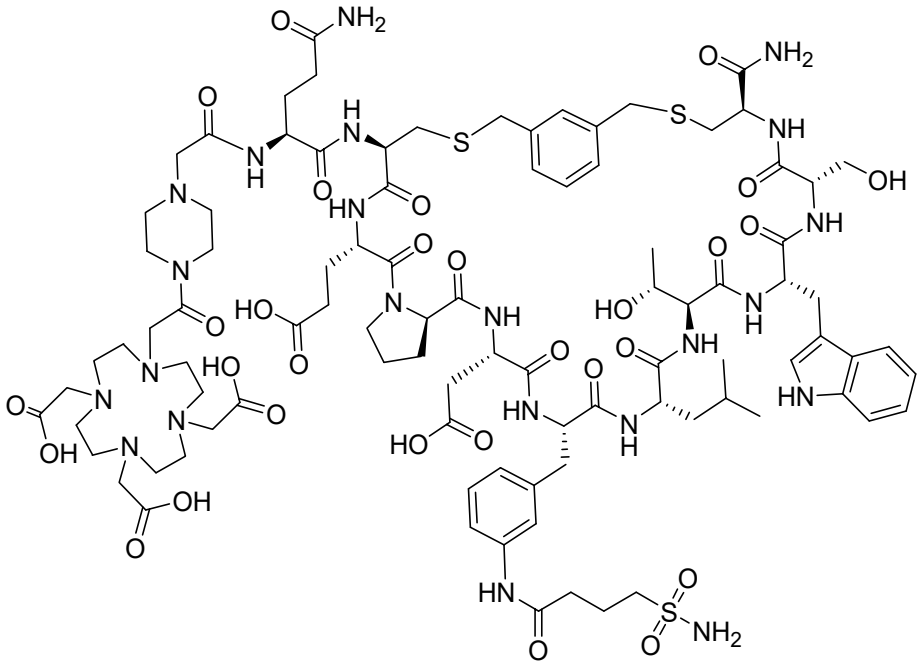
al. *Aliment Pharmacol Ther* 2003, 18(8), 837-46; Yang et al. *Pathol Oncol Res* 2018, 24 (4): 899-906; Strapcova et al. *Cancers (Basel)* 2020, 12(8); van Kuijk et al. *Front Oncol* 2016, 6, 69). Importantly, CAIX expression in non-cancerous (healthy) tissues is rare and generally restricted to the epithelia of the stomach, gallbladder, pancreas, and intestine (Pastorekova et al. *Gastroenterology* 1997, 112(2), 398-408).

The tumor expression of CAIX, complemented by a restricted profile in healthy tissues, provides an opportunity for therapeutic targeting and personalized medicine. It is therefore an object of the present invention to provide a compound for use in a method of treating a CAIX positive disease in a human patient, which achieves improved delivery and therapeutic efficacy (antitumor activity).

It is a further object of the present invention to provide a compound for use in a method of diagnosing and/or treating a CAIX positive disease in a human patient, which achieves improved delivery and therapeutic efficacy, while the side effects due to accumulation of radioactivity in non-cancerous (healthy) tissues are reduced or remain acceptable.

SUMMARY

In one aspect, the present disclosure refers to use of a compound in the manufacture of a medicament for treating a carbonic anhydrase IX (CAIX) positive disease in a human patient, wherein: (i) optionally, an imaging dose of the compound labeled with ^{68}Ga is to be administered to the patient, to obtain an image of body parts or tissues to be examined, and (ii) a treatment dose of the compound labeled with ^{177}Lu is to be administered to the patient, to treat the CAIX positive disease; wherein the compound is represented by the following Formula (1):



Formula (1)

wherein the DOTA moiety comprised in the compound of Formula (1) chelates the ^{68}Ga or ^{177}Lu to form the compound labeled with ^{68}Ga or ^{177}Lu; wherein, preferably the compound labeled with ^{177}Lu to be administered in step (ii) is to be administered once per cycle of one to six weeks, preferably once per cycle of four to six weeks, and most preferably once per cycle of four weeks; and wherein, if the patient is not to be administered an imaging dose of the compound labeled with ^{68}Ga in step (i), the compound labeled with ^{177}Lu to be administered in step (ii) is to be administered once per cycle of one to six weeks, preferably once per cycle of four to six weeks, and most preferably once per cycle of four weeks.

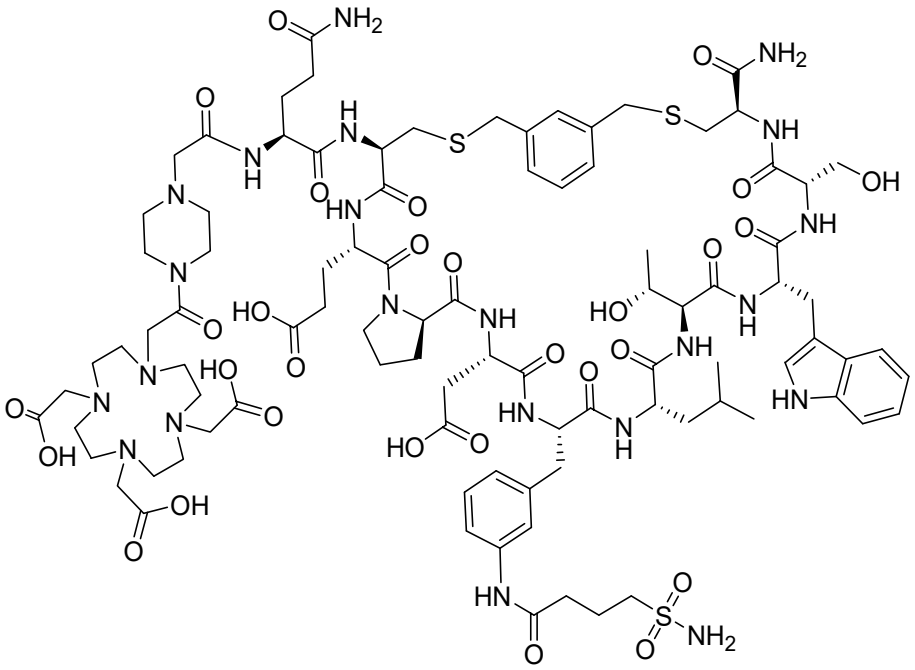
The present disclosure provides a compound for use in a method of treating CAIX positive diseases in a human patient. The present inventors have found that administering a treatment dose of a compound of the disclosure labeled with ^{177}Lu may lead to sufficient uptake of the radiolabeled compound in the tumor cells, while unspecific accumulation in healthy tissues (e.g., in the kidneys or other tissues endogenously expressing CAIX) is minimal/below an acceptable level. The compound labeled with ^{177}Lu may therefore have excellent therapeutic efficacy and minimal side effects. The inventors have also found that administering to human patients an imaging dose of a compound of the disclosure labeled with ^{68}Ga enables excellent imaging of the tumor tissues, thereby enabling the identification of patients that are likely to benefit from treatment with the compound of the disclosure labeled with ^{177}Lu.

The present disclosure thus relates to a compound for use in a method of treating a CAIX positive disease in a human patient comprising the steps of:

(i) optionally administering to the patient an imaging dose of the compound labeled with ^{68}Ga to obtain an image of body parts or tissues to be examined, and

(ii) administering to the patient a treatment dose of the compound labeled with ^{177}Lu to treat the CAIX positive disease;

wherein the compound is represented by the following formula (1):



Formula (1)

wherein the DOTA moiety comprised in the compound of formula (1) chelates the ^{68}Ga or ^{177}Lu to form the compound labeled with ^{68}Ga or ^{177}Lu.

The present disclosure in particular includes the following examples ("Items"):

1. A compound for use in a method of treating a carbonic anhydrase IX (CAIX) positive disease in a human patient, the method comprising the steps of:

(i) optionally administering to the patient an imaging dose of the compound labeled with ^{68}Ga, to obtain an image of body parts or tissues to be examined, and

(ii) administering to the patient a treatment dose of the compound labeled with ^{177}Lu, to treat the CAIX-positive disease;

wherein the compound is represented by the following Formula (1):

carcinoma (RCC), in particular clear cell renal cell carcinoma (ccRCC), colorectal carcinoma (CRC), pancreatic ductal adenocarcinoma (PDAC), glioblastoma (GBM), mesothelioma, cholangiocarcinoma (CCA), ovarian carcinoma, non-small cell lung cancer (NSCLC), in particular squamous non-small cell lung cancer (SNSCLC), brain cancer, pancreatic cancer, thyroid cancer, lung cancer, renal cancer, breast cancer, in particular triple-negative breast cancer (TNBC), head and neck cancer, in particular squamous carcinoma of head and neck (SCCHN), urothelial carcinoma and bladder cancer.

12. The compound for use according to any of items 1 to 11, wherein the CAIX positive disease is a cancer selected from the group consisting of ccRCC, CRC, PDAC, SNSCLC, TNBC and SCCHN, and preferably from ccRCC, CRC and PDAC.

13. The compound for use according to any of items 1 to 12, wherein the compound chelating ^{68}Ga and/or the compound chelating ^{177}Lu is administered after one or more other therapeutic agents or therapies, such as DNA damage response (DDR) inhibitors, chemotherapeutic agents, immunomodulatory agents, proton pump inhibitors (PPIs), histamine H_2-receptor antagonists, tyrosine kinase inhibitors, cell therapy, external beam radiation, or any other targeted therapies.

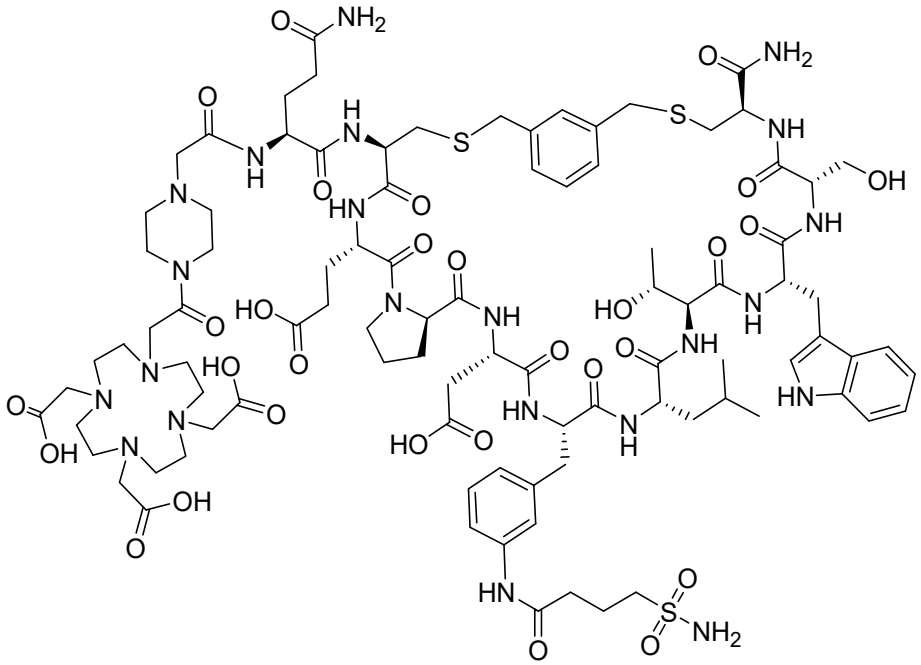
In one example, the present disclosure includes the following examples ("Items"):

1. A compound for use in a method of treating a carbonic anhydrase IX (CAIX) positive disease in a human patient, the method comprising the steps of:

   (i) administering to the patient an imaging dose of the compound labeled with ^{68}Ga, to obtain an image of body parts or tissues to be examined, and

   (ii) administering to the patient a treatment dose of the compound labeled with ^{177}Lu, to treat the CAIX positive disease;

   wherein the compound is represented by the following Formula (1):



Formula (1)

wherein the DOTA moiety comprised in the compound of Formula (1) chelates the ^{68}Ga or ^{177}Lu to form the compound labeled with ^{68}Ga or ^{177}Lu.

2. The compound for use according to item 1, wherein

(a) the imaging dose of the compound labeled with ^{68}Ga is from 50 to 250 MBq, preferably from 100 to 200 MBq, more preferably from 145 to 225 MBq, such as about 185 MBq, and/or

(b) the treatment dose of the compound labeled with ^{177}Lu is from 1.0 to 25.0 GBq, preferably from 2.0 to 20.0 GBq, more preferably from 3.0 to 19 GBq.

3. The compound for use according to item 1 or 2, wherein the compound labeled with ^{177}Lu is administered once per cycle of one to six weeks, preferably once per cycle of four to six weeks, and most preferably once per cycle of four weeks.

4. The compound for use according to any of items 1 to 3, wherein the compound labeled with ^{177}Lu-labeled is administered over one to ten cycles, preferably over four to eight cycles, and more preferably over four to six cycles.

5. The compound for use according to any of items 1 to 4, wherein the treatment dose of the compound labeled with ^{177}Lu that is administered in at least one cycle, and preferably in each cycle, is selected from the following:

(1) a treatment dose of from 2.0 to 6.0 GBq, such as about 3.7 GBq,
(2) a treatment dose of from 6.0 to 10.0 GBq, such as about 7.4 GBq,
(3) a treatment dose of from 10.0 to 14.0 GBq, such as about 11.1 GBq,
(4) a treatment dose of from 14.0 to 18.0 GBq, such as about 14.8 GBq, and
(5) a treatment dose of from 18.0 to 20.0 GBq, such as about 18.5 GBq.

6. The compound for use according to any of items 1 to 5, wherein the compound labeled with ^{68}Ga and/or the compound labeled with ^{177}Lu is administered intravenously, and preferably intravenously by infusion.

7. The compound for use according to any of items 1 to 6, wherein the compound labeled with ^{68}Ga and/or the compound labeled with ^{177}Lu is provided as a solution in a pharmaceutically acceptable injectable carrier.

8. The compound for use according to item 7, wherein the solution of the compound labeled with ^{68}Ga has a concentration of from 250 to 950 MBq/8.1 mL, and the solution of the compound labeled with ^{177}Lu has a concentration of from 150 to 900 MBq/mL.

9. The compound for use according to any of items 1 to 8, wherein the CAIX positive disease is cancer, and preferably the human patient has unresectable, locally advanced, or metastatic solid tumors.

10. The compound for use according to any of items 1 to 9, wherein the CAIX positive disease is a cancer selected from the group consisting of renal cell carcinoma (RCC), in particular clear cell renal cell carcinoma (ccRCC), colorectal carcinoma (CRC), pancreatic ductal adenocarcinoma (PDAC), glioblastoma (GBM), mesothelioma, cholangiocarcinoma (CCA), ovarian carcinoma, non-small cell lung cancer (NSCLC), in particular squamous non-small cell lung cancer (SNSCLC), brain cancer, pancreatic cancer, thyroid cancer, lung cancer, renal cancer, breast cancer, in particular triple-negative breast cancer (TNBC), head and neck cancer, in particular squamous carcinoma of head and neck (SCCHN), urothelial carcinoma and bladder cancer.

11. The compound for use according to any of items 1 to 10, wherein the CAIX positive disease is a cancer selected from the group consisting of ccRCC, CRC, PDAC, SNSCLC, TNBC and SCCHN, and preferably from ccRCC, CRC and PDAC.

12. The compound for use according to any of items 1 to 11, wherein the compound labeled with ^{68}Ga and/or the compound labeled with ^{177}Lu is administered after one or more other therapeutic agents or therapies, such as DNA damage response (DDR) inhibitors, chemotherapeutic agents, immunomodulatory agents, proton pump inhibitors (PPIs), histamine H_2-receptor antagonists, tyrosine kinase inhibitors, cell therapy, external beam radiation, or any other targeted therapies.

FIGURES

Figure 1 - *In vivo* efficacy in terms of tumor volume (A), impact on relative body weight (B) and tumor uptake (C) of ^{177}Lu-DPI-4452 in the HT-29 xenograft mouse model.

Figure 2 - *In vivo* uptake of ^{177}Lu-DPI-4452 in kidneys (A) and liver (B) as well as the comparison of the uptake of ^{177}Lu-DPI-4452 and ^{68}Ga-DPI-4452 in kidney, liver, and tumor (C) in the HT-29 xenograft mouse model.

Figure 3 - *In vivo* images of intravenously injected ^{68}Ga-DPI-4452 at 1 hour p.i. and ^{177}Lu-DPI-4452 at 4 hours p.i. in the HT29 xenograft mouse model. Representative axial, coronal and maximal intensity (bottom) projection (MIP) images of two mice are shown (Fig. 17A: first mouse, Fig. 17B: second mouse). Uptake is presented as percent injected dose per gram tissue (%ID/g).

Figure 4 - *In vivo* efficacy in terms of tumor volume (A), impact on relative body weight (B) and tumor uptake (C) of ^{177}Lu-DPI-4452 in the SK-RC-52 xenograft mouse model.

Figure 5 - *In vivo* uptake of ^{177}Lu-DPI-4452 in kidneys (A) and liver (B) as well as the comparison of the uptake of ^{177}Lu-DPI-4452 and ^{68}Ga-DPI-4452 in kidney, liver and tumor (C) in the SK-RC-52 xenograft mouse model.

Figure 6 - *In vivo* imaging of ^{177}Lu-DPI-4452 in the SK-RC-52 xenograft mouse model. Representative axial, coronal and maximal intensity (bottom) projection (MIP) images for two mice are shown. Uptake is presented as percent injected dose per gram tissue (%ID/g).

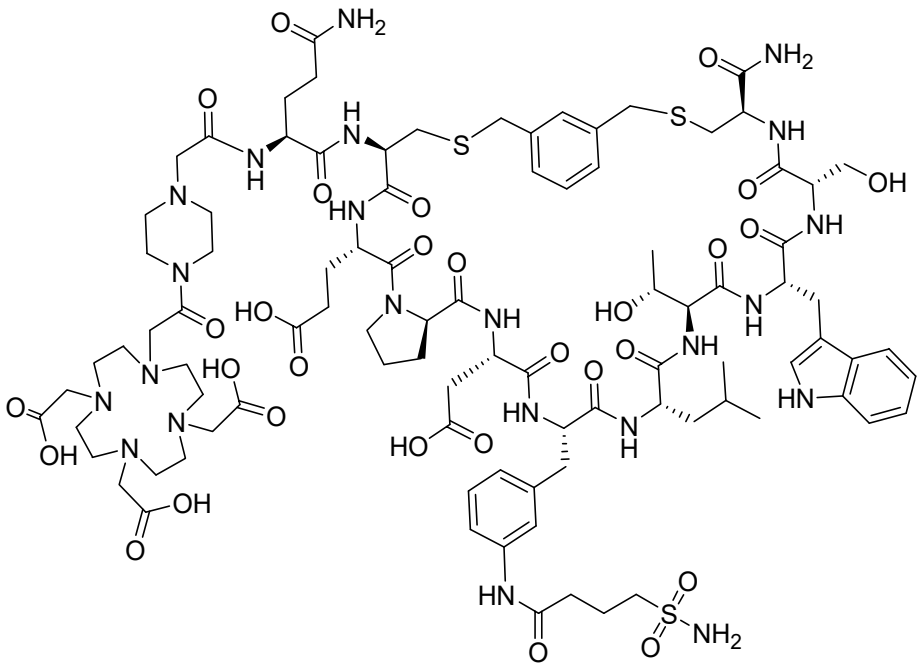
CLAIMS

1. Use of a compound in the manufacture of a medicament for treating a carbonic anhydrase IX (CAIX) positive disease in a human patient, wherein:

(i) optionally, an imaging dose of the compound labeled with ^{68}Ga is to be administered to the patient, to obtain an image of body parts or tissues to be examined, and

(ii) a treatment dose of the compound labeled with ^{177}Lu is to be administered to the patient, to treat the CAIX positive disease;

wherein the compound is represented by the following Formula (1):



Formula (1)

wherein the DOTA moiety comprised in the compound of Formula (1) chelates the ^{68}Ga or ^{177}Lu to form the compound labeled with ^{68}Ga or ^{177}Lu;

wherein, preferably the compound labeled with ^{177}Lu to be administered in step (ii) is to be administered once per cycle of one to six weeks, preferably once per cycle of four to six weeks, and most preferably once per cycle of four weeks; and

wherein, if the patient is not to be administered an imaging dose of the compound labeled with ^{68}Ga in step (i), the compound labeled with ^{177}Lu to be administered in step (ii) is to be administered once per cycle of one to six weeks, preferably once per cycle of four to six weeks, and most preferably once per cycle of four weeks.

2. The use according to claim 1, wherein:

(i) an imaging dose of the compound labeled with ^{68}Ga is to be administered to the patient, to obtain an image of body parts or tissues to be examined, and

(ii) a treatment dose of the compound labeled with ^{177}Lu is to be administered to the patient, to treat the CAIX positive disease.

3. The use according to claim 1 or 2, wherein

(a) the imaging dose of the compound labeled with ^{68}Ga is from 50 to 250 MBq, preferably from 100 to 200 MBq, more preferably from 145 to 225 MBq, such as about 185 MBq, and/or

(b) the treatment dose of the compound labeled with ^{177}Lu is from 1.0 to 25.0 GBq, preferably from 2.0 to 20.0 GBq, more preferably from 3.0 to 19 GBq.

4. The use according to any of claims 1 to 3, wherein the compound labeled with ^{177}Lu is to be administered once per cycle of one to six weeks, preferably once per cycle of four to six weeks, and most preferably once per cycle of four weeks.

5. The use according to any of claims 1 to 4, wherein the compound labeled with ^{177}Lu-labeled is to be administered over one to ten cycles, preferably over four to eight cycles, and more preferably over four to six cycles.

6. The use according to any of claims 1 to 5, wherein the treatment dose of the compound labeled with ^{177}Lu that is to be administered in at least one cycle, and preferably in each cycle, is selected from the following:

(1) a treatment dose of from 2.0 to 6.0 GBq, such as about 3.7 GBq,
(2) a treatment dose of from 6.0 to 10.0 GBq, such as about 7.4 GBq,
(3) a treatment dose of from 10.0 to 14.0 GBq, such as about 11.1 GBq,
(4) a treatment dose of from 14.0 to 18.0 GBq, such as about 14.8 GBq, and

(5) a treatment dose of from 18.0 to 20.0 GBq, such as about 18.5 GBq.

7. The use according to any of claims 1 to 6, wherein the compound labeled with ^{68}Ga and/or the compound labeled with ^{177}Lu is to be administered intravenously, and preferably intravenously by infusion.

8. The use according to any of claims 1 to 7, wherein the compound labeled with ^{68}Ga and/or the compound labeled with ^{177}Lu is provided as a solution in a pharmaceutically acceptable injectable carrier.

9. The use according to claim 8, wherein the solution of the compound labeled with ^{68}Ga has a concentration of from 250 to 950 MBq/8.1 mL, and the solution of the compound labeled with ^{177}Lu has a concentration of from 150 to 900 MBq/mL.

10. The use according to any of claims 1 to 9, wherein the CAIX positive disease is cancer, and preferably the human patient has unresectable, locally advanced, or metastatic solid tumors.

11. The use according to any of claims 1 to 10, wherein the CAIX positive disease is a cancer selected from the group consisting of renal cell carcinoma (RCC), in particular clear cell renal cell carcinoma (ccRCC), colorectal carcinoma (CRC), pancreatic ductal adenocarcinoma (PDAC), glioblastoma (GBM), mesothelioma, cholangiocarcinoma (CCA), ovarian carcinoma, non-small cell lung cancer (NSCLC), in particular squamous non-small cell lung cancer (SNSCLC), brain cancer, pancreatic cancer, thyroid cancer, lung cancer, renal cancer, breast cancer, in particular triple-negative breast cancer (TNBC), head and neck cancer, in particular squamous carcinoma of head and neck (SCCHN), urothelial carcinoma and bladder cancer.

12. The use according to any of claims 1 to 11, wherein the CAIX positive disease is a cancer selected from the group consisting of ccRCC, CRC, PDAC, SNSCLC, TNBC and SCCHN, and preferably from ccRCC, CRC and PDAC.

13. The use according to any of claims 1 to 12, wherein the compound labeled with ^{68}Ga and/or the compound labeled with ^{177}Lu is to be administered after one or more other therapeutic agents or therapies, such as DNA damage response (DDR) inhibitors, chemotherapeutic agents, immunomodulatory agents, proton

pump inhibitors (PPIs), histamine H_2-receptor antagonists, tyrosine kinase inhibitors, cell therapy, external beam radiation, or any other targeted therapies.