The recently published EANM practice guidelines for MTC imaging recommend ^{68}Ga-labeled somatostatin analogues, [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) and [^{18}F]fluorodihydroxyphenylalanine ([^{18}F]F-DOPA) [15]. In a retrospective analysis, [^{18}F]F-DOPA PET/CT displayed enhanced detection rates (72%) in patients with recurrent MTC compared to [^{18}F]FDG PET/CT (17%) or PET/CT performed with ^{68}Ga-labeled somatostatin analogues (33%) [16]. Interestingly, [^{18}F]F-DOPA PET reveals good sensitivity in primary tumors (86%) but only moderate (57%) to low (6%) sensitivity in lymph node (LN) and distant metastases, respectively [17]. Moreover, as reported in a recent meta-analysis of the literature, the per-patient detection rate of [^{18}F]F-DOPA PET or PET/CT is only 66% (95% confidence interval, 58–74%) in patients with suspected recurrent MTC [18].

For patients with metastatic disease, treatment options are still limited. Neither external beam radiation, nor conventional chemotherapy have shown sufficient therapeutic efficiency and are therefore not recommended [1,19,20]. Unlike common forms of thyroid cancer, MTC originates from malignant de-differentiation of parafollicular cells. As these cells do not accumulate iodine, radioactive iodine therapy is not a treatment option [21,22]. For this reason, total thyroidectomy and central compartment neck dissection are still performed most frequently in case of MTC [1,23]. However in general, 10-year survival rate for patients with local and distant metastases was 76% and 40%, respectively [6]. Tyrosine kinase inhibitors such as selpercatinib, vandetanib or cabozantinib have been shown to prolong (mainly progression-free) survival [1]. However, therapy is associated with a variety of relevant side effects such as hypertension, renal toxicity and hepatotoxicity, amongst others [1,24].

Over the last decades, the field of nuclear medicine emerged as a powerful alternative due to its non-invasive imaging and therapy opportunities [13,14]. As a supplement to the screening methods mentioned earlier, localization of tumors and metastases could be thus determined via molecular imaging. In the 1990s, diagnosis of MTC was first accomplished via somatostatin receptor scintigraphy (SRS), applying Somatostatin receptor subtype 2 (sstr2)-specific ligands. Although decent improvement in diagnosis, lots of MTC-negative scans were still reported, especially in patients with metastatic spreading [25]. For this reason, new options for MTC targeting, particularly for progressed disease and metastasis were warranted.

As was reported by *Reubi et al.* in 1997, MTC overexpresses cholecystokinin receptors A (CCK-A) and B (CCK-B), with the latter also known as gastrin receptor or CCK-2 receptor (CCK-2R) [26]. In 2006, *Gotthardt et al.* showed that CCK-2R expression is extensively higher in MTC-derived metastases than sstr2 expression (94% to 40%, respectively) [27]. Ever since, the development of CCK-2R-specific tracers that are based on the endogenous ligands CCK or minigastrin, increased [28,29].

In view of the above there is an ongoing need for further options to diagnose and treat CCK-2R-expressing cancer, such as MTC. This need is addressed by the present invention.

Summary

In one aspect, the present disclosure refers to a tetrapeptide binding to Cholecystokinin 2 receptor (CCK-2R), wherein the tetrapeptide is represented by formula (I)

Xaa1-Xaa2-Xaa3-Xaa4 (formula (I))

or salt thereof, wherein

Xaa1 is Trp, (β-(3-benzothienyl)-alanine, Trp, wherein one or more of the H atoms of the 1*H*-indol-3-yl are replaced by a substituent that is for each H atom independently selected from a C_1 to C_3 alkyl, -OH, -SH, -F, and -Cl, Phe, 1-Nal, 2-Nal, Tyr or p-Amino-Phe,
Xaa2 is an N-methyl amino acid, wherein the N-methyl group is at the alpha carbon, and preferably an N-methyl amino acid containing an aliphatic side chain, wherein the N-methyl group is at the alpha carbon,
Xaa3 is an amino acid with an acidic side chain at neutral pH, and
Xaa4 is an amino acid with an aromatic side chain or an amide thereof.

In one aspect, the present disclosure refers to a conjugate comprising within a single molecule:

(a) the tetrapeptide as described herein, and

(b) one or more chelating groups capable of complexing a nonradioactive or radioactive cation or one or more chelating groups containing a chelated nonradioactive or radioactive cation.

In one aspect, the present disclosure refers to a conjugate compound binding to Cholecystokinin 2 receptor (CCK-2R) that is represented by formula (IV)

$$R^L\text{-dap}(R^{SiFA})\text{-}R^{GABA}\text{-L-}R^H \text{ (IV)}$$

wherein:

R^L is DOTA or DOTAGA, optionally containing a chelated nonradioactive or radioactive cation;

dap(R^{SiFA}) is a dap group carrying a silicon-based fluoride acceptor moiety R^{SiFA};

R^{GABA} is present or absent, and, if present, is one or more γ-aminobutryic acid (GABA), preferably $(GABA)_{1-3}$;

L is a linking moiety comprising at least 5, preferably at least 6 α- or γ-glu and most preferably 6 to 9 α- or γ-glu, whereby γ-glu is preferred over α-glu; and

R^H is or comprises Ala-Tyr-Gly-Trp-Nle-Asp-Phe-NH_2.

Detailed Description

Accordingly, the present invention relates in a first aspect to a tetrapeptide binding to Cholecystokinin 2 receptor (CCK-2R), wherein the tetrapeptide is represented by formula (I) Xaa1-Xaa2-Xaa3-Xaa4 (formula (I)) or salt thereof, wherein Xaa1 is Trp, (β-(3-benzothienyl)-alanine, Trp, wherein one or more