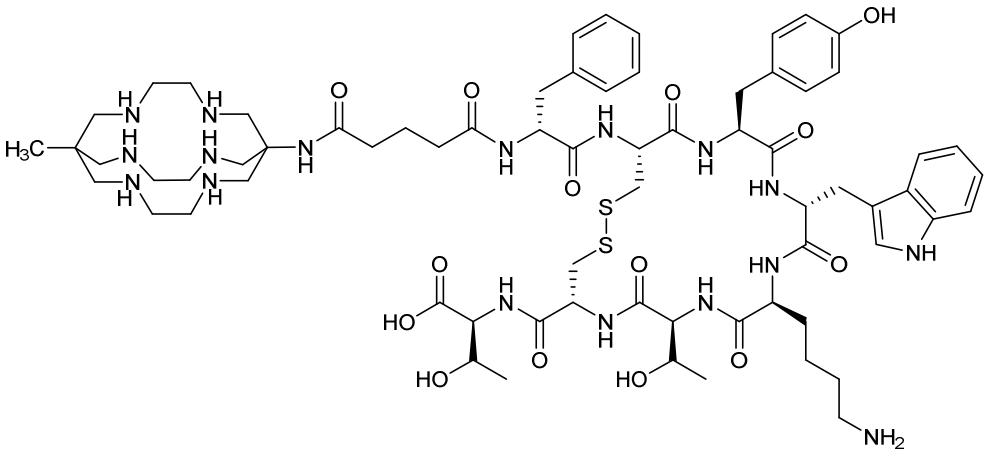
[0011] The present inventors have also found that the administration of the compound of Formula (I) complexed with a copper radionuclide allows for the delivery of a high dose of radiation to the desired site while concurrently limiting off-target effects of radiation. This therefore minimises unwanted damage to healthy tissue and related side effects. Without wishing to be bound by theory, the present inventors believe that the compound of Formula (I) complexed with ^{67}Cu allows for improved treatment of neuroendocrine cancers, since the radiolabelled complex shows greater specificity for somatostatin receptors and better retains the radioisotope. This then allows for better targeting of the cancer site and reduced leakage or loss of the radioisotope. As the radioactivity is localised at the cancer site, this reduces adverse events, such as off-target radiation effects and damage to healthy tissue. In addition to a reduction of adverse radiation-related effects, the present inventors believe that the methods disclosed herein also have reduced adverse effects generally as classified according to criteria known and accepted in the art for adverse event reporting. The reduction of off-target radiation damage and minimisation of adverse events allows for better treatment of patients, increased patient comfort and compliance and subsequently, improved outcomes for treatment.

[0012] The present inventors have also found that the compound of Formula (I) complexed with ^{67}Cu allows for a greater dose of radiation to be administered to the subject, owing to the improved retention of the radioisotope. Since a greater dose of radiation may be administered (and tolerated) in accordance with the methods disclosed herein, treatment of the neuroendocrine cancer with the compound of Formula (I) complexed with ^{67}Cu is improved, which results in greater survival of the subject.

[0013] The present inventors also believe that the radiolabelled compounds of Formula (I) provide an approach for the diagnosis of a neuroendocrine cancer, which may be used in conjunction with the treatment methodology as discussed herein. That is, one of the main advantages of the present invention is that the use of the compound of formula (I) can be used in both diagnosing and treating a cancer by simply switching between the Cu radioisotope species. Where the compound of Formula (I) is coordinated with a ^{64}Cu copper, the complex may be used in conjunction with PET and/or CT imaging in order to visualise the biodistribution and localisation of the radiolabelled compound, which in turn indicates the sites at which the membrane is expressed and potentially cancerous. Based on the information provided by imaging the location of the ^{64}Cu-labelled compound, the compound of Formula (I) coordinated with a suitable copper radioisotope, for example ^{67}Cu, may be used for therapeutic

purposes since the compound will bind and localise at the same sites as those determined by imaging of the subject. Imaging of the subject by SPECT, PET and/or CT after administration of the radiolabelled compound of Formula (I) for the purposes of treatment may be performed to confirm the localisation of the radiolabelled compound and targeted treatment.

[0014] In one aspect, the present invention provides a method for the treatment of a neuroendocrine cancer, the method comprising administering to a subject in need thereof an aqueous formulation of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed to a ^{67}Cu radioisotope in a therapeutically effective amount:

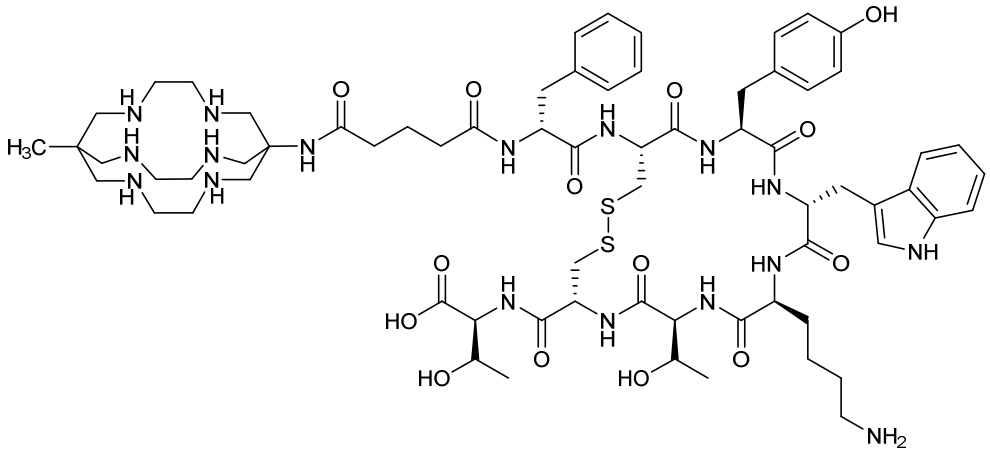


Formula (I)

wherein the dose of radiation delivered by the radioisotope is sufficient to reduce the size of one or more lesions associated with the cancer.

[0014a] Disclosed herein is a use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed to a ^{67}Cu radioisotope in a therapeutically effective amount in the manufacture of a medicament for the treatment of a neuroendocrine cancer, wherein the dose of radiation delivered by the radioisotope is sufficient to reduce the size of one or more lesions associated with the cancer.

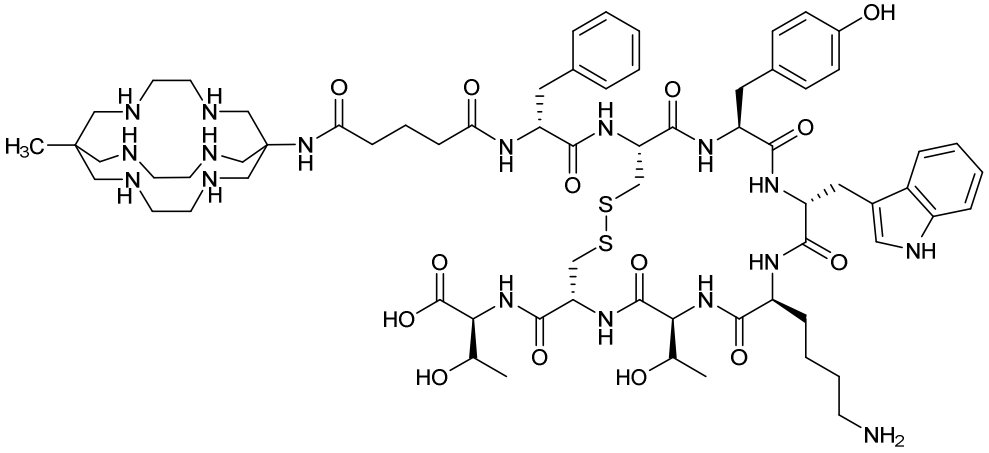
[0015] In one aspect, the present invention provides a method for the treatment of a neuroendocrine cancer, the method comprising administering to a subject in need thereof an aqueous formulation of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed to a ^{67}Cu radioisotope in a therapeutically effective amount:



Formula (I)

wherein the aqueous formulation is optionally administered one, two or three additional times at the same or lower amount of the compound of Formula (I);
wherein the total dose of ^{67}Cu radiation delivered to the bone marrow of the subject is less than about 2 Gy and the total dose of radiation delivered to the kidneys of the subject is less than about 30 Gy.

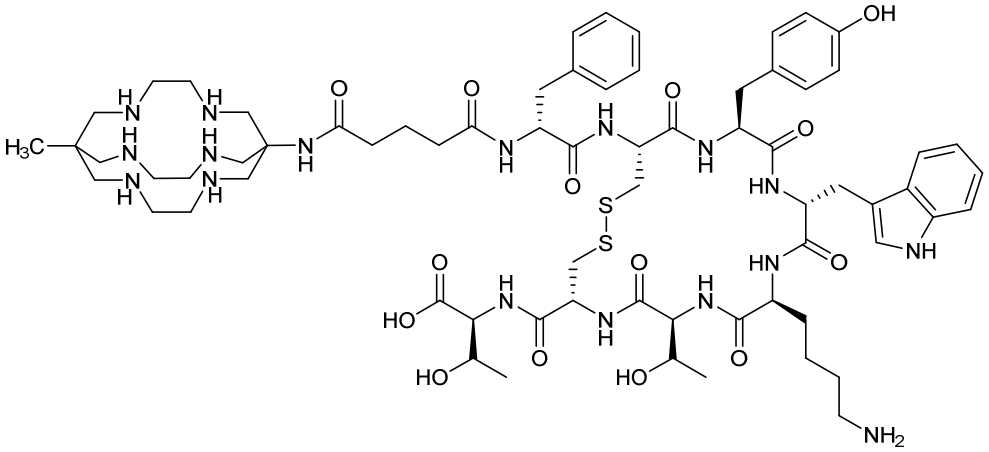
[0016] In another aspect, the present invention provides a method for the treatment of a neuroblastoma, the method comprising administering to a subject in need thereof an aqueous formulation of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope in a therapeutically effective amount:



Formula (I)

wherein the dose of radiation delivered by the radioisotope is sufficient to reduce the size of one or more lesions associated with the neuroblastoma.

[0017] In another aspect, the present invention provides a method for the treatment of a neuroendocrine cancer, the method comprising administering to the subject in need thereof an aqueous formulation of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope in a therapeutically effective amount:



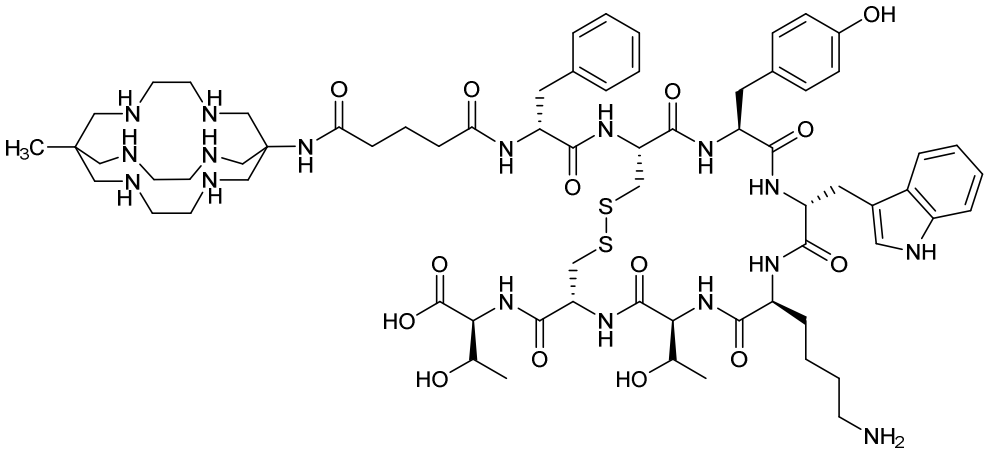
Formula (I)

wherein the subject does not experience any adverse events classified as Grade 3 or higher.

[0018] In other embodiments, the subject does not experience any adverse events classified as Grade 2 or higher.

[0019] In other embodiments, the subject does not experience any adverse events classified as Grade 1 or higher.

[0020] In another aspect, the present invention also provides a method for the treatment of a neuroblastoma, the method comprising administering to the subject in need thereof an aqueous formulation of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope in a therapeutically effective amount:



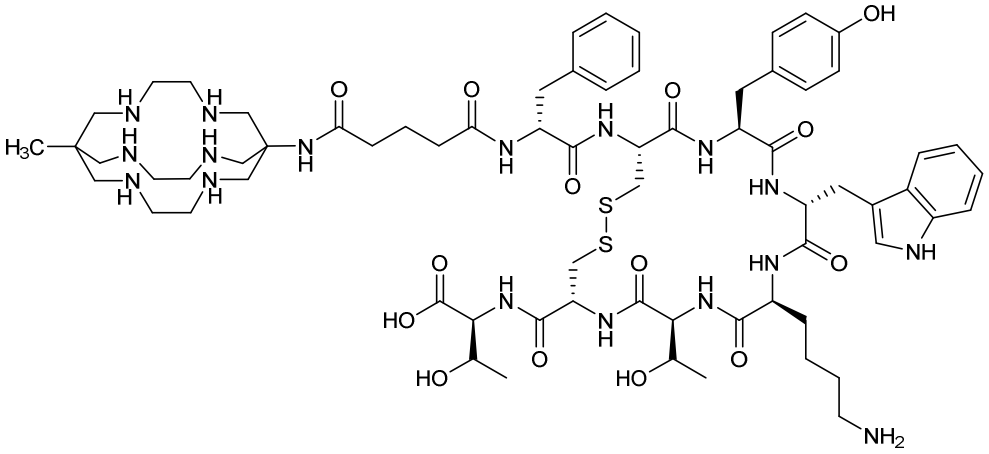
Formula (I)

wherein the subject does not experience any adverse events classified as Grade 3 or higher.

[0021] In other embodiments, the subject does not experience any adverse events classified as Grade 2 or higher.

[0022] In other embodiments, the subject does not experience any adverse events classified as Grade 1 or higher.

[0023] In a further aspect, the present invention provides a method for the treatment of a neuroendocrine tumour, the method comprising administering to the subject in need thereof an aqueous formulation of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope in a therapeutically effective amount:

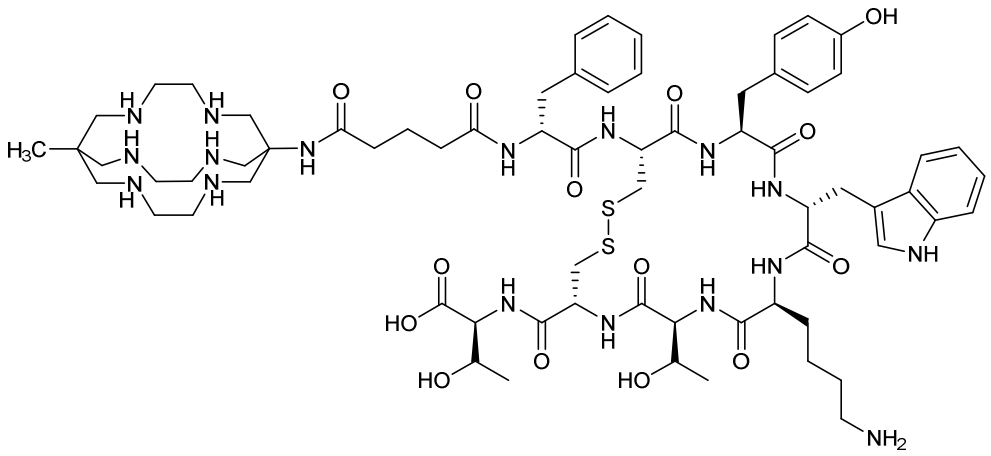


Formula (I)

wherein the dose of radiation is not associated with any dose limiting toxicities in the subject.

[0024] In another aspect, the present invention provides a method for the treatment of a neuroendocrine cancer in a patient in need of such treatment, the method comprising:

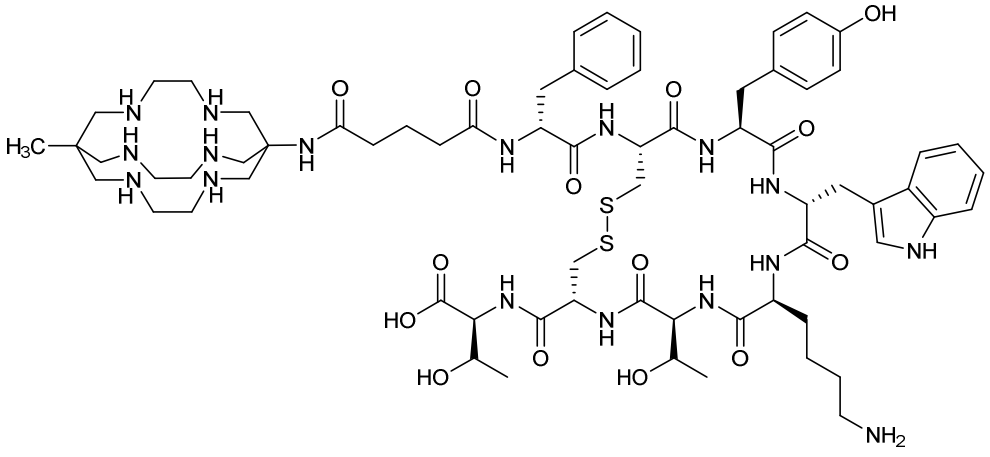
1) optionally administering an amino acid infusion to said patient followed by an IV infusion of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope:



Formula (I)

in a therapeutically effective amount of about 75 MBq/kg to about 475 MBq/kg.

[0025] In yet another aspect, the present invention provides a method for the treatment of a neuroblastoma, the method comprising administering to a subject in need thereof an aqueous formulation of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope in a therapeutically effective amount,



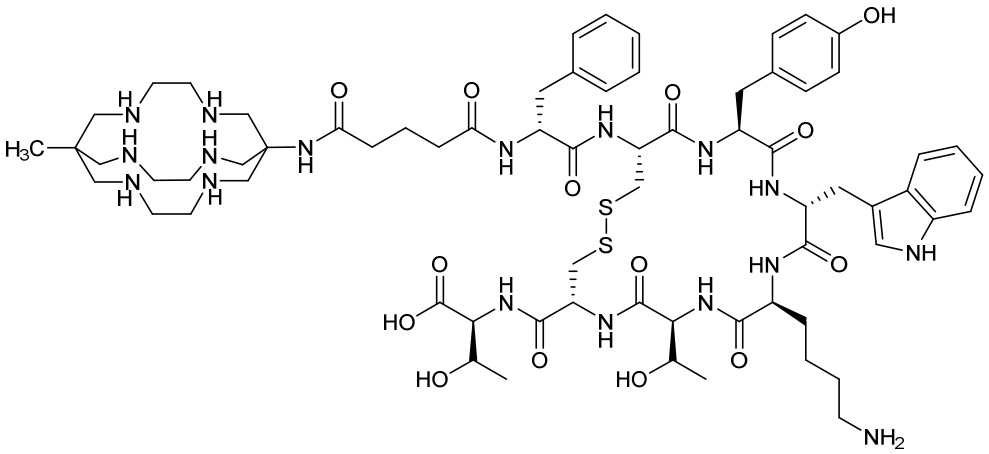
Formula (I)

wherein the aqueous formulation is optionally administered one, two or three additional times at the same or lower amount of the compound of Formula (I);

wherein the total dose of ^{67}Cu radiation delivered to the bone marrow of the subject is less than about 2 Gy and the total dose of radiation delivered to the kidneys of the subject is less than about 30 Gy.

[0026] In a further aspect, the present invention provides a method for the treatment of a neuroblastoma in a patient in need of such treatment, the method comprising:

1) optionally administering an amino acid infusion to said patient followed by an IV infusion of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope:



Formula (I)

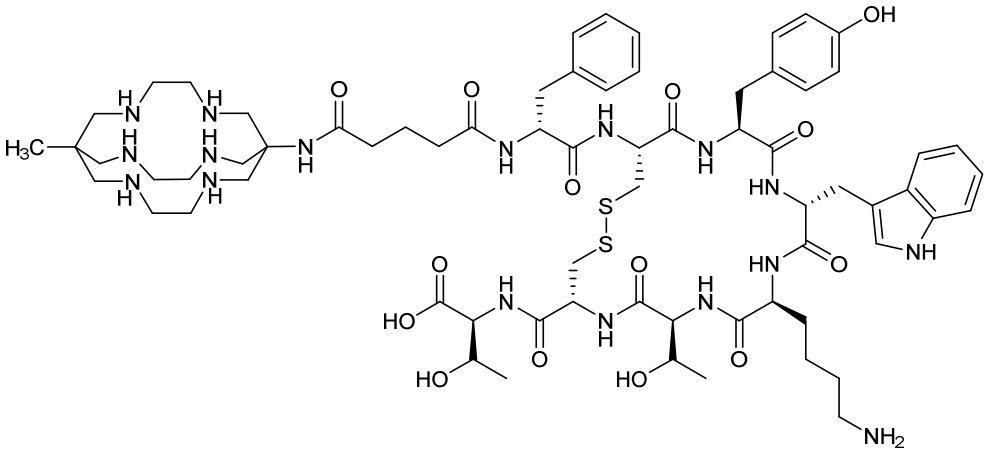
in a therapeutically effective amount of about 75 MBq/kg to about 475 MBq/kg.

[0027] In an embodiment and with reference to the second or third aspect, the method also may further comprise the step of:

2) repeating the therapy cycle 1) one, two or three additional times at the same or lower dose of Formula (I) so that the overall dose of radiation delivered to the kidneys of the patient does not exceed 30 Gy.

[0028] In a further aspect, the present invention provides a method for the treatment of a neuroendocrine cancer in a patient in need of such treatment, the method comprising:

1) optionally administering an amino acid infusion to said patient followed by an IV infusion of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope:



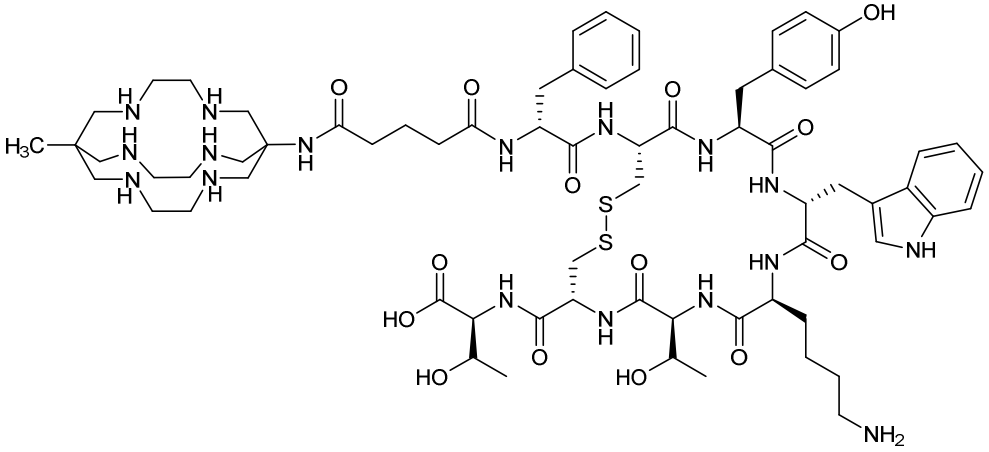
Formula (I)

in a therapeutically effective amount of about 75 MBq/kg to about 475 MBq/kg, and

2) repeating the therapy cycle 1) one, two or three additional times at the same or lower amount of Formula (I) so that the overall dose delivered to the patient does not exceed a 30 Gy kidney limit based on the patients weight.

[0029] In a further aspect, the present invention provides a method for the treatment of a neuroblastoma in a patient in need of such treatment, the method comprising:

1) optionally administering an amino acid infusion to said patient followed by an IV infusion of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope:



Formula (I)

in a therapeutically effective amount of about 75 MBq/kg to about 475 MBq/kg, and

2) repeating the therapy cycle 1) one, two or three additional times at the same or lower amount of Formula (I) so that the overall dose delivered to the patient does not exceed a 30 Gy kidney limit based on the patients weight.

[0030] In certain embodiments, the overall dose of radiation delivered as a result of administration of the compound of Formula (I) does not result in a dose of radiation delivered to the kidneys that exceeds about 30 Gy, about 29 Gy, about 28 Gy, about 27 Gy, about 26 Gy, about 25 Gy, about 24 Gy or about 23 Gy to the kidney based on the patient's weight.

[0031] In specific embodiments the effectiveness of the treatment method may be assessed by the diagnosis methods disclosed herein which may be conducted between therapy cycles with the ^{64}Cu radioisotope. Accordingly, one of the advantages of the present invention is that the same compound of Formula (I) may be used for both diagnosing and treating a tumor, as well as the progress of the treatment regime, by simply switching out the ^{64}Cu radioisotope with the ^{67}Cu radioisotope.

[0032] In an embodiment and with reference to the above aspects the neuroendocrine cancer is neuroblastoma. In an embodiment and with reference to the above aspects the neuroendocrine cancer is high-risk neuroblastoma. In an embodiment and with reference to the above aspects the neuroendocrine cancer is pediatric high-risk neuroblastoma. In an embodiment and with reference to the above aspects the patient is a child, adolescent or adult.

[0033] In some embodiments, the dose of radiation delivered by the ^{67}Cu radioisotope is about 75 MBq/kg, about 175 MBq/kg, about 275 MBq/kg, about 375 MBq/kg or about 475 MBq/kg. In some embodiments, the dose of radiation delivered by the ^{67}Cu radioisotope to the subject is tailored for the subject specifically. In certain embodiments, the dose of radiation delivered to the subject is determined by prior radioimaging of the subject by administration of the compound of Formula (I) complexed with a suitable radioisotope.

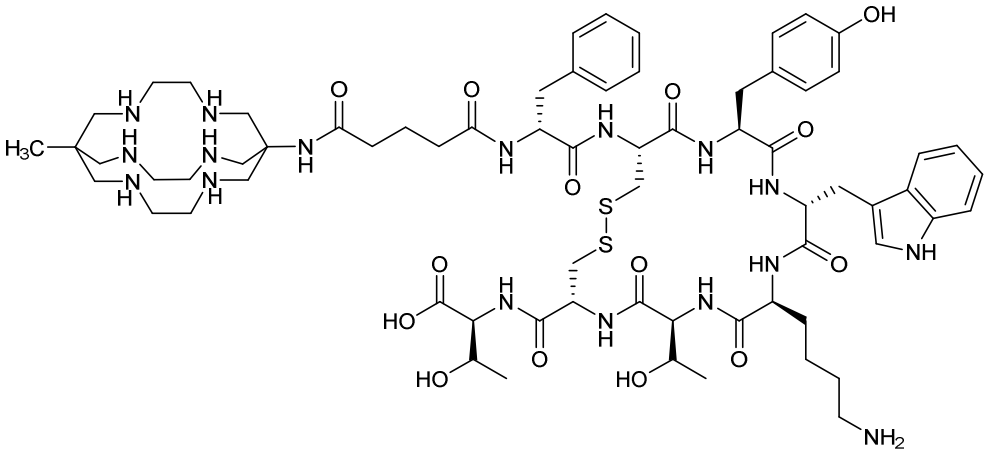
[0034] In an embodiment, the method of treatment further comprises monitoring of the subject by radioimaging by PET, SPECT and/or CT. In some embodiments, the monitoring of the subject by radioimaging may occur between therapy cycles.

[0035] In certain embodiments, the methods disclosed herein do not result in any adverse events classified as Grade 3 or above, according to the CTCAE v5.0.

[0036] In other embodiments, the methods disclosed herein do not result in any adverse events classified as Grade 2 or above, according to the CTCAE v5.0.

[0037] In other embodiments, the methods disclosed herein do not result in any adverse events classified as Grade 2 or above, according to the CTCAE v5.0.

[0038] In a further aspect, the present invention provides a method of radioimaging a neuroendocrine cancer, the method comprising administering to a subject in need thereof an aqueous formulation of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{64}Cu radioisotope:

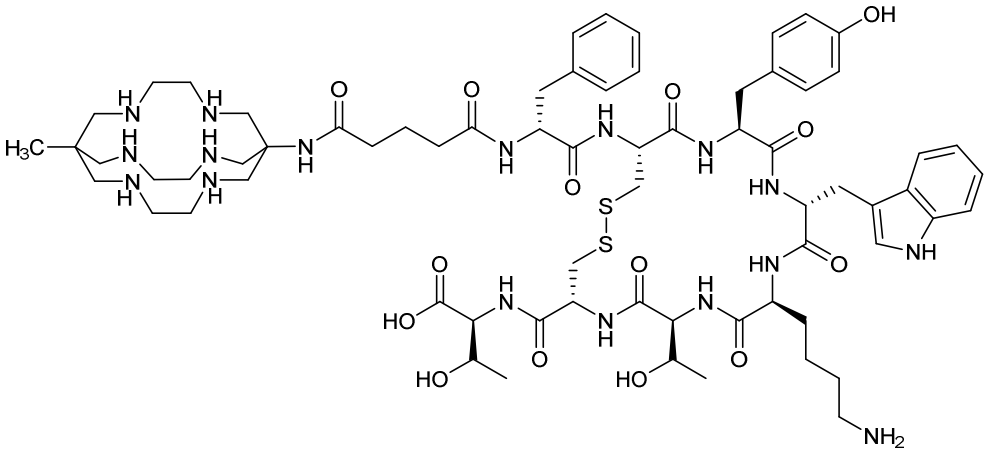


Formula (I)

wherein the dose of radiation delivered by the radioisotope is about 2 MBq/kg.

[0038a] Disclosed herein is a use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{64}Cu radioisotope in the manufacture of a medicament for the treatment of a neuroendocrine cancer, wherein the dose of radiation delivered by the radioisotope is about 2 MBq/kg.

[0039] In another aspect, the present invention provides a method of radioimaging a neuroblastoma, the method comprising administering to a subject in need thereof an aqueous formulation of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{64}Cu radioisotope:



Formula (I)

wherein the dose of radiation delivered by the radioisotope is about 2 MBq/kg.

[0040] Thus present invention also provides use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed to a ^{64}Cu radioisotope for radioimaging a neuroendocrine cancer, preferably the total dose of radiation for an adult patient delivered by the radioisotope from administration of more than one dose of the aqueous formulation is about 150 to about 250 MBq, or about 200 MBq.

[0041] Without wishing to be bound by theory, the present inventors believe that administration of more than one dose of the formulations described herein for the treatment of a neuroendocrine cancer leads to higher absorbed radiation doses at the cancer site, which leads to greater efficacy of treatment. This means that repeat administrations of the formulation containing the compound of Formula (I) complexed with a radioisotope may lead to greater survival of the subject, when compared with single administrations of the formulations as disclosed herein. The method of the first aspect may comprise administration of multiple doses of the aqueous formulation of the complex containing the compound of Formula (I) and the radioisotope.

[0042] In an embodiment, the method comprises the sequential administration of more than one dose of the aqueous formulation described in the first aspect. In some embodiments, two doses of the aqueous formulation described in the first aspect are administered. In other embodiments, three doses of the aqueous formulation described in the first aspect are administered. In further embodiments, four doses of the aqueous formulation described in the first aspect are administered. In other embodiments, more than four doses of the aqueous formulation described in the first aspect are administered.

[0043] In some embodiments, the sequential doses of the aqueous formulation are administered between about 1 week and about 16 weeks apart. In an embodiment, the sequential doses of the aqueous formulation are administered about 1 week apart. In some embodiments, the sequential doses of the aqueous formulation are administered between about 1 and about 12 weeks apart. In further embodiments, the sequential doses of the aqueous formulation are administered between about 1 and about 10 weeks apart. In some embodiments, the sequential doses of the aqueous formulation are administered between about 1 and about 8 weeks apart. In some embodiments, the sequential doses of the aqueous formulation are administered between about 1 and about 6 weeks apart. In some embodiments, the sequential doses of the aqueous formulation are administered between about 1 and about 4 weeks apart. In some embodiments, the sequential doses of the aqueous formulation are administered between about 1 and about 2 weeks apart. In some embodiments, the sequential doses of the aqueous formulation are administered about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or about 16 weeks apart. In an embodiment, the total dose of radiation delivered to the bone marrow of the subject is less than about 2 Gy. In another embodiment, the total dose of radiation delivered to the kidneys of the subject is less than about 23-28 Gy. In another embodiment, the total dose of radiation delivered to the submandibular gland of the subject is less than about 24 Gy.

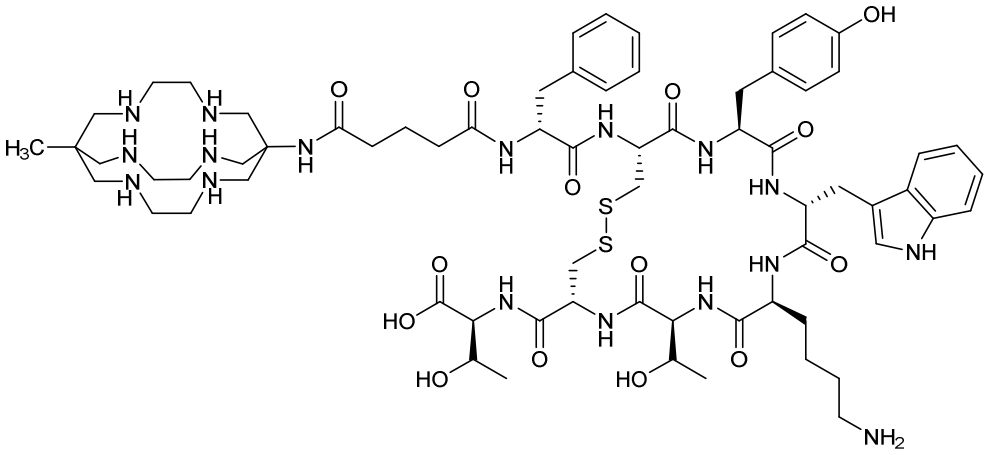
[0044] The method of the aspects above may comprise administration of multiple doses of the complex containing the compound of Formula (I) and the radioisotope, where the doses administered are the same or different. In some embodiments, where multiple doses are administered, the second and any subsequent doses are higher than the original dose. In some embodiments, multiple doses are administered, until the cumulative dose of radiation delivered to the kidneys of the subject reaches about 23 Gy. In some embodiments, multiple doses are administered, until the cumulative dose of radiation delivered to the submandibular gland of the subject reaches about 24 Gy and does not exceed 28 Gy.

[0045] In an embodiment, the aqueous formulation is administered intravenously. In another embodiment, the aqueous formulation is administered by slow infusion. In a preferred embodiment, the aqueous formulation is administered intravenously by slow infusion.

[0046] The methods disclosed herein include the administration of a radioisotope that emits ionising radiation. Since the kidneys are responsible for blood filtration, the kidneys of a

subject to which the formulations comprising the compound of Formula (I) and a radioisotope has been administered are at risk of absorbing unwanted radiation as a result of active reabsorption and retention of the radiolabelled compound of Formula (I). Prevention of nephrotoxicity may be achieved by co-administration of cationic amino acids that competitively inhibit the reabsorption of the compound of Formula (I) and thus the radioisotope. In some embodiments, the method of the first aspect further comprises the administration of a formulation containing one or more amino acids, or salts thereof. In some embodiments, one or more amino acids are in a cationic form. In some embodiments, the formulation containing one or more amino acids comprises lysine, or a salt thereof. In other embodiments, the formulation containing one or more amino acids comprises arginine, or a salt thereof. In a preferred embodiment, the method comprises the administration of a formulation comprising lysine and arginine, or salts thereof.

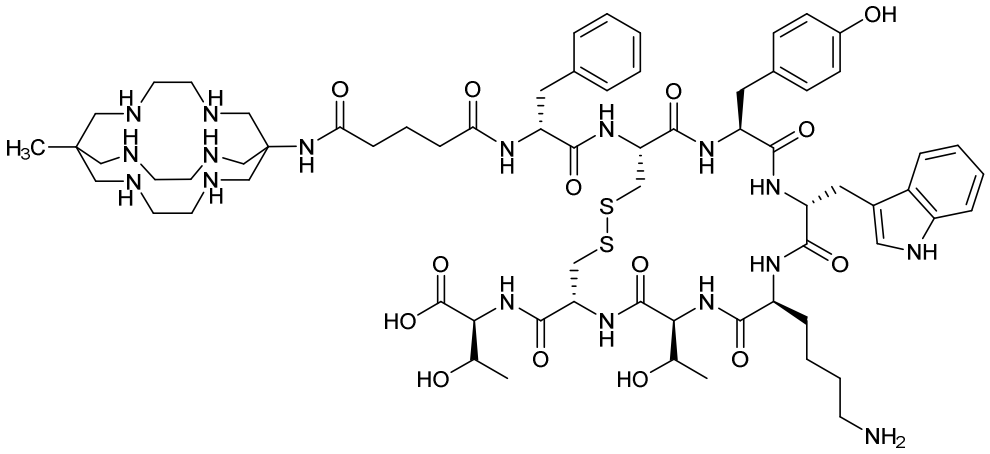
[0047] In a further aspect, the present invention provides use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed to a ^{67}Cu radioisotope:



Formula (I)

in the manufacture of an aqueous formulation for the treatment of a neuroendocrine cancer, wherein the dose of radiation delivered by the radioisotope is sufficient to reduce the size of one or more lesions associated with the cancer.

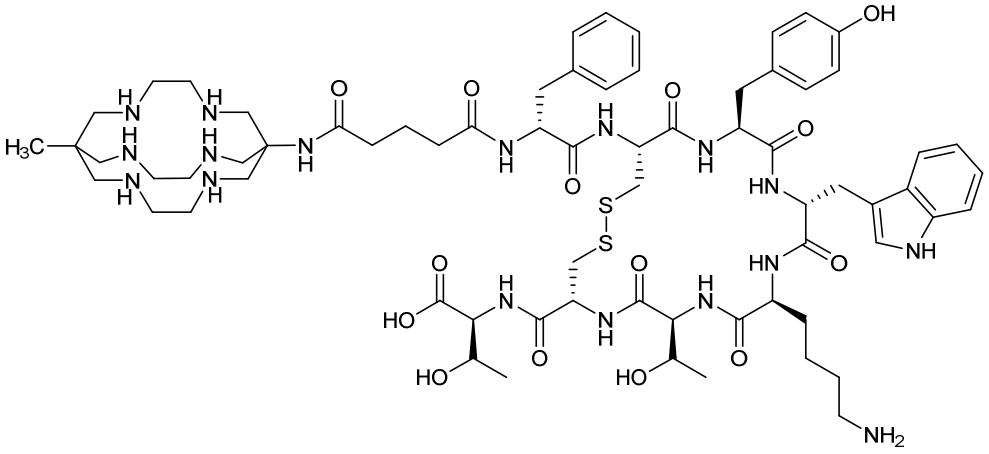
[0048] In yet a further aspect, the present invention provides the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed to a ^{67}Cu radioisotope:



Formula (I)

in the manufacture of an aqueous formulation for the treatment of a neuroblastoma, wherein the dose of radiation delivered by the radioisotope is sufficient to reduce the size of one or more lesions associated with the neuroblastoma.

[0049] In another aspect, the present invention provides the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope in a therapeutically effective amount in the manufacture of a medicament for the treatment of a neuroendocrine cancer:



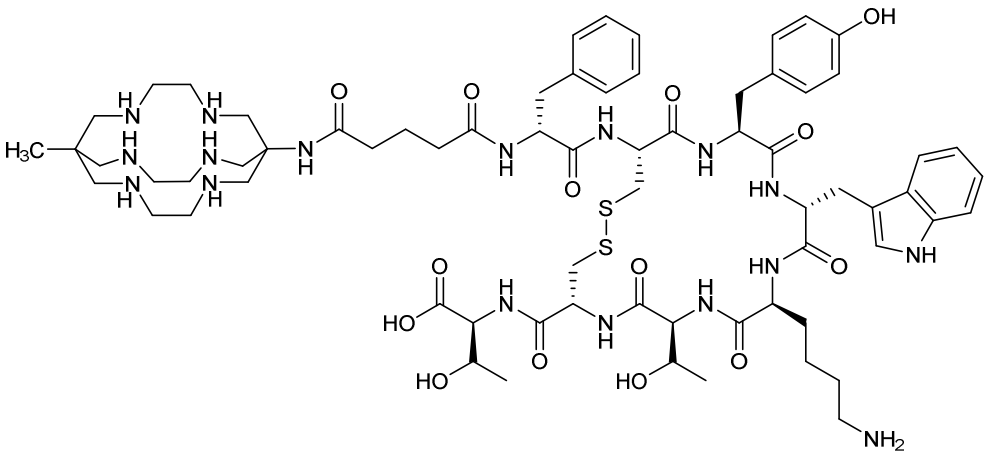
Formula (I)

wherein the administration of the medicament is not associated with any adverse events classified as Grade 3 or higher.

[0050] In other embodiments, the administration of the medicament is not associated with any adverse events classified as Grade 2 or higher.

[0051] In other embodiments, the administration of the medicament is not associated with any adverse events classified as Grade 1 or higher.

[0052] In another aspect, the present invention also provides the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope in a therapeutically effective amount in the manufacture of a medicament for the treatment of a neuroblastoma:



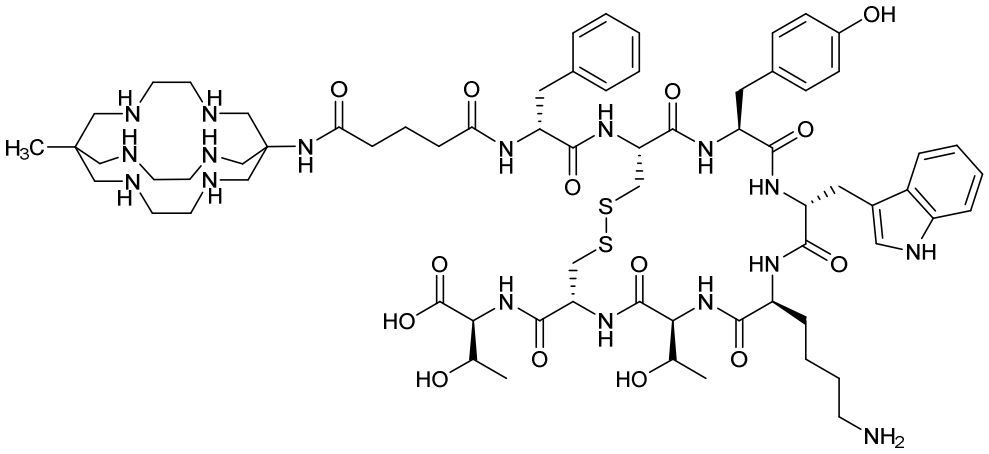
Formula (I)

wherein the administration of the medicament is not associated with any adverse events classified as Grade 3 or higher.

[0053] In other embodiments, the administration of the medicament is not associated with any adverse events classified as Grade 2 or higher.

[0054] In other embodiments, the administration of the medicament is not associated with any adverse events classified as Grade 1 or higher.

[0055] In a further aspect, the present invention provides the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope in a therapeutically effective amount in the manufacture of a medicament for the treatment of a neuroendocrine tumour:



Formula (I)

wherein the dose of radiation is not associated with any dose limiting toxicities in the subject.

[0056] In other embodiments, the administration of the medicament is not associated with any adverse events classified as Grade 3 or higher.

[0057] In other embodiments, the administration of the medicament is not associated with any adverse events classified as Grade 2 or higher.

[0058] In other embodiments, the administration of the medicament is not associated with any adverse events classified as Grade 1 or higher.

[0059] In some embodiments, the dose of radiation delivered by the ^{67}Cu radioisotope is about 75 MBq/kg, about 175 MBq/kg, about 275 MBq/kg, about 375 MBq/kg or about 475 MBq/kg.

[0060] In another aspect, the present invention provides use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope for the treatment of a neuroendocrine cancer.

[0061] In another aspect, the neuroendocrine cancer is a neuroendocrine tumour. In certain embodiments, the neuroendocrine tumour is a paediatric neuroendocrine tumour.

[0062] In a preferred embodiment, the neuroendocrine tumour is a neuroblastoma. In some embodiments, the subject is less than 10 years of age, less than 5 years of age or less than 1 year of age. In some embodiments, the neuroblastoma is a high-risk neuroblastoma. In some

embodiments, the neuroblastoma is a high-risk neuroblastoma with failure to respond to prior chemotherapy, radiation therapy and/or surgery. In other embodiments, the subject is less than about 30 years of age, less than about 25 years of age, less than about 20 years of age or less than about 15 years of age.

[0063] In another embodiment the neuroendocrine tumour is a meningioma. In another embodiment, the neuroendocrine tumour is a gastrointestinal tumour. In another embodiment, the neuroendocrine tumour is a pancreatic tumour. In another embodiment, the neuroendocrine tumour is a lung tumour. In another embodiment, the neuroendocrine tumour is a stomach tumour. In another embodiment, the neuroendocrine tumour is a Merkel cell carcinoma. In another embodiment, the neuroendocrine tumour is a neurofibromatosis.

Brief description of the figures

[0064] Figure 1. Images of a patient after (A) administration of ^{123}I-MIBG and imaging by SPECT, and the same patient after (B) administration of ^{64}Cu-Sartate and imaging by PET. The image obtained by PET imaging after administration of ^{64}Cu-Sartate shows greater resolution compared to the images obtained by SPECT after administration of ^{123}I-MIBG. Furthermore, images obtained by PET/^{64}Cu-Sartate can identify additional lesions that were not observed under imaging by SPECT/^{123}I-MIBG.

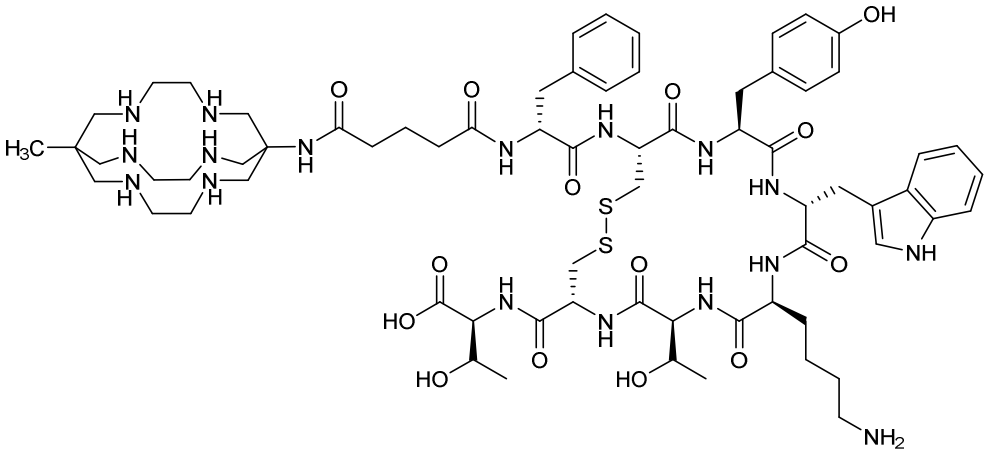
Detailed description

[0065] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

[0066] The term "about" or "approximately" as used herein means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system.

[0067] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the invention belongs. For the purposes of the present invention, the following terms are defined below.

[0068] The compound of Formula (I) contains an octreotate ligand and a sarcophagine and is capable of targeting somatostatin receptors, namely type 2 (SSTR2) receptors. The compound may be referred to as “MeCOSar” or “SARTATE” and contains a macrocyclic sarcophagine fragment (i.e. 5-[[8-amino-3,6,10,13,16,19-hexaazabicyclo-[6.6.6]eico-1-yl)amino]-5-oxo-pentanyl) and an octreotate fragment (i.e. D-Phe-Cys-Tyr-D-Trp-Lys-Thr-Cys-Thr-OH). The compound of Formula (I) has the following structure:



Formula (I)

[0069] The compound of Formula (I) contains multiple stereocentres. All stereoisomers, for example enantiomers and diastereomers, of the compound and its salts are also contemplated by the present invention.

[0070] The term "pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the above-identified compounds, and include pharmaceutically acceptable acid addition salts and base addition salts. Suitable pharmaceutically acceptable acid addition salts of compounds of Formula (I) may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric acid, sulfuric acid, phosphoric acid, methane sulfonic acid, camphor sulfonic acid, oxalic acid, maleic acid, succinic acid, citric acid, formic acid, hydrobromic acid, benzoic acid, tartaric acid, fumaric acid, salicylic acid, mandelic acid, and carbonic acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, heterocyclic carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, fumaric, maleic, alkyl sulfonic and arylsulfonic acids. Pharmaceutically acceptable salts also include those in which the main compound functions as an acid and is

reacted with an appropriate base to form, e.g., sodium, potassium, calcium, magnesium, ammonium, and choline salts. Those skilled in the art will further recognize that acid addition salts may be prepared by reaction of a compound with the appropriate inorganic or organic acid via any of a number of known methods. Alternatively, alkali and alkaline earth metal salts can be prepared by reacting a compound with the appropriate base via a variety of known methods. The following are further examples of acid salts that can be obtained by reaction with inorganic or organic acids: acetates, adipates, alginates, citrates, aspartates, benzoates, benzenesulfonates, bisulfates, butyrates, camphorates, digluconates, cyclopentanepropionates, dodecylsulfates, ethanesulfonates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, fumarates, hydrobromides, hydroiodides, 2-hydroxy-ethanesulfonates, lactates, maleates, methanesulfonates, nicotinates, 2-naphthalenesulfonates, oxalates, palmoates, pectinates, persulfates, 3-phenylpropionates, picrates, pivalates, propionates, succinates, tartrates, thiocyanates, tosylates, mesylates and undecanoates. Additional information on pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 19th Edition, Mack Publishing Co., Easton, PA 1995. In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds, agents and salts may exist in different crystalline or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulae.

[0071] The formulations for injection comprise pharmaceutically acceptable sterile aqueous solutions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. The formulations may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of micro-organisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminium monostearate and gelatin. The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use. The pharmaceutical formulation may further comprise a pH controller. Examples of suitable pH controllers include

hydrochloric acid, sodium hydroxide and the like. Identification of preferred pH ranges (where appropriate) and suitable excipients is routine in the art, for example, as described in Katdare and Chaubel (2006) Excipient Development for Pharmaceutical, Biotechnology and Drug Delivery Systems (CRC Press).

[0072] The formulations as disclosed herein may be provided in a pharmaceutically acceptable carrier or diluent. As will be appreciated by those skilled in the art, the choice of pharmaceutically acceptable carrier or diluent will be dependent on the route of administration and on the nature of the condition and subject to be treated. The particular carrier or diluent and route of administration may be readily determined by a person skilled in the art. The carrier or diluent and route of administration should be carefully selected so as to ensure that the complex of the compound of Formula (I) and the ^{67}Cu radioisotope remains intact both before and after administration.

[0073] The pharmaceutical forms suitable for injectable use include sterile injectable solutions or dispersions and sterile powders for the preparation of sterile injectable solutions. Such forms should be stable under the conditions of manufacture and storage and may be preserved against reduction, oxidation and microbial contamination. For injection, compositions of the invention may be formulated in aqueous solutions, suitably in physiologically compatible buffers such as Hanks' solution, Ringer's solution or physiological saline buffer.

[0074] For the purposes of imaging or treatment of a neuroendocrine cancer, the compound of Formula (I) is complexed with a ^{64}Cu or ^{67}Cu radioisotope. The present inventors have found that the sarcophagine fragment of Formula (I) has a strong affinity for copper isotopes and is capable of complexing and retaining a radioisotope for a time that is sufficient for the purposes of imaging and treatment, even after administration to a subject. The half-life of the ^{67}Cu radioisotope is approximately 60 hours and undergoes beta decay, thus making the isotope suitable for localised radiotherapy. Since decay of the ^{67}Cu radioisotope is accompanied by gamma radiation, the treatment of a subject to which the compound of Formula (I) complexed with ^{67}Cu may be monitored and imaged by single-photon emission computed tomography (SPECT). In an embodiment, the method for treating a subject in need thereof by administration of a compound of Formula (I) complexed with ^{67}Cu includes monitoring and/or imaging single-photon emission tomography. Other imaging techniques during treatment may also be used, for example, MRI and CT. In a preferred embodiment, the method for treatment includes

imaging by SPECT and/or CT using a ^{64}Cu radioisotope. Since radioisotopes of ^{64}Cu have a half-life of approximately 12 hours and undergo beta decay with positron emission, the compound of Formula (I) complexed with ^{64}Cu is suitable for use as a radioimaging agent. The present inventors have found that the half-life of ^{64}Cu together with the binding affinity of the octreotate fragment to SSTR2 means that the administration of the radiolabelled compound can be used for radioimaging. Since ^{64}Cu decays by positron emission, radioimaging by positron emission tomography (PET) allows for the localisation of the radiolabelled compound of Formula (I) in the subject to be imaged and subsequently, the identification of neuroendocrine tumour sites.

[0075] For the purposes of treatment, the dose of radiation to be administered and delivered to the subject by a ^{67}Cu radioisotope may be determined based on both bodyweight of the subject and the quality of the images obtained via radioimaging after administration of the compound of Formula (I) complexed with a ^{64}Cu radioisotope. In some embodiments, the radiolabelled compound of Formula (I) complexed with a ^{64}Cu radioisotope is used to model the distribution of the corresponding compound of Formula (I) complexed with a ^{67}Cu radioisotope.

[0076] The units of radioactivity as recited herein are given in gray (Gy) or becquerel (Bq). It will be appreciated that the dose of radiation may be converted from one unit to another using known conversion factors and that other units for the amount of radioactivity that are not explicitly recited herein may also be used.

[0077] In some embodiments, the dose of radiation to be administered to the subject is about 75 MBq/kg, about 100 MBq/kg, about 125 MBq/kg, about 150 MBq/kg, about 175 MBq/kg, about 200 MBq/kg, about 225 MBq/kg, about 250 MBq/kg, about 275 MBq/kg, about 300 MBq/kg, about 325 MBq/kg, about 350 MBq/kg, about 375 MBq/kg, about 400 MBq/kg, about 425 MBq/kg, about 450 MBq/kg, or about 475 MBq/kg. In certain embodiments, the dose of radiation to be administered to the subject is about 75 MBq/kg, about 175 MBq/kg, about 275 MBq/kg, about 375 MBq/kg or about 475 MBq/kg. In certain embodiments, the dose of radiation is delivered by a ^{64}Cu radioisotope. In other embodiments, the dose of radiation is delivered by a ^{67}Cu radioisotope.

[0078] As used herein the terms "treating", "treatment", “preventing”, “prevention" and grammatical equivalents refer to any and all uses which remedy the stated neuroendocrine

tumour, prevent, retard or delay the establishment of the disease, or otherwise prevent, hinder, retard, or reverse the progression of the disease. Thus the terms "treating" and “preventing” and the like are to be considered in their broadest context. For example, treatment does not necessarily imply that a patient is treated until total recovery. Where the disease displays or a characterized by multiple symptoms, the treatment or prevention need not necessarily remedy, prevent, hinder, retard, or reverse all of said symptoms, but may prevent, hinder, retard, or reverse one or more of said symptoms.

[0079] The term "subject" as used herein refers to mammals and includes humans, primates, livestock animals (e.g. sheep, pigs, cattle, horses, donkeys), laboratory test animals (e.g. mice, rabbits, rats, guinea pigs), performance and show animals (e.g. horses, livestock, dogs, cats), companion animals (e.g. dogs, cats) and captive wild animals. Preferably, the mammal is human or a laboratory test animal. Even more preferably, the mammal is a human.

[0080] As used herein, the term “cancer” broadly encompasses neoplastic diseases characterised by abnormal cell growth with the potential to invade or spread to other parts of the body. The cancer may be benign, which does not spread to other parts of the body. The cancer may be malignant, meaning that the cancer cells can spread through the circulatory system or lymphatic system. The term as used herein includes all malignant, i.e. cancerous, disease states. The cancer may be present as a tumour.

[0081] As used herein, the term “neuroendocrine cancer” refers to a cancer that neuroendocrine system of the body is responsible for creating, storing and secreting peptides and hormones. Neuroendocrine cancers often present as tumours and are typically found in the gastrointestinal or respiratory system, however neuroendocrine cancers may also be found in other sites such as the adrenal glands, the nervous system and skin. Specific sites for neuroendocrine tumours include the large bowel and appendix, small intestine, pancreas, stomach and the lungs. In certain embodiments, the neuroendocrine cancer is present as a tumour. In certain embodiments, the neuroendocrine cancer is a tumour in the large bowel of the patient. In other embodiments, the neuroendocrine cancer is a tumour in the appendix of the patient. In other embodiments, the neuroendocrine cancer is a tumour in the small intestine of the patient. In other embodiments, the neuroendocrine cancer is a tumour in the pancreas of the patient. In other embodiments, the neuroendocrine cancer is a tumour in the stomach of the patient. In other embodiments, the neuroendocrine cancer is a tumour in the lungs of the patient.

[0082] As used herein, the term neuroblastoma refers to a neuroendocrine cancer, where the cancer forms in early nerve tissue (i.e. neuroblasts) of the sympathetic nervous system. A neuroblastoma can be found anywhere in the sympathetic nervous system, including the adrenal glands, neck, chest and spinal cord. In certain embodiments, the neuroblastoma originates in the adrenal glands of the patient. In other embodiments, the neuroblastoma originates in tissues of the neck. In other embodiments, the neuroblastoma originates in tissues of the chest. In other embodiments, the neuroblastoma originates in tissues of the spinal cord.

[0083] The term “child” or “children” as used herein refers to subjects that are less than 18 years of age. In an embodiment, the child may be an adolescent, for example, between about 13 and about18 years of age. In another embodiment, the child may be a toddler, for example, between about 1 and about 3 years of age. In yet another embodiment, the child may be an infant, for example, less than 1 year of age. In certain embodiments, the subject is a child and is 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or less than 1 year of age.

[0084] The term "therapeutically effective amount" or "effective amount" is an amount sufficient to effect beneficial or desired clinical results. An effective amount can be administered in one or more administrations. For the purposes of radioimaging, an effective amount is sufficient for an image showing the localisation of the compound of Formula (I) administered to the subject, owing to the detection of the products of decay from the radioisotope that is complexed with the compound. For the purposes of treatment, an effective amount is typically sufficient to palliate, ameliorate, stabilize, reverse, slow and/or delay the progression of the neuroendocrine cancer.

[0085] In addition the treatment regime will typically involve a number of cycles of radiation treatment with the cycles being continued until such time as the condition has been ameliorated. Once again the optimal number of cycles and the spacing between each treatment cycle will depend upon a number of factors such as the height and weight of the subject, the severity of the condition being treated, the health (or lack thereof) of the subject being treated and their previous reactions to radiotherapy and/or radioimaging.

[0086] The formulations defined in the present specification for methods of treatment of a neuroendocrine tumour may be administered parenterally, with intravenous administration preferred. In an embodiment, the aqueous formulation comprising a radiolabelled compound of Formula (I) is administered intravenously, either by bolus administration or slow infusion.

In an embodiment, the compound of Formula (I) radiolabelled with a ^{67}Cu radioisotope is administered intravenously by slow infusion.

[0087] The aqueous formulations comprising the compound of Formula (I) may be a formulation comprising sodium chloride. In some embodiments, the formulation comprises a saline solution. In certain embodiments, the saline solution comprises about 0.9% sodium chloride. In some embodiments, the aqueous formulation comprises a buffer solution. In some embodiments, the buffer solution comprises a phosphate ion. In some embodiments, the buffer solution comprises sodium phosphate. In some embodiments, the buffer solution is a sodium phosphate buffer at a concentration of about 0.1 M.

[0088] The aqueous formulations comprising the compound of Formula (I) may comprise other excipients. In certain embodiments, the formulation comprises an antioxidant. In other embodiments, the formulation comprises one or more antioxidants. In some embodiments, the formulation comprises gentisic acid or a salt thereof. In some embodiments, the formulation comprises gentisic acid as a sodium salt, or sodium gentisate. In certain embodiments, the formulation comprises gentisic acid at a concentration of about 0.056% w/v. In other embodiments, the formulation comprises gentisic acid at a concentration of no more than about 0.72 mg/ml. In other embodiments, the formulation comprises ascorbic acid or a salt thereof. In some embodiments, the formulation comprises ascorbic acid as a sodium salt, or sodium ascorbate. In some embodiments, the formulation comprises ascorbic acid at a concentration of no more than about 50 mg/ml. In some embodiments, the formulation comprises ethanol. In some embodiments, the formulation comprises ethanol at a concentration of about 10% v/v.

[0089] In certain embodiments, the aqueous formulation administered as part of a method for the treatment of a neuroendocrine cancer or a neuroblastoma comprises the compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a 67Cu radioisotope, a sodium phosphate buffer solution, gentisic acid or a salt thereof and ascorbic acid or a salt thereof. In certain embodiments, the aqueous formulation further comprises saline.

[0090] In certain embodiments, the aqueous formulation administered as part of a method for the treatment of a neuroendocrine cancer or a neuroblastoma comprises the compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a 67Cu radioisotope,

a sodium phosphate buffer solution, gentisic acid or a salt thereof, ascorbic acid or a salt thereof and saline.

[0091] In certain embodiments, the aqueous formulation administered as part of a method for the treatment of a neuroendocrine cancer or a neuroblastoma comprises the compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a 67Cu radioisotope, a sodium phosphate buffer solution at a concentration of about 0.1 M, gentisic acid or a salt thereof in an amount of no more than about 0.72 mg/ml, ascorbic acid or a salt thereof in an amount of no more than about 50 mg/ml, and saline.

[0092] In certain embodiments, the aqueous formulation administered as part of a method for the radioimaging of a neuroendocrine cancer or a neuroblastoma comprises the compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a 67Cu radioisotope, ethanol and gentisic acid or a salt thereof. In certain embodiments, the aqueous formulation further comprises saline.

[0093] In certain embodiments, the aqueous formulation administered as part of a method for the radioimaging of a neuroendocrine cancer or a neuroblastoma comprises the compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a 67Cu radioisotope, ethanol, gentisic acid or a salt thereof and saline.

[0094] In certain embodiments, the aqueous formulation administered as part of a method for the radioimaging of a neuroendocrine cancer or a neuroblastoma comprises the compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a 67Cu radioisotope, ethanol in an amount of about 10% v/v, gentisic acid or a salt thereof in an amount of no more than about 0.056% w/v and saline.

[0095] It will be understood that the specific dose of the radiolabelled compound of Formula (I) for any particular subject will depend upon a variety of factors including, for example, the age, body weight and indication of the individual to be treated, the time of administration, rate of excretion, and combination with any other treatment or therapy. Single or multiple administrations can be carried out with dose levels and pattern being selected by the treating physician. A broad range of doses may be applicable. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a given dose delivering a certain

amount of radiation may be calculated as a fraction of the total radiation to be delivered to the subject. Dosage regimens may comprise the administration of multiple doses of the radiolabelled compound of Formula (I), where the doses are the same or different. In some embodiments, the methods for treatment of a neuroendocrine cancer comprise the administration of multiple doses of a compound of Formula (I) complexed with ^{67}Cu, where the doses of radiation that are administered are the same. In other embodiments, the methods comprise the administration of multiple doses, where the second and subsequent doses of radiation are higher than the first dose administered to the subject.

[0096] In some embodiments, the methods comprise the administration of two doses of an aqueous formulation described herein. In some embodiments, the methods comprise the administration of three doses of an aqueous formulation as described herein. In some embodiments, the methods comprise the administration of four doses of an aqueous formulation as described herein. In some embodiments, the methods comprise the administration of five doses of the aqueous formulation as described herein. In some embodiments, the methods comprise the administration of six doses of the aqueous formulation as described herein. In some embodiments, the methods comprise the administration of seven or more doses of the aqueous formulation as described herein.

[0097] The methods for radioimaging by administration of a radiolabelled complex of a compound of Formula (I) as disclosed herein allow for the diagnosis of a neuroendocrine cancer in a subject. In combination with the methods for treatment where the compound of Formula (I) having a different isotope is administered, the methods disclosed herein represent a theranostic approach, i.e. a therapeutic and diagnostic approach, to the treatment of neuroendocrine cancers. This is because administration of the compound of Formula (I) when complexed with a suitable radioisotope for the purposes of radioimaging of the subject, while administration of the same compound of Formula (I) that is instead complexed with ^{67}Cu allows for treatment of the subject. Radioimaging allows for visualisation of where the compound of Formula (I) accumulates, which then corresponds to the site of treatment. Without wishing to be bound by theory, the present inventors believe that the methods and uses disclosed herein allow for more efficacious treatment of neuroendocrine cancers. The use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with a ^{67}Cu radioisotope allows for a higher dose of radioactivity to be delivered in a single dose. Since the compound of Formula (I) is specific for SSTR2 and retains the copper radioisotope for a longer

time (when compared to other metal chelators), the radioactivity is delivered to the cancer site and localised more efficiently. The compound of Formula (I) also shows better clearance from key organs. This in turn reduces any off-target effects of the radioisotope and limits unwanted damage to healthy tissue attributed to dissociation and subsequent circulation of the radioisotope. Better clearance of the radiolabelled compound of Formula (I) and retention at the targeted cancer site leads to images of higher contrast and subsequently more reliable diagnostic images. The ability to deliver a more sustained radiation dose by administration of the compound of Formula (I) complexed with a copper radioisotope also leads to more efficient treatment overall, as smaller amounts of the compound of Formula (I) and the radioisotope are required. Where the requisite radiation is delivered in fewer doses, this results in better tolerance and adherence to the treatment regime.

[0098] The methods of the present invention relate to the treatment of a neuroendocrine cancer in a subject in need thereof. In an embodiment, the neuroendocrine cancer is a neuroblastoma. In an embodiment, the neuroblastoma is a paediatric neuroblastoma. In some embodiments, the subject has had prior treatment with surgery and/or chemotherapy. In some embodiments, the subject requires additional therapies, for example, induction chemotherapy, surgery, radiotherapy (distinct from the methods disclosed herein), high-dose chemotherapy with autologous stem cell rescue and/or biologic and immunotherapeutic maintenance therapy.

[0099] The methods of treatment disclosed herein are for the treatment of a neuroendocrine cancer in a subject. In some embodiments, the neuroendocrine cancer is a tumour. In some embodiments, the neuroendocrine cancer is found in the gastrointestinal system, respiratory system, nervous system or skin. In a preferred embodiment, the neuroendocrine cancer is found in the nervous system. In other embodiments, the neuroendocrine tumour is a meningioma. In another embodiment, the neuroendocrine tumour is a gastrointestinal tumour. In another embodiment, the neuroendocrine tumour is a pancreatic tumour. In another embodiment, the neuroendocrine tumour is a lung tumour. In another embodiment, the neuroendocrine tumour is a stomach tumour. In another embodiment, the neuroendocrine tumour is a Merkel cell carcinoma. In another embodiment, the neuroendocrine tumour is a neurofibromatosis.

[0100] In one embodiment, the neuroendocrine cancer is a neuroblastoma. In another embodiment, the neuroblastoma is a paediatric neuroblastoma. In certain embodiments, the

neuroblastoma is found in early nerve tissue of the sympathetic nervous system. In some embodiments, the neuroblastoma is found in the adrenal glands, neck, chest and spinal cord.

[0101] In a preferred embodiment, the neuroendocrine tumour is a neuroblastoma. In some embodiments, the subject is less than 10 years of age, less than 5 years of age or less than 1 year of age. In some embodiments, the neuroblastoma is a high-risk neuroblastoma. In some embodiments, the neuroblastoma is a high-risk neuroblastoma with failure to respond to prior chemotherapy, radiation therapy and/or surgery.

[0102] It will be understood that the specific dose of the radiolabelled compound of Formula (I) for any particular subject will depend upon a variety of factors including, for example, the age, body weight and indication of the individual to be treated, the time of administration, rate of excretion, and combination with any other treatment or therapy. In preferred embodiments, the subject is human.

[0103] In some embodiments, the subject is an infant. As used herein, the term "infant" refers to a subject that has an age of about 1 day to about 12 months. In some embodiments, the subject is an infant that is about 12 months, about 11 months, about 10 months, about 9 months, about 8 months, about 7 months, about 6 months, about 5 months, about 4 months or about 3 months in age.

[0104] In other embodiments, the subject is a child. As used herein, the term "child" refers to a subject has an age of about 1 year to about 10 years. In some embodiments, the subject is a child of at least 1 year of age. In some embodiments, the subject is a child of from 1 year to about 10 years of age. In other embodiments, the subject is about 10 years, about 9 years, about 8 years, about 7 years, about 6 years, about 5 years, about 4 years, about 3 years, about 2 years, about 1 year or less than 1 year of age.

[0105] In other embodiments, the subject is an adolescent. As used herein, the term "adolescent" refers to a subject that has an age of about 10 years to about 19 years. In other embodiments, the subject is an adolescent of from about 10 years to about 19 years of age. In other embodiments, the subject is about 10 years, about 11 years, about 12 years, about 13 years, about 14 years, about 15 years, about 16 years, about 17 years, about 18 years or about 19 years of age.

[0106] In some embodiments, the subject is an adult. As used herein, the term "adult" refers to a subject that has an age of more than about 19 years. In certain embodiments, the subject is an adult with neuroblastoma, where the adult has had an earlier diagnosis of neuroblastoma. w

[0107] In some embodiments, the subject has a bodyweight of about 5 kg, about 6 kg, about 7 kg, about 8 kg, about 9 kg, about 10 kg, about 11 kg, about 12 kg, about 13 kg, about 14 kg, about 15 kg, about 16 kg, about 18 kg, about 20 kg, about 22 kg, about 24 kg, about 26 kg, about 28 kg, about 30 kg, about 35 kg, about 40 kg, about 45 kg, about 50 kg, about 55 kg, about 60kg, about 65 kg, about 70 kg, about 75 kg, about 80 kg, about 85 kg, about 90 kg, about 95 kg, about 100 kg, about 105 kg, about 110 kg, about 115 kg or about 120 kg.

[0108] Single or multiple administrations can be carried out with dose levels and pattern being selected by the treating physician. A broad range of doses may be applicable. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a given dose delivering a certain amount of radiation may be calculated as a fraction of the total radiation to be delivered to the subject. Dosage regimens may comprise the administration of multiple doses of the radiolabelled compound of Formula (I), where the doses are the same or different. In some embodiments, the methods for treatment of a neuroendocrine cancer comprise the administration of multiple doses of a compound of Formula (I) complexed with a copper radioisotope, where the doses are the same. In other embodiments, the methods comprise the administration of multiple doses, where the second and subsequent doses are higher than the first dose administered to the subject. In some embodiments, the dose administered for the purpose of treatment or therapy is determined by prior radioimaging of the subject by administration of the compound of Formula (I) complexed with a ^{64}Cu radioisotope in order to locate the cancer sites, estimate the amount of the compound retained by the subject (and subsequently the amount of radioactivity delivered) and assess the nature of the cancer sites. The present inventors believe that the use of the compound of Formula (I) or a pharmaceutically acceptable salt thereof for both radioimaging and radiotherapy represents a theranostic approach to neuroendocrine cancers. Without wishing to be bound by theory, the present inventors believe that the use a compound that may be used in a theranostic manner presents a more tailored approach to cancer therapy.

[0109] In combination with the methods for radioimaging a neuroendocrine cancer where the compound of Formula (I) having a different isotope is administered, the methods disclosed herein represent a theranostic approach, i.e. a therapeutic and diagnostic approach, to the treatment of such cancers. This is because administration of the compound of Formula (I) may also be complexed with a radioisotope that allows for the radioimaging of a subject, while administration of the compound of Formula (I) that is complexed with ^{67}Cu allows for treatment of the subject. Radioimaging allows for visualisation of where the compound of Formula (I) accumulates, which then corresponds to the site of treatment. Without wishing to be bound by theory, the present inventors believe that the methods and uses disclosed herein allow for more efficacious treatment of a neuroendocrine cancer. The use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with a copper radioisotope allows for a higher dose of radioactivity to be delivered in a single dose. Since the compound of Formula (I) is specific for a neuroendocrine cancer and retains the copper radioisotope for a longer time (when compared to other metal chelators), the radioactivity is delivered to the cancer site and localised more efficiently. The compound of Formula (I) also shows better clearance from key organs. This in turn reduces any off-target effects of the radioisotope and limits unwanted damage to healthy tissue attributed to dissociation and subsequent circulation of the radioisotope. Better clearance of the radiolabelled compound of Formula (I) and retention at the targeted cancer site leads to images of higher contrast and subsequently more reliable diagnostic images. The ability to deliver a more sustained radiation dose by administration of the compound of Formula (I) complexed with a copper radioisotope also leads to more efficient treatment overall, as smaller amounts of the compound of Formula (I) and the radioisotope are required. Where the requisite radiation is delivered in fewer doses, this results in better tolerance to treatment by the subject.

[0110] The methods of the present invention also contemplates combination therapies, wherein the radiolabelled compound of Formula (I) as described herein is co-administered with other suitable agents that may facilitate the desired therapeutic or prophylactic outcome. The term "co-administered" mean simultaneous administration in the same formulation or in two different formulations via the same or different routes or sequential administration by the same or different routes. The term "concomitant" refers to the administration of more than one formulation, where the formulations are administered to the subject at the same time. The term "simultaneously" means that the active agents are administered at substantially the same time.

The term “sequential” administration means a time difference of from seconds, minutes, hours or days between administrations of the agents. Administration may be in any order.

[0111] Since the methods disclosed herein relate to the administration of a radioisotope that emits ionising radiation, co-administration of one or more amino acids with the aqueous formulations comprising a radiolabelled compound of Formula (I) as disclosed herein may prevent or limit nephrotoxicity resulting from retention of the radiopharmaceutical. The one or more amino acids co-administered to a subject undergoing treatment for a neuroendocrine cancer competitively inhibit the reabsorption of the radiolabelled compound of Formula (I) by the proximal tubules of the kidneys. The present inventors believe that limiting reuptake of the radiolabelled compound of Formula (I) and therefore reducing nephrotoxicity of the subject allows for higher doses of the compound to be administered and therefore increase the efficiency of treatment. The methods for the treatment of a neuroendocrine cancer as disclosed herein further comprise the administration of one or more amino acids, or salts thereof, to the subject. In one embodiment, a formulation comprising one or more amino acids or salts thereof is co-administered with an aqueous formulation comprising a compound of Formula (I) complexed with a ^{67}Cu radioisotope. In one embodiment, the one or more amino acids includes lysine or a salt thereof. In another embodiment, the one or more amino acids includes arginine or a salt thereof. In a preferred embodiment, the method for the treatment of a neuroendocrine cancer further comprises the administration of lysine and/or arginine, or salts thereof. In a preferred embodiment, the method for the treatment of a neuroendocrine cancer further comprises the administration of lysine and arginine or salts thereof. In a preferred embodiment, the method for the treatment of a neuroendocrine cancer further comprises the co-administration of lysine and arginine or salts thereof with the compound of Formula (I) complexed with a ^{67}Cu radioisotope. In some embodiments, the one or more amino acids, or salts thereof, are administered as an intravenous infusion. In some embodiments, the formulation comprising one or more amino acids comprises L-lysine or a salt thereof. In other embodiments, the formulation comprising one or more amino acids comprises L-arginine or a salt thereof. In some embodiments, the one or more amino acids are present as a hydrochloride salt. In some embodiments, the one or more amino acids are each present at a concentration of about 2.5% w/v.

[0112] In an embodiment, the method for the treatment of a neuroendocrine cancer comprising administering to a subject in need thereof an aqueous formulation of a compound of Formula

(I) or a pharmaceutically acceptable salt thereof complexed to with ^{67}Cu in a therapeutically effective amount, and an aqueous formulation of one or more amino acids. In a preferred embodiment, the formulations comprising the radiolabelled compound of Formula (I) complexed with ^{67}Cu and one or more amino acids are administered concurrently. In another preferred embodiment, the formulation comprising one or more amino acids is administered to the subject prior to the administration of the compound of Formula (I) complexed with ^{67}Cu.

[0113] As used herein, the term “amino acid” refers to a molecule which contains both an amino and a carboxyl functional group. The amino acid may be a natural or unnatural amino and may also be in equilibrium with its zwitterionic form. The amino acid may contain modifications at either the amino and/or carboxyl terminus, or may contain a free amino group or carboxyl group. Further modification of the amino acid side chain or additional substitutions at other parts of the amino acid are also contemplated.

[0114] In cerain embdoiments, the amino acids are commonly found in nature. These are glycine (Gly, G), alanine (Ala, A), valine (Val, V), leucine (Leu, L), isoleucine (Ile, I), methionine (Met, M), proline (Pro, P), phenylalanine (Phe, F), tryptophan (Trp, W), serine (Ser, S), threonine (Thr, T), asparagine (Asn, N), glutamine (Gln, Q), tyrosine (Tyr, Y), cysteine (Cys, C), lysine (Lys, K), arginine (Arg, R), histidine (His, H), aspartic acid (Asp, D), and glutamic acid (Glu, E).

[0115] The methods of the present invention may further comprise the administration of an anti-emetic agent. In one embodiment, the methods of the present invention further comprises the administration of an anti-emetic agent to the subject. In some embodiments, the anti-emetic is administered concurrently with or prior to the compound of Formula (I) complexed with ^{67}Cu.

[0116] As used herein, the classification of adverse events associated with a method as disclosed herein is in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 as issued by the National Cancer Institute (NCI). The CTCAE is a descriptive terminology which is used in the art for adverse event (AE) reporting. A grading (or severity) scale is used to classify each AE term. In accordance with the definition provided in the CTCAE, an "adverse event (AE) is any unfavourable and unintended sign, (including an abnormal laboratory finding), symptom, or disease temporally located with the use of a medical

treatment or procedure that may or may not be considered related to the medical treatment or procedure". Previous versions of the CTCAE may also be used, however the broader description of the grades in the latest version (v5.0) is reproduced below:

Grade	Description of severity
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Activities of Daily Living (ADL) *Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. **Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

[0117] As used herein, a reference to, for example, a Grade 2 AE is an event having the severity as described in the table above. One skilled in the art would understand that initial identification of the AE in accordance to the System Organ Class (SOC) as described in the CTCAE v5.0 is then followed by grading in accordance with the table above.

[0118] In certain embodiments of the methods disclosed herein, the subject does not experience any adverse events classified as Grade 3 or higher, in accordance with the definition provided in the CTCAE.

[0119] In certain embodiments of the methods disclosed herein, the subject does not experience any adverse events classified as Grade 2 or higher, in accordance with the definition provided in the CTCAE.

[0120] In other embodiments, the subject does not experience any adverse events classified as Grade 1 or higher, in accordance with the definition provided in the CTCAE.

[0121] In other embodiments, the subject does not experience any adverse events classified as Grade 1 or Grade 2, in accordance with the definition provided in the CTCAE.

[0122] In other embodiments, the subject does not experience any adverse events classified as Grade 1, Grade 2 or Grade 3 in accordance with the definition provided in the CTCAE.

[0123] The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

[0124] Those skilled in the art will appreciate that the invention described herein in susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications which fall within the spirit and scope. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

Examples

[0125] The following examples are illustrative of the disclosure and should not be construed as limiting in any way the general nature of the disclosure of the description throughout this specification.

Example 1 - Dose Selection of ^{67}Cu-SARTATE (Formula I)

[0126] In the Dose Escalation Phase of the study, patients received a single administration of ^{67}Cu- SARTATE. The dose levels used in the escalation phase were 75 MBq/kg, 175 MBq/kg, 275 MBq/kg and 375 MBq/kg.

[0127] Preliminary data from a cohort of patients receiving 75 MBq/kg and a cohort of patients receiving 175 MBq/kg (all of whom have received a single Therapy Cycle of ^{67}Cu-SARTATE) showed that no Dose Limiting Toxicities (DLTs) were reported to date. This result indicates

that ^{67}Cu-SARTATE administration is well tolerated, which suggested that a higher dose of at least 275 MBq/kg could be used.

[0128] The averaged radiation dosimetry estimates of [^{64}Cu]Cu-SARTATE from three subjects for the PET & SPECT imaging components of a trial (see *J. Nucl. Med.* (2022) Bailey *et al*.) in meningioma patients are shown in Table 1. The highest organ dose per MBq was in spleen followed by kidneys, liver, adrenals and small intestine. This was consistent for both [^{64}Cu]Cu-SARTATE and [^{67}Cu]Cu-SARTATE. This data can then be extrapolated to estimate dosimetry of both [^{64}Cu]Cu-SARTATE and [^{67}Cu]Cu-SARTATE in children.

Table 1. Averaged radiation dosimetry estimates of [^{64}Cu]Cu-SARTATE and [^{67}Cu]Cu-SARTATE in meningioma patients.

Organ	[^{64}Cu]Cu-SARTATE Mean Absorbed Dose (mGy/MBq)	[^{67}Cu]Cu-SARTATE Mean Absorbed Dose (mGy/MBq)	Ratio of Dose (mGy) ^{67}Cu:^{64}Cu
Adrenals	8.30×10^{-2}	1.79×10^{-1}	2.2
Brain	1.29×10^{-2}	4.12×10^{-2}	3.2
Breasts	1.32×10^{-2}	3.85×10^{-2}	2.9
Gallbladder Wall	2.42×10^{-2}	5.43×10^{-2}	2.2
LLI Wall	3.68×10^{-2}	1.13×10^{-1}	3.1
Small Intestine	5.00×10^{-2}	1.58×10^{-1}	3.2
Stomach Wall	2.07×10^{-2}	4.88×10^{-2}	2.4
ULI Wall	2.00×10^{-2}	5.14×10^{-2}	2.6
Heart Wall	2.06×10^{-2}	5.42×10^{-2}	2.6
Kidneys	2.46×10^{-1}	5.45×10^{-2}	2.2
Liver	9.90×10^{-2}	1.73×10^{-1}	1.7
Lungs	3.85×10^{-2}	8.50×10^{-2}	2.2
Muscle	1.56×10^{-2}	2.54×10^{-2}	1.6
Ovaries	1.79×10^{-2}	4.85×10^{-2}	2.7
Pancreas	4.12×10^{-2}	7.98×10^{-2}	1.9
Red Marrow	2.11×10^{-2}	6.19×10^{-2}	2.9
Osteogenic Cells	3.22×10^{-2}	1.30×10^{-1}	4.0
Skin	1.20×10^{-2}	3.66×10^{-2}	3.0
Spleen	4.78×10^{-1}	6.42×10^{-1}	1.3
Testes	1.19×10^{-2}	4.08×10^{-2}	3.4
Thymus	1.46×10^{-2}	4.08×10^{-2}	2.8
Thyroid	1.35×10^{-2}	5.34×10^{-2}	3.9
Urinary Bladder Wall	3.81×10^{-2}	6.22×10^{-2}	1.6
Uterus	1.77×10^{-2}	5.23×10^{-2}	3.0
Total Body	2.32×10^{-2}	5.19×10^{-2}	2.2

[0129] Once the Dose Escalation Phase is completed and an acceptable safety and tolerability profile has been established, 2 Therapy Cycles of ^{67}Cu-SARTATE can be administered to patients in the Cohort Expansion Phase. In peptide receptor nuclide therapy (PRRT), larger

cumulative administered activities result in higher absorbed radiation doses to the tumor and have been shown to correlate with efficacy. This has been observed in preclinical studies of ^{67}Cu-SARTATE, where repeat administrations have resulted in greater survival than single administrations.

[0130] The dose-limiting organs in PRRT are usually the kidneys and bone marrow. The kidneys are at risk due the active reabsorption and retention of the radiopharmaceutical. In order to reduce nephrotoxicity, co-administration of positively charged amino acids that competitively inhibit reabsorption of the radio-peptide by the proximal tubules is often implemented. Co-injection of a cocktail of basic amino acids, such as lysine and arginine has been shown to reduce kidney uptake of radiopharmaceuticals by about 33% allowing for higher treatment doses to be administered. Dose-limiting total radiation to kidneys, derived from external beam radiation therapy (EBRT), may be quoted as 23 Gy or more conservatively, 18 Gy.

[0131] To avoid nephrotoxicity, the modelled cumulative administered activity of ^{67}Cu-SARTATE will not exceed the 23 Gy to the kidneys. In the event the planned cumulative administered activity across the total Therapy Cycles exceeds this modelled limit, the activity of the second and subsequent administrations of ^{67}Cu-SARTATE may be adjusted down to ensure that the modelled kidney radiation dose will not exceed 23 Gy in total. The weight-derived maximum allowable cumulative administered activity is calculated for each participant, with example doses depicted in Table 2.

[0132] The proposed 23 Gy kidney radiation dose limit will not take into account of radiation exposure to the kidney from previous treatment with radiopharmaceuticals. Based on the requirements of the protocol, it is likely that previous radiation therapy will only involve ^{131}I-MIBG therapy and/or EBRT as participants treated with PRRT are excluded. The dose levels administered during ^{131}I-MIBG therapy may vary based on institutional protocols, ranging from 37 – 666 MBq/kg. A kidney absorbed dose of 0.164 mGy/MBq has been reported following treatment with ^{131}I-MIBG in the high-risk refractory or recurrent neuroblastoma population, which is considered relatively low compared to SSTR-targeting radiopharmaceuticals. The main target organs with the highest radiation dose received during ^{131}I-MIBG therapy are the liver, lungs and bone marrow and the primary adverse effects are mostly hematologic.

[0133] Similarly, other previous investigations have also not accounted for any prior radiotherapy which may have affected renal function, except for ensuring that all patients had an adequate kidney function before trial entry.

[0134] However, to mitigate the risk of potential cumulative renal toxicity, participants who had previous ^{131}I-MIBG treatment within 12 months treatment or EBRT to a kidney at any time, will be required to have a higher estimated glomerular filtration (eGFR) compared to participants that did not. Additionally, participants who had EBRT that affected both kidneys or a single functioning kidney in the previous 12 months will be excluded. Thus, ensuring that only participants that have good kidney function reserve following prior radiation therapy is important.

Example 2 - Dosimetry of ^{64}Cu-SARTATE

[0135] The radiation dosimetry of ^{64}Cu-Sartate was determined using methods for establishing radiation dose.

i) ^{64}Cu-SARTATE PET/CT scans acquired at 1-, 4-, 12-, 24- and/or 48 hours post injection of ^{64}Cu-SARTATE were used to determine:
    a. Absorbed dose (mGy/MBq) in organs and effective dose (mSv/MBq) from 64Cu-SARTATE
    b. Modeled absorbed dose (mGy/MBq) in organs from ^{67}Cu-SARTATE
    c. Modeled estimated total cumulative administered activity of ^{67}Cu-SARTATE (GBq) that does not exceed the specific organ tolerance limits (23 Gy to the kidney, 2 Gy to the bone marrow)
ii) Additional later scans may be performed if adequate residual activity levels remain in the subject.

Example 3 - Dosimetry of ^{67}Cu-SARTATE

[0136] The radiation dosimetry of ^{67}Cu-Sartate may be determined using methods for establishing radiation dose.

i) ^{67}Cu-SARTATE SPECT/CT scans were acquired at 1-, 4-, 12-, 24- and/or 48 hours post injection of ^{67}Cu-SARTATE (additional later scans were performed if adequate residual activity levels remained in the participant) to determine:

a. Absorbed dose (mGy/MBq) in organs and effective dose (mSv/MBq) from ^{67}Cu-SARTATE
b. Modeled absorbed dose (mGy/MBq) in organs from ^{67}Cu-SARTATE
c. Modeled estimated total cumulative administered activity of ^{67}Cu-SARTATE (GBq) that does not exceed the specific organ tolerance limits (23 Gy to the kidney, 2 Gy to the bone marrow)

ii) Additional later scans may be performed if adequate residual activity levels remain in the subject.

Example 4 – Calculating the maximum dosage of ^{67}Cu-SARTATE

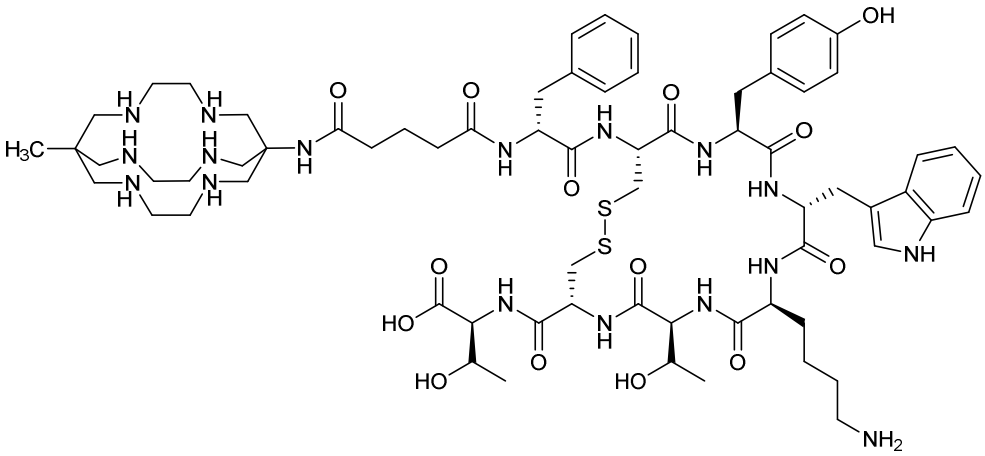
[0137] The maximum dosage of ^{67}Cu-SARTATE that can be administered without exceeding the renal limit of 23 Gy is based on the weight of the patient. Based on the maximum dose to the kidneys, the maximum cumulative dose of ^{67}Cu-SARTATE can then be calculated (see Table 2). Where upper renal limit is 30 Gy based on the weight of the patient, the maximum cumulative dose of ^{67}Cu-SARTATE can also be calculated. Similar cumulative doses may also be calculated according to the upper renal limit.

Table 2. Weight-based maximum cumulative dose of ^{67}Cu-SARTATE

Participant Weight (kg)	**Estimated Dose to Kidney (mGy/MBq)**	**Maximum Allowable Administered Activity Equivalent to 23 Gy Kidney Dose (GBq)**
10	2-5	1-15
20	1-4	1-21
30	1-4	7-27
40	0.5-3	13-33
50	0.5-3	20-40
60	0.25-2.5	24-44
70	0.2-2.5	30-50

The claims defining the invention are as follows:

1. Use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed to a ^{67}Cu radioisotope in a therapeutically effective amount in the manufacture of a medicament for the treatment of a neuroendocrine cancer,



Formula (I)

wherein the dose of radiation delivered by the radioisotope is sufficient to reduce the size of one or more lesions associated with the cancer.

2. Use according to claim 1, wherein an amino acid infusion is to be administered before the medicament.

3. Use according to claim 1 or 2, wherein the dose of radiation is not associated with any dose limiting toxicities.

4. Use according to any one of claims 1 to 3, wherein the dose of radiation is not associated with any adverse events classified as Grade 3 or higher.

5. Use according to any one of claims 1 to 4, wherein the dose of radiation is not associated with any adverse events classified as Grade 2 or higher.

6. Use according to any one of claims 1 to 5, wherein the dose of radiation is not associated with any adverse events classified as Grade 1 as higher.

7. Use according to any one of claims 1 to 6, wherein the medicament is to be administered in an amount of about 75 MBq/kg to about 475 MBq/kg.

8. Use according to any one of claims 1 to 7, wherein the medicament is to be administered one, two or three additional times at the same or lower amount such that the overall dose delivered to the patient does not exceed a 30 Gy kidney limit based on the patient's weight.

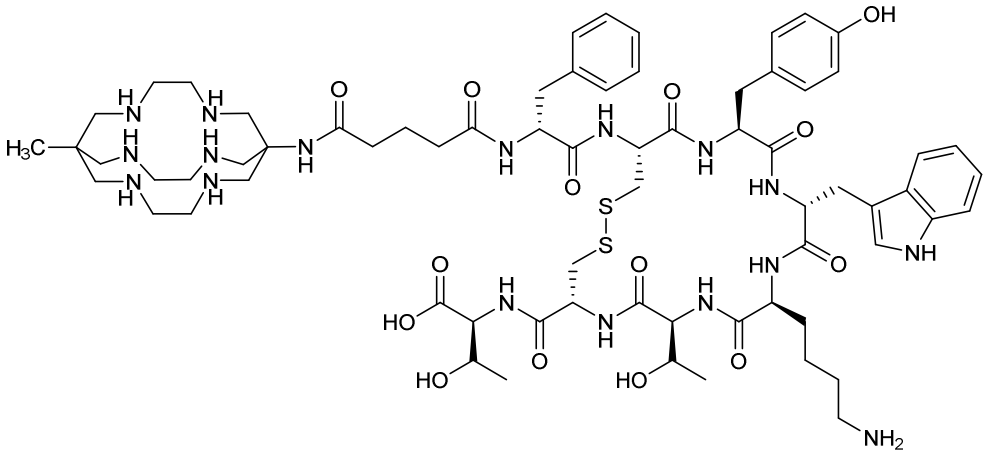
9. Use according to any one of claims 1 to 8, wherein the dose of radiation delivered by the ^{67}Cu radioisotope to the subject in a single dose of the compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed to a ^{67}Cu radioisotope is about 75 MBq/kg, about 175 MBq/kg, about 275 MBq/kg, about 375 MBq/kg or about 475 MBq/kg.

10. Use according to claim 2, wherein the amino acid infusion comprises lysine and/or arginine, or salts thereof.

11. Use according to any one of claims 1 to 10, wherein the effectiveness of the compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{67}Cu radioisotope is assessed by positron emission tomography (PET) or single-photon emission coupled tomography (SPECT) with the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed to a ^{64}Cu radioisotope.

12. Use according to any one of claims 1 to 11, wherein the medicament is to be administered to a subject before radioimaging of the subject by PET and/or CT.

13. Use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof complexed with a ^{64}Cu radioisotope:



Formula (I)

in the manufacture of a medicament for the treatment of a neuroendocrine cancer, wherein the dose of radiation delivered by the radioisotope is about 2 MBq/kg.

14. Use according to any one of claims 1 to 13, wherein the neuroendocrine cancer is a neuroendocrine tumour.

15. Use according to any one of claims 1 to 13, wherein the neuroendocrine cancer is a neuroblastoma.