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(54) Titre : RGD (ARG-GLY-ASP) COUPLE A DES (NEURO)PEPTIDES

(54) Title: RGD (ARG-GLY-ASP) COUPLED TO (NEURO)PEPTIDES

(57) **Abrégé/Abstract:**

The invention relates to compounds having a binding affinity for both the  $\alpha v \beta 3$  receptor and a (neuro)peptide receptor, in particular the somatostatin receptor, which compound comprises a first peptide part comprising at least once the amino acid sequence Arg-Gly-Asp, and a second peptide part coupled thereto, optionally via a linker, which second peptide part is a (neuro)peptide.

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(54) Title: RGD (ARG-GLY-ASP) COUPLED TO (NEURO)PEPTIDES

(57) Abstract: The invention relates to compounds having a binding affinity for both the  $\alpha\text{v}\beta\text{3}$  receptor and a (neuro)peptide receptor, in particular the somatostatin receptor, which compound comprises a first peptide part comprising at least once the amino acid sequence Arg-Gly-Asp, and a second peptide part coupled thereto, optionally via a linker, which second peptide part is a (neuro)peptide.

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**RGD (ARG-GLY-ASP) COUPLED TO (NEURO)PEPTIDES**

The present invention relates to compounds that have a binding affinity for both the  $\alpha\beta 3$  receptor and a (neuro)peptide receptor, in particular the somatostatin receptor.

The integrin  $\alpha\beta 3$  receptor is predominantly expressed in growing and migrating endothelial cells, and has been identified as a marker of the angiogenic phenotype of vascular cells during e.g. tumor angiogenesis. The  $\alpha\beta 3$  integrin itself is expressed by tumor cells as well. The  $\alpha\beta 3$  receptor is thus a potential target for tumor seeking molecules.

Another type of receptor that occurs in tumors are the somatostatin receptors. Their presence has been demonstrated in a variety of tumors and also on immune cells by classical biochemical binding techniques, autoradiography, in situ hybridization and RT-PCR. Binding of a ligand to a somatostatin receptor most often results in internalization of the ligand/somatostatin-receptor complex.

The natural ligand to the somatostatin receptors is somatostatin, a 14 or 28 amino acid neuropeptide, which binds with high affinity to all somatostatin receptor subtypes (sst). Somatostatin is rapidly degraded in plasma, but enzymatic degradation-stable somatostatin analogs have been developed. The clinically most widely used analogues are octreotide and lanreotide, these compounds bind with high affinity to the sst 2, 3 and 5.

It was contemplated according to the invention to combine ligands having an affinity for both types of receptors in one compound in order to improve on the overall affinity of the compound for tumors.

To this end the invention relates to compounds having a binding affinity for both the  $\alpha\beta 3$  receptor and a (neuro)peptide receptor, in particular the somatostatin receptor, which compound comprises a first peptide part

comprising at least once the amino acid sequence Arg-Gly-Asp, and a second peptide part coupled thereto, optionally via a linker, which second peptide part is a (neuro)peptide.

5           The invention is not only applicable to somatostatin, but also to other (neuro)peptides. Consequently, the second peptide part is preferably selected from the group consisting of CCK, gastrin, substance P, bombesin, VIP (vasoactive intestinal  
10 peptide), PACAP (pituitary adenylate cyclase activating peptide), somatostatin and analogues of these. Analogues may be modified versions of the original peptide to improve stability or activity or may be parts of the peptides that still retain their biological activity.

15           In a preferred embodiment, the second peptide part is a somatostatin analogue, preferably selected from the group consisting of octreotate, octreotide, lantreotide, vapreotide or derivatives thereof.

          The first peptide part is a so-called RGD-  
20 peptide, which is a peptide having at least once the Arg-Gly-Asp motif. Analogues of the original RGD-peptide may comprise additional amino acids, such as Tyrosine for iodination. In a preferred embodiment of the RGD-analogue an additional Asp is present between the Tyr and the  
25 linker. This Asp serves for cyclisation of the RGD-peptide part to make it more stable.

          A suitable linker is for example Lysine, which has two NH<sub>2</sub>-groups. One of these can be used for coupling to the RGD-peptide while the COOH group is used for  
30 coupling to the (neuro)peptide. The remaining NH<sub>2</sub>-group can then be used for coupling to a chelator. The chelator is used for complexing a (radioactive) label.

          Radiolabeling of these neuropeptide-RGD compounds, either directly or via a chelator (with or  
35 without spacer), makes these compounds suitable as radiodiagnostics or radiopharmaceuticals. Suitable isotopes for radiolabeling are the following <sup>213</sup>Bi, <sup>186</sup>Re, <sup>188</sup>Re, <sup>77</sup>As, <sup>90</sup>Y, <sup>66</sup>Ga, <sup>67</sup>Cu, <sup>169</sup>Er, <sup>114m</sup>In, <sup>117m</sup>Sn, <sup>121</sup>Sn, <sup>127</sup>Te,

3

<sup>142</sup>Pr, <sup>143</sup>Pr, <sup>198</sup>Au, <sup>199</sup>Au, <sup>149</sup>Tb, <sup>161</sup>Tb, <sup>109</sup>Pd, <sup>165</sup>Dy, <sup>149</sup>Pm, <sup>151</sup>Pm, <sup>153</sup>Sm, <sup>157</sup>Gd, <sup>159</sup>Gd, <sup>166</sup>Ho, <sup>172</sup>Tm, <sup>169</sup>Yb, <sup>175</sup>Yb, <sup>177</sup>Lu, <sup>105</sup>Rh, <sup>103m</sup>Rh, <sup>195m</sup>Pt, <sup>111</sup>Ag, <sup>124</sup>I, <sup>131</sup>I and <sup>211</sup>At, <sup>99m</sup>Tc, <sup>203</sup>Pb, <sup>67</sup>Ga, <sup>68</sup>Ga, <sup>72</sup>As, <sup>111</sup>In, <sup>113m</sup>In, <sup>97</sup>Ru, <sup>62</sup>Cu, <sup>64</sup>Cu, <sup>52</sup>Fe, <sup>52m</sup>Mn, <sup>51</sup>Cr, <sup>123</sup>I, <sup>131</sup>I, <sup>75</sup>Br, <sup>76</sup>Br, <sup>77</sup>Br and <sup>82</sup>Br. An example of such a radiolabeled compound is the <sup>111</sup>In-DTPA-somatostatin analogue-RGD compound.

RGD-peptides coupled to somatostatin analogues (or other (neuro)-peptides and their analogues) may bind to and enter the cell via either the RGD-receptor ( $\alpha v\beta 3$ ) or one of the somatostatin receptors. With the compound binding to two different receptors, namely the (neuro)peptide receptor and  $\alpha v\beta 3$  integrin, it can thus be expected to find the compound on different target cells like tumor cells, as well as on the cells of the tumor vascularization. This may contribute to a higher target-background ratio.

A prototype for compounds of the invention is RGD-octreotide. Octreotide is a stable peptide (resistant to plasma degradation) that binds to the somatostatin receptor (sst) subtypes 2, 3 and 5. Other compounds are as described in the examples.

It was found in autoradiography experiments with tissues having either sst-receptors or  $\alpha v\beta 3$ -receptors that although both original peptides are combined in one new compound they both retain their binding affinity for their own receptors. Binding of the novel compound to the respective receptors could be blocked with an excess of the different competing analogues.

The present invention will be further illustrated in the Examples that follow and that are in no way intended to limit the invention.

**EXAMPLES****EXAMPLE 1**

General method for synthesis of RGD-(neuro)peptides conjugates and their corresponding DTPA- or DOTA- derivatives.

The following is a general method for the preparation of compounds of the invention.

Solid phase peptide synthesis (SPPS) is performed using a PE Biosystems "Pioneer" synthesizer employing Fmoc strategy. A linear peptide consisting of all amino acids of the compound is prepared on a 0.1 mmol scale with Fmoc-AA<sub>1</sub>(OtBu)-PEG-PS (PE Biosystems, 0.18 mmol/g loading), wherein AA<sub>1</sub> is the C-terminal amino acid, as the starting resin. Fmoc-protected amino acids (0.4 mmol) are activated with N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene]-N-methylmethan-aminium hexafluorophosphate N-oxide (HATU). All the amino acids and peptide synthesis reagents were purchased commercially.

On-board amide cyclization of the peptide is achieved using the "Allyl Deblock" protocol (Pd(PPh<sub>3</sub>)<sub>4</sub>, N-methylmorpholine, acetic acid, chloroform) followed by 7-Azabenzotriazole-1-yloxytris(pyrrolidino)-phosphonium hexafluorophosphate (PyAOP) activation. The resin containing the protected, cyclized peptide is then removed from the instrument.

The resin is suspended in 8 mL of dimethylformamide containing 92 mg of thallium trifluoroacetate. The mixture is shaken for 2-3 hours, filtered, successively washed with 10 mL of DMF, 10 mL of DMF-water (1:1), 10 mL of DMF and THF to yield protected peptide (III) attached to the resin. The resin is then divided into two portions.

The peptide is cleaved from the resin and deprotected using 85% TFA/5% water/5% phenol/5% thianisole for 10-12 hours. The crude peptide is isolated by precipitation with t-butyl methyl ether followed by centrifugation and purified by reverse phase HPLC using

an acetonitrile/water gradient containing 0.1% TFA (Solvent A: 0.1% TFA/H<sub>2</sub>O, Solvent B: 0.1% TFA/10% H<sub>2</sub>O/CH<sub>3</sub>CN; Gradient: Hold at 95% A/5% B for 2.0 min. followed by solvent A (100%) to 50%A:50%B over a period of 20 minutes).

The Mtt protecting group of the lysine is removed by treatment with 5% TFA/5% triisopropylsilane (TIPS)/90% dichloromethane (2 x 30 min.). The resin is washed with dichloromethane and tetrahydrofuran and suspended in DMF (2.5 mL) containing DIEA (35 μl, 0.2 mmol). In a separate vessel, tri-t-butyl DTPA anhydride or DOTA (112 mg, 0.2 mmol) is dissolved in DMF containing HBTU/HOBt (0.2 mmol, 1.0 mL of a 0.2 mmol/mL solution) and DIEA (35 μl, 0.2 mmol) to give a 5 mL solution. After 15 agitating for one hour, the activated DTPA derivative is added to the previously suspended resin.

The reaction is permitted to continue overnight before washing the resin with DMF and THF.

The peptide was cleaved from the resin and deprotected using 85% TFA/5% water/5% phenol/ 5% thianisole for 10-12 hours. The crude peptide is isolated by precipitation with t-butyl methyl ether followed by centrifugation and purified by reverse phase HPLC using an acetonitrile/water gradient containing 0.1% TFA (Solvent A: 0.1% TFA/H<sub>2</sub>O, Solvent B: 0.1% TFA/10% H<sub>2</sub>O/CH<sub>3</sub>CN; Gradient: Hold at 95% A/5% B for 2.0 min. followed by solvent A to B over a period of 20 minutes).

## EXAMPLE 2

### 30 Synthesis of RGD-octreotate (IV) and the corresponding DTPA-derivative (V)

In accordance with the method as described in Example 1 an RGD-octreotate and its corresponding DTPA-derivative were prepared according to the following 35 reaction scheme:

6

Arg(Pmc)-Gly-Asp(OtBu)-DTyr(OtBu)-Asp( $\beta$ -OAll)-Lys(Mtt)-DPhe-Cys(Acm)-Tyr(OtBu)-  
DTrp(tBoc)-Lys(tBoc)-Thr(OtBu)-Cys(Acm)-Thr(OtBu)-O-RESIN

(I)

↓

5

Arg(Pmc)-Gly-Asp(OtBu)-DTyr(OtBu)-Asp-Lys(Mtt)-DPhe-

|

|

HN ————— CO

10 Cys(Acm)-Tyr(OtBu)-DTrp(tBoc)-Lys(tBoc)-Thr(OtBu)-Cys(Acm)-Thr(OtBu)-O-RESIN

(II)

↓

T1 (OCOCF<sub>3</sub>)<sub>2</sub>

15

Arg(Pmc)-Gly-Asp(OtBu)-DTyr(OtBu)-Asp-Lys(Mtt)-DPhe-

|

|

HN ————— CO

20 Cys(Acm)-Tyr(OtBu)-DTrp(tBoc)-Lys(tBoc)-Thr(OtBu)-Cys(Acm)-Thr(OtBu)-O-RESIN

|

|

S ————— S

(III)

25

85%TFA, 5%H<sub>2</sub>O,  
5%phenol, 5%thioaniosole

|

|

i. 5%TFA, 5%TIPS, 90%CH<sub>2</sub>Cl<sub>2</sub>  
ii. tri-t-butyl mono DTPA anhydride  
iii. 85%TFA, 5%H<sub>2</sub>O,  
5%phenol, 5%thioaniosole

30

↓

↓

(IV)

(V)

35 RGD-octreotate (IV):

Arg-Gly-Asp-DTyr-Asp-Lys-DPhe-Cys-Tyr-DTrp-Lys-Thr-Cys-Thr-OH

|

|

|

|

HN ————— CO S ————— S

40

Lys( $\epsilon$ -DTPA)RGD-octreotate (V):

<sup>ε</sup>NH-DTPA

|

45

Arg-Gly-Asp-DTyr-Asp-Lys-DPhe-Cys-Tyr-DTrp-Lys-Thr-Cys-Thr-OH

|

|

|

|

HN ————— CO S ————— S

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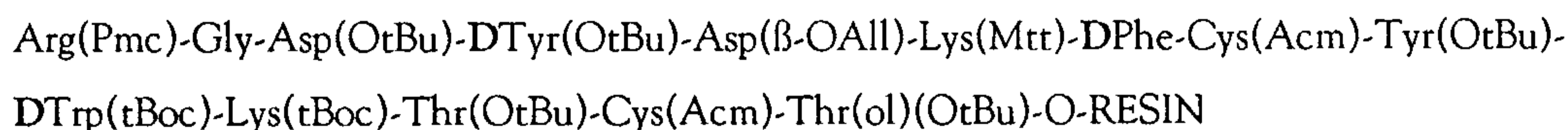
The mass spectrometer data for the RGD octreotate conjugate (IV) are as follows: Calculated 1766.6, Found: 884.8 ((M+2)/2).

The mass spectrometer data for the DTPA-5 derivative of the RGD-octreotate conjugate (V) are as follows: Calculated 2139.9, Found: 1071.2 ((M+2)/2).

### EXAMPLE 3

#### 10 Synthesis of RGD-octreotide (iv) and the corresponding DOTA-derivative (v)

In accordance with the method as described in Example 1 an RGD-octreotide and its corresponding DTPA-derivative were prepared according to the following  
15 reaction scheme:

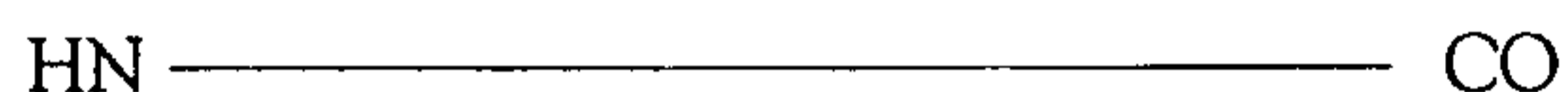


(i)

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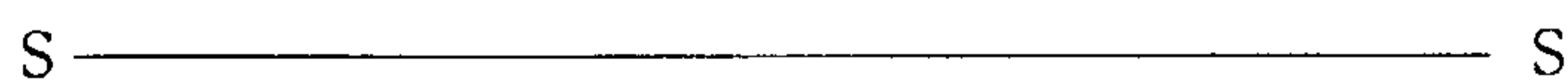
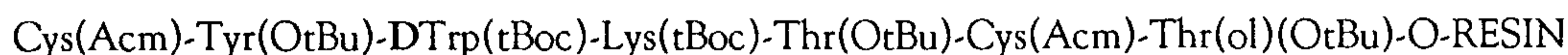
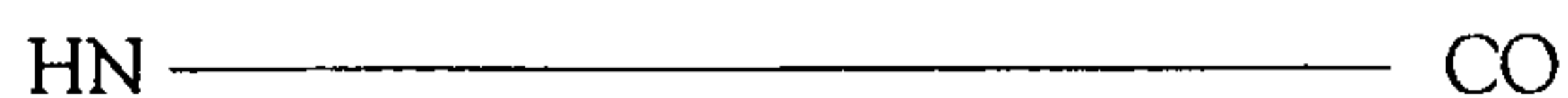


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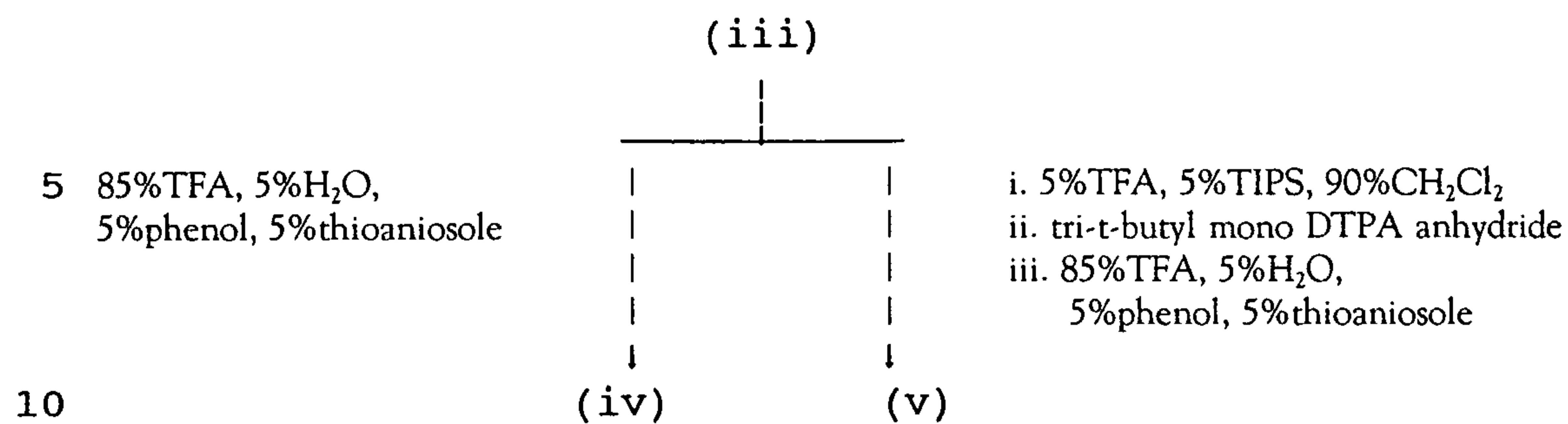


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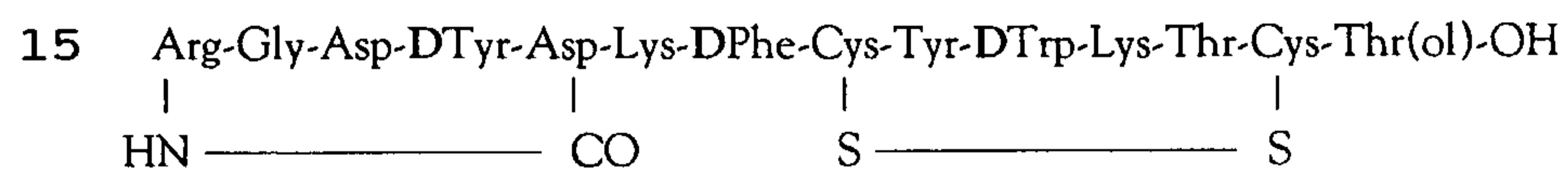


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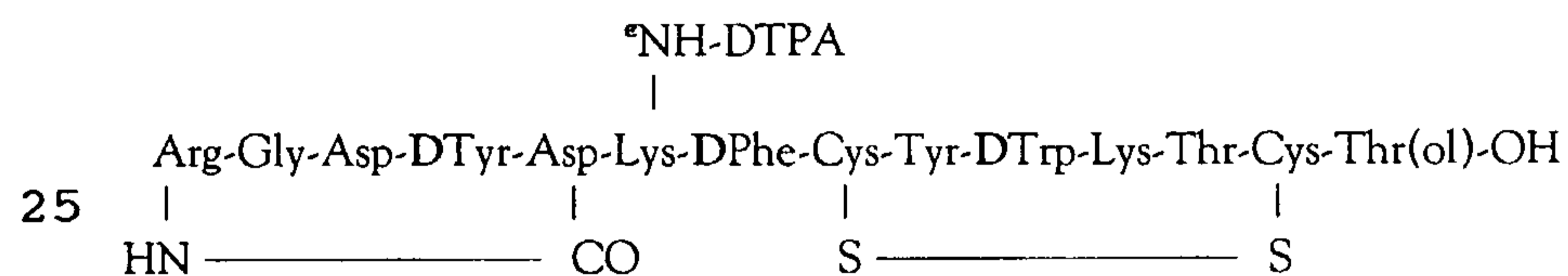
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RGD-octreotide (iv):



20 Lys( $\epsilon$ -DTPA)RGD-octreotide (v):



## SEQUENCE LISTING

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**THE EMBODIMENTS OF THE INVENTION FOR WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:**

1. A compound comprising a somatostatin receptor binding peptide or analog thereof that binds a somatostatin receptor, a linker amino acid at the N-terminus of said somatostatin receptor binding peptide, a metal chelating group coupled to said linker and an apoptosis-inducing molecule comprising an amino acid sequence Arg-Gly-Asp-DTyr-Asp wherein the N-terminal Arg and the C-terminal Asp of said amino acid sequence are cyclized, and wherein the C-terminal Asp of said amino acid sequence is coupled to said linker amino acid.
2. The compound as in Claim 1, wherein said apoptosis-inducing molecule activates Caspase-3.
3. The compound as in Claim 1, wherein said analog is selected from the group consisting of octreotate, octreotide, lantreotide, vapreotide, and derivatives thereof.
4. The compound as in Claim 1, wherein said metal chelating group is a metal chelating group suitable for radiolabeling.
5. The compound as in claim 4, wherein said linker amino acid is lysine, para-amino phenylalanine, or diamino propionic acid.
6. The compound as in claim 4, wherein said metal chelating group suitable for radiolabeling is DTPA or DOTA.

7. The compound as in claim 4, wherein said metal chelating group is radiolabeled with a radioisotope selected from the group consisting of  $^{213}\text{Bi}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{77}\text{As}$ ,  $^{90}\text{Y}$ ,  $^{66}\text{Ga}$ ,  $^{67}\text{Cu}$ ,  $^{169}\text{Er}$ ,  $^{114\text{m}}\text{In}$ ,  $^{117\text{m}}\text{Sn}$ ,  $^{121}\text{Sn}$ ,  $^{127}\text{Te}$ ,  $^{142}\text{Pr}$ ,  $^{143}\text{Pr}$ ,  $^{198}\text{Au}$ ,  $^{199}\text{Au}$ ,  $^{149}\text{Tb}$ ,  $^{161}\text{Tb}$ ,  $^{109}\text{Pd}$ ,  $^{165}\text{Dy}$ ,  $^{149}\text{Pm}$ ,  $^{151}\text{Pm}$ ,  $^{153}\text{Sm}$ ,  $^{157}\text{Gd}$ ,  $^{159}\text{Gd}$ ,  $^{166}\text{Ho}$ ,  $^{172}\text{Tm}$ ,  $^{169}\text{Yb}$ ,  $^{175}\text{Yb}$ ,  $^{177}\text{Lu}$ ,  $^{105}\text{Rh}$ ,  $^{103\text{m}}\text{Rh}$ ,  $^{195\text{m}}\text{Pt}$ ,  $^{111}\text{Ag}$ ,  $^{124}\text{I}$ ,  $^{131}\text{I}$ ,  $^{121}\text{At}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{203}\text{Pb}$ ,  $^{67}\text{Ga}$ ,  $^{68}\text{Ga}$ ,  $^{72}\text{As}$ ,  $^{111}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{97}\text{Ru}$ ,  $^{62}\text{Cu}$ ,  $^{64}\text{Cu}$ ,  $^{52}\text{Fe}$ ,  $^{52\text{m}}\text{Mn}$ ,  $^{51}\text{Cr}$ ,  $^{123}\text{I}$ ,  $^{131}\text{I}$ ,  $^{75}\text{Br}$ ,  $^{76}\text{Br}$ ,  $^{77}\text{Br}$ , and  $^{82}\text{Br}$ .

8. The compound as in claim 6, wherein said metal chelating group is radiolabeled with a radioisotope selected from the group consisting of  $^{213}\text{Bi}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{77}\text{As}$ ,  $^{90}\text{Y}$ ,  $^{66}\text{Ga}$ ,  $^{67}\text{Cu}$ ,  $^{169}\text{Er}$ ,  $^{114\text{m}}\text{In}$ ,  $^{117\text{m}}\text{Sn}$ ,  $^{121}\text{Sn}$ ,  $^{127}\text{Te}$ ,  $^{142}\text{Pr}$ ,  $^{143}\text{Pr}$ ,  $^{198}\text{Au}$ ,  $^{199}\text{Au}$ ,  $^{149}\text{Tb}$ ,  $^{161}\text{Tb}$ ,  $^{109}\text{Pd}$ ,  $^{165}\text{Dy}$ ,  $^{149}\text{Pm}$ ,  $^{151}\text{Pm}$ ,  $^{153}\text{Sm}$ ,  $^{157}\text{Gd}$ ,  $^{159}\text{Gd}$ ,  $^{166}\text{Ho}$ ,  $^{172}\text{Tm}$ ,  $^{169}\text{Yb}$ ,  $^{175}\text{Yb}$ ,  $^{177}\text{Lu}$ ,  $^{105}\text{Rh}$ ,  $^{103\text{m}}\text{Rh}$ ,  $^{195\text{m}}\text{Pt}$ ,  $^{111}\text{Ag}$ ,  $^{124}\text{I}$ ,  $^{131}\text{I}$ ,  $^{121}\text{At}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{203}\text{Pb}$ ,  $^{67}\text{Ga}$ ,  $^{68}\text{Ga}$ ,  $^{72}\text{As}$ ,  $^{111}\text{In}$ ,  $^{113\text{m}}\text{In}$ ,  $^{97}\text{Ru}$ ,  $^{62}\text{Cu}$ ,  $^{64}\text{Cu}$ ,  $^{52}\text{Fe}$ ,  $^{52\text{m}}\text{Mn}$ ,  $^{51}\text{Cr}$ ,  $^{123}\text{I}$ ,  $^{131}\text{I}$ ,  $^{75}\text{Br}$ ,  $^{76}\text{Br}$ ,  $^{77}\text{Br}$ , and  $^{82}\text{Br}$ .