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(57) Abrégé/Abstract:
Cyclic or linear somatostatin peptides bearing a specific chelating group on the terminal amino group, in free or salt form, are complexed with a β-, γ- or positron-emitting element and are useful as radiopharmaceuticals.

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POLYPEPTIDES

Abstract of the Invention

Cyclic or linear somatostatin peptides bearing a specific chelating group on the terminal amino group, in free or salt form, are complexed with a β-, γ- or positron-emitting element and are useful as radiopharmaceuticals.

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CASE 100-7774

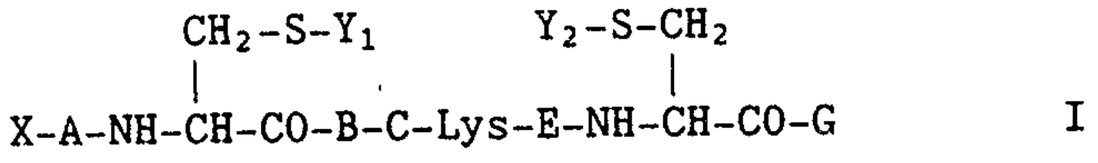
POLYPEPTIDES

The present invention relates to polypeptides, process for their production, pharmaceutical preparations containing them and their use as a pharmaceutical, e.g. for treatment of somatostatin receptor positive tumors or as in vivo imaging agents.

GB-A-2,225,579 discloses somatostatin peptides bearing at least one chelating group which can be labelled for in vivo diagnostic and therapeutic applications. These compounds are capable of binding to somatostatin receptors, e.g. expressed or overexpressed by tumors or metastases.

The present invention provides new somatostatin peptide ligands bearing at least one chelating group which are suitable for e.g. γ- or β-radionuclide or positron labelling and have interesting binding affinity properties to target somatostatin receptors present on tumors. The chelating group may be attached either directly or indirectly through a spacer or bridging group to the somatostatin peptide.

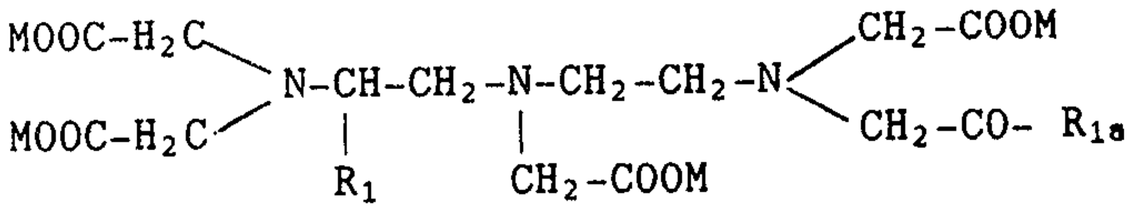
According to the invention there is provided a compound of formula I



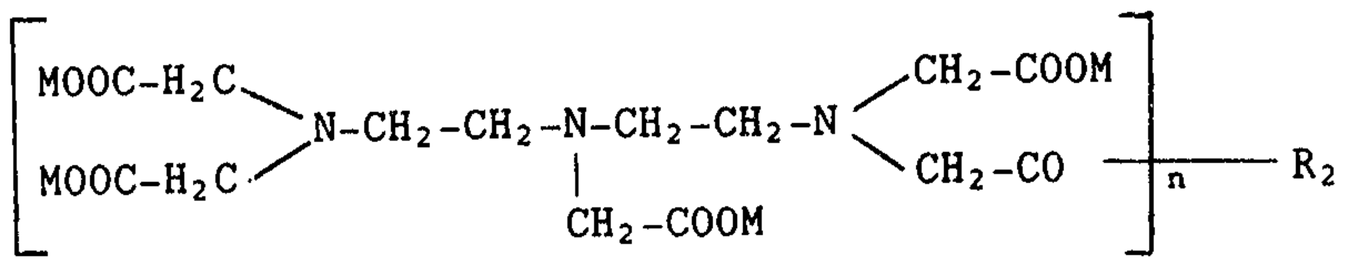
I

wherein

X is a radical of formulae (a) to (e):



(a)



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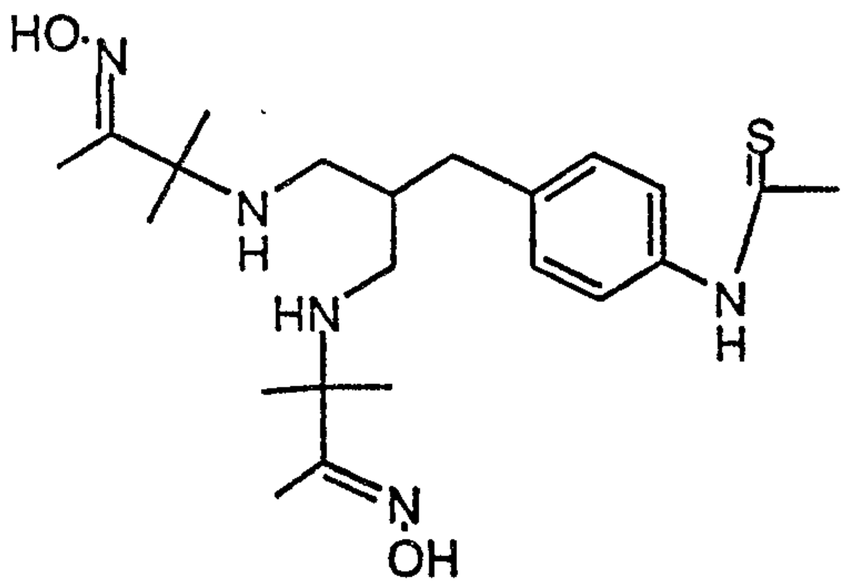
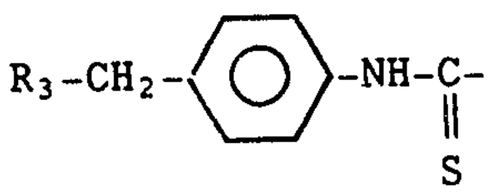
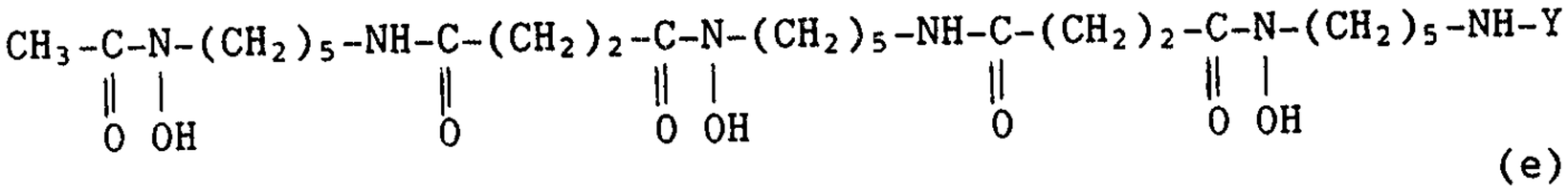


(c)

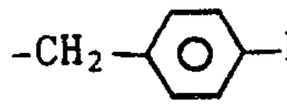


(d)



(e)

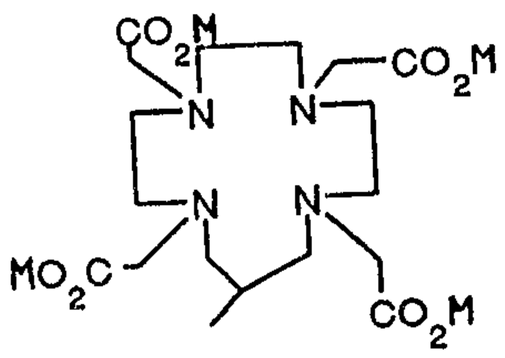
M is hydrogen or the equivalent of a pharmaceutically acceptable cation

either R_1 is hydrogen and R_{1a} is a free bond or R_1 is  and R_{1a} is OM

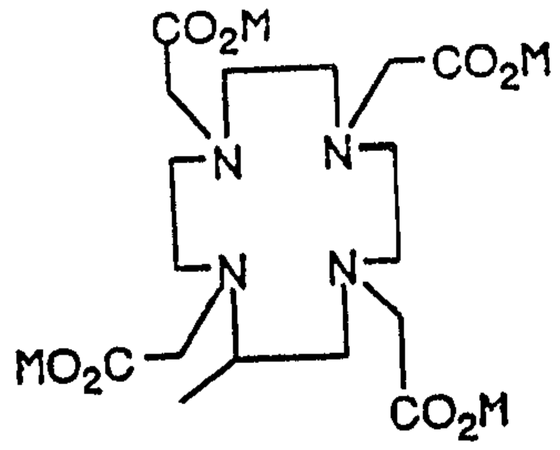
either n is 1 and R_2 is (N^{α})-Lys or (N^{ε})-Lys or

n is 2 and R_2 is (N^{α},N^{ε})-Lys

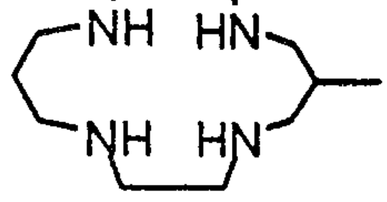
R_3 is a radical of formula (f), (g) or (h)



(f)



(g)



(h)

Y is a divalent spacer group capable of binding the terminal amino group of deferoxamine with the terminal amino group of the peptide,

A is (D)Phe, (D)Trp, or (D)-β-Nal

B is Phe optionally ring substituted by halogen or hydroxy, β-Nal or Thr

C is (D)Trp or Trp

E is Thr, Ser or Val

G is -NH-CH(R_4)-X_1 wherein R_4 is the radical attached to the α-carbon atom of Thr, β-Nal or Trp and X_1 is $-CH_2OR_5$ or

$-CONH_2$ wherein R_5 is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester, and

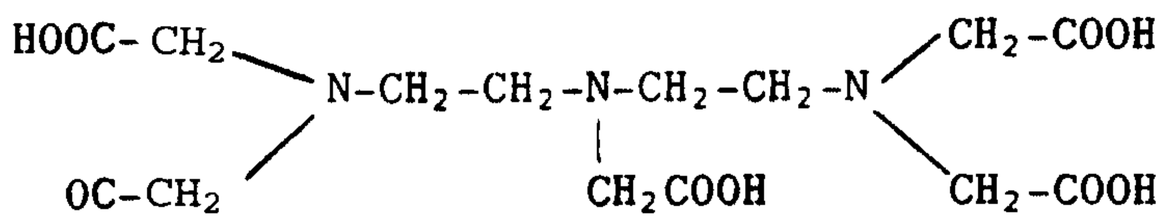
Y_1 and Y_2 represent together a direct bond or each is hydrogen,

the residues B and E having the L-configuration, the residues in the 2- and 7-positions having the L- or D-configuration, and B being Tyr when X is a chelating group of formula (a) wherein R_1 is hydrogen.

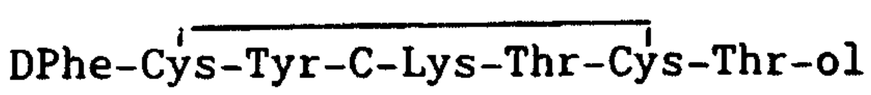
Preferably R_1 is $-CH_2-C_6H_4-NH-CS-$. Y is preferably a radical derived from a dicarboxylic acid, e.g. succinyl. R_5 is preferably hydrogen.

The compounds of formula I may exist e.g. in free or salt form. Salts include acid addition salts with e.g. organic acids, polymeric acids or inorganic acids, for example hydrochlorides and acetates, and salt forms obtainable with the carboxylic groups present in the group X, e.g. those wherein M is an alkali metal cation such as sodium or potassium, or substituted or unsubstituted ammonium.

In a particularly preferred embodiment of the invention there is provided a compound of formula I



I



wherein

C is (D) Trp or Trp in free form or in salt or complex form.

The present invention also includes a process for the production of the compounds of formula I. They may be produced by analogy to known methods.

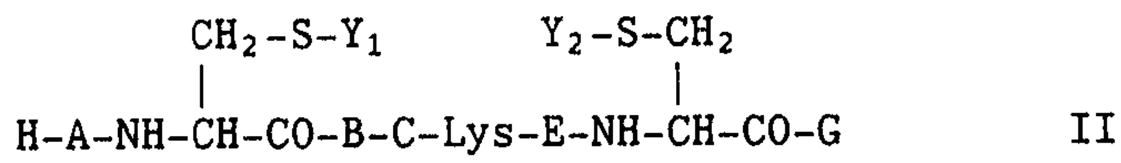
The compounds of formula I may be produced for example as follows:

a) removing at least one protecting group which is present in a protected compound having the sequence indicated in formula I, or

b) linking together by an amide bond two peptide fragments each of them containing at least one amino acid or amino alcohol

in protected or unprotected form and one of them containing the group X, wherein the amide bond is in such a way that the amino acid sequence indicated in formula I is obtained, and stage a) of the process is then optionally effected, or

c) linking together a chelating agent and a compound of formula II



II

in protected or unprotected form, and stage a) is then optionally effected or,

d) removing a functional group of an unprotected or a protected compound of formula I or converting it into another functional group so that another unprotected or protected compound of formula I is obtained and in the latter case stage a) of the process is effected, or

and recovering the compounds of formula I thus obtained in free form or in salt form.

The above reactions may be effected in analogy with known methods, e.g. as described in the following examples, in particular processes a) and c). Where desired, in these reactions, protecting groups which are suitable for use in peptides or for the desired chelating groups may be used for functional groups which do not participate in the reaction. The term protecting group may also include a polymer resin having functional groups.

The peptide fragment bearing the chelating group and used in stage b) may be prepared by reacting the peptide fragment comprising at least one amino acid or amino alcohol in protected or unpro-

tected form with the chelating agent. The reaction may be performed in analogy with stage c).

The chelating agent used in process step c) may be known or prepared in analogy with known procedures. The compound used is such that it allows the introduction of the desired chelating group on the somatostatin peptide, e.g. it may also be used in form of an anhydride or in salt form. 1-p-isothiocyanatobenzyl-diethylene triamine pentaacetic acid, 2-(p-isothiocyanatobenzyl)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, 6-(p-isothiocyanatobenzyl)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione-dioxime, 12-(p-isothiocyanatobenzyl)-1,4,7,10-tetraazacyclotridecane-1,4,7,10-tetraacetic acid, 13-(p-isothiocyanatobenzyl-1,4,8,-11-tetraazacyclotetradecane may be prepared according to known methods, e.g. as disclosed by M. W. Brechbiel and al. in Inorg. Chem., 25, 2772-2781 (1986) or Min K. Moi and C.F. Meares in J. Am. Chem. Soc., 110, 6266-6267 (1988). Deferoxamine (or Desferal) is a known compound (cf. The Merck Index, Tenth Edition, 2839, 1983).

For the production of the compounds of formula I wherein X is a group of formula (b) or (e), either diethylene triamine pentaacetic acid (DTPA) or Deferoxamine may be reacted at first with Lys or a Y yielding compound, e.g. a dicarboxylic acid, and then with a compound of formula II, or alternatively DTPA or deferoxamine may be reacted with a compound of formula II modified with Lys or a spacer group Y on the terminal amino group.

The compounds of formula I may be purified in conventional manner, e.g. by chromatography.

The compounds of formula I in free form or in salt form are ligands. The chelating group X is capable to form a complex with a radionuclide and the corresponding labelled ligands are further capable of binding to somatostatin receptors, e.g. expressed or overexpressed by tumors or metastases.

Accordingly, the present invention also provides the compounds of formula I which are complexed with a positron, β- or γ-emitting radionuclide, in free form or in salt form, their preparation and their use for in vivo diagnostic and therapeutic treatment.

Suitable γ-emitting radionuclides include those which are useful in diagnostic techniques. The γ-emitting radionuclides advantageously have a half-life of from 1 hour to 40 days, preferably from 5 hours to 4 days, more preferably from 12 hours to 3 days. Examples are radionuclides derived from Gallium, Indium, Technetium, Yttrium, Ytterbium, Rhenium and Thallium e.g. ^{67}Ga, ^{111}In, ^{99m}Tc, ^{90}Y, ^{169}Yb and ^{186}Re. Preferably the γ-radionuclide is selected depending on the metabolism of the compound of formula I used. More preferably the compound of formula I is chelated with a γ-radionuclide having a longer half-life than the half-life of the non modified somatostatin peptide on the tumor.
Suitable positron-emitting radionuclides are e.g. ^{68}Ga.
Suitable β-emitting radionuclides include those which are useful in therapeutic applications, e.g. as mentioned in GB-A-2,225,579 for example those derived from Y and Re. The β-radionuclide advantageously have a half-life of from 2.3 hrs to 14.3 d, preferably from 2.3 to 100 hrs. Preferably the β-emitting radionuclide is selected in order to have a longer half-life than the half-life of the non modified somatostatin peptide on the tumor.

Preferred are ^{111}In, ^{90}Y, ^{99m}Tc and ^{68}Ga.

The chelated compounds of formula I may be prepared e.g. as disclosed in GB-A-2,225,579 e.g. by reacting the compound of formula I with a corresponding radionuclide yielding compound, e.g. a metal salt, preferably a water-soluble salt.

Preferably the complexing of the compound of formula I is effected at a pH at which the compound of formula I is physiologically stable.

Radionuclides such as for example Technetium-99m may be used in oxidized form, e.g. Tc-99m pertechnetate, which may be complexed under reducing conditions.

The chelated compounds of formula I and their pharmaceutical acceptable salts exhibit pharmaceutical activity and are therefore useful either as an imaging agent, e.g. visualisation of an accumulation of somatostatin receptors, e.g. as in somatostatin receptor positive tumors and metastases, when complexed with a γ-emitting or positron-emitting radionuclide, or as a radiopharmaceutical for the treatment in vivo of tumours, particularly somatostatin receptor positive tumors and metastases when complexed with a β-radionuclide, as indicated by standard tests.

The affinity of the chelated compounds of formula I for somatostatin receptors expressed or overexpressed by tumors and metastases, has been determined in standard in vitro binding assays, e.g. as disclosed in GB-A-2,225,579. It is observed that e.g. the compound of Example 4 binds with high affinity to the somatostatin receptors (IC_{50} = 3 nM).

The affinity of the chelated compounds of formula I for somatostatin receptors can also be shown by in vivo testing, according to standard test methods, e.g. as disclosed in GB-A-2,225,579.

After administration of a compound of formula I chelated with a γ-radionuclide, at a dosage of from 1 to 5 µg/kg of compound of formula I labeled with 0.1 to 2 mCi radionuclide the tumor site becomes detectable together with the organs where excretion essentially takes place.

Accordingly, in a series of specific or alternative embodiments, the present invention also provides:

1. A method for <u>in vivo</u> detection of tumors, particularly soma-

tostatin receptor positive tumors or metastases in a subject which comprises a) administering a compound of formula I chelated with a γ- or positron-emitting radionuclide to said subject and b) recording the localisation of the tumors targeted by said chelated compound.

The chelated compounds of formula I for use as an imaging agent may be administered parenterally, preferably intravenously, e.g. in the form of injectable solutions or suspensions, preferably in a single injection. The appropriate dosage will of course vary depending upon, for example, the compound of formula I and the radionuclide used. A suitable dose to be injected is in the range to enable imaging by photoscanning procedures known in the art. A chelated compound of formula I may advantageously be administered in a dose having a radioactivity of from 0.1 to 50 mCi, preferably 0.1 to 30 mCi, more preferably 0.1 to 20 mCi. An indicated dosage range may be of from 1 to 200 µg compound of formula I labeled e.g. with 0.1 to 20 mCi, preferably 3 to 15 mCi γ-emitting radionuclide, depending on the γ-emitting radionuclide used. For example with In, it is preferred to use a radioactivity in the lower range, whereas with Tc, it is preferred to use a radioactivity in the upper range.

The enrichment in the tumorigenic sites with the chelated compounds of formula I may be followed by the corresponding imaging techniques, e.g. using nuclear medicine imaging instrumentation, for example a scanner, γ-camera , rotating γ-camera, each preferably computer assisted; PET-scanner (Positron emission tomography); MRI equipment or CAT scanning equipment.

2. A method for <u>in vivo</u> treatment of tumors, e.g. somatostatin receptor positive tumors and metastases in a subject in need of such a treatment which comprises administering to said

subject a therapeutically effective amount of a compound of formula I chelated with a β-emitting radionuclide.

Dosages employed in practising the therapeutic method of the present invention will of course vary depending e.g. on the particular condition to be treated, for exemple the volume of the tumor, the particular chelated compound employed, for exemple the half-life of the chelated compound of formula I in the tumor, and the therapy desired. In general, the dose is calculated on the basis of radioactivity distribution to each organ and on observed target uptake. For example the β-chelated compound of formula I may be administered at a daily dosage range having a radioactivity of from 0.1 to 3mCi/kg body weight, e.g. 1 to 3 mCi, preferably 1 to 1.5 mCi/kg body weight. An indicated dosage range is of from 1 to 200 µg compound of formula I labeled with e.g. 0.1 to 3 mCi/kg body weight, preferably 0.1 to 1.5 mCi/kg body weight β-emitting radionuclide.

The β-emitting chelated compounds of formula I may be administered by any conventional route, in particular parenterally, e.g. in the form of injectable solutions or suspensions. They may also be administered advantageously by infusion, e.g. an infusion of 30 to 60 min. Depending on the site of the tumor, they may be administered as close as possible to the tumor site, e.g. by means of a catheter. The mode of administration selected may depend on the dissociation rate of the chelated compound used and the excretion rate.

The chelated compounds of formula I may be administered in free form or in pharmaceutically acceptable form. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

The chelated compounds of formula I for use in the method of the

present invention may preferably be prepared shortly before the administration to a subject, i.e. the radiolabeling with the desired β-, γ- or positron-emitting radionuclide, may be performed shortly before the administration.
The chelated compounds of formula I may be suitable for imaging or treating tumors such as pituitary, gastroenteropancreatic, central nervous system, breast, prostatic, ovarian or colonic tumors, small cell lung cancer, kidney cancer, paragangliomas, neuroblastomas, pheochromocytomas, lymphomas, medullary thyroid carcinomas, myelomas, Hodgkin' and non-Hodgkin's disease, bone tumors etc. and metastases thereof.

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula I optionally chelated with a β-, γ- or positron-emitting radionuclide, in free or in pharmaceutically acceptable salt form, together with one or more pharmaceutically acceptable carriers or diluents therefor.

Such compositions may be manufactured in conventional manner.

A composition according to the invention may also be presented in separate package with instructions for mixing the compound of formula I with the radionuclide and for the administration of the resulting labeled compound. It may also be presented in twin-pack form, that is, as a single package containing separate unit dosages of the compound of formula I and the radionuclide with instructions for mixing them and for administration of the chelate. A diluent or carrier may be present in the unit dosage forms.

In the following examples, all temperatures are in ° C and $[\alpha]_D^{20}$-values uncorrected. The following abbreviations are employed:

Boc tert.-butoxycarbonyl
TFA trifluoroacetic acid

AcOH acetic acid

DMF dimethyl formamide

Fmoc 9-fluorenylmethoxycarbonyl

DOTA 1,4,7,10-tetra-azacyclododecane-1,4,7,10-tetraacetic acid

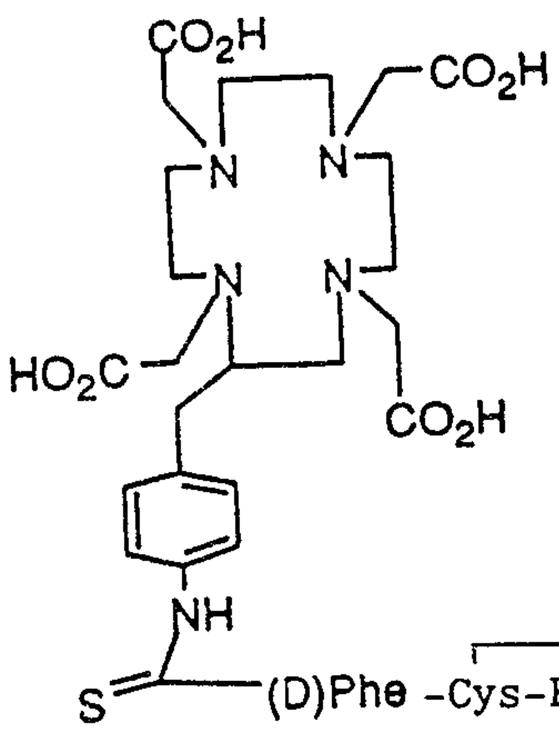
DTPA diethylene triamine pentaacetic acid

HMPAO 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione-dioxime

TITRA 1,4,7,10-tetraazacyclotridecane-1,4,7,10-tetraacetic acid

TETRA 1,4,8,11-tetraazacyclotetradecane

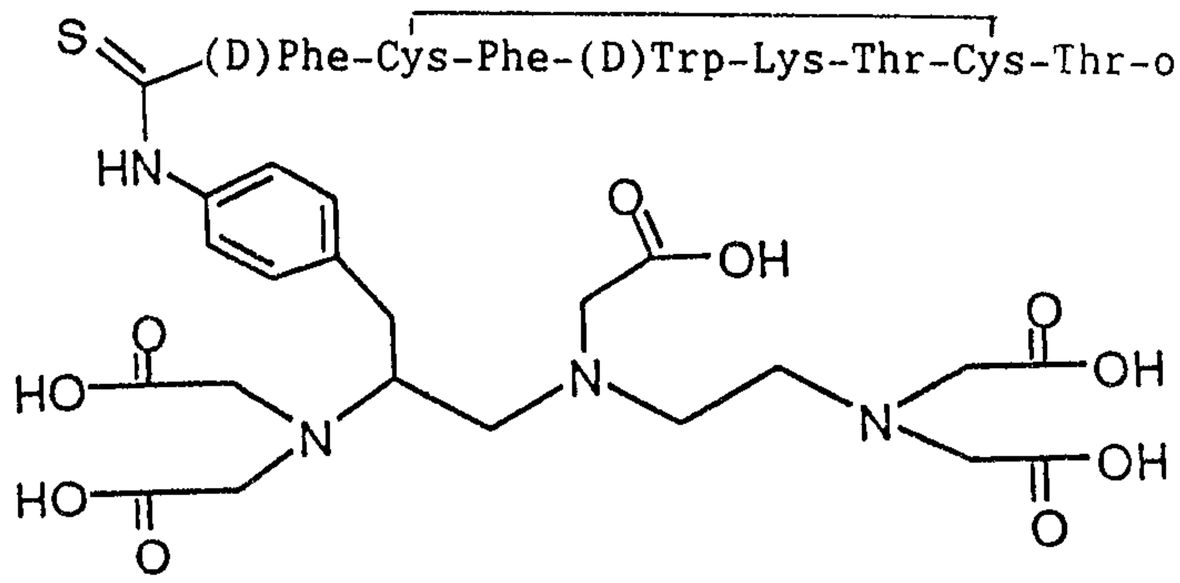
EXAMPLE 1:



To a solution of 220 mg H-DPhe-Cys-Phe-DTrp-Lys(ε-Fmoc)-Thr-Cys-Thr-ol in 20 ml acetonitrile/water (3/1 v/v) and 0.14 ml triethylamine there is added 110 mg 2-(p-isothiocyanatobenzyl)-DOTA. After a reaction time of 9 hours at room temperature the solution is diluted with water and freeze dried. The residue is purified by silica gel chromatography and then treated for 10 minutes with 10 ml piperidine/DMF (1/4 v/v). After removal of the solvent and the base, the raw compound is purified by chromatography on silica gel and desalted by RP-HPLC chromatography using a water/acetonitrile/acetic acid buffer system. The resulting title compound is lyophilized.

FAB-MS: 1570.9

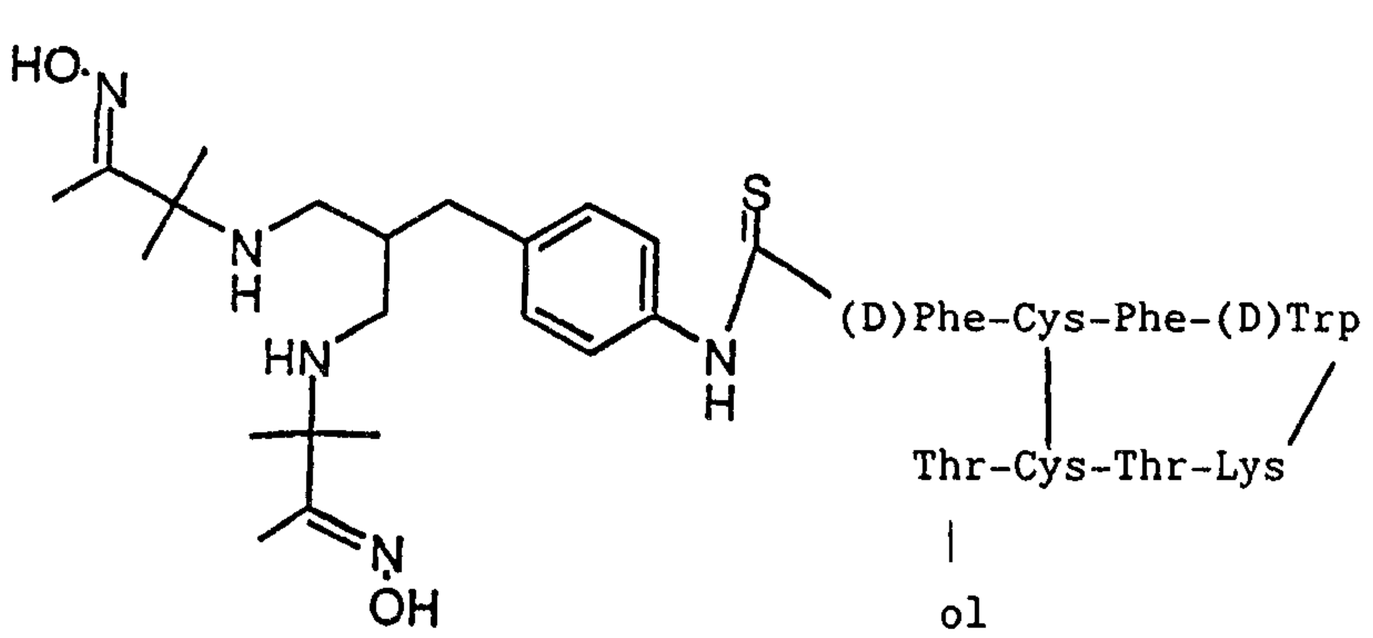
EXAMPLE 2:



By repeating the procedure of Example 1 but using 1-(p-isothiocyanatobenzyl)-DTPA instead of 2-(p-isothiocyanatobenzyl)-DOTA, the title compound is obtained.

FAB-MS: 1573.8 $[\alpha]_D^{20}$ =-10.0° (c = 0.12 in 95% AcOH)

EXAMPLE 3:



By repeating the procedure of Example 1 but using 6-(p-isothiocyanatobenzyl)-HMPAO instead of 2-(p-isothiocyanatobenzyl)-DOTA, the title compound is obtained.

FAB-MS: 1458.8

This compound is particularly suitable for ^{99m}Tc labelling.

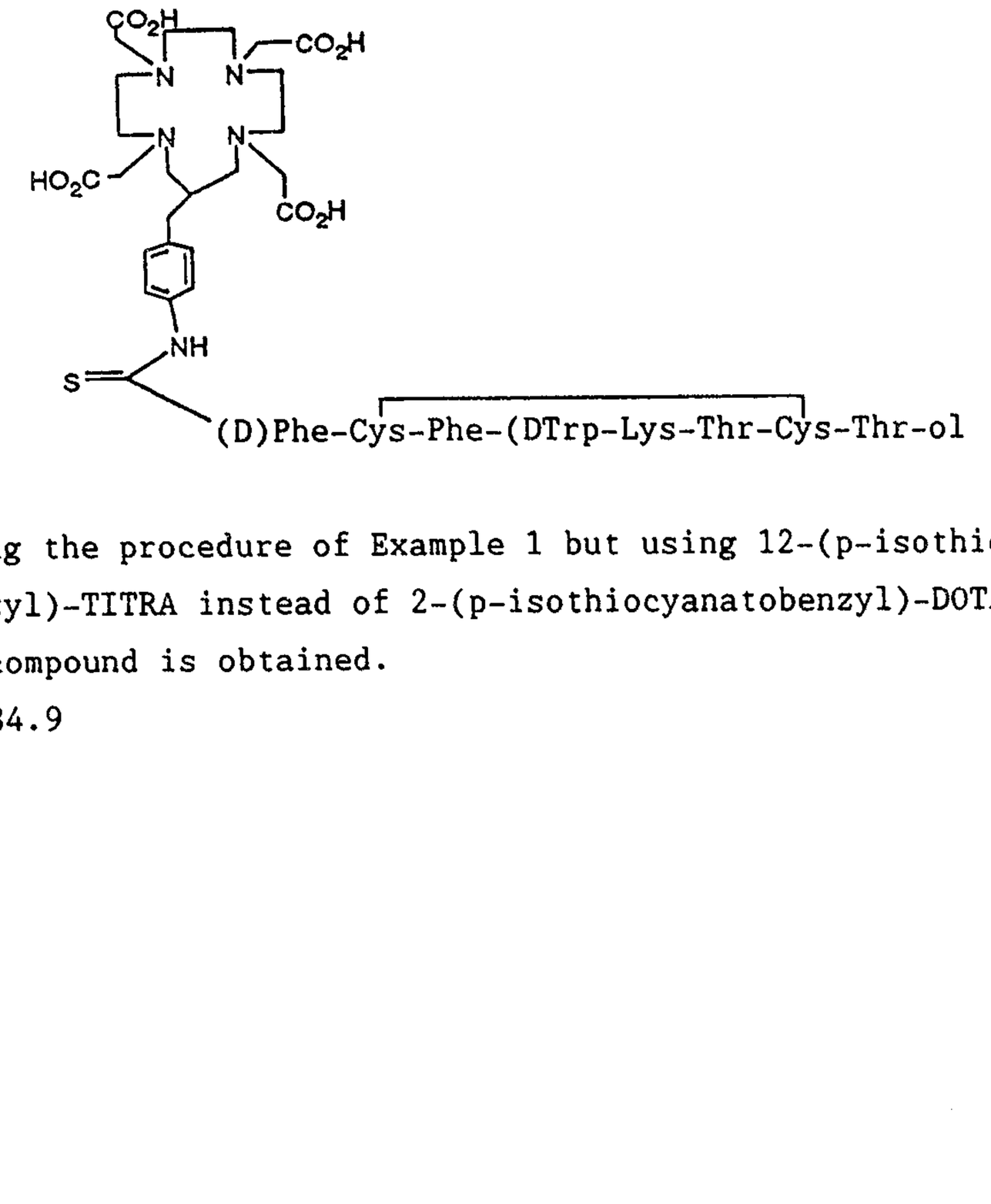
6-(p-isothiocyanatobenzyl)-HMPAO used as chelating agent may be prepared from 6-(p-nitrobenzyl)-HMPAO which is reduced to 6-(p-aminobenzyl)-HMPAO as follows:

15 ml methanol and 15 ml water are mixed and adjusted to pH 11 with 0.1 N NaOH. 25 mg catalyst based on Pd/alox are added and after clearing of with hydrogen, prehydrogenation is performed. After 15 min. when a constant hydrogen level is reached, a solution of 0.25 g 6-(p-nitrobenzyl)-HMPAO in 15 ml 1:1 methanol/-water is added and the mixture is stirred overnight. The resulting mixture is then filtered on Hyflo Super Cel, concentrated and dried under vacuo.

The resulting 6-(p-aminobenzyl)-HMPAO is then reacted with phosgen as disclosed by M. W. Brechbiel et al in Inorg. Chem. 25, 2772-2781, 1986.

6-(p-nitro-benzyl)-HMPAO may be prepared as disclosed by Parker et al. in Tetrahedron 45, No.1, 21 (1989) and Meares et al. in Anal. Biochem., 142, 68 (1984).

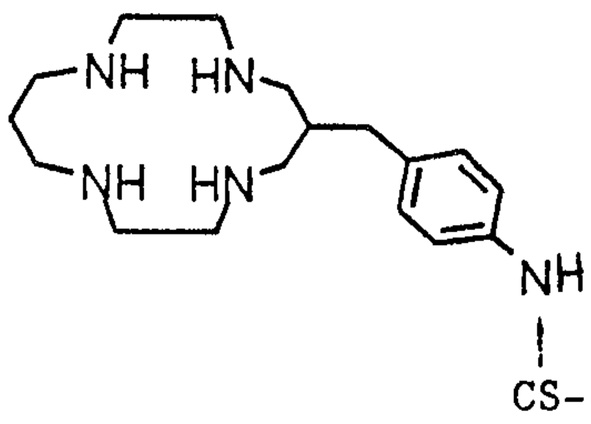
EXAMPLE 4:



By repeating the procedure of Example 1 but using 12-(p-isothiocyanatobenzyl)-TITRA instead of 2-(p-isothiocyanatobenzyl)-DOTA, the title compound is obtained.

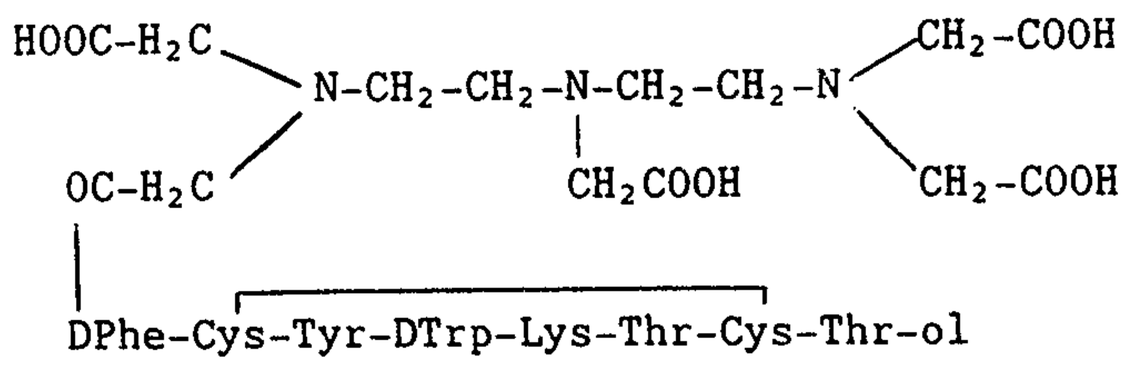
FAB-MS: 1584.9

EXAMPLE 5:



By repeating the procedure of Example 1 but using 1-(p-isothiocyanatobenzyl)-1,4,8,11-tetraazacyclotetradecane instead of 2-(p-isothiocyanatobenzyl)-DOTA, the title compound is obtained.
FAB-MS: 1366.8

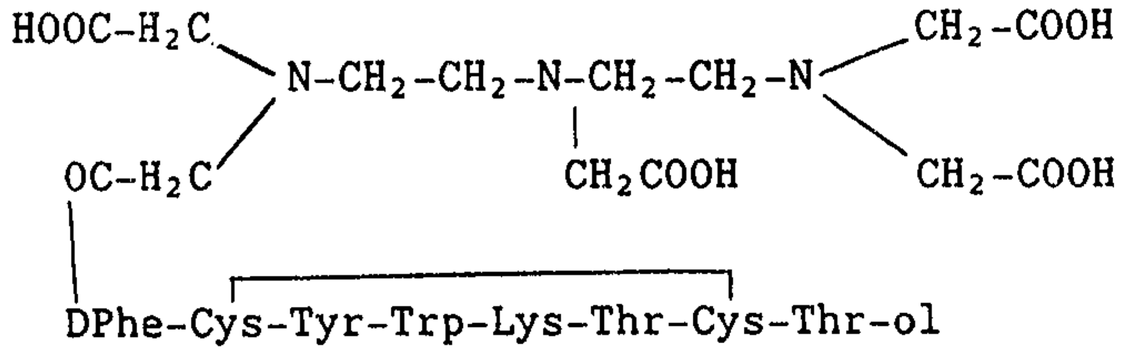
EXAMPLE 6:



1.2 g of H-DPhe-Cys-Tyr-DTrp-Lys(ε-Boc)-Thr-Cys-Thr-ol in free base (1 mM), are dissolved in 5 l of dioxan/H_2O 1/1 (v/v) and reacted with 5 g $NaHCO_3$. 520 mg DTPA dianhydride is slowly added with stirring. The reaction mixture is stirred for a further 30 min and dry-frozen. The residue is dissolved in 250 ml water and the pH is adjusted to pH 2.5 with concentrated HCl. The precipitated product is filtered out, washed and dried over phosphorus pentoxide. After cleavage of the Boc group by treatment with TFA, chromatography on a silica-gel column and desalting on a

Duolite resin, the title compound is obtained.
$[\alpha]_D^{20}$ = -6.4° (c = 0.25 in 95% AcOH)

EXAMPLE 7:



By repeating the procedure of Example 6 for coupling with DTPA but using DPhe-Cys-Tyr-Trp-Lys(ε-Fmoc)-Thr-Cys-Thr-ol and removing Fmoc as disclosed in Example 1 the title compound is obtained.

$[\alpha]_D^{20}$ = -3.4° (c = 0.25 in 95% AcOH)

EXAMPLE 8: Desferal-succinyl-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol

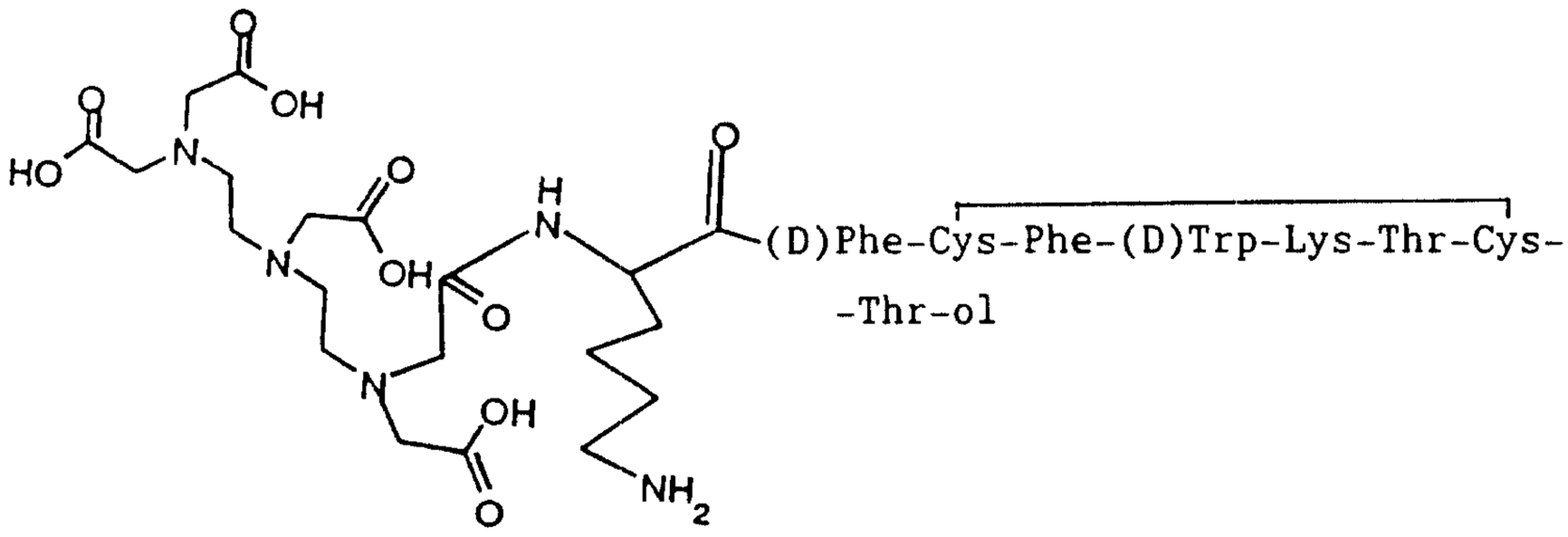
200 mg (0.164 mM) HOOC-CH_2CH_2-CO-DPhe-Cys-Phe-DTrp-Lys(εFmoc)-Thr-Cys-Thr-ol in solution in 20 ml DMF are cooled to -15°. There is added subsequently: 101 mg (0.18 mM) Desferal in base free form, 45 mg (0.33 mM) 1-hydroxybenzotriazole and 51.5 mg (0.25 mM) dicyclohexylcarbodiimide. The reaction mixture is warmed to room temperature and left for 18 hours at room temperature. After evaporation of the solvent under high vacuo, the residue is chromatographed on 50 g silica gel using a 8:2.0.125:0.125 mixture of chloroform/methanol/glacial acetic acid/water as eluent. The fractions containing the title compound are applied on 50 ml Duolite, washed salt free with water and eluted with a dioxan/-water/1% acetic acid gradient. The resulting title compound is lyophilized.

MS = MH^+ 1661 $[\alpha]_D^{20}$ = -7.4° (c = 0.25 in 95% AcOH)

The compound used as starting material may be prepared as follows:

224 g (0.2 mM) H-DPhe-Cys-Tyr-DTrp-Lys(ε-Boc)-Thr-Cys-Thr-ol are dissolved in 6 ml dioxan/water 1/1 and the solution is cooled to 4°. There is added 0.1 ml (0.58 mM) N-ethyldiisopropylamine and 24 mg (0.24 mM) succinic acid anhydride. After 1 hour the solution is lyophilized. The residue is treated with 10 ml methylene chloride, filtered and dried. The resulting product can be used tel quel for the reaction with Desferal.

EXAMPLE 9:



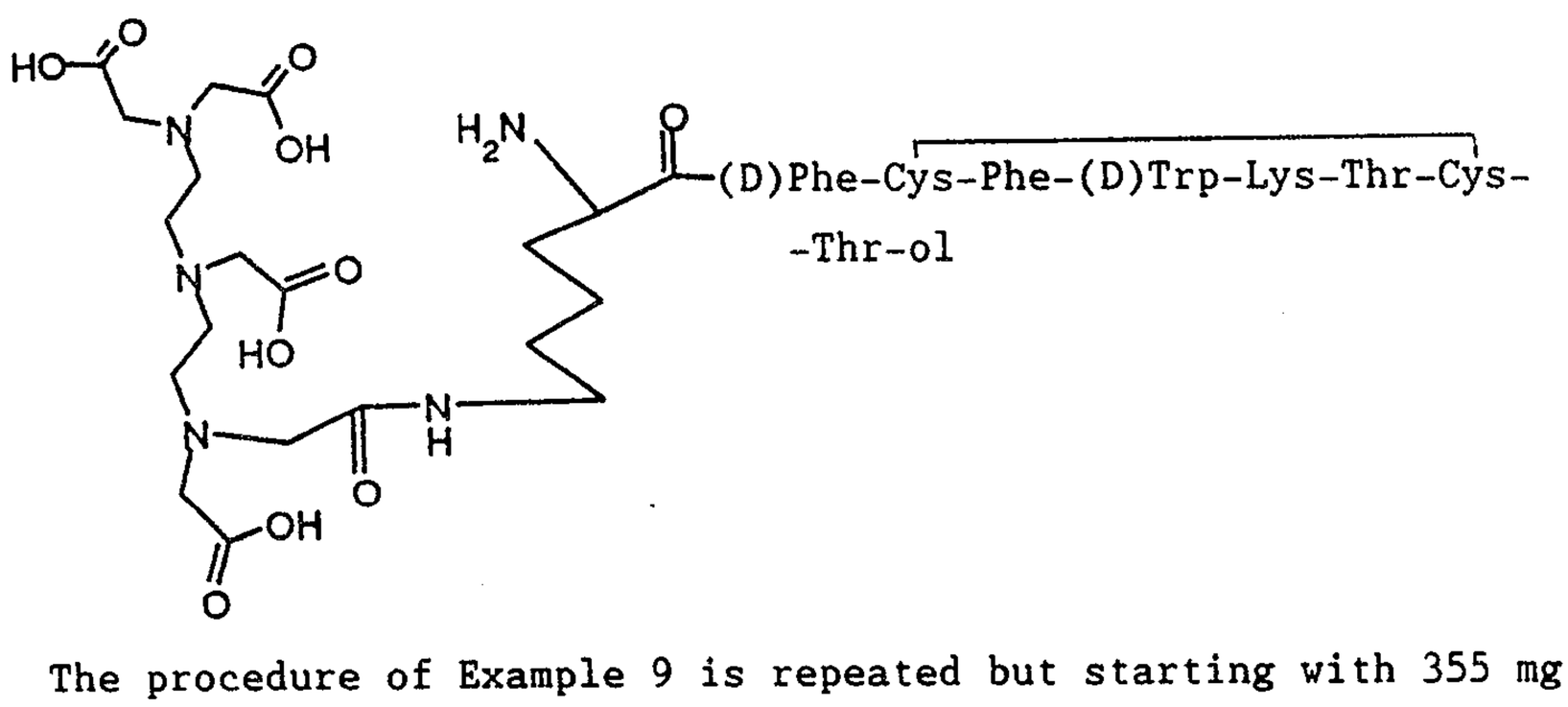
250 mg of (N^{ε}-Fmoc)-Lys-DPhe-Cys-Tyr-DTrp-Lys(ε-Fmoc)-Thr-Cys-Thr-ol is dissolved in 5 ml DMF and cooled to 4°C. To the solution there is added 0.131 ml N-ethyldiisopropylamin and 6.5 ml (0.183 mM) DTPA-azide solution. After 2 to 5 hrs at room temperature, the Fmoc protecting groups are removed with 1 ml piperidin. After 15 min. the mixture is evaporated, chromatographed on silica gel using a 7:5:2:2 chloroform/methanol/acetic acid/water mixture as eluent and evaporated. The residue is put on 50 g Duolite™, washed

salt free with water and rinsed with a 50/49/1 dioxane/water/acetic acid, yielding the title compound.

FAB-MS: 1522.8 $[\alpha]_D^{RT}$ = -18.8° (c = 0.6 in 95% AcOH)

DTPA-azide may be prepared as follows: 720 mg DTPA-hydrazide are dissolved in 50 ml DMF and cooled to -15°. To this solution is added dropwise 0.188 ml (1.67mM) t.-butyl nitrite and the resulting solution is stirred for 30 min. It can be used directly in the above procedure.

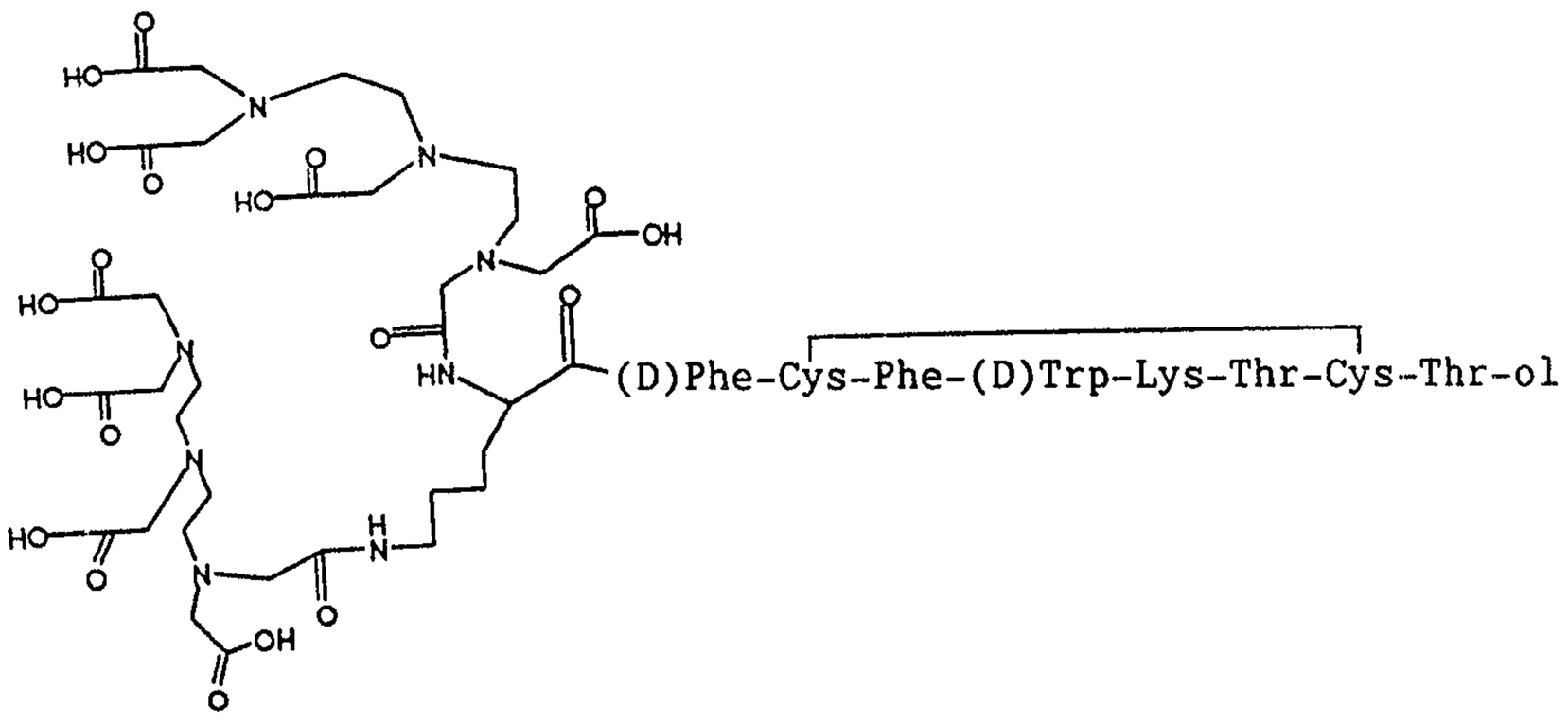
EXAMPLE 10:



The procedure of Example 9 is repeated but starting with 355 mg (N$^{\alpha}$-Fmoc, N$^{\varepsilon}$-Boc)-Lys-DPhe-Cys-Phe-DTrp-Lys(Fmoc)-Thr-Cys-Thr-ol. Before coupling is effected, Boc is removed by treatment with 5ml TFA, stirring for 15 min at room temperature, addition of 100 ml diisopropyl ether and 5 ml 3N etheric HCl and filtration.

FAB-MS: 1522.8 $[\alpha]_D^{20}$ = -29° (c = 0.31 in 95% AcOH)

EXAMPLE 11:

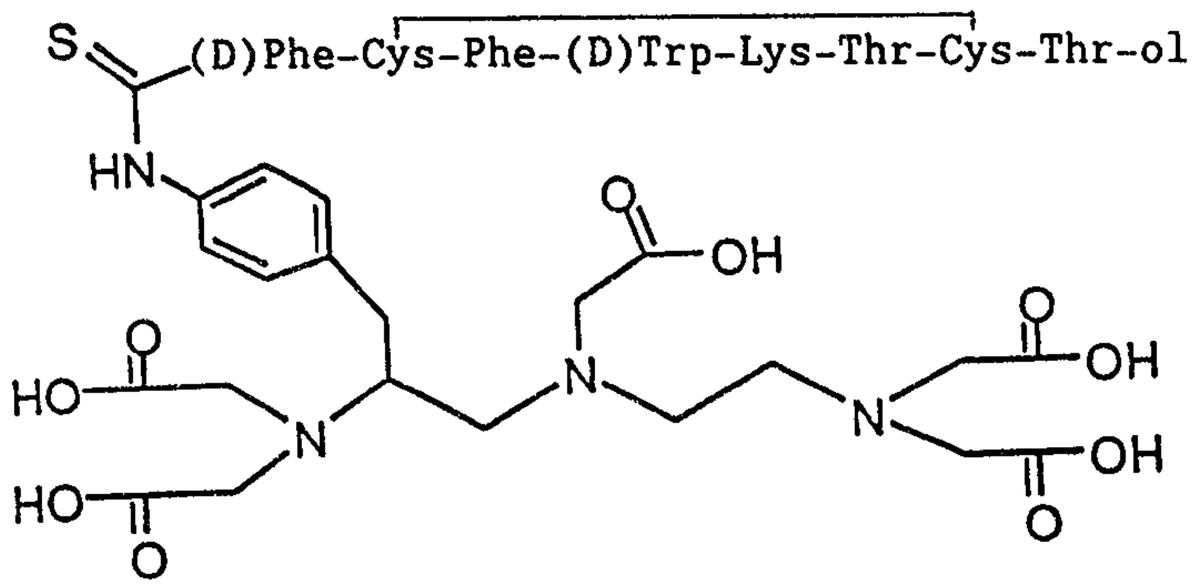


The procedure of Example 9 is repeated but starting with (N$^{\alpha}$-Boc, N$^{\varepsilon}$-Boc)-Lys-DPhe-Cys-Phe-DTrp-Lys(Fmoc)-Thr-Cys-Thr-ol and using the double amount of DTPA-azide and N-ethyl-diisopropyl-amine. Prior to the coupling the Boc groups are removed as disclosed in Example 10.

FAB-MS: 1898.1 $[\alpha]_D^{20}$ = -18.5° (c = 0.3 in 95% AcOH)

EXAMPLE 12:

^{111}In labeled



1 mg of the compound of Example 2 is dissolved in 5 ml 0.01M acetic acid. The resulting solution is passed through a 0.22µ

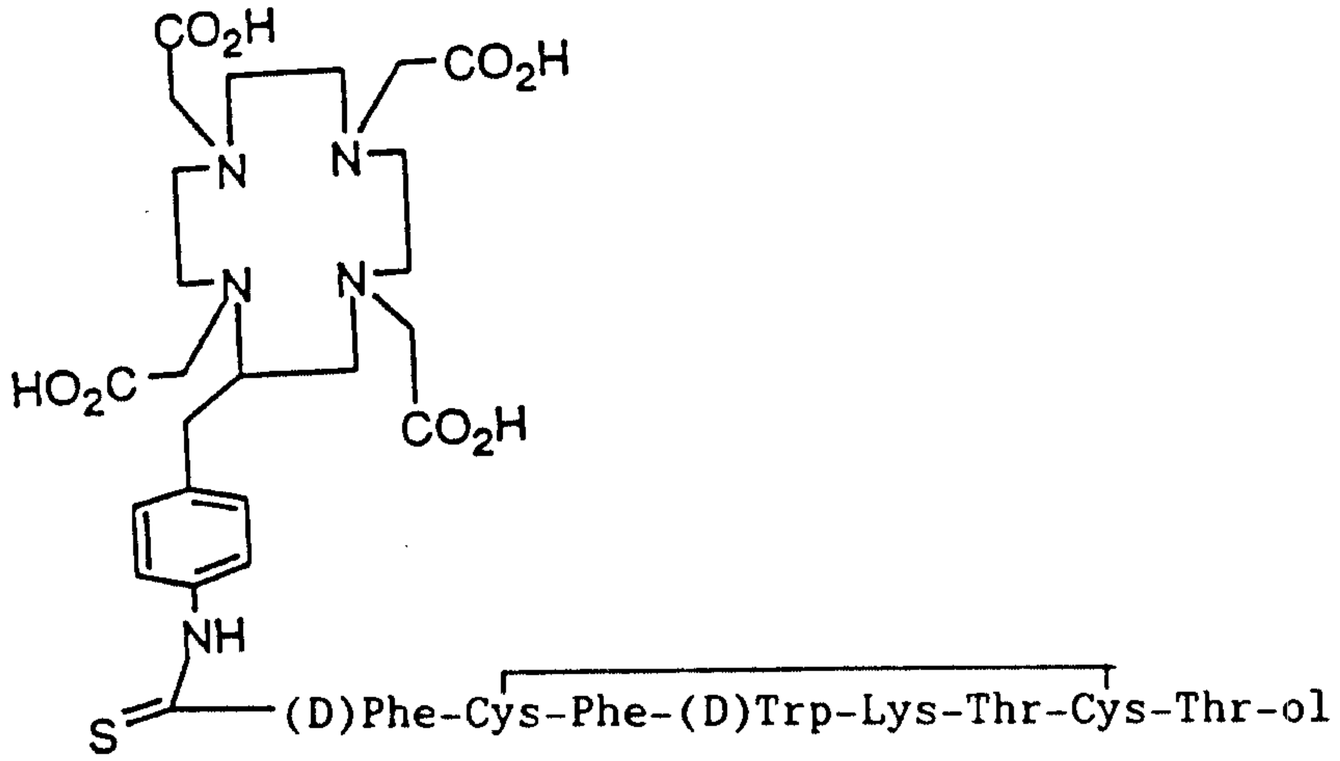
Millex™-GV filter and dispensed in 0.1 ml portions and stored at -20°C. $^{111}InCl_3$ (Amersham™, 1 mCi/100 µl) is prediluted in an equal volume of 0.5M sodium acetate and labeling is carried out by mixing the ligand with the $InCl_3$ solution and gentle homogenisation at room temperature.

HEPES buffer, pH 7.4, is then added to make a solution 10^{-6} M.

Compounds of Examples 4, 6 and 7 are also labeled with ^{111}In in accordance with the procedure of Example 12.

EXAMPLE 13 :

^{90}Y labeled



^{90}Y is obtained from a ^{90}Sr-^{90}Y radionuclide generator. The construction of the generator, its elution and the conversion of the [^{90}Y]EDTA to the acetate complex are performed in accordance with the method disclosed by M.Chinol and D.J. Hnatowich in J. Nucl. Med. 28, 1465-1470 (1987). 1 mg of the compound of Example 1 dissolved in 5ml 0.01M acetic acid is allowed to warm to room temperature and 1.0 mCi of ^{90}Y in 50 µl sterile 0.5M acetate is added. The mixture is then left undisturbed for 30 min to 1 hr to

maximize chelation.

Compounds of Examples 1, 2, 4 and 5 are labeled with ^{90}Y in accordance with the procedure of Example 13.

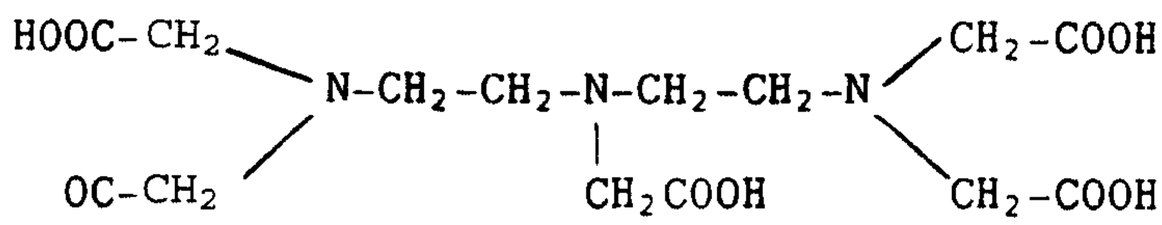
EXAMPLE 14: ^{68}Ga labeled Desferal-succinyl-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol

A ^{68}Ga generator based on tin oxide is eluted with 10 ml 5 mM Na_2EDTA at pH 7-8 at a flow rate of 1 ml/min. The resulting eluate is added to 15 ml 10 M HCl and 25 ml diethyl ether. After mixing the phases the aqueous layer is rejected. The ether layer is further washed with 3 x 8 ml 6 M HCl. The ether layer is reduced to dryness and redissolved in 300 µl ammonium acetate buffer (pH 4.5-5.0).

This ^{68}Ga solution is added to 2 µg of the compound of Example 8 and the solution is vortexed for 20 seconds. There is added ca. 15µl 1 M NaCl to render the solution isotonic prior to injection.

CLAIMS:

1. A compound of formula I



I

DPhe-Cys-Tyr-C-Lys-Thr-Cys-Thr-ol

wherein
C is (D) Trp or Trp in free form or in salt or complex form.

2. A compound of formula I according to claim 1 complexed with a β-, γ- or positron emitting radionuclide.

3. A compound of formula I according to claim 1 complexed with ^{111}In, in free form or in salt form.

4. A compound according to claim 2 or 3, in free form or in salt form, for use as a radiopharmaceutical.

5. A compound according to claim 3 in free form or in salt form, for use as an imaging agent to detect somatostatin receptor positive tumors and metastases.

6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3, in free form or in pharmaceutically acceptable salt form in association with a pharmaceutically carrier or diluent.

7. A package containing unit dosages of a compound of formula I in free form or in salt form according to claim 1 and of a γ- or positron emitting radionuclide with instructions for mixing them and for the use as imaging agent.