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(54) BENZIMIDAZOLE COMPOUNDS THAT ARE VITRONECTIN RECEPTOR ANTAGONISTS

BENZIMIDAZOLDERIVATE MIT VITRONECTINREZEPTOR-ANTAGONISTISCHER WIRKUNG

COMPOSES DE BENZIMIDAZOLE UTILISES COMME ANTAGONISTES DU RECEPTEUR DE LA VITRONECTINE

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(56) References cited:
WO-A-95/32710 **WO-A-96/00730**

- **NICOLAOU K C ET AL: "Design, synthesis and biological evaluation of nonpeptide integrin antagonists" BIOORGANIC & MEDICINAL CHEMISTRY, vol. 6, no. 8, August 1998 (1998-08), pages 1185-208, XP000908906**

EP 1 135 374 B9

Description

FIELD OF THE INVENTION

[0001] This invention relates to compounds which are vitronectin receptor antagonists and are useful for the treatment of cancer, retinopathy, cardiovascular disorders, such as atherosclerosis and restenosis, and diseases wherein bone resorption is a factor, such as osteoporosis.

BACKGROUND OF THE INVENTION

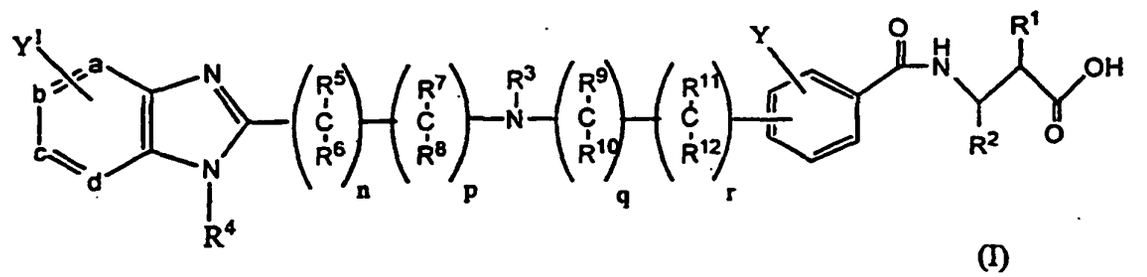
[0002] Integrins are a superfamily of cell adhesion receptors, which are transmembrane glycoproteins expressed on a variety of cells. These cell surface adhesion receptors include gpIIb/IIIa, also known as the " fibrinogen receptor," and $\alpha_v\beta_3$, also known as the "vitronectin receptor." The fibrinogen receptor gpIIb/IIIa is expressed on the platelet surface, and it mediates platelet aggregation and the formation of a hemostatic clot at the site of a bleeding wound. Philips, *et al., Blood.,* **1988,** 71, 831. The vitronectin receptor $\alpha_v\beta_3$ is expressed on a number of cells, including endothelial, smooth muscle, osteoclast, and tumor cells, and, thus, it has a variety of functions. The $\alpha_v\beta_3$ receptor expressed on the membrane of osteoclast cells mediates the bone resorption process and contributes to the development of osteoporosis. Ross, *et al., J. Biol, Chem.,* 1987, **262,** 7703. The $\alpha_v\beta_3$ receptor expressed on human aortic smooth muscle cells stimulates their migration into neointima, which leads to the formation of atherosclerosis and restenosis after angioplasty. Brown *et al., Cardiovascular Res.,* **1994**, 28, 1815. Additionally, a recent study has shown that a $\alpha_v\beta_3$ antagonist is able to promote tumor regression by inducing apoptosis of angiogenic blood vessels. Brooks, *et al., Cell,* **1994,** 79, 1157. Thus, agents that would block the vitronectin receptor would be useful in treating diseases mediated by this receptor, such as osteoporosis, atherosclerosis, restenosis and cancer.

[0003] The vitronectin receptor is known to bind to bone matrix proteins, such as osteopontin, bone sialoprotein and thrombospondin, which contain the tri-peptide Arg-Gly-Asp (or RGD) motif. Thus, Horton, *et al., Exp. Cell Res.* **1991,** 195, 368, disclose that RGD-containing peptides and an anti-vitronectin receptor antibody (23C6) inhibit dentine resorption and cell spreading by osteoclasts. In addition, Sato, *et al., J. Cell Biol.* **1990**, 111, 1713 disclose that echistatin, a snake venom peptide which contains the RGD sequence, is a potent inhibitor of bone resorption in tissue culture, and inhibits attachment of osteoclasts to bone. Fisher, *et al.*, *Endocrinology* **1993**, 132, 1411, has further shown that echistatin inhibits bone resorption in *vivo* in the rat. Bertolini *et al., J. Bone Min. Res.,* 6, Sup. 1, S146,252 have shown that cyclo-S,S-N$^{\alpha}$- acetyl-cysteinyl- N$^{\alpha}$- methyl-argininyl-glycyl-aspartyl-penicillamine inhibits osteoclast attachment to bone. EP 0 528 587 and EP 0 528 586 report substituted phenyl derivatives which inhibit osteoclast mediated bone resorption.

[0004] Alig et al., EP 0 381033, Hartman, et al., EP 0 540 334, Blackburn, et al., WO 93/08174, Bondinell, et al., WO 93/00095, Blackburn, et al., WO 95/04057, Egbertson, et al., EP 0 478 328, Sugihara, et al., EP 0 529 858, Porter, et al., EP 0 542 363, and Fisher, et al., EP 0 635 492 disclose certain compounds that are useful for inhibiting the fibrinogen receptor. WO 96/00730 discloses certain compounds that are vitronectin receptor antagonists. Nicobou et al., Bioorganic & Medicinal Chemistry (1998), 6, 1185-1208; discloses the design, synthesis and biological evaluation of nonpeptide integrin antagonists. Two such compounds are patent inhibitors of $\alpha_{IIb}\beta_3$ and are compound shaved in vivo inhibition of angiogenesis.

SUMMARY OF THE INVENTION

[0005] We have invented novel compounds that are antagonists at the vitronectin receptor, i.e., they have a high affinity for the vitronectin receptor, thereby making them useful for treating disorders or diseases mediated by the vitronectin receptor, e.g., cancer, retinopathy, artherosclerosis, vascular restenosis and osteoporosis. The compounds of our invention have the formula:



(I)

wherein n, p, q and r are each independently selected from 0 or 1;

a, b, c, and d each independently represents a carbon or nitrogen atom, with the proviso that no more than two of a, b, c, and d are nitrogen atoms;

Y and Y^1 each independently represents 1-4 optional substituents selected from alkyl, alkoxy, halo, $-CF_3$, and -C(O)OH;

R^1 is H, alkyl, aryl, aralkyl, arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, heteroaralkyl, cycloalkylalkyl, heterocycloalkylalkyl, $-NHR^A$, $-NHC(O)R^A$, $-NHSO_2R^A$, $NHC(O)NHR^A$ or $-NHC(O)OR^A$, R^1 being optionally substituted by 1-3 groups selected from halo, alkyl, $-CF_3$, -CN, $-OR^B$, $-SR^B$, $-CO_2R^B$, $-C(O)R^B$, $-OC(O)R^B$, $-OC(O)OR^B$ and- SO_2R^B, and R^A and R^B are independently selected from H, alkyl, aryl, arallcyl, arylcycloallcyl, heteroaryl, cycloalkyl, heterocycloalkyl, heteroaralkyl, cycloalkylalkyl or heterocycloalkylalkyl, with the proviso that when R^1 is alkyl, R^1 is not substituted with halo, the proviso that when R^1 is $-NHSO_2R^A$ or $-NHC(O)OR^A$, R^A is not H, and the proviso that for $-SO_2R^B$ or $-OC(O)OR^B$, R^B is not H;

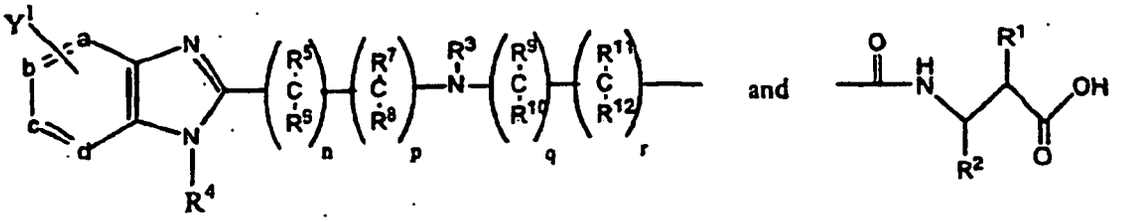
R^2 is H, alkyl, aryl, aralkyl, arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, heteroaralkyl, cycloalkylalkyl, or heterocycloalkylalkyl, R^2 being optionally substituted by 1-3 groups selected from halo, alkyl, $-CF_3$, -CN, $-OR^C$, SR^C, $-CO_2R^C$, $-C(O)R^C$, $-OC(O)R^C$, $-OC(O)OR^C$ and $-SO_2R^C$, wherein R^C is selected from H, alkyl, aryl, arallcyl, arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, heteroaralkyl, cycloalkylalkyl or heterocycloalkylalkyl, with the proviso that when R^2 is alkyl, R^2 is not substituted with halo, and the proviso that for $-SO_2R^C$ or $-OC(O)OR^C$, R^C is not H;

R^3 is H, alkyl, aralkyl, arylcycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, heteroaralkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-C(O)R^D$, $-C(O)OR^D$, $-SO_2R^E$, $-C(O)NR^FR^G$, $-C(O)NR^FSO_2R^E$, or $-C(=S)NR^FR^G$, wherein R^D, R^E, R^F and R^G are independently selected from H, alkyl, aryl, aralkyl, arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl or heterocycloalkylalkyl, or R^F and R^G taken together complete a 5-7 member ring containing 0 to 1 oxygen or sulfur atoms, and 1 to 2 nitrogen atoms, R^3 being optionally substituted by 1-3 groups selected from halo, alkyl, aryl, $-CF_3$, -CN, $-OR^H$, $-SR^H$, $-CO_2R^H$, $-C(O)R^H$, $-OC(O)R^H$, $-OC(O)OR^H$, $-SO_2R^H$ and $-NR^HR^H$, wherein R^H is selected from H, alkyl, aryl, aralkyl, arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, heteroaralkyl, cycloalkylalkyl or heterocycloalkylalkyl, with the proviso that when R^3 is alkyl, R^3 is not substituted with halo, the proviso that when R^3 is $-SO_2R^E$, $-C(O)NR^FSO_2R^E$, or $-CO(O)R^D$, R^D and R^E are not H, and the proviso that for $-SO_2R^H$ or $-OC(O)OR^H$, R^H is not H;

R^4 is H, alkyl, aralkyl, arylcycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, heteroaralkyl, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, R^4 being optionally substituted by 1-3 groups selected from halo, alkyl, $-CF_3$, -CN, $-OR^J$, $-SR^J$, $-CO_2R^J$, $-C(O)R^J$, $-OC(O)R^J$, $-OC(O)OR^J$ and $-SO_2R^J$, wherein R^J is selected from H, alkyl, aryl, aralkyl, arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, heteroaralkyl, cycloallcylalkyl or heterocycloalkylalkyl, with the proviso that when R^4 is alkyl, R^4 is not substituted with halo, and the proviso that for $-SO_2R^J$ or $-OC(O)OR^J$, R^J is not H;

R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are independently selected from H or C_1-C_3 alkyl;

and wherein



are positioned meta or para relative to each other;
or a biolabile ester thereof, or a pharmaceutically acceptable salt thereof;
wherein the following terms have the following meanings:

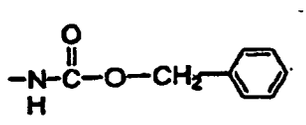
"alkyl" refers to straight or branched chain groups having 1 to 20 carbon atoms;
"cycloalkyl" refers to non-aromatic carbocyclic ring or multi-carbocyclic ring system of from 3 to 20 carbon atoms;

"cycloalkylalkyl" refers to groups having the formula cycloalkyl-R-, wherein R is alkyl;
"heterocycloalkyl" refers to a cycloalkyl group, wherein one or more of the carbon atoms of such groups are replaced with a heteroatom selected from O, S and N;
"heterocycloalkylalkyl" refers to groups having the formula hetcrocycloalkyl-R-, wherein R is alkyl;
"aryl" refers to aromatic carbocyclic groups;
"aralkyl" refers to groups having the formula aryl-R-, wherein R is alkyl;
"heteroaryl" refers to aromatic carbocyclic groups, wherein one or more of the carbon atoms of such groups are replaced with a heteroatom selected from O, S and N;
"heteroaralkyl" refers to groups having the formula heteroaryl-R-, wherein R is alkyl;
"arylcycloalkyl" refers to groups having the formula aryl-R-, wherein R is cycloalkyl;

and wherein said biolabile esters are alkyl, alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl and alkoxycarbonyloxyalkyl esters, including cycloalkyl and aryl substituted derivatives thereof, aryl esters and cycloalkyl esters, wherein said alkyl, alkanoyl or alkoxy groups may contain from 1 to 8 carbon atoms and be branched-chain or straight-chain, said cycloalkyl groups may contain from 3-7 carbon atoms and said cycloalkanoyl groups from 4-8 carbon atoms wherein both are optionally benzo-fused, and said aryl and aroyl groups include substituted phenyl, naphthyl or indanyl ring systems.

DETAILED DESCRIPTION OF THE INVENTION

[0006] R^1 is preferably H, -NHR^A -$NHC(O)R^A$, $NHC(O)OR^A$,-$NHC(O)NHR^A$, or -$NHSO_3R^A$, R^1 is more preferably -$NHC(O)OR^A$. R^1 is most preferably,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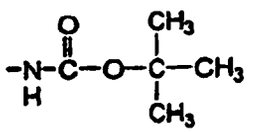
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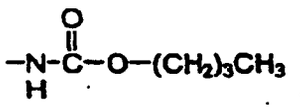
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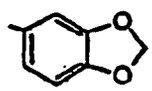
R^2 preferably H.
R^3 is preferably selected from H, alkyl, -$C(O)R^D$, -$C(O)OR^D$, -$C(O)NR^FR^G$, and -$C(=S)NR^FR^G$. R^D is preferably selected from phenyl, alkyl, aralkyl, arylcycloalkyl, cycloalkyl, and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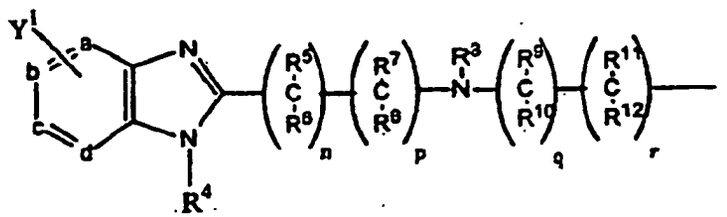
wherein R^D is optionally substituted by 1-3 substituents selected from alkoxy, halo, cycloalkyl, -S-CH_3, phenyloxy, -$OC(O)CH_3$, -$C(O)OC_2H_5$ and -$N(OH_3)_2$. R^F and R^G are preferably selected from H, alkyl, phenyl, cycloalkyl, and aralkyl, wherein R^F and R° are optionally substituted by alkoxy, halo or -CO_2R^H.
R^4 is preferably H or alkyl, most preferably H.
R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are each preferably H.

[0007] Preferably, the sum of n + p is 1.
[0008] Preferably, the sum of q + r is 1.
[0009] Preferably; a, b, c, and d are Carbon atoms.
[0010] Preferably,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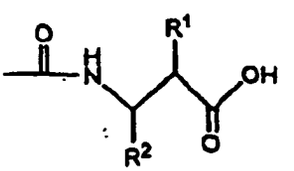
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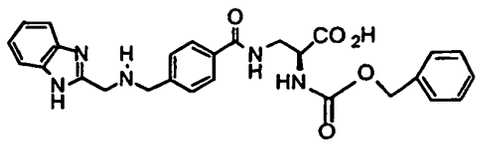
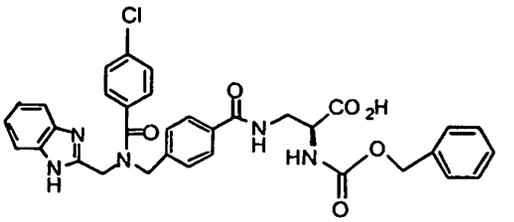
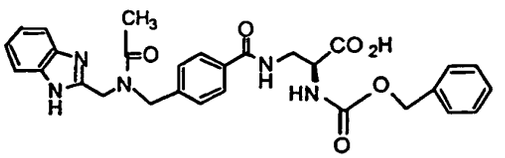
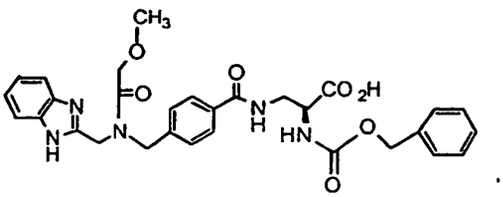
are positioned para relative to each other.

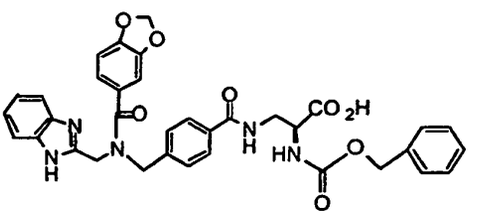
[0011] The following compounds, including biolabile esters, or pharmaceutically acceptable salts thereof, are particularly preferred:

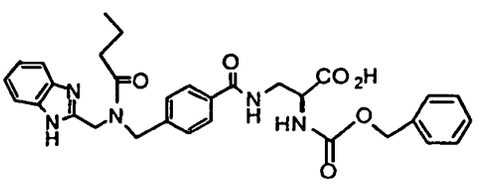


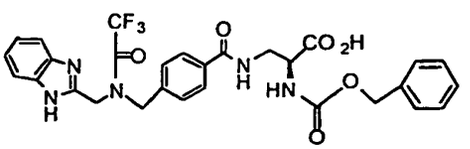


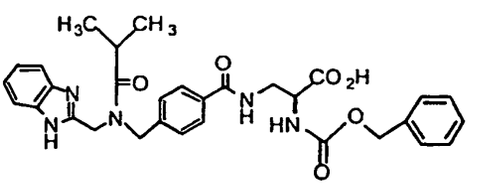


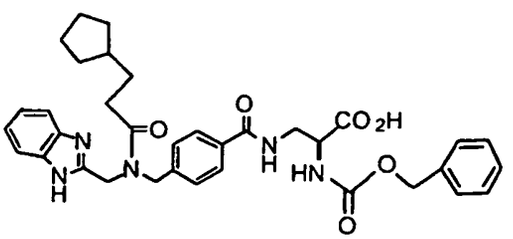


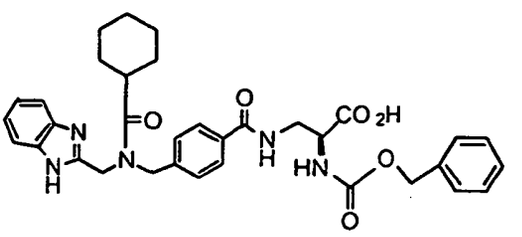


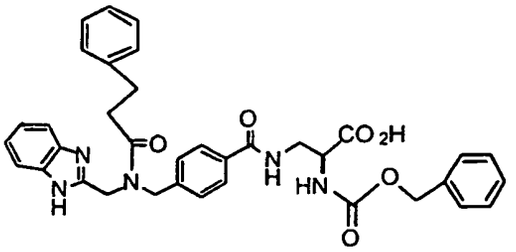


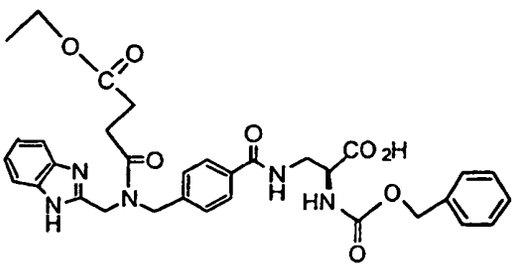


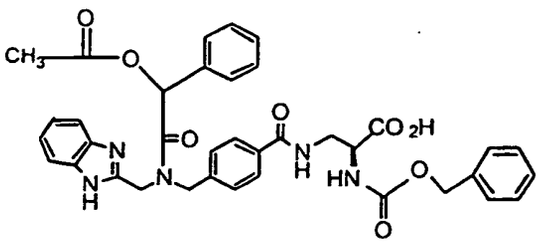


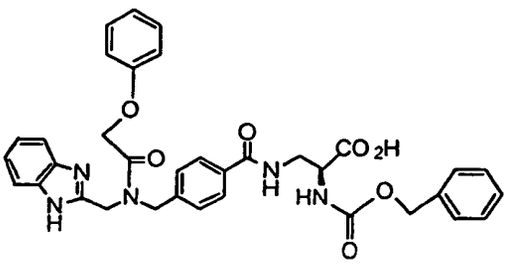


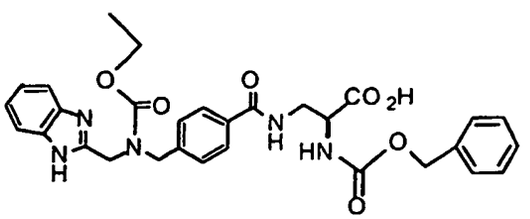


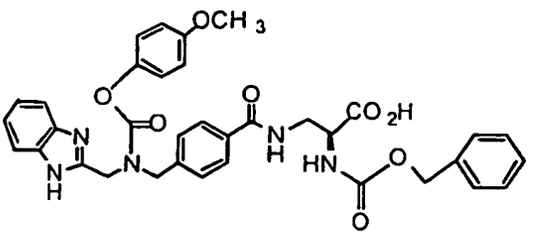


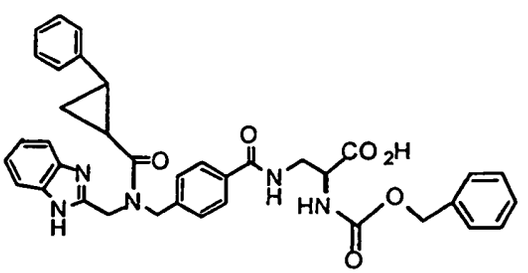


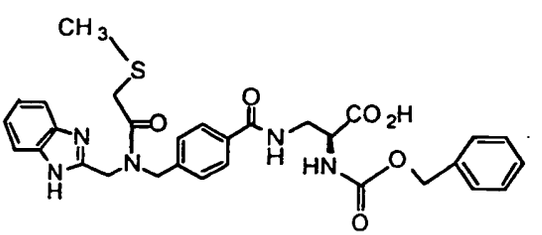


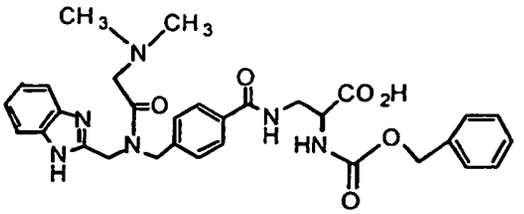


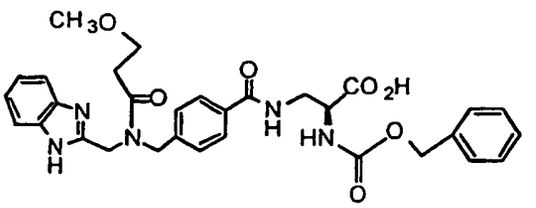


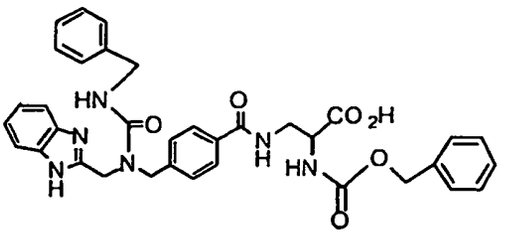


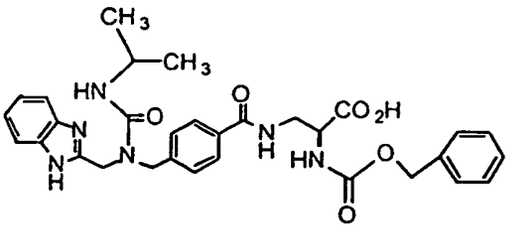


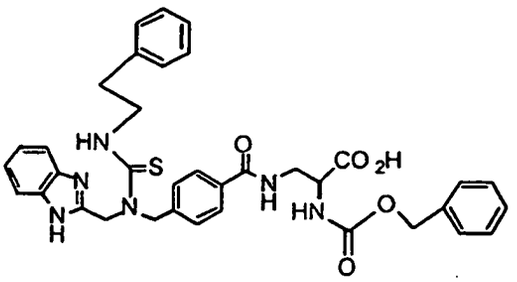


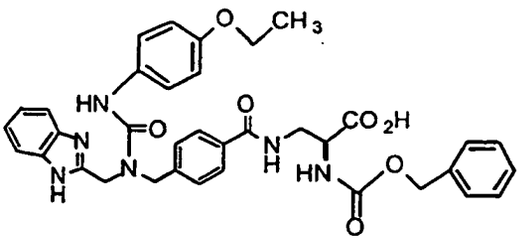


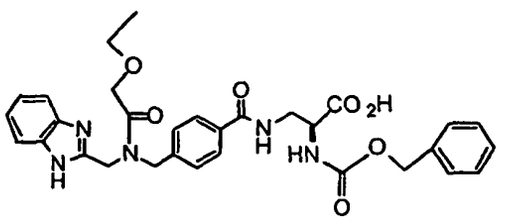


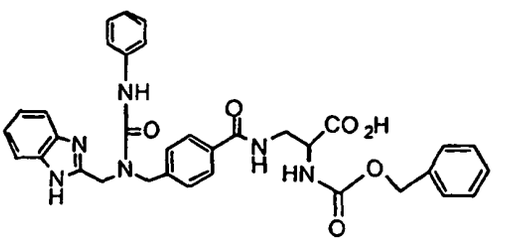


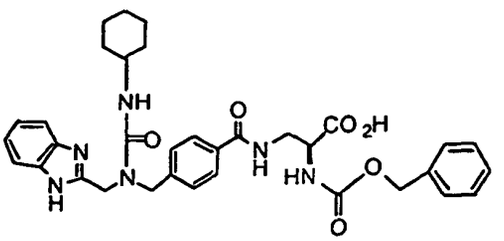


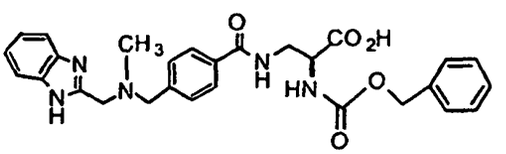


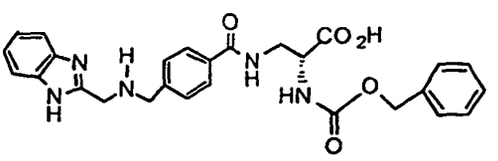


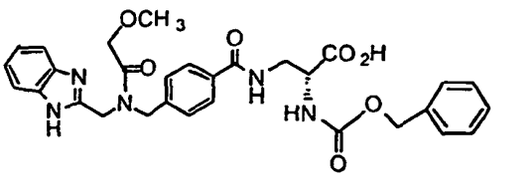


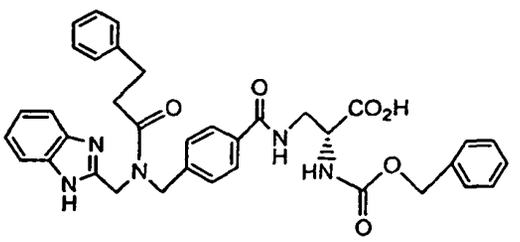


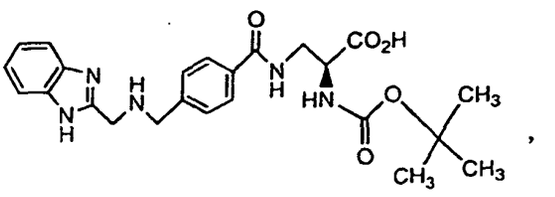


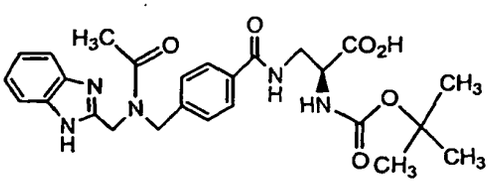


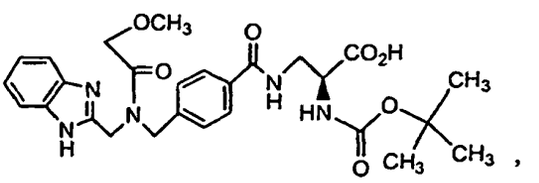


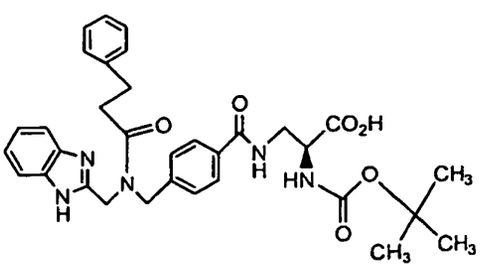


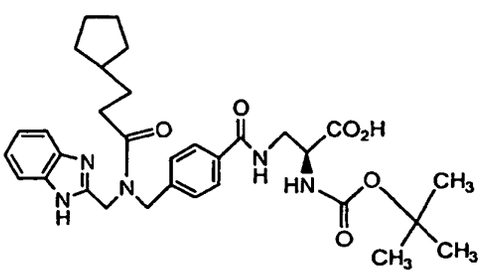


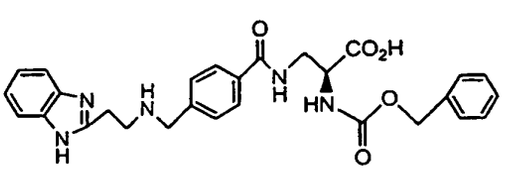


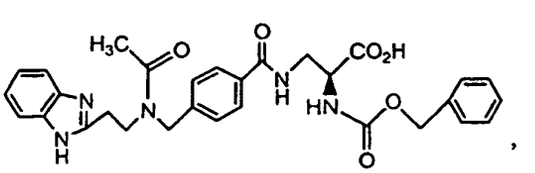


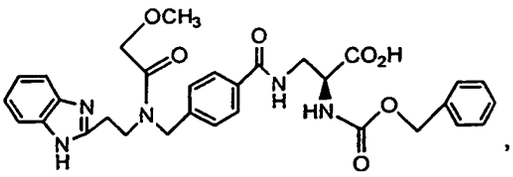


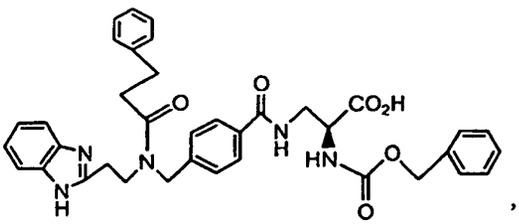


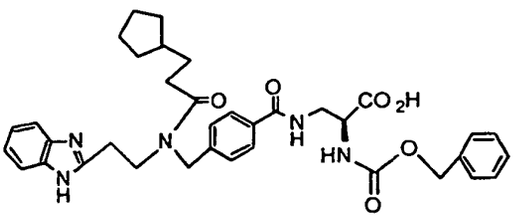


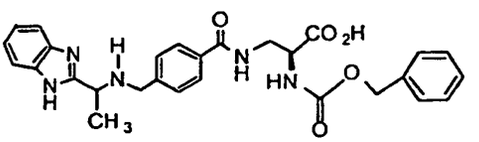


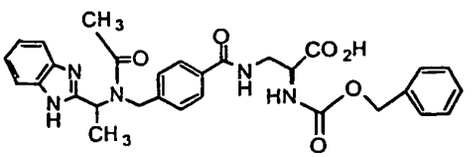


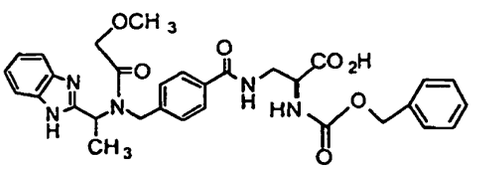


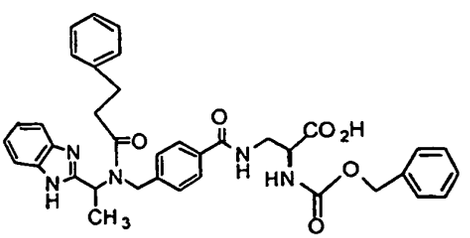


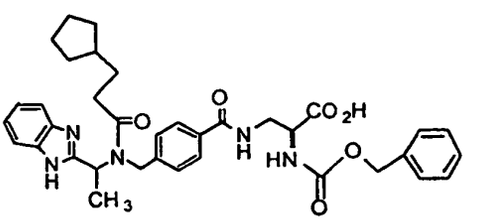


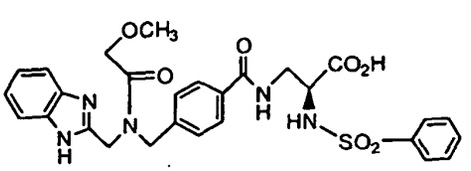


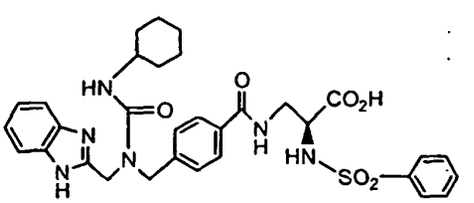


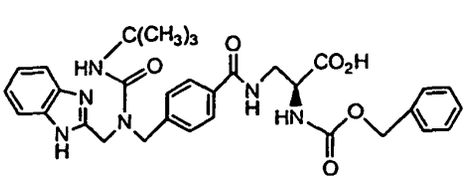


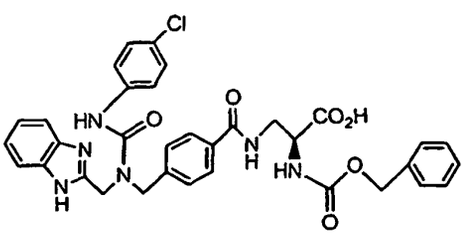


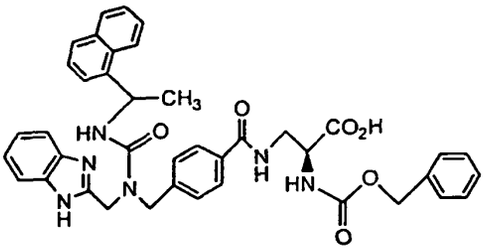








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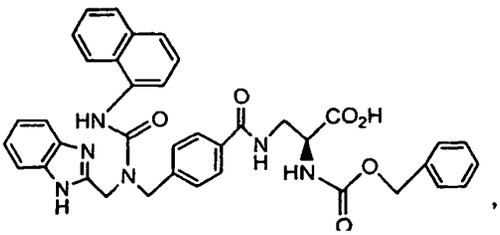
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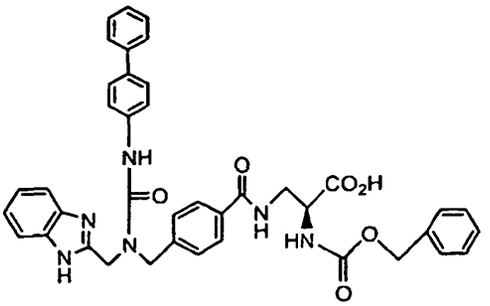
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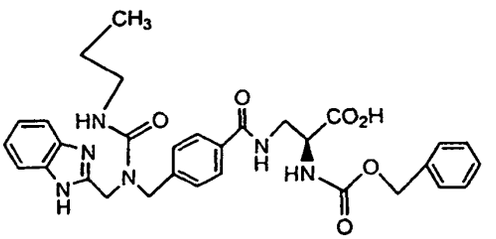
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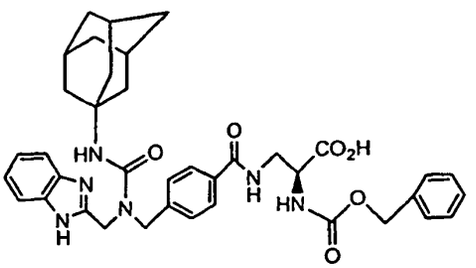
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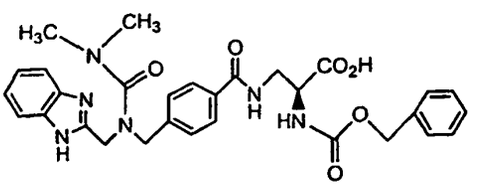
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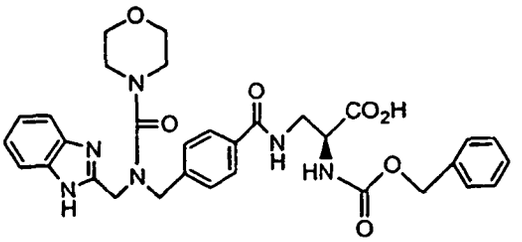
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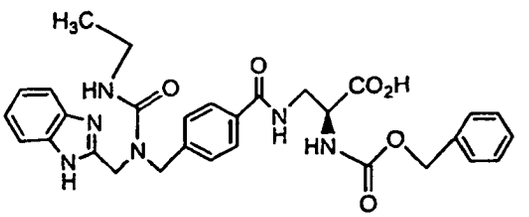
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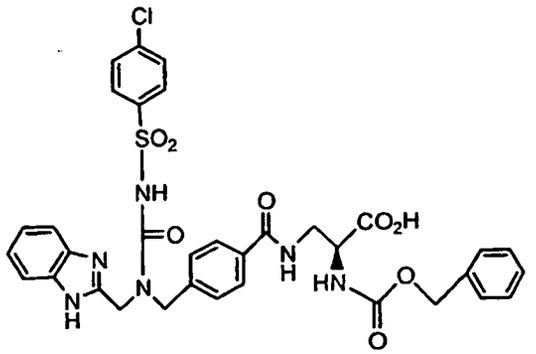
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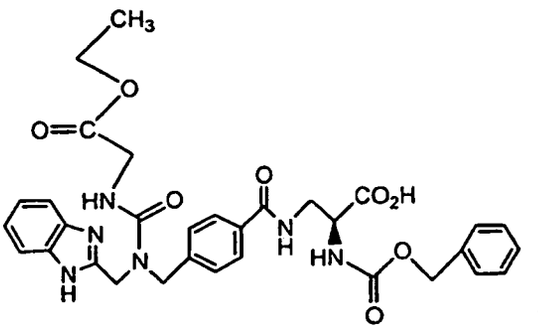
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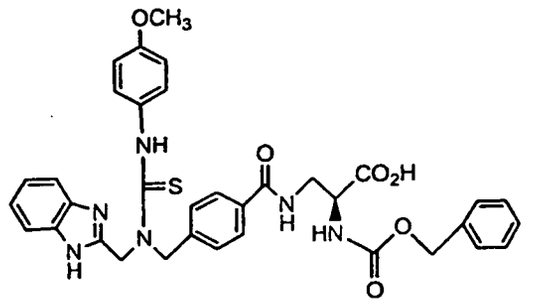
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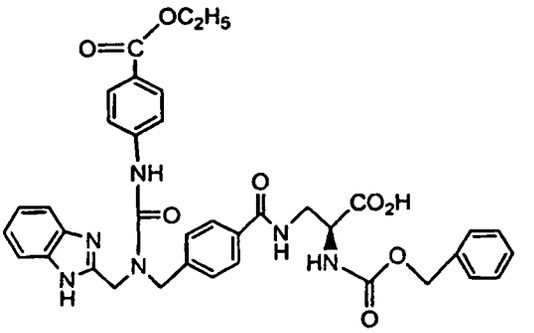
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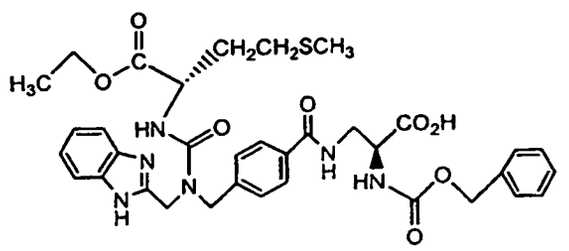
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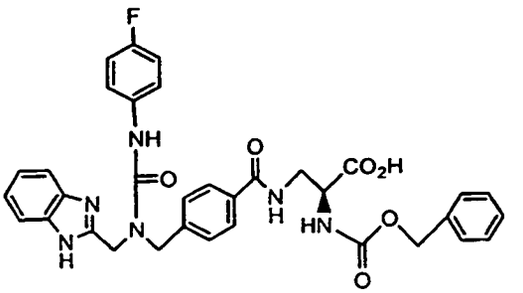
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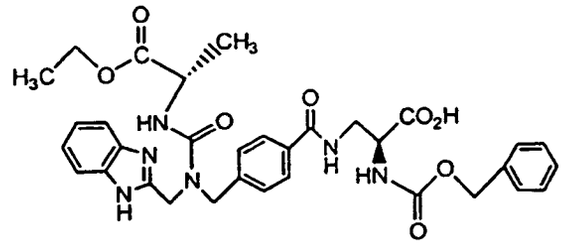
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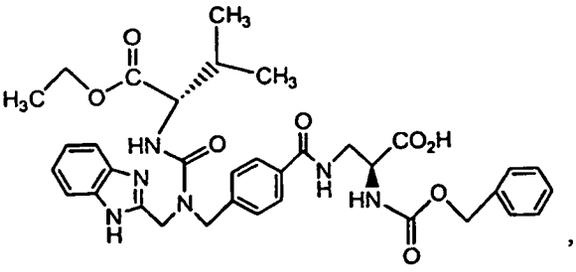
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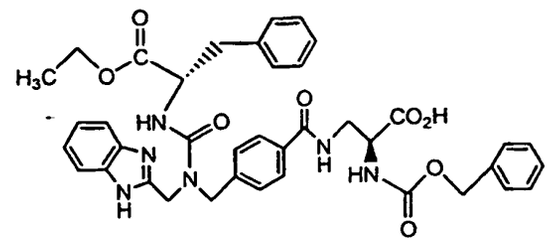
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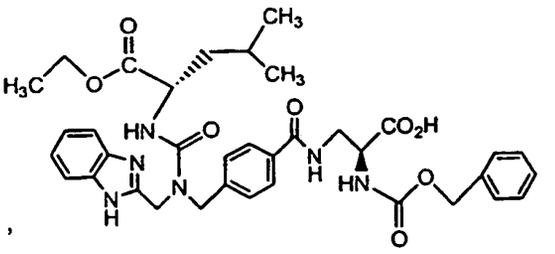
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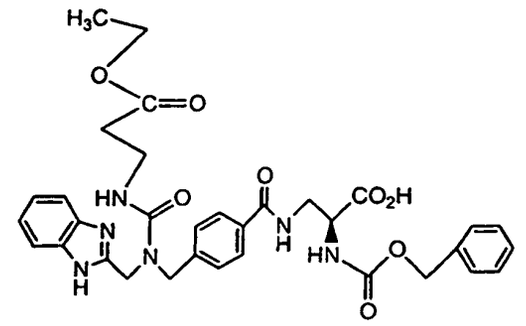
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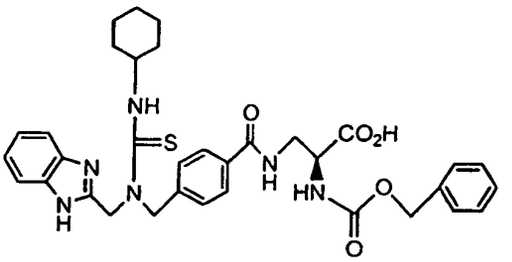
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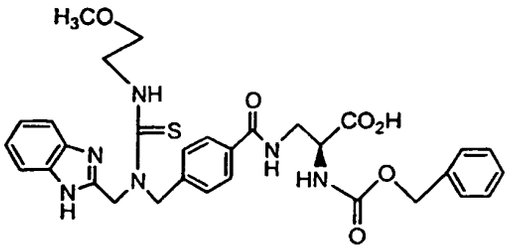
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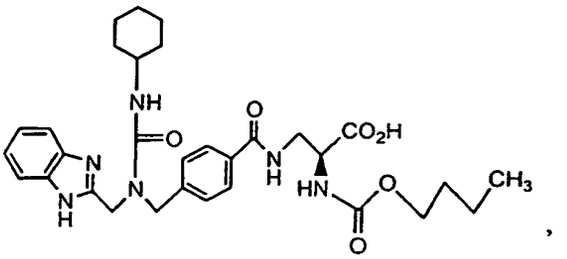
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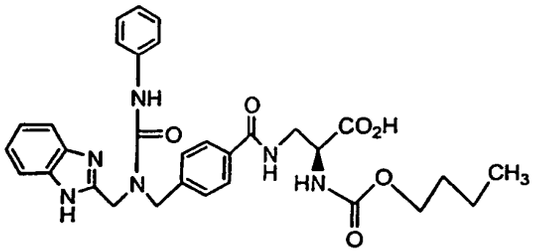
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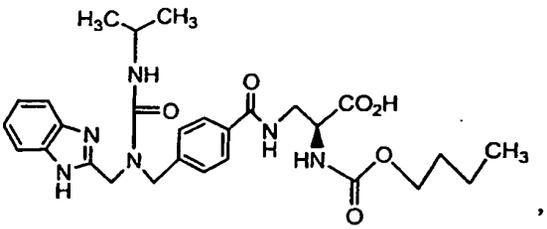
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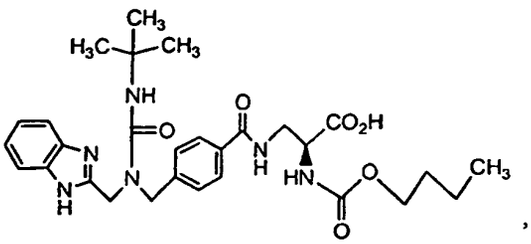
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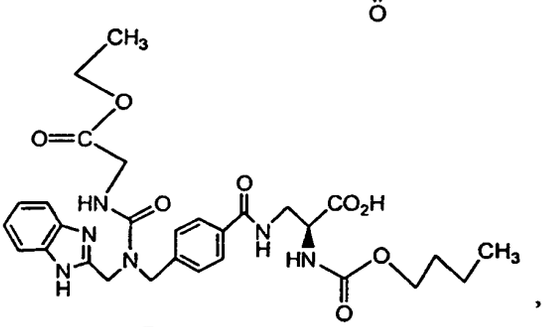
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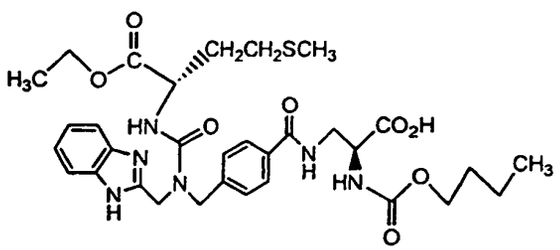
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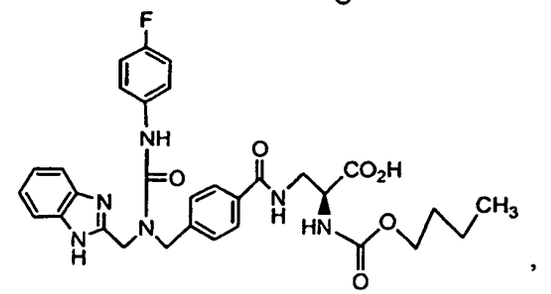
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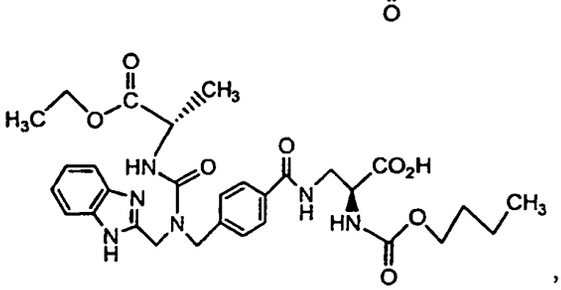
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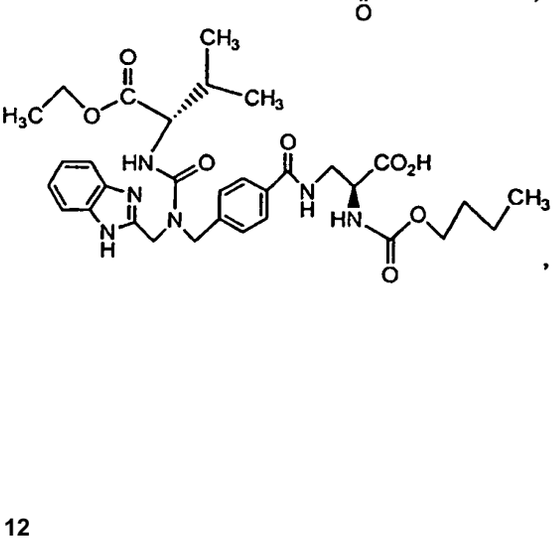
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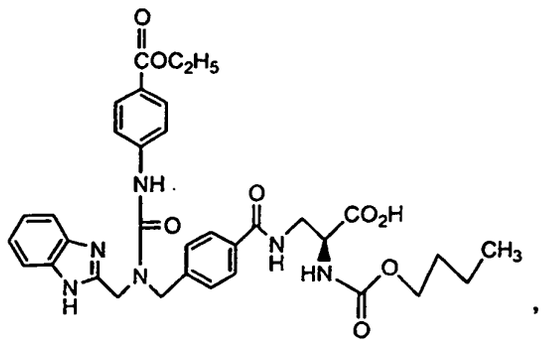
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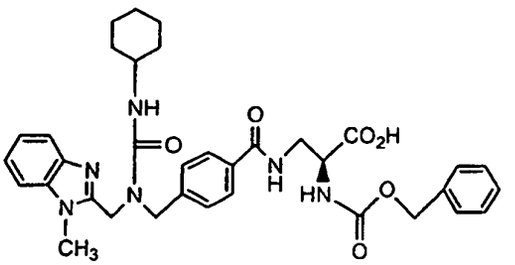
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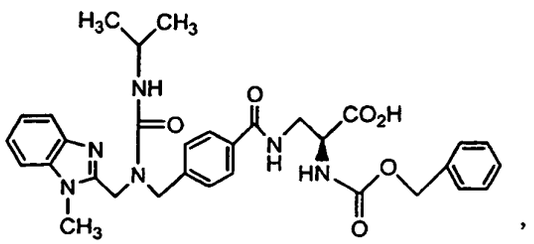
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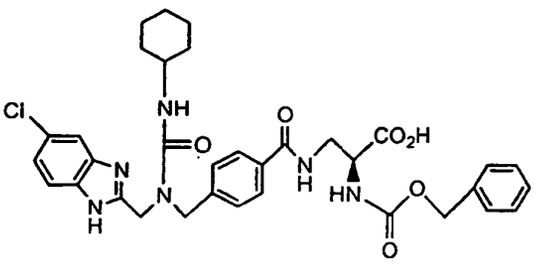
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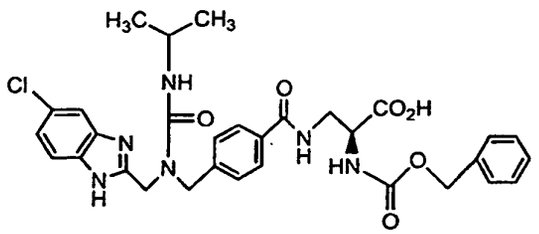
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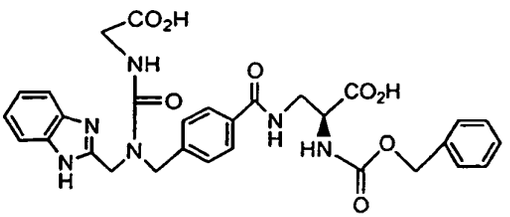
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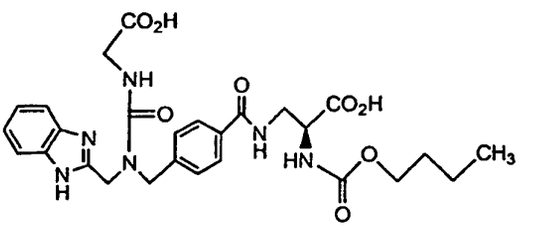
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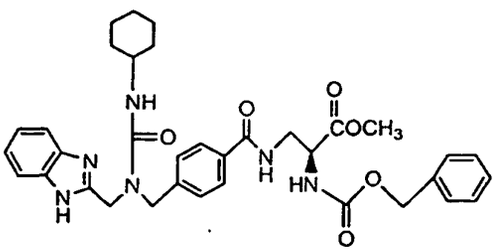
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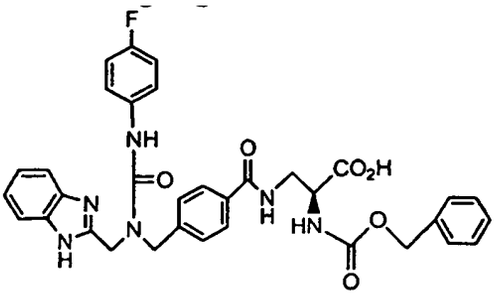
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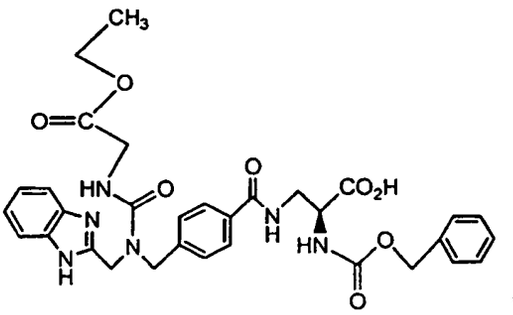
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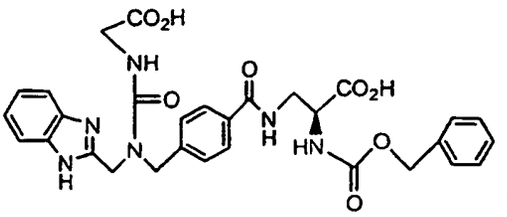
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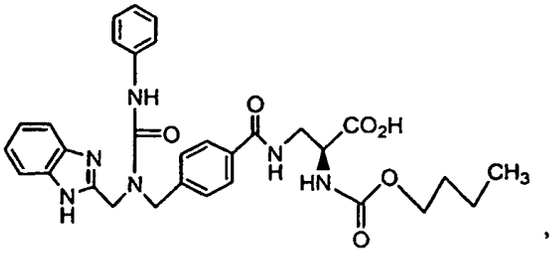
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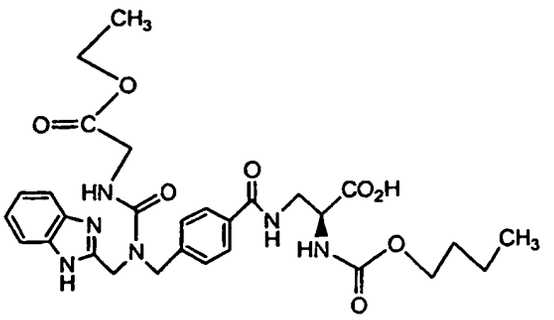
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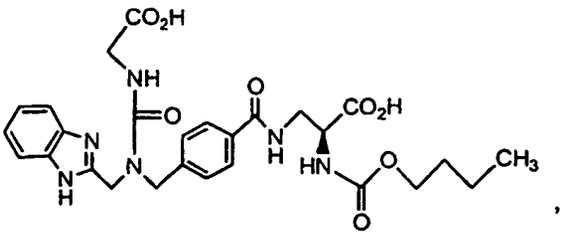
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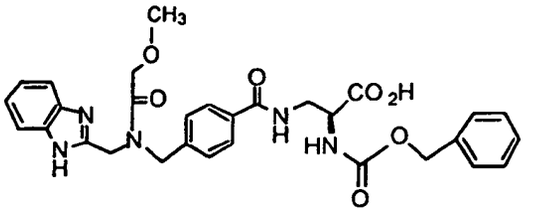
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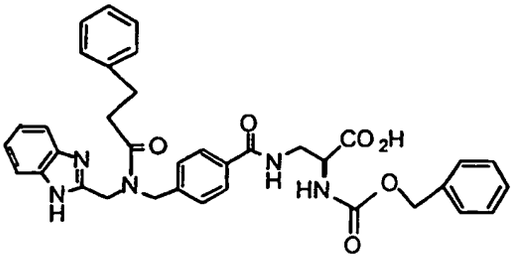
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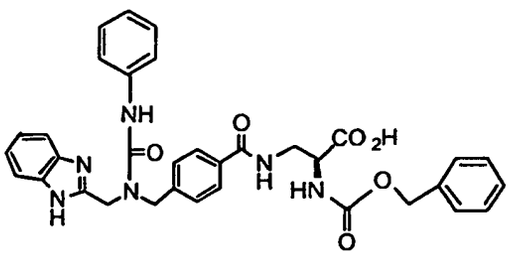
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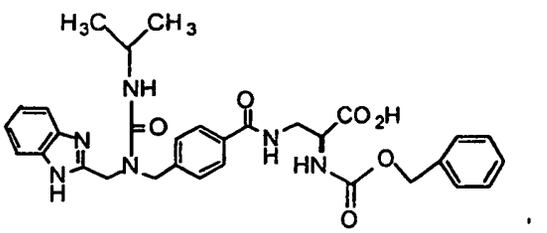
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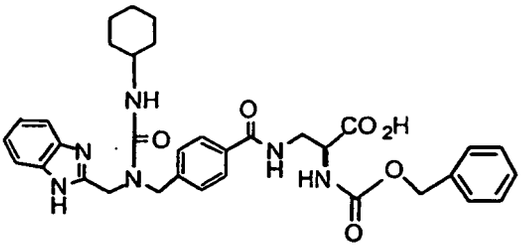


are particularly preferred.

[0013] Preferably, the compounds of the present invention are selected from those having affinities that are greater than 100 fold more specific for $\alpha_v\beta_3$ than for $\alpha_{IIb}\beta_3$.

[0014] As used herein, the following terms have the following meanings, unless defined otherwise:

"Alkyl" refers to straight or branched hydrocarbon chain groups having 1 to 20 carbon atoms, preferably, 1 to 6 carbon atoms.
"Alkoxy" refers to groups having the formula -OR, wherein R is alkyl.
"Aryl" refers to carbocyclic groups having at least one aromatic ring.
"Aralkyl" refers to groups having the formula aryl-R-, wherein R is alkyl.
"Arylcycloalkyl" refers to groups having the formula aryl-R-, wherein R is cycloalkyl.
"Arylalkoxy" refers to groups having the formula aryl-R-O-, wherein R is alkyl.
"Carboxy" refers to a group having the formula -C(O)OH.
"Carboxyalkyl" refers to groups having the formula, -R-C(O)OH, wherein R is alkyl.
"Carbamoyl" refers to a group having the formula $-C(O)NH_2$.
"Carbamoylalkyl" refers to groups having the formula $-R-C(O)NH_2$, wherein R is alkyl.
"Cbz" refers to benzyloxycarbonyl.
" CycloaDcyt" refers to a non-aromatic carbocyclic ring or multi-carbocyclic ring system of from 3 to 20 carbon atoms, preferably, 3 to 7 carbon atoms.
"Cycloalkylalkyl" refers to groups having the formula cycloalkyl-R-, wherein R is alkyl.
"Finoc" refers to 9-fluorenylmethoxycarbonyl.
"Heteroaryl" refers to aromatic carbocyclic groups, wherein one or more of the carbon atoms of such groups are replaced with a heteroatom selected from O, S and N.
"Heteroaralkyl" refers to groups having the formula heteroaryl-R-, wherein R is alkyl.
"Heterocycloalkyl" refers to a cycloalkyl group, wherein one or more of the carbon atoms of such group is replaced with O, S, NH, or N-alkyl.
"Hetetocycloalkylalkyl" refers to groups having the formula heterocycloalkyl-R-, wherein R is alkyl.
"Halo" refers to a halogen substituent.

[0015] The term "biolablile ester" means a pharmaceutically acceptable, biologically degradable ester derivative of a compound of formula (I), that is a prodrug which, upon administration to a animal or human being, is converted in the body to a compound of formula (I). Biolabile esters of the invention are as defined previously.

[0016] The term "vitronectin - mediated disorder" refers to a disease state or malady which is caused or exacerbated by a biological activity of vitronectin receptors. Disorders mediated by the vitronectin receptor include, without limitation, cancer, retinopathy, artheroselerosis, vascular restenosis, and osteoporosis.

[0017] The term "effective amount" refers to an amount of vitronectin receptor antagonist compound sufficient to exhibit a detectable therapeutic effect. The therapeutic effect may include, for example, without limitation, inhibiting the growth of undesired tissue or malignant cells, or increasing bone density. The precise effective amount for a subject will depend upon the subject's size and health, the nature and severity of the condition to be treated, and the like. The effective amount for a given situation can be determined by routine experimentation based on the information provided herein.

[0018] The following abbreviations are used for the solvents and reagents discussed herein: ethanol ("EtOH"); methanol ("MeOH"); acetic acid ("AcOH"); ethyl acetate ("EtOAc"); 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate ("HBTU"); 1-hydroxybenzotriazole ("HOBt"); bromo-tris-pyrrolidino-phosphonium hexafluorophosphate ("PyBroP"); N,N-dimethylformamide (" DMF"); trifluoroacetic acid ("TFA"); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (" EDCI"); and diisopropylethylamine ("DIPEA"). In addition, "Ph" represents a phenyl group; "tBu" represents a $-C(CH_3)_3$ group; "OtBu" represents an $-O-C(CH_3)_3$ group, "n-Bu" or "Bu-n" represents an n-butyl

group, "Et" represents an ethyl group, "Me" represents a methyl group, "Ac" represents an acetyl group, and "Boc" represents t-butoxycarbonyl.

[0019] The compounds of the invention have asymmetric carbon atoms, and therefore, all isomers, including enantiomers and diastereomers are within the scope of this invention. The invention includes *d* and *l* isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting chiral starting materials, or by separating isomers of compounds of formula (I).

[0020] Certain compounds of the present invention will be acidic in nature (e.g., those which have a carboxyl or phenolic hydroxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. The salt may be prepared by treating a solution of the compound with the appropriate base. Non-limitative examples of such salts are sodium, potassium, calcium, aluminum, gold and silver salts, and salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

[0021] Certain compounds of the invention will be basic in nature, and may form pharmaceutically acceptable salts with organic and inorganic acids. Non-limitative examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt.

[0022] It may be desirable when providing the compounds of the invention for oral administration to use the compounds of formula (I) in the form of a biolabile ester. The suitability of any particular ester-forming group can be assessed by conventional *in vivo* animal or *in vitro* enzyme hydrolysis studies. Thus, desirably, for optimum effect, the ester should only be hydrolysed after absorption is complete. Accordingly, the ester should be resistant to premature hydrolysis by digestive enzymes before absorption, but should be productively hydrolysed by, for example, gutwall, plasma or liver enzymes. In this way, the active acid is released into the bloodstream following oral absorption of the prodrug.

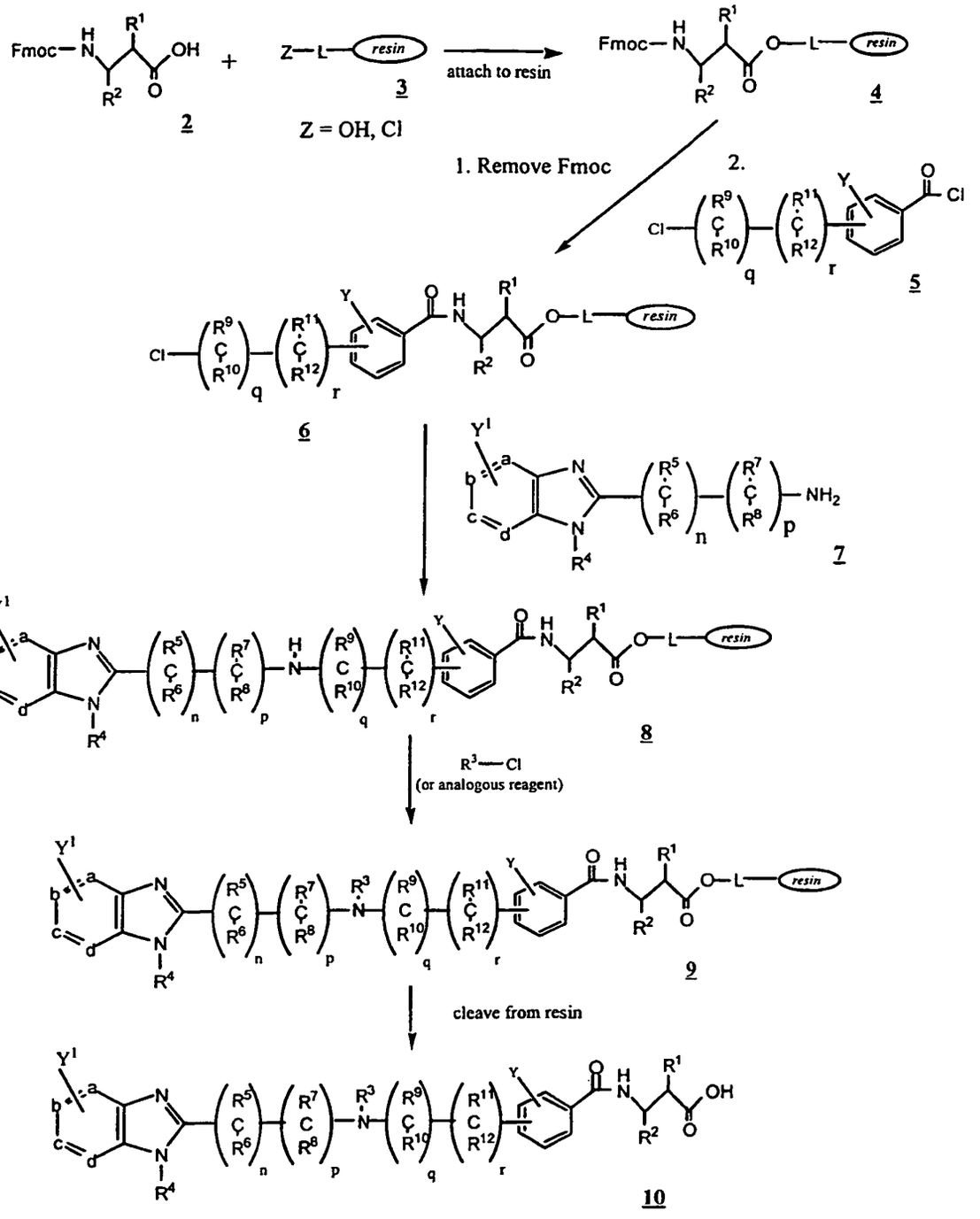
[0023] Suitable biolabile esters may include alkyl, alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl and alkoxycarbonyloxyalkyl esters, including cycloalkyl and aryl substituted derivatives thereof, aryl esters and cycloalkyl esters, wherein said alkyl, alkanoyl or alkoxy groups may contain from 1 to 8 carbon atoms and be branched-chain or straight-chain, said cycloalkyl groups may contain from 3-7 carbon atoms and said cycloalkanoyl groups from 4-8 carbon atoms wherein both are optionally benzo-fused, and said aryl and aroyl groups include substituted phenyl, naphthyl or indanyl ring systems. Preferably, the biolabile esters of the invention are C_1-C_4 alkyl esters. More preferably, they are methyl, ethyl and pivaloyloxymethyl esters.

[0024] Biolabile esters may be obtained from the acids of formula (I) by standard reactions well known to persons skilled in the art. For example, aryl and alkyl esters can be synthesized via activation of a carboxylic acid group of (I) in a variety of ways, such as by forming the acyl chloride, followed by reaction with the required phenol or alcohol. Alternatively, alkyl esters are obtainable by alkylation of a suitable alkali, or alkaline earth, metal carboxylate salt of a compound of formula (I).

[0025] The compounds of the present invention may be prepared according to the following reaction scheme (Scheme I):

SCHEME 1

[0026]



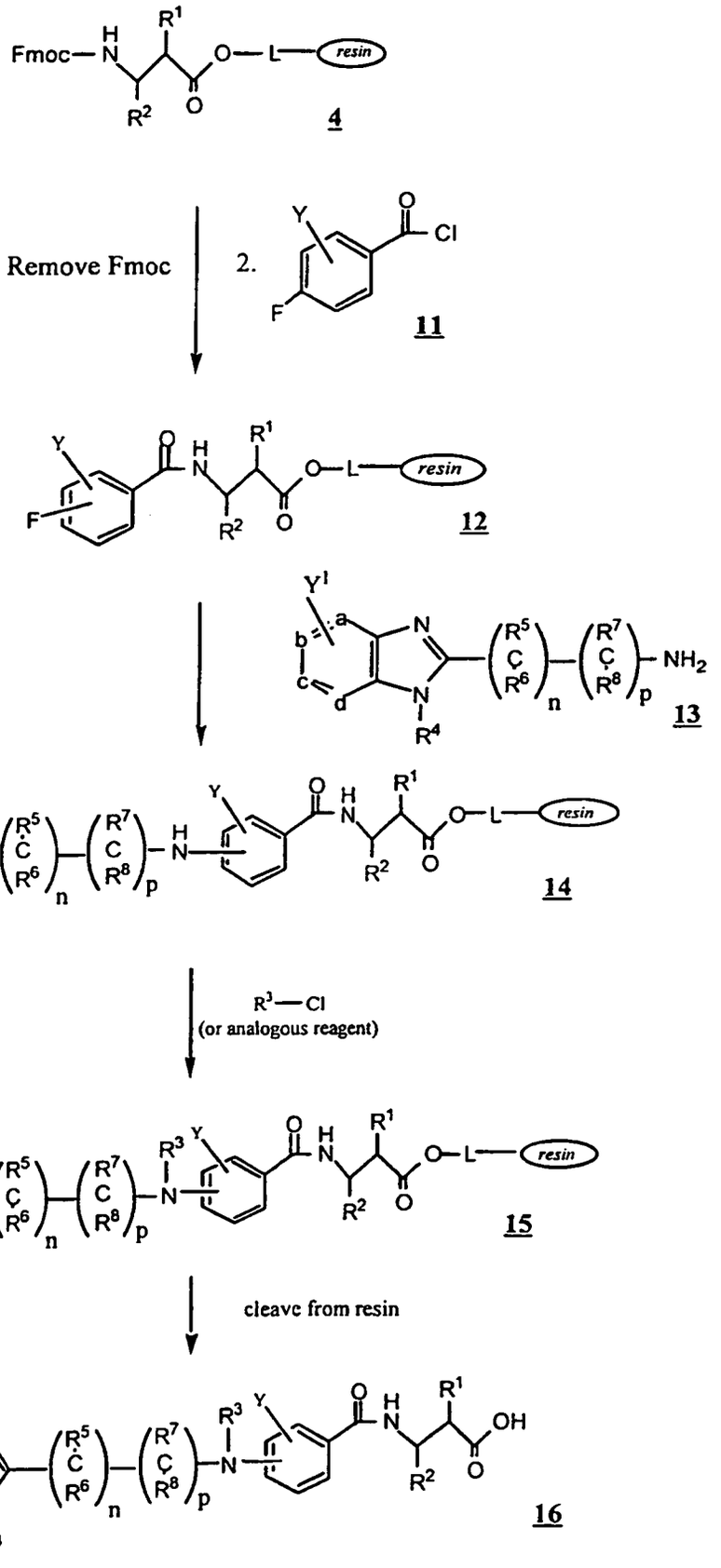
[0027] In Scheme 1, which depicts a solid phase preparation of compounds wherein at least one of q or r is 1, compound **2** is attached by conventional means to a polymeric resin 3 (e.g., a cross-linked polystyrene or a polyethylene glycol/polystyrene copolymer) through a cleavable acid labile linker, L, having an -OH or -Cl group, e.g., Wang, Sasrin and chlorotrityl resin, to form resin compound **4**. For example, the attachment to the resin may be carried out by reacting compound **2** with the resin **3** (Cl-form) in the presence of DIPEA in an organic solvent, e.g., DMF or methylene chloride. The Fmoc group of compound **4** is removed by conventional means, e.g., by treating with piperidine in DMF at 0˚ to 80˚C, and acylated with benzoyl chloride **5** to form amide **6**. The acylation is preferably carried out in an organic solvent (e.g., methylene chloride or DMF) at 0˚ to 80˚C in the presence of a tertiary amine, preferably DIPEA. Amide **6** is reacted with benzimidazole-amine **7** in a displacement reaction to produce compound **8**. The displacement reaction is preferably carried out by shaking the reactants in DMF for an extended period, preferably 1-2 days. For compounds in which the R^3 group is not H, such compounds may be made by subjecting compound **8** to conventional reactions to add the R^3 substituent to form compound **9**. For example, depending on the desired substituent, compound **8** may be reacted with

a carboxylic acid, an acyl chloride, acyl anhydride, isocyanate, carbamoyl chloride, isothiocyanate, alkyl halide, alkyl sulfonate, or epoxide, or alternatively, compound **8** may be subjected to reductive alkylation with an aldehyde or ketone. Compound 10 is formed by cleavage from the linker and the resin portion of compound **9** by conventional means, e.g., by treating with dilute TFA in methylene chloride at ambient temperature for 10 to 60 minutes. If desired, compound 10 may be converted to a biolabile ester by standard esterification methods.

[0028] Compounds wherein q and r are both 0 may be prepared according to the solid phase synthesis shown in Scheme 2, below.

SCHEME 2

[0029]



[0030] In Scheme 2, compound **4,** prepared as described in Scheme 1, is treated with piperidine in DMF at 0˚ to 80˚C, and acylated with benzoyl chloride **11** to form amide **12.** The acylation is preferably carried out in an organic solvent

(e.g., methylene chloride or DMF) at 0˚ to 80˚C in the presence of a tertiary amine, preferably DIPEA. Amide **12** is subsequently reacted with a benzimidazole **13** to form compound **14,** and if desired, reacted with a suitable reagent to add the R^3 group under the conditions described for Scheme 1 to form compound **15.** Compound **16** is formed by cleavage from the linker and resin portion of compound **15** under the conditions described in Scheme 1. If desired, compound **16** may be converted to a biolabile ester by standard esterification methods. The starting compounds and reagents used in the foregoing schemes are either commercially available or may be prepared by methods well-known to those skilled in the art.

[0031] Those skilled in the art will recognize that reactive groups in the foregoing reaction schemes (e.g., carboxyl, amino, hydroxy) may be protected if desired or necessary with conventional protecting groups that can be subsequently removed by standard procedures. See, e.g., McOmie, Protecting groups In Organic Chemistry, Plenum Press, N.Y., 1973, and Greene and Wuts, Protecting Groups In Organic Synthesis, 2nd Ed., John Wiley & Sons, N.Y. 1991.

[0032] As an alternative to solid phase synthesis, the compounds of the present invention may be prepared by solution synthesis, employing appropriate protective groups for reactive groups. Particularly useful for carboxy protection are t-butyl esters, although other groups such as allyl and benzyl are also suitable. Intermediate esters may be converted to the acids by appropriate deprotection methods.

[0033] For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

[0034] For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

[0035] Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral inj ection.

[0036] Liquid form preparations may also include solutions for intranasal administration.

[0037] Opthalmic preparations may be formulated using commercially available vehicles such as Sorbi-care® (Allergan) or Neodecadron® (Merck, Sharp & Dohme).

[0038] Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

[0039] Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

[0040] The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

[0041] Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

[0042] The quantity of active compound in a unit dose of preparation may be varied or adjusted from 0.01 mg to 1000 mg, more preferably from 0.1 mg to 200 mg, most preferably from 5 mg to 100 mg, according to the particular application.

[0043] The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

[0044] The amount and frequency of administration of the compounds of the invention will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 0.02 mg to 4,000 mg/day, preferably 0.2 mg to 800 mg/day, most preferably 10 mg to 400 mg/day in two to four divided doses to block tumor growth.

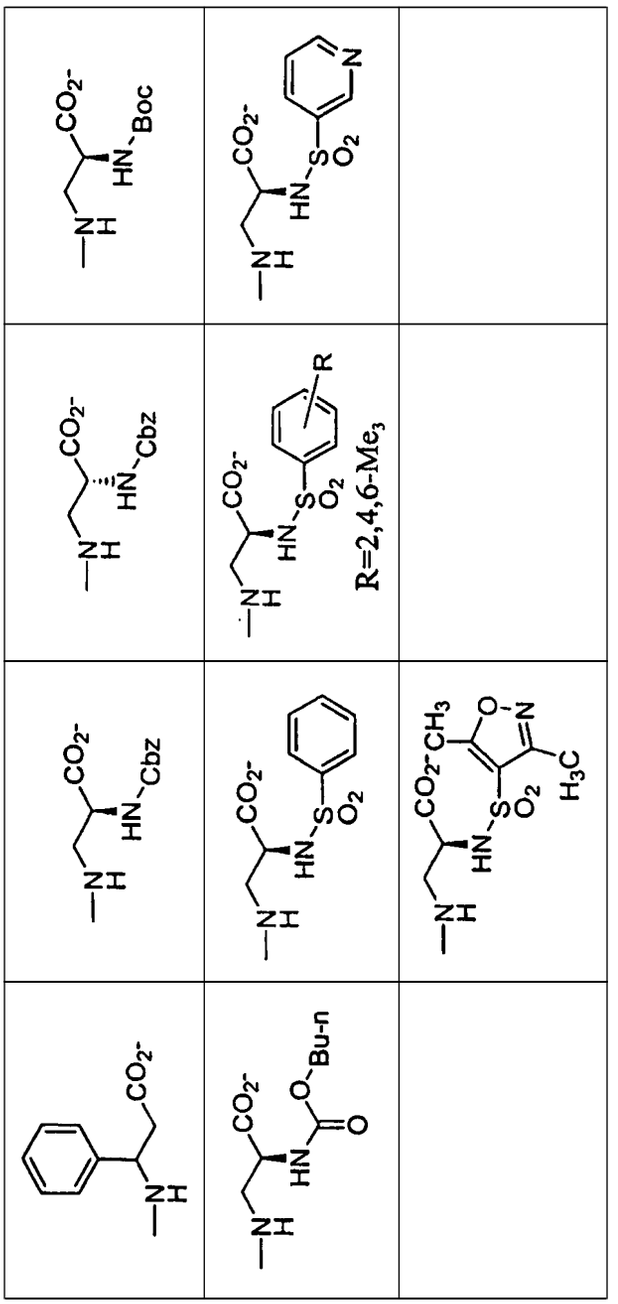
[0045] The following examples illustrate the foregoing invention, although such examples should not be construed as limiting the scope of the invention. Alternative mechanistic pathways and analagous structures within the scope of the invention will be apparent to those skilled in the art.

EXAMPLES

[0046] In the Examples below, the "funnel apparatus" is a sintered glass funnel for agitating the contents with nitrogen and removal of the solvent by filtration. Where resins are "washed" with solvent, e.g., (20 mL x 5), the resin in solvent

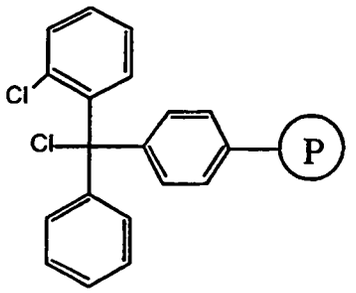
(20 mL) is agitated for 2 minutes in a funnel apparatus, and solvent is removed by filtration (draining), and this sequence is repeated 4 additional times.

[0047] For the Examples below, "AA" refers to

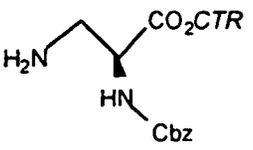

R=2,4,6-Me3

depending on the particular compounds used from the preparative examples. "-U-" refers to $-CH_2-$, $-CH_2-CH_2-$, or $-CH(CH_3)-$, depending on the particular compounds used from the preparative examples.

[0048] "2-chlorotrityl resin, chloride form" refers to



wherein  represents the resin (polymer) portion. "*CTR*" refers to 2-chlorotrityl resin. Thus, for example, N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin refers to



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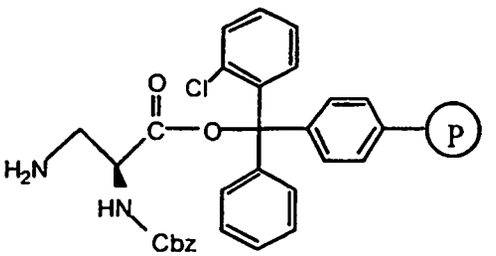
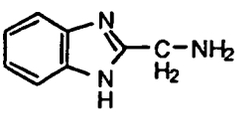


Preparation 1

2-(Aminomethyl)benzimidazole

[0049]

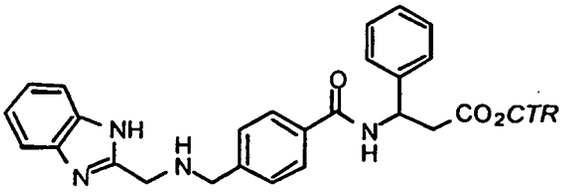


[0050] Add 2-(aminomethyl)bcnzimidazole, dihydrochloride, hydrate (18.50 g) to a solution of potassium hydroxide (9.50 g) in methanol (400 mL). Stir the resulting mixture at room temperature for 30 minutes, filter, and concentrate the filtrate *in vacuo.* Extract the residue with EtOAc (5 x 500 mL) and filter. Concentrate the filtrate *in vacuo* to give the title compound as a white solid (9.60 g).

Preparation 2

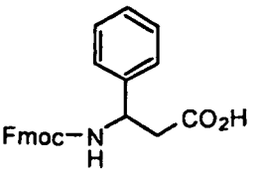
[3-[4-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl]amino]-3-phenyl-propionic acid on 2-chlorotrityl resin

[0051]



Step 1. 3-Fmoc-amino-3-phenylpropionic acid

[0052]

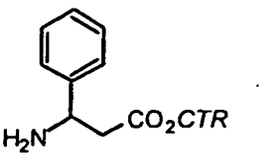


[0053] Combine 3-amino-3-phenylpropionic acid (3.70 g, 22.4 mmol) and $NaHCO_3$ (8.42 g, 100 mmol) in acetone (50 mL) and water (50 mL). Cool in an ice-bath. Add Fmoc-O-hydroxysuccinimide (9.40 g, 28.0 mmol), and stir the resulting mixture for 3 hours while the ice melts. Concentrate the mixture *in vacuo,* and extract the aqueous portion with EtOAc. Wash the EtOAc solution with 5% glacial acetic acid in water (3 x 300 mL), 5% NaHCO3 solution (3 x 300 mL) and brine (3 x 300 mL). Concentrate the dried ($MgSO_4$) EtOAc solution *in vacuo* to give the title compound (contains Fmoc-O-hydroxysuccinimide) as a white foam which is used in Step 2.

[0054] Reference: W. M. Kazmierski, Int. J. Pep. Prot. Res., **45**, 242 (1995).

Step 2. 3-Amino-3-phenylpropionic acid on 2-chlorotrityl resin

[0055]



[0056] **Step 2a**. To a solution of DIPEA (1.6 mL) in DMF (10 mL), add the crude product (Preparation 2, Step 1) (0.64 g). Add 2-chlorotrityl resin, chloride form (2.00 g, 0.65 mmol/g). Agitate the resulting mixture for 30 minutes. Add MeOH (0.44 mL), agitate the mixture for 10 minutes, and drain. Wash the resin with DMF (30 mL x 5) and then CH_2Cl_2 (30 mL x 5) to give 3-Fmoc-amino-3-phenylpropionic acid on 2-chlorotrityl resin.

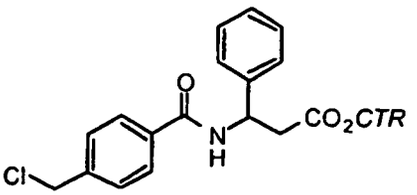
[0057] **Step 2b.** Wash the resin (Preparation 2, Step 2a) with DMF (20 mL x 5). Add 20% piperidine in DMF (30 mL), agitate for 15 minutes, and collect the filtrate. Repeat two times. To determine loading level, combine filtrates in 100 mL volumetric flask, and add DMF to 100 mL (Solution A). Dilute Solution A (0.2 mL) to 100 mL in a volumetric flask. UV absorbance at 301 nM: 0.374

$$0.374 \times \text{concentration}/7800$$

$$0.374 \times 20{,}000/7800 = 0.959 \text{ mmol}/ 2 \text{ g } (0.479 \text{ mmol/g})$$

Step 3. 3-(4-Chloromethylbenzoyl)amino-3-phenylpropionic acid on 2-chlorotrityl resin

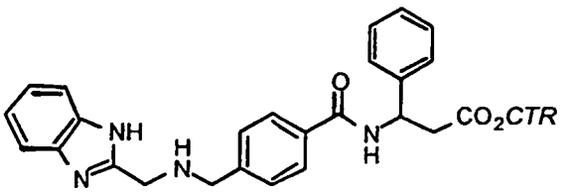
[0058]



[0059] Place resin (Preparation 2, Step 2b) (2.00 g, 0.959 mmol) in CH_2Cl_2 (5 mL) in a vial, and treat with DIPEA (1.84 mL, 10.6 mmol), followed by 4-chloromethylbenzoylchloride (1.89 g, 9.6 mmol). Seal vial and place on a shaker for 2.5 hours. Transfer resin to funnel apparatus. Wash the resin with CH_2Cl_2 (20 mL x 3), DMF (20 mL x 3) and then CH_2Cl_2 (20 mL x 3) to yield title resin.

Step 4. 3-[4-(Benzimidazol-2-ylmethyl)aminomethylbenzoylamino-3-phenylpropionic acid on 2-chlorotrityl resin

[0060]

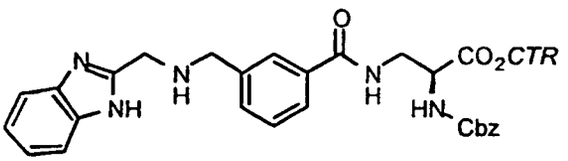


[0061] Shake the resin (Preparation 2, Step 3) (2.00 g, 0.479 mmol) and 2-(aminomethyl)benzimidazole (9.6 g) (Preparation 1) in DMF (25 mL) in a sealed vial for 44 hours. Transfer resin to funnel apparatus, and wash the resin with DMF (25 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give the title resin.

Preparation 3

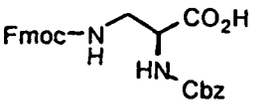
N^3-[3-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl]-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0062]



Step 1. N^3-Fmoc-N^2-Cbz-L-2,3-diaminopropionic acid

[0063]

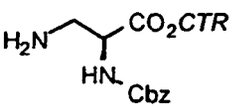


[0064] Combine N^2-Cbz-L-2,3-diaminopropionic acid (2.66 g, 11.27 mmol) and NaHCO3 (4.21 g, 50 mmol) in acetone (25 mL) and water (25 mL). Cool in an ice-bath. Add Fmoc-O-hydroxysuccinimide (4.70 g, 14.0 mmol), and stir the resulting mixture for 3 hours while the ice melts. Concentrate the mixture *in vacuo,* and extract the aqueous portion with EtOAc. Wash the EtOAc solution with 5% glacial acetic acid in water (3 x 125 mL), 5% NaHC03 solution (3 x 100 mL) and brine (3 x 100 mL). Concentrate the dried ($MgSO_4$) EtOAc solution *in vacuo* to give the title compound (contains Fmoc-O-hydroxysuccinimide) as a white foam (5.12 g) which is used in Step 2.

[0065] Reference: W. M. Kazmierski, Int. J. Pep. Prot. Res., **45**, 242 (1995).

Step 2. N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0066]



[0067] **Step 2a**. To a solution of DIPEA (1.47 mL) in DMF (30 mL), add the crude product of Preparation 3, Step 1 (1.5 g). Add 2-chlorotrityl resin, chloride form (2.0 g, 0.65 mmol/g). Agitate the resulting mixture for 30 minutes. Add MeOH (0.86 mL), and agitate the mixture for 10 minutes, and drain. Wash the resin with DMF (30 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give N^3-Fmoc-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin.

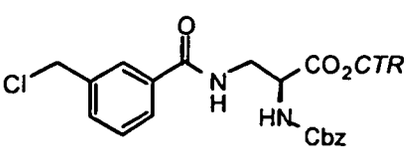
[0068] **Step 2b**. Wash the resin (Preparation 3, Step 2a) with DMF (20 mL x 5). Add 20% piperidine in DMF (30 mL), agitate for 15 minutes, and collect the filtrate. Repeat two times. Determine the loading as in Preparation 2. Measure UV absorbance at 301 nM: 0.391

$$0.391 \times \text{concentration}/7800$$

$$0.391 \times 20{,}000/7800 = 1.0026 \text{ mmol}/\ 2 \text{ g } (0.501 \text{ mmol/g})$$

Step 3. N^3-(3-Chloromethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0069]

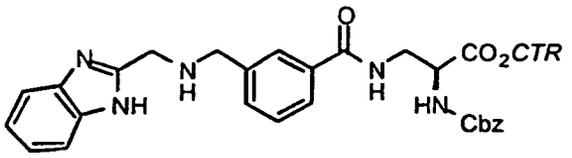


[0070] Place resin (Preparation 3, Step 2b) (1.00 g, 0.50 mmol) in CH_2Cl_2 (5 mL) in a vial, and treat with DIPEA (0.96 g, 5.5 mmol), followed by 3-chloromethylbenzoyl chloride (0.95 g, 5 mmol). Seal vial and place on a shaker for 2.5 hours. Transfer resin to funnel apparatus. Wash the resin with CH_2Cl_2 (20 mL x 3), DMF (20 mL x 3) and then CH_2Cl_2 (20 mL

x 3) to yield title resin.

Step 4. N^3-[3-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0071]

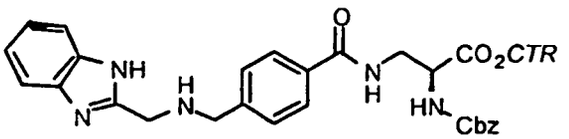


[0072] Shake the resin from Preparation 3, Step 3 (1.00 g, 0.5 mmol) and 2-(aminomethyl)benzimidazole (5 g) (Preparation 1) in DMF (25 mL) in a sealed vial for 44 hours. Transfer resin to funnel apparatus, and wash the resin with DMF (25 mL x 5) and then CH_2Cl_2 (20 mL x 3) to give the title resin.

Preparation 4

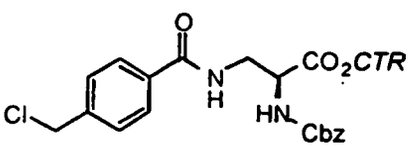
N^3-[4-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0073]



Step 1. N^3-(4-Chloromethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

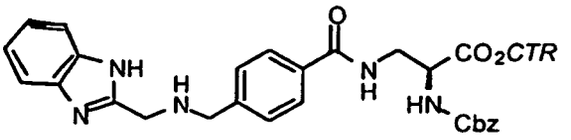
[0074]



[0075] Place resin (Preparation 3, Step 2b) (1.00 g, 0.50 mmol) in CH_2Cl_2 (5 mL) in a vial, and treat with DIPEA (0.96 g, 5.5 mmol,) followed by 4-chloromethylbenzoyl chloride (0.95 g, 5 mmol). Seal vial and place on a shaker for 2.5 hours. Transfer resin to funnel apparatus. Wash the resin with CH_2Cl_2 (20 mL x 3), DMF (20 mL x 3) and then CH_2Cl_2 (20 mL x 3) to yield title resin.

Step 2. N^3-[4-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0076]

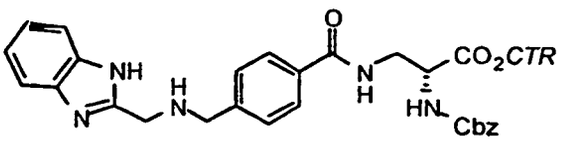


[0077] Shake the resin from Step 1 (1.0 g, 0.5 mmol) and 2-(aminomethyl)benzimidazole (5.00 g) (Preparation 1) in DMF (25 mL) in a sealed vial for 44 hours. Transfer resin to funnel apparatus, and wash the resin with DMF (25 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give the title resin.

Preparation 5

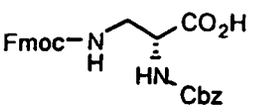
N^3-[4-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl]-N^2-Cbz-D-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0078]



Step 1. N^3-Fmoc-N^2-Cbz-D-2,3-diaminopropionic acid

[0079]

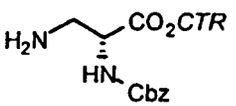


[0080] Combine N^2-Cbz-D-2,3-diaminopropionic acid (1.3 g, 5.6 mmol) and $NaHCO_3$ (2.10 g, 25 mmol) in acetone (15 mL) and water (15 mL). Cool in an ice-bath. Add Fmoc-O-hydroxysuccinimide (2.35 g, 7.0 mmol), and stir the resulting mixture for 3 hours while the ice melts. Concentrate the mixture *in vacuo,* and extract the aqueous portion with EtOAc. Wash the EtOAc solution with 5% glacial acetic acid in water (3 x 60 mL), 5% NaHC03 solution (3 x 50 mL) and brine (3 x 50 mL). Concentrate the dried ($MgSO_4$) EtOAc solution *in vacuo* to give the title compound (contains Fmoc-O-hydroxysuccinimide) as a white foam which is used Step in 2.

[0081] Reference: W. M. Kazmierski, Int. J. Pep. Prot. Res., **45**, 242 (1995).

Step 2. N^2-Cbz-D-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0082]



[0083] **Step 2a**. To a solution of DIPEA (0.8 mL) in DMF (10 mL), add the crude product from Preparation 5, Step 1 (0.81 g). Add 2-chlorotrityl resin, chloride form (1.00 g) (0.65 mmol/g). Agitate the resulting mixture for 30 minutes. Add

MeOH (0.4 mL), and agitate the mixture for 10 minutes, and drain. Wash the resin with DMF (30 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give N^3-Fmoc-N^2-Cbz-D-2,3-diaminopropionic acid on 2-chlorotrityl resin.

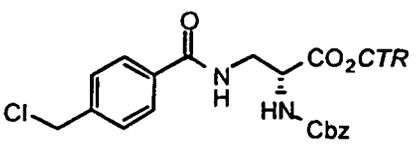
[0084] **Step 2b**. Wash the resin from Preparation 5, Step 2a with DMF (20 mL x5). Add 20% piperidine in DMF (30 mL), agitate for 15 minutes, and collect the filtrate. Repeat two times. Determine the loading as in Preparation 2. Measure UV absorbance at 301 nM: 0.154

$$0.154 \times \text{concentration}/7800$$

$$0.154 \times 20{,}000/7800 = 0.394 \text{ mmol/ g}$$

Step 3. N^3-(4-Chloromethylbenzoyl)-N^2-Cbz-D-2,3-diaminopropionic acid on 2-chlorotrityl resin

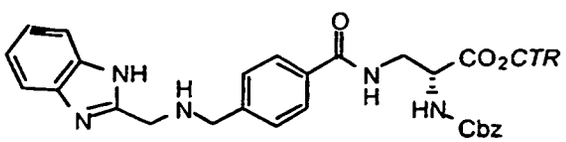
[0085]



[0086] Place resin (Preparation 5, Step 2b) (1.00 g, 0.394 mmol) in CH_2Cl_2 (5 mL) in a vial, and treat with DIPEA (0.75 mL, 4.33 mmol) followed by 4-chloromethylbenzoyl chloride (0.75 g, 3.94 mmol). Seal vial and place on a shaker for 2.5 hours. Transfer resin to funnel apparatus. Wash the resin with CH_2Cl_2 (20 mL x 3), DMF (20 mL x 3) and then CH_2Cl_2 (20 mL x 3) to yield title resin.

Step 4. N^3-[4-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl)-N^2-Cbz-D-2,3-diaminopropionic acid-2-chlorotrityl resin

[0087]

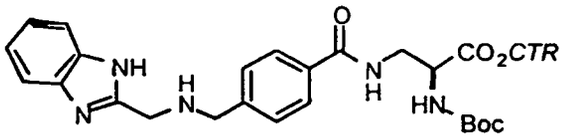


[0088] Shake the resin (Preparation 5, Step 3) (1.00 g, 0.394 mmol) and 2-(aminomethyl)benzimidazole (5.00 g) (Preparation 1) in DMF (25 mL) in a sealed vial for 44 hours. Transfer resin to funnel apparatus, and wash the resin with DMF (25 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give the title resin.

Preparation 6

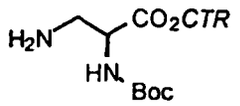
N^3-[4-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl]-N^2-Boc-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0089]



Step 1. N^2-Boc-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0090]



[0091] **Step 1a**. To a solution of DIPEA (1.60 mL) in DMF (10 mL), add (N^3-Fmoc- N^2-Boc-L-2,3-diaminopropionic acid) (0.72 g). Add the 2-chlorotrityl resin, chloride form (2.00 g) (0.65 mmol/g). Agitate the resulting mixture for 30 minutes. Add MeOH (0.8 mL), agitate the mixture for 10 minutes, and drain. Wash the resin with DMF (30 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give N^3-Fmoc-N^2-Boc-L-2,3-diaminopropionic acid on 2-chlorotrityl resin.

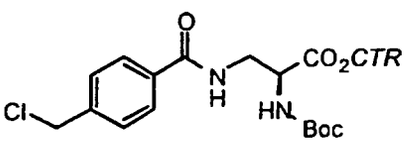
[0092] **Step 1b.** Wash the resin (Preparation 6, Step 1) with DMF (20 mL x 5). Add 20% piperidine in DMF (30 mL), agitate for 15 minutes, and collect the filtrate. Repeat two times. Determine the loading as in Preparation 2. Measure UV absorbance at 301 nM: 0.216

$$0.216 \times \text{concentration}/7800$$

$$0.216 \times 20{,}000/7800 = 0.276 \text{ mmol/ g}$$

Step 2. N^3-(4-Chloromethylbenzoyl)-N^2-Boc-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

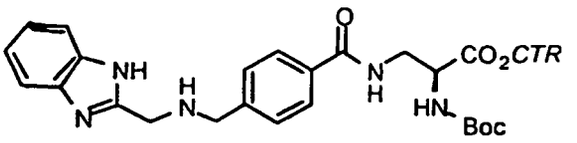
[0093]



[0094] Place resin (Preparation 6, Step 1b) (2.00 g, 0.55 mmol) in CH_2Cl_2 (5 mL) in a vial, and treat with DIPEA (1.05 g, 6.08 mmol) followed by 4-chloromethylbenzoyl chloride (1.04 g, 5.52 mmol). Seal vial and place on a shaker for 2.5 hours. Transfer resin to funnel apparatus. Wash the resin with CH_2Cl_2 (20 mL x 3), DMF (20 mL x3) and then CH_2Cl_2 (20 mL x 3) to yield title resin.

Step 3. N^3-[4-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl)-N^2-Boc-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0095]

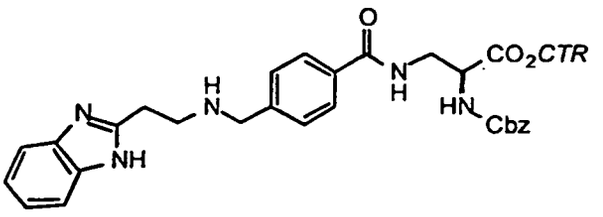


[0096] Shake the resin (Preparation 6, Step 2) (2.00 g, 0.55 mmol) and 2-(aminomethyl)benzimidazole (5.00 g) (Preparation 1) in DMF (25 mL) in a sealed vial for 44 hours. Transfer resin to funnel apparatus, and wash the resin with DMF (25 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give the title resin.

Preparation 7

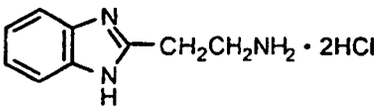
N^3-[4-[2-(Benzimidazol-2-yl)ethyl]aminomethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0097]



Step 1a. 2-[2-(Aminoethyl)]benzimidazole dihydrochloride

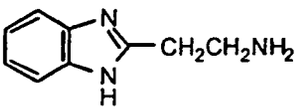
[0098]



[0099] Combine o-phenylenediamine (10.8 g, 100 mmol) and β-alanine (13.4 g, 150 mmol) in 6N HCl (100 mL). Heat at reflux 25 hours, allow to cool, and chill at -15˚C. Filter the solid and wash with cold 6N HCl, then cold EtOH. Dissolve the solid in 80% EtOH (125 mL), treat with decolorizing charcoal, and concentrate *in vacuo* to 40 g. Warm while adding EtOH (80 mL). Allow to cool, filter, and wash with EtOH to obtain the product as plates.

Step 1b. 2-[2-(Aminoethyl)]benzimidazole

[0100]

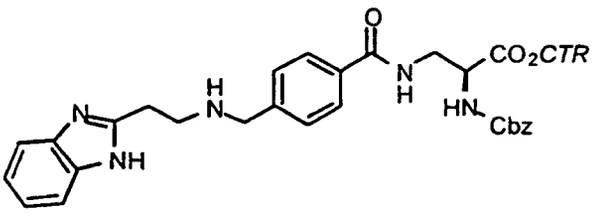


[0101] Add the product (Preparation 7, Step 1a) (7.18 g) to a solution of potassium hydroxide (3.45 g) in methanol

(120 mL). Stir the resulting mixture at room temperature for 30 minutes, filter, and concentrate the filtrate *in vacuo.* Extract with EtOAc (3 x 500 mL) and filter. Concentrate the filtrate *in vacuo* to give the title compound as a white solid (3.33 g).

Step 2. N^3-[4-[2-(Benzimidazol-2-yl)ethyl)aminomethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0102]

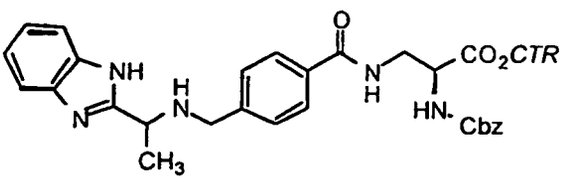


[0103] Shake the resin (Preparation 4, Step 1) (0.8 g, 0.4 mmol) and 2-[2-(aminoethyl)]benzimidazole (3.25 g) in DMF (25 mL) in a sealed vial for 44 hours. Transfer resin to funnel apparatus, and wash the resin with DMF (25 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give the title resin.

Preparation 8

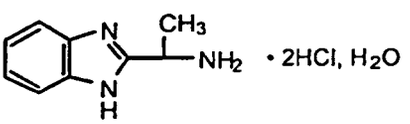
N^3-[4-[1-(Benzimidazol-2-yl)ethyl]aminomethylbenzoyl]-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0104]



Step 1a. 2-(1-Aminoethyl)benzimidazole dihydrochloride hydrate

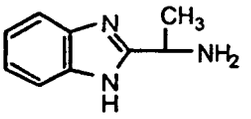
[0105]



[0106] Combine *o*-phenylenediamine (10.8 g, 100 mmol) and d,1-alanine (13.4 g, 150 mmol) in 6N HCl (100 mL) Heat at reflux 75 hours, allow to cool, and chill at -15˚C. Filter to remove 2.4 g solid. Decolorize the filtrate with charcoal, concentrate *in vacuo* to 30 g, and dilute with 95% EtOH (90 mL). Chill at -15˚C, filter and wash with cold 90% EtOH to obtain the title compound as a white powder.

Step 1b. 2-(1-Aminoethyl)benzimidazole

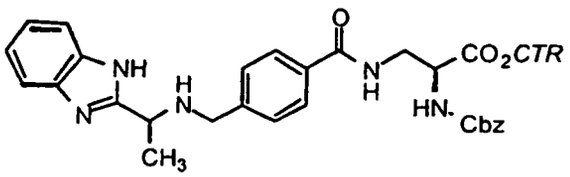
[0107]



[0108] Add the product (Preparation 8, Step 1a) (6.99 g) to a solution of potassium hydroxide (3.36 g) in methanol (120 mL). Stir the resulting mixture at room temperature for 30 minutes, filter, and concentrate the filtrate *in vacuo.* Extract the residue with EtOAc (3 x 500 mL) and filter. Concentrate the filtrate *in vacuo* to give the title compound as a white solid (4.23 g).

Step 2. N^3-[4-[1-(Benzimidazol-2-yl)ethyl]aminomethylbenzoyl]-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0109]

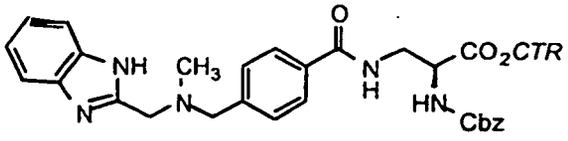


[0110] Shake the resin (Preparation 4, Step 1) (1.0 g, 0.5 mmol) and 2-(1-aminoethyl)benzimidazole (4.20 g) in DMF (25 mL) in a sealed vial for 44 hours. Transfer resin to funnel apparatus, and wash the resin with DMF (25 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give the title resin.

Preparation 9

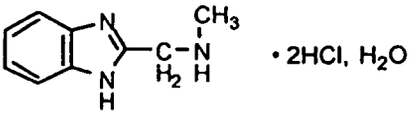
N^3-[4-[(Benzimidazol-2-yl)methyl]methylaminomethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0111]



Step 1a. 2-(Methylaminomethyl)benzimidazole dihydrochloride hydrate

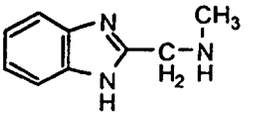
[0112]



[0113] Combine *o*-phenylenediamine (10.8 g, 100 mmol) and sarcosine (13.4 g, 150 mmol) in 6N HCl (100 mL). Heat at reflux 90 hours, allow to cool, and concentrate *in vacuo* to 45 g. Add EtOH (50 mL) and chill at -15˚C. Filter the solid and wash with cold 90% EtOH. Dissolve in 80% EtOH (150 mL) and decolorize with charcoal. Concentrate *in vacuo* to 28 g, warm with 95% EtOH (160 mL), allow to cool, and filter to provide colorless rods.

Step 1b. 2-(Methylaminomethyl)benzimidazole

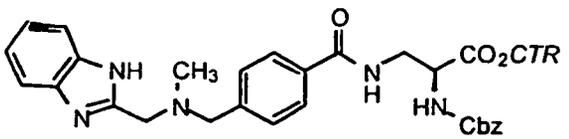
[0114]



[0115] Add the product (Preparation 9, Step 1 a) (2.33 g) to a solution of potassium hydroxide (1.21 g) in methanol (50 mL). Stir the resulting mixture at room temperature for 30 minutes, filter, and concentrate the filtrate *in vacuo.* Extract the with EtOAc (400 mL) and filter. Concentrate the filtrate *in vacuo* to give the title compound as a white solid (1.28 g).

Step 2. N^3-[4-[(Benzimidazol-2-yl)methyl]methylaminomethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0116]

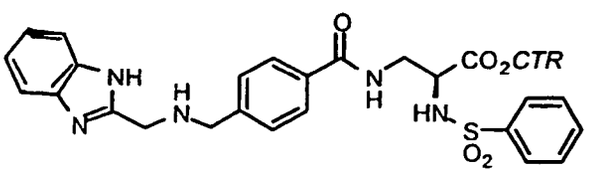


[0117] Shake the resin (Preparation 4, Step 1) (0.30 g, 0.15 mmol) and 2-(methylaminomethyl)benzimidazole (1.25 g) in DMF (20 mL) in a sealed vial for 44 hours. Transfer resin to funnel apparatus, and wash the resin with DMF (25 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give the title resin.

Preparation 10

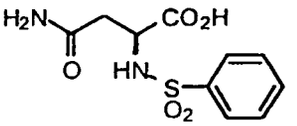
N^3-[4-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl]-N^2-benzenesulfonyl-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0118]



Step 1a. N^2-Benzenesulfonyl-L-Asparagine

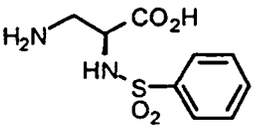
[0119]



[0120] To L-Asparagine (10 g), add sodium hydroxide (3.4 g) and dioxane/water (50 mL / 50 mL). Cool resulting solution in an ice bath and add benzenesulfonyl chloride (10.6 mL), sodium hydroxide (3.4 g), and water (80 mL). Stir for 3 hours. Add water (200 mL) and extract with EtOAc. Acidify the aqueous solution to pH 3 with concentrated HCl and cool to give a precipitate. After 1 hour collect the solid and dry it in vacuo at 40˚ C to give the title compound.

Step 1b. N^2-Benzenesulfonyl-L-diaminopropionic acid

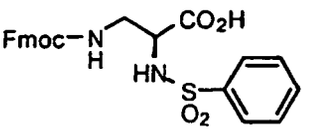
[0121]



[0122] Prepare a solution of sodium hydroxide (10.5 g) in water (50 g), cool, and add bromine (2.5 mL). Add product from Step Ia (10 g) and sodium hydroxide (2.9 g) in water (35 mL) and stir for 30 minutes. Heat at 90˚ C for 30 minutes and cool in an ice bath. Adjust to pH 7 with concentrated HCl. Collect the title compound as a white solid, mp 203-206˚ C.

Step 1c. N^3-Fmoc-N^2-benzenesulfonyl-L-2,3-diaminopropionic acid

[0123]

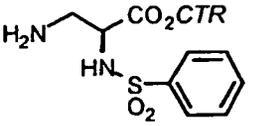


[0124] Combine N^2-benzenesulfonyl-L-2,3-diaminopropionic acid (2.92 g, 12.0 mmol) and NaHCO3 (4.57 g) in acetone (40 mL) and water (40 mL). Cool in a ice-bath. Add Fmoc-O-hydroxysuccinimide (4.97 g, 19.2 mmol), and stir the resulting mixture for 3 hours while the ice melts. Add additional NaHCO3 (1.5 g), acetone (40 mL) and water (40 mL), and dioxane (80 mL) and stir for 20 hours. Concentrate the mixture *in vacuo,* and extract the aqueous portion with EtOAc. Wash the EtOAc solution with 5% glacial acetic acid in water (3 x 300 mL), 5% NaHCO3 solution (3 x 300 mL) and brine (3 x 300 mL). Concentrate the dried ($MgSO_4$) EtOAc solution *in vacuo* to give the title compound (contains Fmoc-O-hydroxysuccinimide) as a light yellow solid which is used in Step 2.

[0125] Reference: W. M. Kazmierski, Int. J. Pep. Prot. Res., **45**, 242 (1995).

Step 2. N^2-Benzenesulfonyl-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0126]



[0127] **Step 2a**. To a solution of DIPEA (1.60 mL) in DMF (10 mL), add (N^3-Fmoc- N^2-benzenesulfonyl-L-2,3-diaminopropionic acid) (0.787 g). Add the 2-chlorotrityl resin, chloride form (2.00 g) (0.65 mmol/g). Agitate the resulting mixture for 30 minutes. Add MeOH (0.8 mL), agitate the mixture for 10 minutes, and drain. Wash the resin with DMF (30 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give N^3-Fmoc-N^2-benzenesulfonyl-L-2,3-diaminopropionic acid on 2-chlorotrityl resin.

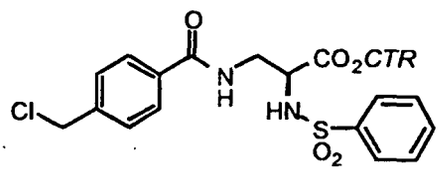
[0128] **Step 2b**. Wash the resin (Preparation 10, Step 2a) with DMF (20 mL x 5). Add 20% piperidine in DMF (30 mL), agitate for 15 minutes, and collect the filtrate. Repeat two times. Determine the loading as in Preparation 1. Measure UV absorbance at 301 nM: 0.389

$$0.389 \times \text{concentration}/7800$$

$$0.389 \times 20{,}000/7800 = 0.9958/2 \text{ g } (0.498 \text{ mmol/ g})$$

Step 3. N^3-(4-Chloromethylbenzoyl)-N^2-benzenesulfonyl-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

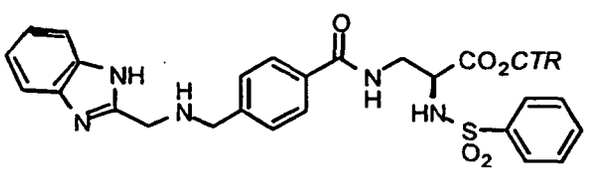
[0129]



[0130] Place resin (Preparation 10, Step 2b) (1.00 g, 0.498 mmol) in CH_2Cl_2 (5 mL) in a vial, and treat with DIPEA (0.95 mL, 5.48 mmol) followed by 4-chloromethylbenzoyl chloride (0.94 g, 4.98 mmol). Seal vial and place on a shaker for 2.5 hours. Transfer resin to funnel apparatus. Wash the resin with CH_2Cl_2 (20 mL x 3), DMF (20 mL x3) and then CH_2Cl_2 (20 mL x 3) to yield title resin.

Step 4. N^3-[4-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl)-N^2-benzenesulfonyl-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0131]

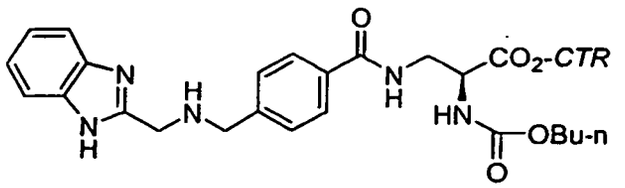


[0132] Shake the resin (Preparation 10, Step 3) (1.00 g, 0.55 mmol) and 2-(aminomethyl)benzimidazole (5.00 g) (Preparation 1) in DMF (25 mL) in a sealed vial for 44 hours. Transfer resin to funnel apparatus, and wash the resin with DMF (25 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give the title resin.

Preparation 11

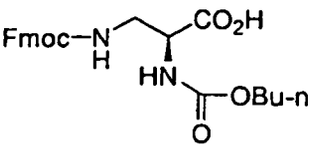
N^3-[4-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl]-N^2-n-butoxycarbonyl-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0133]



Step 1. N^3-Fmoc-N^2-n-butoxycarbonyl-L-2,3-diaminopropionic acid

[0134]

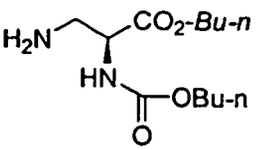


[0135] Combine N^2-n-butoxycarbonyl-L-2,3-diaminopropionic acid (18.0 g, 88.2 mmol) and NaHC03 (38.2 g) in acetone (400 mL) and water (400 mL). Cool in a ice-bath. Add Fmoc-O-hydroxysuccinimide (42.7 g, 126.6 mmol), and stir the resulting mixture for 3 hours while the ice melts. Continue stirring overnight for 20 hours. Concentrate the *mixture in vacuo,* and extract the aqueous portion with EtOAc. Wash the EtOAc solution with 5% glacial acetic acid in water (3 x 100 mL), 5% NaHC03 solution (8 x 100 mL) and brine (3 x 100 mL). Concentrate the dried ($MgSO_4$) EtOAc solution *in vacuo.* Chase with heptane, dry in vacuum oven overnight, and then transfer to a large dish and dry in a stream of air (to remove AcOH) to give the title compound (contains Fmoc-O-hydroxysuccinimide) as a light yellow solid which is used Step 2.

[0136] Reference: W. M. Kazmierski, Int. J. Pep. Prot. Res., 45, 242 (1995).

Step 2. N^2-n-Butoxycarbonyl-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0137]



[0138] **Step 2a**. Add Dissolve (N^3-Fmoc- N^2-n-butoxycarbonyl-L-2,3-diaminopropionic acid) (16.7 g) in DMF (100 mL), warm, add DMF (50 mL), and filter. Add DIPEA (14 mL), and then add the 2-chlorotrityl resin, chloride form (15.00 g) (0.65 mmol/g). Agitate the resulting mixture for 45 minutes. Add MeOH, agitate the mixture for 10 minutes, and drain. Wash the resin with DMF (100 mL x 5) and then CH_2Cl_2 (100 mL x 5) to give N^3-Fmoc-N^2-n-butoxycarbonyl-L-2,3-diaminopropionic acid on 2-chlorotrityl resin.

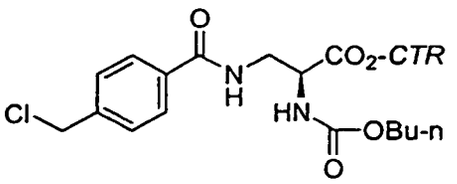
[0139] **Step 2b**. Wash the resin (Preparation 11, Step 2a) with DMF (100 mL x 5). Add 20% piperidine in DMF (100 mL), agitate for 15 minutes, and collect the filtrate. Repeat two times and then DMF (2 x 100 mL). Determine the loading as in Preparation 1 (dilute the filtrate to 1000 mL (solution A); take 1 mL and dilute to 100 mL) Measure UV absorbance at 301 nM: 0.794

0.794 x concentration/7800

0.794 x 10,000/7800 = 10.18 mmol/15 g (0.67 mmol/ g)

Step 3. N^3-(4-Chloromethylbenzoyl)-N^2-n-butoxycarbonyl-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

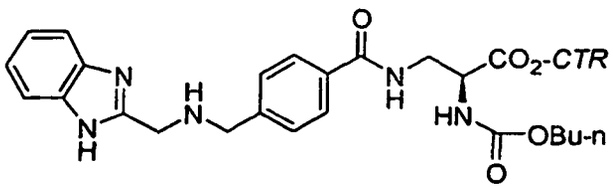
[0140]



[0141] Place resin (Preparation 11, Step 2b) (15.00 g, 10 mmol) in CH_2Cl_2 (50 mL) in a vial, and treat with DIPEA (12.3 mL, 70 mmol) followed by 4-chloromethylbenzoyl chloride (11.5 g, 60 mmol). Gently sparge for 4 hours. Wash the resin with CH_2Cl_2 (100 mL x 3), NMP (100 mL x3) and then CH_2Cl_2 (100 mL x 5) to yield title resin.

Step 4. N^3-[4-(Benzimidazol-2-ylmethyl)aminomethylbenzoyl)-N^2-n-butoxycarbonyl-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0142]

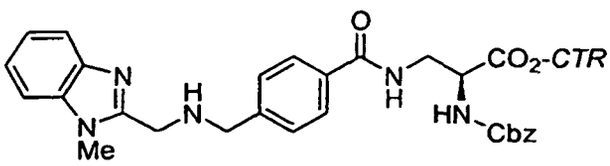


[0143] Shake the resin (Preparation 11, Step 3) (15.00 g, 10 mmol) and 2-(aminomethyl)benzimidazole (80.85 g) (Preparation 1) in NMP (500 mL) in a sealed vial for 24 hours. Transfer resin to funnel apparatus, and wash the resin with NMP (100 mL x 3) and then CH_2Cl_2 (100 mL x 5) to give the title resin.

Preparation 12

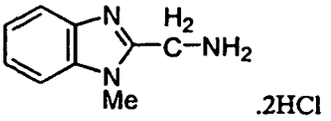
N^3-[4-[(1-Methylbenzimidazol-2-yl)methyl]aminomethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0144]



Step 1a. 1-Methyl-2-(aminomethyl)benzimidazole dihydrochloride

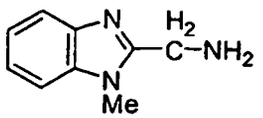
[0145]



[0146] Combine *N*-methyl-o-phenylenediamine (12.2 g, 100 mmol) and glycine (11.3 g, 150 mmol) in 6N HCl (100 mL). Heat at reflux 90 hours, allow to cool, and concentrate *in vacuo* to 60 g. Add EtOH (50 mL) and chill at -15˚C. Filter the solid and wash with cold 90% EtOH. Dissolve the blue solid in water (30 mL), add EtOH (100 mL) and treat with decolorizing charcoal. Wash the solid with 2:1 EtOH-water and concentrate filtrates *in vacuo* to 33 g. Add water (15 mL) and warm while adding EtOH (150 mL). Allow to cool, filter, and wash with 90% EtOH to obtain the product as blue flakes. Process the filtrate to obtain a second crop.

Step 1b. 1-Methyl-2-(aminomethyl)benzimidazole

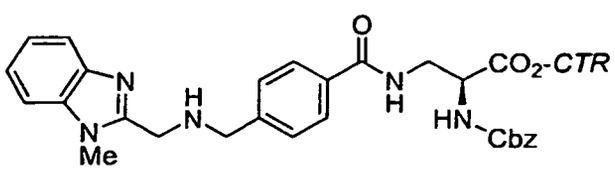
[0147]



[0148] Add the product (Preparation 12, Step 1a) (10.3 g) to a solution of potassium hydroxide (5.20 g) in methanol (200 mL). Stir the resulting mixture at room temperature for 30 minutes, filter, and concentrate the filtrate *in vacuo.* Extract the with EtOAc (400 mL) and filter. Concentrate the filtrate *in vacuo* to give the title compound as a white solid (5.60 g).

Step 2. N^3-[4-[(1-Methylbenzimidazol-2-yl)methyl]aminomethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0149]

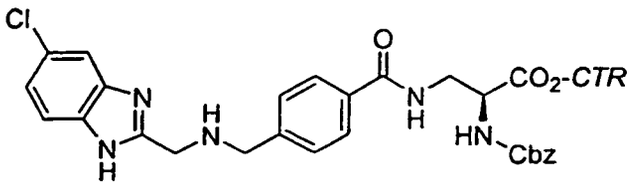


[0150] Shake the resin (Preparation 4, Step 1) (1.50 g, 0.60 mmol) and 1-methyl-2-(aminomethyl)benzimidazole (5.00 g) in DMF (25 mL) in a sealed vial for 18 hours. Transfer resin to funnel apparatus, and wash the resin with DMF (25 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give the title resin.

Preparation 13

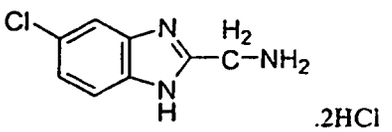
N^3-[4-[(5-Chlorobenzimidazol-2-yl)methyl]aminomethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0151]



Step 1a. 2-(aminomethyl)-5-chlorobenzimidazole dihydrochloride

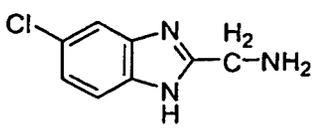
[0152]



[0153] Combine 4-chloro-*o*-phenylenediamine (14.3g, 100mmmol) and glycine (11.3g, 150 mmol) in 6N HCl (100 mL). Heat at reflux 72 hours, allow to cool, add EtOH (30 mL), and chill at -15˚ C. Filter and wash with 3:10 EtOH-water, then water. Combine the filtrates, concentrate *in vacuo* to 50 g, and dilute with EtOH (75 mL). Chill at -15˚ C, filter and wash with cold 90% EtOH. Dry to obtain solid (18.8 g). Take up in 2:1 EtOH-water (120 mL), treat with decolorizing charcoal, concentrate *in vacuo* to 29 g, add water (6 mL), and heat while adding EtOH (120 mL). Boil to 100 mL, add EtOH (50 mL), boil to 125 mL, and allow to cool. Collect the solid and wash with 95% EtOH. Dry to obtain the title compound as a light orange powder.

Step 1b. 2-(Aminomethyl)-5-chlorobenzimidazole

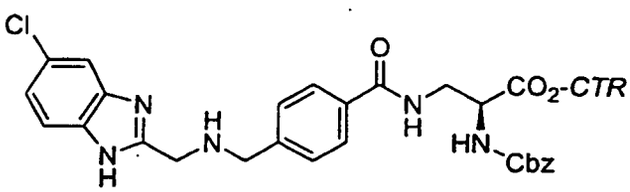
[0154]



[0155] Add the product (Preparation 12, Step 1a) (10.3 g) to a solution of potassium hydroxide (5.20 g) in methanol (200 mL). Stir the resulting mixture at room temperature for 30 minutes, filter, and concentrate the filtrate *in vacuo.* Extract the with EtOAc (400 mL) and filter. Concentrate the filtrate *in vacuo* to give the title compound as a white solid (7.62 g).

Step 2. N^3-[4-[(5-Chlorobenzimidazol-2-yl)methyl]aminomethylbenzoyl)-N^2-Cbz-L-2,3-diaminopropionic acid on 2-chlorotrityl resin

[0156]

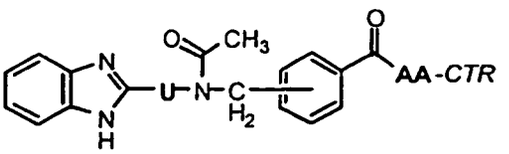


[0157] Shake the resin (Preparation 4, Step 1) (1.50 g, 0.60 mmol) and 1-methyl-2-(aminomethyl)benzimidazole (5.00 g) in DMF (25 mL) in a sealed vial for 18 hours. Transfer resin to funnel apparatus, and wash the resin with DMF (25 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give the title resin.

Example 1

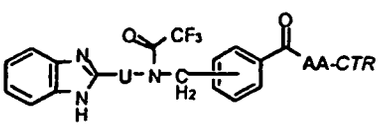
Acetylation of Products from Preparations 2-4 and 6-7

[0158]



[0159] Place the resin (0.16 g, -0.07 mmol) in CH_2Cl_2 (4 mL) in a vial, and treat with DIPEA (0.77 mmol), followed by acetic anhydride (0.70 mmol). Seal the vial and place it on a shaker for 2 hours at room temperature. Place the resin in a funnel apparatus, and wash the resin with CH_2Cl_2 (15 mL x 3), DMF (15 mL x 5), and then CH_2Cl_2 (20 mL x 5) to give a diacylated product. Wash the resin with DMF (15 ml x 5), and then treat the resin with 20% piperidine in DMF (30 mL) with agitation for 1.5 hours. Wash the resin with DMF (15 mL x 5) and then CH_2Cl_2 (20 mL x 5) to yield monoacetylated resin.

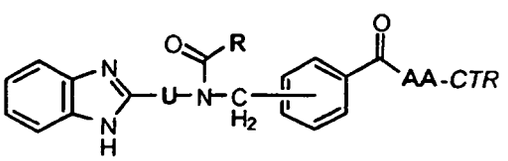
[0160] Using the same method, prepare the following compound



Example 2

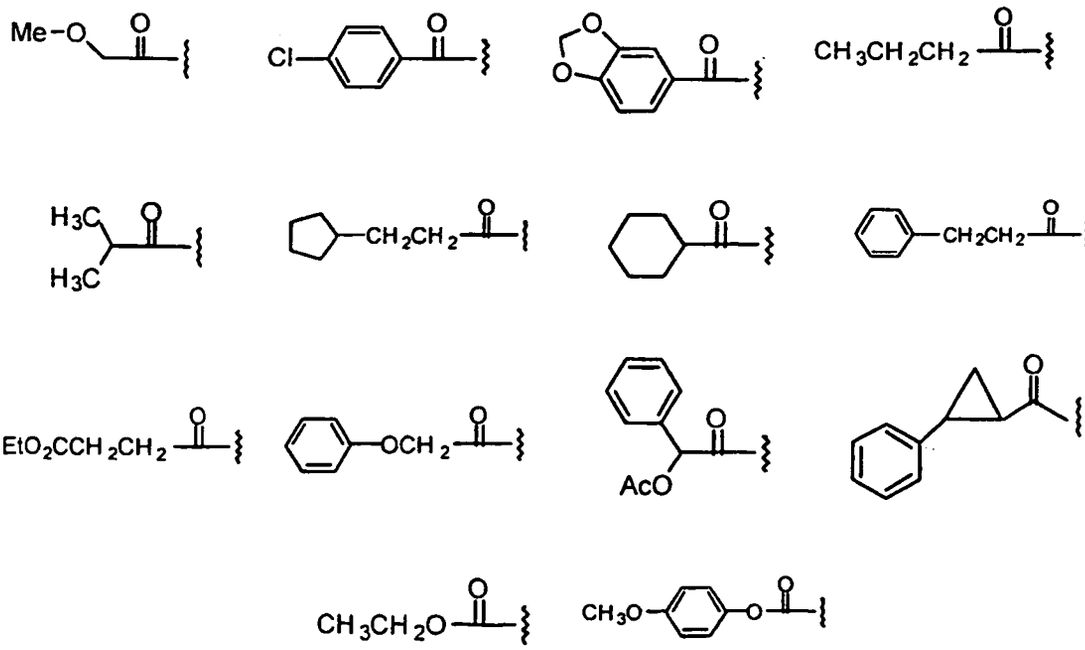
Acylation of Products from Preparations 2-8 with Acid Chlorides and Chloroformates

[0161]



[0162] Place the resin (0.16 g, -0.07 mmol) in CH_2Cl_2 (4 mL) in a vial, and treat with DIPEA (0.77 mmol), followed by acid chloride or chloroformate (0.70 mmol). Seal the vial and place it on a shaker for 2 hours at room temperature. Place the resin in a funnel apparatus, and wash the resin with CH_2Cl_2 (15 mL x 3), DMF (15 mL x 5) and then CH_2Cl_2 (20 mL x 5) to give a diacylated product. Wash the resin with DMF (15 ml x 5), and then treat the resin with 20% piperidine in DMF (30 mL) with agitation for 1.5 hours. Wash the resin with DMF (15 mL x 5) and then CH_2Cl_2 (20 mL x 5) to yield monoacylated resin.

[0163] Acid chlorides and chloroformates used:

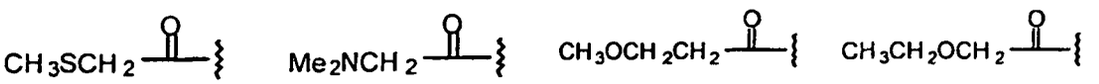


Example 3

Acylation of Products from Preparation 4 with Acids

[0164] Place the resin (0.16 g, ~0.07 mmol) in CH_2Cl_2 (4 mL) in a vial, and treat with DIPEA (0.70 mmol) followed by carboxylic acid (0.35 mmol) and PyBroP (0.35 mmol). Seal the vial and place it on a shaker for 1.5 hours at room temperature. Place the resin in a funnel apparatus and wash the resin with CH_2Cl_2 (15 mL x 3), DMF (15 mL x 5), and then CH_2Cl_2 (20 mL x 5) to give a diacylated product. Wash the resin with DMF (15 ml x 5), and then treat the resin with 20% piperidine in DMF (30 mL) with agitation for 1.5 hours. Wash the resin with DMF (15 mL x 5) and then CH_2Cl_2 (20 mL x 5) to yield monoacylated resin.

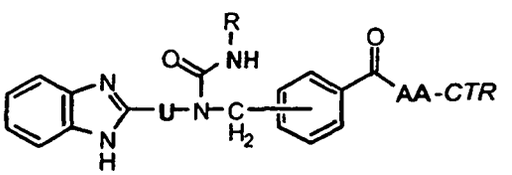
[0165] Acids used:



Example 4

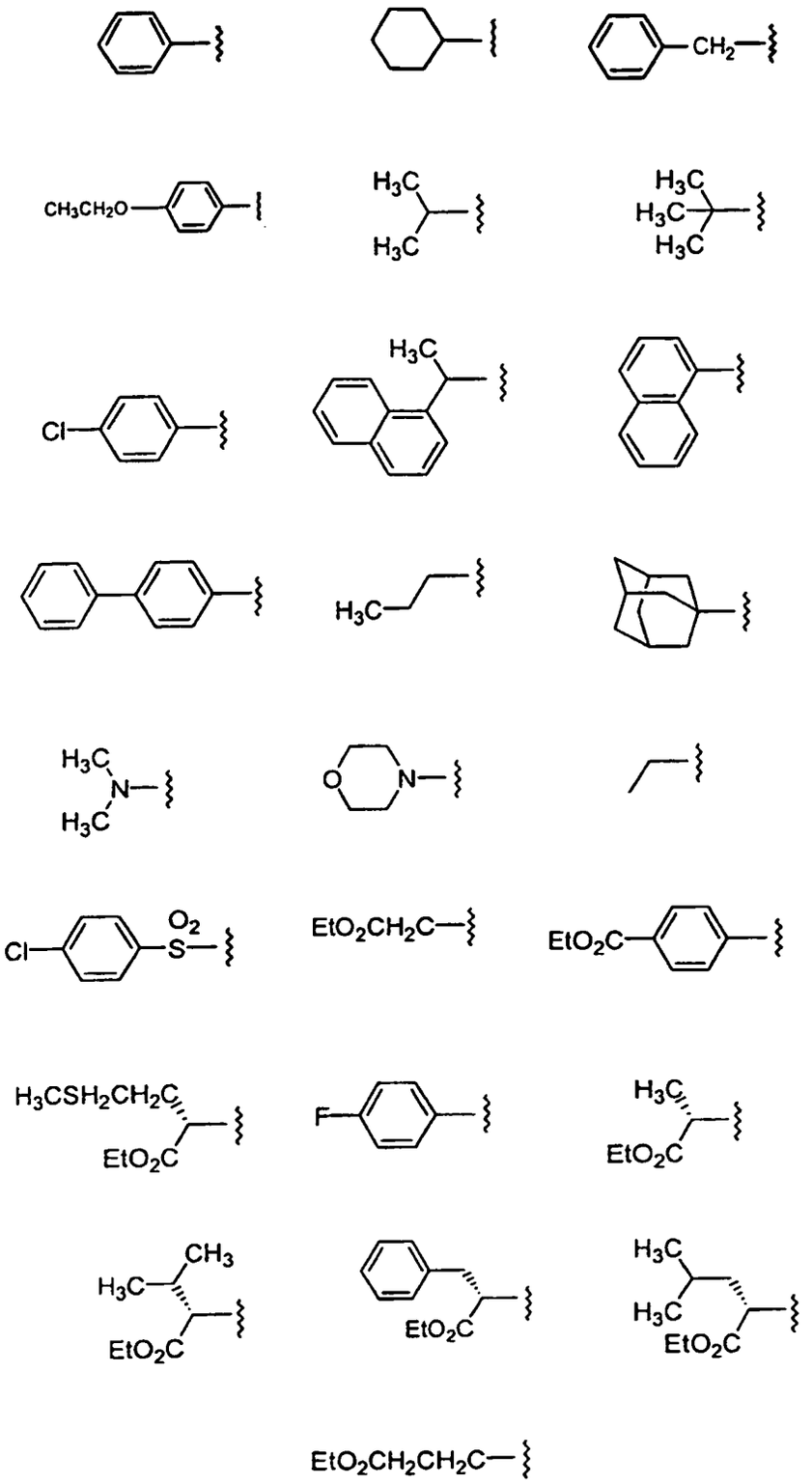
Preparation of Ureas: Reaction of Isocyanates or Isothiocyanates with Products from Preparation 4

[0166]

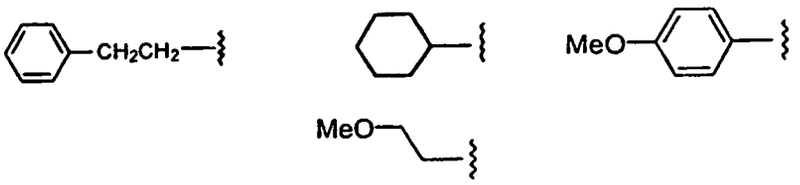


[0167] Place the resin (0.16 g, ~0.107 mmol) in DMF (5 mL) in a vial and add isocyanate (0.22 mmol). Seal the vial and place it on a shaker for 2-2.5 hours at room temperature. Place the resin in a funnel apparatus and wash the resin with CH_2Cl_2 (15 mL x 3), DMF (15 mL x 5), and then CH_2Cl_2 (20 mL x 5) to give the title resin.

[0168] Isocyanates used:



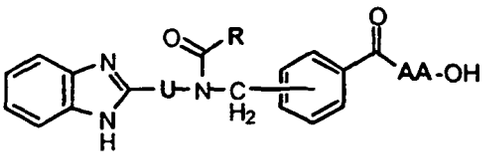
[0169] Isothiocyanate used:



Example 5

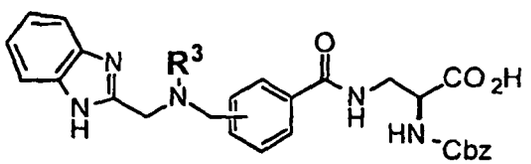
Cleavage of Products from Resin

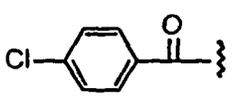
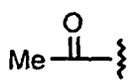
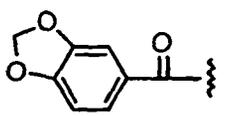
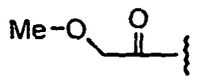
[0170]



[0171] Treat the resins from Preparations 2-13 or Examples 1-4 (~0.16 g) with CH_2Cl_2:TFA:H_2O (99:0.95:0.05) (10 mL) at room temperature for 15 minutes and filter. Repeat this one time. Combine the filtrates, and concentrate on a Speed Vac. Add heptane (1 mL) and concentrate in Speed Vac. Dry the products in a vacuum oven at 40˚ C for 20 hours to yield the following products listed in Tables 1 to 8, below (HPLC condition: Vydac column (218TP5405): 5-95% MeCN-H_2O (0.1% TFA) gradient over 10 minutes, at 1 mL/min. UV detection 254 nM):

TABLE 1.



Example	Benzoyl Substituent	R^3	MS *m/e* [M+H]$^+$	HPLC Retention Time, min
5-1	*para*		502	3.91
5-2	*para*		640	3.95
5-3	*para*		544	4.13
5-4	*para*		650	5.45
5-5	*para*		574	4.15
5-6	*meta*		502	4.02

(continued)

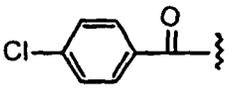
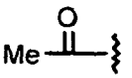
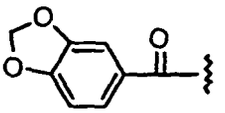
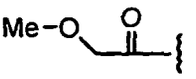
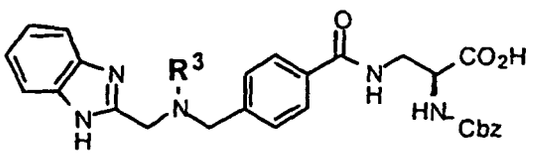
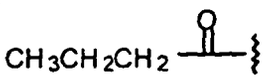
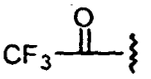
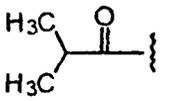
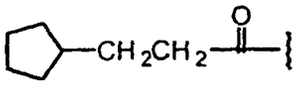
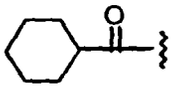
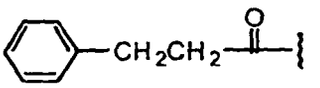
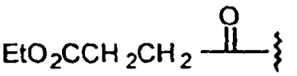
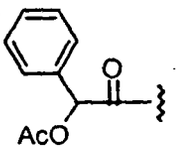
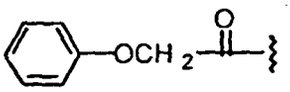
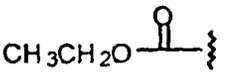
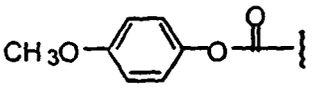
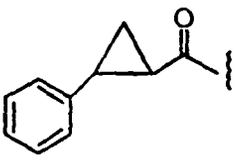
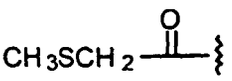
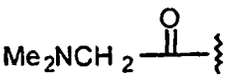
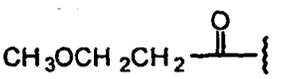
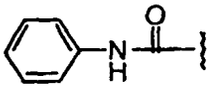
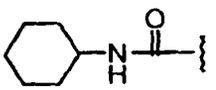
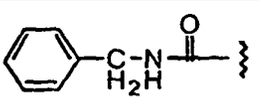
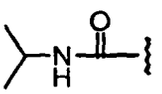
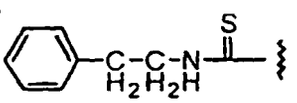
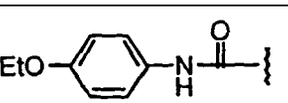
Example	Benzoyl Substituent	R^3	MS *m/e* $[M+H]^+$	HPLC Retention Time, min
5-7	*meta*		640	6.10
5-8	*meta*		544	4.24
5-9	*meta*		650	5.58
5-10	*meta*		574	4.29

TABLE 2.

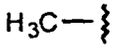
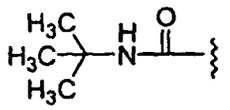
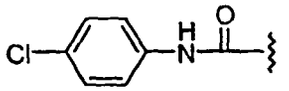
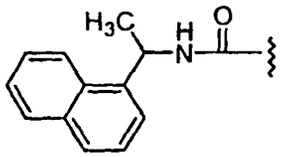
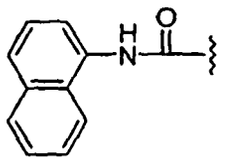
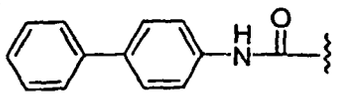
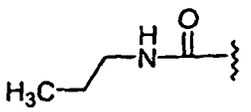
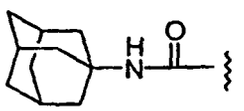
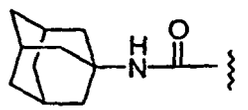
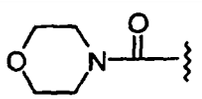
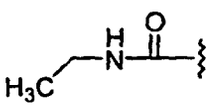
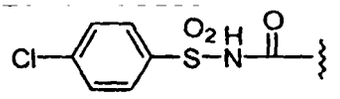
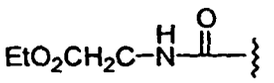


Example	R^3	MS *m/e* $[M+H]^+$	HPLC Retention Time, min
5-11		572	5.84
5-12		598	5.99
5-13		572	5.77
5-14		626	6.85
5-15		612	6.43
5-16		634	6.52
5-17		630	6.36

(continued)

Example	R^3	MS *m/e* $[M+H]^+$	HPLC Retention Time, min
5-18		678	6.33
5-19		636	5.77
5-20		574	6.43
5-21		652	6.57
5-22		646	6.58
5-23		589	5.68
5-24		587	4.92
5-25		588	5.49
5-26		588	5.50
5-27		621	6.22
5-28		627	6.40
5-29		635	6.19
5-30		585	5.72
5-31		665	6.95
5-32		665	6.46

(continued)

Example	R^3	MS *m/e* $[M+H]^+$	HPLC Retention Time, min
5-33		516	5.33
5-34		601	6.06
5-35		655	6.72
5-36		699	6.94
5-37		671	6.54
5-38		697	6.83
5-39		587	5.65
5-40		679	7.10
5-41		573	5.43
5-42*		615	5.38
5-43		573	5.37
5-44		719	6.49
5-45*		631	5.57

(continued)

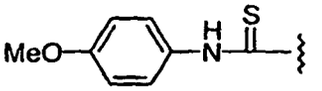
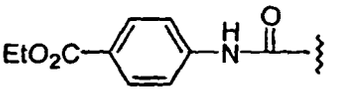
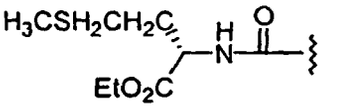
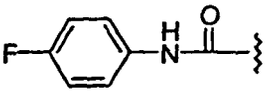
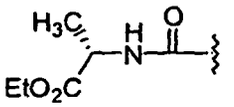
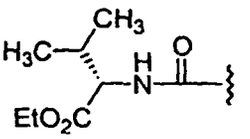
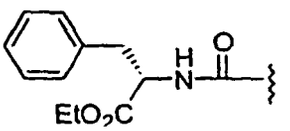
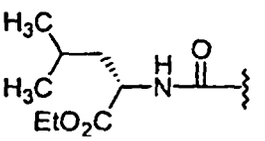
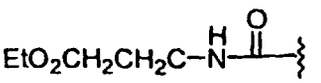
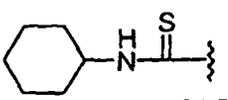
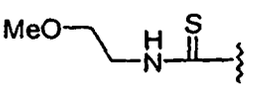
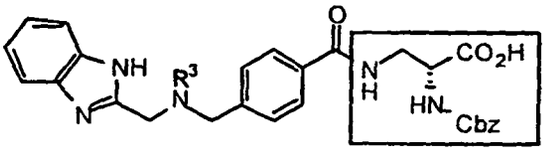
Example	R^3	MS *m/e* $[M+H]^+$	HPLC Retention Time, min
5-46*		667	6.38
5-47*		693	6.53
5-48*		705	6.45
5-49*		639	6.31
5-50*		645	5.91
5-51*		673	6.46
5-52*		721	6.84
5-53*		687	6.77
5-54*		645	5.78
5-55*		643	6.93
5-56*		619	5.97
*Purified by Preparative TLC			

TABLE 3.



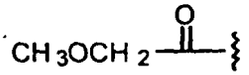
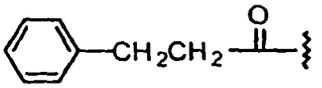
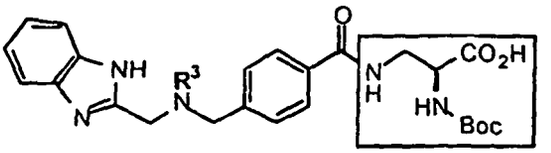
Example	R^3	MS *m/e* $[M+H]^+$	HPLC Retention Time, min
5-57	H	502	5.22
5-58		574	5.30
5-59		634	6.50

TABLE 4.



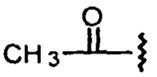
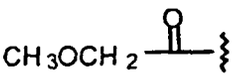
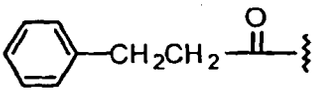
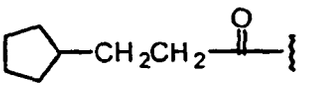
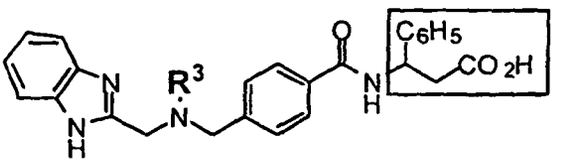
Example	R^3	MS *m/e* $[M+H]^+$	HPLC Retention Time, min
5-60	H	468	4.13
5-61		510	4.84
5-62		540	4.85
5-63		600	6.29
5-64		592	6.64

TABLE 5.



Example	R^3	MS *m/e* $[M+H]^+$	HPLC Retention Time, min
5-65	H	429	4.19

(continued)

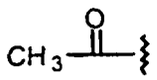
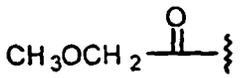
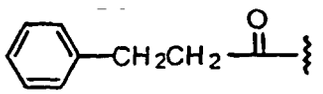
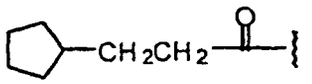
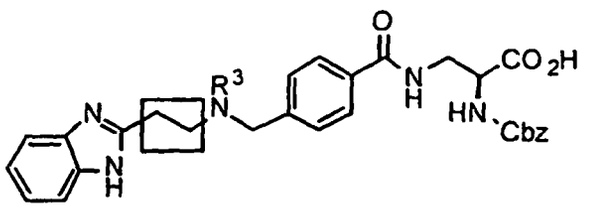
Example	R^3	MS *m/e* [M + H]$^+$	HPLC Retention Time, min
5-66		471	4.93
5-67		501	4.91
5-68		561	6.32
5-69		553	6.69

TABLE 6.



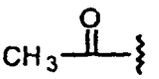
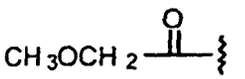
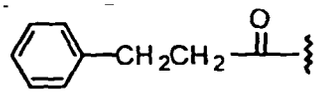
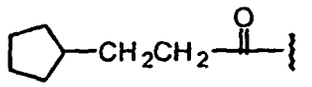
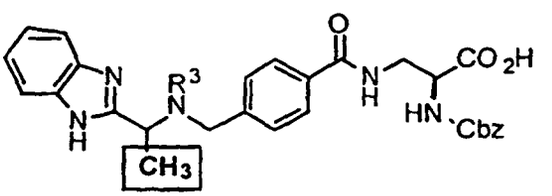
Example	R^3	MS *m/e* [M + H]$^+$	HPLC Retention Time, min
5-70	H	516	4.94
5-71		558	5.25
5-72		588	5.30
5-73		648	6.50
5-74		640	6.78

TABLE 7.



(continued)

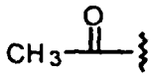
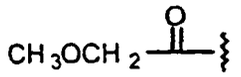
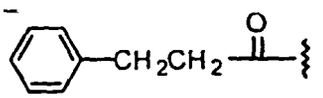
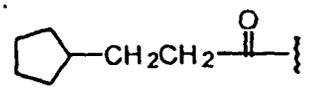
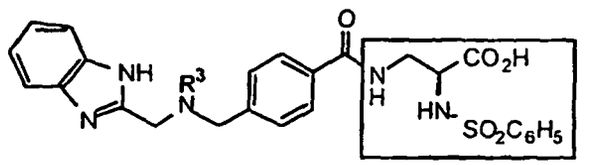
Example	R^3	MS *m/e* [M + H]$^+$	HPLC Retention Time, min
5-75	H	516	5.36
5-76		558	5.23
5-77		588	5.24
5-78		648	6.52
5-79		640	6.84

TABLE 8.



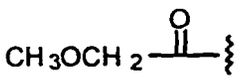
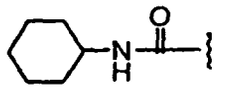
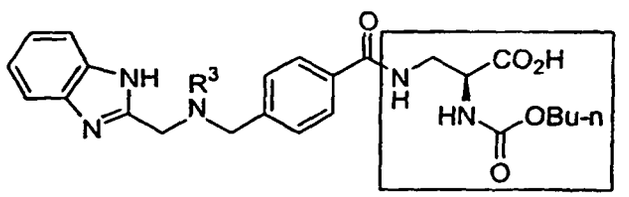
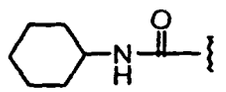
Example	R^3	MS *m/e* [M + H]$^+$	HPLC Retention Time, min
5-80*		579	5.3
5-81*		632	6.23
*Purified by Preparative TLC			

TABLE 8-1.



Example	R^3	MS *m/e* [M+H]$^+$	HPLC Retention Time, min
5-82 *		593	6.17

(continued)

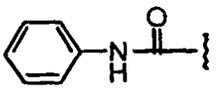
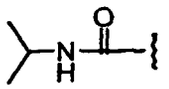
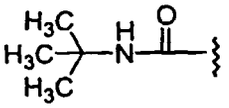
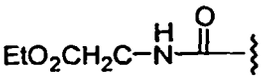
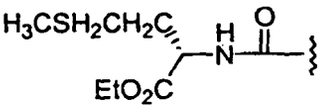
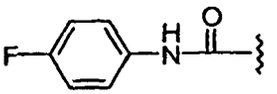
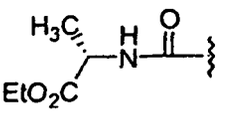
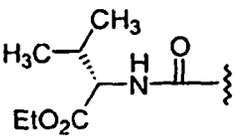
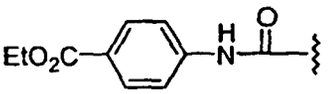
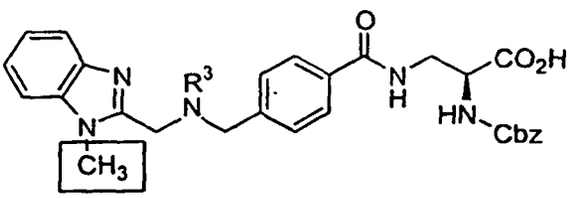
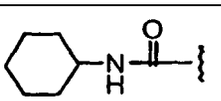
Example	R^3	MS *m/e* $[M+H]^+$	HPLC Retention Time, min
5-83 *		587	6.01
5-84*		553	5.45
5-85*		567	5.91
5-86*		597	5.54
5-87*		671	6.25
5-88*		605	6.16
5-89*		611	5.74
5-90*		639	6.30
5-91*		659	6.46
*Purified by Preparative TLC			

TABLE 8-2.



Example	R^3	MS *m/e* $[M + H]^+$	HPLC Retention Time, min
5-92*		641	6.32

(continued)

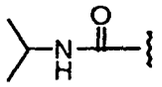
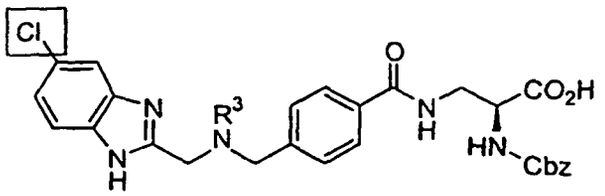
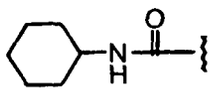
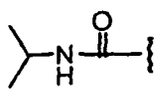
Example	R^3	MS *m/e* $[M + H]^+$	HPLC Retention Time, min
5-93*		601	5.67
* Purified by Preparative TLC			

TABLE 8-3.

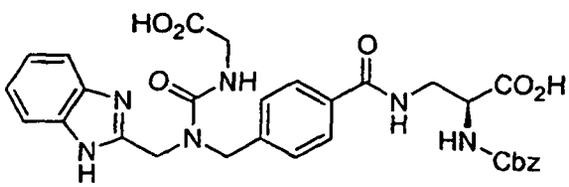


Example	R^3	MS *m/e* $[M+H]^+$	HPLC Retention Time, min
5-94*		661	6.69
5-95*		621	5.98
* Purified by Preparative TLC			

Example 6

N^3-[4-[(Benzimidazol-2-yl)methyl][[(carboxymethyl)amino]carbonyl]aminomethylbenzoyl]-N^2-Cbz-L-2,3-diaminopropionic acid

[0172]

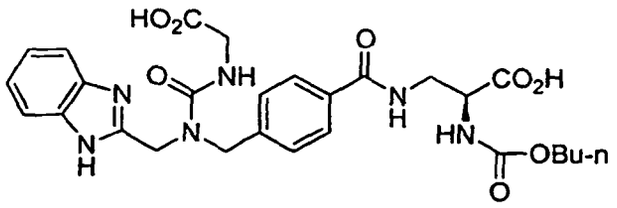


[0173] Dissolve N^3-[4-[(benzimidazol-2-yl)methyl][[(ethoxycarbonylmethyl)amino]-carbonyl]aminomethylbenzoyl]-N^2-Cbz-1-2,3-diaminopropionic acid (5-45) (2.60 g, 4.1 mmol) in MeOH (12 mL) and slowly add 1N NaOH (40 mL). After 3 hours, slowly add 1N HCl (40 mL) and then add 1N HCl to pH 6.5 to give a white precipitate. Decant water and wash with water (2x10 mL). Dry title compound (Table 8-4) in vacuum oven.

Example 7

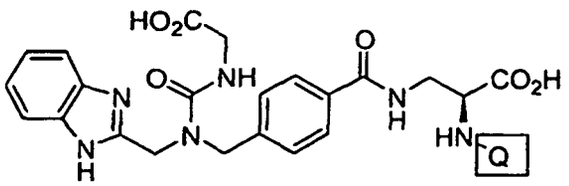
N^3-[4-[(Benzimidazol-2-yl)methyl][[(carboxymethyl)amino]carbonyl]aminomethylbenzoyl]-N^2-(n-butoxycarbonyl)-L-2,3-diaminopropionic acid

[0174]



[0175] Dissolve N^3-[4-[(benzimidazol-2-yl)methyl][[(ethoxycarbonylmethyl)amino]-carbonyl]aminomethylbenzoyl]-N^2-(n- butoxycarbonyl)-L-2,3-diaminopropionic acid (5-86) (0.432 g, 0.72 mmol) in MeOH (5 mL) and slowly add 1N NaOH (4 mL). After 3 hours, evaporate the MeOH under a steam of nitrogen. Slowly add 1N HCl (4 mL) and then add 1N HCl to pH 6.5 to give a white gum. Decant water dry title compound (Table 8-4) in vacuum oven.

TABLE 8-4.

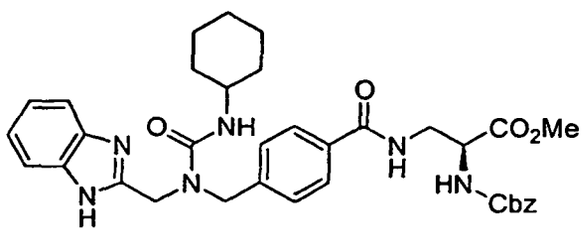


Example	Q	MS *m/e* [M + H]$^+$	HPLC Retention Time, min
5-96	**Cbz**	603	5.22
5-97	**n-BO$_2$C**	569	4.98

Example 8

Methyl N^3-[4-[(Benzimidazol-2-yl)methyl][[(cyclohexyl)amino]carbonyl]aminomethylbenzoyl]-N^2-(n-butoxycarbonyl)-L-2,3-diaminopropionate

[0176]



[0177] Add 3M HCl in MeOH (5 mL) to N^3-[4-[(benzimidazol-2-yl)methyl][[(cyclohexyl)amino]carbonyl] amino-methylbenzoyl]-N^2-(n-butoxycarbonyl)-L-2,3-diaminopropionic acid (0.155 g) in MeOH (20 mL) and heat under reflux for 7 hours. The reaction mixture was concentrated in vacuo. MeOH was added and concentrated in vacuo to give the title compound as a white solid. MS *m/e* [M + H] 641: HPLC retention time: 6.77 min.

[0178] The following assay procedure, which is a competition radioligand binding assay, was carried out to determine the activity of the foregoing compounds as $\alpha_v\beta_3$ antagonists. The competitive assay procedure described in Kumar, et. al., "Biochemical Characterization Of The Binding Of Echistatin To Integrin $\alpha_v\beta_3$ Receptor", Journal Of Pharmacology And Experimental Therapeutics, Vol. 283, No. 2, pp. 843-853 (1997) was employed. Thus, binding of ^{125}I-echistatin (radiolabeled by the chloramine-T method to a specific activity of 2000 Ci/mmol (Amersham, Chicago, Il.)) to $\alpha_v\beta_3$ receptor (purified from human placenta), both prepared as described in Kumar, et al., was competed by the compounds prepared in the foregoing examples. Purified $\alpha_v\beta_3$ receptor was coated onto Microlite-2 plates at a concentration of 50 ng/well. ^{125}I-echistatin was added to the wells to a final concentration of 0.05 nM in binding buffer (50 μl/well) in the presence of the competing test compound. The competing test compounds were employed at serially diluted concentrations ranging from 1 pM to 100 nM. After a 3 hour incubation at room temperature, the wells were washed, and

radioactivity, reflecting binding by ^{125} I-echistatin to $\alpha_v\beta_3$ receptors, was determined with Top Count (Packard). Each data point is an average of values from triplicate wells.

[0179] Specific binding of ^{125}I-echistatin was calculated as the difference between the amount of ^{125}I-echistatin bound in the absence (total binding) and the amount of ^{125}I-echistatin bound in the presence of a 200-fold molar excess of unlabeled echistatin (nonspecific binding). The efficacy of the test compounds for inhibiting specific binding of ^{125}I-echistatin to $\alpha_v\beta_3$ receptors was determined by plotting a graph of specific binding (y-axis) as a function of test compound concentration (x-axis). The concentration of test compound required to inhibit 50% of the specific binding (IC_{50}) was determined from the plot. The IC_{50} may be directly converted mathematically to Ki, which is a measure of the receptor binding affinity of the compounds under the defined assay conditions.

[0180] To measure the relative affinity of the test compounds for $\alpha_v\beta_3$ receptors versus affinity for $\alpha_{IIb}\beta_3$ receptors, similar competitive assays were carried out using purified $\alpha_{IIb}\beta 3$ receptor and ^{125}I-echistatin (iodinated using the lactoperoxidase method). The specificity index, which is a measure of the relative binding affinity for $\alpha_v\beta_3$, versus $\alpha_{IIb}\beta_3$, may be determined by dividing the IC_{50} value for $\alpha_{IIb}\beta_3$ by the IC_{50} value for $\alpha_v\beta_3$.

[0181] The $\alpha_v\beta_3$ IC_{50} values determined by the foregoing assay for the compounds identified in the preceding examples, and the specificity index (IC_{50} $\alpha_{IIb}\beta_3$/ IC_{50} $\alpha v\beta_3$) are summarized in the tables below.

TABLE 9.

Example	IC_{50}, nM
5-1	5.4
5-2	6.5
5-3	1.9
5-4	2.9
5-5	0.42
5-6	~500
5-7	~ 500
5-8	~500
5-9	~500
5-10	~500

TABLE 10.

Example	IC_{50}, nM	SPECIFICITY $\alpha_{IIb}\beta_3$ / $\alpha_v\beta_3$
5-11	3.4	70
5-12	5.6	87
5-13	3.1	38
5-14	5.8	117
5-15	4.3	95
5-16	4.4	899
5-17	4.6	76
5-18	4.4	82
5-19	8.9	34
5-20	7.2	15
5-21	4.4	41
5-22	6.4	26
5-23	5.5	22

(continued)

Example	IC_{50}, nM	SPECIFICITY $\alpha_{IIb}\beta_3$ / $\alpha_v\beta_3$
5-24	5.3	14
5-25	4.5	52
5-26	3.5	91
5-27	1.56	481
5-28	0.65	1136
5-29	4.3	144
5-30	2.3	296
5-31	6.0	80
5-32	6.5	151
5-33	17	128
5-34	2.3	421
5-35	8.1	240
5-36	11.7	129
5-37	5.3	203
5-38	13.6	49
5-139	3.1	223
5-40	5.7	288
5-41	2.8	19
5-42	1.8	39
5-43	2.2	585
5-44	19.6	66.3
5-45	2.2	1333
5-46	2.7	1065
5-47	2.2	1252
5-48	1.0	2028
5-49	4.2	504
5-50	3.0	805
5-51	1.1	1210
5-52	4.0	448
5-53	3.8	483
5-54	2.0	413
5-55	2.5	620
5-56	1.6	514

TABLE 11.

Example	IC_{50}, nM	Specificity $\alpha_{IIb}\beta_3$ / $\alpha_v\beta_3$
5-57	1293	1.43
5-58	118	46

(continued)

Example	IC_{50}, nM	Specificity $\alpha_{IIb}\beta_3$ / $\alpha_v\beta_3$
5-59	129	65

TABLE 12.

Example	IC_{50}, nM	Specificity $\alpha_{IIb}\beta_3$/ $\alpha_v\beta_3$
5-60	25	90
5-61	17	324
5-62	30	419
5-63	20	293
5-64	16	499

TABLE 13.

Example	IC_{50}, nM	Specificity $\alpha_{11b}\beta_3$ / $\alpha_v\beta_3$
5-65	9,227	0.4
5-66	9,468	0.4
5-67	7,373	0.5
5-68	6,630	0.4
5-69	10,514	0.4

TABLE 14.

Example	IC_{50} nM	Specificity $\alpha_{II}\beta_3$ / $\alpha_v\beta_3$
5-70	413	0.2
5-71	266	0.3
5-72	559	0.5
5-73	170	0.7
5-74	238	0.6

TABLE 15.

Example	IC_{50}, nM	Specificity $\alpha_{IIb}\beta_3$ / $\alpha_v\beta_3$
5-75	306	10.2
5-76	50	6.7
5-77	49	12.4
5-78	21	33.9
5-79	33	19.0

TABLE 16.

Example	IC_{50}, nM	Specificity $\alpha_{IIb}\beta_3 / \alpha_v\beta_3$
5-80	4.4	11
5-81	8.2	8.0
5-82	2.2	1259
5-83	1.8	1689
5-84	3.6	712
5-85	1.8	1223
5-86	3.3	793
5-87	2.0	1569
5-88	2.0	1657
5-89	3.3	1094
5-90	2.6	1697
5-91	2.8	1183
5-92	7.6	174
5-93	6.7	124
5-94	3.8	399
5-95	1.7	775
5-96	3.4	528
5-97	4.3	2600

Pharmaceutical Dosage Form Examples

[0182] The following are examples of pharmaceutical dosage forms which contain a compound (i.e., "active compound") of the invention. The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided.

EXAMPLE 9

Tablets

[0183]

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	5
2.	Lactose USP	122	40
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	25
4.	Corn Starch, Food Grade	45	25
5.	Magnesium Stearate	3	5
	Total	300	100

Method of Manufacture

[0184] Mix Item Nos. 1 and 2 in a suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE 10

Capsules

[0185]

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	5
2.	Lactose USP	106	45
3.	Corn Starch, Food Grade	40	45
4.	Magnesium Stearate NF	7	5
Total		253	100

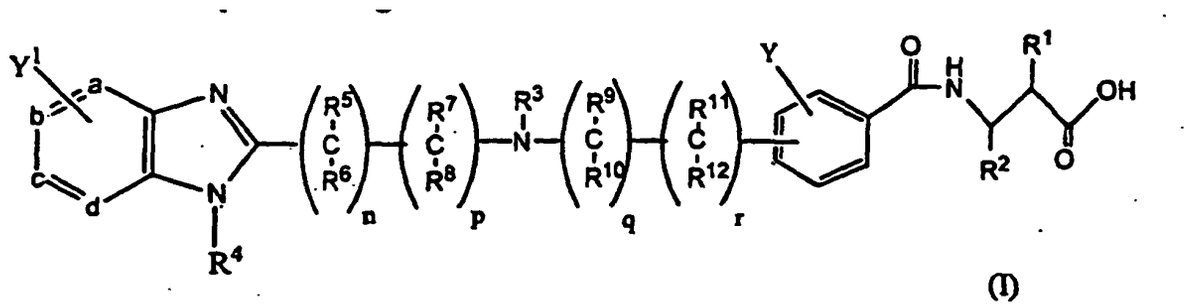
Method of Manufacture

[0186] Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

[0187] While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

Claims

1. A compound having the formula:



(I)

wherein n, p, q and.r are each independently selected from 0 or 1;

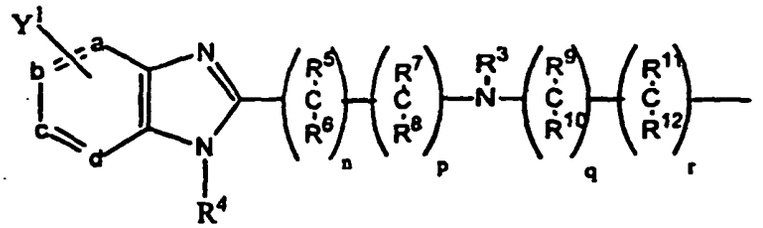
a, b, c, and d each independently represents a carbon or nitrogen atom, with the proviso that no more than two of a, b, c, and d are nitrogen atoms;

Y and Y^1 each independently represents 1-4 optional substituents selected from alkyl, alkoxy, halo, $-CF_3$, and -C(O)OH;

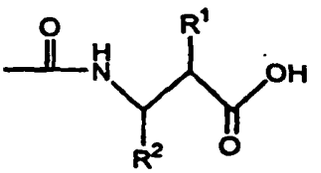
R^1 is H, alkyl, aryl, aralkyl, arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, heteroaralkyl, cycloalkylalkyl, heterocycloalkylalkyl, $-NHR^A$, $-NHC(O)R^A$, $-NHSO_2R^A$, $NHC(O)NHR^A$ or $-NHC(O)OR^A$, R^1 being optionally substituted by 1-3 groups selected from halo, alkyl, $-CF_3$, -CN, $-OR^B$, $-SR^B$, $-CO_2R^B$, $-C(O)R^B$, $-OC(O)R^B$, $-OC(O)OR^B$ and $-SO_2R^B$, and R^A and R^B are independently selected from H, alkyl, aryl, aralkyl, arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, heteroaralkyl, cycloalkylalkyl or heterocycloalkylalkyl, with the proviso that when R' is alkyl, R^1 is not substituted with halo, the proviso that when R^1 is $-NHSO_2R^A$ or $-NHC(O)OR^A$,

R^A is not H, and the proviso that for $-SO_2R^B$ or $-OC(O)OR^B$, R^B is not H;
R^2 is H, alkyl aryl, aralkyl, arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, heteroaralkyl, cycloalkylalkyl, or heterocycloalkylalkyl, R^1 being optionally substituted by 1-3 groups selected from halo, alkyl, $-CF_3$, -CN, $-OR^C$, $-SR^C$, $-CO_2R^C$, $-C(O)R^C$, $-OC(O)R^C$, $-OC(O)OR^C$ and $-SO_2R^F$, wherein R^C is selected from H, alkyl, aryl, aralkyl arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, heteroaralkyl, cycloalkylalkyl or heterocycloalkylalkyl, with the proviso that when R^1 is alkyl, R^2 is not substituted with halo, and the proviso that for $-SO_2R^C$ or $-OC(O)OR^C$, R^C is not H;
R^3 is H, alkyl, aralkyl, arylcycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, heteroaralkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, $-C(O)R^D$, $-C(O)OR^D$, $-SO_2R^E$,- $C(O)NR^FR^G$, $-C(O)NR^FSO_2R^E$, or $-C(=S)NR^FR^G$, wherein R^D, R^E, R^F and R^G are independently selected from H, alkyl, aryl, aralkyl, arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl or heterocycloalkylalkyl, or R^F and R^G taken together complete a 5-7 member ring containing 0 to 1 oxygen or sulfur atoms, and 1 to 2 nitrogen atoms, R^3 being optionally substituted by 1-3 groups selected from halo, alkyl, aryl, $-CF_3$, -CN, $-OR^H$, $-SR^H$, $-CO_2R^H$, $-C(O)R^H$, $-OC(O)R^H$, $-OC(O)OR^H$, $-SO_2R^H$ and $-NR^HR^H$, wherein R^H is selected from H, alkyl, aryl, aralkyl, arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, heteroaralkyl, cycloalkylalkyl or heterocycloalkylalkyl, with the proviso that when R^3 is alkyl, R^3 is not substituted with halo, the proviso that when R^3 is $-SO_2R^E$, $-C(O)NR^FSO_2R^E$, or $-CO(O)R^D$, R^D and R^E are not H, and the proviso that for $-SO_2R^H$ or $-OC(O)OR^H$, R^H is not H;
R^4 is H, alkyl, aralkyl, arylcycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, heteroaralkyl, aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, R^4 being optionally substituted by 1-3 groups sheeted from halo, alkyl, $-CF_3$, -CN, $-OR^J$, $-SR^J$, $-CO_2R^J$, $-C(O)R^J$, $-OC(O)R^J$, $-OC(O)OR^J$ and $-SO_2R^J$, wherein R^J is selected from H, alkyl, aryl, aralkyl, arylcycloalkyl, heteroaryl, cycloalkyl, heterocycloalkyl, heteroaralkyl, cycloalkylalkyl or heterocycloalkylalkyl, with the proviso that when R^4 is alkyl, R^4 is not substituted with halo, and the proviso that for $-SO_2R^J$ or $-OC(O)OR^J$, R^J is not H;
R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are independently selected from H or C_1-C_3 alkyl;

and wherein



and



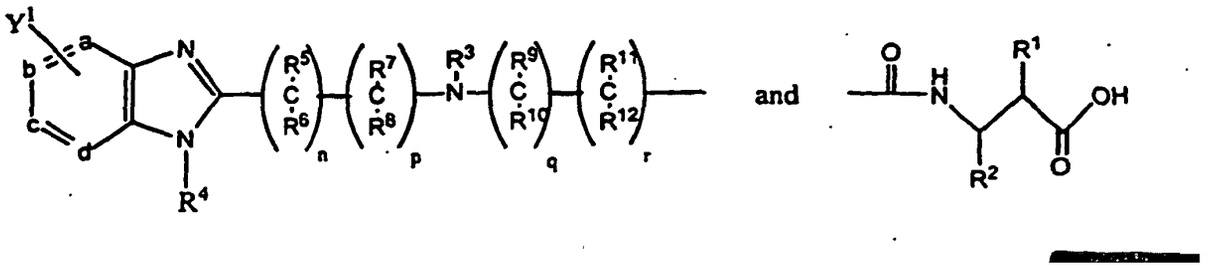
are positioned meta or para relative to each other;
or a biolabile ester thereof, or a pharmaceutically acceptable salt thereof;
wherein the following terms have the following meanings:

"alkyl" refers to straight or branched chain groups having 1 to 20 carbon atoms;
"cycloalkyl" refers to non-aromatic carbocyclic ring or multi-carbocyclic ring system of from 3 to 20 carbon atoms;
"cycloalkylalkyl" refers to groups having the formula cycloalkyl-R-, wherein R is alkyl;
"heterocycloalkyl" refers to a cycloalkyl group, wherein one or more of the carbon atoms of such groups are replaced with a heteroatom selected from O, S and N;
"heterocycloalkylalkyl" refers to groups having the formula heterocycloalkyl-R-, wherein R is alkyl;
"aryl" refers to aromatic carbocyclic groups;
"aralkyl" refers to groups having the formula aryl-R-, wherein R is alkyl; "heteroaryl" refers to aromatic carbocyclic groups, wherein one or more of the carbon atoms of such groups are replaced with a heteroatom selected from O, S and N;
"heteroaralkyl" refers to groups having the formula heteroaryl-R-, wherein R is alkyl;
"arylcycloalkyl" refers to groups having the formula aryl-R-, wherein R is cycloalkyl;

and wherein said biolabile esters are alkyl, alkanoyloxyalkyl, cycloalkanoyloxyalkyl, aroyloxyalkyl and alkoxycarbonyloxyalkyl esters, including cycloalkyl and aryl substituted derivatives thereof, aryl esters and cycloalkyl esters, wherein said alkyl, alkanoyl or alkoxy groups may contain from 1 to 8 carbon atoms and be branched-chain or straight-chain, said cycloalkyl groups may contain from 3-7 carbon atoms and said cycloalkanoyl groups from 4-8

carbon atoms wherein both are optionally benzo-fused, and said aryl and aroyl groups include substituted phenyl, naphthyl or indanyl ring systems.

2. The compound of claim 1 wherein



are positioned para relative to each other.

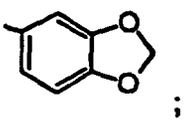
3. The compound of claim 2, wherein R^4 is H.

4. The compound of claim 3, wherein R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are each H.

5. The compound of claim 4, wherein the sum of n + p is 1 and the sum of q + r is1.

6. The compound of claim 5, wherein a, b, c, and d are each carbon atoms, and R^2 is H.

7. The compound of claim 6, wherein R^3 is selected from H, alkyl, $-C(O)R^D$, $-C(O)OR^D$, $-C(O)NR^FR^G$, and $-C(=S)NR^FR^G$; wherein R^D is selected from phenyl, alkyl, aralkyl, cycloalkyl, arylcycloalkyl, and

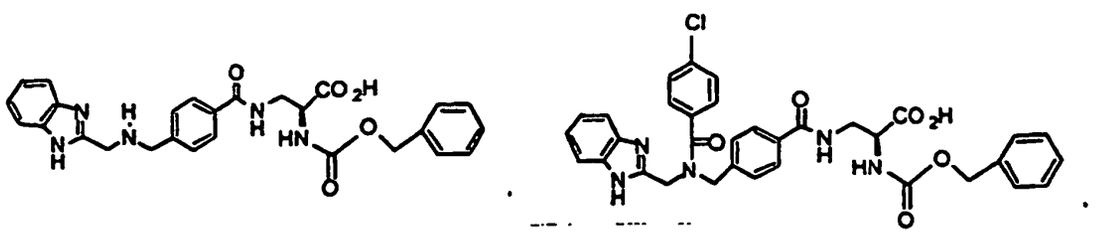


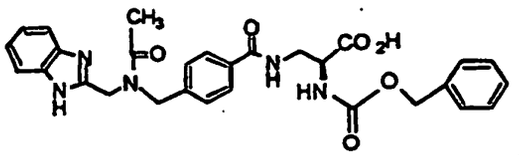
;

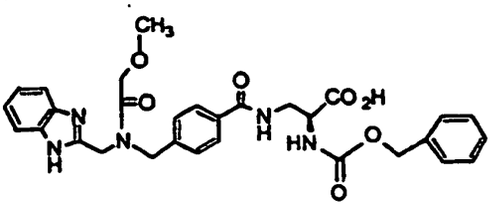
wherein R^D is optionally substituted by 1-3 substituents selected from alkoxy, halo, cycloalkyl, $-S-CH_3$, phenyloxy, $-OC(O)CH_3$, $-C(O)OC_2H_5$ and $-N(CH_3)_2$; wherein R^F and R^G are selected from H, alkyl, phenyl, cycloalkyl, and aralkyl; and wherein R^F and R^G are optionally substituted by alkoxy, halo or $-CO_2R^H$.

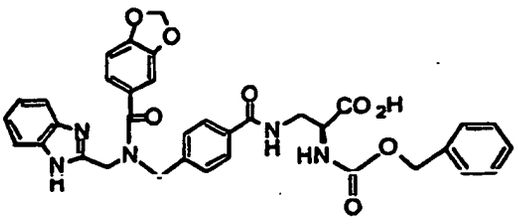
8. The compound of claim 7, wherein R^1 is H, $-NHR^A$, $-NHC(O)R^A$, $-NHC(O)OR^A$, $-NHC(O)NHR^A$ or $-NHSO_2R^A$.

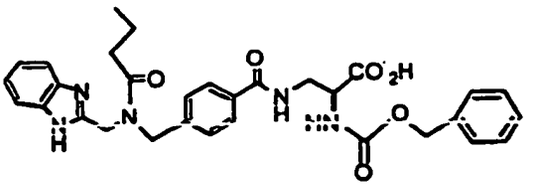
9. The compound of claim 1, wherein said compound is selected from the group consisting of

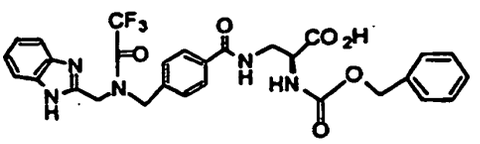


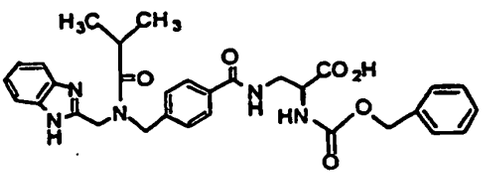


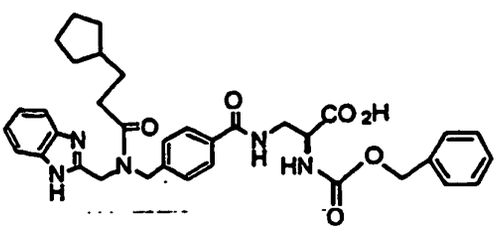


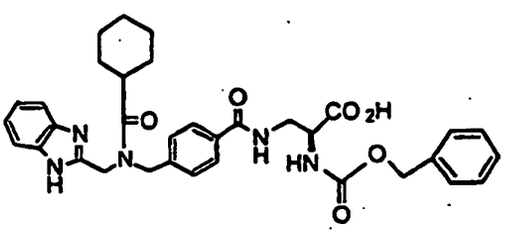


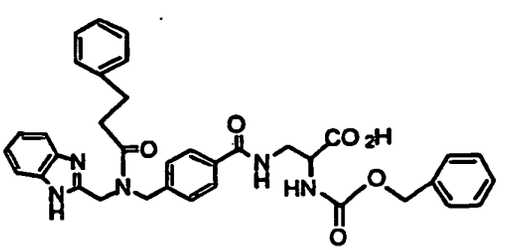


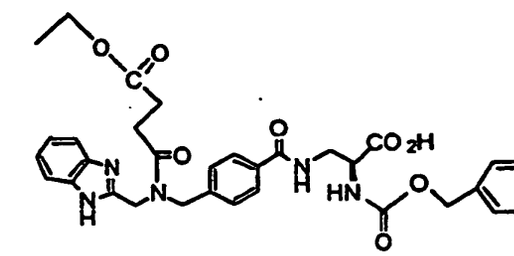


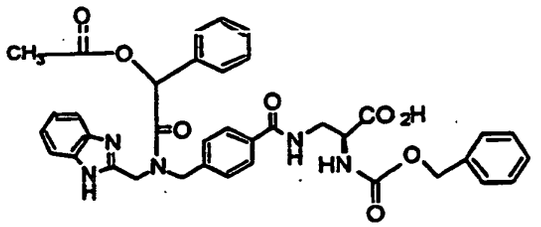


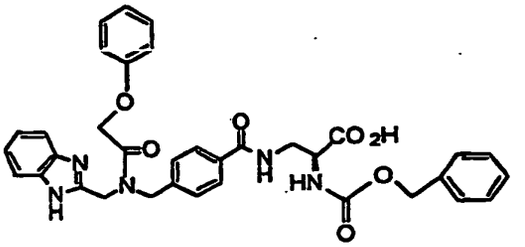


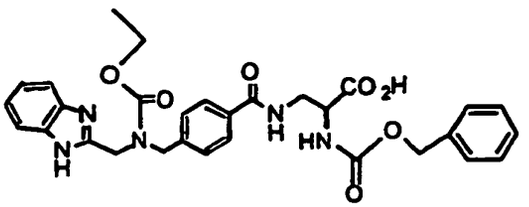


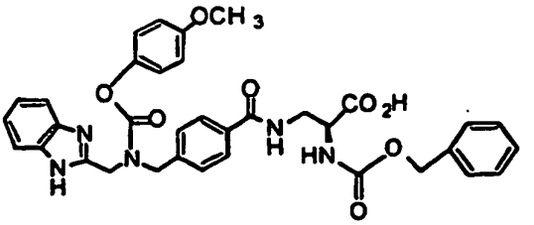


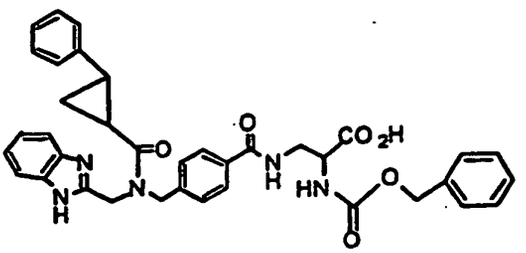


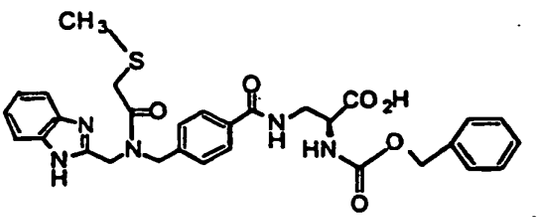


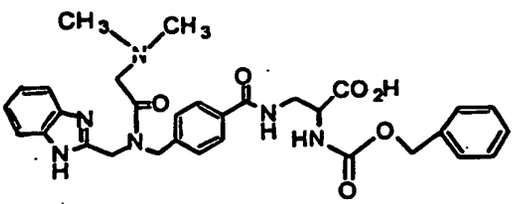


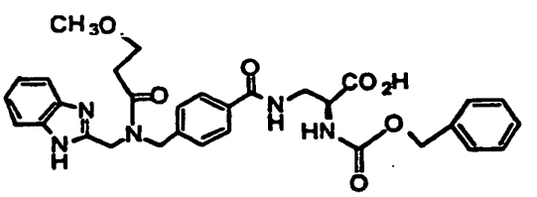


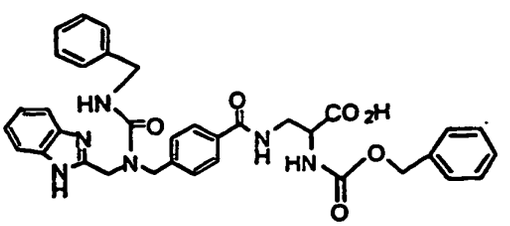


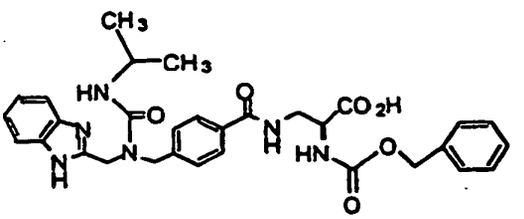


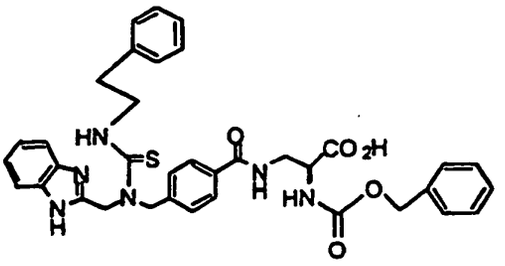


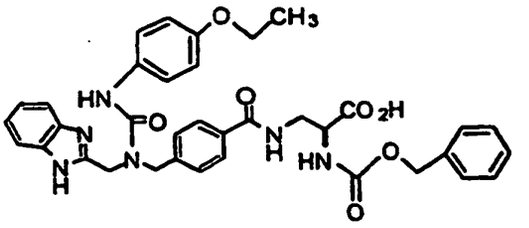


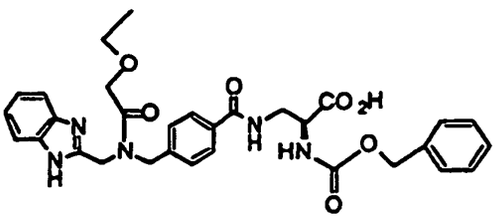


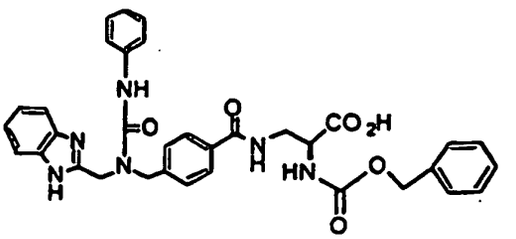


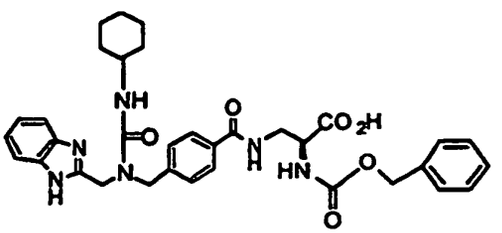


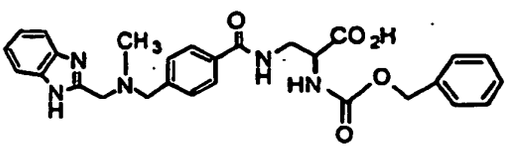


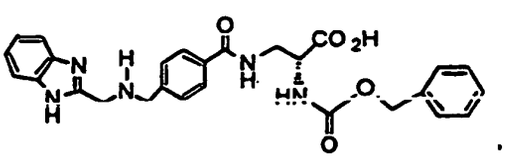


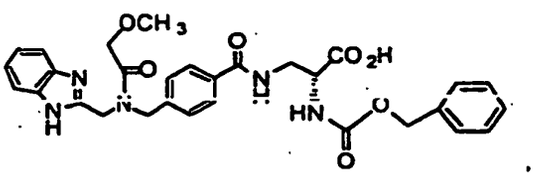


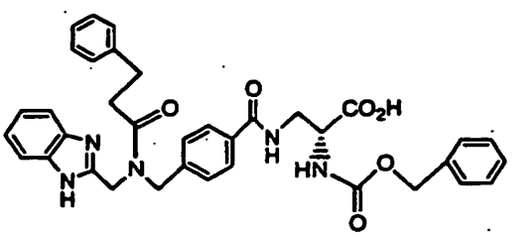


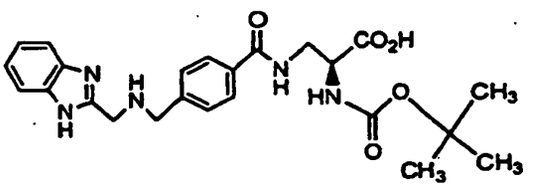


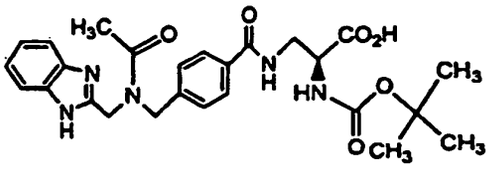


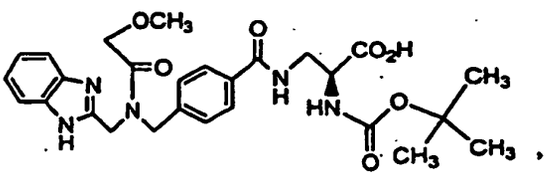


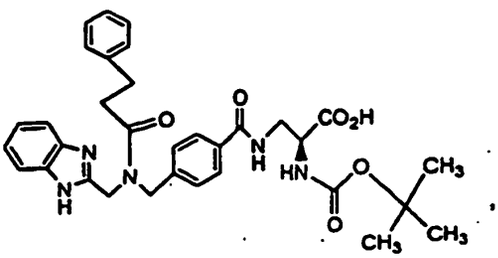


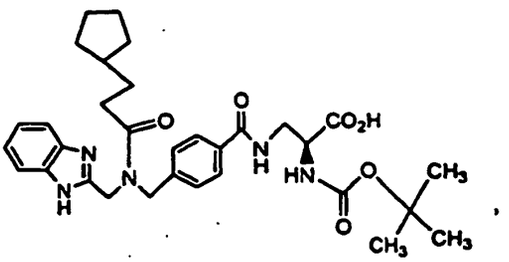


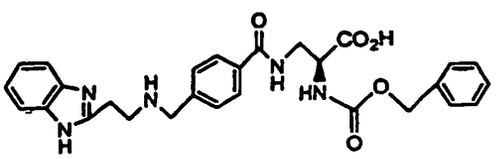


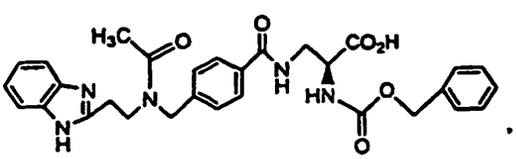


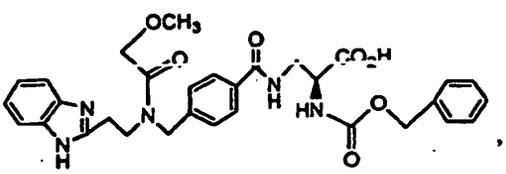


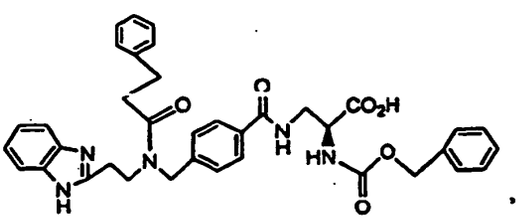


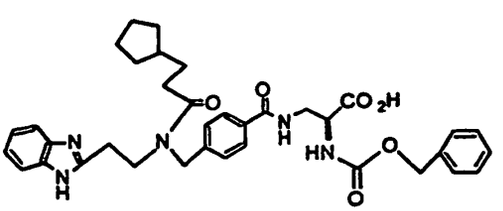


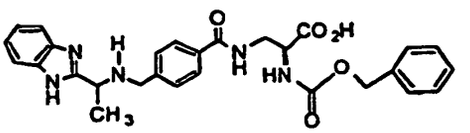


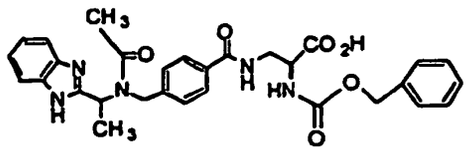


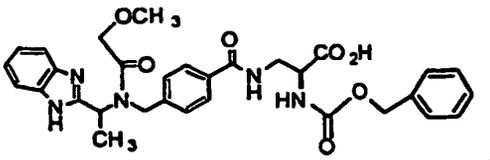


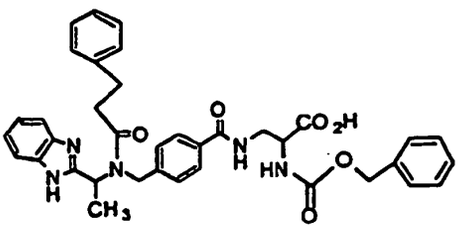


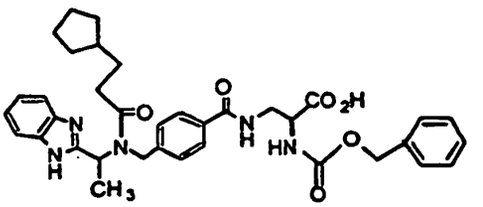


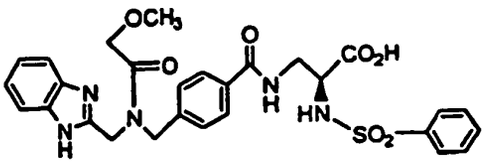


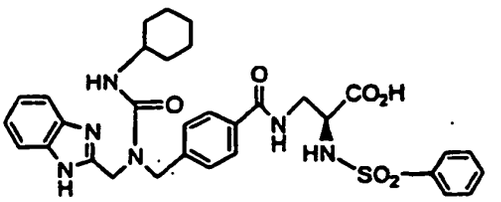


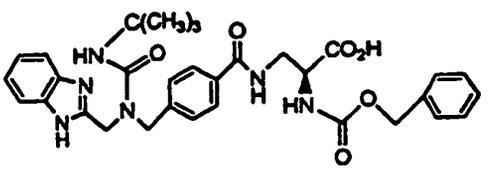


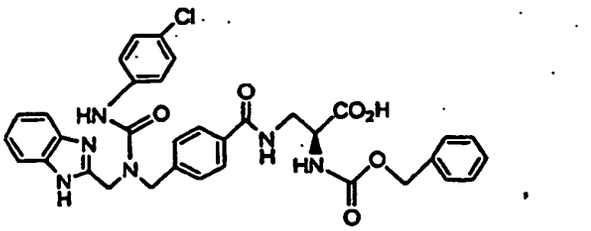


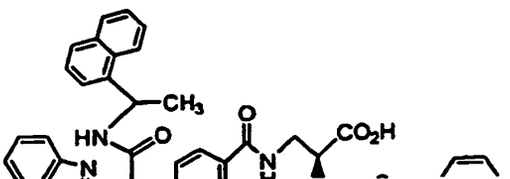


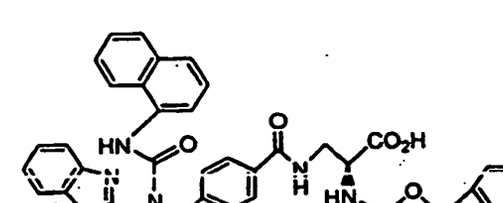


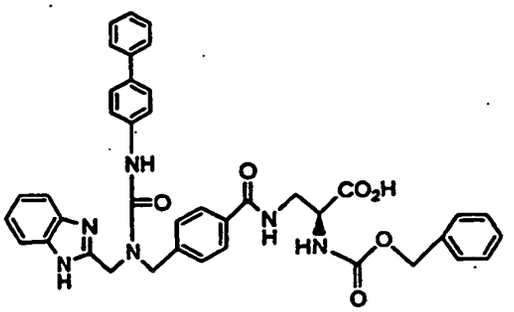












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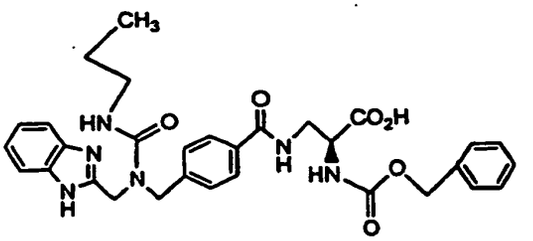

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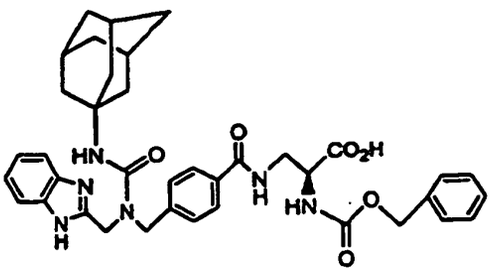

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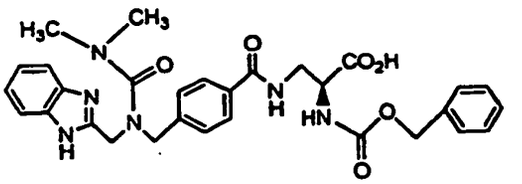

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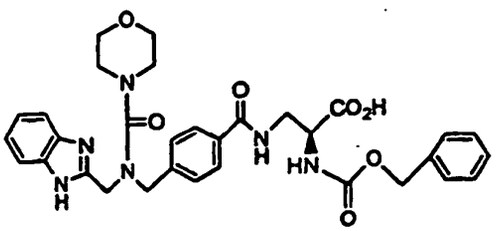

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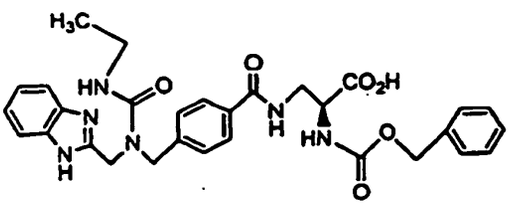

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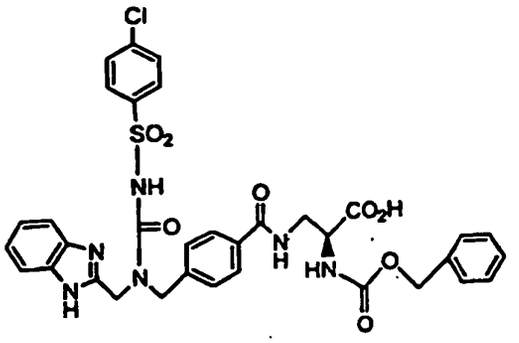
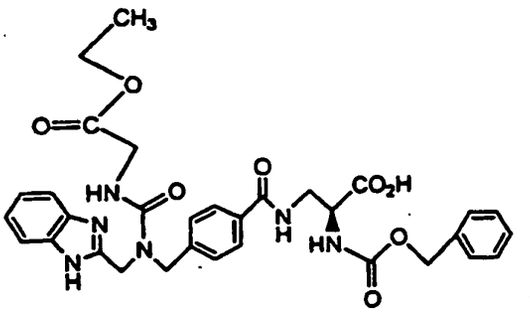
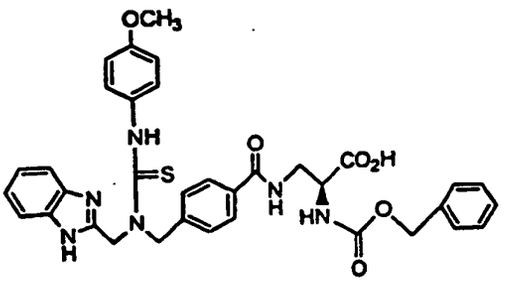
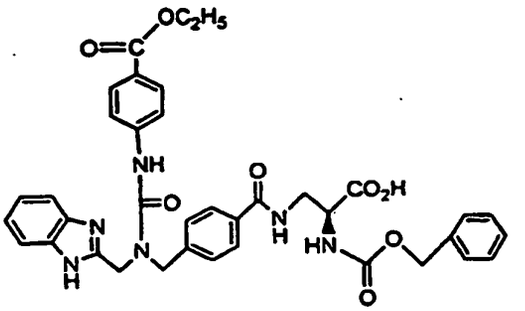
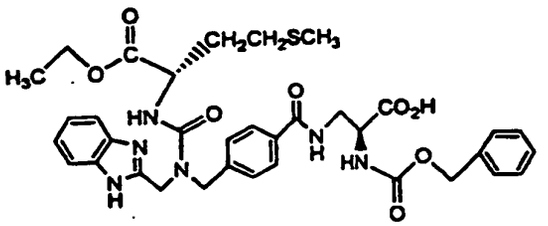
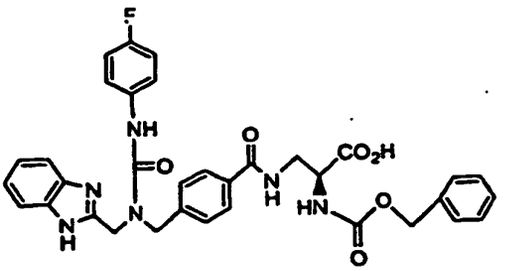


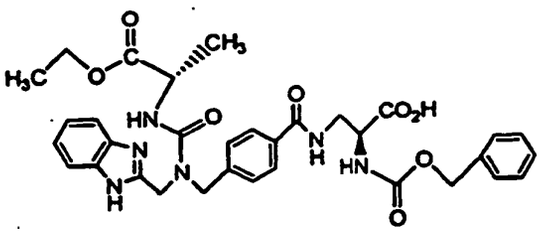


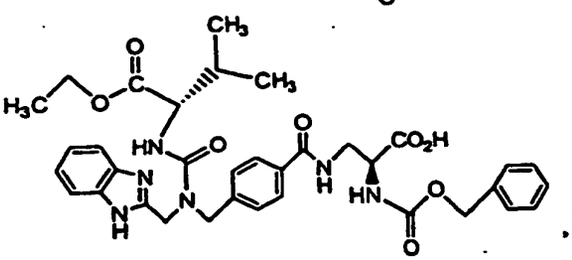


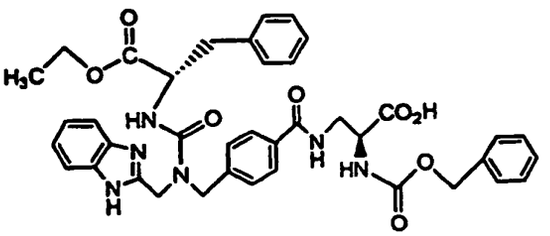


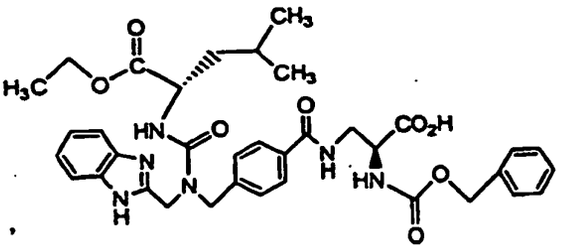


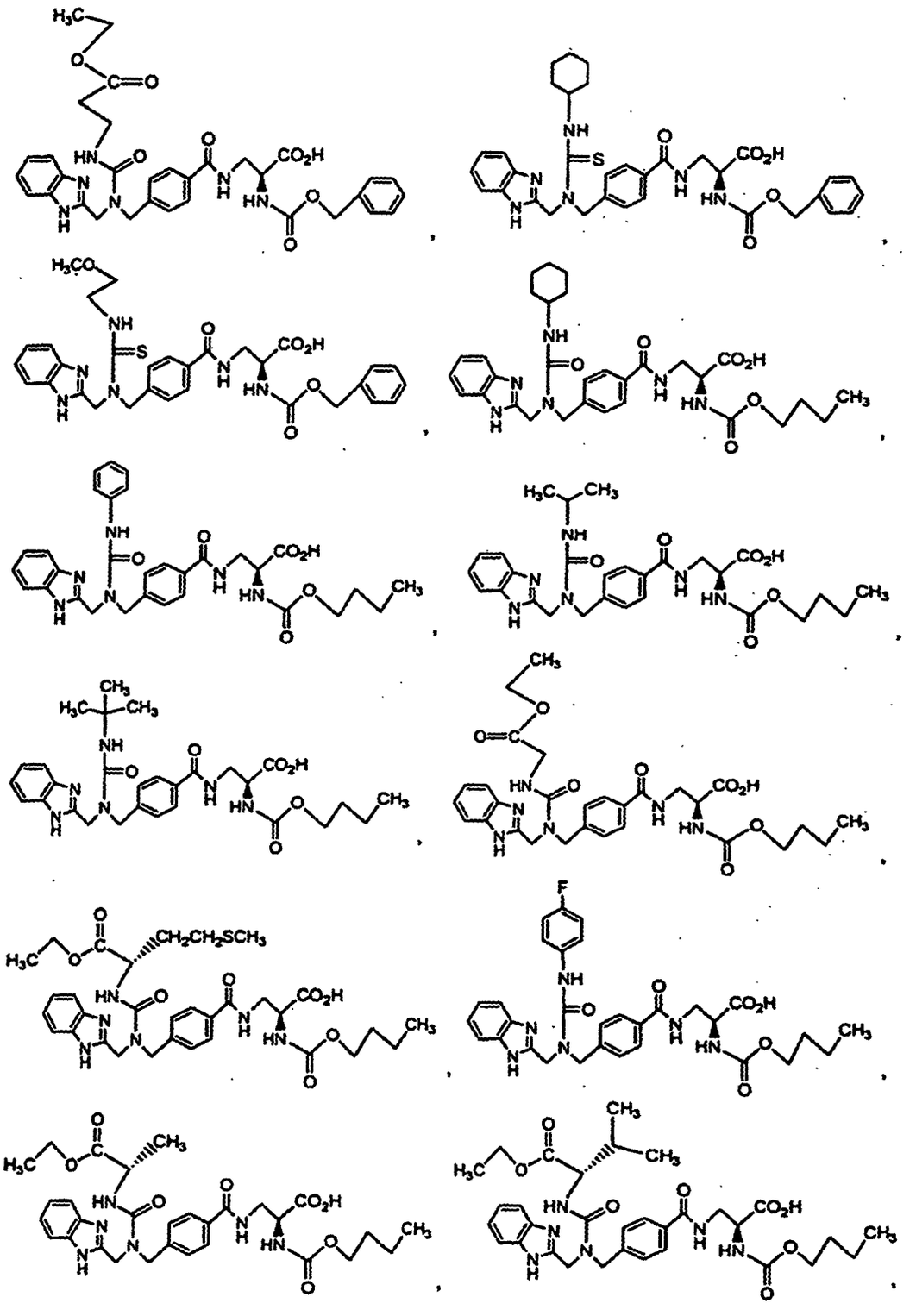


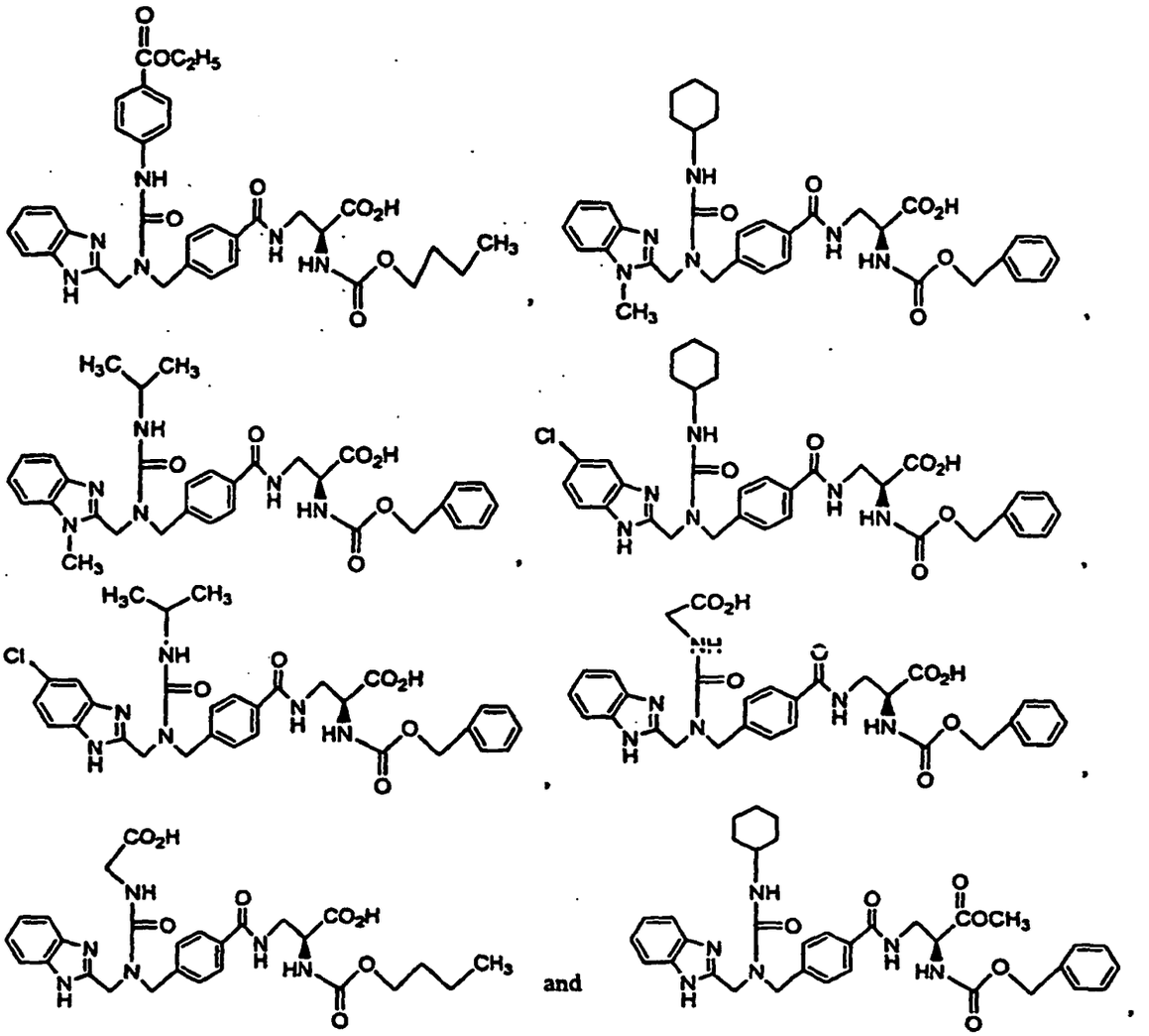






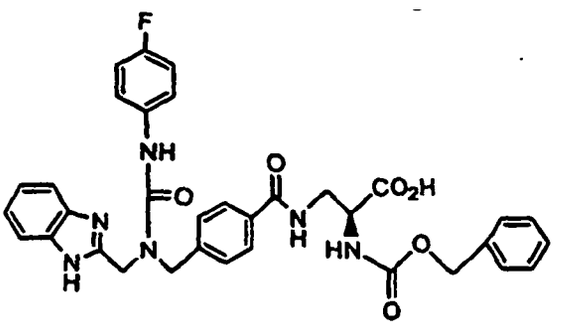






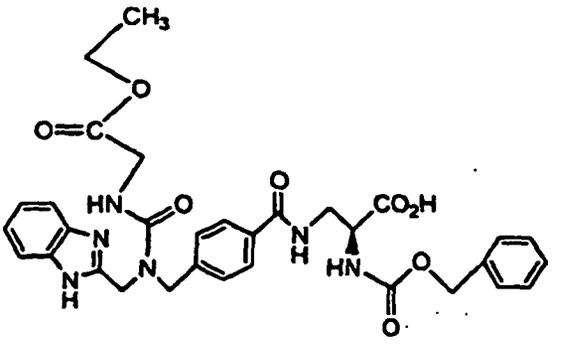
or a biolabile ester thereof, or a pharmaceutically acceptable salt thereof.

10. The compound of claim 9, wherein said compound is



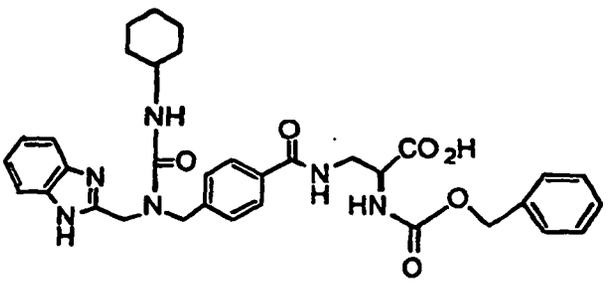
or a biolabile ester thereof, or a pbannaceutically acceptable salt thereof.

11. The compound of claim 9, wherein said compound is



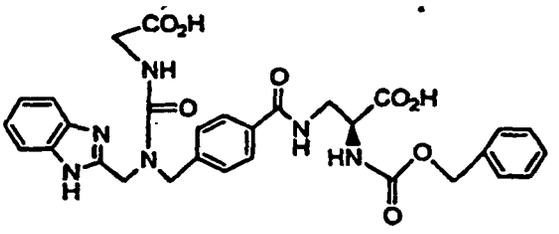
or a biolabile ester thereof, or a pharmaceutically acceptable salt thereof.

12. The compound of claim 9, wherein said compound is



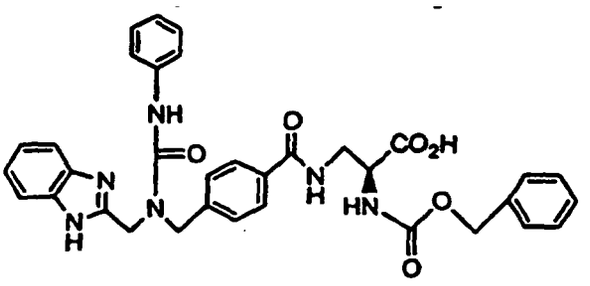
or a biolabile ester thereof, or a pharmaceutically acceptable salt thereof.

13. The compound of claim 9. wherein said compound is



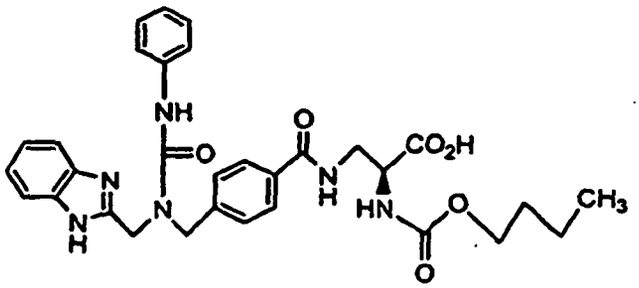
or a biolabile ester thereof, or a pharmaceutically acceptable salt thereof.

14. The compound of claim 9, wherein said compound is



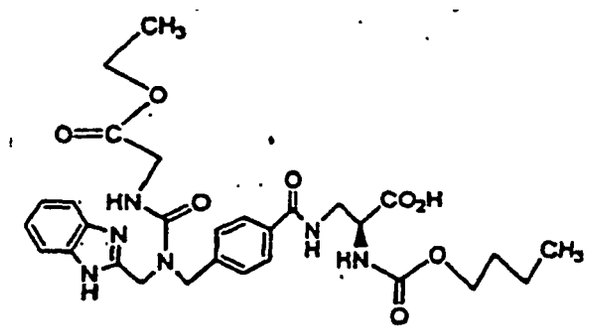
or a biolabile ester thereof, or a pharmaceutically acceptable salt thereof.

15. The compound of claim 9, wherein said compound is



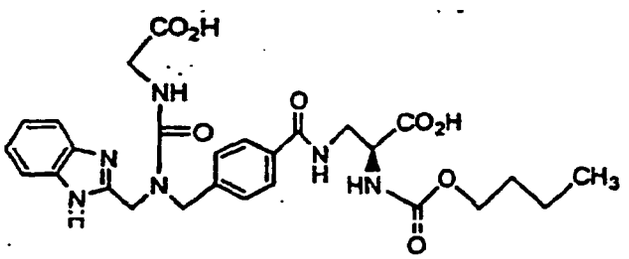
or a biolabile ester thereof, or a pharmaceutically acceptable salt thereof.

16. The compound of claim 9, wherein said compound is



or a biolabile ester thereof, or a pharmaceutically acceptable salt thereof.

17. The compound of claim 9, wherein said compound is

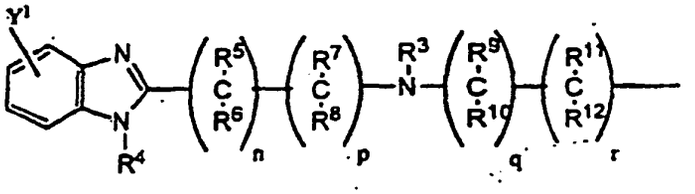


or a biolabile ester thereof, or a pharmaceutically acceptable salt thereof.

18. Use of a compound according to any preceding claim for the manufacture of a medicament for treating a mammal afflicted with a vitronectin-mediated disorder.

19. The use of claim 18, wherein the vitronectin-mediated disorder is cancer, retinopathy, atherosclerosis, vascular restenosis, or osteoporosis.

20. The use of claim 19, wherein a, b, c, and d are each carbon atoms;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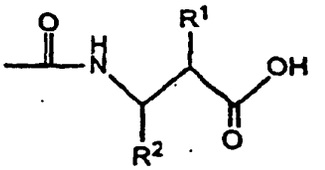
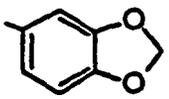


are positioned para relative to each other;

R^2, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are each H;
the sum of n + p is 1 and the sum of q + r is 1;
R^1 is H, -NHR^A, -$NHC(O)R^A$, -$NHC(O)OR^A$, -$NHC(O)NHR^A$ or -$NHSO_2R^A$;
R^3 is selected from H, alkyl, -$C(O)R^D$, -$C(O)OR^D$, -$C(O)NR^FR^G$, and- $C(=S)NR^FR^G$; wherein R^D is selected from phenyl, alkyl, aralkyl, cycloalkyl arylcycloalkyl, and

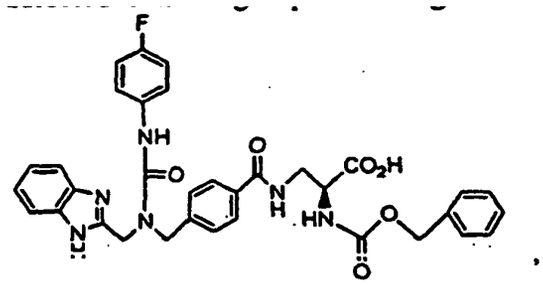

;

wherein R^D is optionally substituted by 1-3 substitutents selected from alkoxy, halo, cycloalkyl, -S-CH_3, phenyloxy, -$OC(O)CH_3$, -$C(O)OC_2H_5$ and -$N(CH_3)_2$; wherein R^F and R^G are selected from H, alkyl, phenyl, cycloalkyl, and aralkyl; and wherein R^F and R^G are optioonally substituted by alkoxy, halo, or -CO_2R^H.

[deletion(s)]

21. The use of claim 20, wherein the disorder is cancer.

22. The use of claim 18, wherein the disorder is cancer and the compound is selected from the group consisting of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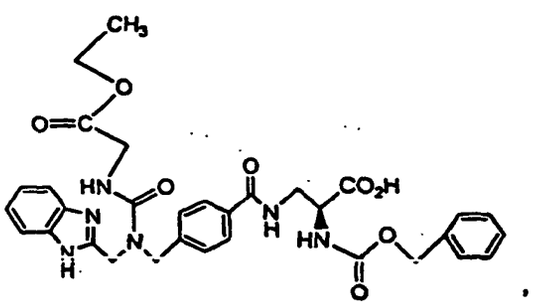
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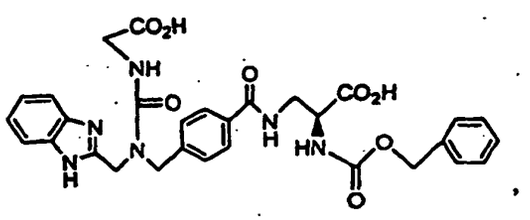
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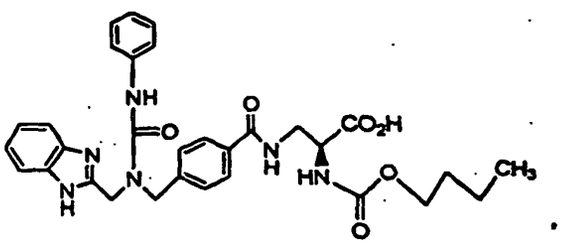
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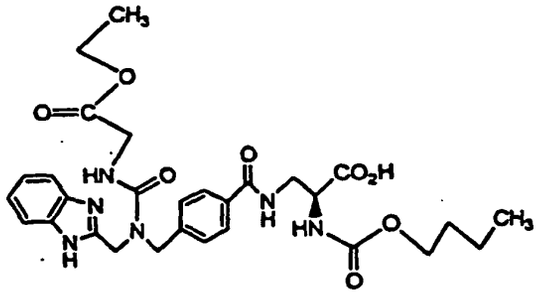
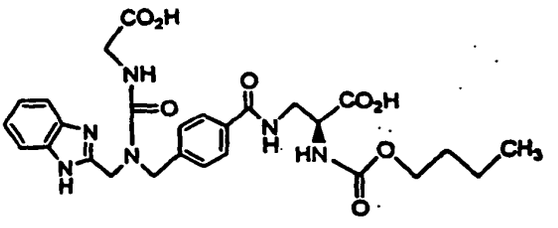
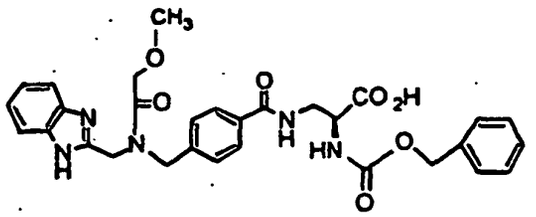
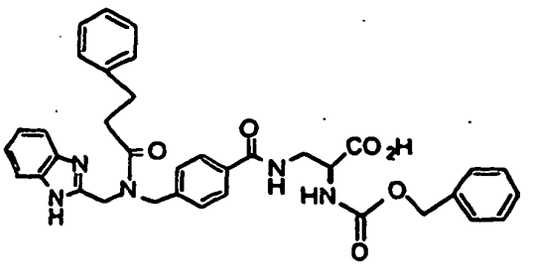
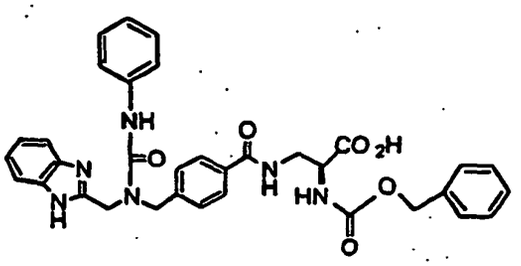
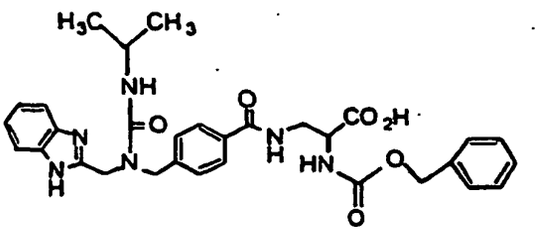




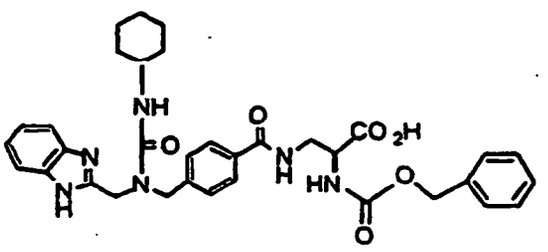








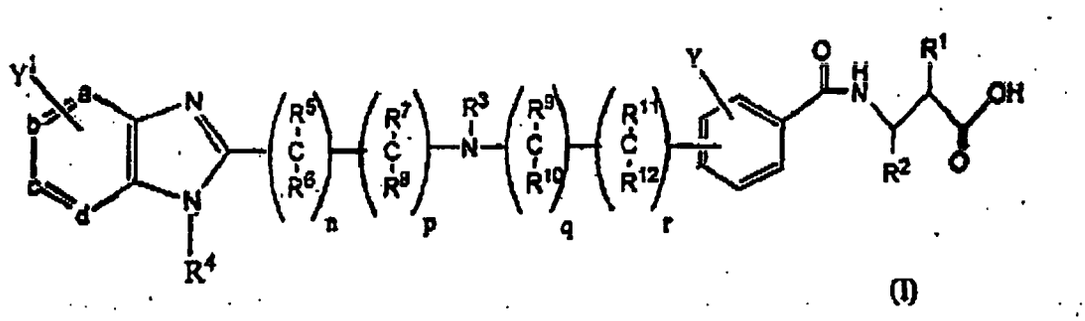
and



or a biolabile ester thereof, or a pharmaceutically acceptable salt thereof.

Patentansprüche

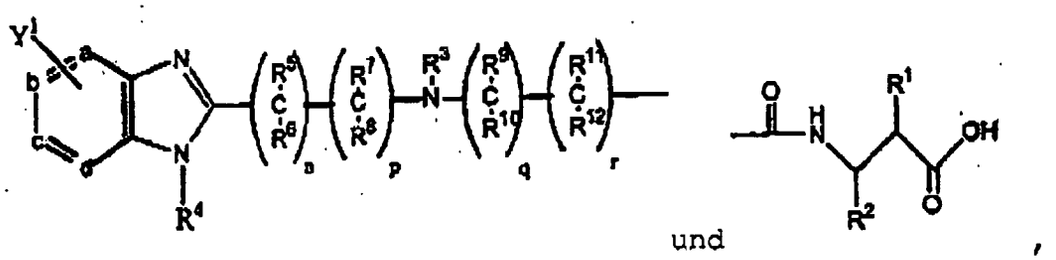
1. Verbindung mit der Formel:



(I)

wobei n, p, q und r jeweils unabhängig ausgewählt sind aus 0 oder 1;
a, b, c und d jeweils unabhängig für ein Kohlenstoff- oder Stickstoffatom stehen, mit der Maßgabe, dass nicht mehr als zwei von a, b, c und d Stickstoffatome sind;
Y und Y^1 jeweils unabhängig für 1 bis 4 optionale Substituenten ausgewählt aus Alkyl, Alkoxy, Halogen, $-CF_3$ und -C(O)OH stehen;
R^1 H, Alkyl, Aryl, Aralkyl, Arylcycloalkyl, Heteroaryl, Cycloalkyl, Heterocycloalkyl, Heteroaralkyl, Cycloalkylalkyl, Heterocycloalkylalkyl, $-NHR^A$, $-NHC(O)R^A$, $-NHSO_2R^A$, $NHC(O)NHR^A$ oder $-NHC(O)OR^A$ ist, wobei R^1 gegebenenfalls mit 1 bis 3 Gruppen ausgewählt aus Halogen, Alkyl, $-CF_3$, -CN, $-OR^B$, $-SR^B$, $-CO_2R^B$, $-C(O)R^B$, $-OC(O)R^B$, $-OC(O)\ OR^B$ und $-SO_2R^B$ substituiert ist, und R^A und R^B unabhängig ausgewählt sind aus H, Alkyl, Aryl, Aralkyl, Arylcycloalkyl, Heteroaryl, Cycloalkyl, Heterocycloalkyl, Heteroaralkyl, Cycloalkylalkyl oder Heterocycloalkylalkyl, mit der Maßgabe, dass, wenn R^1 Alkyl ist, R^1 nicht mit Halogen substituiert ist, mit der Maßgabe, dass, wenn R^1 $-NHSO_2R^A$ oder $-NHC(O)OR^A$ ist, R^A nicht H ist, und mit der Maßgabe, dass bei $-SO_2R^B$ oder $-OC(O)OR^B$ R^B nicht H ist;
R^2 H, Alkyl, Aryl, Aralkyl, Arylcycloalkyl, Heteroaryl, Cycloalkyl, Heterocycloalkyl, Heteroaralkyl, Cycloalkylalkyl oder Heterocycloalkylalkyl ist, wobei R^2 gegebenenfalls mit 1 bis 3 Gruppen ausgewählt aus Halogen, Alkyl, $-CF_3$, -CN, $-OR^C$, $-SR^C$, $-CO_2R^C$, $-C(O)R^C$, $-OC(O)R^C$, $-OC(O)OR^C$ und $-SO_2R^c$ substituiert ist, wobei R^C ausgewählt ist aus H, Alkyl, Aryl, Aralkyl, Arylcycloalkyl, Heteroaryl, Cycloalkyl, Heterocycloalkyl, Heteroaralkyl, Cycloalkylalkyl oder Heterocycloalkylalkyl, mit der Maßgabe, dass, wenn R^2 Alkyl ist, R^2 nicht mit Halogen substituiert ist, und mit der Maßgabe, dass bei $-SO_2R^C$ oder $-OC(O)OR^C$ R^C nicht H ist;
R^3 H, Alkyl, Aralkyl, Arylcycloalkyl, cycloalkylalkyl, Heterocycloalkylalkyl, Heteroaralkyl, Aryl, Heteroaryl, Cycloalkyl, Heterocycloalkyl, $-C(O)R^D$, $-C(O)OR^D$, $-SO_2R^E$, -C(O) NR^FR^G, $-C(O)NR^FSO_2R^E$ oder -C (=S) NR^FR^G ist, wobei. R^D, R^E, R^F und R^G unabhängig ausgewählt sind aus H, Alkyl, Aryl, Aralkyl, Arylcycloalkyl, Heteroaryl, Cycloalkyl, Heterocycloalkyl, Cycloalkylalkyl oder Heterocycloalkylalkyl, oder R^F und R^G zusammengenommen einen 5- bis 7-gliedrigen Ring vervollständigen, der 0 bis 1 Sauerstoff- oder Schwefelatome und 1 bis 2 Stickstoffatome enthält, wobei R^3 gegebenenfalls mit 1 bis 3 Gruppen ausgewählt aus Halogen, Alkyl, Aryl, $-CF_3$, -CN, $-OR^H$, $-SR^H$, $-CO_2R^H$,-C(O)R^H, $-OC(O)R^H$, $-OC(O)OR^H$, $-SO_2R^H$ und $-NR^HR^H$ substituiert ist, wobei R^H ausgewählt ist aus H, Alkyl, Aryl, Aralkyl, Arylcycloalkyl, Heteroaryl, Cycloalkyl, Heterocycloalkyl, Heteroaralkyl, Cycloalkylalkyl oder Heterocycloalkylalkyl mit der Maßgabe, dass, wenn R^3 Alkyl ist, R^3 nicht mit Halogen substituiert ist, mit der Maßgabe, dass, wenn R^3 $-SO_2R^E$, $-C(O)NR^FSO_2R^E$ oder $-CO(O)R^D$ ist, R^D und R^E nicht H sind, und mit der Maßgabe, dass bei $-SO_2R^H$ oder $-OC(O)OR^H$ R^H nicht H ist;
R^4 H, Alkyl, Aralkyl, Arylcycloalkyl, Cycloalkylalkyl, Heterocycloalkylalkyl, Heteroaralkyl, Aryl, Heteroaryl, Cycloalkyl oder Heterocycloalkyl ist, wobei R^4 gegebenenfalls mit 1 bis 3 Gruppen ausgewählt aus Halogen, Alkyl, $-CF_3$, -CN, $-OR^J$, $-SR^J$, $-CO_2R^J$, -C (O) R^J, -OC (O) R^J, $-OC(O)OR^J$ und $-SO_2R^J$ substituiert ist, wobei R^J ausgewählt ist aus H, Alkyl, Aryl, Aralkyl, Arylcycloalkyl, Heteroaryl, Cycloalkyl, Heterocycloalkyl, Heteroaralkyl, Cycloalkylalkyl oder Heterocycloalkylalkyl mit der Maßgabe, dass, wenn R^4 Alkyl ist; R^4 nicht mit Halogen substituiert ist, und mit der Maßgabe, dass bei $-SO_2R^J$ oder $-OC(O)OR^J$ R^J . nicht H ist;
R^5,R^6, R^7, R^8, R^9, R^{10}, R^{11} und R^{12} unabhängig ausgewählt sind aus H oder C_1- bis C_3-Alkyl;

und worin:



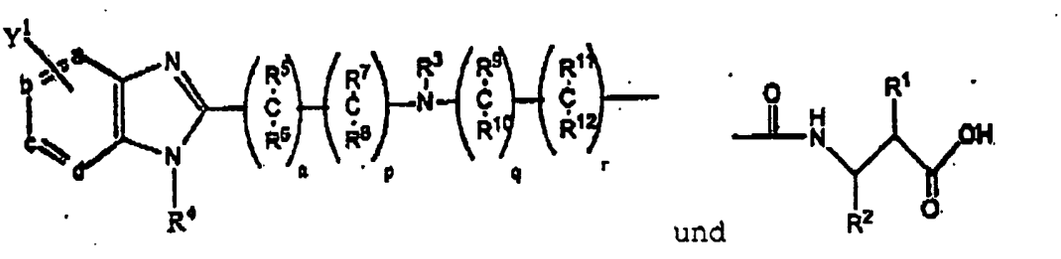
und

meta oder para relativ zueinander angeordnet sind;
oder ein biolabiler Ester oder ein pharmazeutisch annehmbares Salz davon;
wobei die folgenden Begriffe die folgenden Bedeutungen haben:

"Alkyl" bezieht sich auf geradkettige oder verzweigte Gruppen mit 1 bis 20 Kohlenstoffatomen;
"Cycloalkyl" bezieht sich auf einen nicht-aromatisches carbocyclisches Ring oder ein multi-barbocyclisches Ringsystem mit 3 bis 20 Kohlenstoffatomen;
"Cycloalkylalkyl" bezieht sich auf Gruppen mit der Formel Cycloalkyl-R-, wobei R Alkyl ist;
"Heterocycloalkyl" bezieht sich auf eine Cycloalkylgruppe, worin ein oder mehrere der Kohlenstoffatome dieser Gruppen durch ein Heteroatom ausgewählt aus O, S und N ersetzt worden sind;
"Heterocycloalkylalkyl" bezieht sich auf Gruppen mit der. Formel Heterocycloalkyl-R-, wobei R Alkyl ist;
"Aryl" bezieht sich auf aromatische carbocyclische Gruppen;
"Aralkyl" bezieht sich auf Gruppen mit der Formel Aryl-R-, wobei R Alkyl ist;
"Heteroaryl" bezieht sich auf aromatische carbocyclische Gruppen, worin ein oder mehrere der Kohlenstoffatome dieser Gruppen durch ein Heteroatom ausgewählt aus 0, S und N ersetzt worden sind;
"Heteroaralkyl" bezieht sich auf Gruppen mit der Formel Heteroaryl-R-, wobei R Alkyl ist;
"Arylcycloalkyl" bezieht sich auf Gruppen mit der Formel Aryl-R-, wobei R Cycloalkyl ist;

und wobei die biolabilen Ester Alkyl-, Alkanoyloxyalkyl-, Cycloalkanoyloxyalkyl-, Aroyloxyalkyl- und Alkoxycarbonyloxyalkylester einschließlich cycloalkyl- und arylsubstituierten Derivaten davon, Arylester und Cycloalkylester sind, wobei die Alkyl-, Alkanoyl- oder Alkoxygruppen 1 bis 8 Kohlenstoffatome enthalten können und verzweigt oder geradkettig sind, wobei die Cycloalkylgruppen 3 bis 7 Kohlenstoffatome enthalten können und die Cycloalkanoylgruppen 4 bis 8 Kohlenstoffatome enthalten können, wobei beide gegebenenfalls benzokondensiert sind, und wobei die Aryl- und Aroylgruppen substituierte Phenyl-, Naphthyl- oder Indanylringsysteme einschließen.

2. Verbindung nach Anspruch 1, wobei



und

para relativ zueinander angeordnet sind.

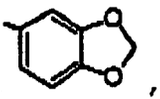
3. Verbindung nach Anspruch 2, bei der R^4 H ist.

4. Verbindung nach Anspruch 3, wobei R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} und R^{12} jeweils H sind.

5. Verbindung nach Anspruch 4, wobei die Summe aus n + p 1 ist und die Summe aus q + r 1 ist.

6. Verbindung nach Anspruch 5, wobei a, b, c und d jeweils Kohlenstoffatome sind und R^2 H ist.

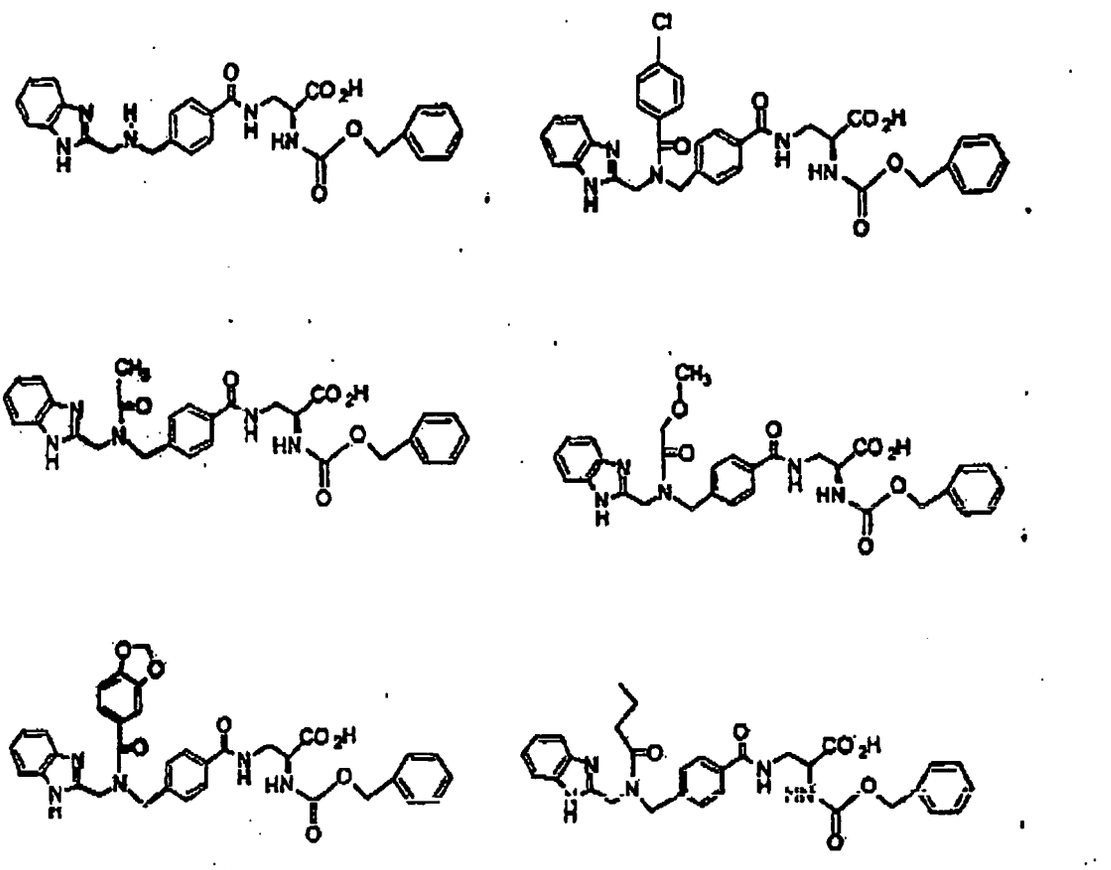
7. Verbindung nach Anspruch 6, wobei R^3 ausgewählt ist aus H, Alkyl, -C(O)R^D, -C(O)OR^D, -C(O)N$R^F R^G$ und -C(=S)N-$R^F R^G$, wobei R^D ausgewählt ist aus Phenyl, Alkyl, Aralkyl, Cycloalkyl, Arylcycloalkyl und

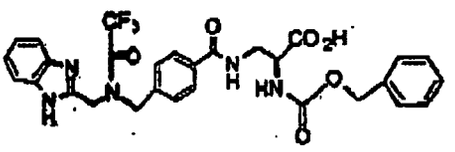


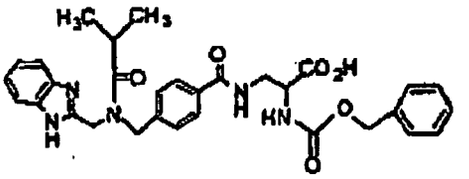
wobei R^D gegebenenfalls mit 1 bis 3 Substituenten ausgewählt aus Alkoxy, Halogen, Cycloalkyl, -S-CH_3, Phenyloxy, -OC (O) CH_3, -C(O)OC_2H_5 und -N$(CH_3)_2$ ausgewählt ist, wobei R^F und R^G ausgewählt sind aus H, Alkyl, Phenyl, Cycloalkyl und Aralkyl, und wobei R^F und R^G gegebenenfalls mit Alkoxy, Halogen oder -CO_2R^H substituiert sind.

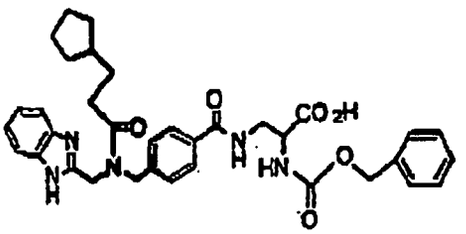
8. Verbindung nach Anspruch 7, wobei R^1 H, -NHR^A, -NHC(O)R^A, -NHC(O)OR^A, -NHC (O) NHR^A oder -NHSO_2R^A ist.

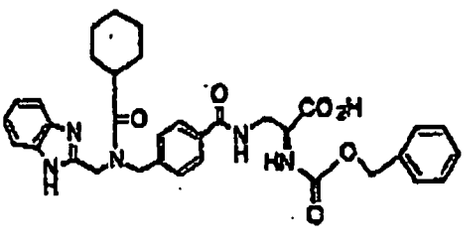
9. Verbindung nach Anspruch 1, die ausgewählt ist aus der Gruppe bestehend aus:

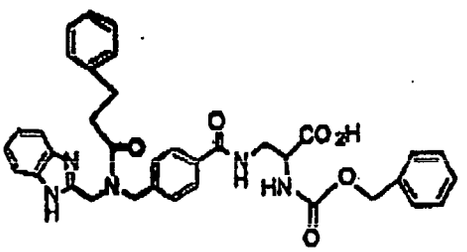


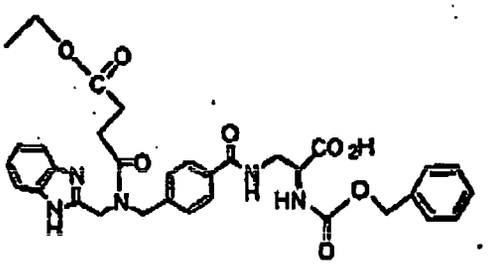


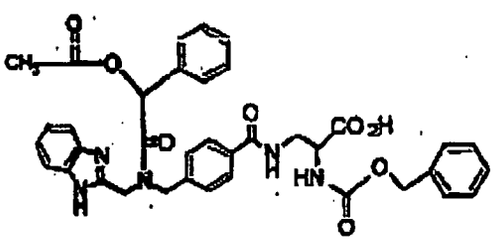


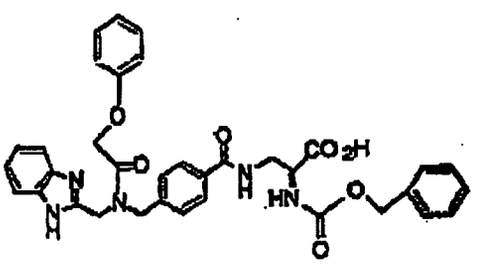


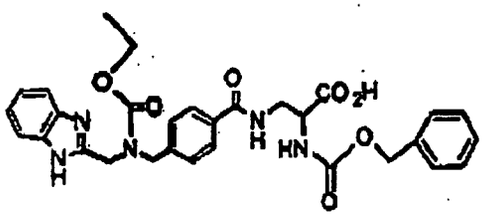


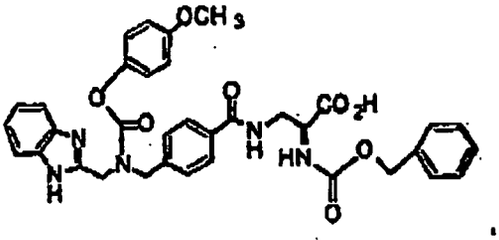


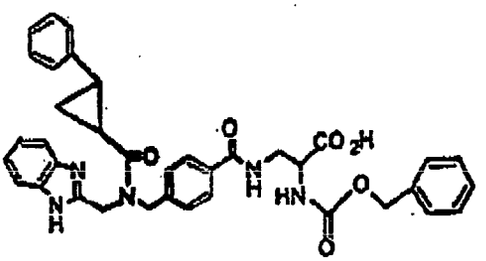


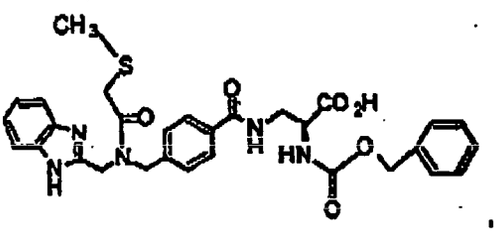


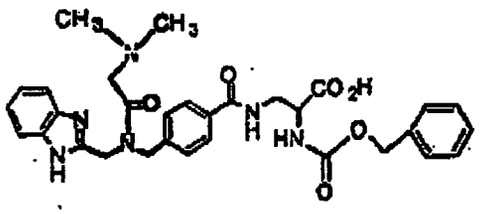


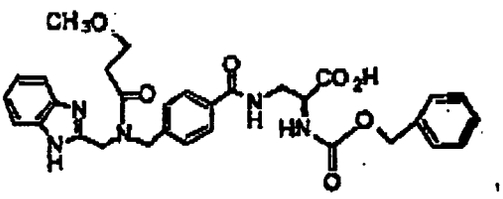


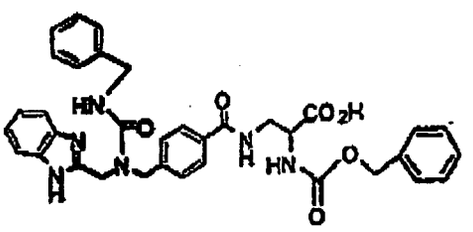


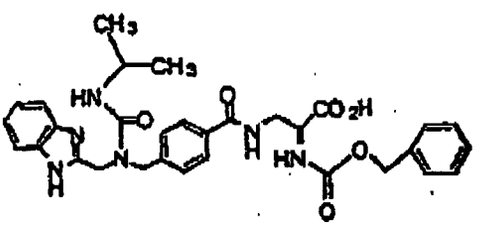


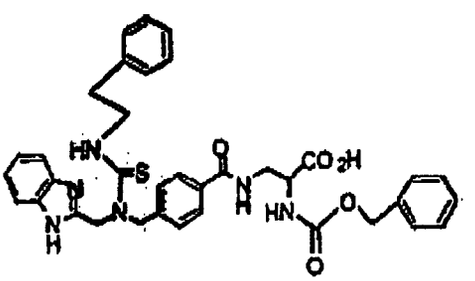


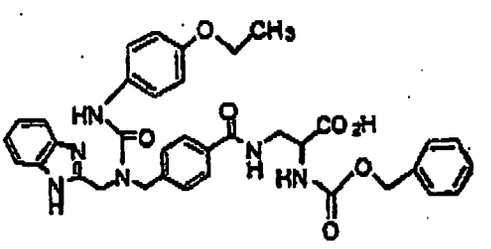


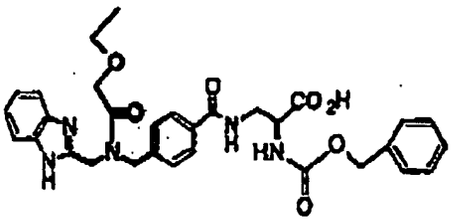


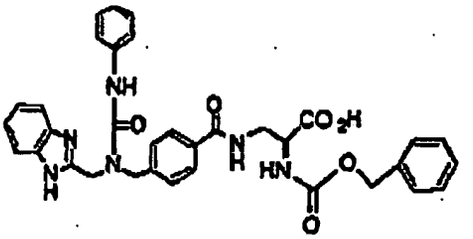


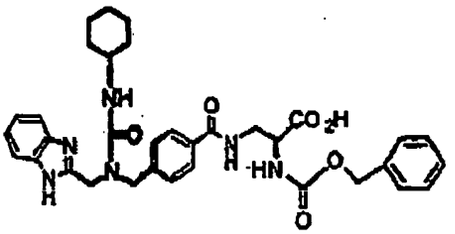


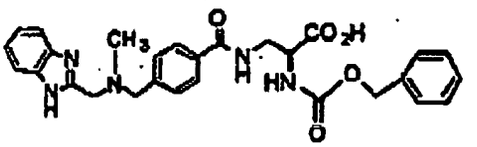


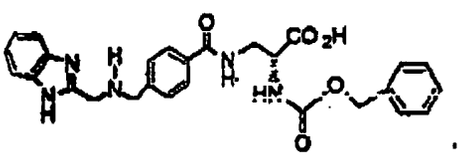


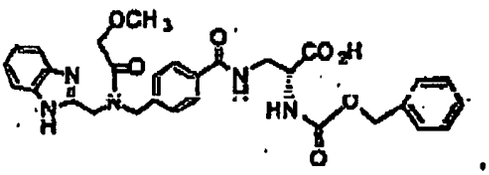


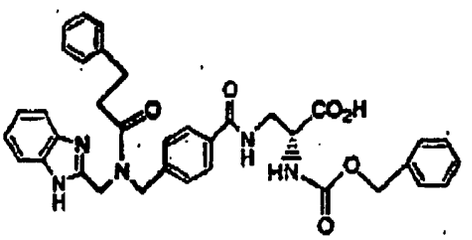


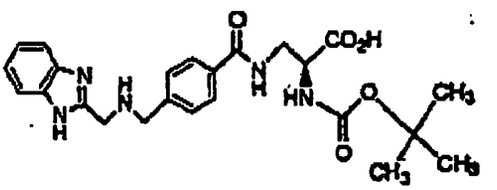


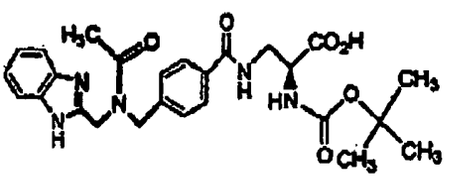


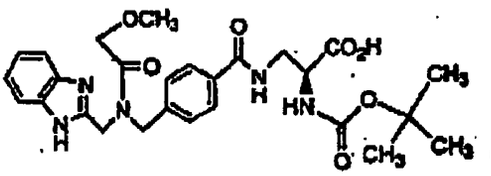


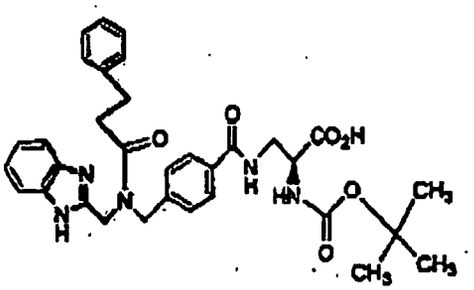


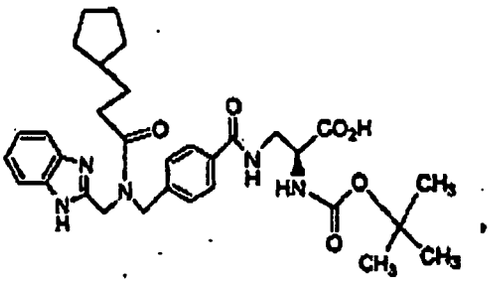


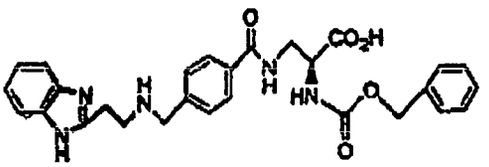


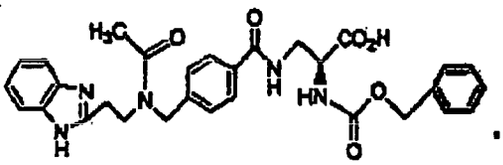


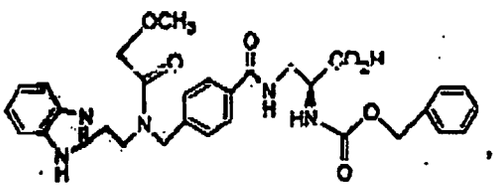


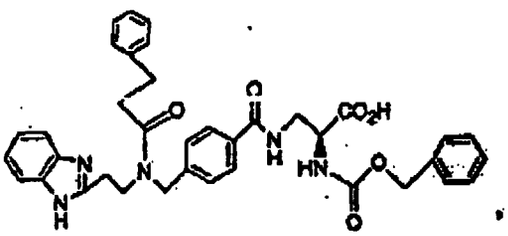


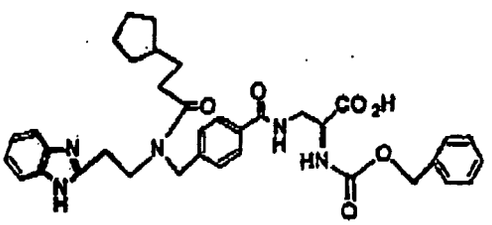


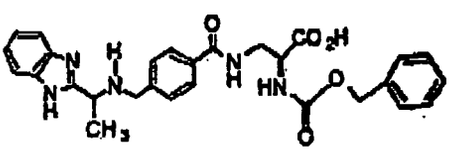


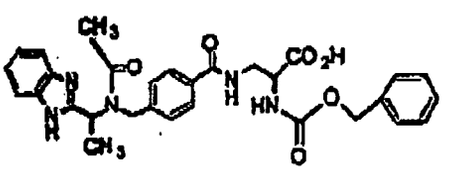


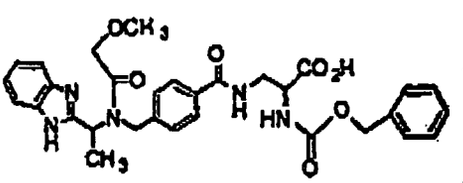


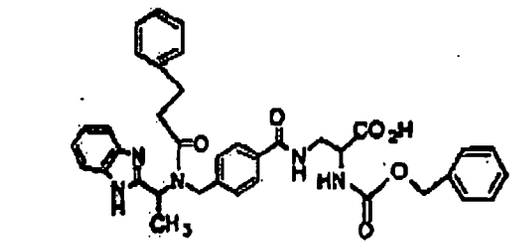


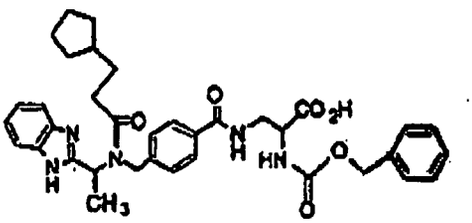


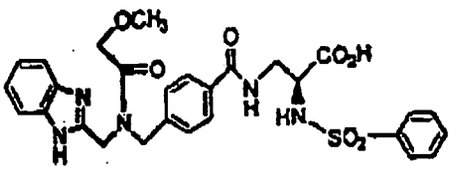


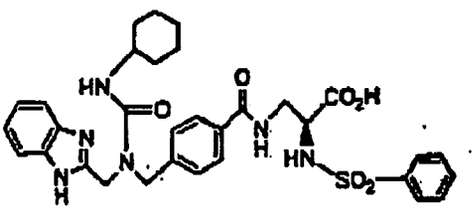


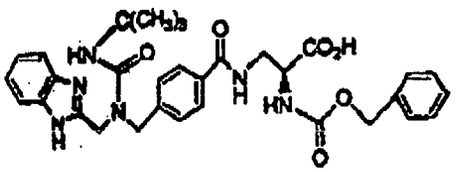


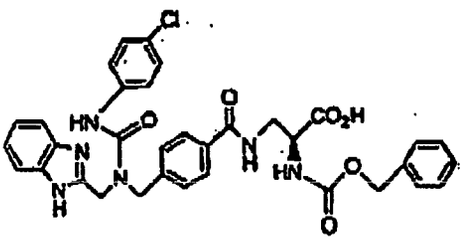


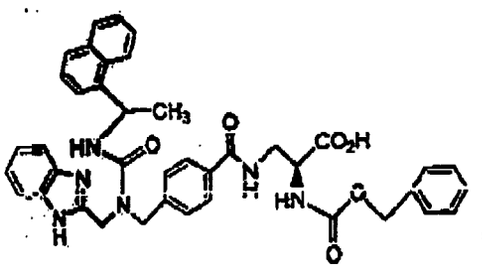


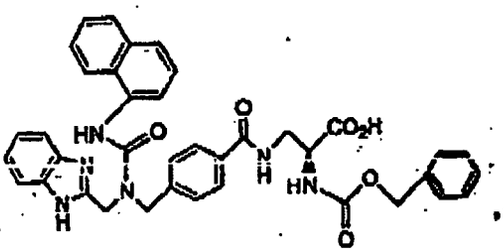


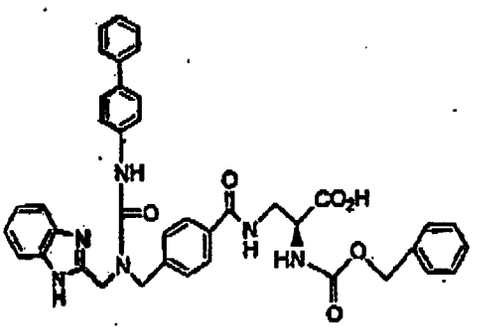


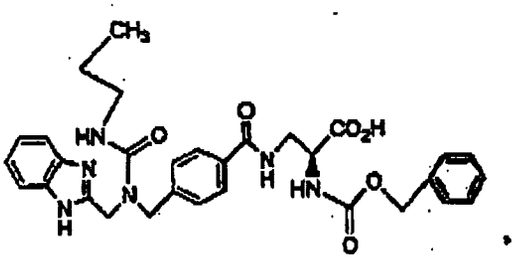


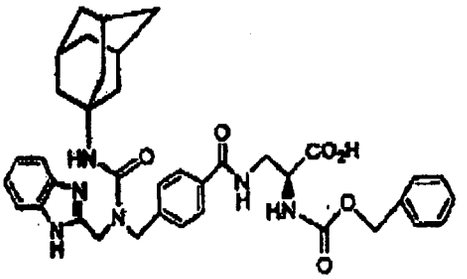


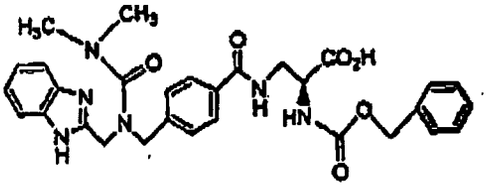


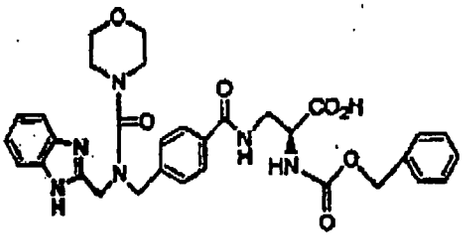


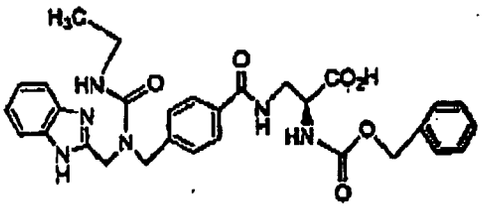


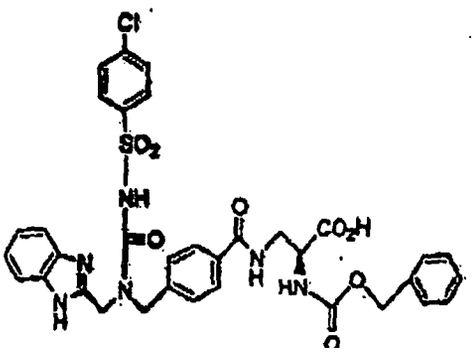


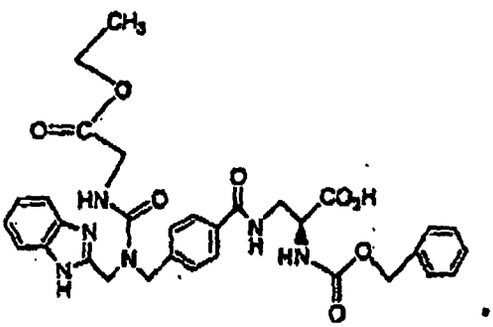


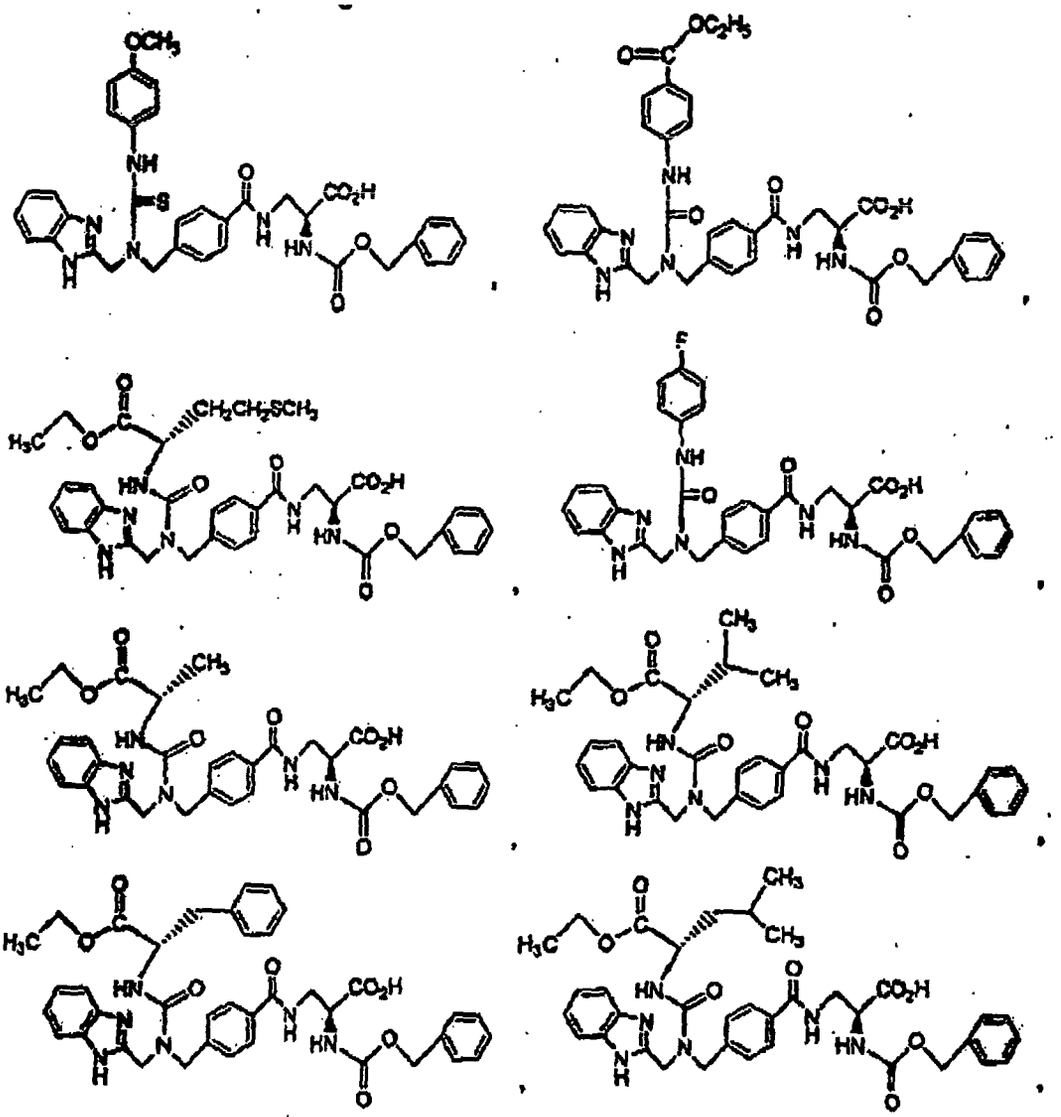


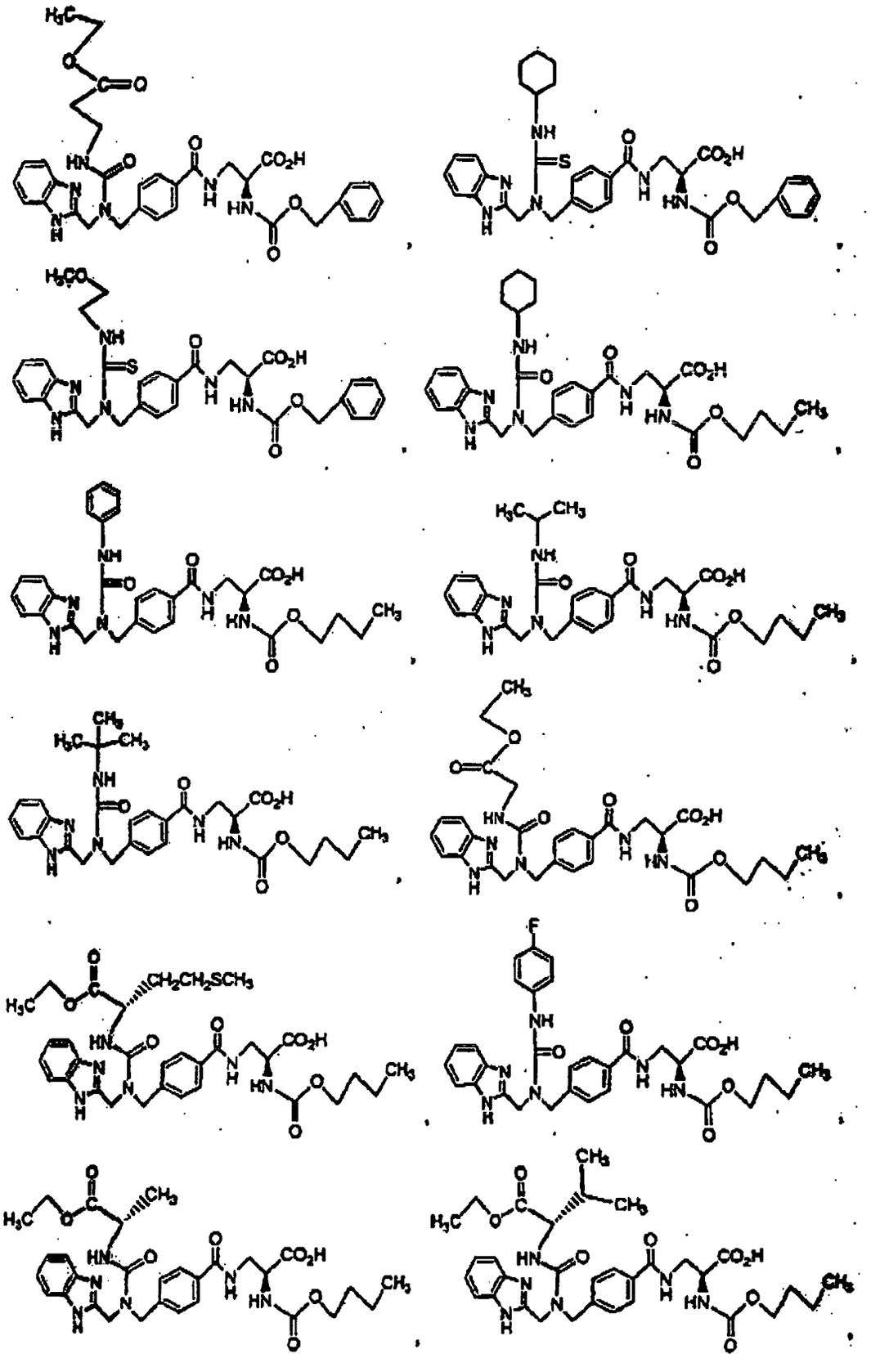


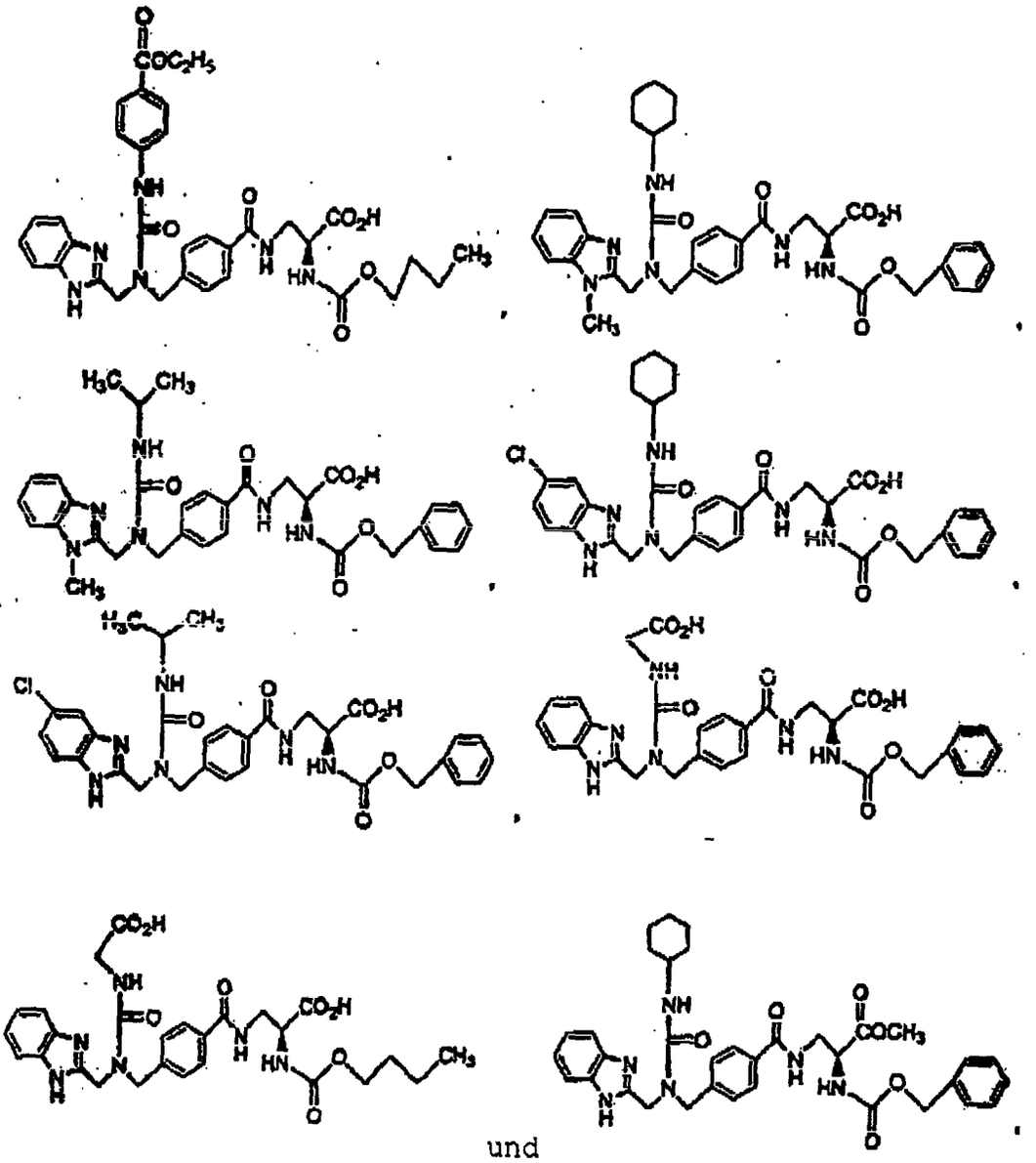








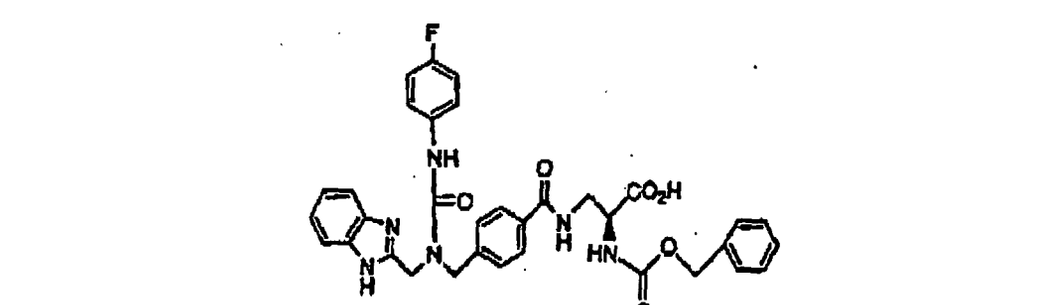




und

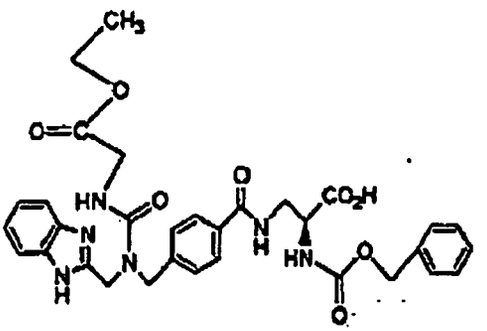
oder ein biolabiler Ester oder ein pharmazeutisch annehmbares Salz davon.

10. Verbindung nach Anspruch 9, wobei die Verbindung



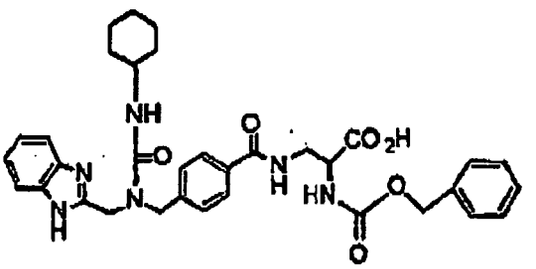
oder ein biolabiler Ester oder ein pharmazeutisch annehmbares Salz davon ist.

11. Verbindung nach Anspruch 9, wobei die Verbindung



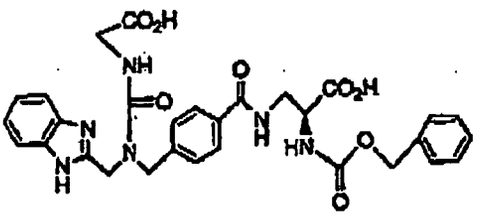
oder ein biolabiler Ester oder ein pharmazeutisch annehmbares Salz davon ist.

12. Verbindung nach Anspruch 9, wobei die Verbindung



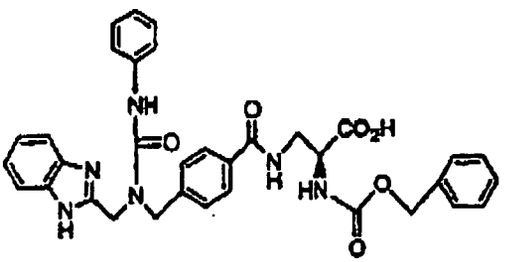
oder ein biolabiler Ester oder ein pharmazeutisch annehmbares Salz davon ist.

13. Verbindung nach Anspruch 9, wobei die Verbindung



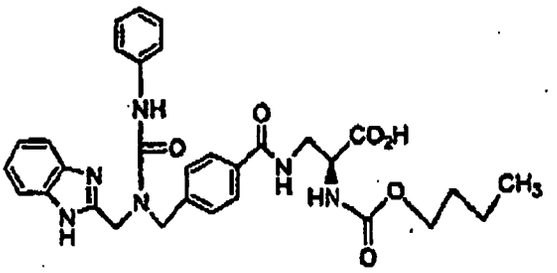
oder ein biolabiler Ester oder ein pharmazeutisch annehmbares Salz davon ist.

14. Verbindung nach Anspruch 9, wobei die Verbindung



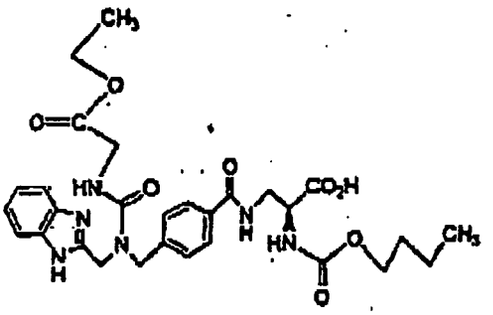
oder ein biolabiler Ester oder ein pharmazeutisch annehmbares Salz davon ist.

15. Verbindung nach Anspruch 9, wobei die Verbindung



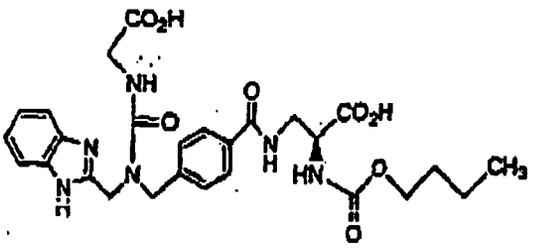
oder ein biolabiler Ester oder ein pharmazeutisch annehmbares Salz davon ist.

16. Verbindung nach Anspruch 9, wobei die Verbindung



oder ein biolabiler Ester oder ein pharmazeutisch annehmbares Salz davon ist.

17. Verbindung nach Anspruch 9, wobei die Verbindung

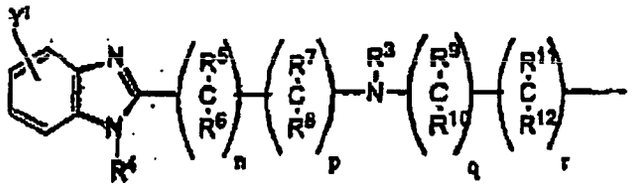


oder ein biolabiler Ester oder ein pharmazeutisch annehmbares Salz davon ist.

18. Verwendung einer Verbindung nach einem der vorhergehenden Ansprüche zur Herstellung eines Medikaments zur Behandlung eines Säugers, der von einer vitronectinvermittelten Erkrankung befallen ist.

19. Verwendung nach Anspruch 18, wobei die Vitronectin-vermittelte Erkrankung Krebs, Retinopathie, Atherosklerose, Gefäß-Restenose oder Osteoporose ist.

20. Verwendung nach Anspruch 19, wobei a, b, c und d jeweils Kohlenstoffatome sind,



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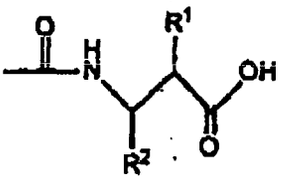
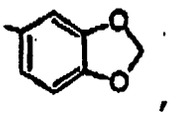


para relativ zueinander angeordnet sind,

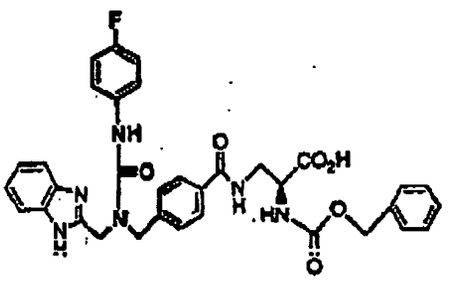
R^2, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} und R^{12} jeweils H sind; die Summe aus n + p 1 ist, und die Summe aus q + r 1 ist:
R^1 H, $-NHR^A$, -NHC (O) R^A, -NHC (O) OR^A, -NHC (O) NHR^A oder $-NHSO_2R^A$ ist;
$-R^3$ ausgewählt ist aus H, Alkyl, -C (O) R^D, -C (O) OR^D, -C (O) NR^FR^G und C (O) NR^FR^G und $-C(=S)NR^FR^G$, wobei R^D ausgewählt ist aus Phenyl, Alkyl, Aralkyl, Cycloalkyl, Arylcycloalkyl, und

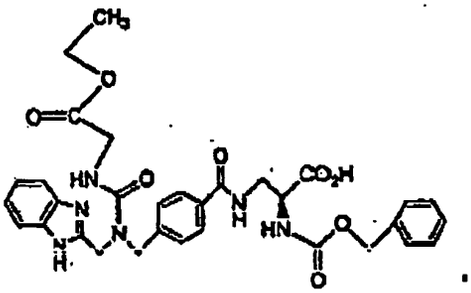


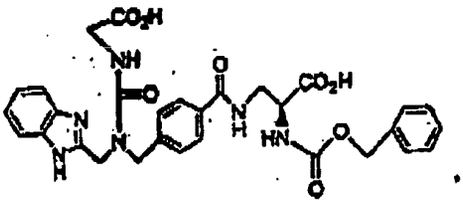
wobei R^D gegebenenfalls mit 1 bis 3 Substituenten ausgewählt aus Alkoxy, Halogen, Cycloalkyl, $-S-CH_3$, Phenyloxy, -OC (O) CH_3, -C (O) OC_2H_5 und -N $(CH_3)_2$ ausgewählt ist, wobei R^F und R^G ausgewählt sind aus H, Alkyl, Phenyl, Cycloalkyl und Aralkyl, und wobei R^F und R^G gegebenenfalls mit Alkoxy, Halogen oder $-CO_2R^H$ substituiert sind.

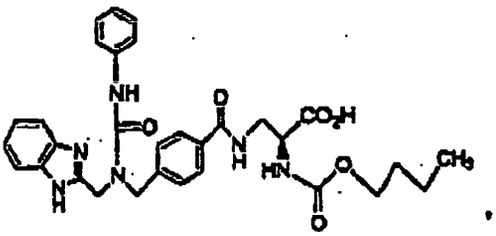
21. Verwendung nach Anspruch 20, wobei die Erkrankung Krebs ist..

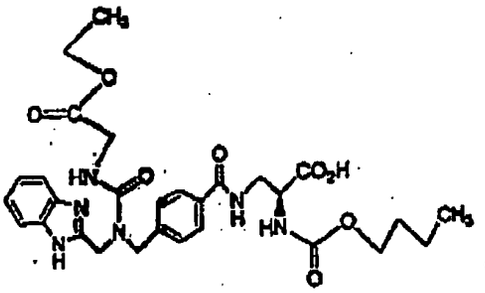
22. Verwendung nach Anspruch 18, wobei die Erkrankung Krebs ist und die Verbindung ausgewählt ist aus der Gruppe bestehend aus:

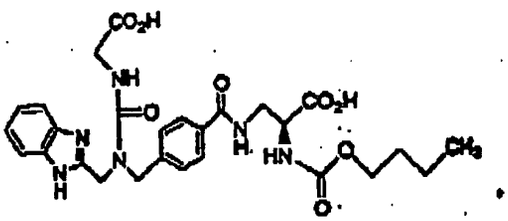


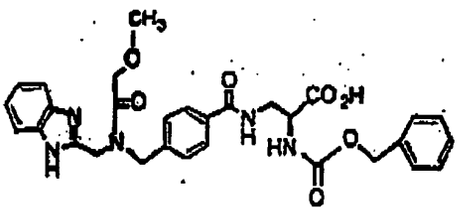


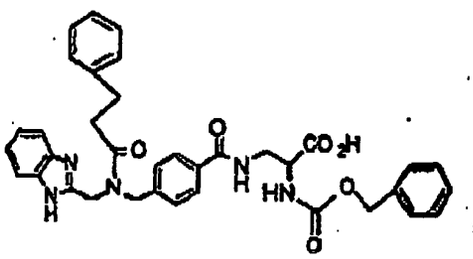


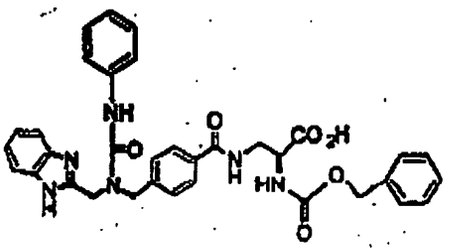


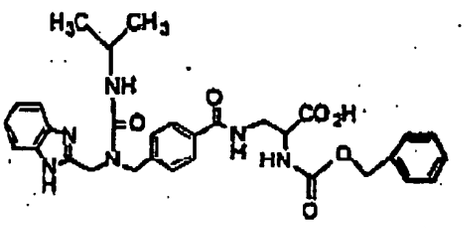












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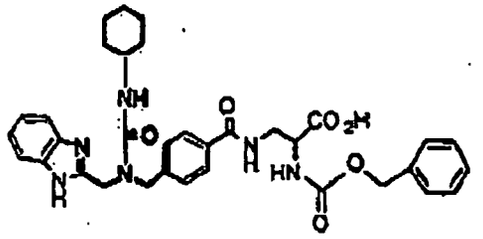
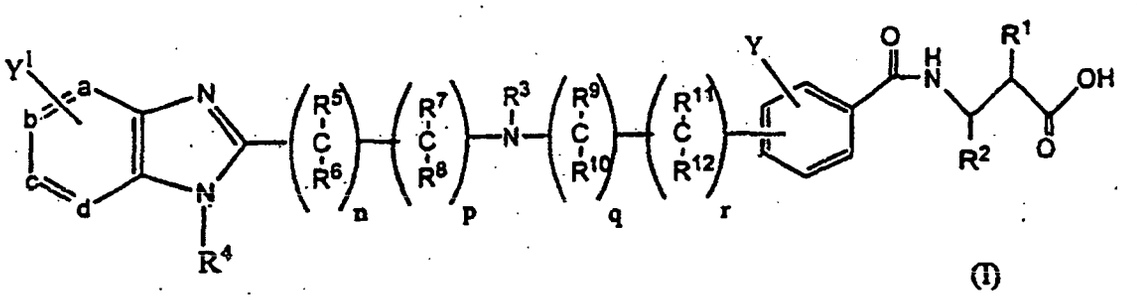


oder einem biolabilen Ester oder einem pharmazeutisch annehmbaren Salz davon.

Revendications

1. Composé de formule :



(I)

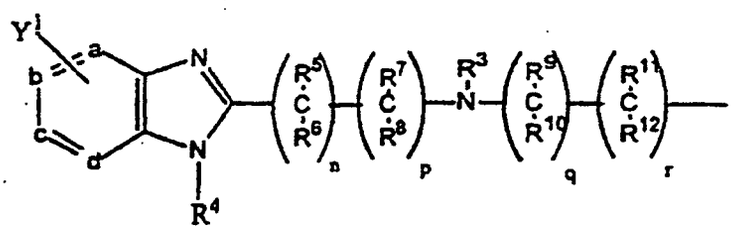
dans laquelle

- n, p, q et r représentent chacun, indépendamment, 0 ou 1 ;
- a, b, c et d représentent chacun, indépendamment, un atome de carbone

ou d'azote, sous réserve qu'au plus deux de ces symboles a, b, c et d représentent des atomes d'azote,

- Y et Y^1 représentent chacun, indépendamment, 1 à 4 éventuels substituants choisis parmi les atomes d'halogène et les groupes alkyle, alcoxy, trifluorométhyle $-CF_3$ et carboxyle -C(O)OH ;
- R^1 représente un atome d'hydrogène, un groupe alkyle, aryle, aralkyle, aryl-cycloalkyle, hétéroaryle, cycloalkyle, hétérocycloalkyle, hétéroaryl-alkyle, cycloalkyl-alkyle ou hétérocycloalkyl-alkyle, ou un groupe de formule $-NHR^A$, $-NHC(O)R^A$, $-NHSO_2R^A$, $-NHC(O)NHR^A$ ou $-NHC(O)OR^A$, le groupe représenté par R' pouvant, en option, porter 1 à 3 substituants choisis parmi les atomes d'halogène, les groupes alkyle, trifluorométhyle $-CF_3$ et cyano -CN et les groupes de formule $-OR^B$, $-SR^B$, $-CO_2R^B$, $-C(O)R^B$, $-OC(O)R^B$, $-OC(O)OR^B$ ou $-SO_2R^B$, et R^A et R^B représentent chacun, indépendamment, un atome d'hydrogène ou un groupe alkyle, aryle, aralkyle, aryl-cycloalkyle, hétéroaryle, cycloalkyle, hétérocycloalkyle, hétéroaryl-alkyle, cycloalkyl-alkyle ou hétérocycloalkyl-alkyle, sous réserve que, si R^1 représente un groupe alkyle, ce groupe ne porte aucun substituant halogéno, que, si R^1 représente un groupe de formule $-NHSO_2R^A$ ou $-NHC(O)OR^A$, R^A ne représente pas un atome d'hydrogène, et que, pour les groupes de formules $-OC(O)OR^B$ et $-SO_2R^B$, R^B ne représente pas un atome d'hydrogène ;
- R^2 représente un atome d'hydrogène ou un groupe alkyle, aryle, aralkyle, aryl-cycloalkyle, hétéroaryle, cycloalkyle, hétérocycloalkyle, hétéroaryl-alkyle, cycloalkyl-alkyle ou hétérocycloalkyl-alkyle, le groupe représenté par R^2 pouvant, en option, porter 1 à 3 substituants choisis parmi les atomes d'halogène, les groupes alkyle, trifluorométhyle $-CF_3$ et cyano -CN et les groupes de formule $-OR^C$, $-SR^C$, $-CO_2R^C$, $-C(O)R^C$,
- $OC(O)R^C$, $-OC(O)OR^C$ ou $-SO_2R^C$, où R^C représente un atome d'hydrogène ou un groupe alkyle, aryle, aralkyle, aryl-cycloalkyle, hétéroaryle, cycloalkyle, hétérocycloalkyle, hétéroaryl-alkyle, cycloalkyl-alkyle ou hétérocycloalkyl-alkyle, sous réserve que, si R^2 représente un groupe alkyle, ce groupe ne porte aucun substituant halogéno, et que, pour les groupes de formules $-OC(O)OR^C$ et $-SO_2R^C$, R^C ne représente pas un atome d'hydrogène ;

- R^3 représente un atome d'hydrogène, un groupe alkyle, aralkyle, aryl-cycloalkyle, cycloalkyl-alkyle, hétérocycloalkyl-alkyle, hétéroaryl-alkyle, aryle, hétéroaryle, cycloalkyle ou hétérocycloalkyle, ou un groupe de formule $-C(O)R^D$, $-C(O)OR^D$, $-SO_2R^E$, $-C(O)NR^FR^G$, $-C(O)NR^FSO_2R^E$ ou $-C(=S)NR^FR^G$, où R^D, R^E, R^F et R^G représentent chacun, indépendamment, un atome d'hydrogène ou un groupe alkyle, aryle, aralkyle, aryl-cycloalkyle, hétéroaryle, cycloalkyle, hétérocycloalkyle, cycloalkyl-alkyle ou hétérocycloalkyl-alkyle, ou bien R^F et R^G représentent conjointement le complément d'un cycle de 5 à 7 chaînons comportant 1 ou 2 atomes d'azote et 0 ou 1 atome d'oxygène ou de soufre, le groupe représenté par R^3 pouvant, en option, porter 1 à 3 substituants choisis parmi les atomes d'halogène, les groupes alkyle, aryle, trifluorométhyle $-CF_3$ et cyano -CN et les groupes de formule $-OR^H$, $-SR^H$, $-CO_2R^H$, $-C(O)R^H$, $-OC(O)R^H$, $-OC(O)OR^H$, $-SO_2R^H$ ou $-NR^HR^H$, où R^H représente un atome d'hydrogène ou un groupe alkyle, aryle, aralkyle, aryl-cycloalkyle, hétéroaryle, cycloalkyle, hétérocycloalkyle, hétéroaryl-alkyle, cycloalkyl-alkyle ou hétérocycloalkyl-alkyle, sous réserve que, si R^3 représente un groupe alkyle, ce groupe ne porte aucun substituant halogéno, que, si R^3 représente un groupe de formule $-C(O)NR^FSO_2R^E$, $-SO_2R^E$ ou $-C(O)OR^D$, R^D ou R^E ne représente pas un atome d'hydrogène, et que, pour les groupes de formules $-OC(O)OR^H$ et $-SO_2R^H$, R^H ne représente pas un atome d'hydrogène ;
- R^4 représente un atome d'hydrogène ou un groupe alkyle, aralkyle, aryl-cycloalkyle, cycloalkyl-alkyle, hétérocycloalkyl-alkyle, hétéroaryl-alkyle, aryle, hétéroaryle, cycloalkyle ou hétérocycloalkyle, le groupe représenté par R^4 pouvant, en option, porter 1 à 3 substituants choisis parmi les atomes d'halogène, les groupes alkyle, trifluorométhyle $-CF_3$ et cyano -CN et les groupes de formule $-OR^J$, $-SR^J$, $-CO_2R^J$, $-C(O)R^J$, $-OC(O)R^J$, $-OC(O)OR^J$ ou $-SO_2R^J$, où R^J représente un atome d'hydrogène ou un groupe alkyle, aryle, aralkyle, aryl-cycloalkyle, hétéroaryle, cycloalkyle, hétérocycloalkyle, hétéroaryl-alkyle, cycloalkyl-alkyle ou hétérocycloalkyl-alkyle, sous réserve que, si R^4 représente un groupe alkyle, ce groupe ne porte aucun substituant halogéno, et que, pour les groupes de formules $-OC(O)OR^J$ et $-SO_2R^J$, R^J ne représente pas un atome d'hydrogène ;
- R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} et R^{12} représentent chacun, indépendamment, un atome d'hydrogène ou un groupe alkyle en C_{1-3};
- et les fragments



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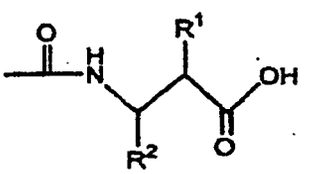


sont placés en positions méta ou para l'un par rapport à l'autre ;

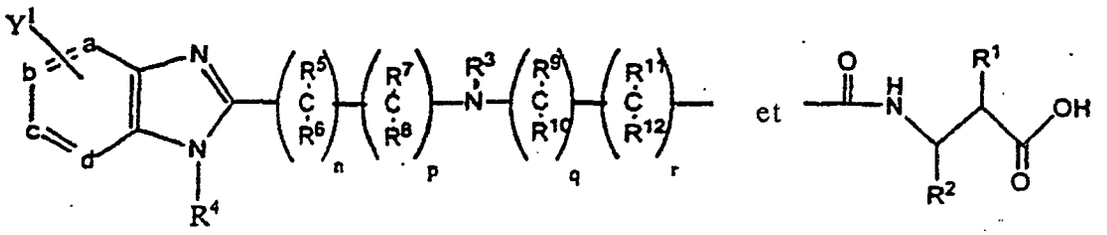
ou ester biolabile d'un tel composé, ou sel pharmacologiquement admissible d'un tel composé ;
étant entendu que les termes suivants ont les significations indiquées ci-dessous :

- "alkyle" désigne un groupe à chaine linéaire ou ramifiée, comportant 1 à 20 atomes de carbone ;
- "cycloalkyle" désigne un groupe carbocyclique ou polycarbocyclique non-aromatique, comportant 3 à 20 atomes de carbone ;
- "cycloalkyl-alkyle" désigne un groupe de formule Cycloalkyl-R- où R représente un groupe alkyle;
- "hétérocycloalkyle" désigne un groupe cycloalkyle au sein duquel un ou plusieurs atomes de carbone ont été remplacés par un ou des hétéroatomes choisis parmi les atomes d'azote, d'oxygène et de soufre ;

- "hétérocycloalkyl-alkyle" désigne un groupe de formule Hétérocycloalkyl-R- où R représente un groupe alkyle ;
- "aryle" désigne un groupe carbocyclique aromatique ;
- "aralkyle" désigne un groupe de formule Aryl-R- où R représente un groupe alkyle ;
- "hétéroaryle" désigne un groupe carbocyclique aromatique au sein duquel un ou plusieurs atomes de carbone ont été remplacés par un ou des hétéroatomes choisis parmi les atomes d'azote, d'oxygène et de soufre ;
- "hétéroaryl-alkyle" désigne un groupe de formule Hétéroaryl-R- où R représente un groupe alkyle ;
- et "aryl-cycloalkyle" désigne un groupe de formule Aryl-R- où R représente un groupe cycloalkyle ;

et que lesdits esters biolabiles sont des esters d'alkyle, d'alcanoyloxyalkyle, de cycloalcanoyloxyalkyle, d'aroyloxyalkyle ou d'alcoxycarbonyloxyalkyle, y compris leurs dérivés à substituant cycloalkyle ou aryle, des esters d'aryle et des esters de cycloalkyle, dans lesquels lesdits groupes alkyle, alcanoyle ou alcoxy peuvent comporter 1 à 8 atomes de carbone formant une chaîne linéaire ou ramifiée, lesdits groupes cycloalkyle peuvent comporter 3 à 7 atomes de carbone et lesdits groupes cycloalcanoyle peuvent comporter 4 à 8 atomes de carbone, les groupes de ces deux derniers types pouvant, en option, être benzo-condensés, et lesdits groupes aryle et aroyle englobent les systèmes cycliques phényle, naphtyle ou indanyle à substituant(s).

2. Composé conforme à la revendication 1, dans lequel les fragments



sont placés en positions para l'un par rapport à l'autre.

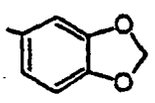
3. Composé conforme à la revendication 2, dans lequel R^4 représente un atome d'hydrogène.

4. Composé conforme à la revendication 3, dans lequel R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} et R^{12} représentent chacun un atome d'hydrogène.

5. Composé conforme à la revendication 4, dans lequel la somme n+p vaut 1 et la somme q+r vaut 1.

6. Composé conforme à la revendication 5, dans lequel a, b, c et d représentent chacun un atome de carbone et R^2 représente un atome d'hydrogène.

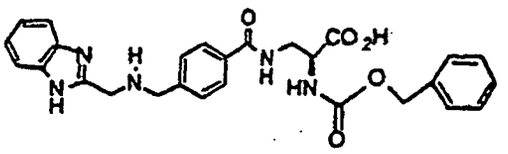
7. Composé conforme à la revendication 6, dans lequel R^3 représente un atome d'hydrogène, un groupe alkyle ou un groupe de formule $-C(O)R^D$, $-C(O)OR^D$, $-C(O)NR^FR^G$ ou $-C(=S)NR^FR^G$, où R^D représente un groupe phényle, alkyle, aralkyle, cycloalkyle ou aryl-cycloalkyle, ou un groupe de formule

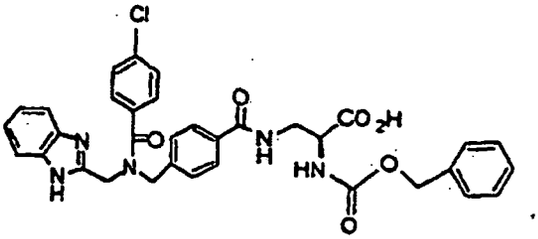


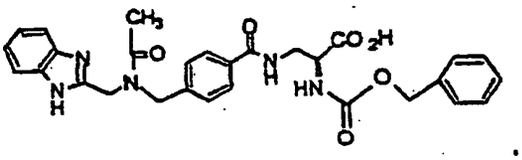
le groupe représenté par R^D pouvant, en option, porter 1 à 3 substituants choisis parmi les atomes d'halogène, les groupes cycloalkyle, alcoxy et phénoxy et les groupes de formule $-SCH_3$, $-OC(O)CH_3$, $-C(O)OC_2H_5$ ou $-N(CH_3)_2$, et R^F et R^G représentent chacun un atome d'hydrogène ou un groupe alkyle, phényle, cycloalkyle ou aralkyle, les groupes représentés par R^F et R^G pouvant, en option, porter un substituant choisi parmi les atomes d'halogène, les groupes alcoxy et les groupes de formule $-CO_2R^H$.

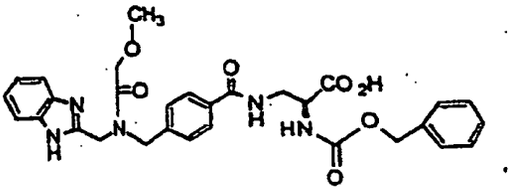
8. Composé conforme à la revendication 7, dans lequel R' représente un atome d'hydrogène ou un groupe de formule $-NHR^A$, $-NHC(O)R^A$, $-NHC(O)OR^A$, $-NHC(O)NHR^A$ ou $-NHSO_2R^A$.

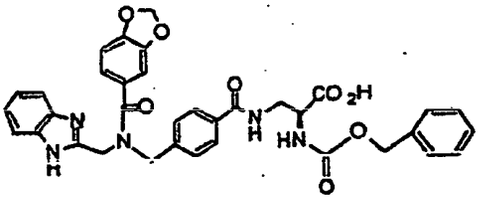
9. Composé conforme à la revendication 1, qui est choisi parmi les suivants :

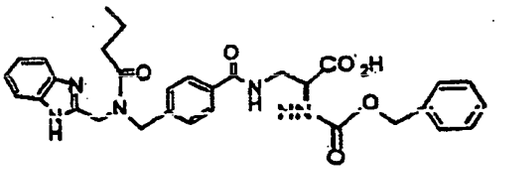


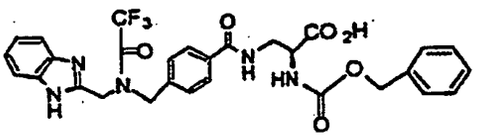


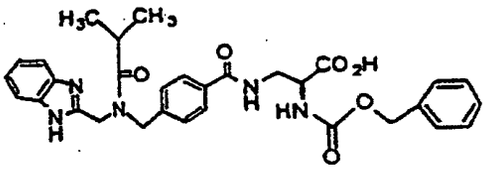


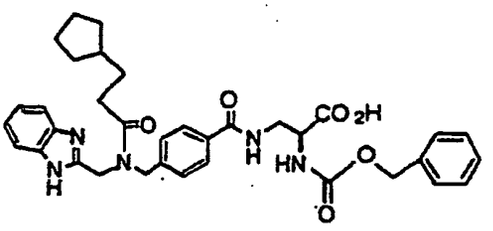


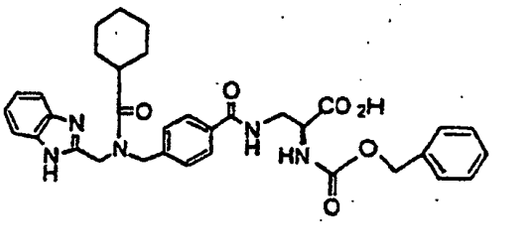


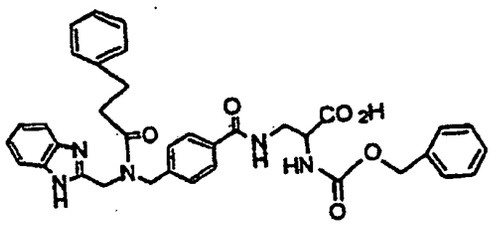


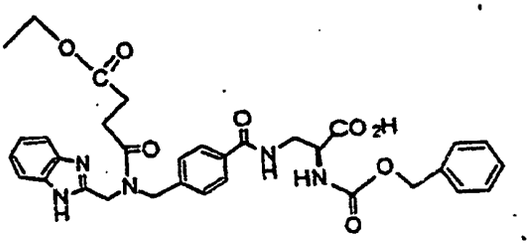


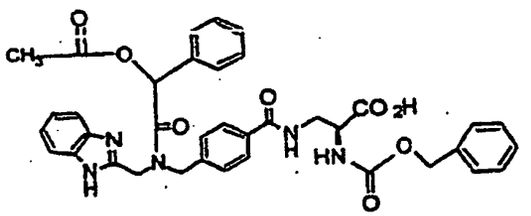


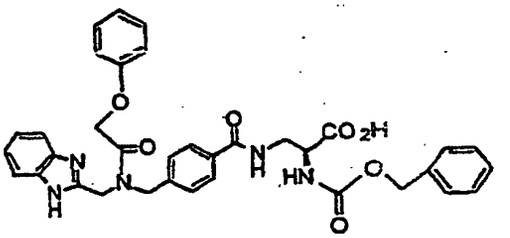


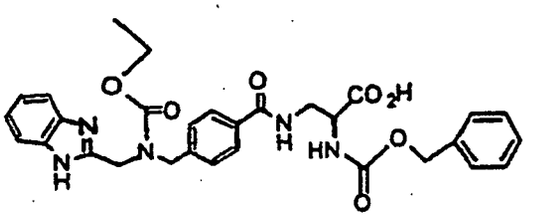


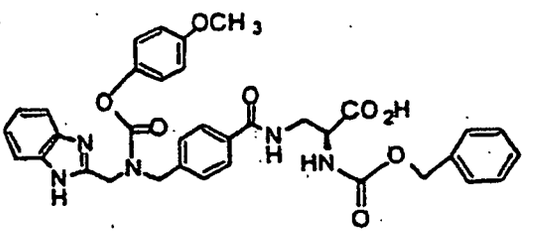


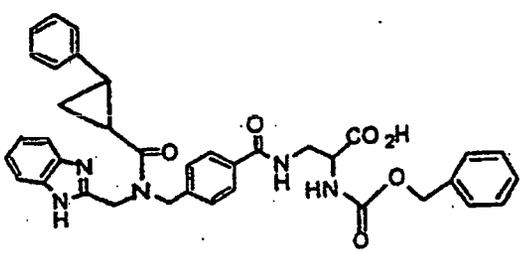


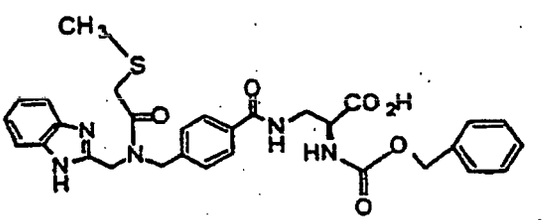


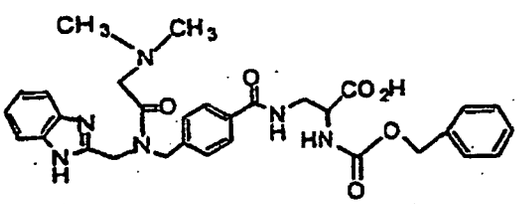


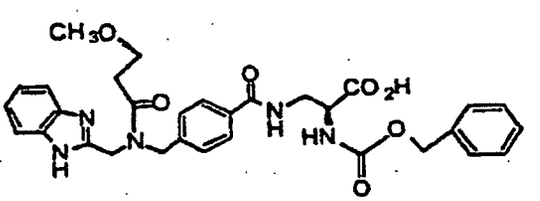


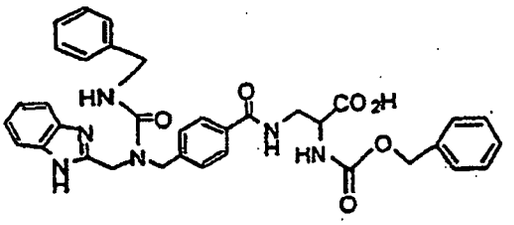


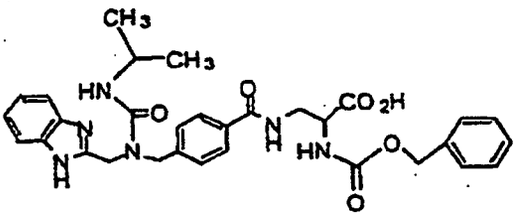


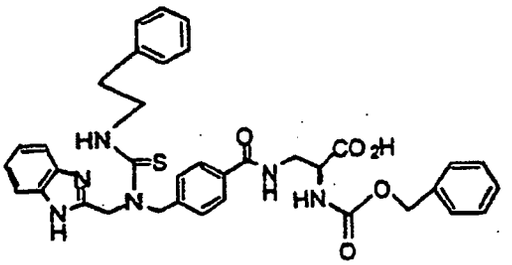


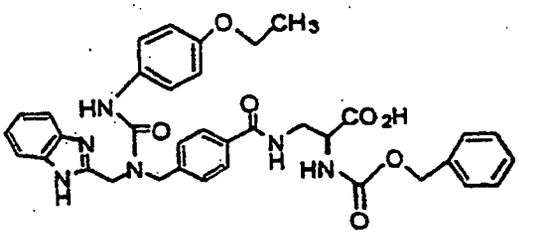


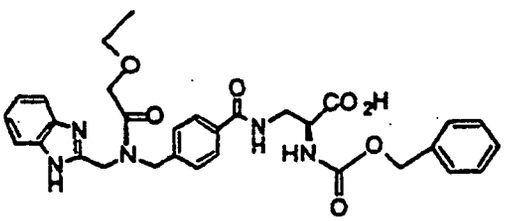


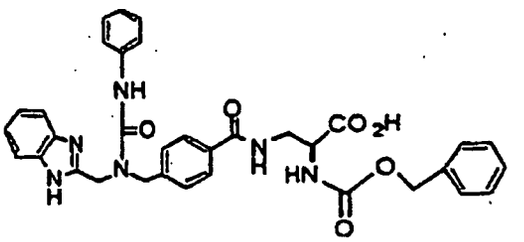


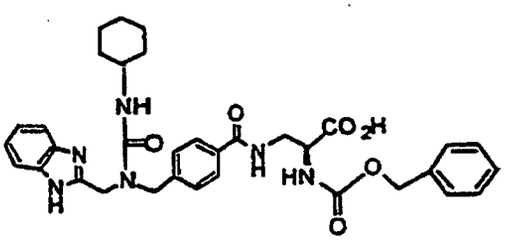


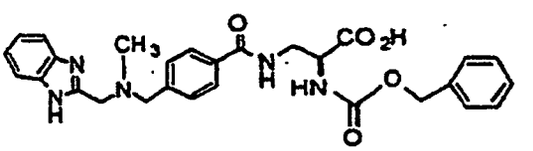


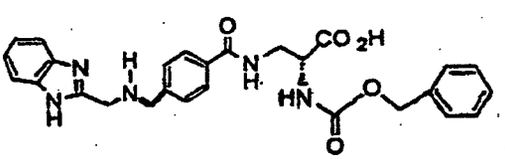


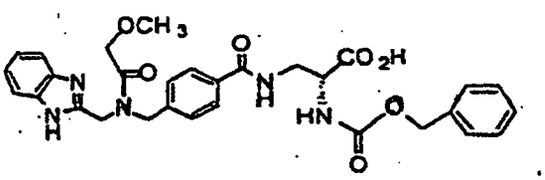


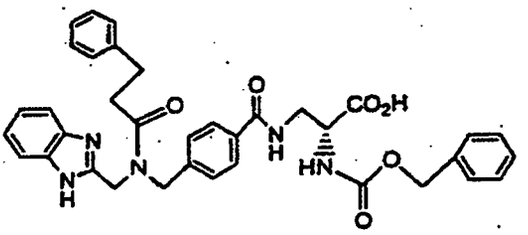


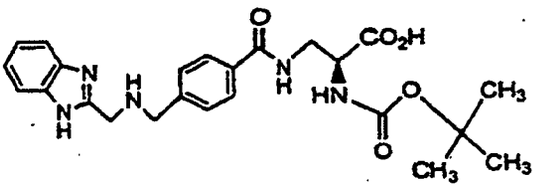


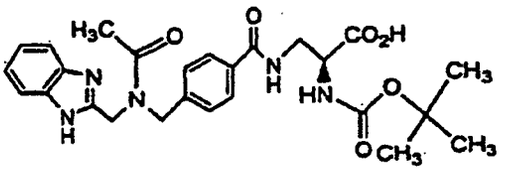


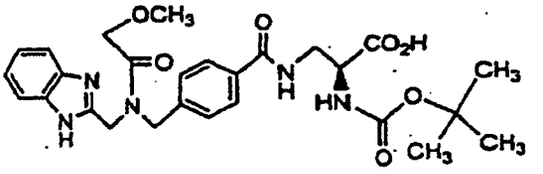


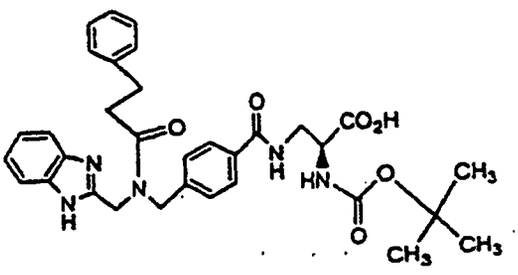


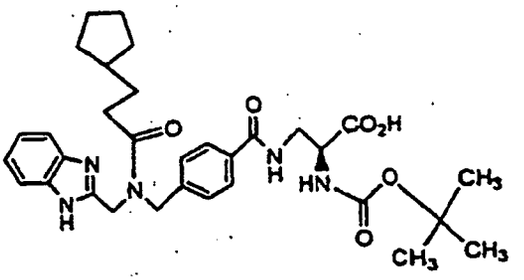


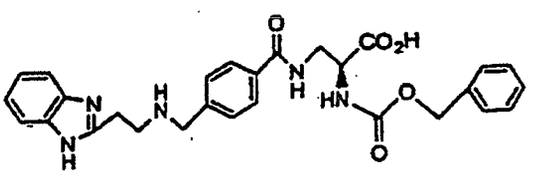


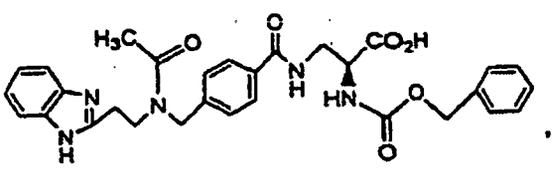


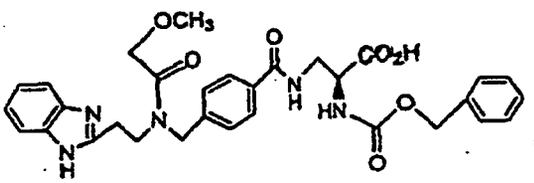


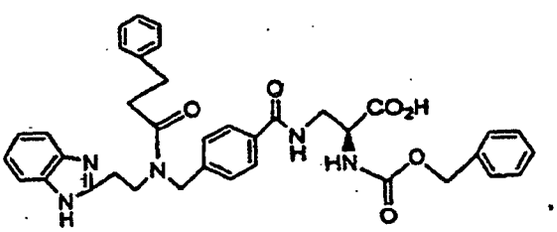


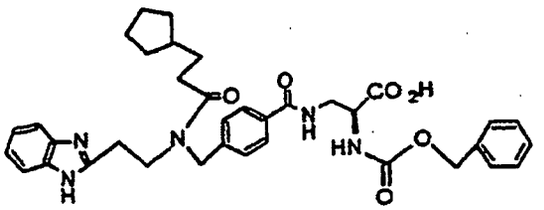


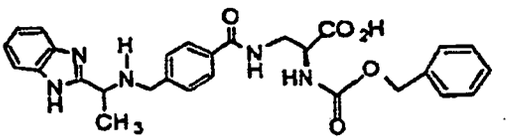


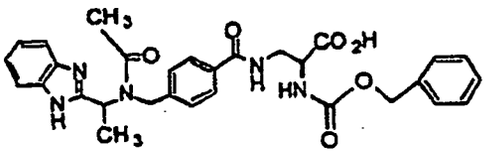


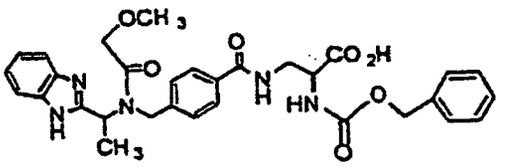


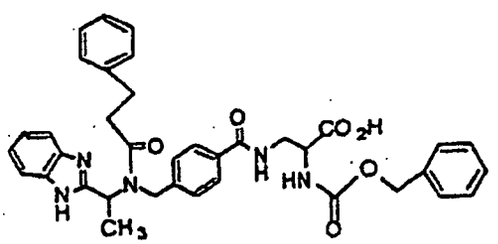


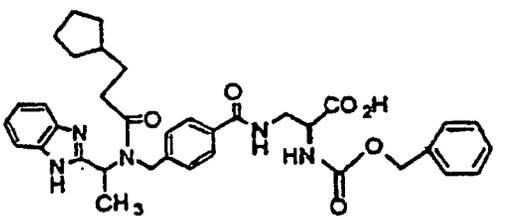


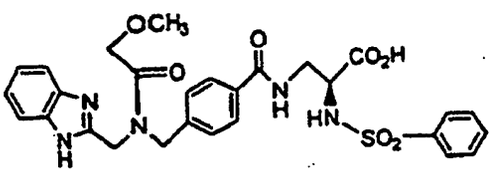


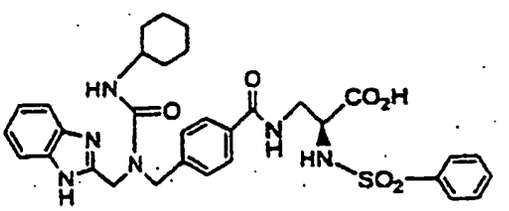


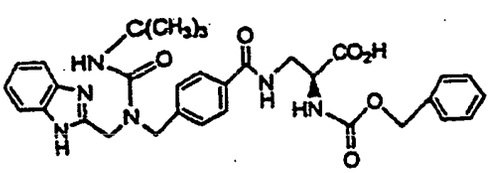


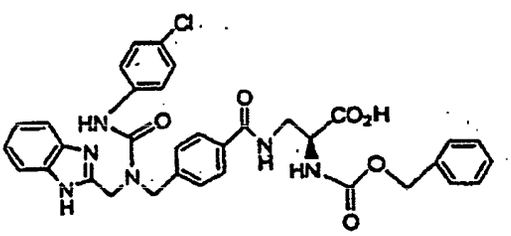


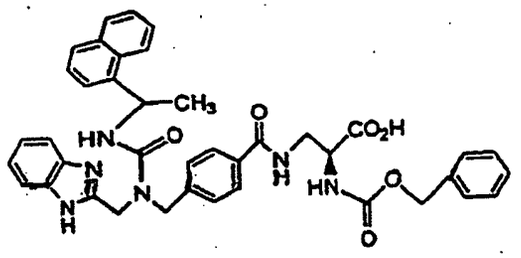


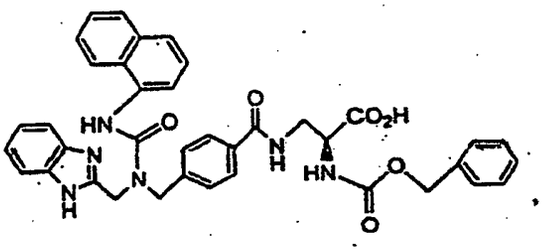


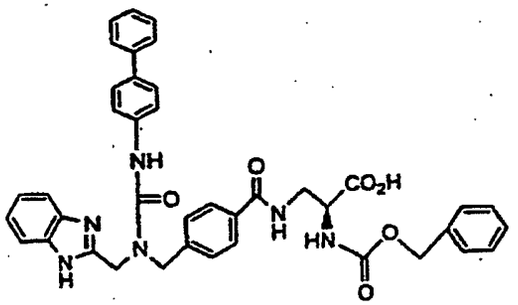


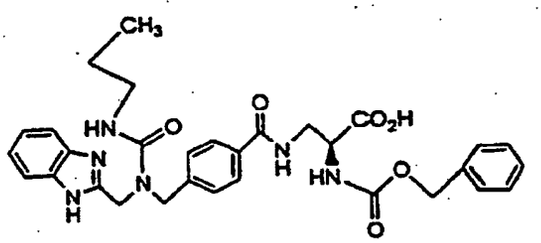


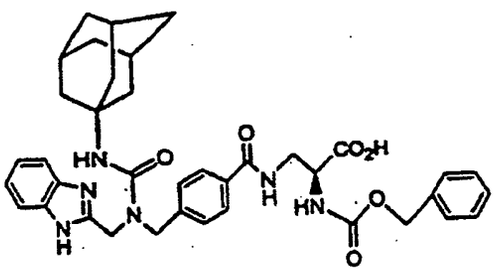


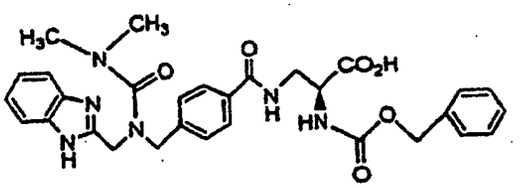


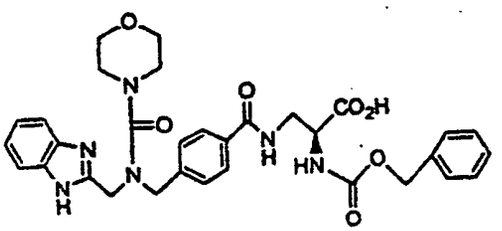


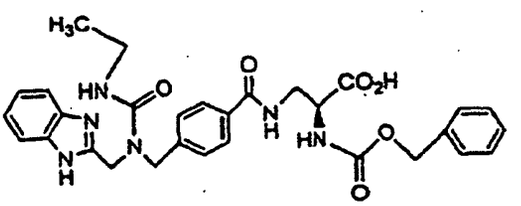


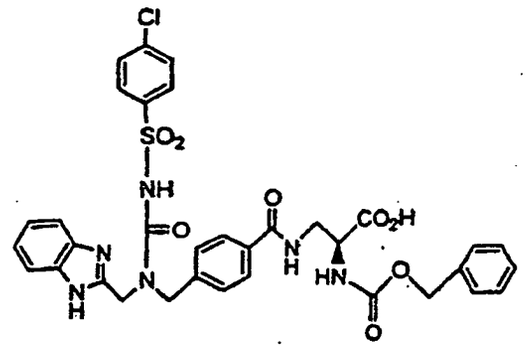


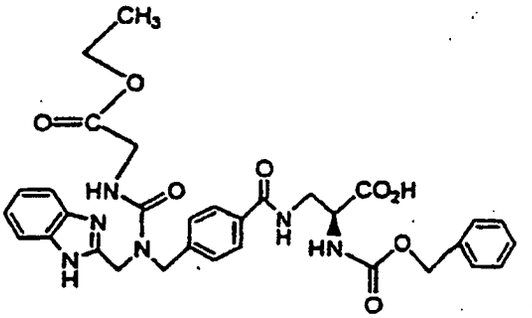


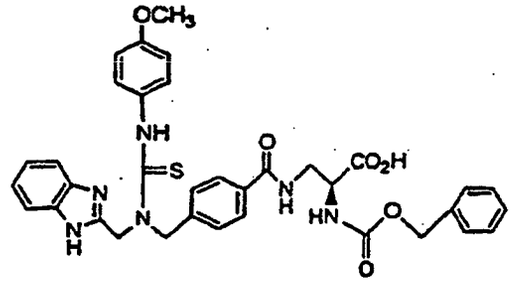


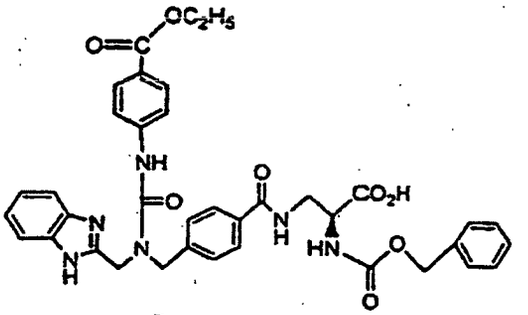


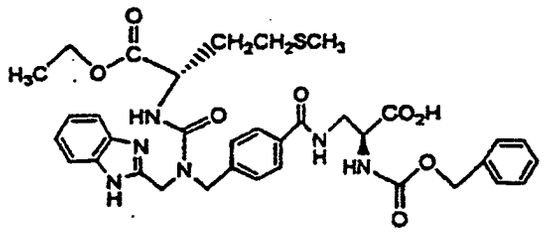


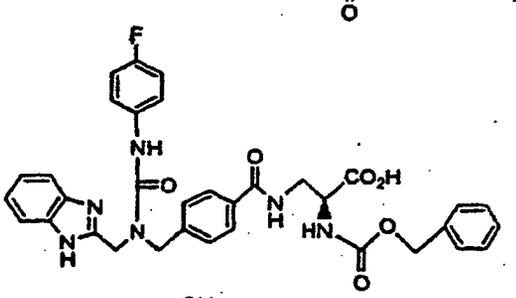


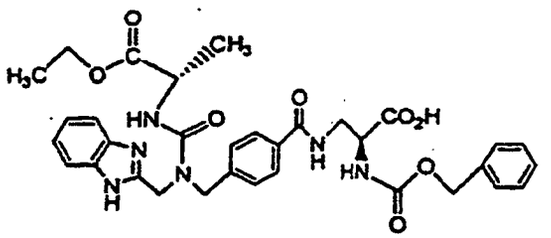


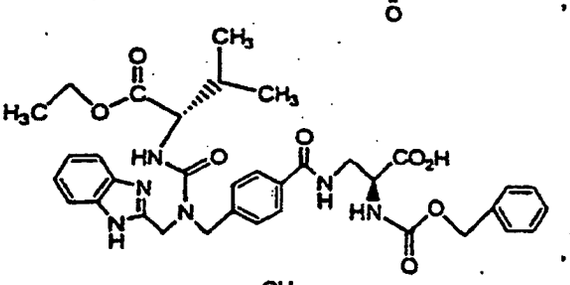


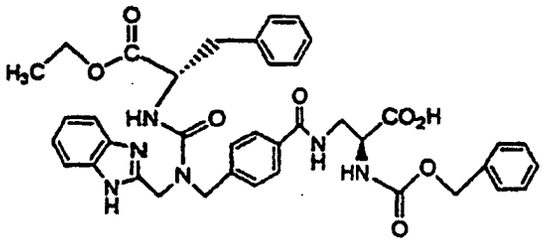


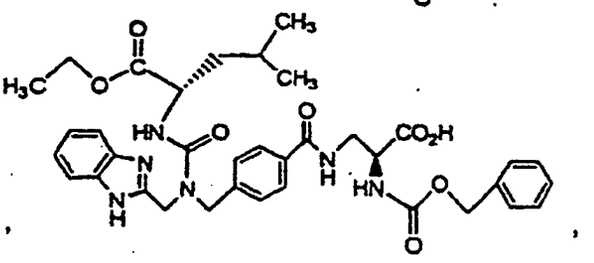


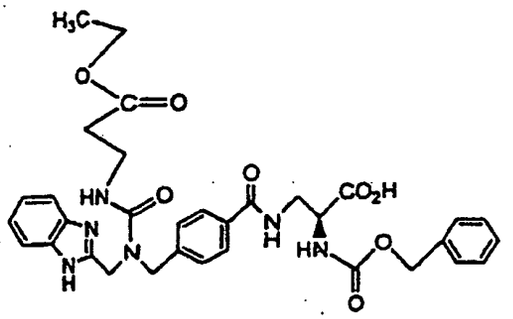


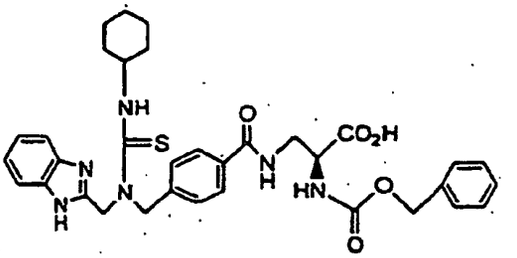


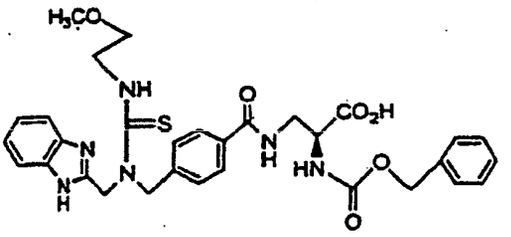


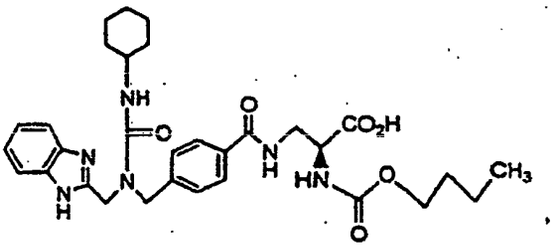


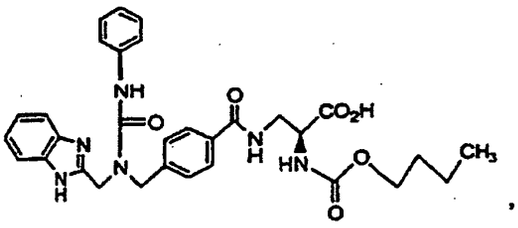


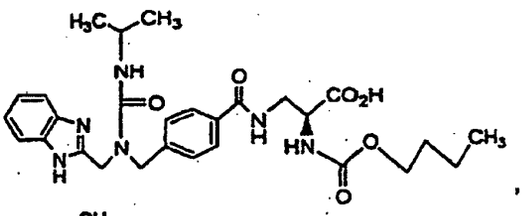


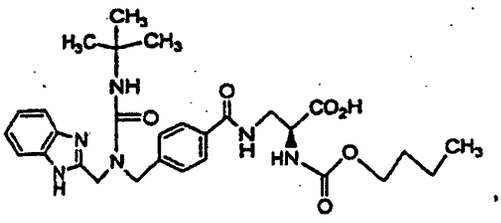


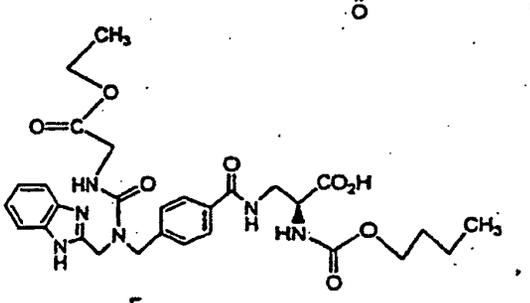


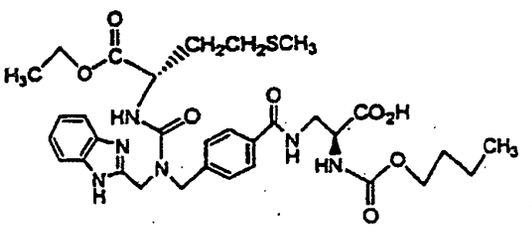


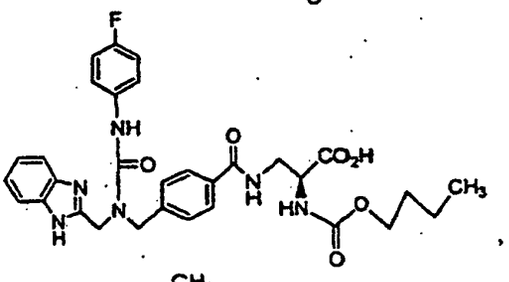


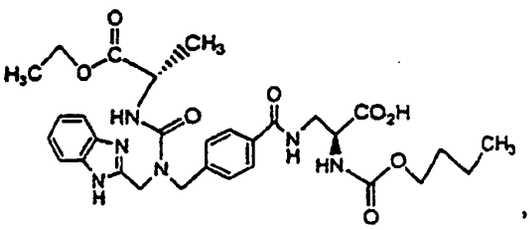


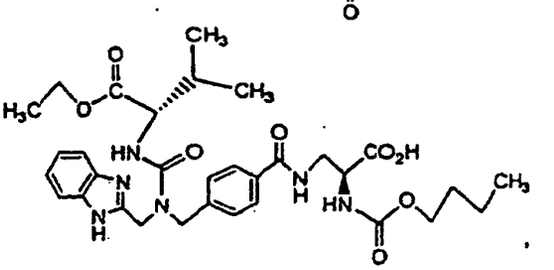


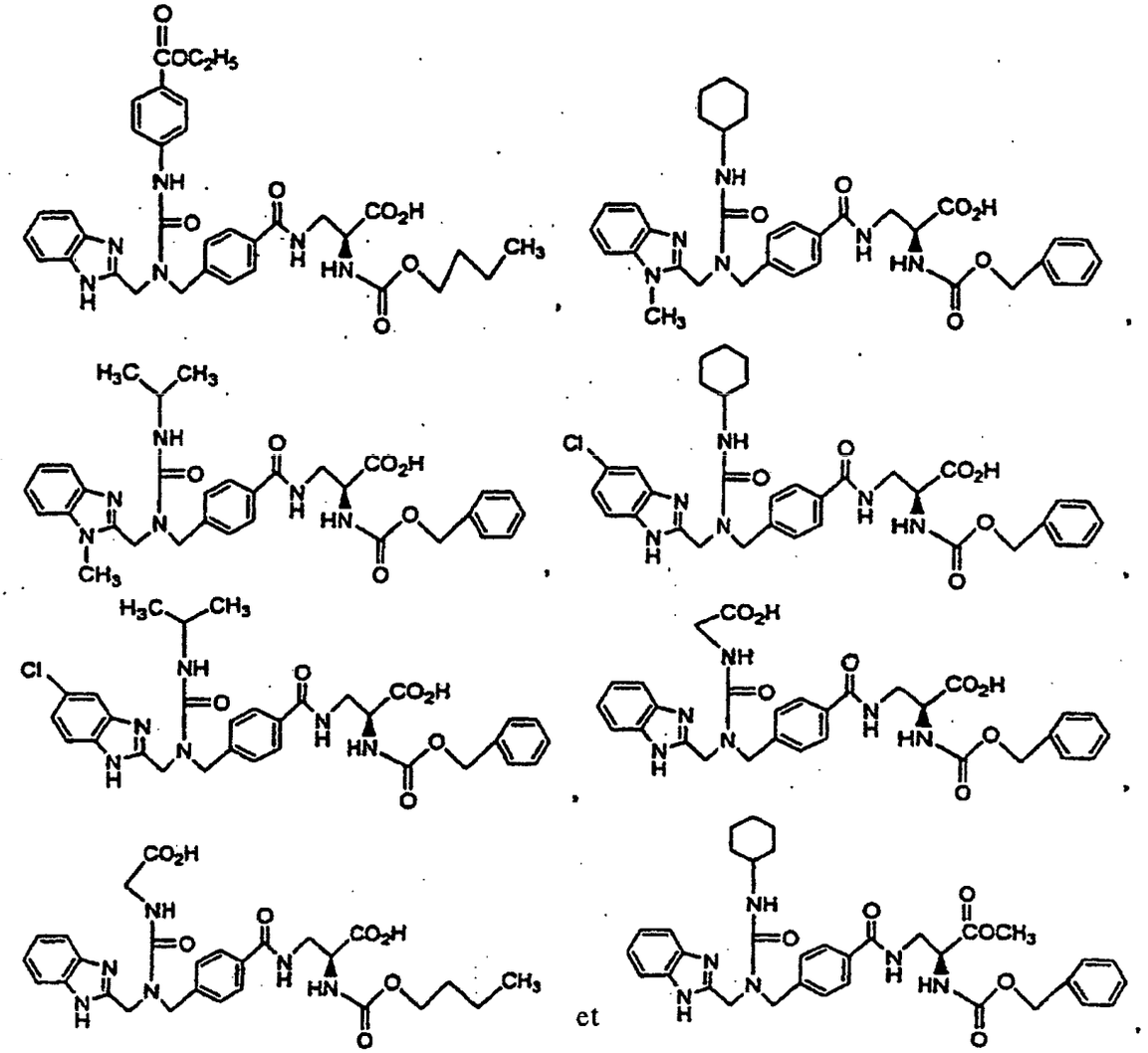








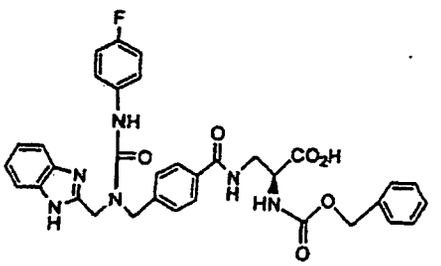




et

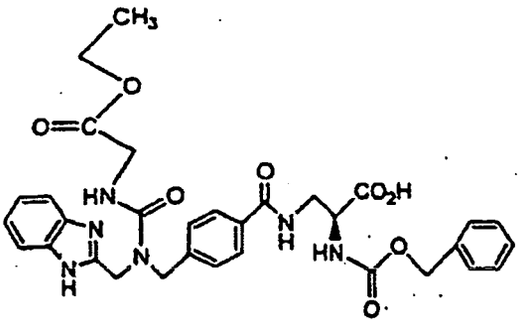
ou ester biolabile d'un tel composé, ou sel pharmacologiquement admissible d'un tel composé.

10. Composé conforme à la revendication 9, qui est le composé de formule



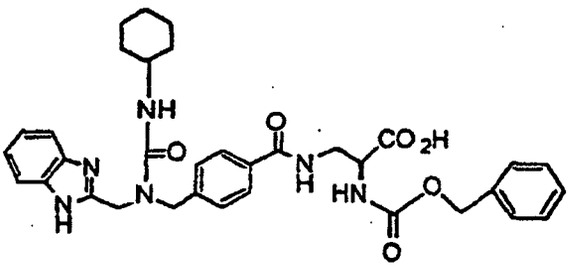
ou ester biolabile de ce composé, ou sel pharmacologiquement admissible de ce composé.

11. Composé conforme à la revendication 9, qui est le composé de formule



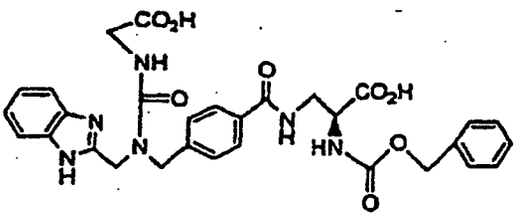
ou ester biolabile de ce composé, ou sel pharmacologiquement admissible de ce composé.

12. Composé conforme à la revendication 9, qui est le composé de formule



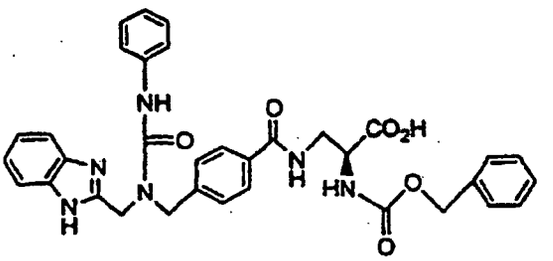
ou ester biolabile de ce composé, ou sel pharmacologiquement admissible de ce composé.

13. Composé conforme à la revendication 9, qui est le composé de formule



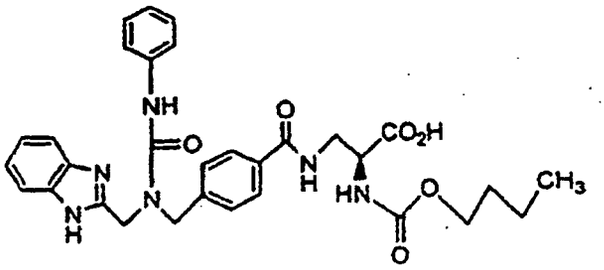
ou ester biolabile de ce composé, ou sel pharmacologiquement admissible de ce composé.

14. Composé conforme à la revendication 9, qui est le composé de formule



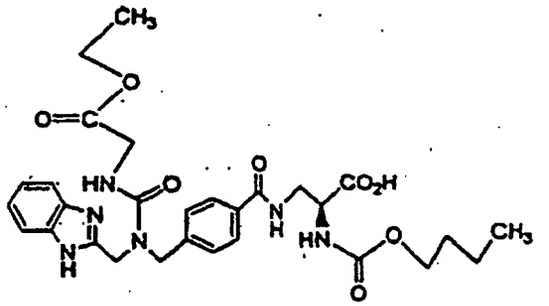
ou ester biolabile de ce composé, ou sel pharmacologiquement admissible de ce composé.

15. Composé conforme à la revendication 9, qui est le composé de formule



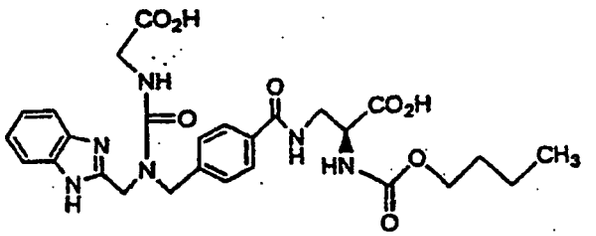
ou ester biolabile de ce composé, ou sel pharmacologiquement admissible de ce composé.

16. Composé conforme à la revendication 9, qui est le composé de formule



ou ester biolabile de ce composé, ou sel pharmacologiquement admissible de ce composé.

17. Composé conforme à la revendication 9, qui est le composé de formule



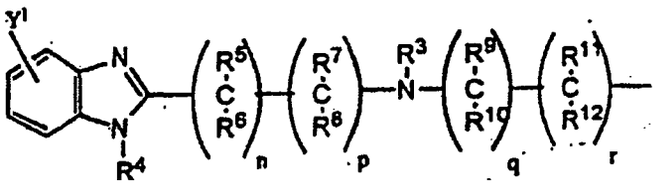
ou ester biolabile de ce composé, ou sel pharmacologiquement admissible de ce composé.

18. Emploi d'un composé conforme à l'une des revendications précédentes en vue de la fabrication d'un médicament destiné au traitement d'un mammifère atteint d'un trouble à médiation par la vitronectine.

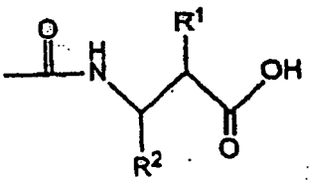
19. Emploi conforme à la revendication 18, le trouble à médiation par la vitronectine étant un cancer, une rétinopathie, l'athérosclérose, une resténose vasculaire ou l'ostéoporose.

20. Emploi, conforme à la revendication 19, d'un composé dans lequel

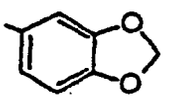
- a, b, c et d représentent chacun un atome de carbone ;
- les fragments



et



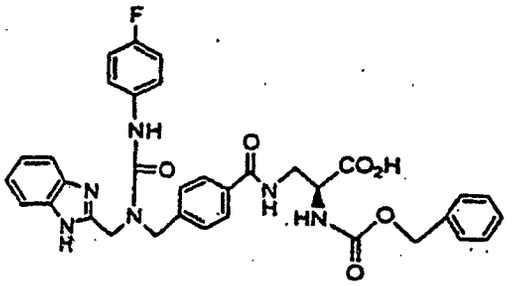
sont placés en positions para l'un par rapport à l'autre ;
- R^2, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} et R^{12} représentent chacun un atome d'hydrogène ;
- la somme n+p vaut 1 et la somme q+r vaut 1 ;
- R^1 représente un atome d'hydrogène ou un groupe de formule $-NHR^A$,
- $NHC(O)R^A$, $-NHC(O)OR^A$, $-NHC(O)NHR^A$ ou $-NHSO_2R^A$;
- R^3 représente un atome d'hydrogène, un groupe alkyle ou un groupe de formule $-C(O)R^D$, $-C(O)OR^D$,$-C(O)NR^FR^G$ ou $-C(=S)NR^FR^G$, où R^D représente un groupe phényle, alkyle, aralkyle, cycloalkyle ou aryl-cycloalkyle, ou un groupe de formule

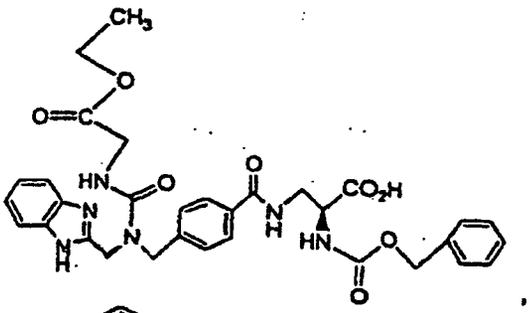


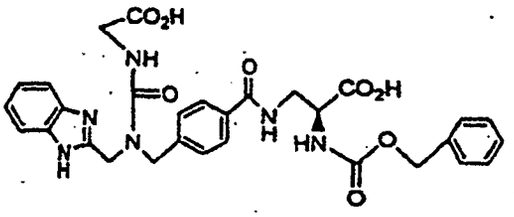
le groupe représenté par R^D pouvant, en option, porter 1 à 3 substituants choisis parmi les atomes d'halogène, les groupes cycloalkyle, alcoxy et phénoxy et les groupes de formule $-SCH_3$, $-OC(O)CH_3$, $-C(O)OC_2H_5$ ou $-N(CH_3)_2$, et R^F et R^G représentent chacun un atome d'hydrogène ou un groupe alkyle, phényle, cycloalkyle ou aralkyle, les groupes représentés par R^F et R^G pouvant, en option, porter un substituant choisi parmi les atomes d'halogène, les groupes alcoxy et les groupes de formule $-CO_2R^H$.

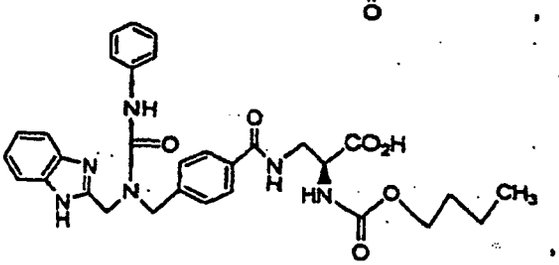
21. Emploi conforme à la revendication 20, ledit trouble étant un cancer.

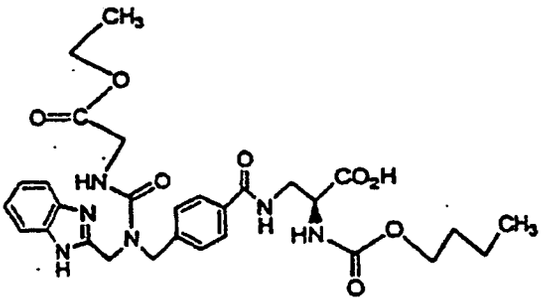
22. Emploi, conforme à la revendication 18, ledit trouble étant un cancer, d'un composé choisi parmi les suivants :

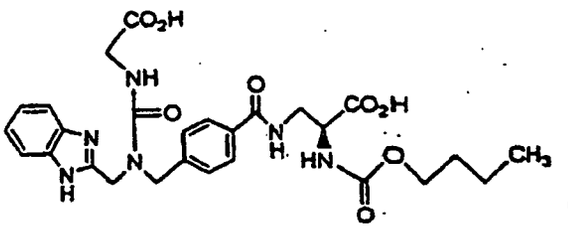


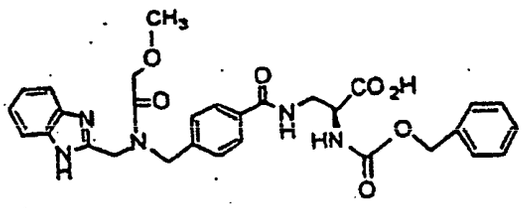


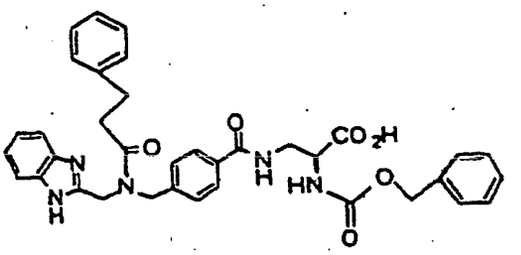


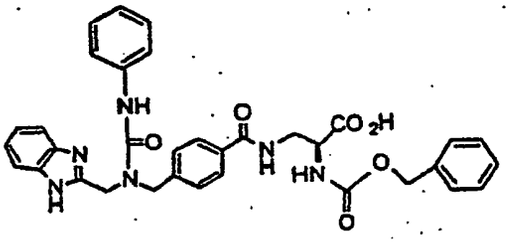


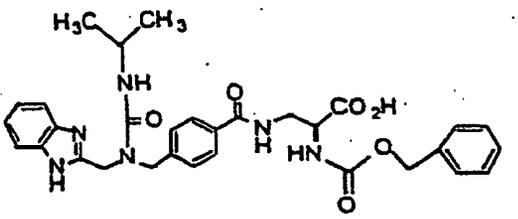




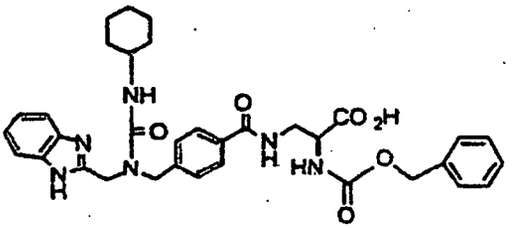








et



ou d'un ester biolabile de l'un de ces composés, ou d'un sel pharmacologiquement admissible de l'un de ces composés.