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(54) **PEPTIDES RADIOMARQUES PERMETTANT DE DIAGNOSTIQUER ET DE TRAITER DES TUMEURS DU SEIN ET DE LA PROSTATE ET DES METASTASES DE CES TUMEURS**

(54) **RADIOLABELED PEPTIDES FOR THE DIAGNOSIS AND TREATMENT OF BREAST AND PROSTATE TUMORS AND METASTASES OF SUCH TUMORS**

(57) Un peptide ou un peptidomimétique radiomarqué qui se lie à des récepteurs libérant des gastrines permet de diagnostiquer et/ou de traiter un cancer du sein et/ou de la prostate.

(57) Breast and/or prostate cancer is diagnosed and/or treated with a radiolabeled peptide or peptidomimetic that binds to GRP (Gastrin Releasing Peptide) receptors.

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(54) Title: RADIOLABELED PEPTIDES FOR THE DIAGNOSIS AND TREATMENT OF BREAST AND PROSTATE TUMORS AND METASTASES OF SUCH TUMORS

(57) Abstract

Breast and/or prostate cancer is diagnosed and/or treated with a radiolabeled peptide or peptidomimetic that binds to GRP (Gastrin Releasing Peptide) receptors.

Radiolabeled Peptides for the Diagnosis and Treatment of Breast and Prostate Tumors and Metastases of Such Tumors

BACKGROUND OF THE INVENTION

This invention relates to compounds and methods for the diagnosis and treatment of tumors of the breast and prostate, as well as metastases of such tumors.

Many tumors have biochemical receptors that cause certain molecules, typically peptides or proteins, to bind to the tumor. One approach to diagnose tumors is to identify a compound that binds to a particular tumor, radiolabel the compound with a suitable radionuclide, administer the compound to the patient (generally via intravenous injection), allow the compound to become bound to the tumor, and then image the location where the radioactive decay occurs. While the concept as thus presented is rather simple, in practice it is quite difficult. The first challenge is to identify a candidate compound. If the compound does not bind very strongly to the tumor and for a sufficient period of time, it will not be possible to obtain adequate diagnosis. Moreover, even if the compound binds to the tumor, if it also binds to surrounding healthy tissue, the diagnosis will be difficult or impossible. Further, it is necessary that the linkage of the compound to the radionuclide not disturb the affinity of the tumor for the compound. Another issue is the potential toxicity of the compound in the patient. Some compounds that may be very suitable from a binding perspective, may be too toxic to use.

A similar approach can be taken in tumor therapy, where one would identify a suitable compound, radiolabel the compound with a suitable radionuclide, and administer the compound to the patient (generally via intravenous injection, but possibly by direct injection into the tumor mass). The radionuclide will then decay,

releasing energy to kill or reduce the growth of the tumor. Again, the concept is simple, but in practice there are many difficulties. In addition to the problems mentioned above, it is necessary that there be very little of the compound anywhere in the body except in the tumor, because of the danger of the high energy radiation to healthy tissue. This means that not only must the compound bind very strongly to the tumor, but there must be no or very little binding to healthy tissues, even if they are not in the vicinity of the tumor.

Attempts to locate suitable compounds have been fraught with difficulty. Because it is desirable to screen large numbers of potential compounds quickly, various "shortcut" assays and models have been developed. Unfortunately, many of these techniques have produced incorrect or misleading data.

Many researchers have used cell line cultures to screen compounds. While the use of cell lines as a screening technique has advantages, it has been found that cell line cultures often have binding affinity for compounds that is not exhibited by actual tumors. Thus, data from this technique produces false positives.

Other researchers have used homogenates of tumors, where a sample of the tumor has been subjected to high shear in a laboratory blender. One problem with this technique is that not only the tumor, but any surrounding tissues that were attached to the tumor are included in the homogenate, thus rendering it impossible to know if any binding affinity is from the tumor or from the surrounding tissues. Further, the shear of the homogenization breaks open the cell membranes, allowing for the possibility of binding that would not occur in an intact cell.

A screening method that produces unambiguous results is a morphological study in which sections (thin slices) of a tumor and surrounding tissue are contacted with a candidate compound that has been labeled with a radionuclide that is suitable for

exposing photographic film. This technique clearly differentiates between receptors that are present in the tumor and those present in the surrounding tissue. Unfortunately, this technique is very labor intensive and depends on having suitable tumor tissue samples available.

Peptides and other compounds have been used without radiolabeling to affect the growth of tumors. While some such compounds may also be useful with radiolabeling for imaging and radiotherapy, the correlation between compounds useful for chemotherapy and those useful for radiotherapy is very low.

Bombesin is a peptide originally isolated from frog skin. It is an example of a compound that binds to GRP (Gastrin Releasing Peptide) receptors. Bombesin has the structure:

pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

Considerable work has been conducted in an attempt to identify tumor and non-tumor GRP receptors. Unfortunately, much of that work has yielded results that are inaccurate or misleading.

Breeman et al. "[^{111}In-DTPA^0, Pro^1 , Tyr^4]bombesin: Studies *In Vitro* and in Rats", *JNM* 39 (1998) 62P teach that high and specific uptake was found in the pancreas and tissues of the GI-tract. Uptake was blocked by iv co-injection of 100 ug of Tyr^4-BN with the radiolabeled peptide, but not when administered 1 hour after the radiotracer indicating the internalization of the radioligand.

Hoffman, Li, Sieckman, and Volkert, "Uptake and Retention of a Rh-105 Bombesin Analogue in GRP Receptor Expressing Neoplasms: An *In Vitro* Study", *JNM* 38 (1997) 188P-189P (abstract) teach that the affinity of a Rh-105 labeled bombesin analog for the GRP receptor was investigated along with its prolonged cellular

retention in the PC-3 human prostate cancer cell line (65% @ 2 h) and CF-PAC1 human pancreatic cell line (41% @ 2 h). The Rh-105 analog was rapidly internalized intracellularly in both cell lines studied. The author states that the selective affinity & prolonged retention in neoplastic cells make this radiolabeled peptide a potential candidate for radiotherapy.

Hoffman, Li, ,Volkert, Sieckman, Higginbotham, and Ochrymowycz, "Synthesis and Characterization of Rh-105 Labelled Bombesin Analogues: Enhancement of GRP Binding Affinity Utilizing Aliphatic Carbon Chain Linkers", *Journal of Labelled Compounds and Radiopharmaceuticals* 40 (1997) 490-492 (abstract) teach that the IC_{50} values (using Swiss 3T3 fibroblasts) were determined for a series of 4 peptides and the non-metalated sulfur macrocyclic analogs expressed similar affinities to the GRP receptor than the parent BBN peptide. Upon Rh(III) complexation, decreasing the proximity of the $Rh(III)Cl_2$-16 and S_4 complex to the binding region of BBN, increases the affinity of the final metalated peptide for the GRP receptor. This data may have implications in preparing other metalated BBN analogues which maintain specificity and high affinity for GRP receptors expressed on neoplastic cells.

Hoffman, Sieckman, Ochrymowycz, Higginbotham, Volkert, and Ketring, "*In Vitro* and *In Vivo* Characterization of a Rh-105-Tetrathiamacrocycle Conjugate of a Labelled Bombesin Analogue", *JNM* 37 (1996) 61P teach that biodistribution studies of the Rh-105 analogue in normal mice showed predominant clearance into the urine and low retention in the kidneys. Data demonstrate the feasibility of forming Rh-105 conjugates with BBN analogs as potential therapeutic agents that specifically target neoplastic cells expressing BBN2 receptors.

Hoffman et al. "Rh-105 Bombesin Analogs: Selective *In Vivo* Targeting of Prostate Cancer with a Radionuclide", *JNM* 39 (1998) 982P teach that an Rh-105 BBN (7-

*rB

14) analog, with a 4 carbon spacer between the sulfur macrocycle and the Q amino acid was evaluated in nude mice possessing PC-3 prostatic tumors. Tumor/Muscle ratios were 7.8, 7.7, and 13.6 @ 4, 24, & 48 hours p.i., respectively. The conclusion is that the selective affinity and prolonged retention of this radiolabeled peptide in prostatic cancer cells makes it an attractive candidate for radiotherapy.

T.J. Hoffman, G.L Sieckman, and W.A. Volkert, " Iodinated Bombesin Analogues: Effect of N-terminal vs. Side Chain Iodine Attachment on BBN-GRP Receptor Binding", *JNM* 37 (1996) 185P teaches that assessed iodinated BBN analogs as potential SCLC targeting vectors. In all cases, the specific binding region, BBN(8-13) or W-A-V-G-H-L, was maintained, as well as amidation of the carboxy terminal end. Measurement of IC_{50} values were conducted utilizing Swiss 3T3 cells with [^{125}I][Tyr^4]BBN. The loss of receptor affinity by the mIP-Lys^7 conjugated peptide suggests that incorporation of Lys between BBN(1-6) may facilitate increased peptide-receptor affinity. The data show that N-terminal iodination of these analogs may provide a viable route to obtain high affinity BBN iodinated peptides.

Schibli, Hoffman, Volkert, et al. "A Tc-99m DITHIA-DI(Bis-Hydroxymethylene) Phosphine conjugate of Bombesin *In Vivo* Studies", *JNM* 39 (1998) 225P teaches that the Tc-99 analogs of bombesin derived from 2 different DADT BFCs and the 14 amino acid peptide Lys-3-bombesin were evaluated in a competitive binding assay vs. [^{125}I][Tyr^4]bombesin using human prostate cancer PC-3 cell membranes. The results indicate that the Tc-99m complexes have the potential to be used in the characterization of bombesin/GRP receptors of prostate cancer non-invasively *in vivo*.

Baidoo et al. "Synthesis and Evaluation of High Affinity Technetium Bombesin Analogs", *JNM* 38(1997) 87P mentions prostate, breast, gastric, colon, pancreatic

and scl cancers. DADT chelates (1 and 2, resulting in neutral or positive cores) were attached to the lysine residue @ N-terminal region of the potent Bn analog Pyr-Q-K-L-G-N-Q-W-A-V-G-H-L-M-NH_2. When a DADT peptide was labeled with Tc-99m or Tc-99, 2 isomers resulted. The Tc-99 analogs exhibited high affinity in a rat cortex membrane binding assay vs. [^{125}I][Tyr^4]bombesin.

B. Rogers, D. Curiel, K. Laffoon, D. Buchsbaum, "Synthesis and Radiolabeling of Bombesin Derivatives with Copper-64 and Binding to Cells Expressing the Gastrin Releasing Peptide Receptor", *Journal of Labelled Compounds and Radiopharmaceuticals* 40 (1997) 482 (abstract) concludes that Cu-64-TETA-Aoc-BBN(7-14) is a potential therapeutic radiopharmaceutical that can be used to treat GRPr positive tumors.

A. Safavy, M. Khazaeli, H. Qin, and D. Buchsbaum, "Synthesis of Bombesin Analogues for Radiolabeling Rhenium-188", *Cancer* 80 (1997) 2354-2359 teaches that 7-amino acid analogue of BBN was synthesized and conjugated to the hydroxamate ligand trisuccin. Radiolabeling with Re-188 were performed in > 90% yield. Cell-binding performed with BNR-11 (3T3 mouse fibroblast cells) and PC-3 human prostate carcinoma GRPA positive cells resulted in positive binding.

B. Rogers et al. "Tumor Localization of a Radiolabeled Bombesin Analog in Mice Bearing Human Ovarian Tumors Induced to Express GRP Receptor by an Adenoviral Vector", *Cancer* 80 (1997) 2419-2424 shows a study was conducted to determine the level of localization of [^{125}I/^{131}I]-mIP-bombesin in tumors.

Rogers, Buchsbaum, et al. "Localization of I-125-mIP-Des-Met14-bombesin(7-13)NH_2 in Ovarian Carcinoma Induced to Express the GRPr by Adenoviral Vector-Mediated Gene Transfer", *JNM* 38 (1997) 1221-1229 teaches that [^{125}I][Tyr^4]bombesin was compared to [^{125}I]-mIP-bombesin (a 7 aa BN analog) for

in vitro binding and internalization into tumor cells and for tumor localization *in vivo*, and results showed that the latter has more favorable characteristics with regards to tumor localization and cellular internalization & retention.

Zinn, Buchsbaum, et al. "Imaging Adenoviral-Mediated Gene Transfer of GRPr Using a Tc-99m-Labelled Bombesin Analogue", *JNM 39* (1998) 224P-225P teaches that BBN analogue (QWAVGHLM) was HYNIC modified and radiolabeled with Tc-99m using tricine as a transchelator. Specific and high affinity binding to GRPr-expressing cells was demonstrated by Scatchard analysis. Favorable biodistribution and imaging were observed.

M.E. Rosenfeld et al., Adenoviral Mediated Delivery of GRPr Results in Specific Tumor Localization of a Bombesin Analogue *In Vivo", Clin. Cancer Res.* 3 (1997), 1187-1194 teaches similar work to previous publication above.

T.J. Hoffman, G.L. Sieckman and W.A. Volkert, "Targeting Small Cell Lung Cancer Using Iodinated Peptide Analogs" teaches that 5 analogs prepared using SPPS and *in vitro* BB2 receptor binding assessed using Swiss T3T fibroblasts. Amino acids #1-6 nor C-terminal Met residue are not essential to maintain receptor specificity. Results imply that incorporation of I-123 or I-131 as a m-iodophenyl moiety may be used to diagnose or treat sclc.

US 5,686,410 Novartis Albert teaches radiolabeled bombesin and antagonists, including use for tumor imaging and therapy (Examples 11 and 12).

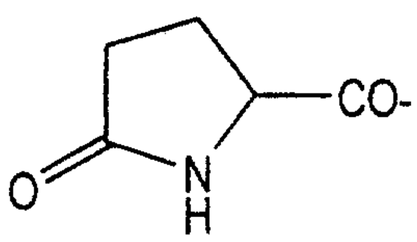
There are numerous articles and patents that discuss the binding of non-radioactive bombesin analogs to various tissues such as SCLC (small cell lung cancer), and petuitary, adrenal, and skin tumors.

SUMMARY OF THE INVENTION

GRP receptors were found to be overexpressed in prostate cancer, breast cancer, and metastases of such cancers. Several novel isosteric modifications at the N-terminal to enable the introduction of chelating groups and at the third position of the bombesin molecules are introduced. This results in the retention of agonist and internalization properties of the molecules. Radiolabeling of these molecules with imaging and therapeutic isotopes have applications in the detection and treatment of GRP and Bombesin receptor positive tumors.

In one respect, the invention concerns three classes of peptides or peptidomimetics either radiolabeled or not, for the diagnosis and/or therapy of GRP receptor positive tumors.

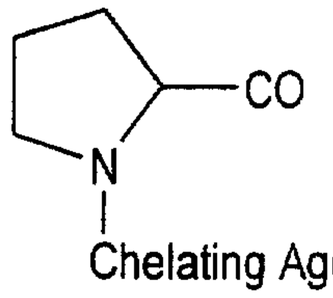
a. For radiolabeling of bombesin and analogs, the presence of p-Glu at the N-terminal of the peptide chain does not lend itself to the attachment of chelating moieties mentioned below either by conventional means or by solid phase methods.



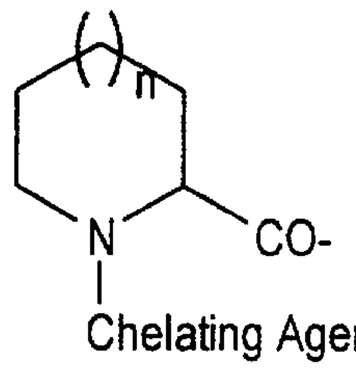
pGlu

The invention relates to the replacement of the p-Glu moiety with cyclic amino acids without the loss of binding characteristics. Replacement moieties include specifically Proline (Pro) and other cyclic analogs to provide the same tertiary structures the N-terminal. Such a replacement provide a reactive moiety for the attachment polyamino carboxylate chelating groups, N_tS_{4-t} chelating agents and others.

Examples of cyclic analogs:



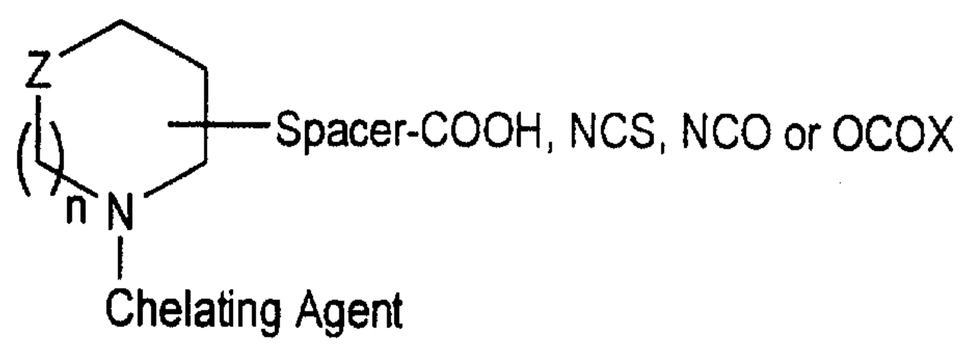
Such an isosteric replacement of pGlu by Pro preserves the binding characteristics of the peptide. Other replacements include pipecolic acid and homologs, and its isomers, and cyclic compounds containing at least one reactive amine to which the chelating agent is attached.



where n = 1 - 5

(Note: n = 0 is Proline, n=1 is pipecolic acid and isomers).

Other cyclic compounds for the replacement of pGlu include the presence of other heteroatom in the carbocyclic ring and the presence of -COOH, NCS (isothiocyanate), NCO (isocyanate), carbomoyl group (OCOX where X is a reactive moiety such as halogen or other reactive moiety). These reactive groups can also be separated from the cyclic moiety by spacer groups.



n = 1-6

Z = O, S, N-R (R = alkyl groups C_1-C_6 normal or branched),

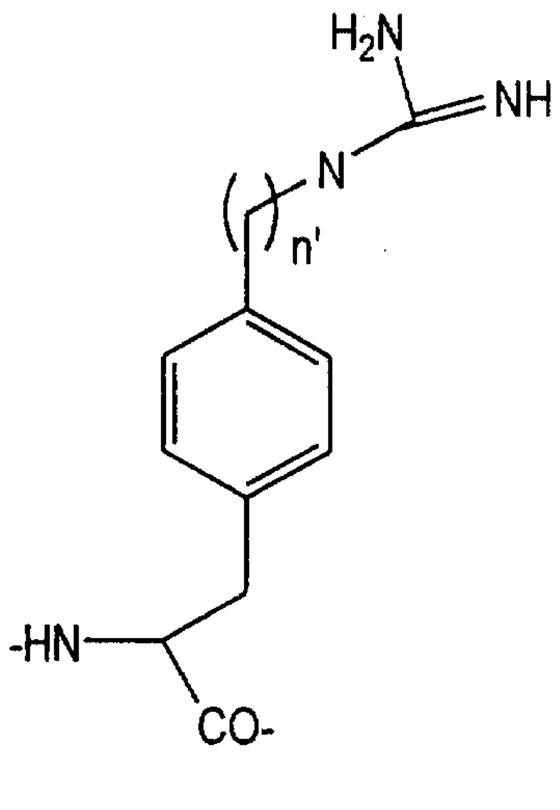
Spacer = branched or normal alkyl chain with or without intervening heteroatoms.

The reactive groups for the attachment to the peptide chain indicated can be located at any position of the ring and can be separated by a spacer.

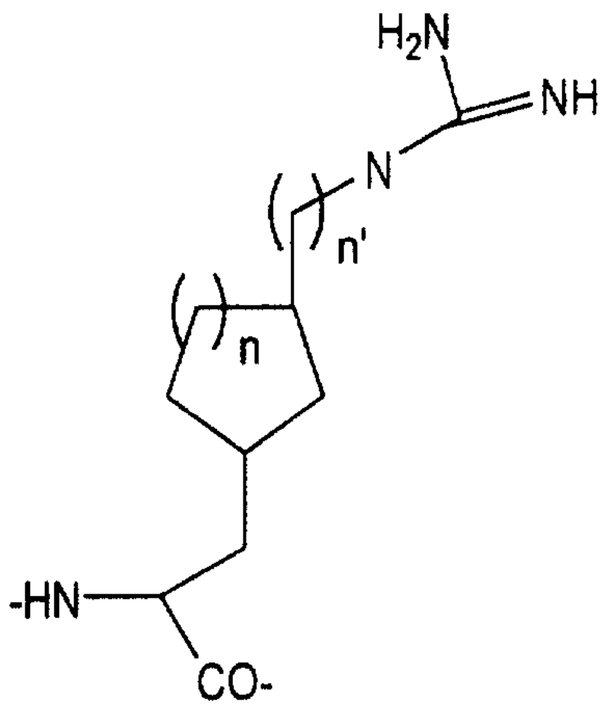
If the attachment of the reactive group is located adjacent to the N- atom containing the chelating moiety or the heteroatom (Z), the attachment can either have either L- or D- configuration.

In all the above the chelating agent is DTPA, DTPA', DOTA, N_tS_{4-t},

b. In another respect, the invention concerns the replacement of the third amino acid of the sequence, Arg, by a chemical equivalent . Such chemical equivalents include, but are not limited to the following.



n' = 0-2 (p-gPhe (n'=0), p-gmPhe (n'=1), p-gePhe (n'=2)



n = 1-3 and n' = 0-3

g-Cpa(n = 1, n' = 0), gm-Cpa (n = 1, n' = 1), ge-Cpa (n = 1, n' = 2), gp-Cpa(n = 1, n' = 3)

g-Cha(n = 2, n' = 0), gm-Cha (n = 2, n' = 1), ge-Cha (n = 2, n' = 2), gp-Cha (n = 2, n' = 3)

g-Chpa(n = 2, n' = 0), gm-Chpa (n = 2, n' = 1), ge-Chpa (n = 2, n' = 2), gp-Chpa (n = 2, n' = 3),

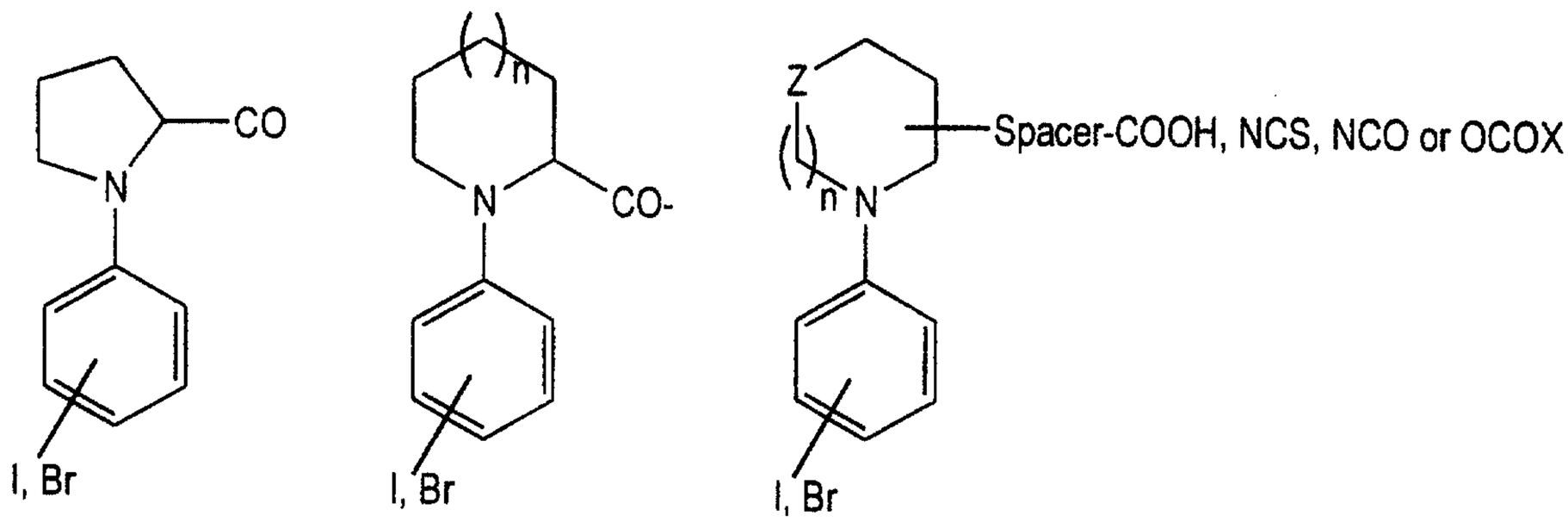
c. In another aspect of the invention, pGlu of bombesin is replaced by L- or D-His-AA_1 or L-His-b-Asp-AA_1 or D-His-Asp-AA_1 (Note: AA_1 is same as in part a, above).

L-(D-)-His-AA_1-Gln-AA_3-AA_4-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-AA_{14}-NH_2

L-(D-)-His-b-Asp-AA_1-Gln-AA_3-AA_4-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-AA_{14}-NH_2

d. In another respect the invention relates to, the attachment of radiohalogens. The following compounds can be used without the loss of binding characteristics of bombesin analogs to the receptors.

For all the above compounds, the chelating agent is replaced by o-, m- or p-Iodo(^{123}I, ^{124}I, ^{131}I for imaging) and ^{125}I, ^{129}I, ^{131}I for therapy).



DETAILED DESCRIPTION OF THE INVENTION

In this specification and claims, numerical values and ranges are not critical unless otherwise stated. that is, the numerical values and ranges may be read as if they were prefaced with the word "about" or "substantially".

The invention provides peptides which are analogs of bombesin. By "analogs of bombesin" is meant any compound that binds to a GRP receptor. A particularly preferred analog of bombesin has the formula:

pGlu-Gln-Arg-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

This compound is also known as Tyr4-bombesin.

Synthesis of the peptides may be accomplished by well known techniques. Suitable techniques generally involve successive condensations of protected amino acids. Such techniques are well known in the art.

Examples of suitable peptides include the following compounds. The compounds are shown with DTPA an an example of a chelating agent. DTPA can be replaced with DTPA', DOTA, I, Br-Bn, His, His-Asp, etc.

pGlu-Gln-Arg-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-Arg-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-Arg-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

(Pip = pipecolic acid)

DTPA-hPip-Gln-Arg-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

(Pip = homopipecolic acid)

DTPA-Pro-Gln-Arg-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Nle-NH_2

DTPA-Pip-Gln-Arg-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Nle-NH_2

(Pip = pipecolic acid)

DTPA-hPip-Gln-Arg-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Nle-NH_2

(Pip = homopipecolic acid)

DTPA-Moc-Gln-Arg-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

(Moc = morpholino 2-carboxylic acid)

DTPA-Mtc-Gln-Arg-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

(Moc = thiomorpholino 2-carboxylic acid)

DTPA-Pro-Gln-gPhe-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-gmPhe-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-gePhe-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-gPhe-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-gmPhe-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-gePhe-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-gPhe-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-gmPhe-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Mtc-Gln-gePhe-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-gCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-gmCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-geCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-gpCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-gCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-gmCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-geCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-gpCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-gChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-gmChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-geChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pro-Gln-gpChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-gCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-gmCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-geCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-gpCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-gCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-gmCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-geCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-gpCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-gChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-gmChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-geChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Pip-Gln-gpChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-gCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-gmCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-geCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-gpCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-gCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-gmCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-geCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-gpCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-gChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-gmChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-geChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-hPip-Gln-gpChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-gCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-gmCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-geCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-gpCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-gCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-gmCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-geCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-gpCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-gChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-gmChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-geChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-gpChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Mtc-Gln-gCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Mtc-Gln-gmCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Mtc-Gln-geCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Mtc-Gln-gpCpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Mtc-Gln-gCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Mtc-Gln-gmCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Mtc-Gln-geCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Mtc-Gln-gpCha-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Mtc-Gln-gChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-gmChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-geChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

DTPA-Moc-Gln-gpChpa-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

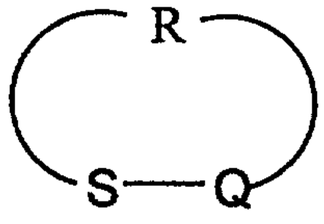
The peptides are bound to a suitable radionuclide. For diagnosis, suitable radionuclides include ^{133m}In, ^{99m}Tc, ^{67}Ga, ^{68}Ga ^{72}As, ^{111}In, ^{97}Ru, ^{203}Pb, ^{62}Cu, ^{64}Cu, ^{52}Fe, ^{52m}Mn, ^{51}Cr, ^{157}Gd, ^{123}I, ^{124}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br, and ^{82}Br with ^{99m}Tc, ^{67}Ga, ^{111}In, and ^{123}I being preferred. For therapy, suitable radionuclides include ^{186}Re, ^{188}Re, ^{77}As, ^{90}Y, ^{67}Cu, ^{169}Er, ^{121}Sn, ^{127}Te, ^{142}Pr, ^{143}Pr, ^{198}Au, ^{199}Au, ^{161}Tb, ^{109}Pd, ^{166}Dy, ^{166}Ho, ^{149}Pm, ^{151}Pm, ^{153}Sm, ^{159}Gd, ^{172}Tm, ^{169}Yb, ^{175}Yb, ^{177}Lu, ^{105}Rh, ^{111}Ag, ^{131}I, ^{129}I, and ^{177m}Sn, with ^{186}Re, ^{188}Re, ^{90}Y, ^{153}Sm, ^{177}Lu, and ^{131}I being preferred.

The radionuclide and the peptide must be bound together. If the radionuclide is a radioactive halogen, the radioactive halogen may be bound directly to the peptide, such as by chemical reaction to a Tyr or Trp moiety of the peptide.

If the radionuclide is a radioactive metal, the radioactive metal may be bound to the peptide by means of a chelating agent. A chelating group may be attached to the peptide by an amide bond or through a spacing group.

Suitable chelating groups for chelating said metal atoms are $N_tS_{(4-t)}$ tetradentate chelating agents, wherein t=2-4, or groups derived from ethylene diamine tetra-acetic acid (EDTA), diethylene triamine penta-acetic acid (DTPA), cyclohexyl 1,2-diamine tetra-acetic acid (CDTA), ethyleneglycol-0,0'-bis(2-aminoethyl)-N,N,N',N'-tetra-acetic acid (EGTA), N,N-bis(hydroxybenzyl)-ethylenediamine-N,N'-diacetic acid (HBED), triethylene tetramine hexa-acetic acid (TTHA), 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetra-acetic acid (DOTA), hydroxyethyldiamine

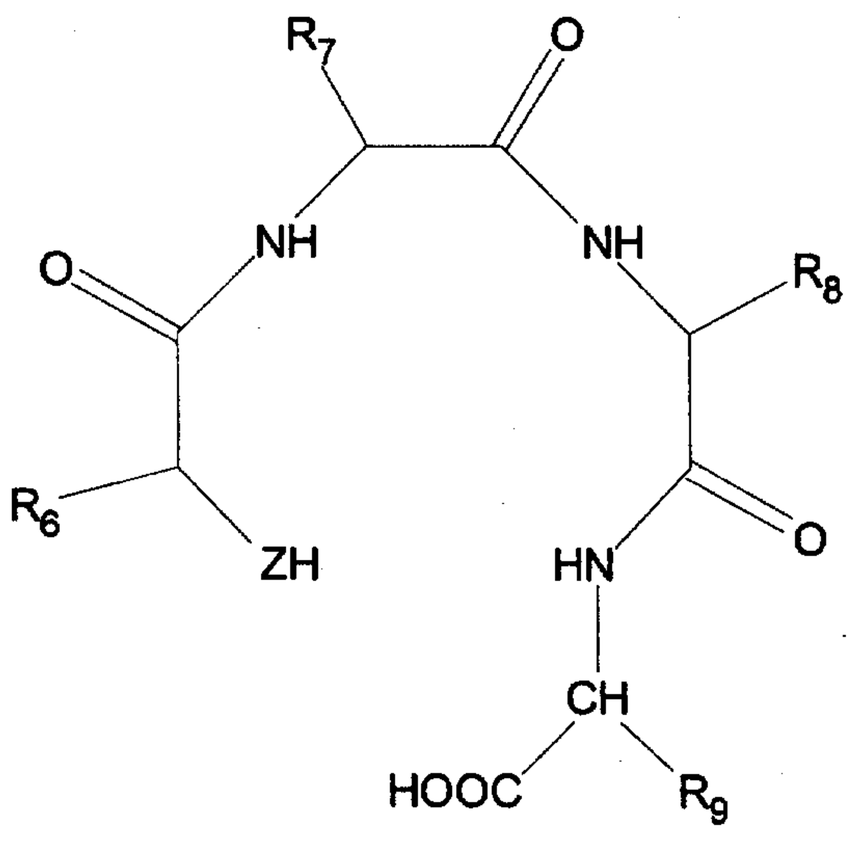
triacetic acid (HEDTA), 1,4,8,11-tetra-azacyclotetradecane-N,N',N",N"'-tetra-acetic acid (TETA), substituted DTPA, substituted EDTA, or from a compound of the general formula



(I)

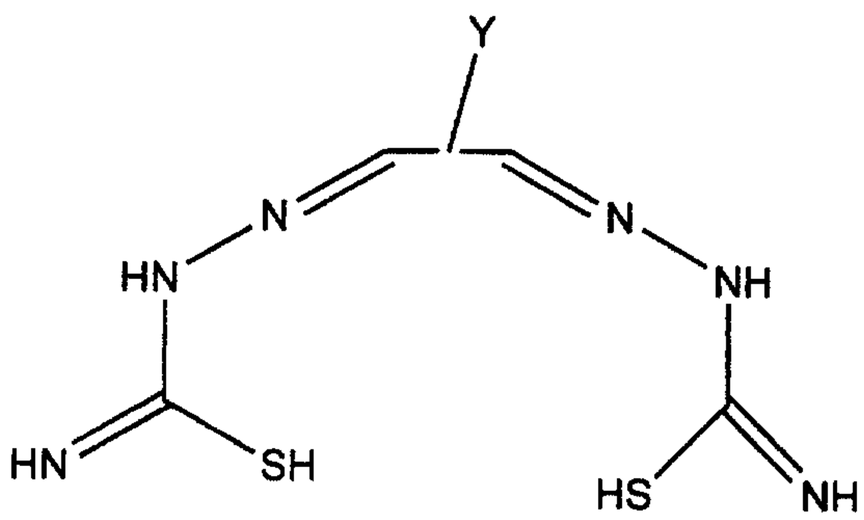
wherein R is a branched or non-branched, optionally substituted hydrocarbyl radical, which may be interrupted by one or more hetero-atoms selected from N, O and S and/or by one or more NH groups, and Q is a group which is capable of reacting with an amino group of the peptide and which is preferably selected from the group consisting of carbonyl, carbimidoyl, N-(C_1-C_6)alkylcarbimidoyl, N-hydroxycarbimidoyl and N-(C_1-C_6)alkoxycarbimidoyl.

$N_tS_{(4-t)}$ chelating agents, wherein t = 2-4, are preferably selected from



(II)

(III)



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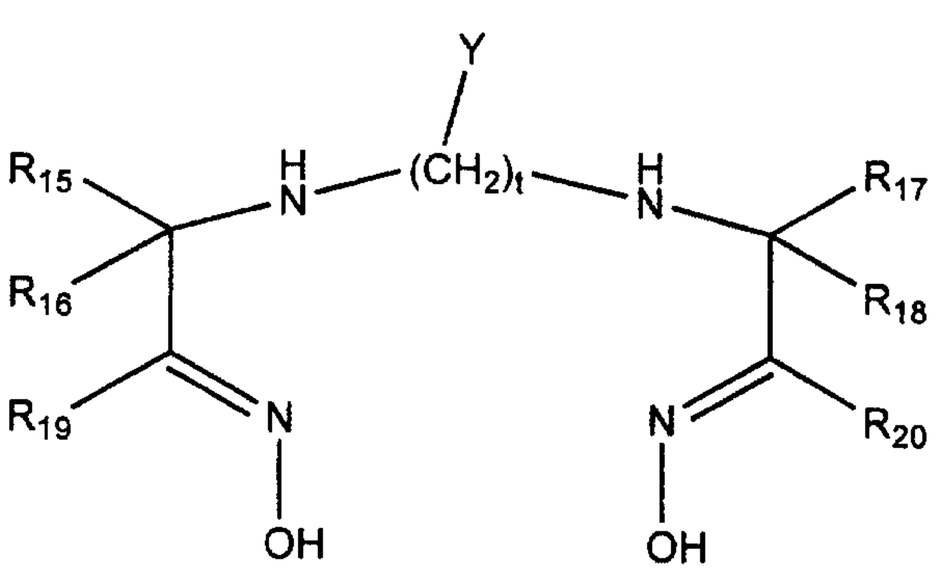
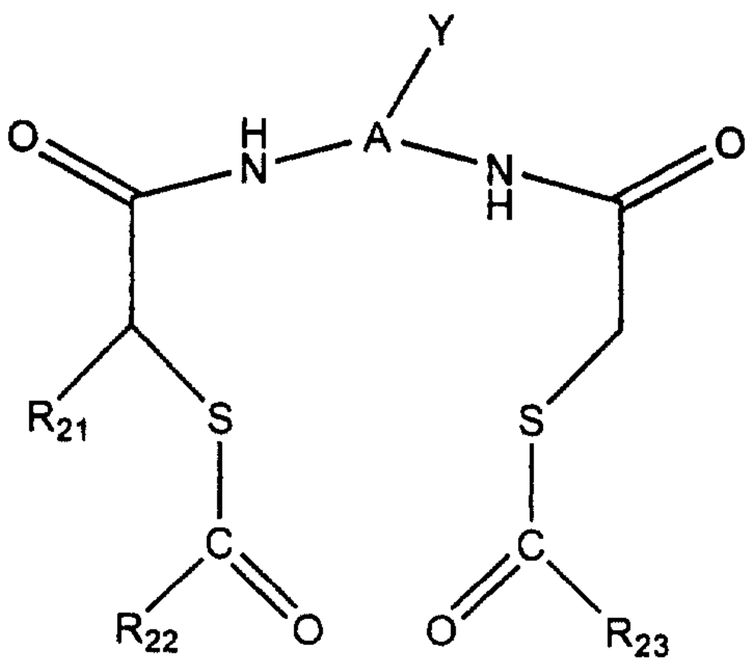
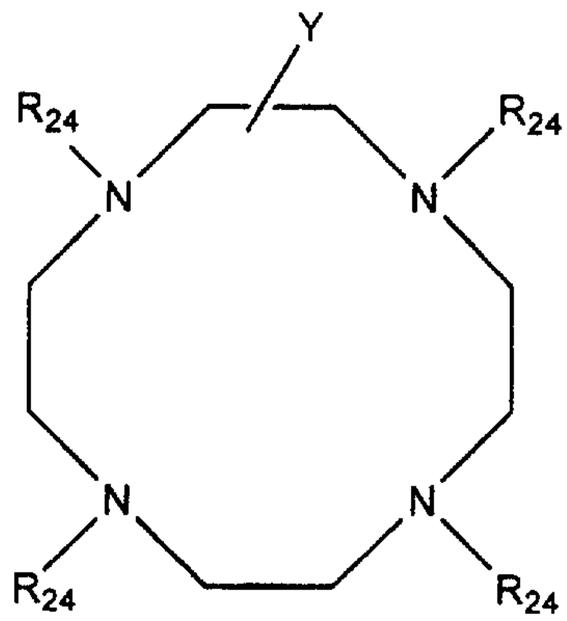


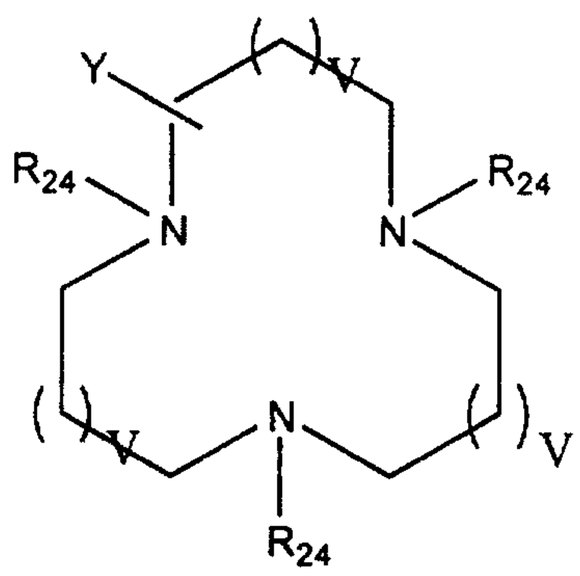
(V)



(VI)



(VII)



(VIII)

wherein:

R_6-R_{20} are each individually hydrogen atoms or (C_1-C_4)alkyl groups, with the proviso that at least one of C_6 to C_9 is the symbol Y;

R_{21} is a hydrogen atom or a CO_2(C_1-C_4)alkyl group;

R_{22} and R_{23} are each individually (C_1-C_4)alkyl groups or phenyl groups;

v is 0 or 1;

t is 2 or 3;

R_{24} is CH_2COOH or a functional derivative thereof;

A is (C_1-C_4)alkylene, if desired substituted with CO_2alkyl, $CH_2COalkyl$, $CONH_2$, $CONHCH_2CO_2alkyl$; phenylene, phenylene substituted by CO_2alkyl, wherein the alkyl groups have 1 to 4 carbon atoms;

G is NH or S;

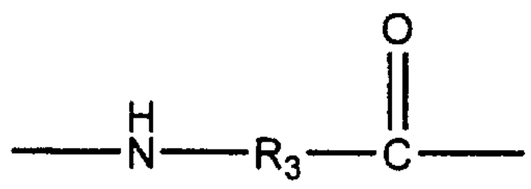
Y is a functional group capable of binding with a free amino group of the peptide or with the spacing group;

and Z is S or O.

Said functional group Y preferably comprises isocyanato, isothiocyanato, formyl, o-halonitrophenyl, diazonium, epoxy, trichloro-s-triazinyl, ethyleneimino, chlorosulfonyl, alkoxycarb-imidoyl, (substituted or unsubstituted) alkylcarbonyloxycarbonyl, alkylcarbonylimidazolyl, succinimido-oxycarbonyl; said group being attached to a (C_1-C_{10})hydrocarbon biradical. Suitable examples of hydrocarbon biradicals are biradicals derived from benzene, (C_1-C_6)alkanes, (C_2-C_6)alkenes and (C_1-C_4)-alkylbenzenes.

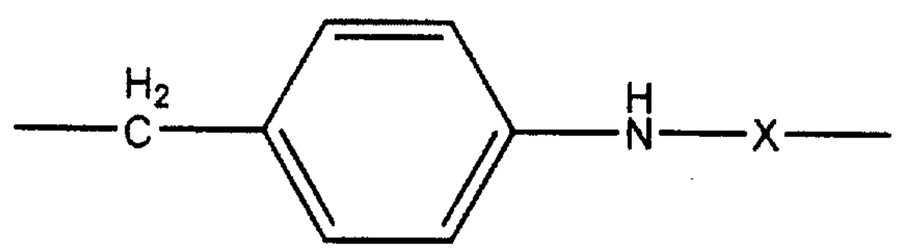
Examples of suitable chelators of the general formula II are described in the international patent application WO 89/07456, such as unsubstituted or substituted 2-imino-thiolanes and 2-imino-thiacyclohexanes, in particular 2-imino-4-mercaptomethylthiolane.

Suitable examples of spacing groups, if present in the metal-labelled peptide molecule, are groups of the general formula



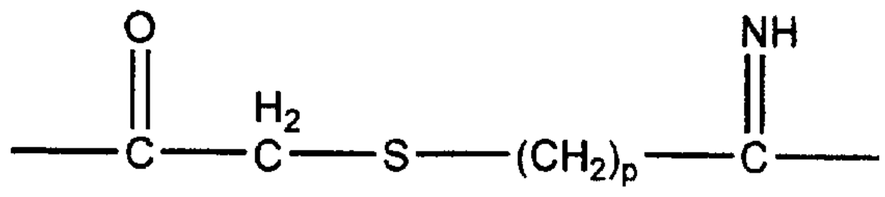
(IX)

or



(X)

wherein R_3 is a C_1-C_{10} alkylene group, a C_1-C_{10} alkylidene group or a C_2-C_{10} alkenylene group, and X is a thiocarbonyl group or a group of the general formula



(XI)

wherein p is 1-5.

Conjugates with avidin or biotin are formed as described by Paganelli et al. (Int. J. Cancer 1988, 2, 121), Kalofonos et al. (J. Nucl. Med. 1990, 31, 1791) and Anderson et al. (FEBS LETT. 1991, 282/1, 35-40).

The labeled peptides may be combined with carrier materials, such as saline, and adjuvants, such as acids or bases added to change the pH, buffers, and preservatives. The use of carriers and adjuvants is well known to those skilled in the art.

The invention may be provided to the user by providing a suitable radiolabeled peptide of the invention in a carrier, with or without adjuvants, or by providing some or all of the necessary components in a kit. The use of a kit is particularly convenient since some of the components have a limited shelf life, particularly when combined. A suitable kit may include one or more of the following components (i) a peptide, (ii) a chelating agent, (iii) a carrier solution, (iv) a radioisotope, (v) a reducing agent, and (vi) instructions for their combination. Depending on the form of the radionuclide, the reducing agent be a necessary to prepare the radionuclide for reaction with the peptide. Suitable reducing agents include Ce(III), Fe(II), Cu(I), Ti(III), Sb(III), and Sn(II). Of these, Sn(II) is particularly preferred.

For reasons of stability, it is generally preferred that the peptide be in a dry, lyophilized condition. The user can add the carrier solution to the dry peptide to reconstitute it. If it is desired to provide the peptide in solution form, it may be necessary to store it at lower temperatures than the dry form.

As mentioned above, the peptide and the chelating agent may be included separately in the kit. Alternatively, the peptide may have already been combined with the chelating agent.

Because of the short half-life of suitable radionuclides, it will frequently be most convenient to provide the kit without the radionuclide to the user, who will order the radionuclide separately when needed for a procedure. If the radionuclide is included in the kit, the kit will most likely be shipped to the user just before it is needed.

For diagnosis of tumors, the radiolabeled compounds are administered in an amount effective to allow imaging of the tumors. The quantitative amount will vary depending on the uptake of the compound by the tumor, the radioisotope chosen, and the sensitivity of the detection device (e.g.: gamma camera). Too little compound will not allow a sufficient radiation to permit diagnosis. Too much compound will cause large concentrations of the compound in the blood or non-targeted organs, and may also present unnecessary risk of toxicity to the patient. The selection of the effective amount is within the skill of one skilled in the art.

For treatment of tumors, the radiolabeled compounds are administered in a therapeutically effective amount. By "therapeutically effective amount" is meant an amount that will at least inhibit the growth or spread of the tumor, and preferably will cause the tumor to shrink or be completely eliminated. The quantitative amount will vary depending on the uptake of the compound by the tumor and the radioisotope chosen. Too little compound will not have sufficient effect. Too much compound will present unnecessary radiation exposure and risk of toxicity to the patient. The selection of the effective amount is within the skill a typical radiation oncologist.

EXAMPLE 1

The peptide

pGlu-Gln-Arg-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

([Tyr^4]bombesin) was synthesized using conventional solid phase techniques. It was labeled with ^{125}I by the chloramine T iodination procedure, according to Greenwood, et al., Biochemical Journal 1963, 89, 114-123. The resulting compound

pGlu-Gln-Arg-Tyr*-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

([^{125}I-Tyr^4]bombesin, the "radioligand") was purified by HPLC, and had a specific activity of 1,000 Ci/mmol.

EXAMPLE 2

Various tumor tissue samples, including surrounding tissue, were harvested from human patients and/or human cadavers, and frozen. The samples were cut on a cryostat, mounted on microscope slides, and then stored at -20°C for at least 3 days to at least 3 days to improve adhesion of the tissue to the slide. The slide-mounted tissue sections were allowed to reach room temperature and preincubated in 50 mmol/l Tris-HCl, 130 mmol/l NaCl, 4.7 mmol/l KCl, 5 mmol/l $MgCl_2$, 1 mmol/l ethylene glycol-bi(b-aminoethylether)-N,N,N',N'-tetraacetic acid, and 0.5% bovine serum albumin, pH 7.4 (preincubation solution), for 30 min. at 25°C. The slides are then incubated in a solution containing the same medium as the preincubation solution except the bovine serum albumin is omitted, and the following compounds are added: 20000 dpm/100 ml of the radioligand of Example 1, 0.025% bacitracin, 1 mmol/l dithiothreitol, 2mg/ml chymostatin, and 4mg/ml leupeptin, pH = 6.5. The slides are incubated at room temperature with the radioligand for 150 min., as described by Mantyh et al. (Gasteroenterology 1994, 107, 1019-30). After the incubation, the slides are rinsed with four washes of 30 sec each in ice-cold preincubation solution, pH 7.4, dipped in ice-cold water, and then quickly dried in a refrigerator under a stream of cold air. The sections are subsequently exposed to a ^{3}H-Ultrofilm for 1 week, to detect the precise location of the radioactivity.

The films were evaluated to determine the ability to distinguish the tumor from the surrounding tissue. The results are shown in Table 1.

TABLE 1

Tissue	Number of Samples	Number Positive	% Positive
Colon Cancer	18	1	6
Gastric Cancer	27	0	0
Pancreatic Cancer	28	0	0
Non Small Cell Lung Carcinoma	34	0	0
Small Cell Lung Carcinoma	10	2	20
Gastrinomas	4	4	100
Melanomas	8	1	12
Glioblastomas	9	6	67
Prostate Cancer	28	28	100
Prostate Cancer Metastases	5	5	100
Breast Cancer	95	66	69
Breast Cancer Metastases	5	5	100
Uterus Leiomyosarcoma Tumor	3	1	33

In Table 1, a tumor is considered "positive" if (1) a traditional histilogical examination of the tissue verifies that the tumor is present, (2) the film shows a clear image of the tumor, distinguishing it from the surrounding tissue, and (3) the film does not show an image of the tumor, if the tissue is first blocked with a non-radiolabeled sample of the peptide.

The data show that (1) gastrinomas, glioblastomas, prostate cancer, prostate cancer metastases, breast cancer, and breast cancer metastases show a high incidence of bombesin receptors (in the case of gastrinomas, prostate cancer, prostate cancer metastases, and breast cancer metastases, 100%); and (2) a number of human tumors that were claimed by the literature to be bombesin receptor positive show no or very little positive results.

The negative data in Table 1 is important in understanding the instant invention. It has been widely reported (see, for example, Moody et al., Peptides, 683-686 (1993)), that small cell lung cancer has bombesin receptors. However, the data in

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Table 1 shows that only 20% of such tumors could be detected. Because of the highly specific nature of the method used to produce the data in Table 1, the data suggests that the techniques used in the prior art had fundamental defects.

EXAMPLE 3

The peptide

DTPA-Pro-Gln-Arg-Tyr-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH_2

[$DTPA^0$-Pro^1,Tyr^4]bombesin) was synthesized using conventional solid phase techniques. DTPA was introduced during the solid phase synthesis using tri-t-butyl DTPA. ^{111}In labeling was performed according to the procedure described by W.H. Bakker, et al., Life Sciences, Vol 49, 1583 (1991), yielding [^{111}In-$DTPA^0$-Pro^1,Tyr^4]bombesin having a specific activity of 100 MBq/μg.

EXAMPLE 4

Gastrin releasing peptide receptor has high affinity for the 14 amino acid peptide bombesin. A bombesin analog, [^{111}In-$DTPA^0$,Pro^1,Tyr^4]bombesin, showed intact high affinity to the bombesin receptor, and agonistic activities on bombesin-stimulated prolactin secretion on 7315b cells with an IC50 of 8 nM. After labeling with IN-111 up to a level of 100 Mbq per μg, the radioligand was radiochemically stable (>95%) for 2 h, as revealed by HPLC. In rats high and specific uptake was found in pancreas and tissues of the GI tract. Uptake of radioactivity could be blocked by iv coinjection of 100 μg Tyr^4bombesin with the radioligand, but not when administered 1 h after the radioligand, indicating its internalisation. A bell-shaped function between injected mass and % ID per g bombesin receptor positive tissues was found at ≈ 0.025-0.1 μg. Dynamic gamma camera showed rapid clearance of radioactivity from the blood compartment, renal uptake and urinary excretion: ≈ 35% in 1 h, 70% in 20 h with a total body retention of 10%. Specific uptake in the bombesin receptor positive prolactinoma 7315b inoculated on female Lewis rats was found and could also be visualized by scintigraphy. The residence

time of radioactivity was in accordance with similar DTPA conjugated peptides. Thus, the radioligand [^{111}In-DTPA^{0},Pro^{1},Tyr^{4}]bombesin is suitable for scintigraphy of bombesin receptors in vivo.

TABLE 2

Tissue RA in % ID/g at 48 h after injection of 0.01-0.05 μg of [^{111}In-DTPA^{0},Pro^{1},Tyr^{4}]bombesin labeled with 2 MBq In-111 in rats (n≥3) and ratio vs. blood( )

μg	Pancreas	Colon	Stomach	Adrenal	Blood
0.01	1.0(1210)	0.072(85)	0.035(40)	0.029(34)	0.0009
0.025	1.2(1217)	0.063(64)	0.065(64)	0.030(30)	0.0010
0.1	0.72(856)	0.061(73)	0.042(50)	0.022(26)	0.0009
0.5	0.43(574)	0.039(52)	0.036(50)	0.014(18)	0.0008

What is claimed is:

1. A peptide that binds to GRP receptors.

2. A peptidomimetic that binds to GRP receptors.

3. A radiolabeled peptide of claim 1.

4. A radiolabeled peptidomimetic of claim 2.

5. A kit for the diagnosis of breast or prostate tumors or metastases of such tumors in a human comprising

(a) a peptide or a peptidomimetic that binds to GRP receptors;

(b) a radioisotope; and

(c) adjuvants suitable for binding the radioisotope to the peptide or peptidomimetic and administering the resultant combination to a human.

6. A composition for the diagnosis of breast or prostate tumors or metastases of such tumors in a human comprising

(a) a radiolabeled peptide or peptidomimetic that binds to GRP receptors; and

(b) adjuvants suitable administering the radiolabeled peptide or peptidomimetic to a human.

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7. A kit for the treatment of breast or prostate tumors or metastases of such tumors in a human comprising

(a) a peptide or peptidomimetic that binds to GRP receptors;

(b) a radioisotope; and

(c) adjuvants suitable for binding the radioisotope to the peptide or peptidomimetic and administering the resultant combination to a human.

8. A composition for the treatment of breast or prostate tumors or metastases of such tumors in a human comprising

(a) a radiolabeled peptide or peptidomimetic that binds to GRP receptors; and

(b) adjuvants suitable for administering the radiolabeled peptide or peptidomimetic to a human.

9. A method of diagnosing breast or prostate tumors or metastases of such tumors in a human patient comprising

(a) administering to the patient a composition including a diagnostic amount of a radiolabeled peptide or peptidomimetic that binds to GRP receptors; and

(b) externally imaging at least a portion of the patient to determine the location of localized radiation from the radiolabeled peptide.

10. A method of selecting a human patient for radiotherapy of a known breast or prostate tumor or metastases of such a tumor comprising

(a) administering to the patient a composition including a diagnostic amount of a radiolabeled peptide or peptidomimetic that binds to GRP receptors; and

(b) externally imaging the portion of the patient having the tumor, to determine if the radiolabeled peptide is localized in the tumor.

11. A method of treating a breast or prostate tumor or metastases of such a tumor in a human patient comprising administering to the patient a composition including a therapeutic amount of a radiolabeled peptide or peptidomimetic that binds to GRP receptors.