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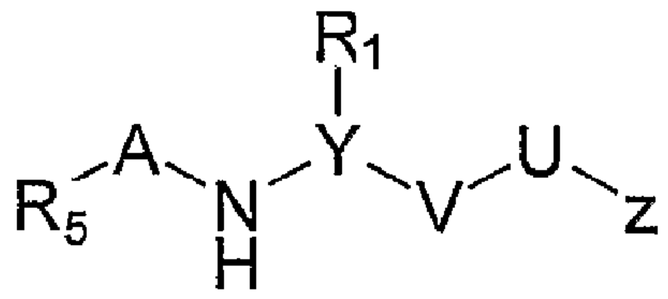
(54) Titre : SUBSTANCES ANALOGUES A LA BENZYLAMINE, A BASE SUBSTITUEE, EN TANT QU'INHIBITEURS DU FACTEUR DE COAGULATION XA, LEUR REALISATION ET LEUR UTILISATION

(54) Title: BASE-SUBSTITUTED BENZYLAMINE ANALOGS FOR USE AS COAGULATION FACTOR XA INHIBITORS, THE PRODUCTION AND USE THEREOF



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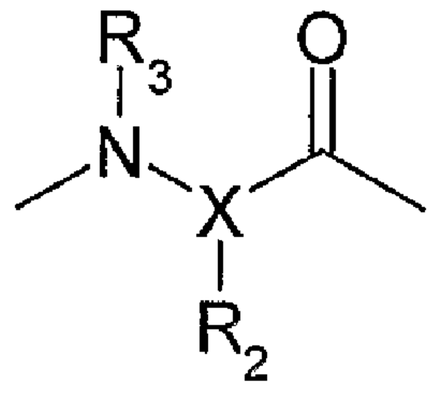

(A)

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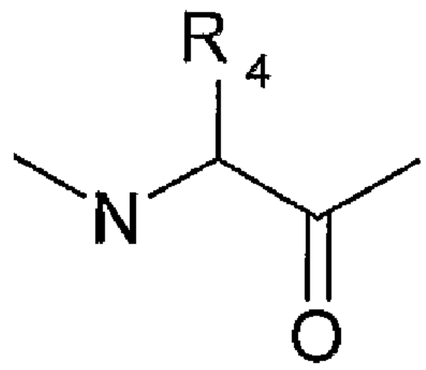

(B)

(57) Abrégé/Abstract:
The invention relates to the novel base-substituted benzylamine analogs of general formula (I), wherein A represents P_2--P_1 with P_1 = (A) and P_2 = (B), for use as coagulation factor Xa inhibitors. The invention also relates to the production and use of said analogs in the therapy and prophylaxis of cardiovascular diseases and thromboembolic events.

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

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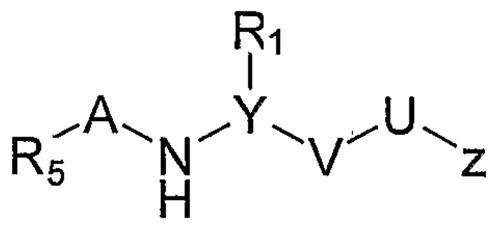
Veröffentlicht:
— *mit internationalem Recherchenbericht*

[Fortsetzung auf der nächsten Seite]

(54) Title: BASE-SUBSTITUTED BENZYLAMINE ANALOGS FOR USE AS COAGULATION FACTOR XA INHIBITORS, THE PRODUCTION AND USE THEREOF

(54) Bezeichnung: BASISCH-SUBSTITUIERTE BENZYLAMINANALOGA ALS INHIBITOREN DES GERINNUNGSFAKTORS XA, IHRE HERSTELLUNG UND VERWENDUNG



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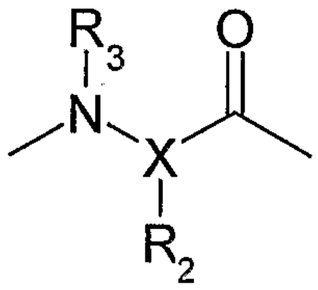
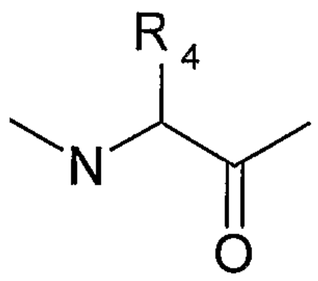


(A)

P_2 =



(B)

(57) Abstract: The invention relates to the novel base-substituted benzylamine analogs of general formula (I), wherein A represents P_2--P_1 with P_1 = (A) and P_2 = (B), for use as coagulation factor Xa inhibitors. The invention also relates to the production and use of said analogs in the therapy and prophylaxis of cardiovascular diseases and thromboembolic events.

(57) Zusammenfassung: Neue basisch-substiutierte Benzlaminanaloga der allgemeinen Formel (I) als Inhibitoren des Gerinnungsfaktors Xa, ihre Herstellung und Verwendung zur Therapie und Prophylaxe von kardiovaskulären Erkrankungen und thromboembolischen Ereignissen.

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— *vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen*

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

Base-substituted benzylamine analogs for use as coagulation factor XA inhibitors, the production and use thereof

The invention relates to novel base-substituted benzylamine analogs as coagulation factor Xa inhibitors, their preparation and use for the therapy and prophylaxis of cardiovascular disorders and thromboembolic events.

The heparin-type anticoagulants currently employed clinically, and the vitamin K antagonist do not comply with all the requirements for an "ideal" antithrombotic agent. For this reason, alternatives are sought with small-molecule inhibitors of coagulation enzymes, specifically of thrombin and factor Xa (F Xa). A particular advantage of F Xa inhibitors compared with thrombin inhibitors might be the smaller tendency to bleeding which has been found in various animal experiments. Thus, antithrombotically effective doses had only a minimal influence on the bleeding time (J.M. Herbert et al., J. Pharmacol. Exp. Ther. 276, 1030-1038, 1996; K. Sato et al., Br. J. Pharmacol. 123, 92-96, 1998).

The first non-peptide compounds having high affinity for F Xa were symmetrical bis-benzamidines (K_i = 13 nM for the most effective compound BABCH) (J. Stürzebecher et al., Thromb. Res. 54, 245-252, 1998). The naphthamidine derivative DX-9065a also has two basic groups and is a selective F Xa inhibitor with K_i = 24 nM (T. Hara et al., Thromb. Haemost. 71, 314-319, 1994). The inhibitor YM-60828 which is structurally related to DX-9065a (K. Sato et al. Eur. J. Pharmacol. 339, 141-146, 1997) is even more effective (K_i = 1.3 nM). In the interim, a whole series of further bisbasic compounds has been described, in which, for example, two benzamidine residues are linked via an oxazoline ring (K_i = 18 nM) (M.L. Quan et al., Bioorg. Med. Chem. Lett. 7, 2813-2818, 1997) or a carboxymethylalkyl chain (K_i = 34 nM) (T.P. Maduskuie et al., J. Med. Chem. 41, 53-62,

1998). The particular disadvantage of the bisbasic compounds is the low bioavailability after oral administration.

F Xa inhibitors comprising only one basic group have also been described. N-Substituted amidinophenoxypyridines (K_i = 0.11 nM for BX-807834) have been developed on the basis of BABCH (R. Mohan et al., Bioorg. Med. Chem. Lett. 8, 1877-1882, 1998; G.B. Phillips et al. J. Med. Chem. 41, 3557-3562, 1998). Amides of Nα-adamantyloxycarbonyl-3-amidinophenylalanine (K_i = 74 nM for the most effective compound) are selective F Xa inhibitors (S. Sperl et al., Biol. Chem. 381, 321-329, 2000), whereas Nα-arylsulfonyl-aminoacylated esters of 3-amidinophenylalanine have a small inhibitory effect (K_i = 840 nM for TAPAM) (J. Stürzebecher et al., Thromb. Res. 54, 245-252, 1998). WO 96/10022 discloses inhibitors which no longer have a strong charge (K_i = 3.0 nM for the most effective compound). A further series of effective factor Xa inhibitors without basic substituents was recently described by Choi-Sledeski et al. (J. Med. Chem. 46, 681-684, 2003).

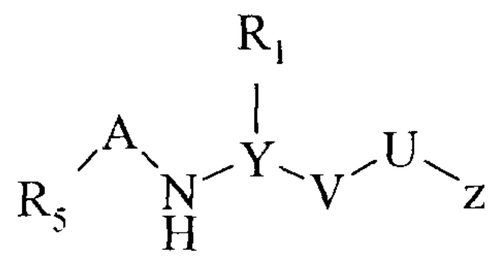
To date, only a few peptides derived from the substrate sequence Ile-Glu-Gly-Arg have been described as F Xa inhibitors. The chloromethyl ketones described by Kettner and Shaw (Thromb. Res. 22, 645-652, 1981) are irreversible F Xa inhibitors and are unsuitable for in vivo applications. By contrast, the peptides SEL 2489 (K_i = 25 nM) and SEL 2711 (K_i = 3 nM) are extremely effective (J. A. Ostrem et al., Biochemistry 37, 1053-1059, 1998). There have also been descriptions of some peptidyl-arginine aldehydes and peptidyl-arginyl ketones which, besides argininal or an arginyl ketone derivative such as, for example, arginyl-ketothiazole in position P3, have a D-arginine or an unnatural basic amino acid such as, for example, 4-amidinophenylalanine, 3- or 4-amidinopiperidinylalanine and 4-guanidinophenylalanine in P3 (Z. H. Jonathan, Bioorg. Med. Lett. 9, 3459-3464, 1999 and review article: Zhu and Scarborough Current Opinion in Cardiovascular, Pulmonary & Renal Investigational Drugs 1999, 1, 63-88).) The application WO 01/96366 discloses inhibitors which are derived from acylated amidinobenzylamine and, besides a natural amino acid in P2, comprise a D-Ser ether or a comparable derivative of an unnatural amino acid. Compounds of this type inhibit both F Xa (K_i = 30 nM for the most effective compound) and the coagulation of human blood

plasma very effectively. However, compounds of this type have only inadequate pharmacokinetic properties for application in vivo; they are scarcely absorbed after oral administration and are very rapidly eliminated from the circulation after i.v. administration in experimental animals.

U.S. Patent No. US 5,914,319 describes thrombin inhibitors which have a d-homophenylalanine or d-homocyclohexylalanine in position P3 and also show a weak factor Xa inhibition with inhibitory constants in the micromolar range (for factor Xa: K_{ass} < 5.5 x 10^6 l/mol, equivalent to about K_i > 0.18 μM). However, these inhibitors have an obligatory imino acid in position P2, i.e. analogs of proline or N(alkyl)glycine derivatives. The thrombin affinity is also distinctly increased, and the selectivity ratio (K_i for thrombin/K_i for F Xa) is < 0.08 for the indicated compounds.

The invention is therefore based on the object of indicating an active ingredient which is suitable for therapeutic applications and which inhibits coagulation factor Xa with high activity and specificity and which preferably circulates for as long as possible in the body after i.v., s.c. or oral administration.

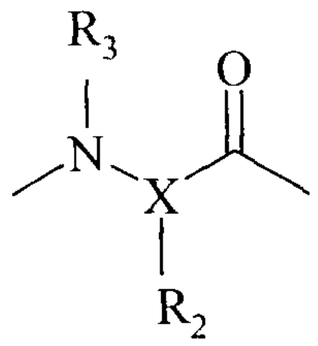
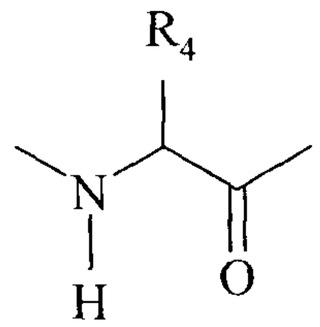
It has surprisingly been found that acylated amidinobenzylamine of the general formula I indicated in claim 1



(I),

where

A is P_2—P_1 with

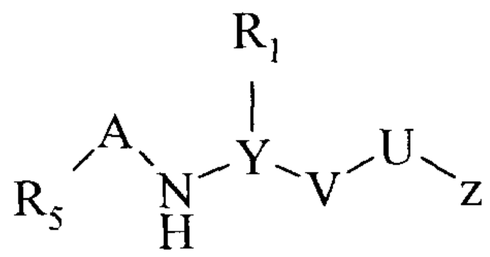
P_1 =  P_2 =  and ,

in particular compounds of 4-amidinobenzylamine both very effectively inactivate factor Xa and are also slowly eliminated from the circulation if, besides the amidino function, further charged or polar groups are introduced, it having emerged in particular that D-homophenylalanine, D-homotyrosine or D-homo-4-pyridylalanine and its derivatives at position P_2 of the general formula I are particularly effective. It was also possible through the use of selected α-amino acids in position P2 to decisively increase the selectivity as factor Xa inhibitors, which was particularly surprising.

For clarification, it is pointed out that the naming of the radicals P_2 and P_1 in the structural segment A of the general formula I does not refer to the otherwise normally used nomenclature of the amino acid residues in peptide substrates of serine proteases and inhibitors derived therefrom, as introduced by Schechter and Berger (Schechter and Berger, Biochem. Biophys. Res. Comm. 27, 157-162 (1967)). The definitions applying in all parts of the invention, i.e. both in the description and in the claims, are as follows:

The letter P in connection with a number from 1 to 3 in normal script, i.e. P1, P2 or P3, is used for amino acid residues and their derivatives in accordance with the Schechter and Berger nomenclature. By contrast, the letter P in connection with a subscript 1 or 2, i.e. P_1 or P_2, represents amino acid residues and their derivatives as constituents of structure A in formula I of the present invention. In this connection, substituted or unsubstituted natural or unnatural amino acid P_1 in the structure A corresponds to P2 according to Schechter and Berger and the substituted or unsubstituted natural or unnatural amino acid P_2 in the structure A corresponds to P3 according to Schechter and Berger.

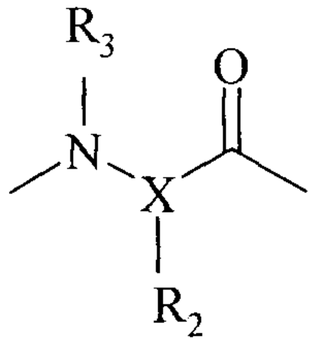
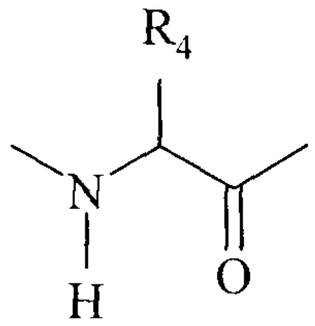
One aspect of the present invention is therefore a compound of the general formula I



(I),

where

A is P_2—P_1 with

P_1 =  and P_2 =  ;

R_1 is an H or $-(CH_2)_aCOOR_6$ with a = 0, 1, 2, 3, 4 or 5, preferably with a= 0, 1 or 2, where R_6 is a branched or unbranched alkyl radical having, preferably, 1 to 6 C atoms, in particular 1 to 3 C atoms, especially ethyl, and R_1 is in particular an H;

R_2 is an H, $-CH_2-OR_7$ or $-CH_2-OCOOR_7$, where R_7 is an H or a branched or unbranched alkyl radical having 1-5, in particular 1-3 C atoms, or R_2 is a $-CH_2-CH_2-COOR_{7*}$, where R_{7*} is an H or a branched or unbranched alkyl radical having 1-5 C atoms, preferably ethyl;

R_3 is an H;

R_4 is $-(CH_2)_f-R_8$ with f = 0 or 2, preferably with f = 2, $-CH_2NHR_8$, $-(CH_2)_2NHR_8$ or $-CH=CH-R_8$, where R_8 is a mono- or polysubstituted or unsubstituted cycloalkyl, aryl or heteroaryl radical, where the cycloalkyl, aryl or heteroaryl radical preferably has 5 to 14, in particular 5 to 6 C atoms in the ring and, in the case of the heteroaryl radical, preferably 1 to 3 N as heteroatoms, or if R_4 is equal to $-(CH_2)_f-R_8$ with R_8 equal to a hydroxycycloalkyl radical with 4 to 14, in particular 6 to 10, especially 6 C atoms, then f is 1, and where P_2 in the

structure A of the general formula I is in the D or L configuration, preferably in the D configuration;

R_5 is $-(CH_2)_i-COOR_9$ with i = 1, 2 or 3, preferably with i = 1, and R_9 is equal to a branched or unbranched alkyl radical having 1-5 C atoms, preferably ethyl, or R_5 is $-SO_2R_{9*}$, $-SO_2-NH-R_{9*}$, where R_{9*} is an H, a branched or unbranched alkyl having 1-10, preferably 1 to 6, in particular 1 to 4, especially 1 to 2 C atoms, a mono- or polysubstituted or unsubstituted aryl, heteroaryl, aralkyl, preferably benzyl, heteroaralkyl radical or a cyclohexylalkyl radical, preferably a cyclohexylmethyl radical, where the substituent may be an -OH, $-O-COOR_7$, $-CH_2-OCOOR_7$, with R_7 as defined above, $-NH_2$, $-NO_2$, $-COOR_{10}$, $-CH_2-COOR_{10}$ group or a Cl, F or Br atom, and where R_{10} is an H or an alkyl radical having 1 to 6, in particular having 1 to 4 C atoms, especially ethyl;

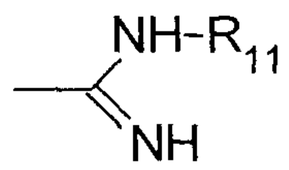
U is a phenyl or cyclohexyl radical;
is an aromatic or nonaromatic heterocyclic radical having 1-10, preferably 6 ring atoms having at least one N, S or O as heteroatom, in particular pyridine, piperidine or pyrimidine, or is a thienyl radical;

V is $(CH_2)_n$ with n = 0 or 1, preferably 0;

X is N or CH, preferably CH;

Y is N or CH, preferably CH;

Z occurs in position 2, 3 or 4, preferably in position 4, and is an aminomethyl, a guanidino function or an amidino group



where R_{11} is H, OH, NH_2, -COR_{12} or -$COOR_{12}$, where R_{12} is a branched or unbranched alkyl radical having 1 to 8, preferably 1 to 6 C atoms or a mono- or polysubstituted or unsubstituted aryl or heteroaryl, aralkyl or heteroaralkyl radical, where the alkyl radical preferably has 1 to 16, in particular 1 to 8, especially 1 to 4 and particularly preferably 1 to 2 C atoms and the aryl or heteroaryl radical preferably has 4 to 14, in particular 6 to 10, especially 6 C atoms and preferably 1 to 3 N as heteroatoms;

or a compound of the general formula I in the form of a prodrug or in the form of its salt.

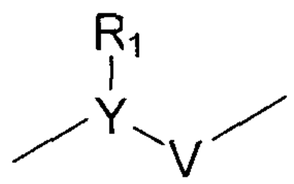
Further particularly suitable compounds are compounds of the general formula I where U is substituted at 1, 2 or 3 positions preferably by a halogen, in particular fluorine or chlorine, or a methyl, ethyl, propyl, methoxy, ethoxy or propoxy radical.

Likewise particularly suitable compounds are compounds of the general formula I where at least one carboxyl group is in protected form as ester, preferably as ethyl ester, and is, in the manner of a prodrug, converted into a carboxyl group only after uptake in the body.

Very generally, a prodrug is a pharmaceutically inactive derivative of the appropriate pharmaceutically active substance and, after oral administration, is biotransformed spontaneously or enzymatically to liberate the pharmaceutically active substance.

Consequently, prodrug means for example compounds of the general formula I in which additionally or exclusively one or more carboxyl groups may be present in the form of their alkyl esters with a branched or unbranched alkyl having 1-5 C atoms, preferably ethyl, and/or in which one or more hydroxyl groups may be present in the form of carbonates in which the terminal radical is equal to R_7 as defined above. A prodrug within the meaning of the present invention is for example also an amidino- or guanidinobenzylamine derivative of the general formula I in which the amidino- or guanidinobenzylamine residue is in the form of hydroxyamidine or hydroxyguanidine or of alkyloxycarbonyl derivative preferably having a branched or unbranched alkyl radical having 1-5 C atoms, preferably ethyl.

Further particularly suitable compound are compounds in which the structural element



of the formula I is a $-CH_2-$ or -NH- group, preferably a $-CH_2-$ group.

Also particularly preferred are compounds in which

R_1 is an H;

R_2 is an H, $-CH_2-CH_2-COOH$, $-CH_2-CH_2-COOCH_2CH_3$ or $-CH_2OH$;

R_3 is an H;

R_4 is a $-(CH_2)_2-R_8$, $-CH_2NHR_8$, $-(CH_2)_2NHR_8$ or a $-CH_2$-4-hydroxycyclohexyl radical, where R_8 is a mono- or polysubstituted or unsubstituted cycloalkyl, aryl or heteroaryl radical, where the cycloalkyl, aryl or heteroaryl radical has 5 or 6 C atoms and, in the case of a heteroaryl radical, 1 or 2 N as heteroatoms, and R_8 is preferably a phenyl, hydroxyphenyl, pyridyl or aminopyridyl radical;

R_5 is a methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, butylsulfonyl, benzylsulfonyl, n-butylsulfonyl, aminobenzylsulfonyl, hydroxybenzylsulfonyl, chlorobenzylsulfonyl, fluorobenzylsulfonyl, carboxybenzylsulfonyl, ethyloxycarbonylbenzylsulfonyl, carboxymethylbenzylsulfonyl, ethyloxycarbonylmethylbenzylsulfonyl, pyridylmethylsulfonyl, N-(oxide)-pyridylmethylsulfonyl, $-CH_2-COOH$ or a $-CH_2COOCH_2CH_3$ radical;

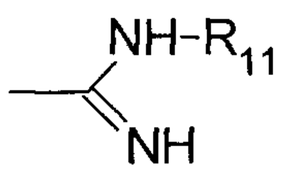
U is a phenyl radical;

V is $(CH_2)_n$ with n = 0;

X is CH;

Y is CH;

Z is present in position 4 and is an amidino group



where R_{11} is H, OH or -$COOR_{12}$ with R_{12} a branched or unbranched alkyl radical having 2, 4 or 6 C atoms.

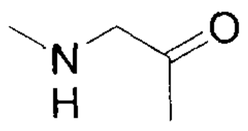
Other particularly suitable compounds are compounds in which R_4 is a -CH_2-CH_2-R_8 radical, where R_8 is an aryl or heteroaryl radical having 4-6 ring atoms, which has 1 or 2 heteroatoms, preferably N, and may be substituted by one or more –NH_2 and/or –OH groups, and preferably P_2 in the structure A of the general formula I is derived from a homophenylalanine, homotyrosine, indanylglycine or 4-pyridylhomoalanine, and the P_2 amino acid is in particular in the D configuration.

Unless defined otherwise, the term "substituent" or "substituted" according to the present invention preferably means -OH, -NH_2, -NO_2, -COOH, -$COOCH_2CH_3$ or a halogen, where the term "halogen" generally means fluorine, chlorine or bromine, in particular fluorine or chlorine.

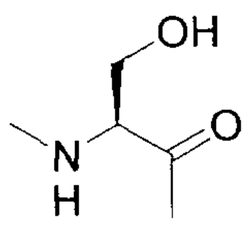
An alkyl radical generally designates, unless defined otherwise, a radical preferably having 1-5 C atoms, in particular ethyl, and cycloalkyl, aryl, aralkyl radical generally designates, unless defined otherwise, a radical preferably having 4 to 14, in particular 6 to 10, especially 6 C atoms as ring atoms. The term "hetero" generally means, unless defined otherwise, preferably N, S or O, in particular N, where at least one C atom of the ring in the heteroaryl radical is replaced by a heteroatom, and preferably 1, 2 or 3 C atoms of the ring are replaced in particular by N.

In detail, particularly preferred compounds of the present invention are compounds according to the claims, or compounds 11 to 20 and 22 to 65 in Table 1.

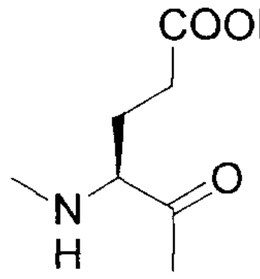
However, the individual particularly preferred compounds also include compounds in which, in the structures mentioned, the glycine residue with the structural element



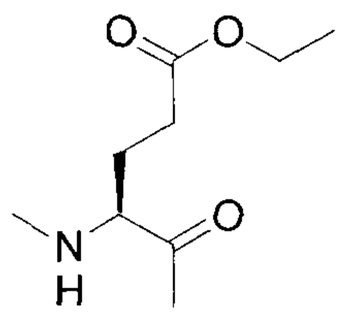
is in each case replaced by a serine residue with the structural element



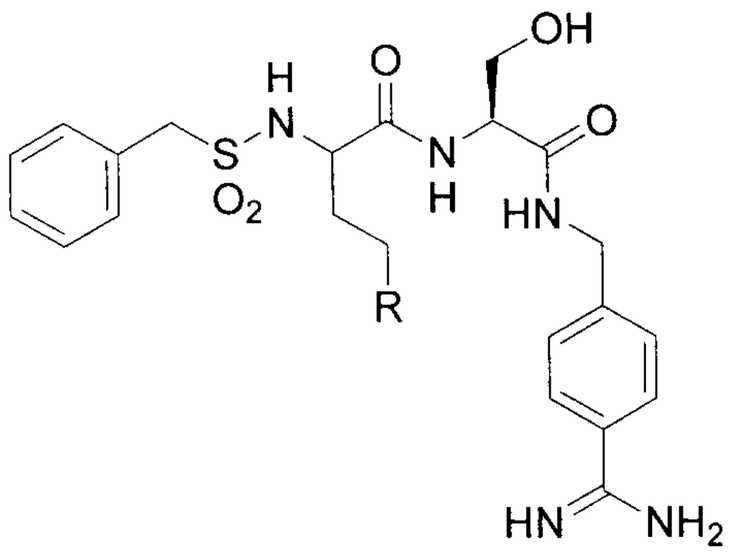
or by a glutamic acid residue with the structural element

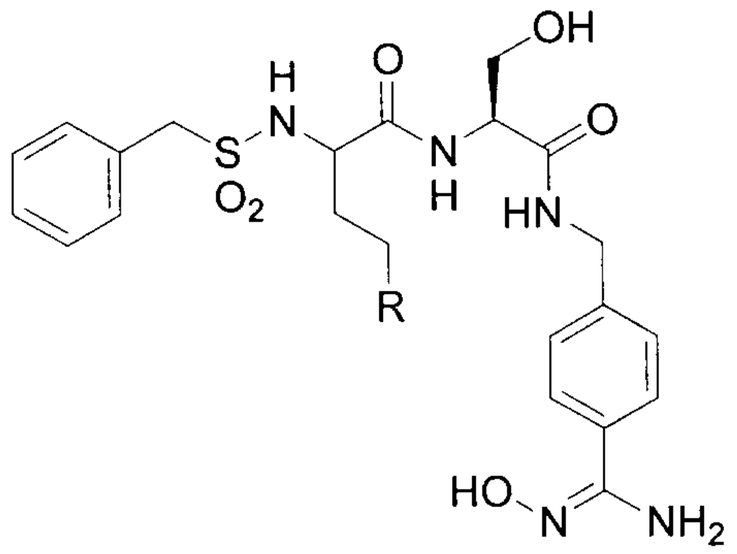


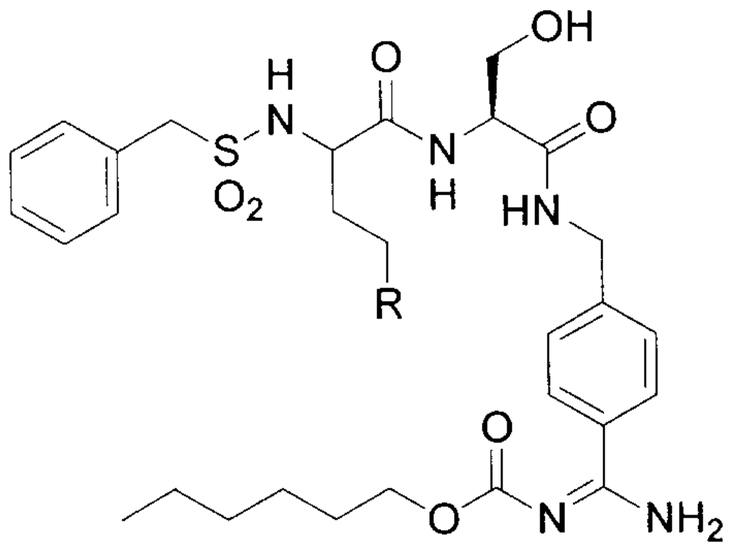
or by a glutamine γ-ethyl ester with the structural element

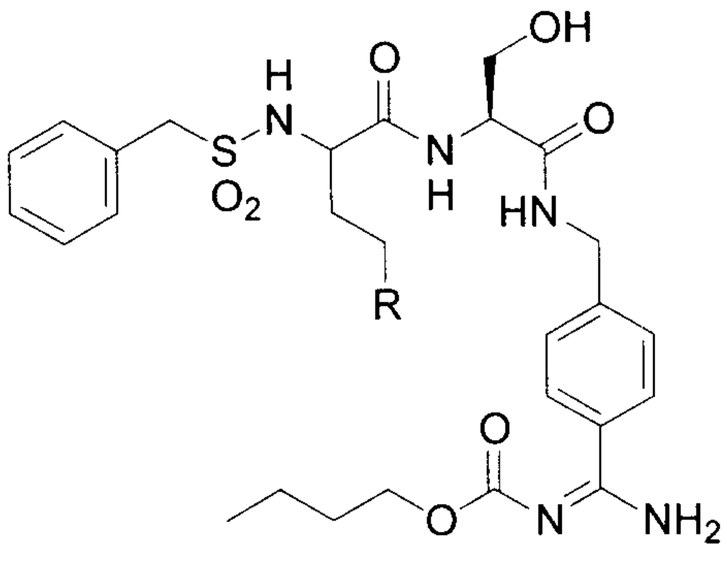


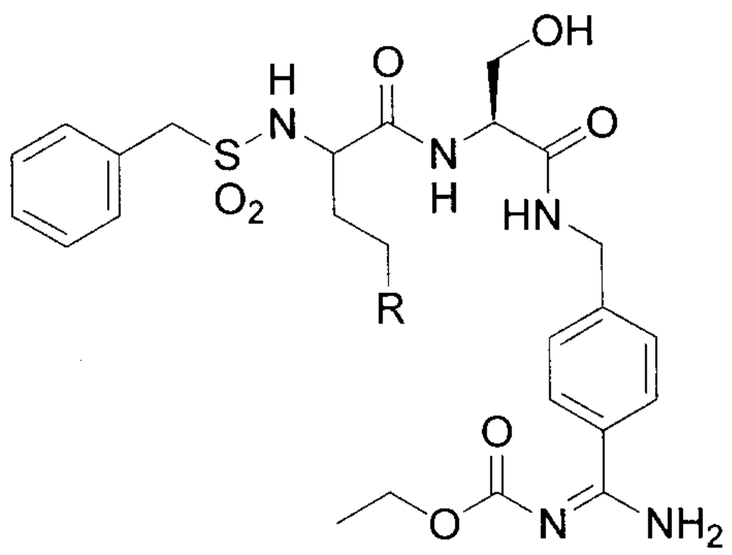
These are for example the following structures having a serine residue:











Further suitable compounds of the present invention:

A further aspect of the present invention are compounds as mentioned above where Z is an amino group. U in such compounds is preferably a phenyl radical, a cyclohexyl radical or an N-atom-heteroaryl radical, preferably a pyridyl radical.

A further aspect of the present invention are compounds as mentioned above with the exception that R_2 is $-(CH_2)_aCONHR_{7*}$ or $-(CH_2)_aCONHR_{7**}$ with a = 1, 2 or 3, where R_{7**} is an aryl radical, preferably a phenyl radical or an aralkyl, preferably a benzyl radical, or a heteroaryl radical having one to two N, S or O heteroatoms, preferably N heteroatoms.

A further aspect of the present invention are compounds as mentioned above, where R_2 is $-(CH_2)_aCONHR_{7*}$ or $-(CH_2)_aCONHR_{7**}$ with a = 1, 2, or 3, and where R_{7**} is substituted by at least one halogen, one methyl, one ethyl, one amino, one hydroxy, one nitro, one -COOH, one $-CH_2COOH$ or one $-CH_2NH_2$- group.

A further aspect of the present invention are compounds as mentioned above, where R_2 is a $-(CH_2)_n-NH_2$ with n= 1, 2, 3, 4 or 5, preferably 1 or 4.

A further aspect of the present invention are compounds as mentioned above, where R_5 R_9 is H.

A further aspect of the present invention are compounds as mentioned above, where R_4 is a $-CH_2-SR_8$ or $-CH_2CH_2-SR_8$ group. Examples of such compounds are in particular those in which R_5 is an $-SO_2R_{9*}$ or an $-SO_2CH_2R_{9*}$ group or in which R_5 is an $-SO_2R_{9*}$ or an $-SO_2CH_2R_{9*}$ group and v is $(CH_2)_n$ with n = 0 or in which R_5 is an $-SO_2R_{9*}$ or an $-SO_2CH_2R_{9*}$ group and v is $(CH_2)_n$ with n = 0 and with U = a phenyl radical, a cyclohexyl radical, an N-heteroaryl, preferably pyridyl radical.

Likewise an aspect of the invention are compounds in which R_5 is an $-SO_2R_{9*}$ or an $-SO_2CH_2R_{9*}$ group or in which R_5 is an $-SO_2R_{9*}$ or an $-SO_2CH_2R_{9*}$ group and v is $(CH_2)_n$ with n = 0 or in which R_5 is an $-SO_2R_{9*}$ or an $-SO_2CH_2R_{9*}$ group and v is $(CH_2)_n$ with n = 0 and U = a phenyl radical, a cyclohexyl radical, an N-heteroaryl, preferably a pyridyl

radical, and in which R_{9*} is a phenyl radical, a cyclohexyl radical, a pyridyl radical or a pyridyl N-oxide radical.

Likewise an aspect of the invention are compounds in which R_5 is an $-SO_2R_{9*}$ or an $-SO_2CH_2R_{9*}$ group or in which R_5 is an $-SO_2R_{9*}$ or $-SO_2CH_2R_{9*}$ group and v is $(CH_2)_n$ with $n = 0$ or in which R_5 is an $-SO_2R_{9*}$ or $-SO_2CH_2R_{9*}$ group and v is $(CH_2)_n$ with $n = 0$ and U = a phenyl radical, a cyclohexyl radical, an N-heteroaryl, preferably a pyridyl, radical and in which R_{9*} is a substituted phenyl or cyclohexyl or pyridyl or pyridyl N-oxide radical, where the substituent may be an -OH, $-O-COOR_7$, $-CH_2OCOOR_7$, with R_7 as defined above, NH_2, NO_2, $-COOR_{10}$, $-CH_2COOR_{10}$ group or a Cl or F or Br atom.

Likewise an aspect of the invention are compounds in which R_5 is an $-SO_2R_{9*}$ or $-SO_2CH_2R_{9*}$ group or in which R_5 is an $-SO_2R_{9*}$ or $-SO_2CH_2R_{9*}$ group and v is $(CH_2)_n$ with $n = 0$ or in which R_5 is an $-SO_2R_{9*}$ or $-SO_2CH_2R_{9*}$ group and v is $(CH_2)_n$ with $n = 0$ and U = a phenyl radical, a cyclohexyl radical or an N-heteroaryl, preferably a pyridyl, radical and in which R_{9*} is a substituted phenyl or cyclohexyl or pyridyl or pyridyl N-oxide radical, where the substituent may be an -OH, $-O-COOR_7$, $-CH_2OCOOR_7$, with R_7 as defined above, NH_2, NO_2, $-COOR_{10}$, $-CH_2COOR_{10}$ group or a Cl or F or Br atom, and in which R_1 is $-(CH_{-2})_aCONHR_6$ or $-(CH_2)_aCONHR_{6*}$ with a = 0, 1, 2, 3, 4 or 5, preferably 0, 1 or 2, where R_{6*} is an aryl radical, preferably a phenyl radical.

Likewise an aspect of the invention are compounds in which R_5 is an $-SO_2R_{9*}$ or an $-SO_2CH_2R_{9*}$ group or in which R_5 is an $-SO_2R_{9*}$ or $-SO_2CH_2R_{9*}$ group and v is $(CH_2)_n$ with $n = 0$ or in which R_5 is an $-SO_2R_{9*}$ or an $-SO_2CH_2R_{9*}$ group and v is $(CH_2)_n$ with $n = 0$ and U = a phenyl radical, a cyclohexyl radical or an N-heteroaryl, preferably a pyridyl, radical and in which R_{9*} is a substituted phenyl or cyclohexyl or pyridyl or pyridyl N-oxide radical, where the substituent may be an -OH, $-O-COOR_7$, $-CH_2OCOOR_7$, with R_7 as defined above, an NH_2, NO_2, $-COOR_{10}$, $-CH_2COOR_{10}$ group or a Cl or F or Br atom, and in which R_2 is $-CH_2-CH_2-CONHR_{7*}$ or $-CH_2CH_2CONHR_{7**}$ or $-CH_2CH_2COOR_{7**}$, where R_{7**} is an aryl radical, preferably a benzyl or phenyl radical.

Likewise an aspect of the invention are compounds in which R_5 is an $-SO_2R_{9*}$ or an $-SO_2CH_2R_{9*}$ group or in which R_5 is an $-SO_2R_{9*}$ or an $-SO_2CH_2R_{9*}$ group and v is $(CH_2)_n$ with n = 0 or in which R_5 is an $-SO_2R_{9*}$ or $-SO_2CH_2R_{9*}$ group and v is $(CH_2)_n$ with n = 0 and U = a phenyl radical, a cyclohexyl radical or a pyridyl radical and in which R_{9*} is a substituted phenyl or cyclohexyl or pyridyl radical, where the substituent may be an -OH, -O-$COOR_7$, $-CH_2OCOOR_7$, with R_7 as defined above, an NH_2, NO_2, $-COOR_{10}$, $-CH_2COOR_{10}$ group or a Cl or F or Br atom, and in which R_4 is a $-CH_2-SR_8$ or $-CH_2CH_2-SR_8$ group..

Likewise an aspect of the invention are compounds as mentioned above, where R_8 is a pyridyl N-oxide radical.

Also an aspect of the invention are compounds in which P_1 is a prolyl radical or an azetidinecarboxylic acid residue.

Likewise an aspect of the invention are compounds in which P_2 is a 4-N-oxide-pyridylhomoalanine residue. Also an aspect of the invention are compounds in which P_2 is a lysyl or an a,ß-diaminopropionic acid residue.

Likewise an aspect of the invention are the compounds one or more or all of the compounds 22 to 65 in table 1.

Besides the inactivation of factor Xa, the additionally charged 4-amidinobenzylamine derivatives of the present invention are, as mentioned above, eliminated very slowly in an advantageous and surprising manner, so that the compounds of the invention represent a novel group of highly active F Xa inhibitors.

The compounds are usually in the form of salts, preferably with mineral acids or suitable organic acids, preferably with hydrochloric acid, sulfuric acid, acetic acid, formic acid, methylsulfonic acid, succinic acid, malic acid or trifluoroacetic acid, especially in the form of their hydrochlorides, sulfates or acetates.

The compounds of the general formula I can be prepared in a manner known in principle as described below, for example as follows, with in general the appropriate amino acids being coupled sequentially onto an amidinobenzylamine which is protected on the amidino group, with the N-terminal amino acid either already carrying the R_5 radical or the latter subsequently being linked thereto.

From the commercially available 4-cyanobenzylamine (Showa Denko, Japan), the Boc-protected 4-acetyloxamidinobenzylamine is obtained by methods known to the skilled worker. Elimination of the Boc-protective group is followed by coupling on the further amino acids and the protective group R_5 by means of standard coupling methods with Boc as N-terminal protective group. The second amino acid can also be coupled directly as N-arylsulfonyl- or N-aralkylsulfonyl-protected amino acid. The peptide analogs are assembled sequentially starting from acetyloxaminobenzylamine. Most of the intermediates crystallize well and can thus be purified easily. Final purification of the inhibitors takes place at the last stage, preferably by preparative reversed phase HPLC.

The invention therefore further relates to a method for preparing a compound of the general formula I, where the appropriate amino acids are coupled sequentially onto an amidinobenzylamine which is protected on the amidino group, for example onto a 4-acetyloxamidinobenzylamine or onto a 4-(benzyloxycarbonylamidino)benzylamine, with the N-terminal amino acid either already carrying the R_5 radical or the latter subsequently being linked thereto.

The invention further relates to a medicament comprising a compound of the invention, and further pharmaceutically suitable excipients and/or additives. Suitable excipients and/or additives, which serve for example to stabilize and/or preserve the medicament, are generally familiar to the skilled worker (e.g. Sucker H. et al., (1991) Pharmazeutische Technologie, 2nd edition, Georg Thieme Verlag, Stuttgart). These include, for example, physiological saline solutions, ringer dextrose, ringer lactate, demineralized water, stabilizers, antioxidants, complexing agents, antimicrobial compounds, proteinase inhibitors and/or inert gases.

The medicament could for example be used in parenteral form, in particular in intraarterial, intravenous, intramuscular or subcutaneous form, in an enteral use form, in particular for oral or rectal use, or in a topical use form, in particular as dermatologic agent. Intravenous or subcutaneous uses are preferred.

In one embodiment of the invention, the medicament is employed for example in the form of a tablet, of a coated tablet, of a capsule, of a pellet, suppository, of a solution, in particular of a solution for injection or infusion, of eyedrops, nose and eardrops, of a syrup, of a capsule, of an emulsion or suspension, of a pessary, stick, aerosol, dusting powder, of a paste, cream or ointment.

The factor Xa inhibitors of the invention or the medicaments mentioned are preferably used for the therapy or prophylaxis of a cardiovascular disorder or of a thromboembolic event, in particular in oral, subcutaneous, intravenous or transdermal form.

The invention is to be explained in more detail below by means of several exemplary embodiments without restricting it.

Methods

Analytical HPLC: Shimadzu LC-10A system, column: Phenomenex-Luna C_{18}, 5 µm (250 x 4 mm) solvents A: 0.1% TFA in water, B: 0.1% TFA in ACN, gradient: 10% B to 70% B in 60 min, 1 ml/min flow rate, detection at 220 or 215 nm.

Preparative HPLC: Shimadzu LC-8A System, column: Phenomenex-Luna C_{18}, 5 µm (250 x 30 mm) solvents A: 0.1% TFA in water, B: 0.1% TFA in ACN, gradient: 5 % B to 50 % B in 120 min, 10 ml/min flow rate, detection at 220 nm.

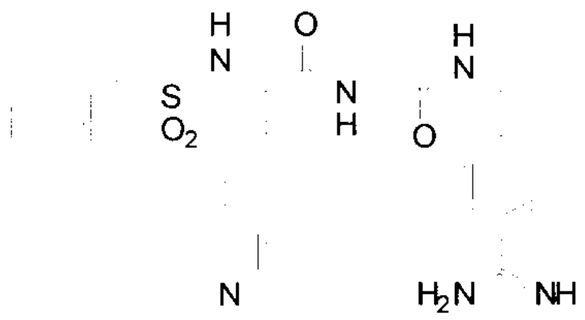
Mass spectroscopy: The mass spectra were recorded on an ESI-MS LCQ from Finnigan (Bremen, Germany).

Abbreviations used

Ac	Acetyl
AcOxam	N-(Acetyloxy)amidine
Amb	Amidomethylbenzene
4-Amba	4-Amidinobenzylamide
Boc	tert.-Butyloxycarbonyl
Bzl	Benzyl
Bzls	Benzylsulfonyl
dCha	d-βCyclohexylalanine
DIEA	Diisopropylethylamine
DCM	Dichloromethane
DMF	N,N-Dimethylformamide
IBCC	Isobutyl chlorocarbonate
i.v.	in vacuo
MS	Mass spectroscopy
NMM	N-Methylmorpholine
PyBOP	Benzotriazol-1-yl-N-oxytris(pyrrolidino)phosphonium hexafluorophosphate
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS-Cl	Trimethylsilyl chloride
tBu	tert.-Butyl

Example 1

Bzls-D,L-homoAla(4-Pyr)-Gly-4Amba x 2 TFA



1a) H-Gly-4-(Acetyloxamidino)benzylamide x HCl (H-Gly-Amb(4AcOxam))

2 g (5.49 mmol) of Boc-Gly-4-(acetyloxamidino)benzylamide (prepared as described in WO 01/96286 A2) were mixed with 30 ml of 1 N HCl in glacial acetic acid. The mixture was occasionally shaken. After 45 min, the solvent was concentrated somewhat, and the product was precipitated by adding diethyl ether, filtered off on a frit with suction, washed with ether and dried in vacuo.

Yield: 1.55 g (5.15 mmol), white solid

1b) Boc-D,L-homoAla(4-Pyr)-Gly-Amb(4AcOxam)

250 mg (0.89 mmol) of Boc-D,L-homoAla(4-Pyr)-OH [RSP Amino Acids DBA, Shirley MA, USA] and 308 mg (1.02 mmol) of product 1a were dissolved in 20 ml of DMF and, at 0°C, 531 mg (1.02 mmol) of PyBop and 533 µl (3.06 mmol) of DIEA were added. The mixture was stirred at 0°C for 20 min and at room temperature for a further 2 h. The solvent was then removed in vacuo, and the residue was taken up in ethyl acetate, washed 1x with NaCl-saturated water, 2x with saturated $NaHCO_3$ solution and 2x with NaCl-saturated water and dried over Na_2SO_4. The solvent was removed in vacuo (yellowish oil).

Yield: about 600 mg (crude product), HPLC: 27.89% B

1c) H-D,L-homoAla(4-Pyr)-Gly-Amb(4AcOxam) x HCl

600 mg of crude product 1b were mixed with 10 ml of 1 N HCl in glacial acetic acid. The mixture was occasionally shaken. After 1 h, the solvent was concentrated somewhat, and the product was precipitated by adding diethyl ether, filtered off on a frit with suction, washed with ether and dried in vacuo.

Yield: 320 mg (0.69 mmol) of pale yellow solid, HPLC: 16.83% B

1d) Bzls-D,L-homoAla(4-Pyr)-Gly-Amb(4AcOxam)

75 mg (0.16 mmol) of crude product 1c and 37 mg (0.19 mmol) of phenylmethanesulfonyl chloride (Bzls-Cl) [Fluka] were dissolved in 10 ml of DMF and, at 0°C, 68 µl (0.39 mmol) of DIEA were added. The mixture was stirred at 0°C for 20 min and at room temperature for a further 2 h. The solvent was then removed in vacuo, and the residue was taken up in ethyl acetate, washed 1x with NaCl-saturated water, 2x with saturated $NaHCO_3$ solution and 2x with NaCl-saturated water und dried over Na_2SO_4. The solvent was removed in vacuo (pale oil).

Yield: about 280 mg (crude product), HPLC: 29.27% B

1e) Bzls-D,L-homoAla(4-Pyr)-Gly-4Amba

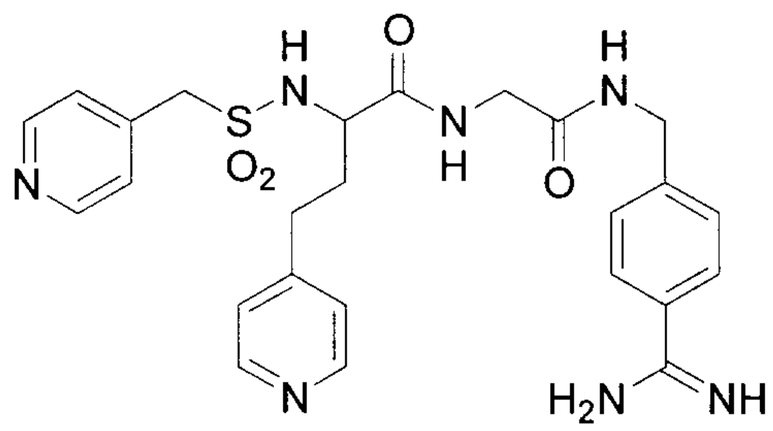
The crude product 1d was dissolved in 50ml of 90% acetic acid, and 20 mg of catalyst (10% Pd/C) were added. The mixture was hydrogenated with hydrogen under atmospheric pressure and at room temperature for 5 h. The catalyst was then filtered off, and the solvent was concentrated in vacuo. The remaining residue was dried in vacuo and purified by preparative reversed-phase HPLC and lyophilized.

Yield: 34.6 mg (0.054 mmol) of lyophilized powder, HPLC: 22.97% B

MS: calculated 522.20 (monoisotopic), found 523.4 $[M+H]^+$

Example 2

4-PMs-D,L-homoAla(4-Pyr)-Gly-4Amba x 3 Acetate



2a) 4-PMs-D,L-homoAla(4-Pyr)-Gly-Amb(4AcOxam)

50 mg (0.11 mmol) of product 1c were suspended in 10 ml of DCM, and 34 µl (0.28 mmol) of chlorotrimethylsilane (= TMS-Cl) [Merck] and 69 µl (0.4 mmol) of DIEA were added, and the mixture was stirred at room temperature for 15 min. Then 41 mg (0.12 mmol) of 4-pyridylmethylsulfonyl chloride x triflate (= 4-PMs-Cl) [Array Biopharma, Boulder, CO, USA] and a further 20 µl (0.11 mmol) of DIEA were added, and stirring was continued at room temperature overnight. The solvent was then removed in vacuo. The residue was employed directly, without further purification, for the next step in the synthesis.

2b) 4-PMs-D,L-homoAla(4-Pyr)-Gly-4Amba

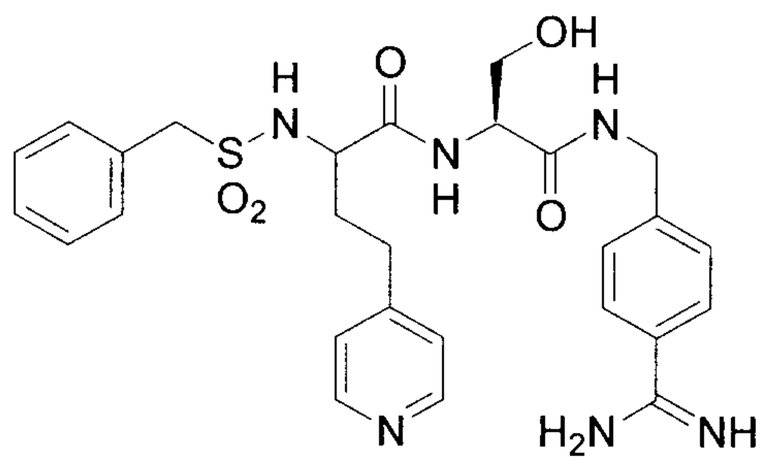
The crude product 2a was dissolved in 50 ml of 90% acetic acid and mixed with 20 mg of catalyst (10% Pd/C). The mixture was hydrogenated with hydrogen under atmospheric pressure and at room temperature overnight. The catalyst was then filtered off, and the solvent was concentrated in vacuo. The remaining residue was dissolved in 5 ml of water and put onto an ion exchange column (Fractogel- EMD COO-column, dimension 16 x 125 mm, equilibrated with water). The column was washed with 85 ml of water, and then the product was eluted with an ammonium acetate gradient. The product-containing fractions (HPLC monitoring) were combined and lyophilized.

Yield: 20 mg (0.034 mmol) of lyophilized powder, HPLC: 13.14% B

MS: calculated 523.20 (monoisotopic), found 524.3 $[M+H]^+$

Example 3

Bzls-D,L-homoAla(4-Pyr)-Ser-4Amba x 2 TFA



3a) Boc-4-Cyanobenzylamide

100 g (0.593 mol) of 4-cyanobenzylamine x HCl were dissolved in 1.2 l of dioxane and 600 ml of 2 N NaOH. 142.3 g (0.652 mol) of di(tert-butyl)pyrocarbonates were added in two portions over 10 min at 0°C. The pH was adjusted to 9-10 by adding 2 N NaOH, and the mixture was stirred for a further 4 h. The solvent was removed in vacuo, and the residue was taken up with ethyl acetate, washed 3x each with 5% $KHSO_4$ and NaCl-

saturated water and then dried over Na_2SO_4. The solvent was removed in vacuo (white solid).

Yield: 132.6 g (0.57 mol) of white solid, HPLC: 51.6% B

3b) Boc-4-Acetyloxamidinobenzylamide

130 g (0.56 mol) of product 3a, 58.4 g (0.84 mol) of hydroxylamine x HCl and 146 ml of DIEA were dissolved in 1.5 l of methanol. The mixture was boiled under reflux for 6 h and then stirred at room temperature overnight. The solvent was removed in vacuo, and the oily residue was dissolved in 1.5 l of acetic acid, mixed with 160 ml (1.68 mol) of acetic anhydride and stirred for 30 min. The solvent was removed in vacuo, and the residue was taken up with ethyl acetate and washed 3x with NaCl-saturated water and then dried over Na_2SO_4. The solvent was removed as far as possible in vacuo, and the product was crystallized from ethyl acetate.

Yield: 110.6 g (0.36 mol) of crystalline solid, HPLC: 39.76% B

3c) H-4-Acetyloxamidinobenzylamine x HCl

50 g (163 mmol) of product 3b were dissolved in 1 l of acetic acid, and 800 ml of 1 N HCl in glacial acetic acid were added. The mixture was shaken and, after a few minutes, the product started to precipitate. After 75 min, the product was filtered off with suction, washed with diethyl ether and dried in vacuo.

Yield: 36 g (147.7 mmol) of white solid, HPLC: 18.97% B

3d) Boc-Ser-4-Acetyloxamidinobenzylamide

25 g (122 mmol) of Boc-Ser-OH were dissolved in 750 ml of DMF and cooled to -15°C. 13.42 ml (122 mmol) of N-methylmorpholine and 15.86 ml (122 ml) of isobutyl chlorocarbonate were added, and the mixture was stirred for 10 min. Then 29.74 g (122 mmol) of product 3c and 13.42 ml (122 mmol) of N-methylmorpholine were added, and the mixture was stirred at –15°C for 1 h and at room temperature overnight. The DMF was then removed in vacuo, and the residue was dissolved in 2 l of ethyl acetate and washed 2x with 300 ml of saturated $NaHCO_3$ solution and 300 ml of NaCl-saturated water and dried over Na_2SO_4, and the solvent was removed in vacuo (oil).

Yield: 43 g of crude product oil, HPLC: 29.87% B

3e) H-Ser-4-Acetyloxamidinobenzylamide x TFA

40 g of the oily crude product 3d were mixed with 200 ml of trifluoroacetic acid and stirred for 1 h. The product was precipitated by adding diethyl ether, filtered off with suction, washed with diethyl ether and dried in vacuo.

Yield: 27 g (66 mmol) of white solid, HPLC: 20.22% B

3f) Boc-D,L-homoAla(4-Pyr)-Ser-Amb(4AcOxam)

100 mg (0.36 mmol) of Boc-D,L-homoAla(4-Pyr)-OH [RSP Amino Acids DBA, Shirley MA, USA] and 161 mg (0.4 mmol) of crude product 3e were dissolved in 15 ml of DMF and, at 0°C, 206 mg (0.4 mmol) of PyBop and 207 µl (1.2 mmol) of DIEA were added. The mixture was stirred at 0°C for 20 min and at room temperature for a further 2 h. The solvent was then removed in vacuo, and the residue was taken up in ethyl acetate, washed 1x with NaCl-saturated water, 2x with saturated $NaHCO_3$ solution and 2x with NaCl-saturated water and dried over Na_2SO_4. The solvent was removed in vacuo (pale oil).

Yield: about 300 mg (crude product), HPLC: 26.8% B and 27.4% B (double peak, racemate)

3g) H-D,L-homoAla(4-Pyr)-Ser-Amb(4AcOxam) x TFA

300 mg of crude product from 3f were mixed with 5 ml of 50% TFA in dichloromethane. The mixture was shaken occasionally. After 45 min, the solvent was concentrated, the residue was solubilized in methanol, and the product was precipitated by adding diethyl ether, filtered off with suction on a frit, washed with ether and dried in vacuo.

Yield: 186 mg (0.33 mmol) of white solid, HPLC: 21.6% B and 22.7% B (double peak, racemate)

3h) Bzls-D,L-homoAla(4-Pyr)-Ser-Amb(4AcOxam)

75 mg (0.13 mmol) of product 3g and 38 mg (0.2 mmol) of phenylmethanesulfonyl chloride (= Bzls-Cl) [Fluka] were dissolved in 10 ml of DMF and, at 0°C, 68 µl (0.39 mmol) of DIEA were added. The mixture was stirred at 0°C for 20 min and at room temperature overnight. The solvent was removed in vacuo (oil).

Yield: about 120 mg (crude product), HPLC: 28.1% B and 28.6% B (double peak)

3i) Bzls-D,L-homoAla(4-Pyr)-Ser-4Amba x 2 TFA

The crude product from 3h was dissolved in 50 ml of 90% acetic acid, and 20 mg of catalyst (10% Pd/C) were added. The mixture was hydrogenated with hydrogen under

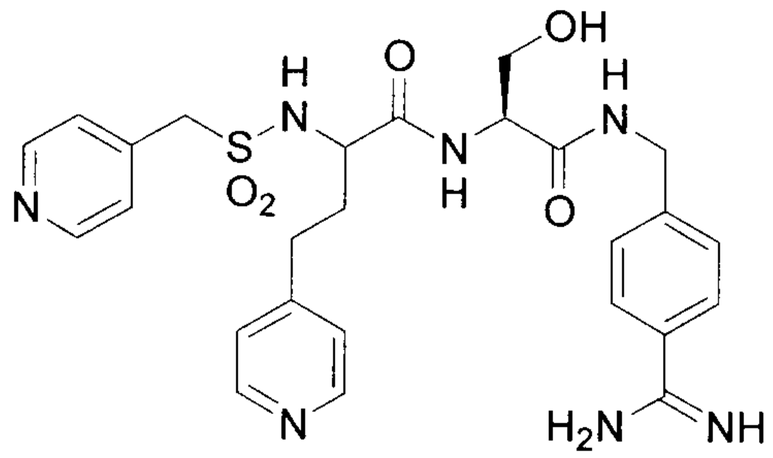
atmospheric pressure and at room temperature overnight. The catalyst was then filtered off, and the solvent was concentrated in vacuo. The remaining residue was dried in vacuo and purified by preparative reversed phase HPLC and lyophilized. It was possible to separate the diastereomers thereby.

HPLC: 22.01% B (compound 3a) and 22.6% B (compound 3b).

MS: calculated 552.22 (monoisotopic), found 553.5 $[M+H]^+$

Example 4

4-PMs-D,L-homoAla(4-Pyr)-Ser-4Amba x 3 acetate



4a) 4-PMs-D,L-homoAla(4-Pyr)-Ser-Amb(4AcOxam)

55 mg (0.1 mmol) of product 3g was suspended in 10 ml of DCM, and 31 µl (0.25 mmol) of chlorotrimethylsilane (= TMS-Cl) [Merck] and 61 µl (0.36 mmol) of DIEA were added, and the mixture was stirred at room temperature for 15 min. Then 36 mg (0.105 mmol) of 4-pyridylmethylsulfonyl chloride x triflate (= 4-PMs-Cl) [Array Biopharma, Boulder, CO, USA] and a further 17.5 µl (0.1 mmol) of DIEA were added, and stirring was continued at room temperature overnight. The solvent was then removed in vacuo. The residue was employed directly, without further purification, for the next step in the synthesis.

4b) 4-PMs-D,L-homoAla(4-Pyr)-Ser-4Amba x 3 acetate

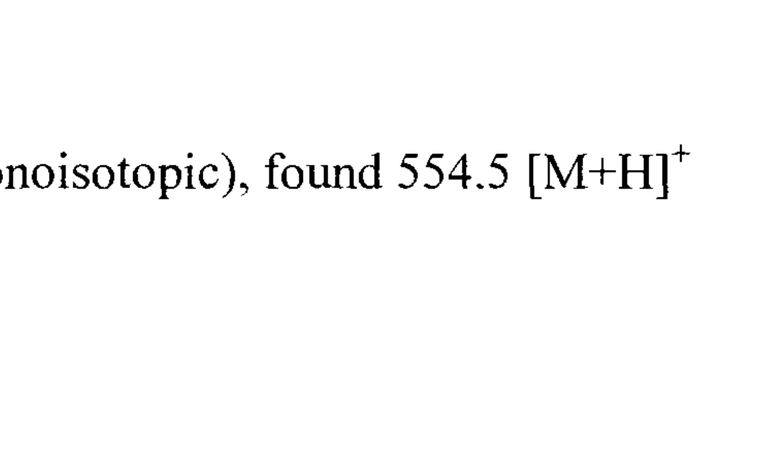
The crude product from 4a was dissolved in 50 ml of 90% acetic acid, and 20 mg of catalyst (10% Pd/C) were added. The mixture was hydrogenated with hydrogen under atmospheric pressure and at room temperature overnight. The catalyst was then filtered off, and the solvent was concentrated in vacuo. The remaining residue was dissolved in 5 ml of water and put onto an ion exchange column (Fractogel- EMD COO column, dimension 16 x 125 mm, equilibrated with water). The column was washed with 85 ml of water and then the product was eluted with an ammonium acetate gradient. The product-containing fractions were combined and lyophilized.

Yield: 17.2 mg (0.028 mmol) of lyophilized powder, HPLC: 12.1 and 12.3% B (double peak, racemate)

MS: calculated 553.21 (monoisotopic), found 554.5 $[M+H]^+$

Example 5

Bzls-d-homoTyr-Gly-4Amba x TFA



5a) Bzls-d-homoTyr-OH

300 mg (1.09 mmol) of H-d-homoTyr-OH x HBr [Chem-Impex International, Wood Dale, IL, USA] were suspended in 20 ml of DCM, and 425 µl (3.37 mmol) of chlorotrimethylsilane (= TMS-Cl) [Merck] and 586 µl (3.37 mmol) of DIEA were added, and the mixture was stirred under reflux at 60°C for 1 h and then cooled again to room temperature. Subsequently, 229 mg (1.2 mmol) of phenylmethanesulfonyl chloride (= Bzls-Cl) [Fluka] and a further 190 µl (1.09 mmol) of DIEA were added, and the mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo, and the residue was taken up in ethyl acetate, washed 1x with 5% $KHSO_4$ solution and 2x with NaCl-saturated water and dried over Na_2SO_4. After removal of the solvent, the product was crystallized from ethyl acetate.

Yield: 353 mg (1.01 mmol) of pale yellow solid, HPLC: 40.9% B

5b) Bzls-d-homoTyr-Gly-Amb(4AcOxam)

50 mg (0.14 mmol) of product 5a and 43 mg (0.14 mmol) of H-Gly-Amb(4AcOxam) (= product 1a) were dissolved in 15 ml of DMF and, at 0°C, 74.4 mg (0.14 mmol) of PyBop and 74.6 µl (0.43 mmol) of DIEA were added. The mixture was stirred at 0°C for 20 min and at room temperature for a further 2 h. The solvent was then removed in vacuo, and the residue was taken up in ethyl acetate, washed 1x with 5% $KHSO_4$ solution and 2x with NaCl-saturated water and dried over Na_2SO_4. A pale oil remained as residue.

Yield: about 200 mg (crude product), HPLC: 39.84% B

5c) Bzls-d-homoTyr-Gly-4Amba

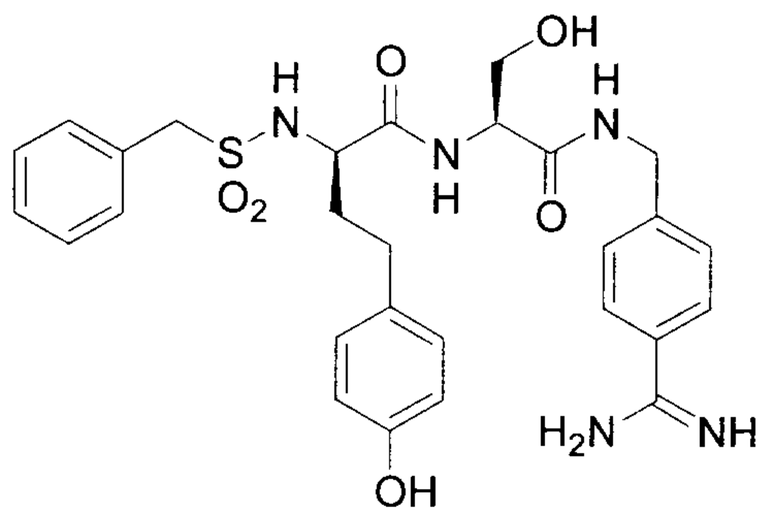
The crude product from 5b was dissolved in 50 ml of 90% acetic acid, and 20 mg of catalyst (10% Pd/C) were added. The mixture was hydrogenated with hydrogen under atmospheric pressure and at room temperature for 6 h. The catalyst was then filtered off, and the solvent was concentrated in vacuo. The remaining residue was dried in vacuo and, without further prepurification, purified by preparative reversed phase HPLC and lyophilized.

Yield: 37.5 mg (0.058 mmol) of lyophilized powder, HPLC: 32.37% B

MS: calculated 537.20 (monoisotopic), found 538.4 $[M+H]^+$

Example 6

Bzls-d-homoTyr-Ser-4Amba x TFA



6a) Bzls-d-homoTyr-Ser-Amb(4AcOxam)

50 mg (0.14 mmol) of product 5a and 58.4 mg (0.14 mmol) of H-Ser-Amb(4AcOxam) (= product 3e) were dissolved in 15 ml of DMF and, at 0°C, 74.4 mg (0.14 mmol) of PyBop and 74.6 µl (0.43 mmol) of DIEA were added. The mixture was stirred at 0°C for 20 min and at room temperature overnight. The solvent was then removed in vacuo, and

the residue was taken up in ethyl acetate, washed 1x with 5% $KHSO_4$ solution and 2x with NaCl-saturated water and dried over Na_2SO_4 (pale oil).

Yield: about 165 mg (crude product), HPLC: 38.49% B

6b) Bzls-d-homoTyr-Ser-4Amba x TFA

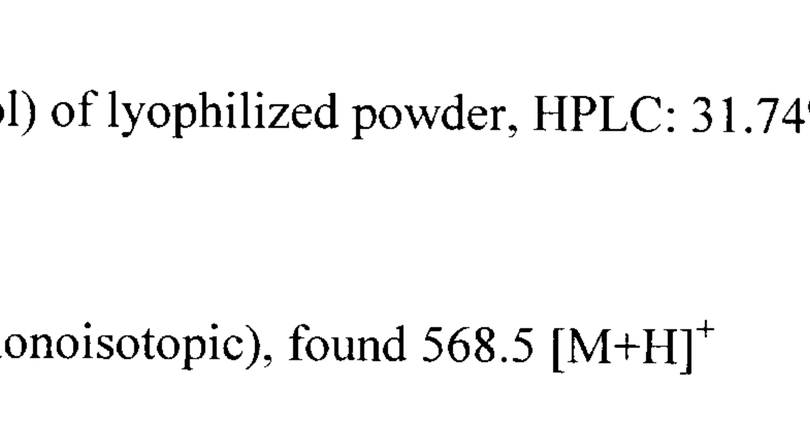
The crude product from 6a was dissolved in 50 ml of 90% acetic acid, and 20 mg of catalyst (10% Pd/C) were added. The mixture was hydrogenated with hydrogen under atmospheric pressure and at room temperature for 6 h. The catalyst was then filtered off, and the solvent was concentrated in vacuo. The remaining residue was dried in vacuo and, without further prepurification, purified by preparative reversed phase HPLC and lyophilized.

Yield: 38 mg (0.056 mmol) of lyophilized powder, HPLC: 31.74% B

MS: calculated 567.22 (monoisotopic), found 568.5 $[M+H]^+$

Example 7

4-PMs-dhomoPhe-Gly-4Amba x 2 TFA



7a) Boc-d-homoPhe-Gly-Amb(4AcOxam)

732 mg (2.62 mmol) of Boc-d-homoPhe-OH [Bachem] and 788 mg (2.62 mmol) of H-Gly-Amb(4AcOxam) (= product 1a) were dissolved in 50 ml of DMF and, at 0°C, 1.36 g (2.62 mmol) of PyBop and 1.37 ml (7.86 mmol) of DIEA were added. The mixture was stirred at 0°C for 20 min and at room temperature for 2 h. The solvent was then removed in vacuo, and the residue was taken up in ethyl acetate, washed 2x each with 5% $KHSO_4$, saturated $NaHCO_3$ solution and NaCl-saturated water and then dried over Na_2SO_4. The solvent was removed in vacuo (pale brown oil).

Yield: about 1.8 g (crude product), HPLC: 47.87% B

7b) H-d-homoPhe-Gly-Amb(4AcOxam) x HCl

600 mg of crude product from 7a were mixed with 15 ml of 1 N HCl in glacial acetic acid. The mixture was shaken occasionally. After 1 h, the solvent was concentrated somewhat and the product was precipitated by adding diethyl ether, filtered off with suction on a frit, washed with ether and dried in vacuo.

Yield: 1.02 g (2.2 mmol) of pale yellow solid, HPLC: 28.11% B

7c) 4-PMs-dhomoPhe-Gly-Amb(4AcOxam)

50 mg (0.11 mmol) of product 7b were suspended in 10 ml of DCM, and 20.5 µl (0.16 mmol) of chlorotrimethylsilane (= TMS-Cl) [Merck] and 49 µl (0.28 mmol) of DIEA were added, and the mixture was stirred at room temperature for 15 min. Then 41 mg (0.12 mmol) of 4-pyridylmethylsulfonyl chloride x triflate (= 4-PMs-Cl) [Array Biopharma, Boulder, CO, USA] and a further 20 µl (0.11 mmol) of DIEA were added, and stirring was continued at room temperature for 2 h. The solvent was then removed

in vacuo. The residue was employed directly, without further purification, for the next step in the synthesis.

7d) 4-PMs-dhomoPhe-Gly-4Amba x 2 TFA

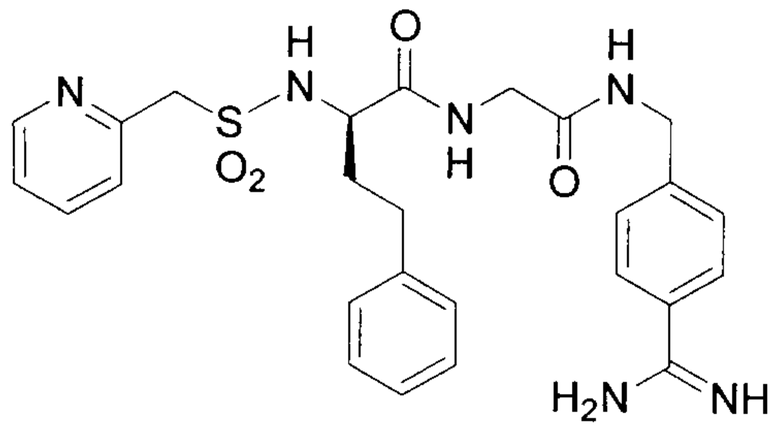
The crude product from 7c was dissolved in 50 ml of 90% acetic acid, and 20 mg of catalyst (10% Pd/C) were added. The mixture was hydrogenated with hydrogen under atmospheric pressure and at room temperature overnight. The catalyst was then filtered off, and the solvent was concentrated in vacuo. The remaining residue was dried in vacuo and, without further prepurification, purified by preparative reversed phase HPLC and lyophilized.

Yield: 30 mg (0.047 mmol) of lyophilized powder, HPLC: 26.01% B

MS: calculated 522.20 (monoisotopic), found 523.3 $[M+H]^+$

Example 8

2-PMs-d-homoPhe-Gly-4Amba x 2 TFA



8a) 2-PMs-dhomoPhe-OH

75 mg (0.42 mmol) of H-d-homoPhe-OH [Bachem] were suspended in 10 ml of DCM, and 116 µl (0.92 mmol) of chlorotrimethylsilane (= TMS-Cl) [Merck] and 160 µl (0.92 mmol) of DIEA were added, and the mixture was stirred under reflux at 60°C for 1 h and then cooled again to room temperature. Then 150 mg (0.44 mmol) of 2-pyridylmethylsulfonyl chloride x triflate (= 2-PMs-Cl) [Array Biopharma, Boulder, CO, USA] and a further 77 µl (0.44 mmol) of DIEA were added, and stirring was continued at room temperature overnight. The solvent was then removed. The residue was employed directly, without further purification, for the next step in the synthesis.

Yield: about 300 mg crude product, HPLC: 32.86% B

8b) 2-PMs-dhomoPhe-Gly-Amb(4AcOxam)

150 mg (about 0.2 mmol) of crude product 8a and 60.2 mg (0.2 mmol) of H-Gly-Amb(4AcOxam (= product 1a) were dissolved in 10 ml of DMF and, at 0°C, 104 mg (0.2 mmol) of PyBop and 104.5 µl (0.6 mmol) of DIEA were added. The mixture was stirred at 0°C for 20 min and at room temperature for a further 2 h. The solvent was then removed in vacuo, and the residue was taken up in ethyl acetate, washed 2x with saturated $NaHCO_3$ solution and 2x with NaCl-saturated water and dried over Na_2SO_4. The solvent was removed in vacuo (pale brown oil).

HPLC: 35.28% B

8c) 2-PMs-dhomoPhe-Gly-4Amba

The crude product from 8b was dissolved in 50 ml of 90% acetic acid, and 20 mg of catalyst (10% Pd/C) were added. The mixture was hydrogenated with hydrogen under

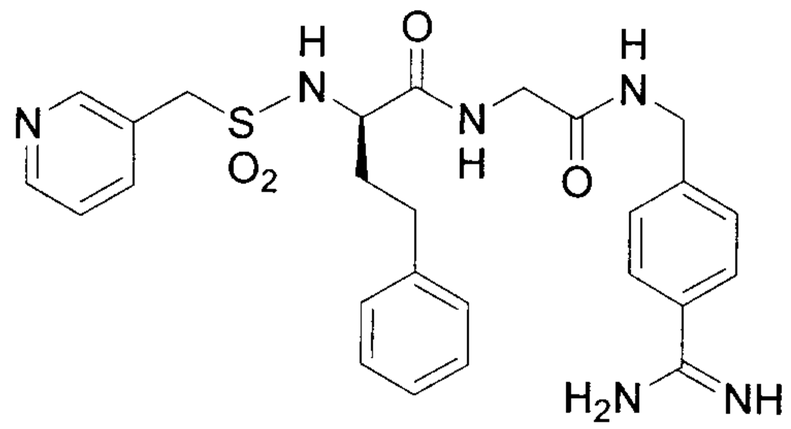
atmospheric pressure and at room temperature for 5 h. The catalyst was then filtered off, and the solvent was concentrated in vacuo. The remaining residue was dried in vacuo and, without further prepurification, purified by preparative reversed phase HPLC, and the product was lyophilized.

Yield: 69 mg (0.11 mmol) of lyophilized powder, HPLC: 31.18% B

MS: calculated 522.20 (monoisotopic), found 523.4 $[M+H]^+$

Example 9

3-PMs-dhomoPhe-Gly-4Amba x 2 TFA



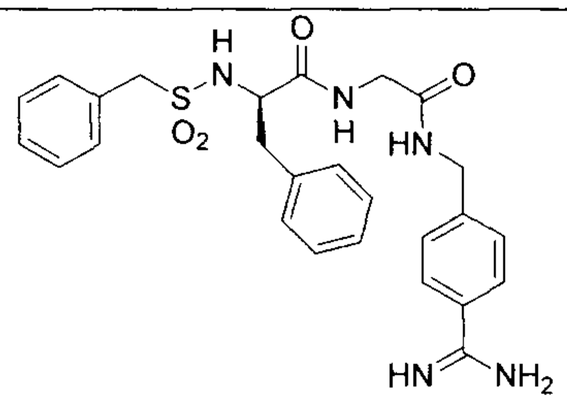
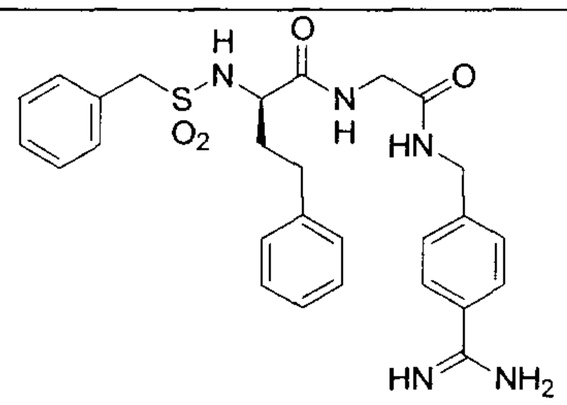
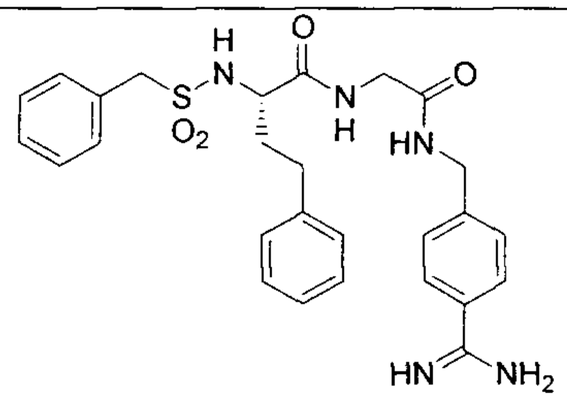
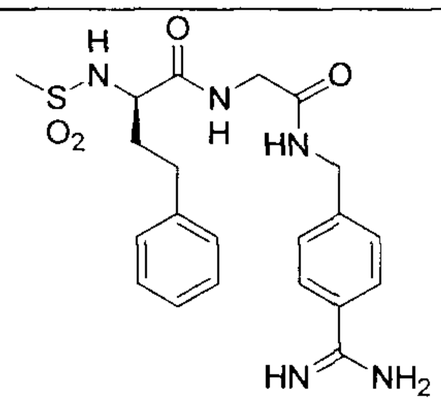
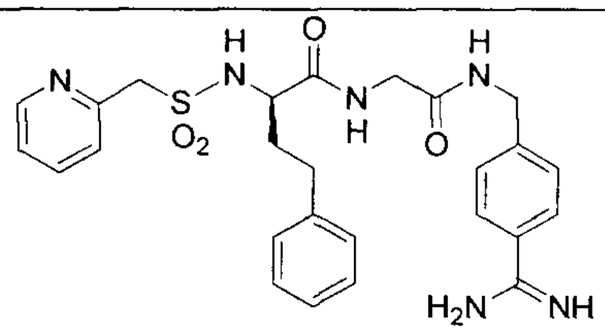
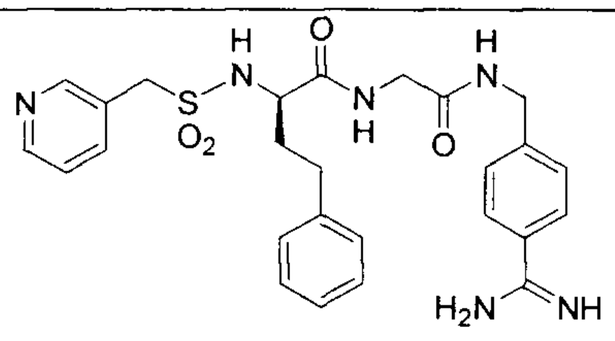
9) 3-PMs-dhomoPhe-Gly-4Amba

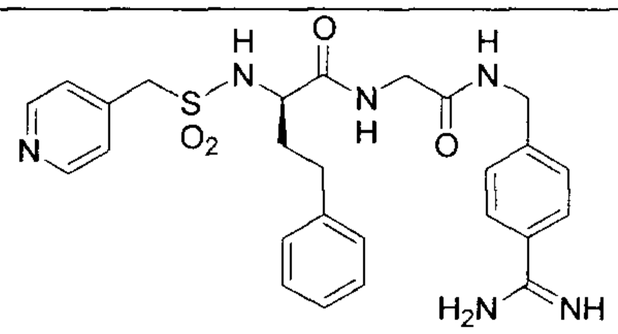
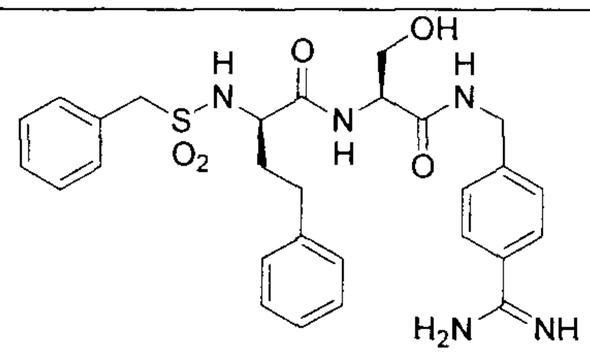
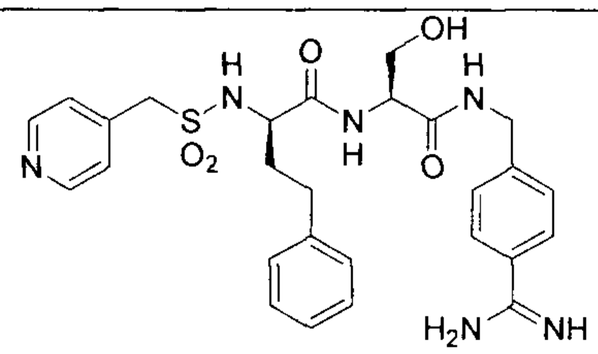
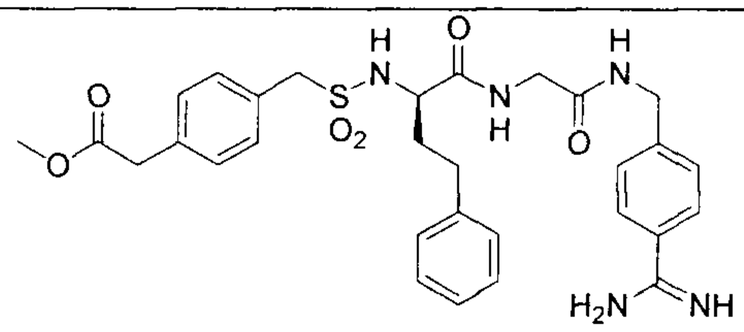
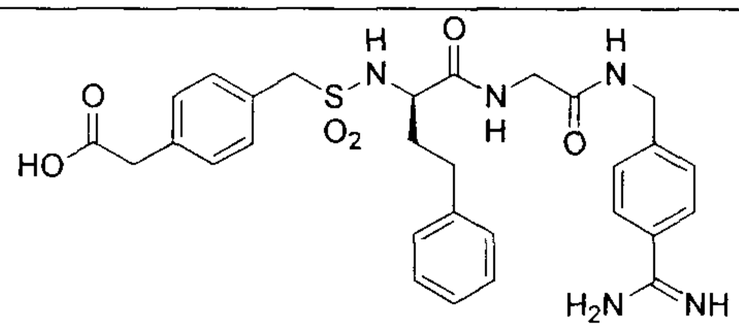
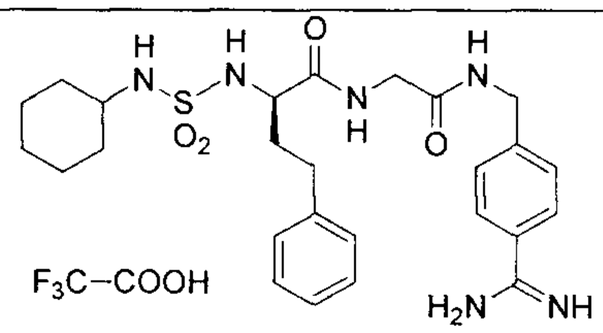
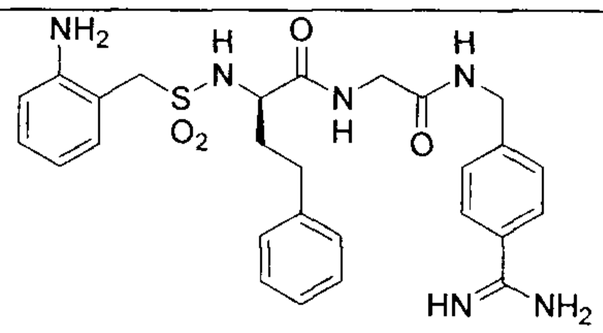
Example 9 was synthesized in analogy to example 8 but using 3-pyridylmethylsulfonyl chloride x triflate (= 3-PMs-Cl) [Array Biopharma, Boulder, CO, USA]. The final product was purified by preparative reversed phase HPLC and lyophilized.

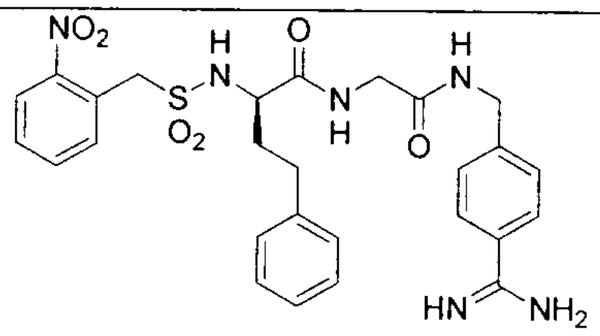
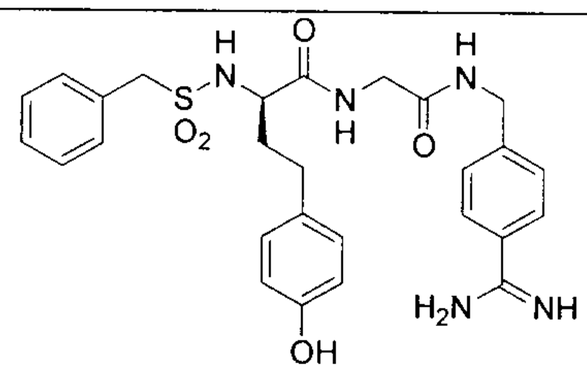
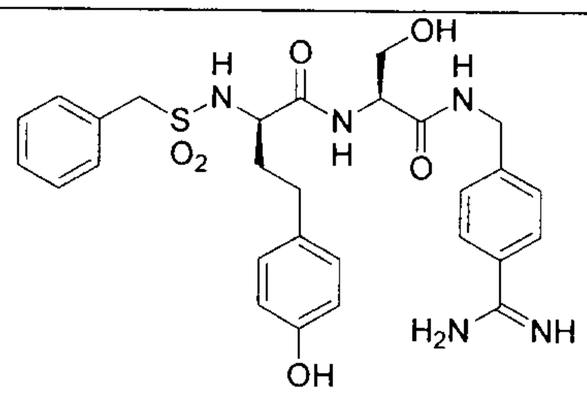
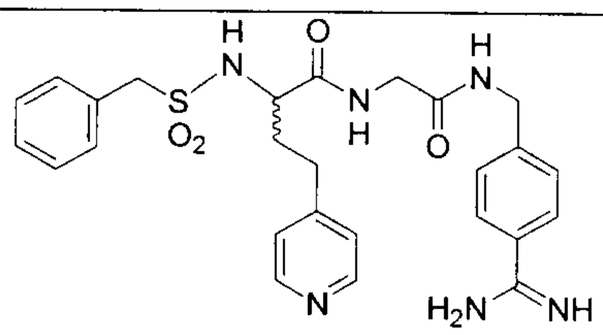
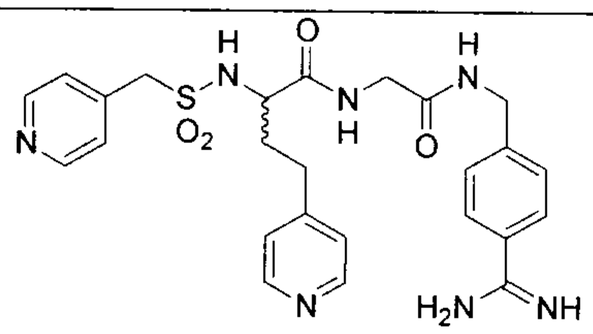
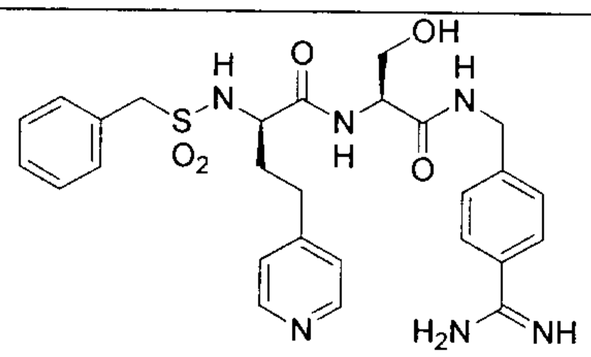
Yield: 62 mg (0.097 mmol) of lyophilized powder, HPLC: 29.08% B

MS: calculated 522.20 (monoisotopic), found 523.4 $[M+H]^+$

Table 1: Determination of the inhibitory constants for factor Xa and thrombin. Also indicated is the selectivity ratio SR (SR = $K_{i\ thrombin}/K_{i\ factor\ Xa}$).

No.	Structure	K_i (μM)		SR
		Factor Xa	Thrombin	
10		0.026	0.068	2.6
11		0.0065	0.047	7.2
12		0.36	11	31
13		1.1	1.3	1.2
8		0.051	4.9	96
9		0.062	5.9	95

14		0.08	3.6	45
15		0.04	0.6	15
7		0.46	3.3	7.2
16		0.038	1.8	47
17		0.054	14	259
18		0.11	5.4	49
19		0.0067	0.92	137

20		0.026	1.2	46
5		0.0027	1.5	556
6		0.019	1.4	74
1		0.0029	2	690
2		0.013	3.2	246
3a		0.0094	0.91	97
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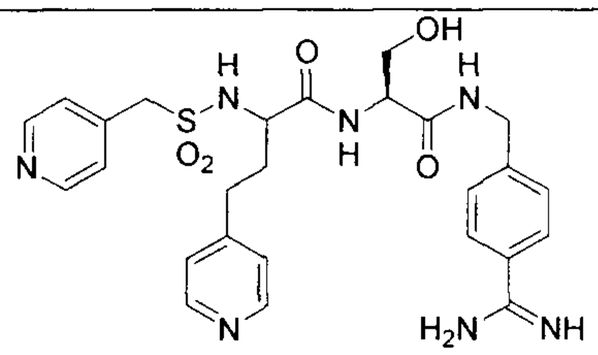
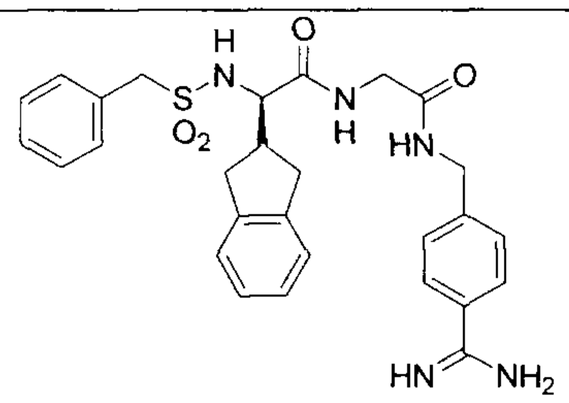
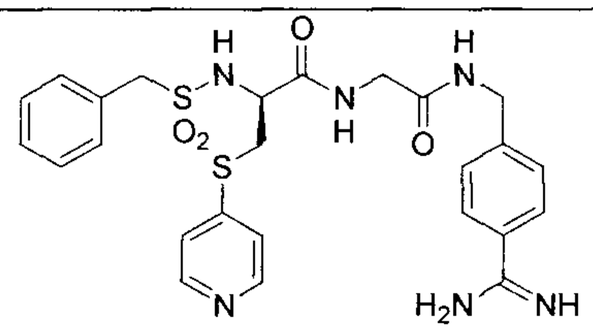
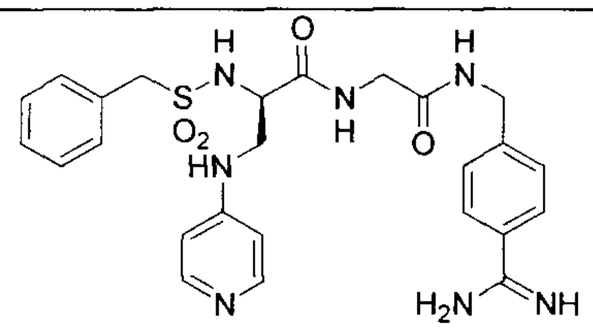
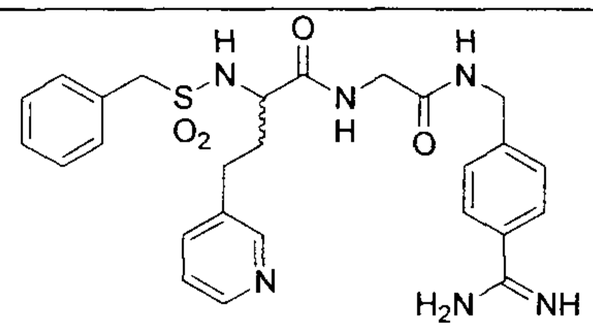
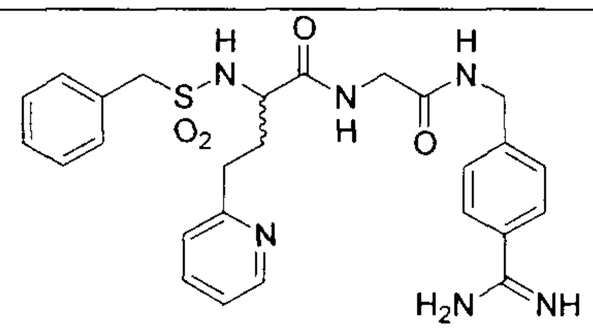
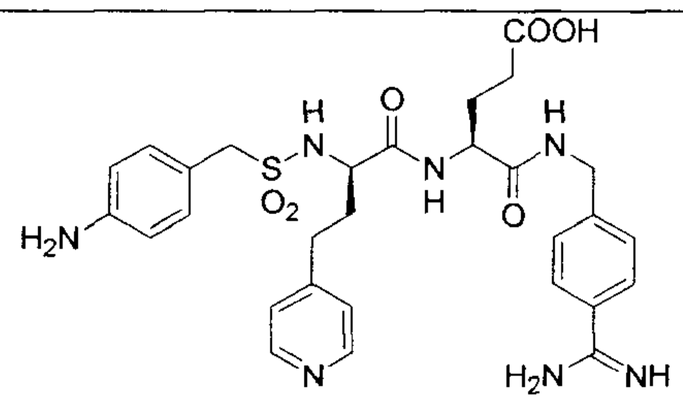
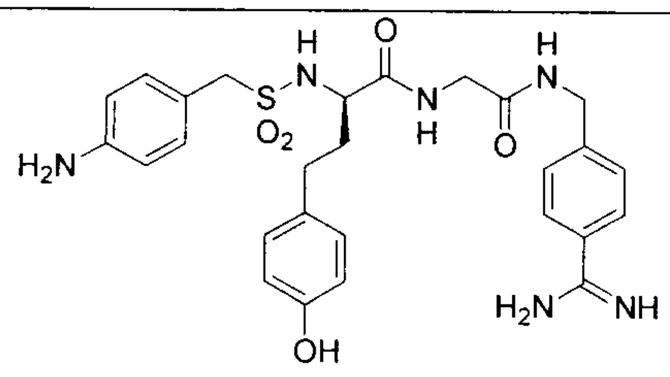
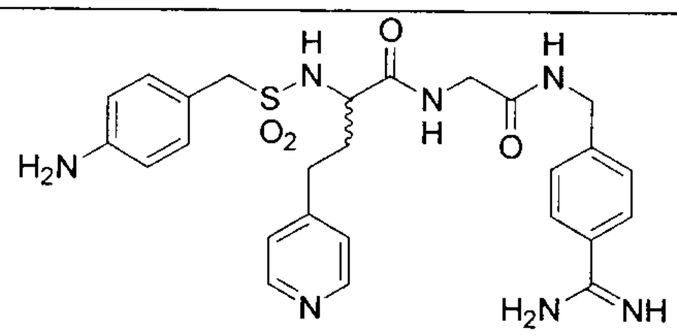
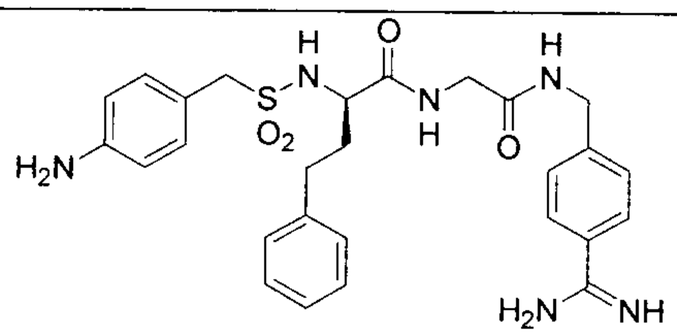
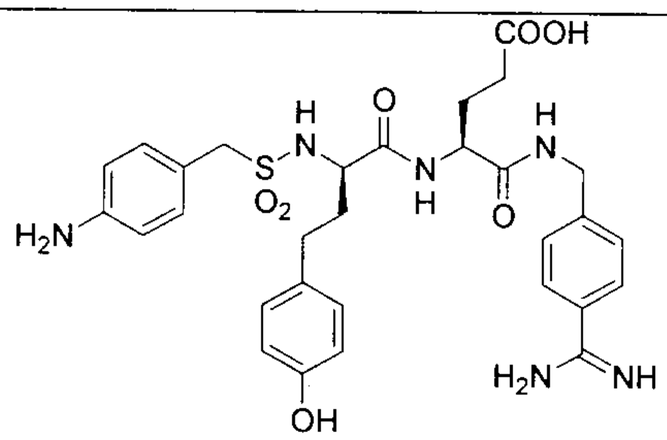
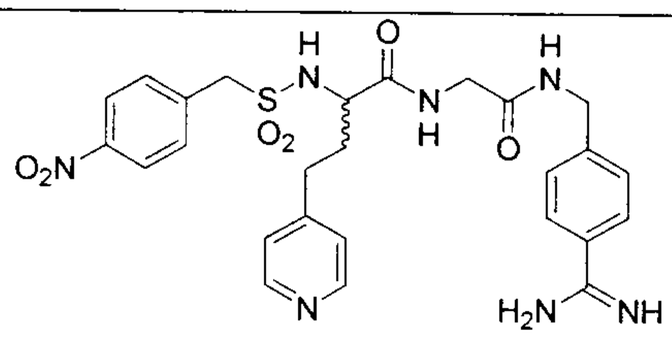
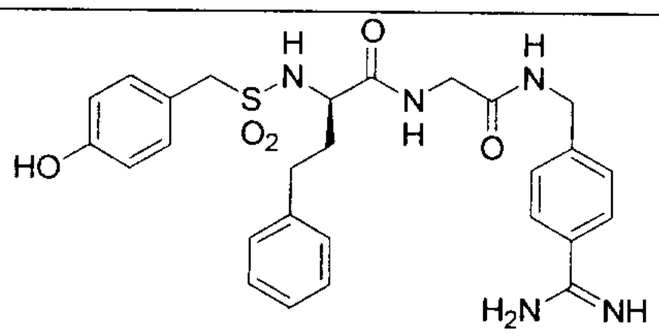
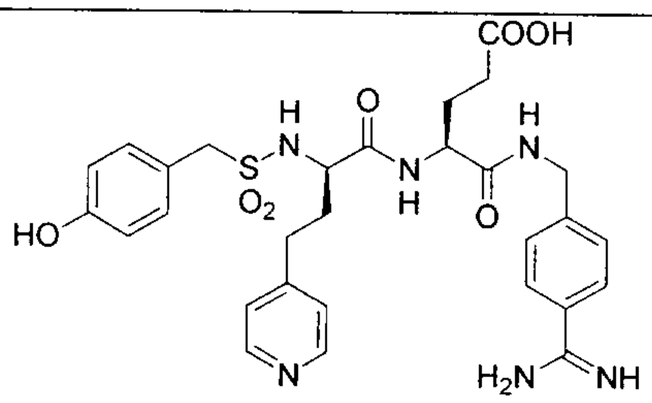
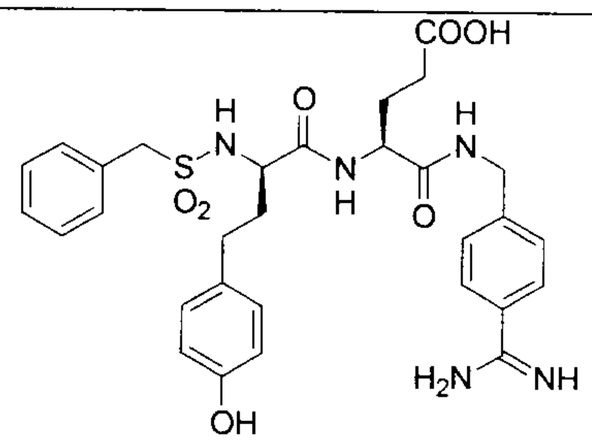
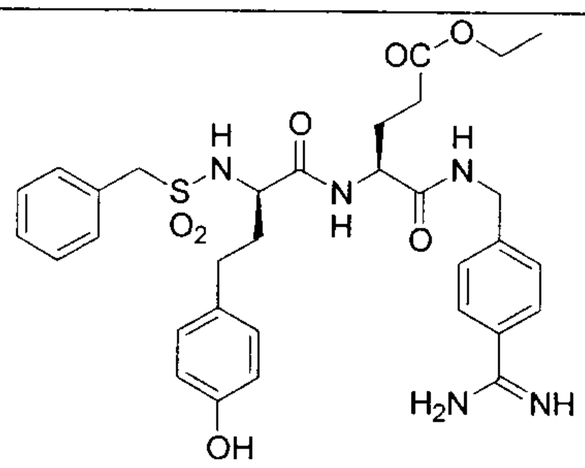
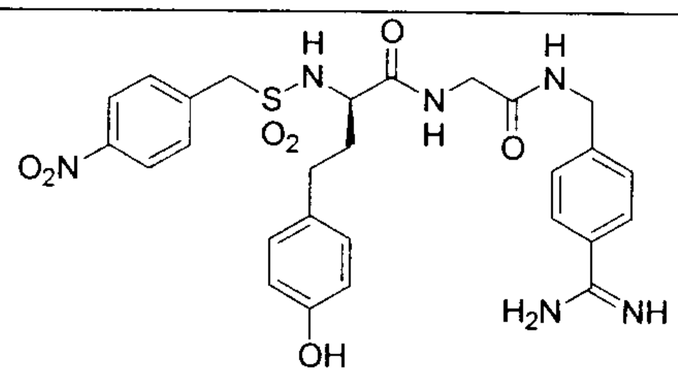
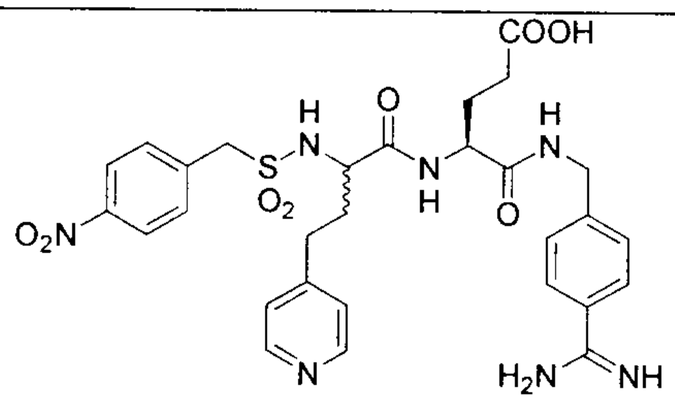
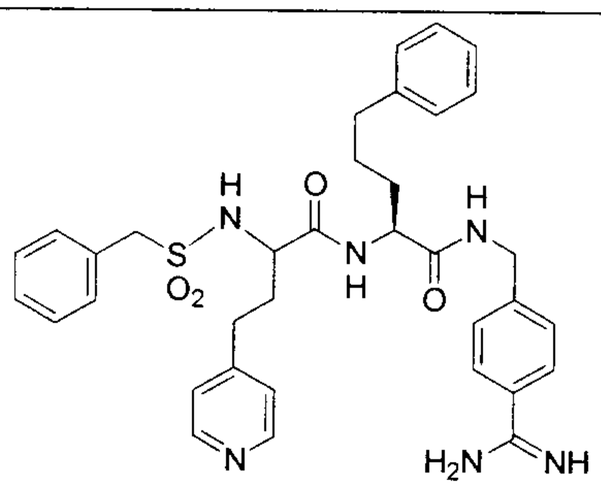
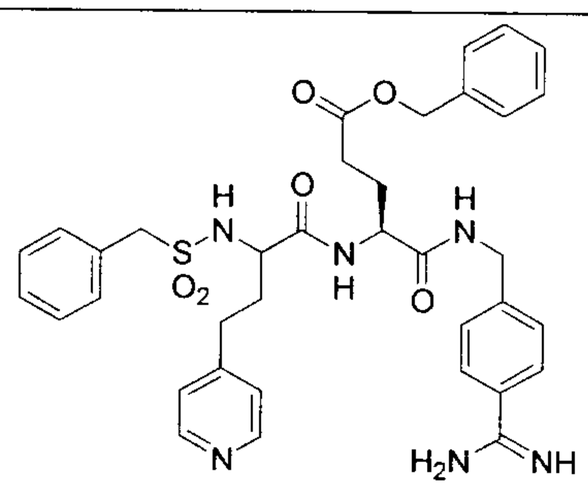
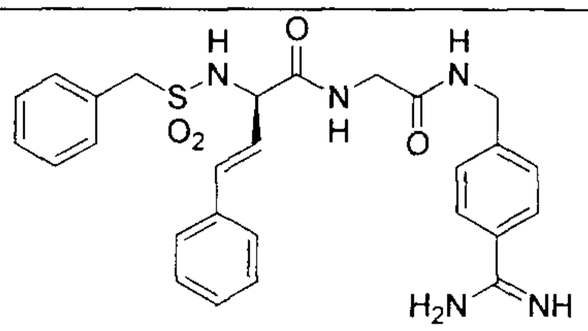
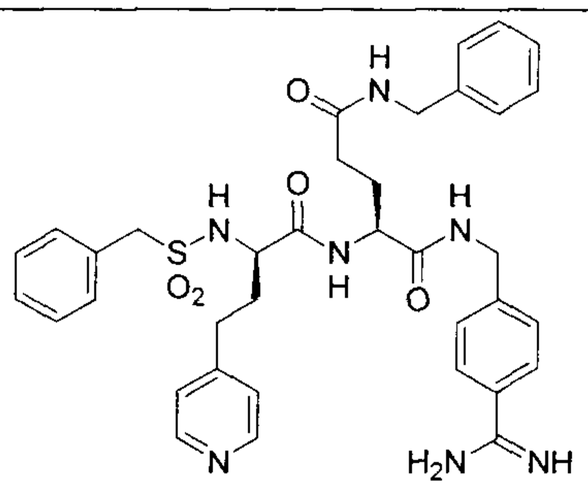
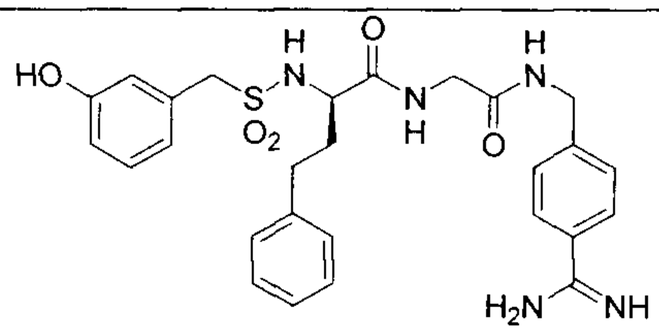
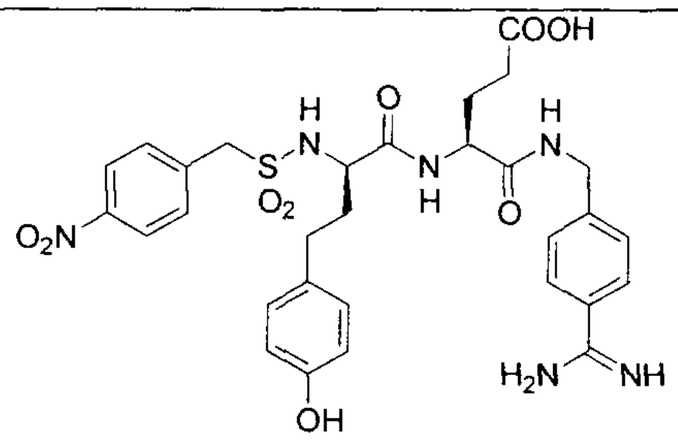
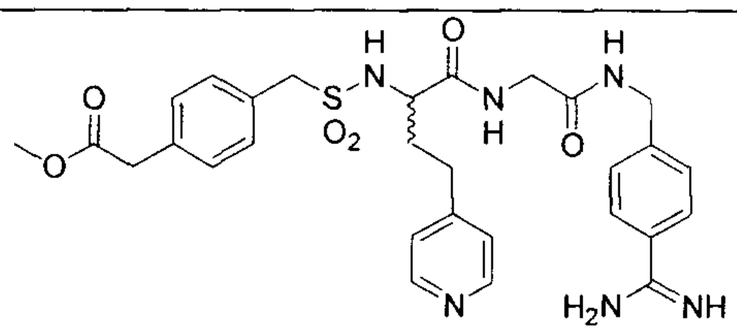
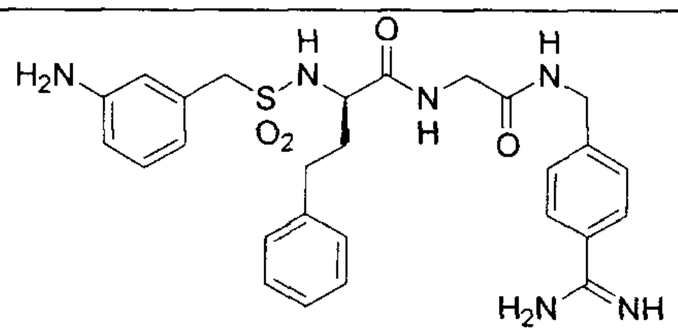
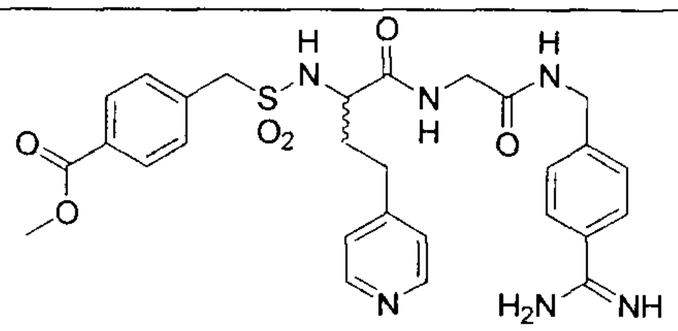
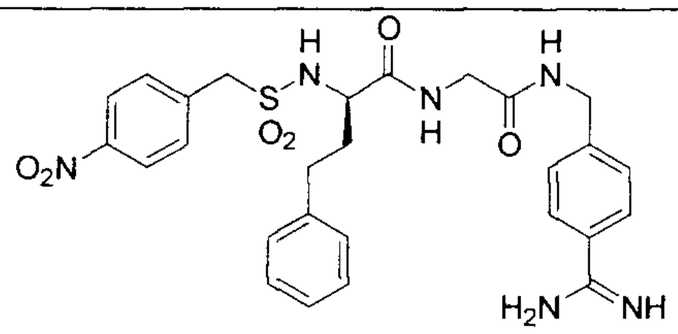
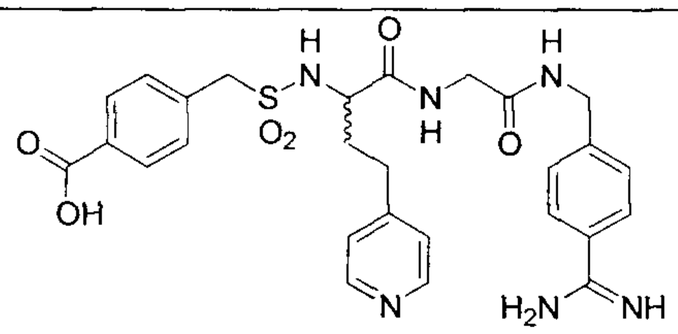
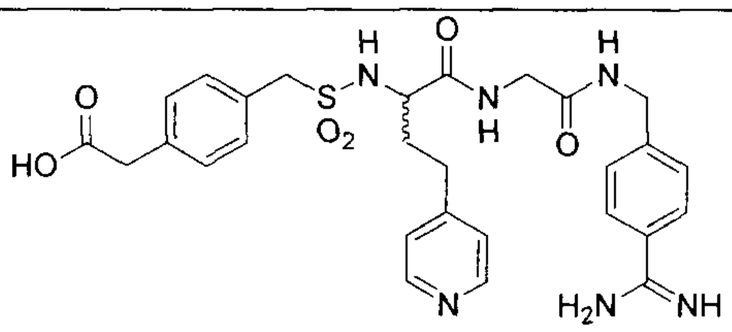
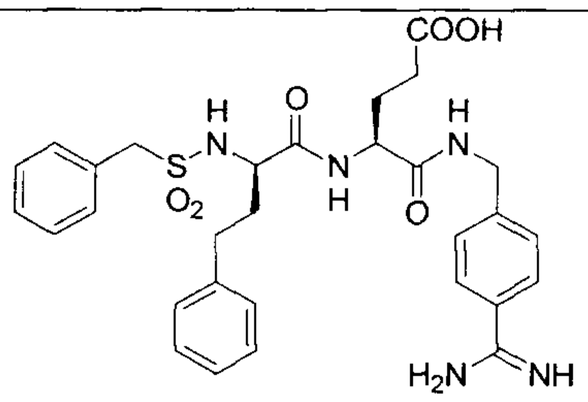
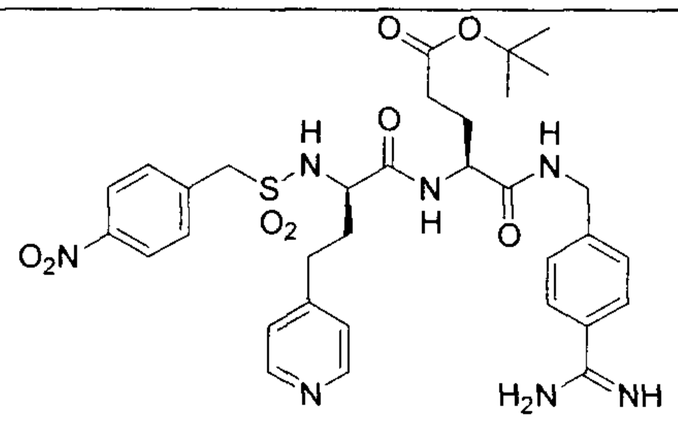
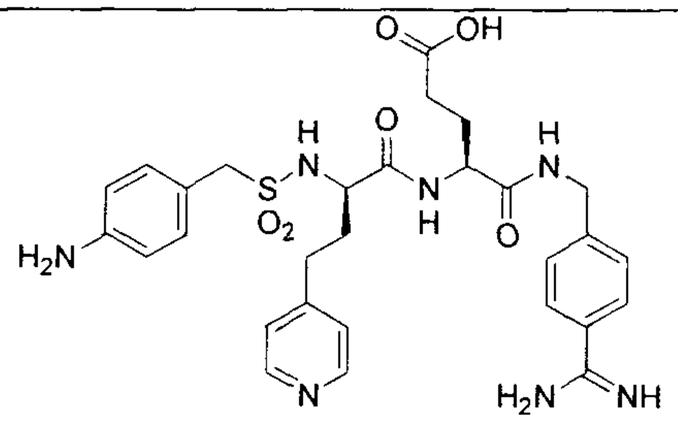
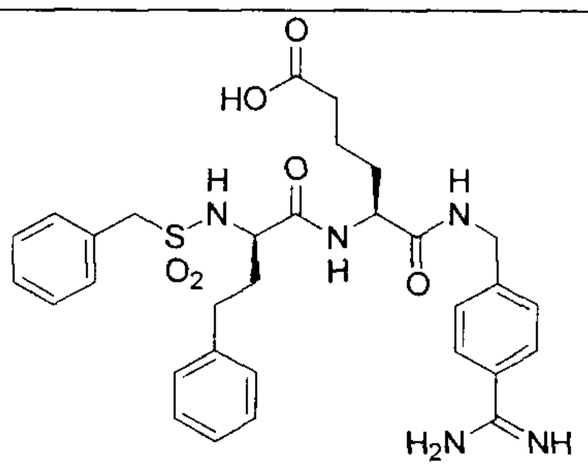
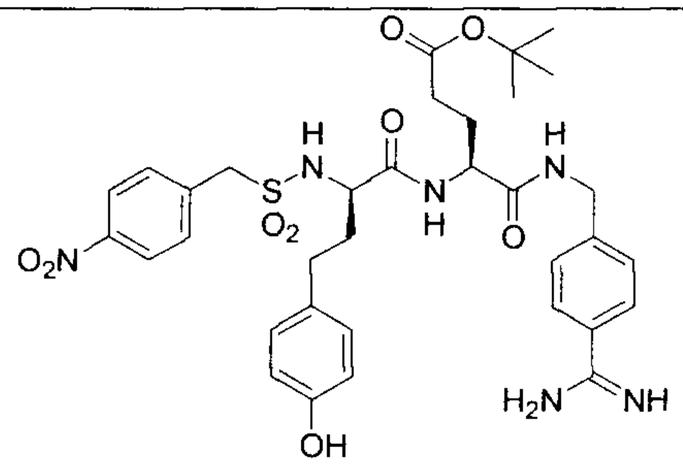
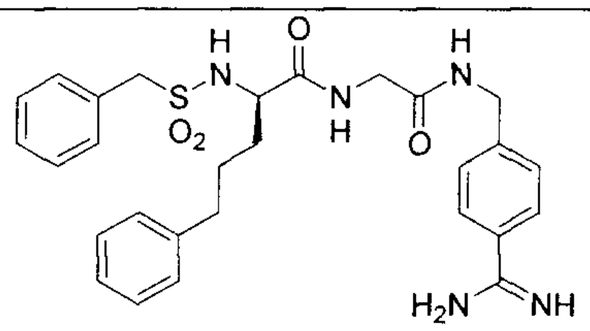
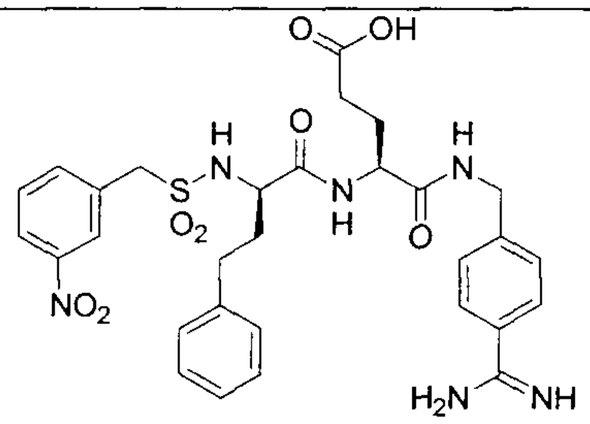
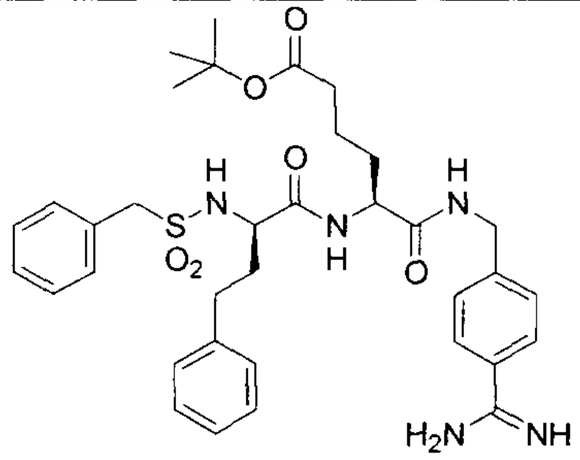
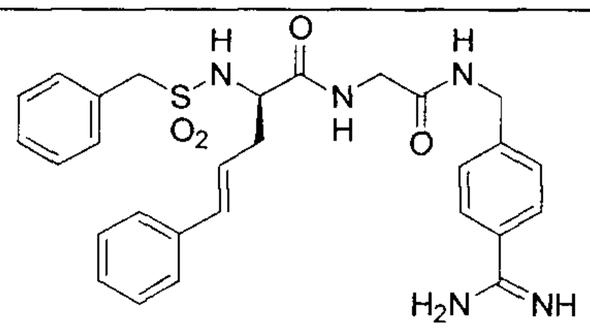
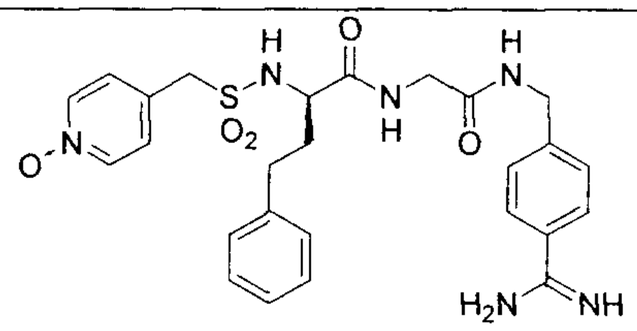
4		0.097	6.3	65
21		0.029	0.15	5.2
22		0.0027	0.7	259
23		0.022	2.8	127
24		0.005	2.0	400
25		0.0021	2.0	952
26		0.0017	25	14705

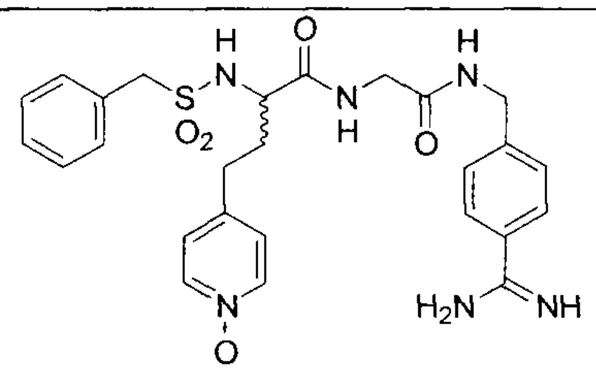
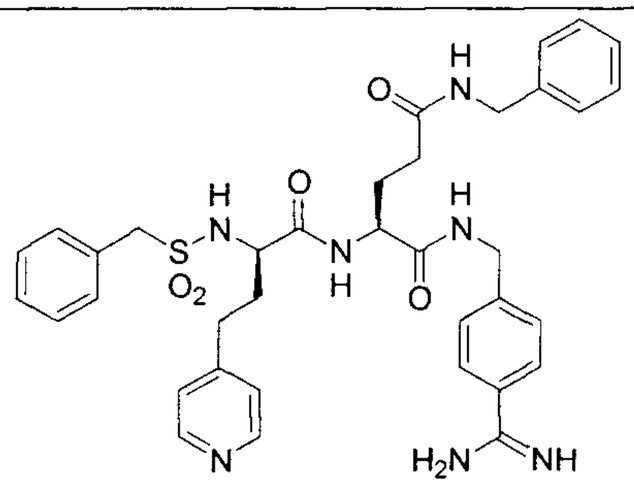
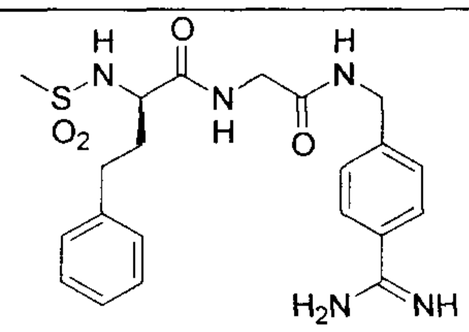
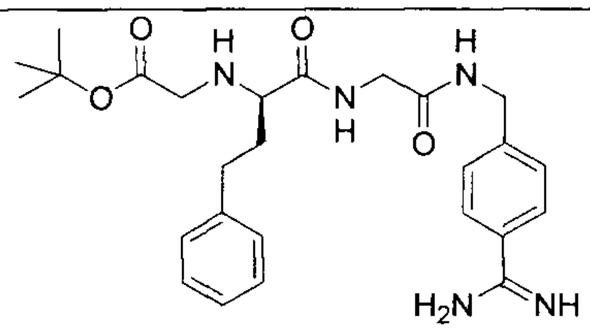
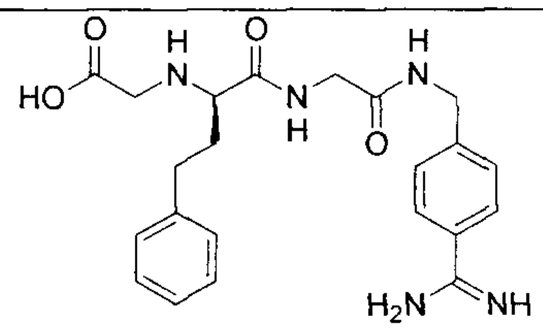
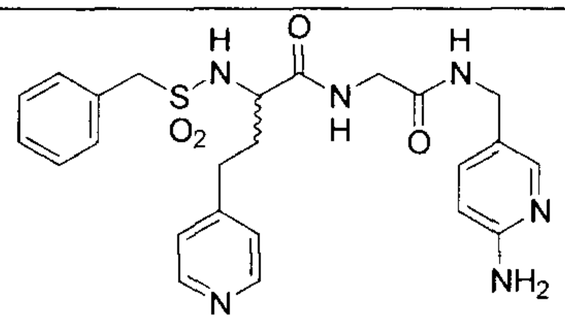
27		0.0019	0.56	295
28		0.0022	1	454
29		0.0026	0.26	100
30		0.0034	78	22940
31		0.0035	1.9	543
32		0.0036	0.38	105
33		0.0036	100	27778

34		0.0037	19	5135
35		0.005	1	200
36		0.0052	0.86	165
37		0.0056	35	6250
38		0.006	0.18	30
39		0.0064	0.17	26

40		0.0065	1.1	170
41		0.0068	1.7	250
42		0.0072	1.5	288
43		0.0075	15	2000
44		0.0082	3.8	463
45		0.0093	1.4	150
46		0.0098	7.6	775

47		0.01	0.71	71
48		0.01	n.b.*	-
49		0.013	38	2923
50		0.013	15	1153
51		0.016	1.4	87
52		0.016	84	5250
53		0.03	0.8	27

54		0.039	0.69	18
55		0.067	0.21	3
56		0.083	13	156
57		0.13	0.46	3.5
58		0.58	1.8	3.1
59		0.97	16	16

60		0.0048	3.5	730
61		0.0068	1.7	250
62		1.06	1.3	1.2
63		0.62	1.5	2.4
64		0.87	28	32
65		0.12	100	833

*n.b. = not determined

Determination of the inhibitory effect

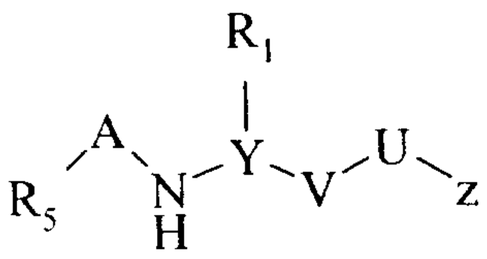
To determine the inhibitory effect, 200 µl of tris buffer (0.05 M, 0.154 M NaCl, 5% ethanol, pH 8.0; contains the inhibitor), 25 µl of substrate (Moc-D-Nle-Gly-Arg-pNA in H_2O; Pentapharm Ltd., Basle, Switzerland) and 50 µl of factor Xa (bovine, Diagnostic Reagents Ltd, Thame, GB) were incubated at 25°C. After 3 min, the reaction was stopped by adding 25 µl of acetic acid (50%), and the absorption at 405 nm was determined using a Microplate Reader (MR 5000, Dynatech, Denkendorf, Germany). The K_i values were found by the Dixon method (Biochem. J. 55, 170-171, 1953) by linear regression using a computer program. The K_i values are the average of at least three determinations. The thrombin inhibition was determined in analogy to a method described earlier (Stürzebecher et al., J. Med. Chem. 40, 3091-3099, 1997).

PCT/EP04/010225
Curacyte Chemistry GmbH

11 July 2005
C62418PC BÖ/KIN

New claims for the international preliminary examination

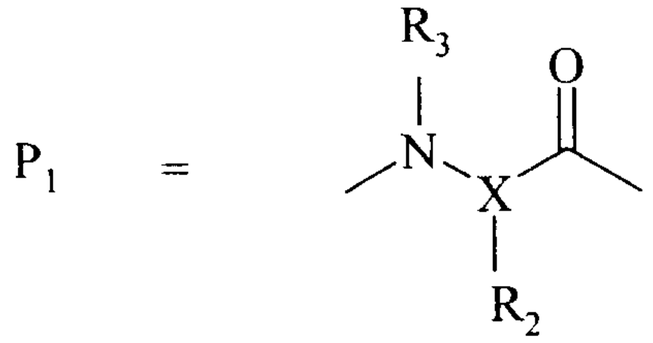
1. A compound of the general formula I



(I),

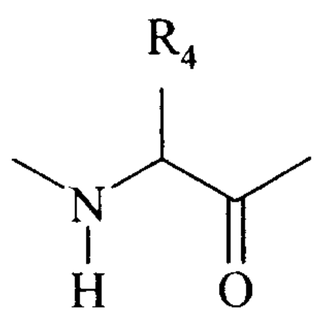
where

A is P_2—P_1 with



and

P_2 =



;

R_1 is an H or $-(CH_2)_aCOOR_6$ with a = 0, 1, 2, 3, 4 or 5, preferably with a = 0, 1 or 2, where R_6 is a branched or unbranched alkyl radical having, preferably, 1 to 6 C atoms, in particular 1 to 3 C atoms, especially ethyl, and R_1 is in particular an H;

R_2 is an H, $-CH_2-OR_7$ or $-CH_2-OCOOR_7$, where R_7 is an H or a branched or unbranched alkyl radical having 1-5, in particular 1-3 C atoms, or R_2 is a $-CH_2-CH_2-COOR_{7*}$, where R_{7*} is an H or a branched or unbranched alkyl radical having 1-5 C atoms, preferably ethyl;

R_3 is an H;

R_4 is $-(CH_2)_f-R_8$ with f = 0 or 2, preferably with f = 2, $-CH_2NHR_8$, $-(CH_2)_2NHR_8$ or $-CH=CH-R_8$, where R_8 is a mono- or polysubstituted or unsubstituted cycloalkyl, aryl or heteroaryl radical, where the cycloalkyl, aryl or heteroaryl radical preferably has 5 to 14, in particular 5 to 6 C atoms in the ring and, in the case of the heteroaryl radical, preferably 1 to 3 N as heteroatoms, or if R_4 is equal to $-(CH_2)_f-R_8$ with R_8 equal to a hydroxycycloalkyl radical with 4 to 14, in particular 6 to 10, especially 6 C atoms, then f is 1, and where P_2 in the structure A of the general formula I is in the D or L configuration, preferably in the D configuration;

R_5 is $-(CH_2)_i-COOR_9$ with i = 1, 2 or 3, preferably with i = 1, and R_9 is equal to a branched or unbranched alkyl radical having 1-5 C atoms, preferably ethyl, or R_5 is $-SO_2R_{9*}$, $-SO_2-NH-R_{9*}$, where R_{9*} is an H, a branched or unbranched alkyl having 1-10, preferably 1 to 6, in particular 1 to 4, especially 1 to 2 C atoms, a mono- or polysubstituted or unsubstituted aryl, heteroaryl, aralkyl, preferably benzyl, heteroaralkyl radical or a cyclohexylalkyl radical, preferably a cyclohexylmethyl radical, where the substituent may be an -OH, $-O-COOR_7$, $-CH_2-OCOOR_7$, with R_7 as defined above, $-NH_2$, $-NO_2$, $-COOR_{10}$, $-CH_2-COOR_{10}$ group or a Cl, F or Br atom, and where R_{10} is an H or an alkyl radical having 1 to 6, in particular having 1 to 4 C atoms, especially ethyl;

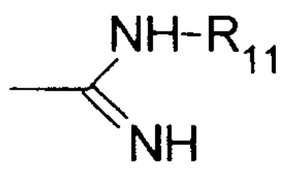
U is a phenyl or cyclohexyl radical;
is an aromatic or nonaromatic heterocyclic radical having 1-10, preferably 6 ring atoms having at least one N, S or O as heteroatom, in particular pyridine, piperidine or pyrimidine, or is a thienyl radical;

V is $(CH_2)_n$ with n = 0 or 1, preferably 0;

X is N or CH, preferably CH;

Y is N or CH, preferably CH;

Z occurs in position 2, 3 or 4, preferably in position 4, and is an aminomethyl, a guanidino function or an amidino group



where R_{11} is H, OH, NH_2, $-COR_{12}$ or $-COOR_{12}$, where R_{12} is a branched or unbranched alkyl radical having 1 to 8, preferably 1 to 6 C atoms or a mono- or polysubstituted or unsubstituted aryl or heteroaryl, aralkyl or heteroaralkyl radical, where the alkyl radical preferably has 1 to 16, in particular 1 to 8, especially 1 to 4 and particularly preferably 1 to 2 C atoms and the aryl or heteroaryl radical preferably has 4 to 14, in particular 6 to 10, especially 6 C atoms and preferably 1 to 3 N as heteroatoms;

or a compound of the general formula I in the form of a prodrug or in the form of its salt.

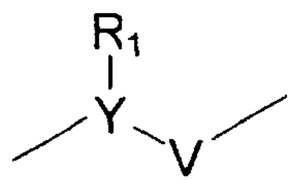
2. The compound as claimed in claim 1, where U is substituted at 1, 2 or 3 positions by a halogen, in particular fluorine or chlorine, or a methyl, ethyl, propyl, methoxy, ethoxy, or propoxy radical.

3. The compound as claimed in claim 1 or 2, where at least one carboxyl group is in protected form as ester, preferably as ethyl ester.

4. The compound as claimed in at least one of claims 1 to 3 in the form of a prodrug in which one or more carboxyl groups are present in the form of their alkyl esters

with a branched or unbranched alkyl having 1-5 C atoms, preferably ethyl, and/or in which one or more hydroxyl groups are in the form of carbonates in which the terminal radical is equal to R_7 as defined above, and/or in which the amidino- or guanidinobenzylamine residue is in the form of hydroxyamidine or hydroxyguanidine or of alkyloxycarbonyl derivative.

5. The compound as claimed in at least one of claims 1 to 4, characterized in that the structural element



of the formula I is a $-CH_2-$ or -NH- group, preferably a $-CH_2-$ group.

6. The compound as claimed in at least one of claims 1 to 5, characterized in that

R_1 is an H;

R_2 is an H, $-CH_2-CH_2-COOH$, $-CH_2-CH_2-COOCH_2CH_3$ or $-CH_2OH$;

R_3 is an H;

R_4 is a $-(CH_2)_2-R_8$, $-CH_2NHR_8$, $-(CH_2)_2NHR_8$ or a $-CH_2$-4-hydroxycyclohexyl radical, where R_8 is a mono- or polysubstituted or unsubstituted cycloalkyl, aryl or heteroaryl radical, where the cycloalkyl, aryl or heteroaryl radical has 5 or 6 C atoms and, in the case of a heteroaryl radical, 1 or 2 N as heteroatoms, and R_8 is preferably a phenyl, hydroxyphenyl, pyridyl or aminopyridyl radical;

R_5 is a methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, butylsulfonyl, n-butylsulfonyl, benzylsulfonyl, aminobenzylsulfonyl, hydroxybenzylsulfonyl, chlorobenzylsulfonyl, fluorobenzylsulfonyl, carboxy-benzylsulfonyl, ethyloxycarbonylbenzylsulfonyl, carboxymethylbenzyl-sulfonyl, ethyloxycarbonylmethylbenzylsulfonyl, pyridylmethylsulfonyl, N-(oxide)-pyridylmethylsulfonyl, $-CH_2-COOH$ or a $-CH_2COOCH_2CH_3$ radical;

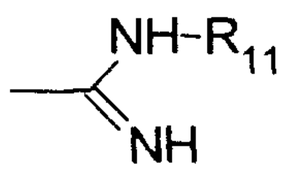
U is a phenyl radical;

V is $(CH_2)_n$ with n = 0;

X is CH;

Y is CH;

Z is present in position 4 and is an amidino group

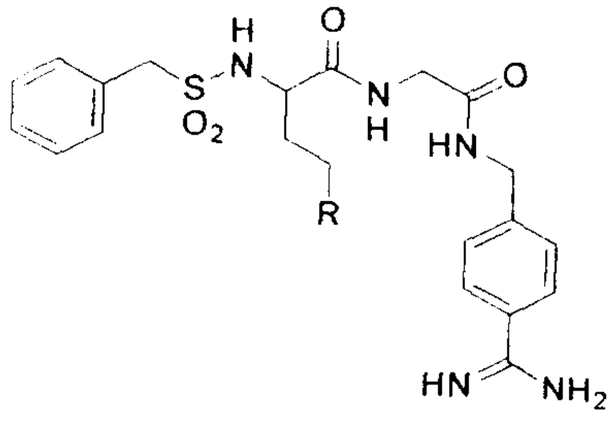


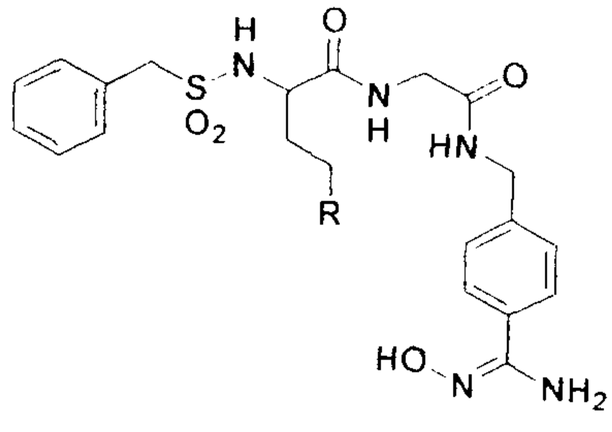
where R_{11} is H, OH or -$COOR_{12}$ with R_{12} a branched or unbranched alkyl radical having 2, 4 or 6 C atoms.

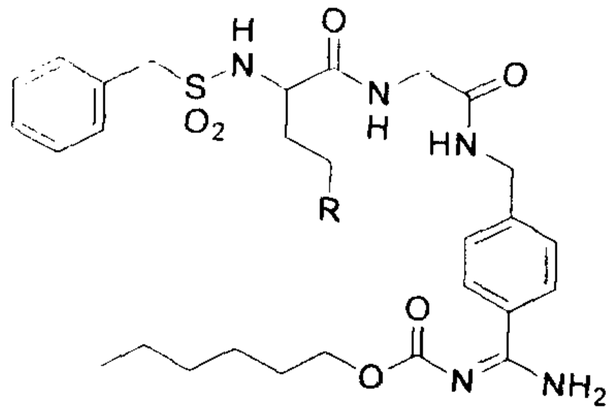
7. The compound as claimed in at least one of claims 1 to 6, characterized in that R_4 is a -CH_2-CH_2-R_8 radical, where R_8 is an aryl or heteroaryl radical having 4-6 ring atoms, which has 1 or 2 heteroatoms, preferably N, and may be substituted by one or more –NH_2 and/or –OH groups, and preferably P_2 in the structure A of the general formula I is derived from a homophenylalanine, homotyrosine, indanylglycine or 4-pyridylhomoalanine, and the P_2 amino acid is in particular in the D configuration.

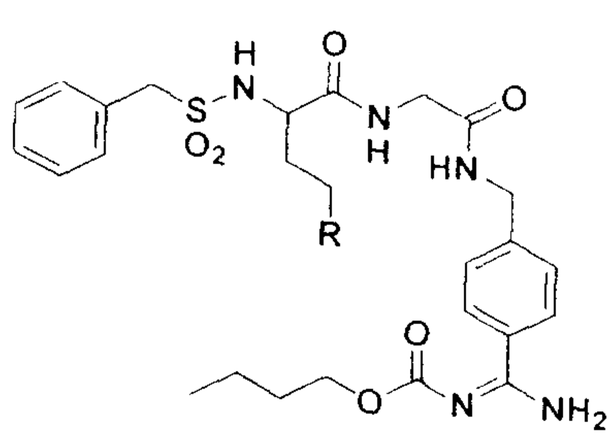
8. The compound as claimed in at least one of claims 1 to 7, characterized in that the substituent is -OH, -NH_2, -NO_2, -COOH, -$COOCH_2CH_3$, a halogen, preferably a fluorine, chlorine or bromine, in particular fluorine or chlorine.

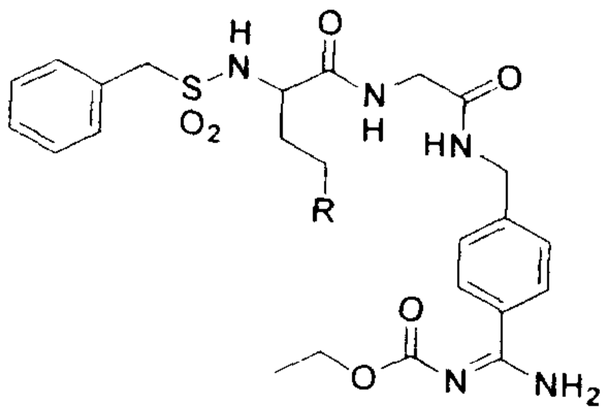
9. The compound as claimed in at least one of claims 1 to 8, characterized in that the compound is selected from the following structures:

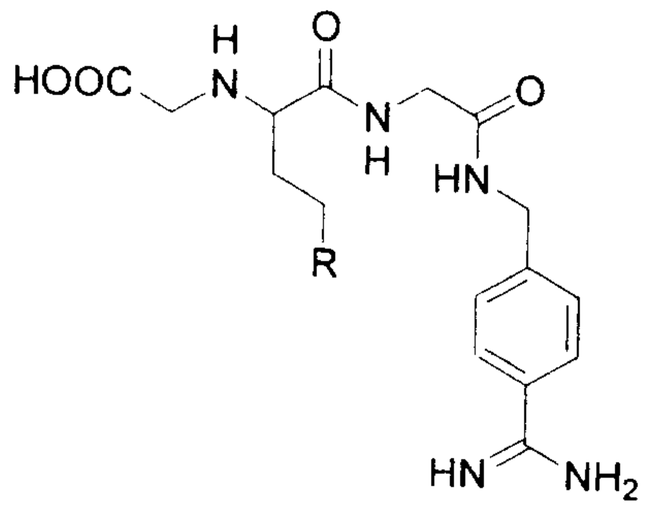


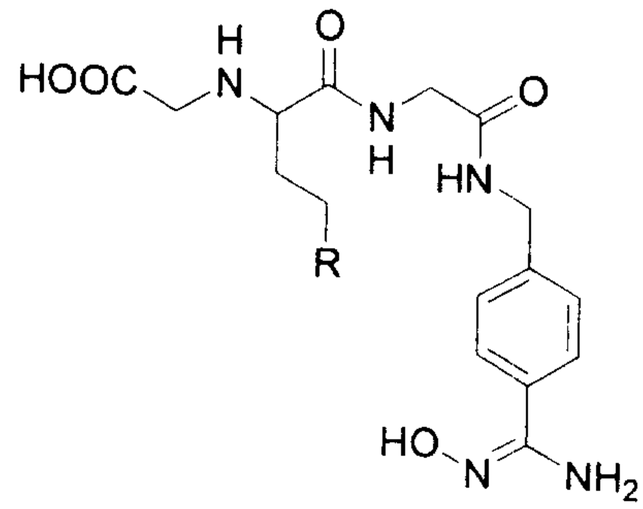


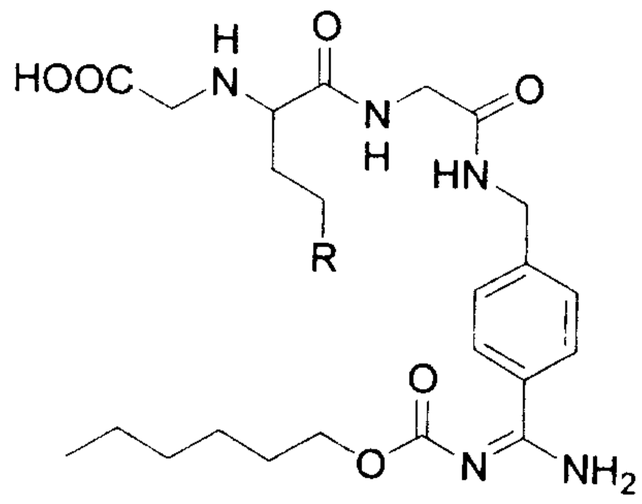


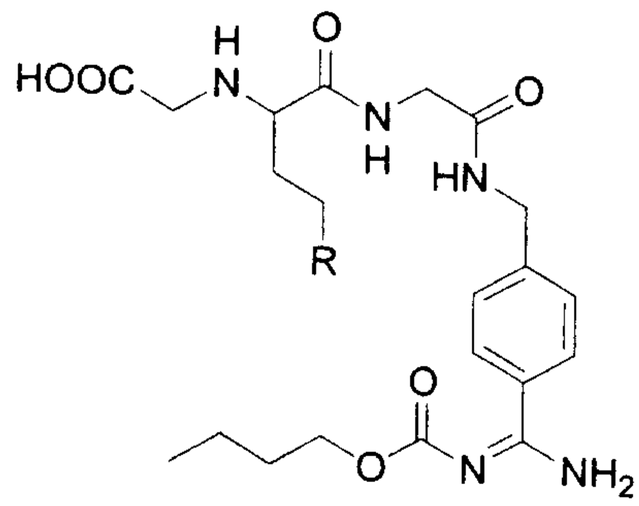


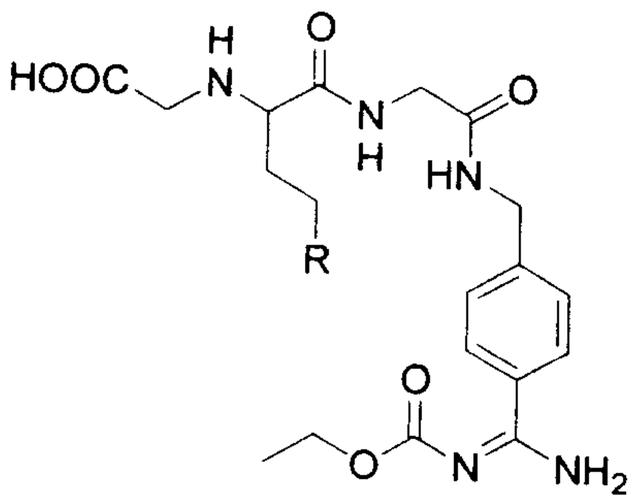


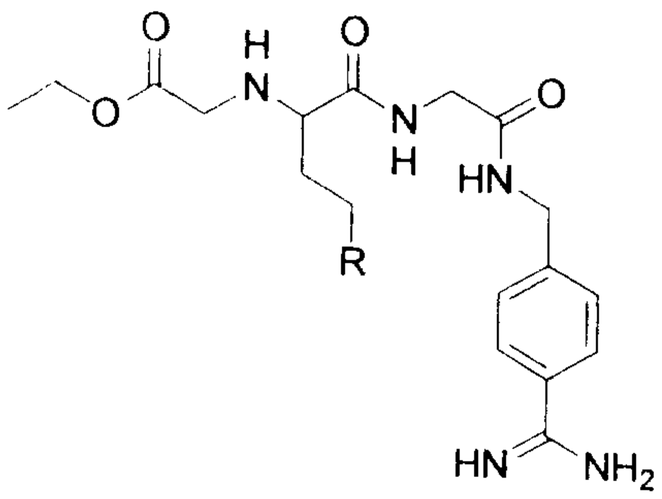


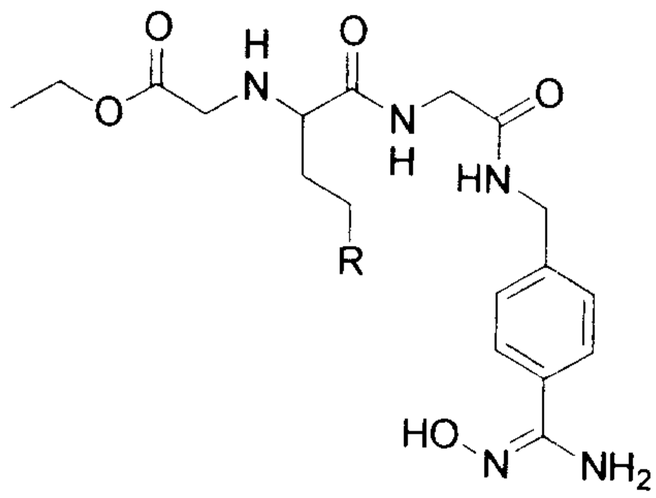


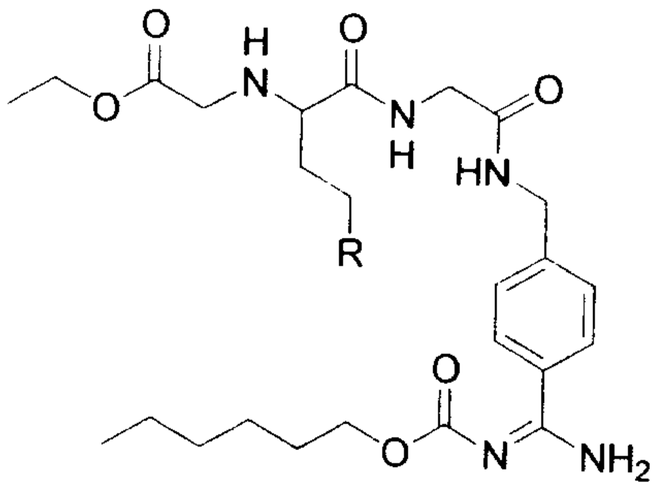


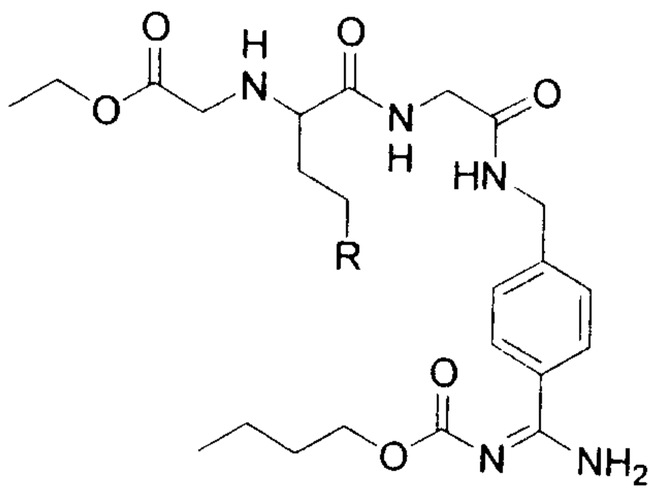


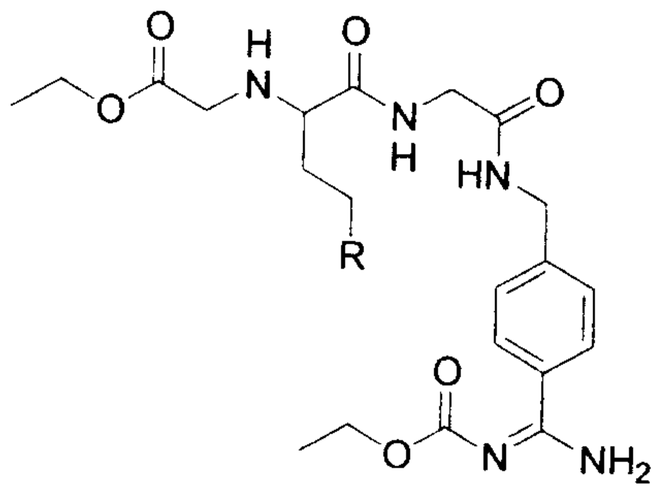


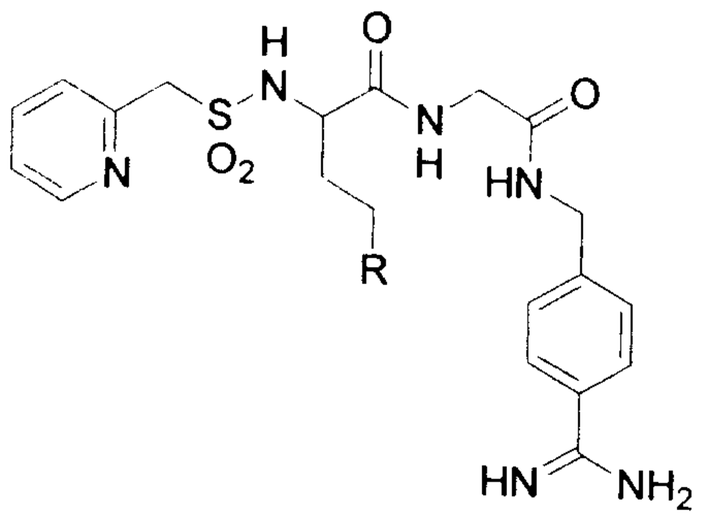


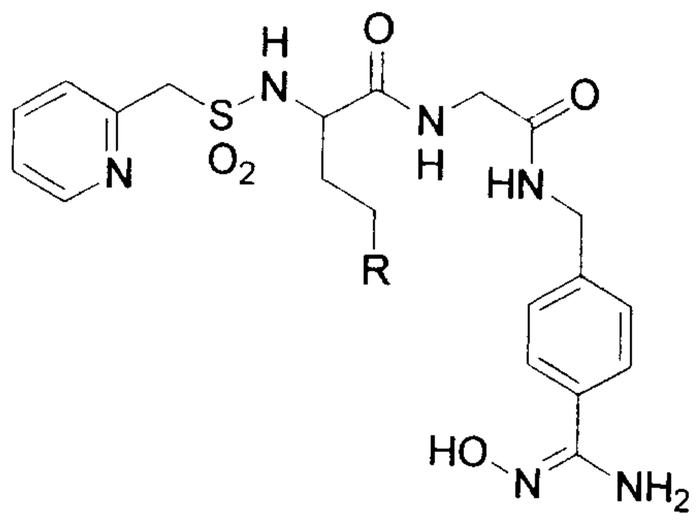


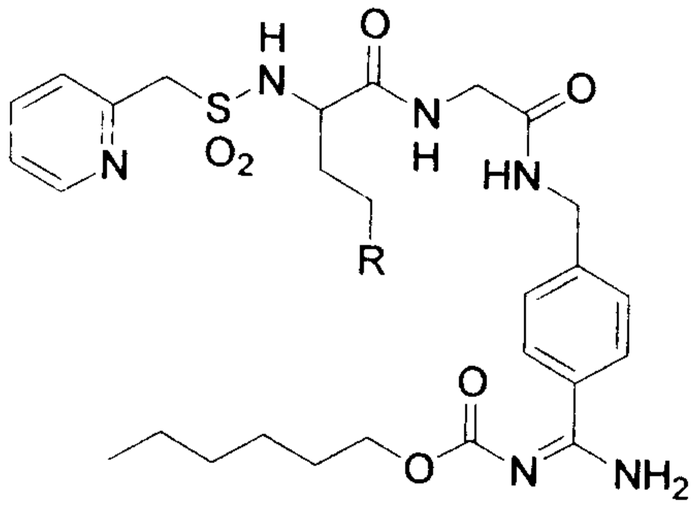


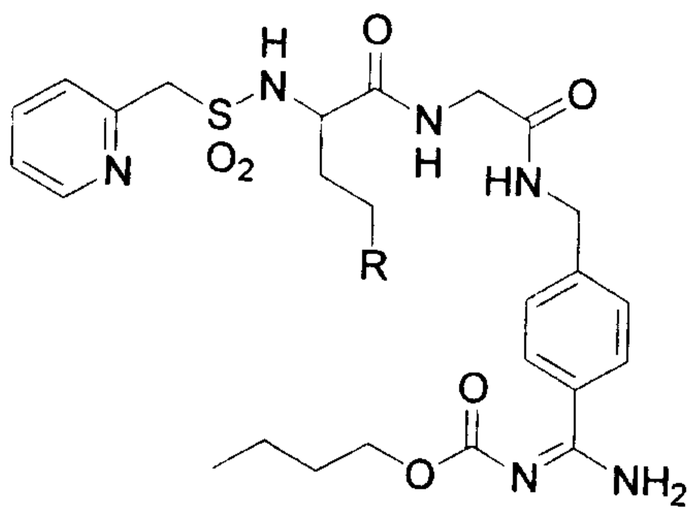


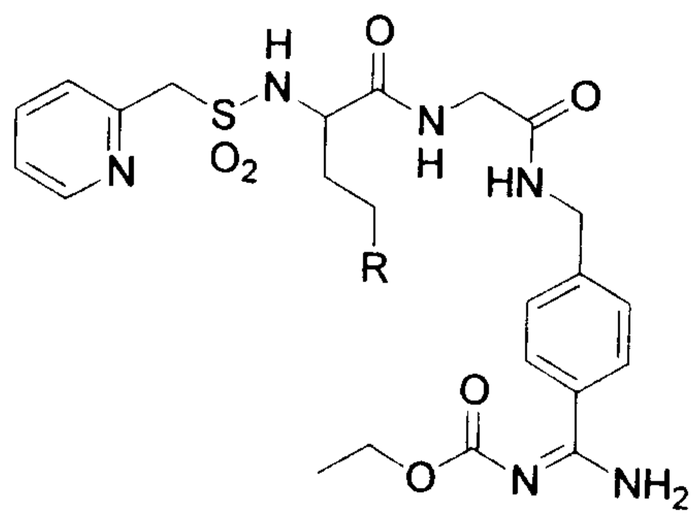


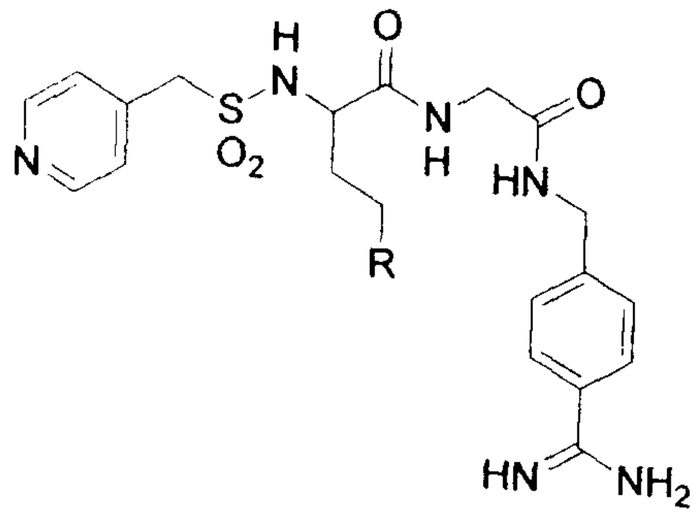


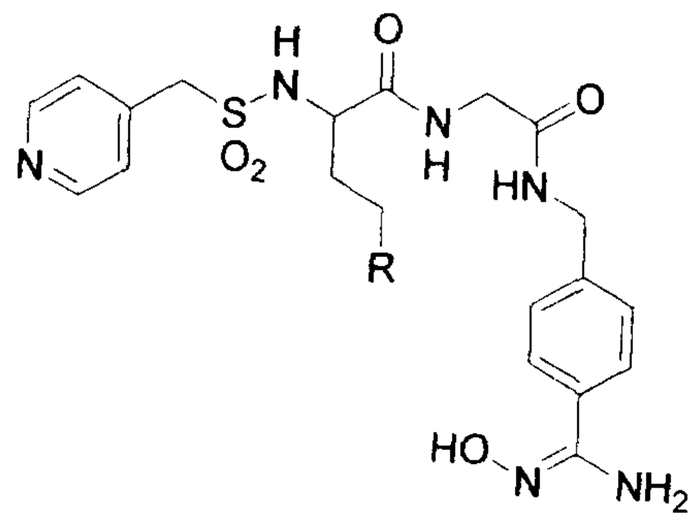


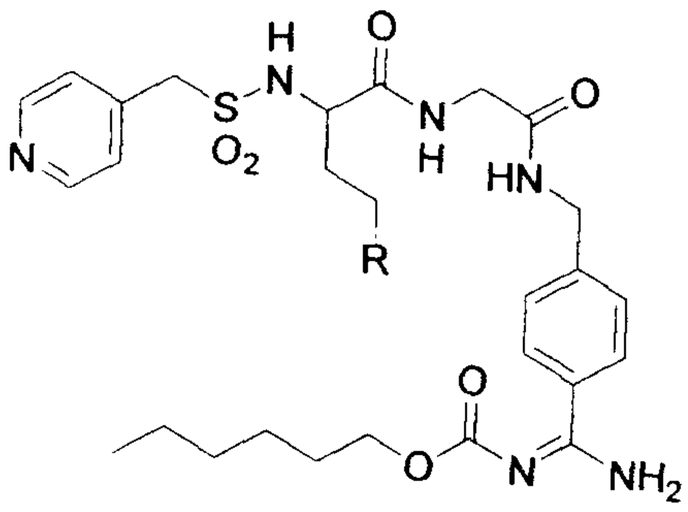


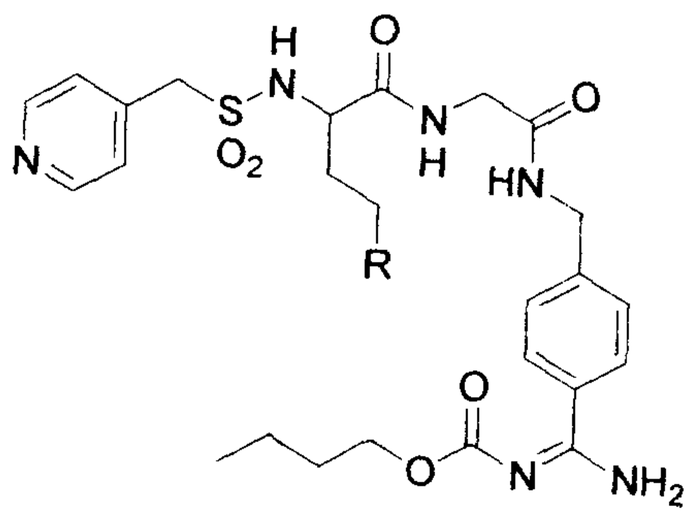


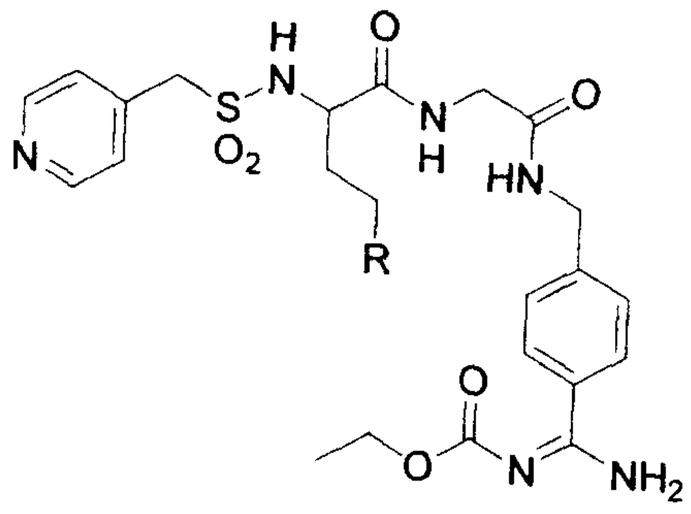


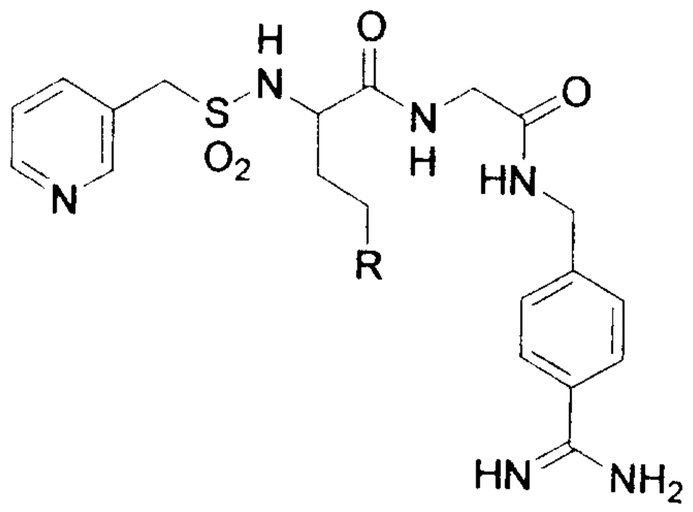


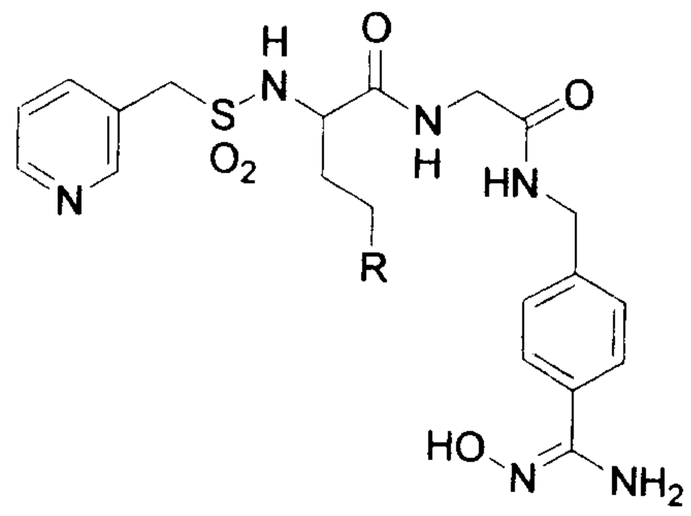


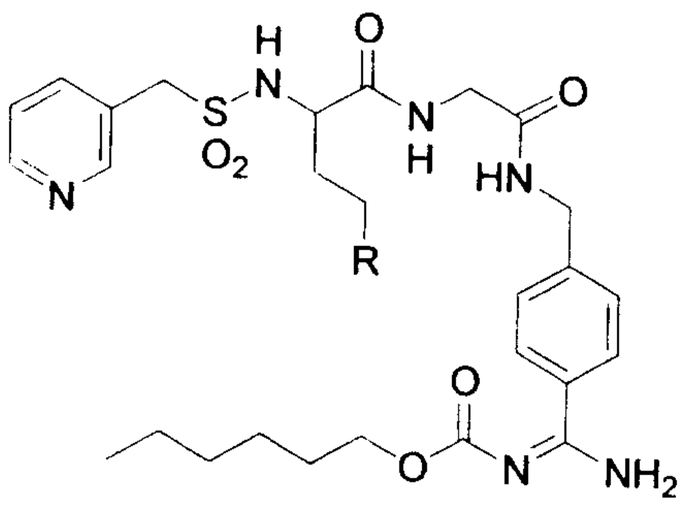


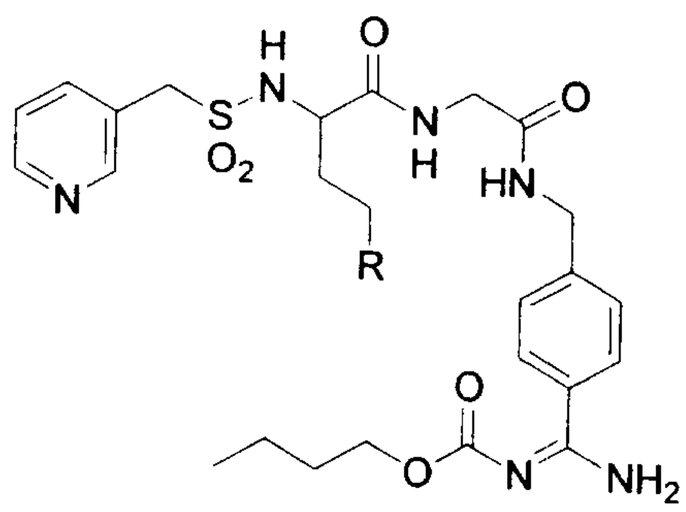


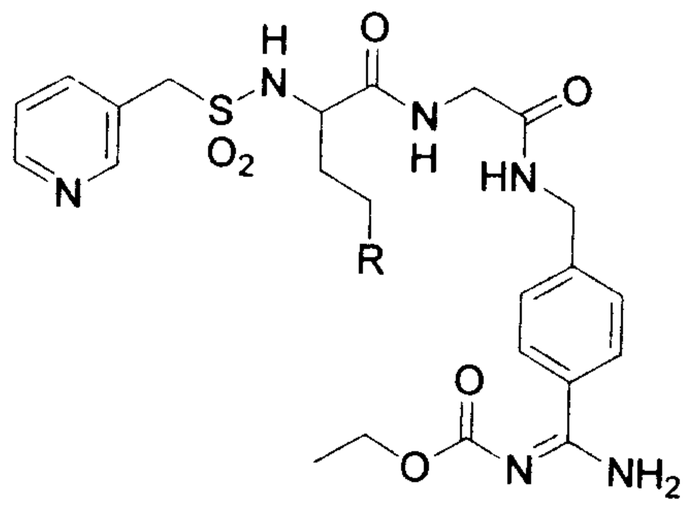


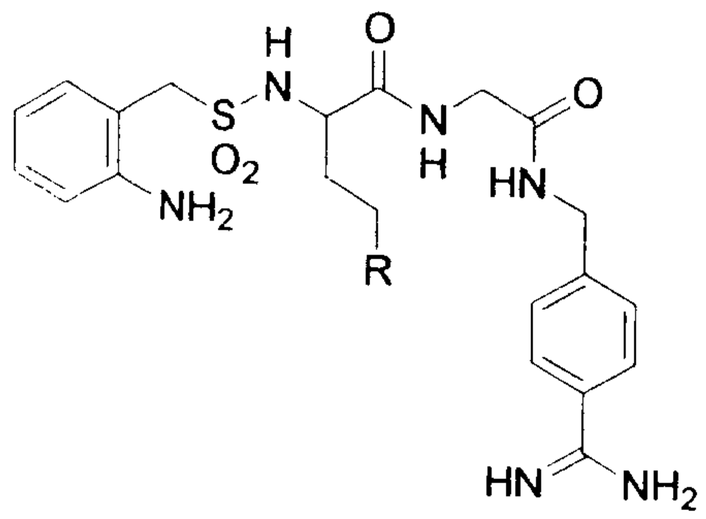


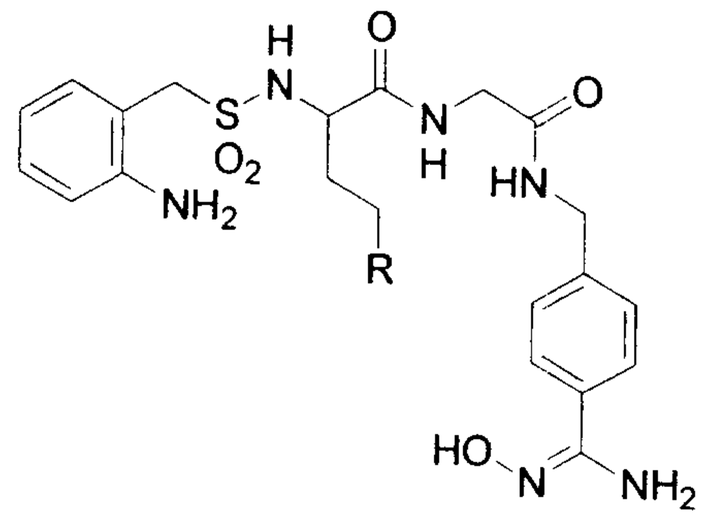


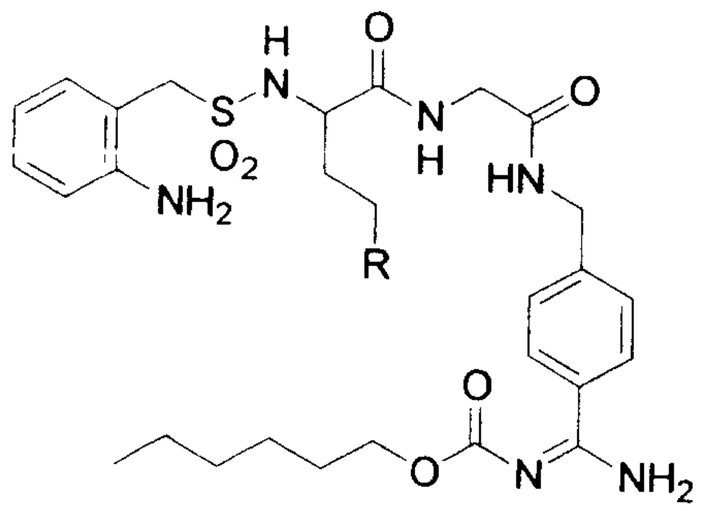


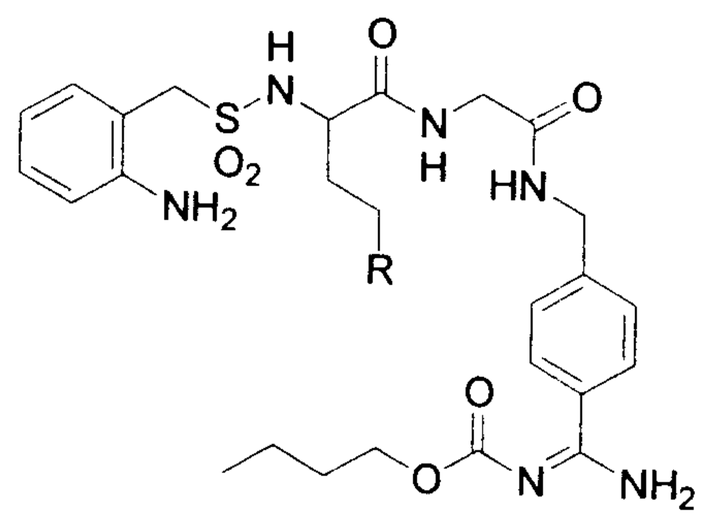


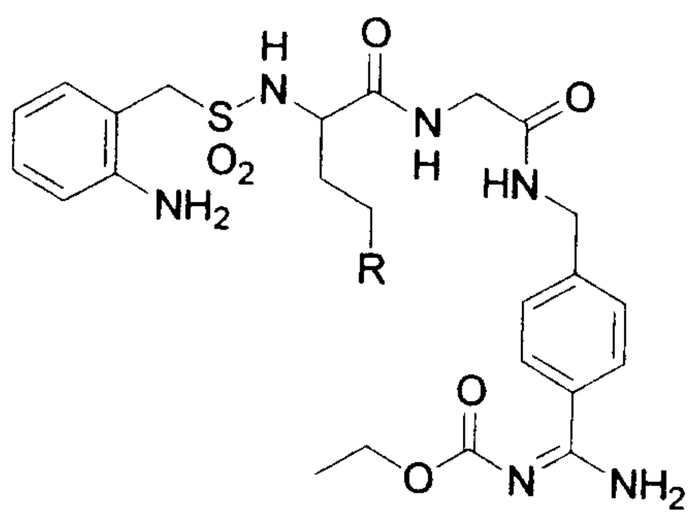


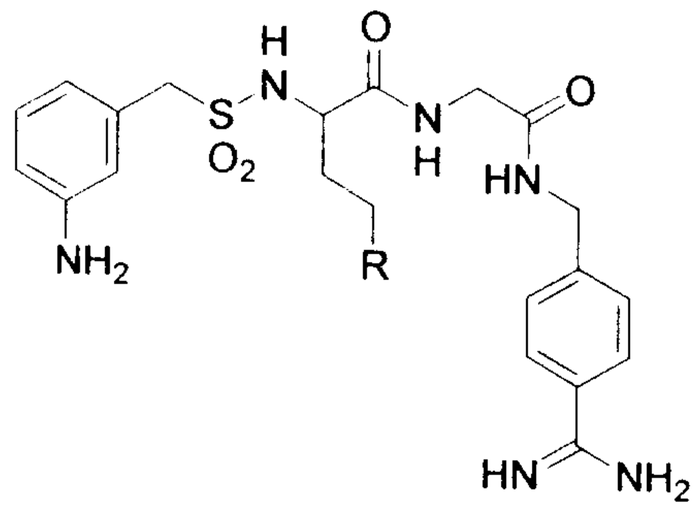


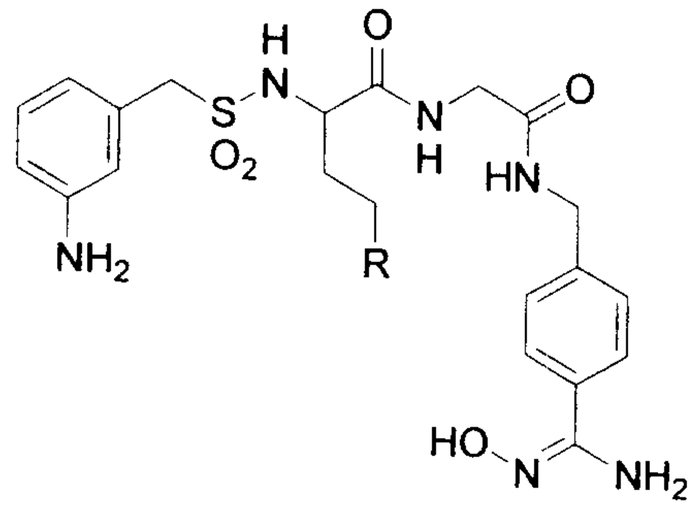


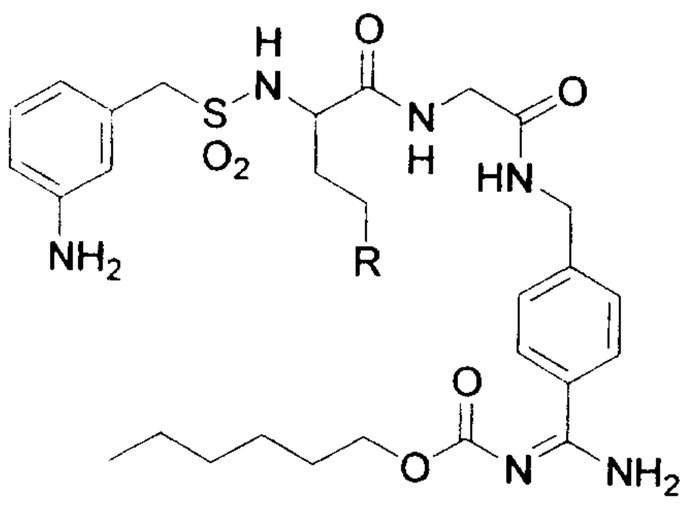


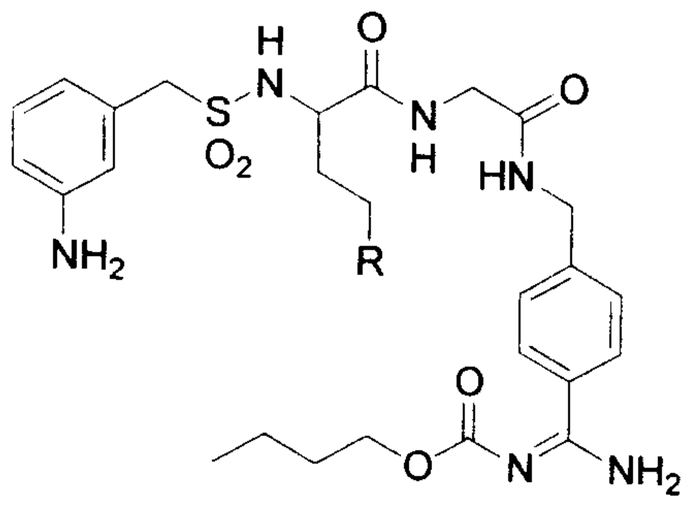


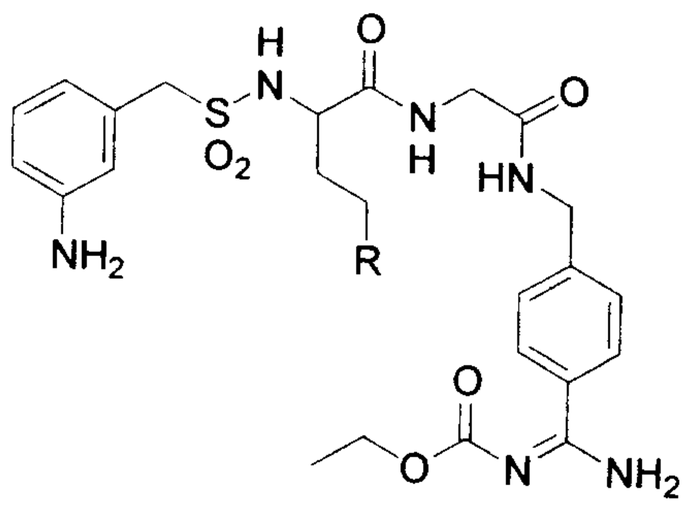


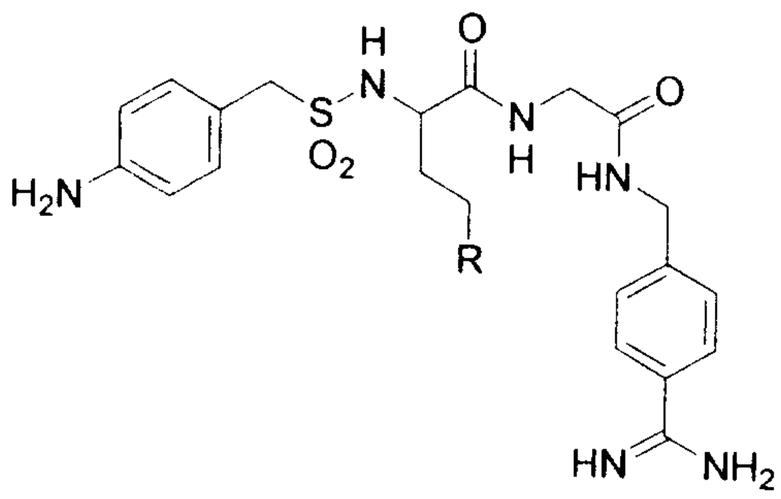


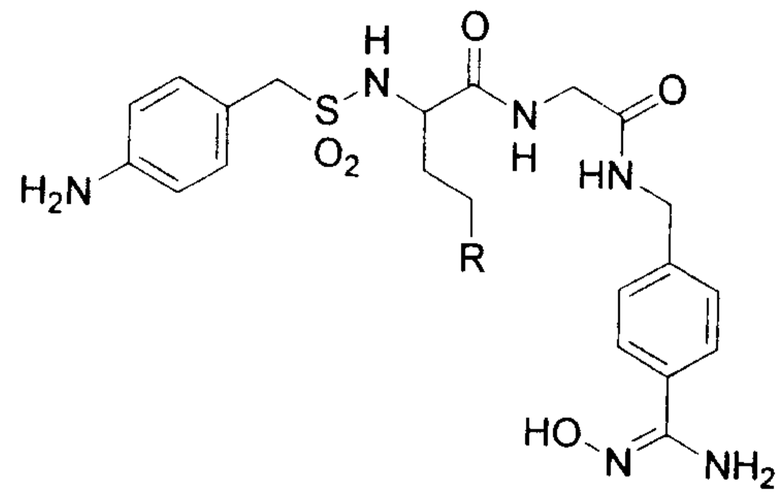


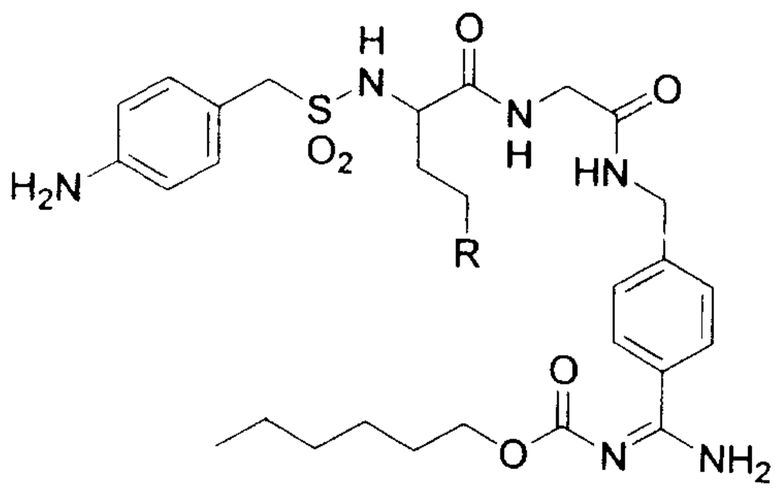


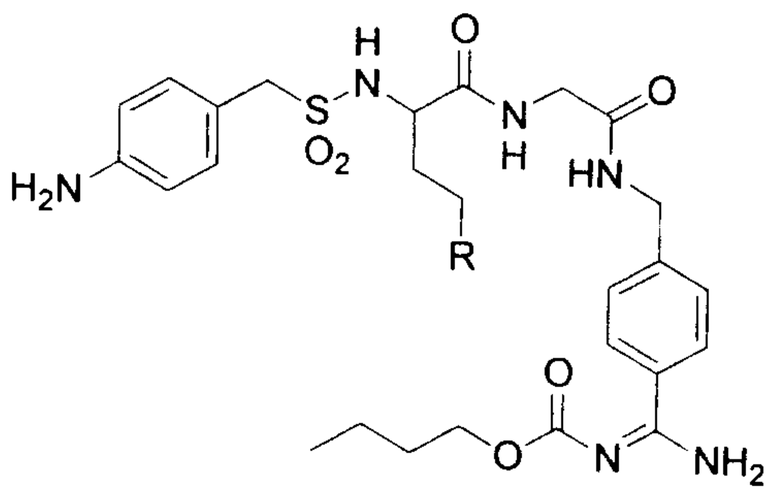


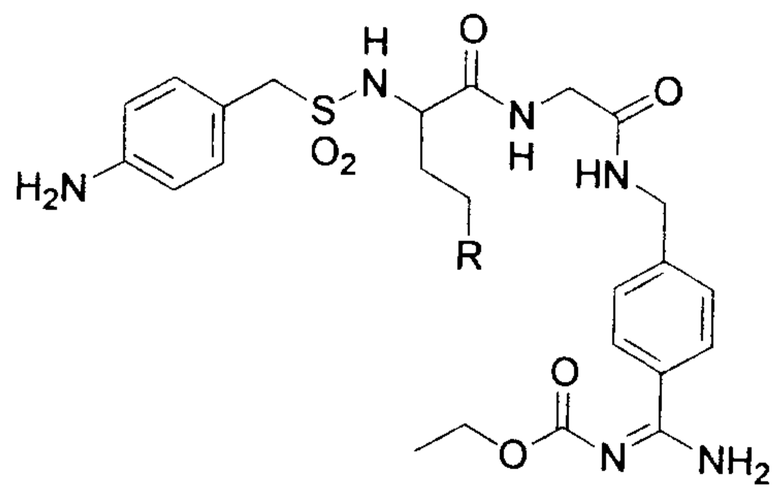


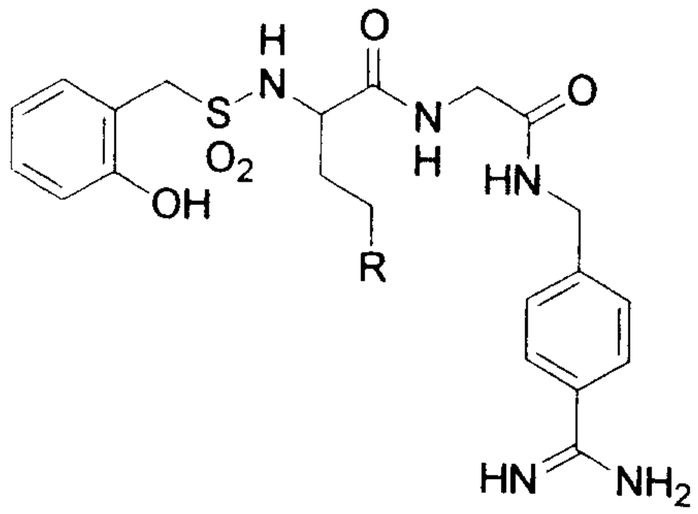


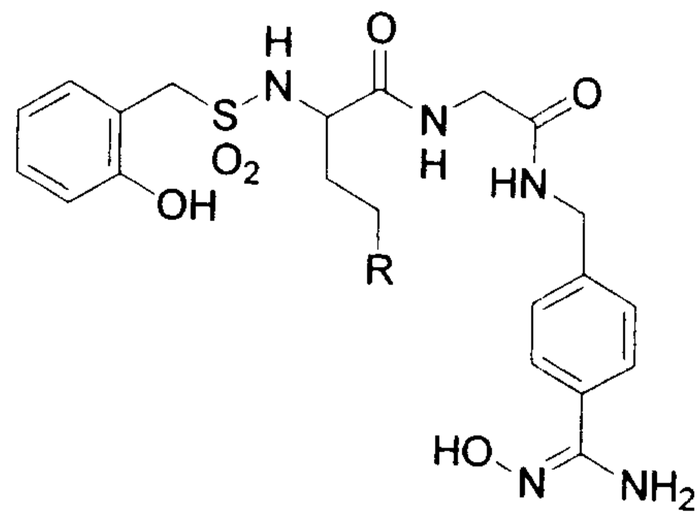


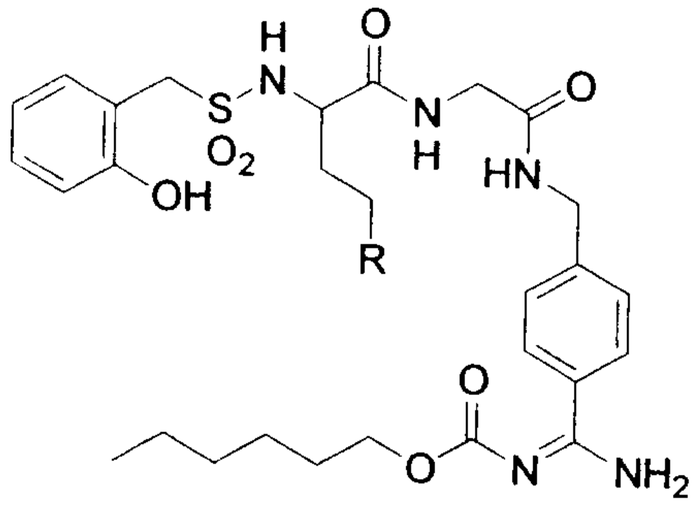


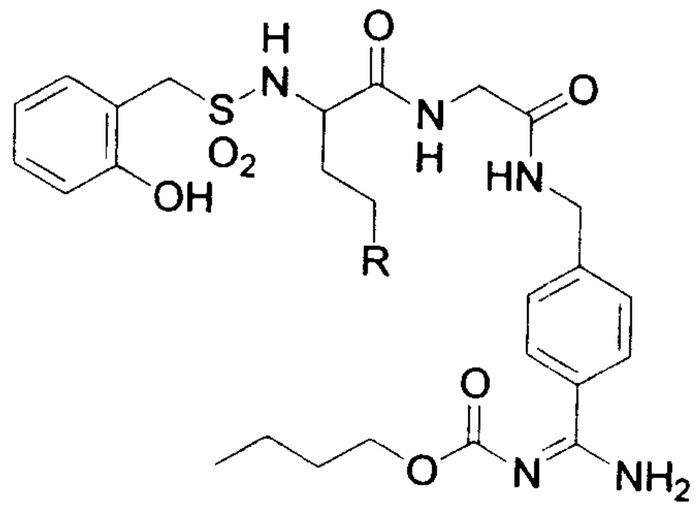


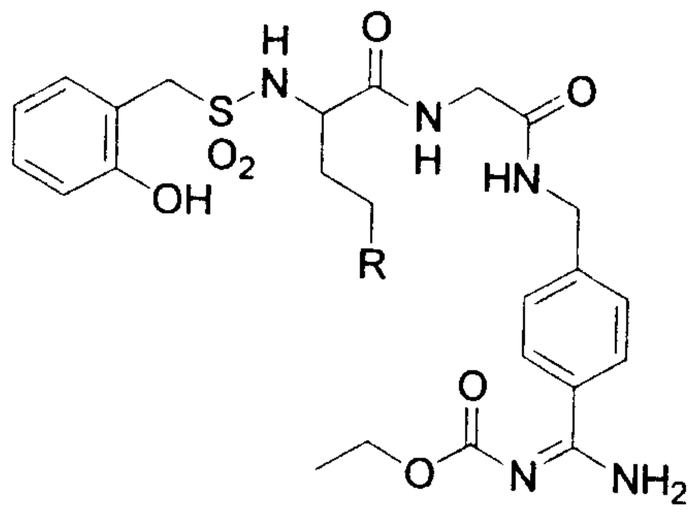


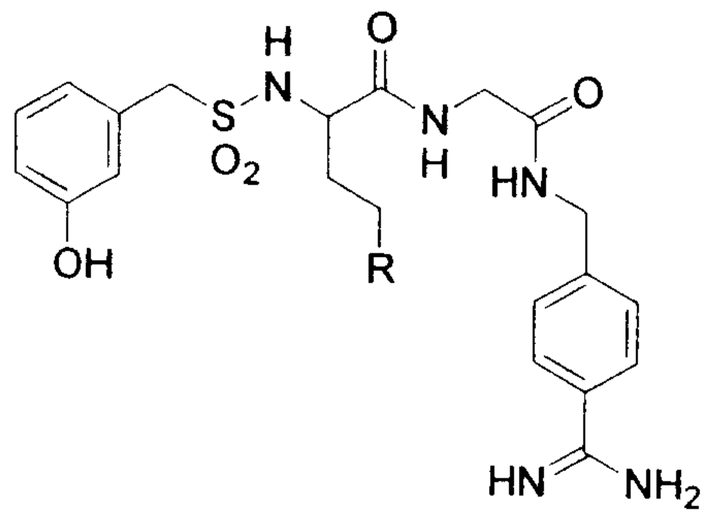


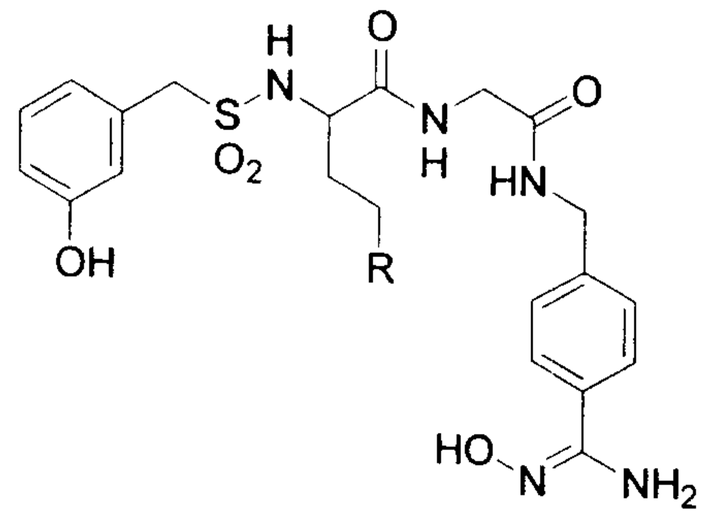


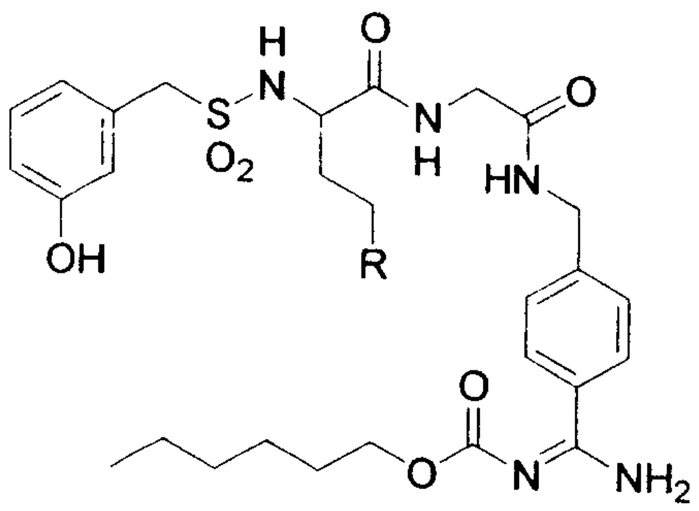


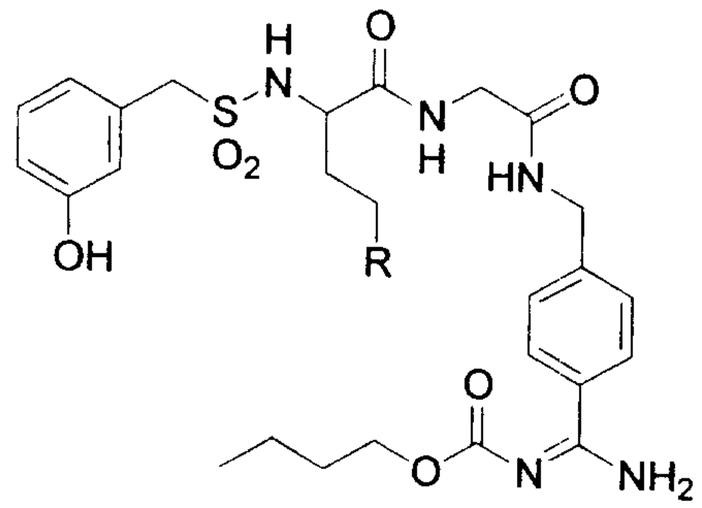


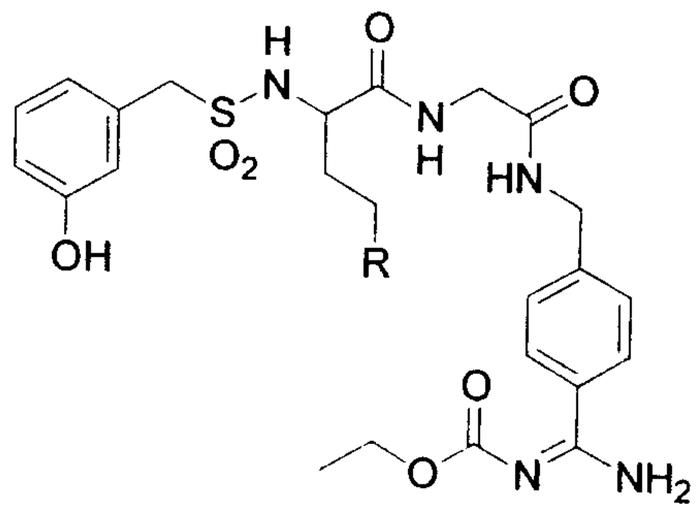


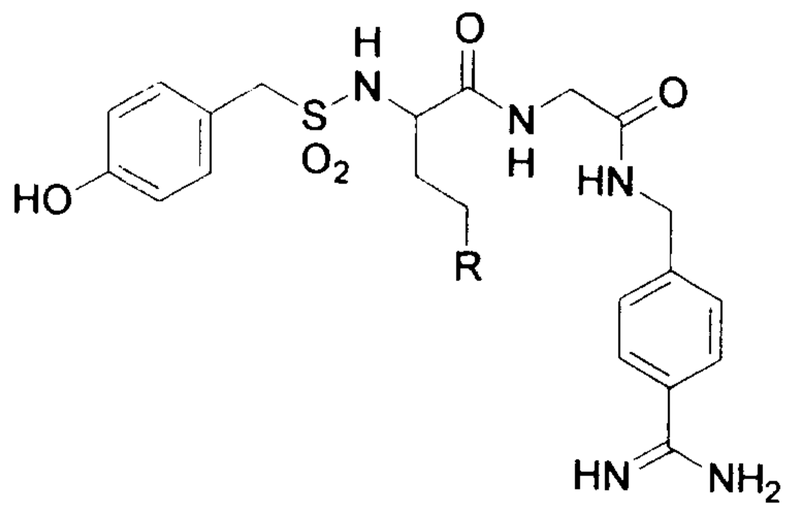


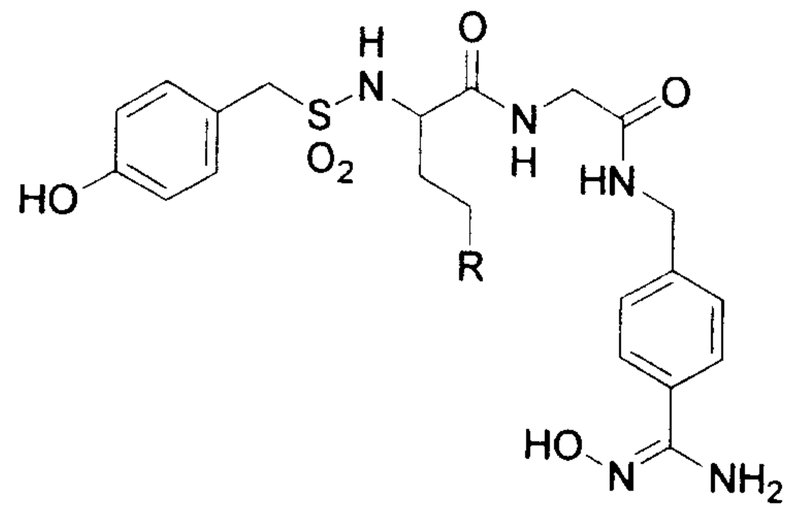


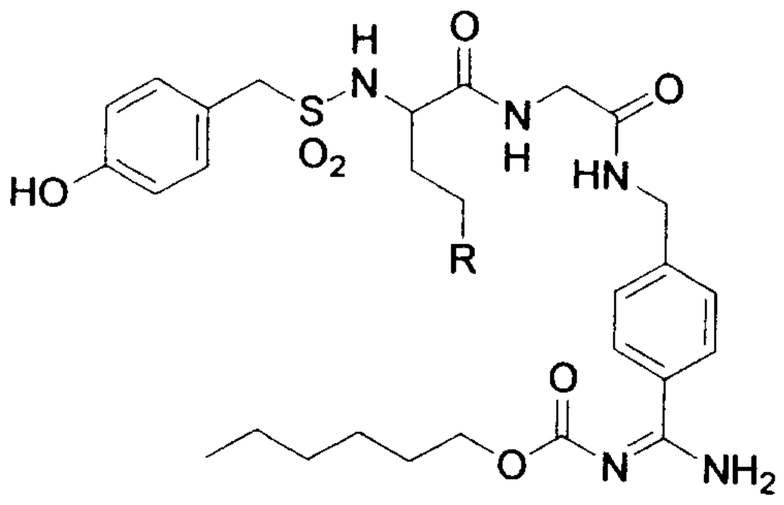


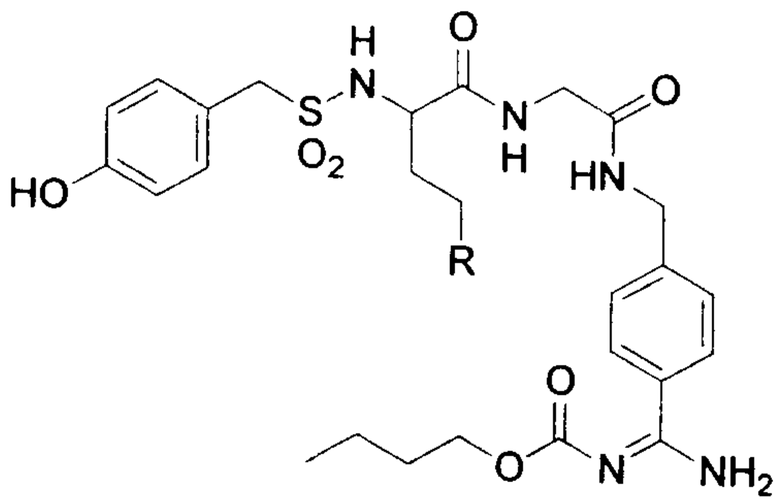


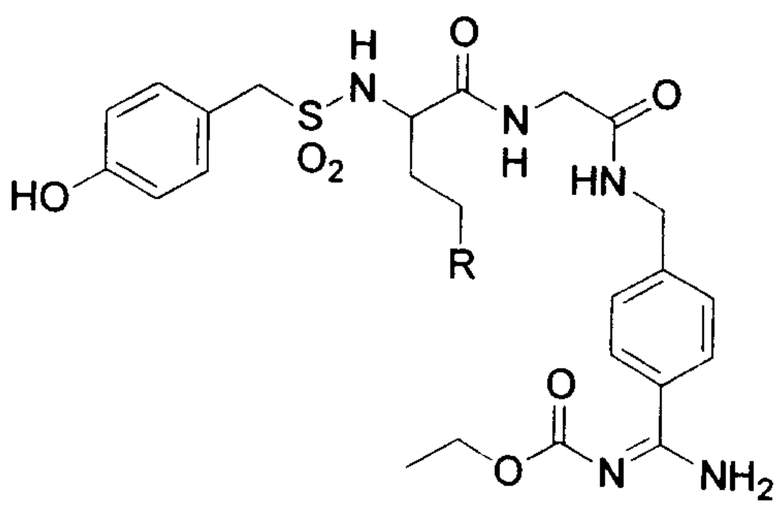


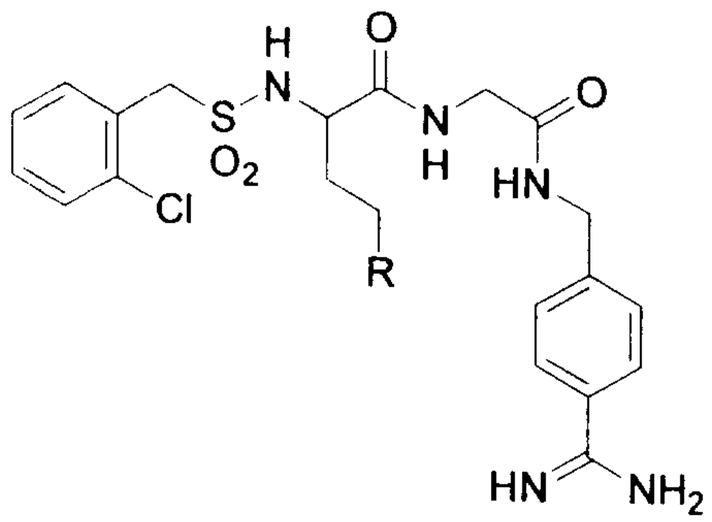


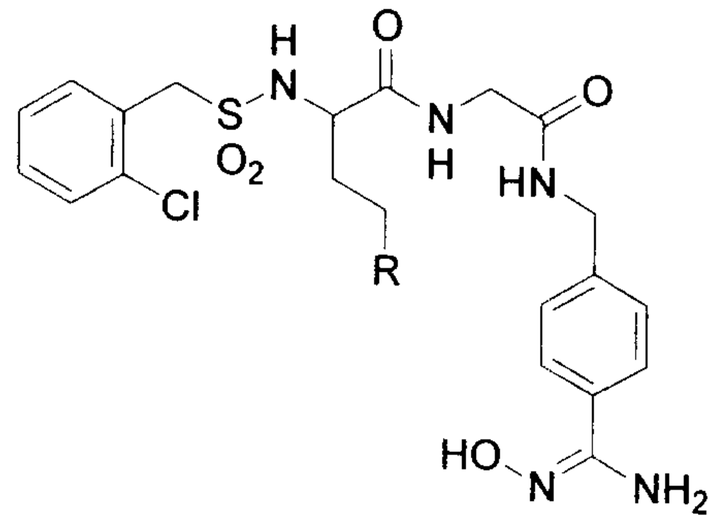


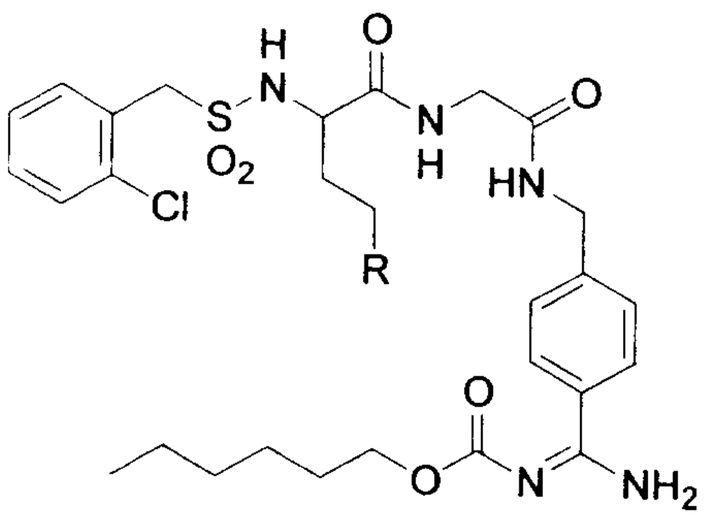


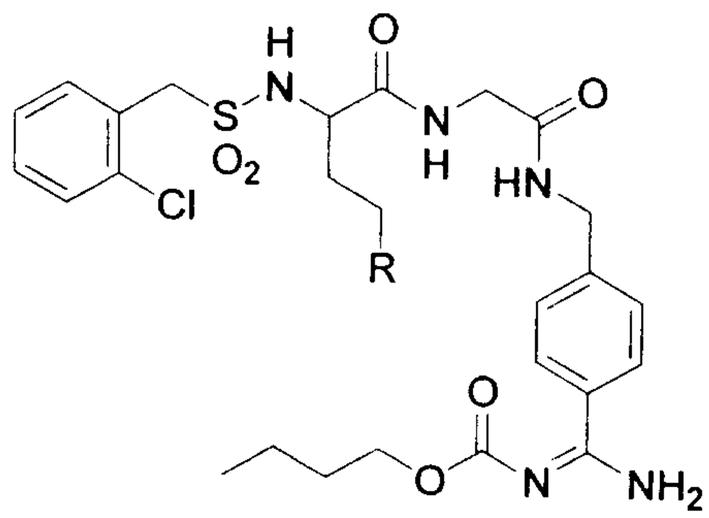


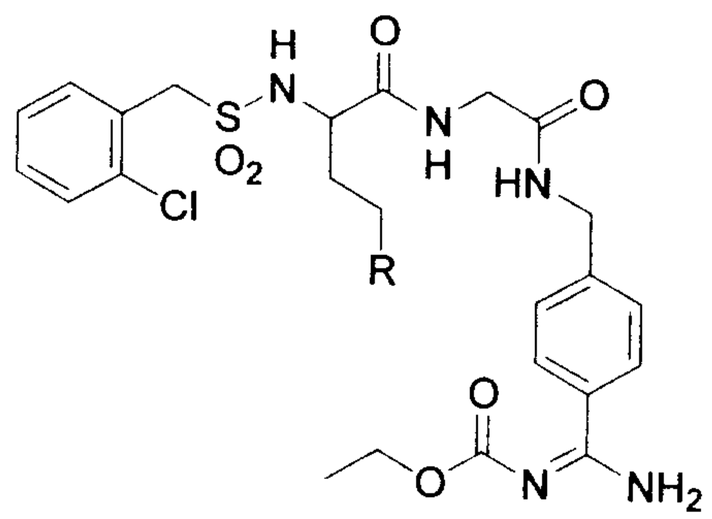


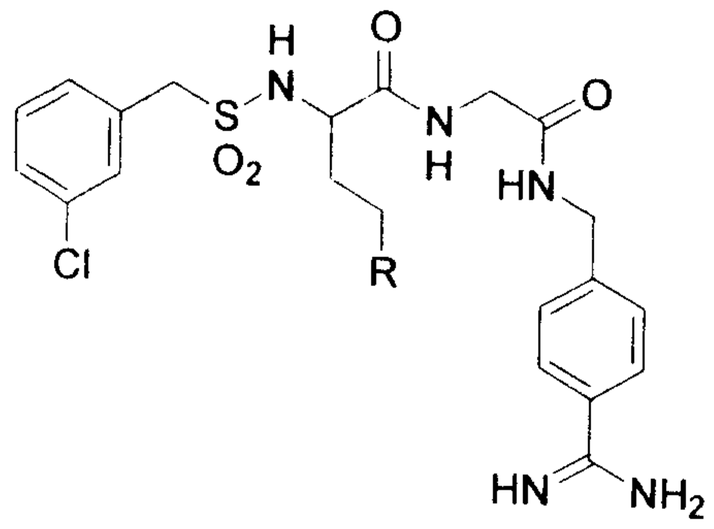


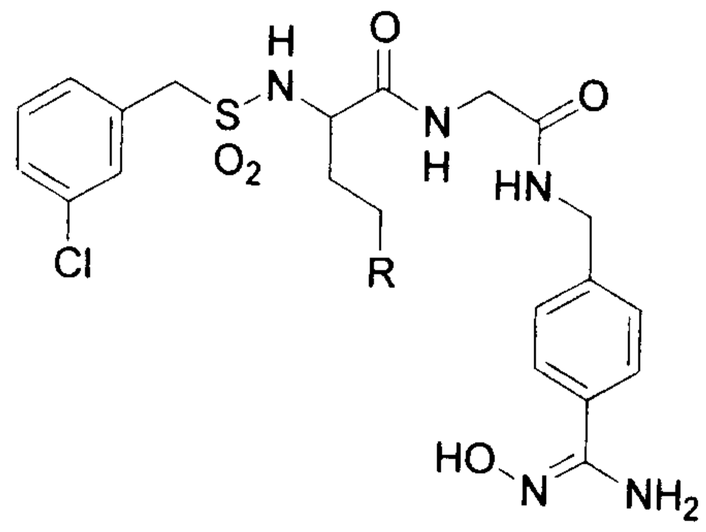


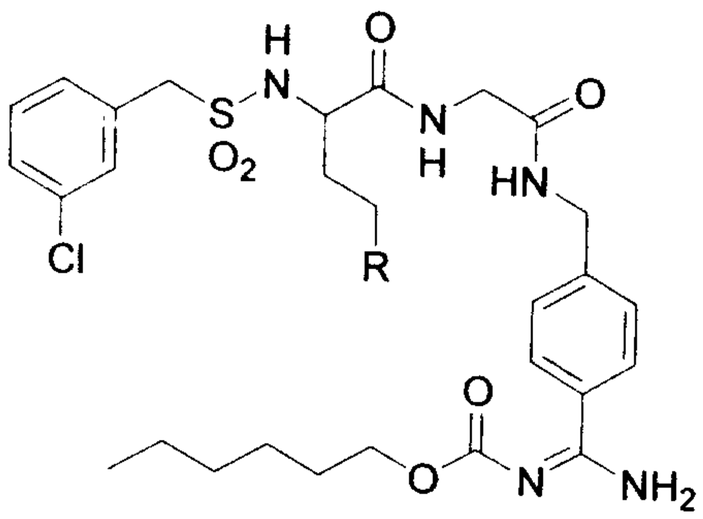


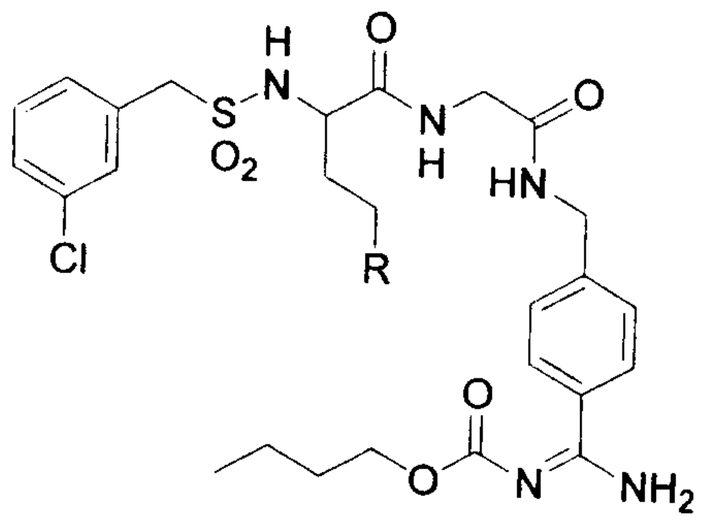


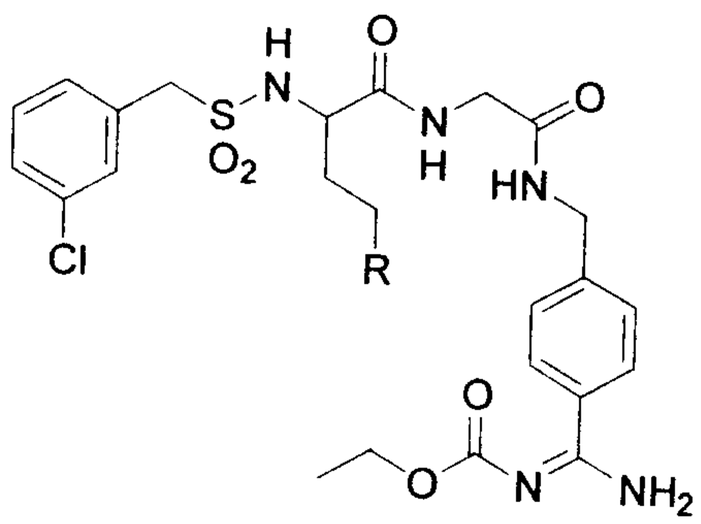


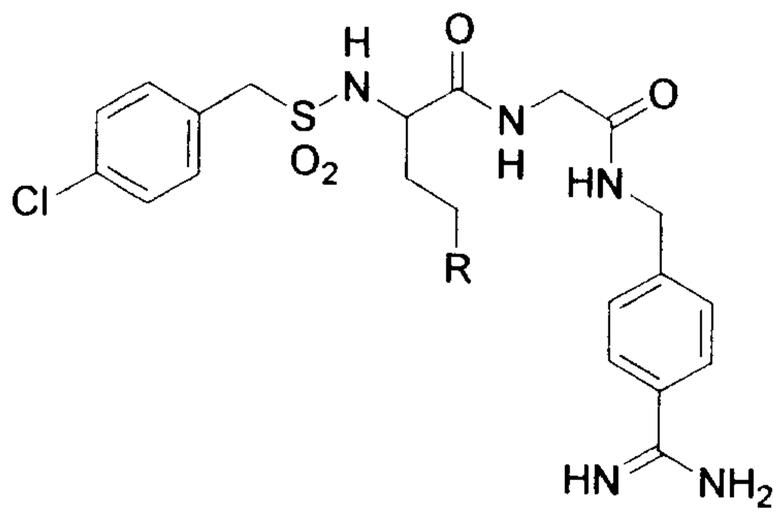


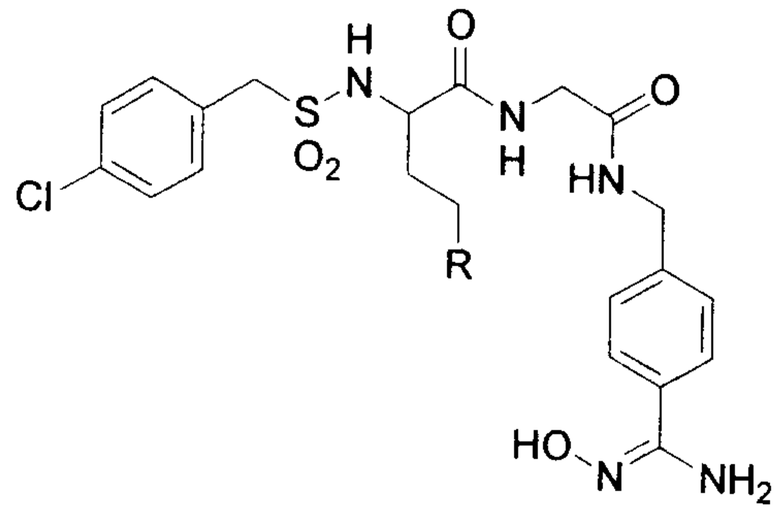


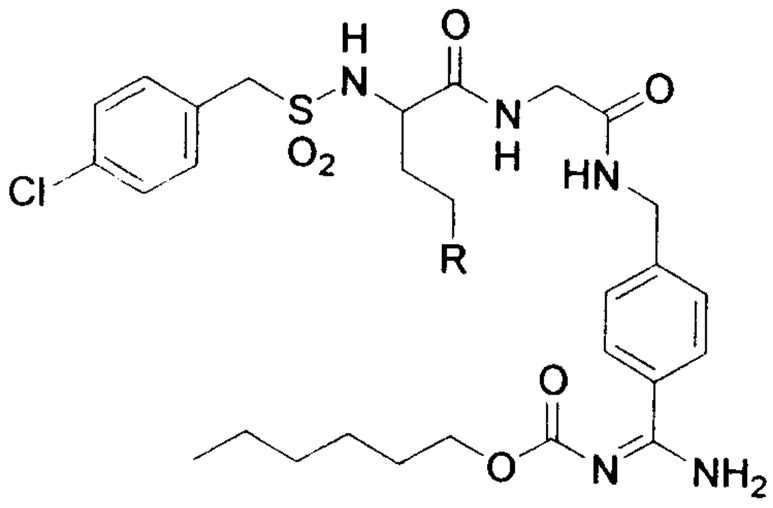


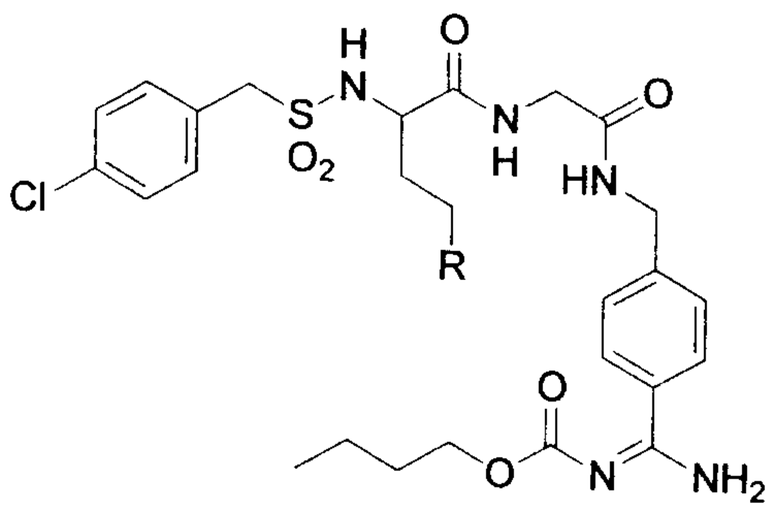


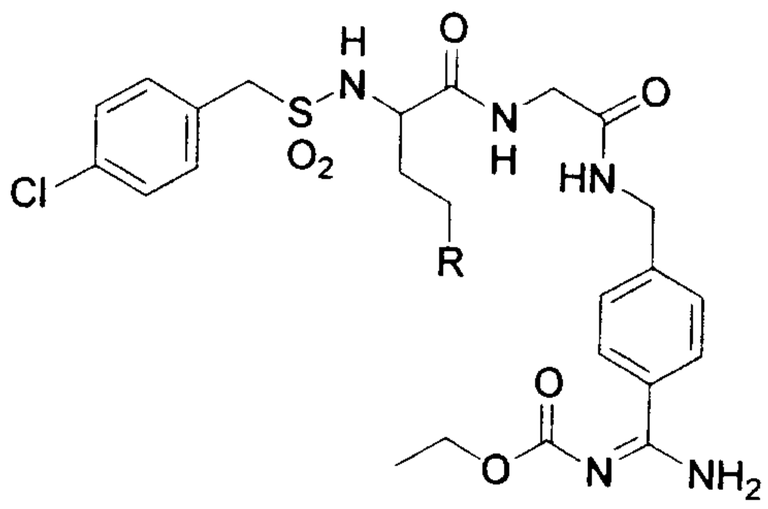


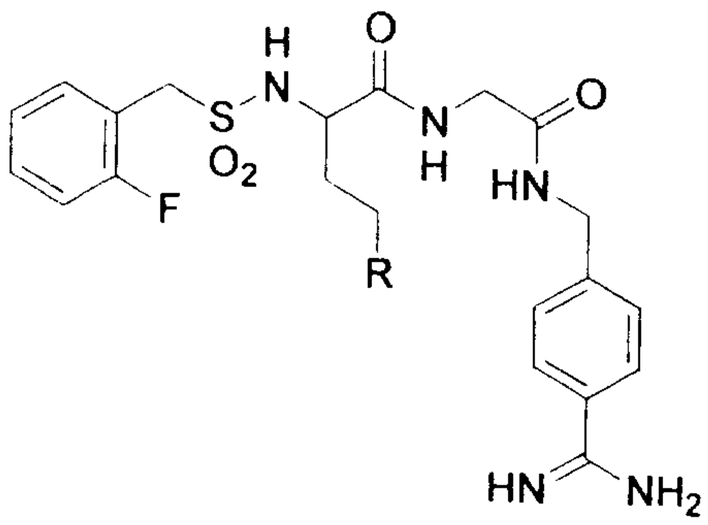


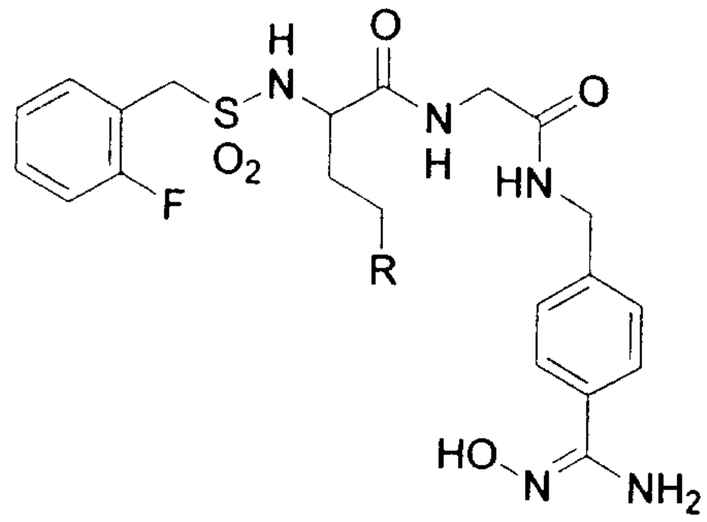


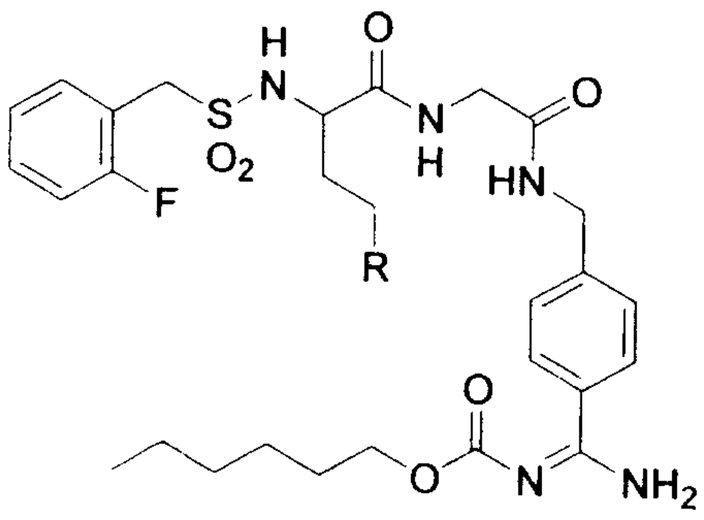


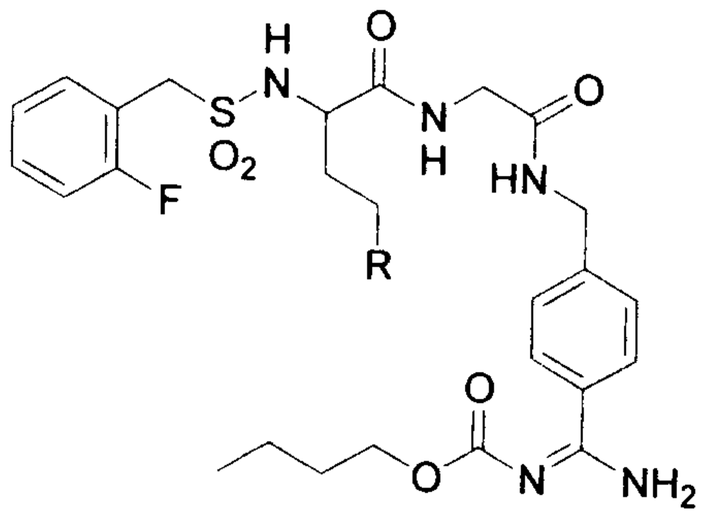


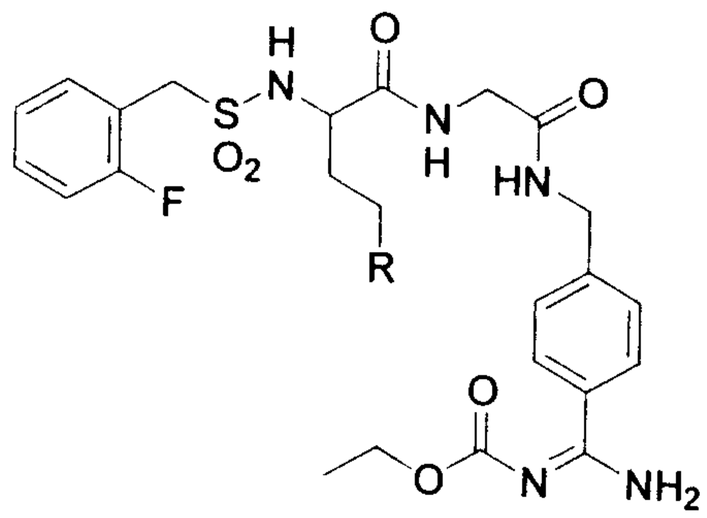


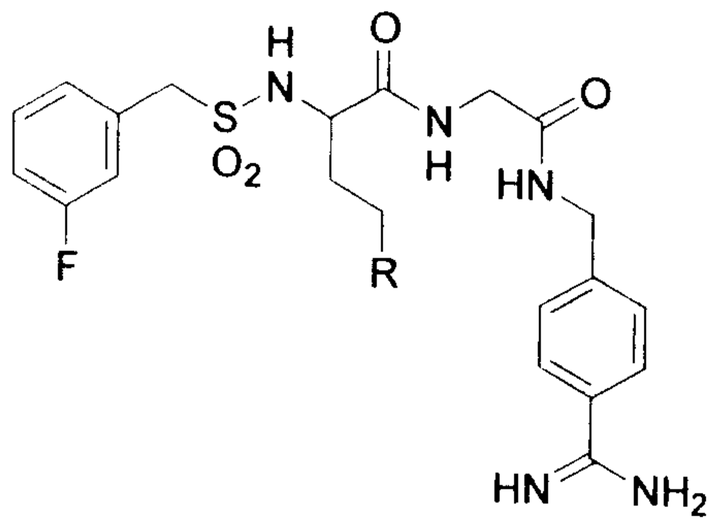


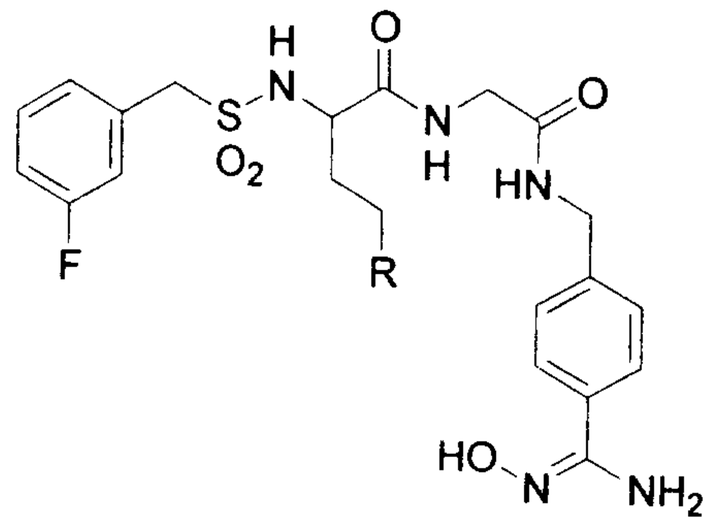


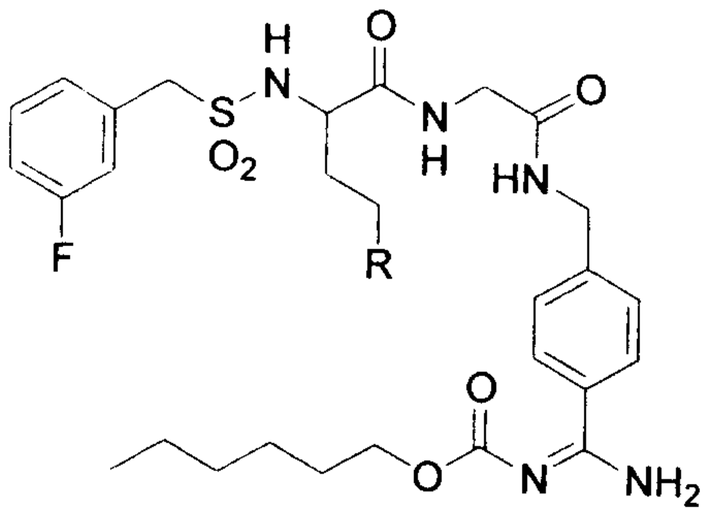


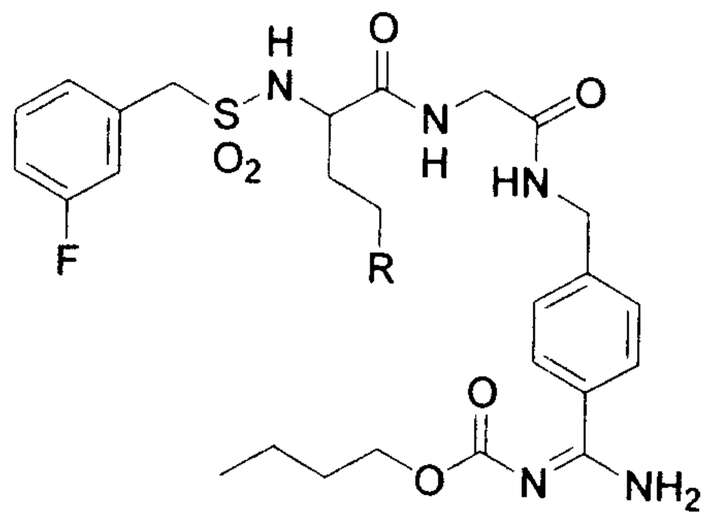


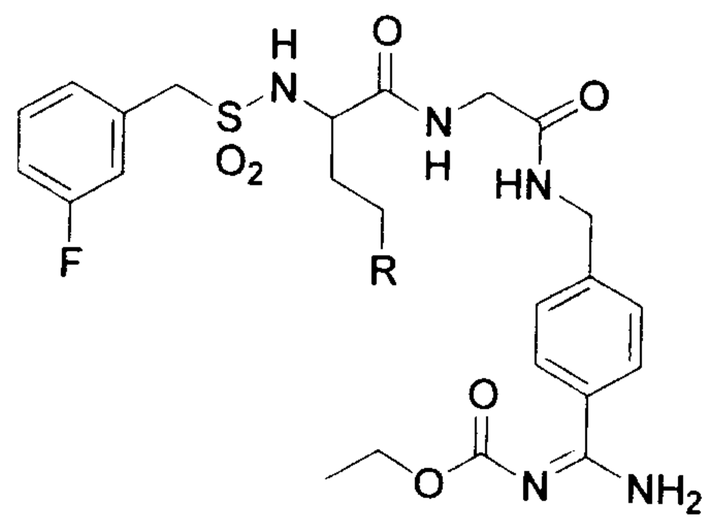


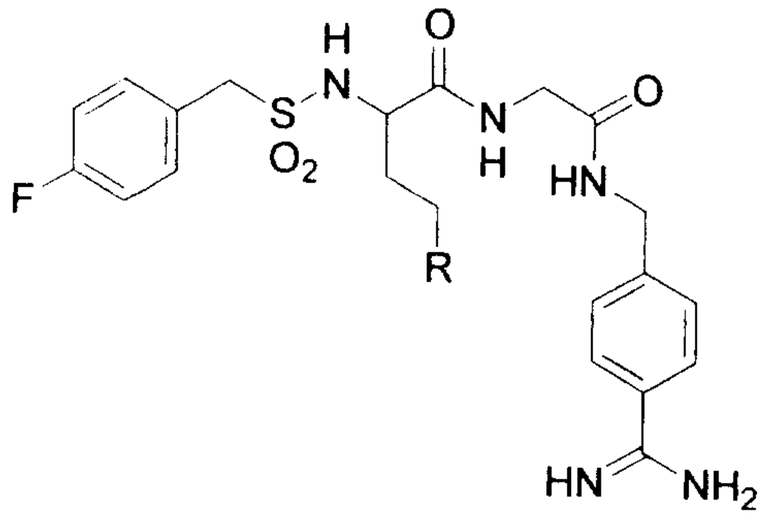


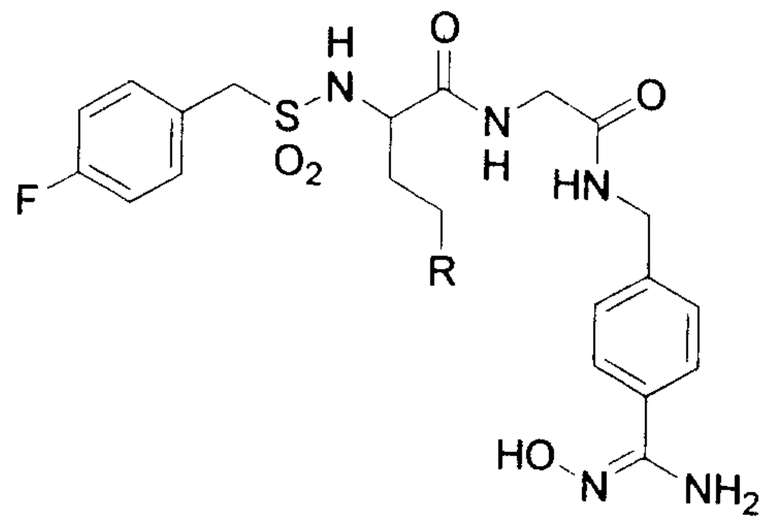


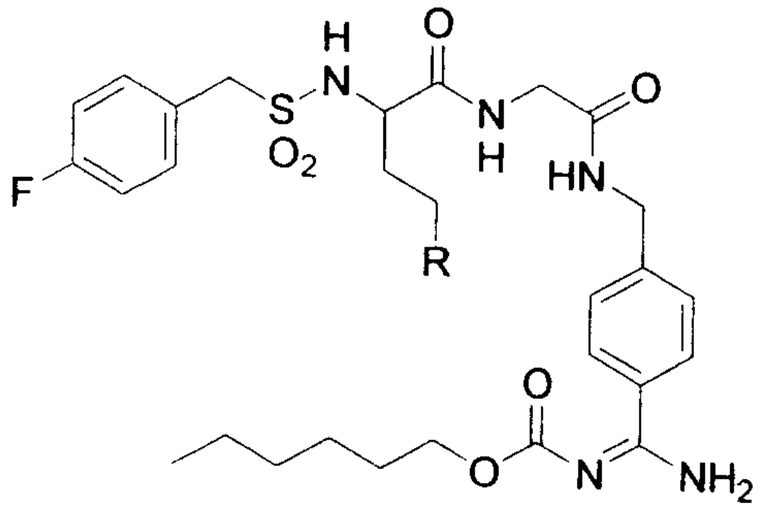


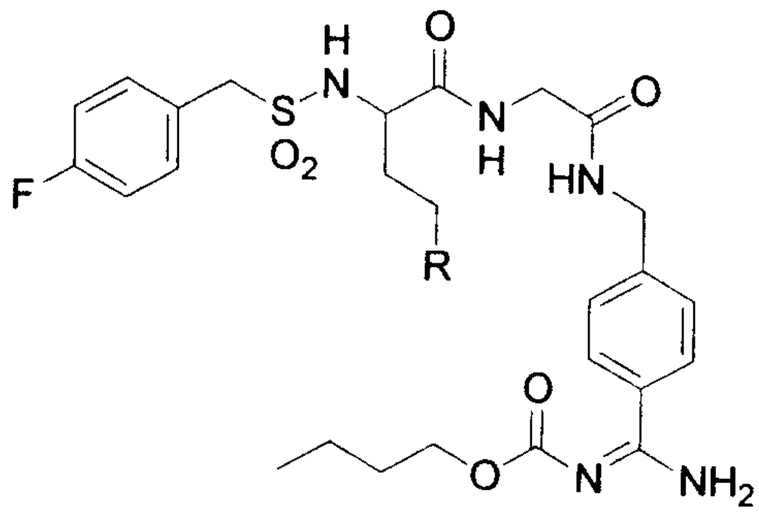


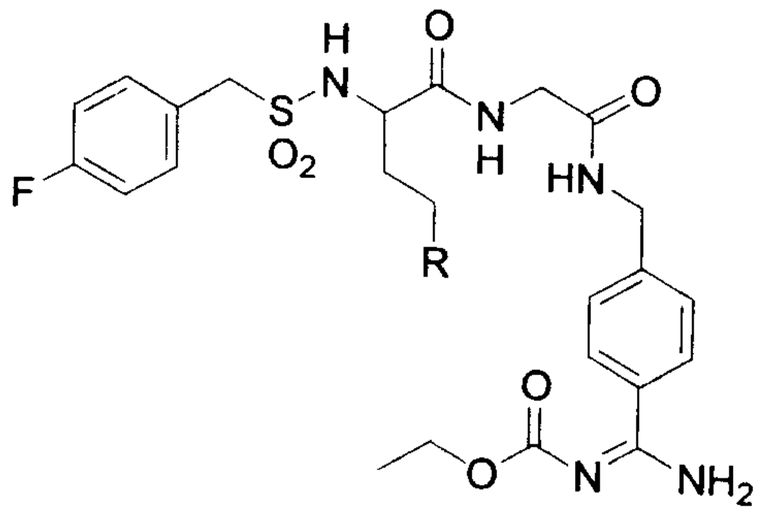


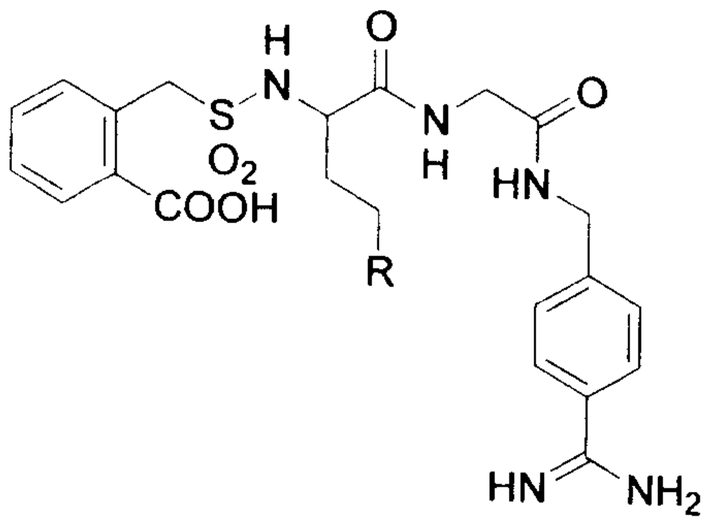


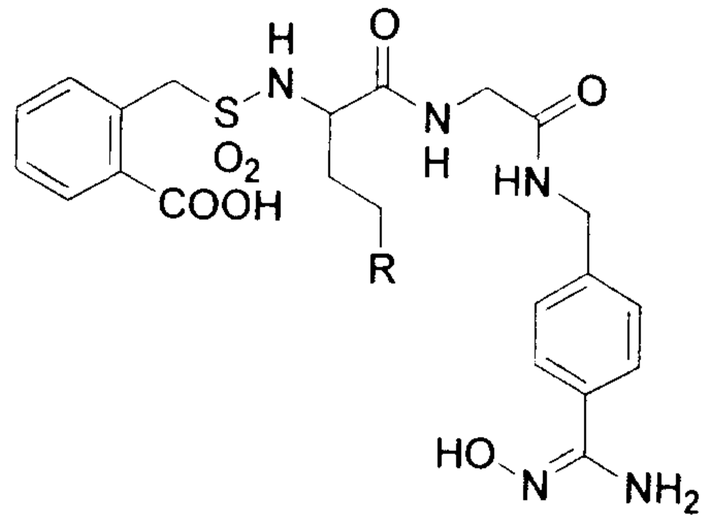


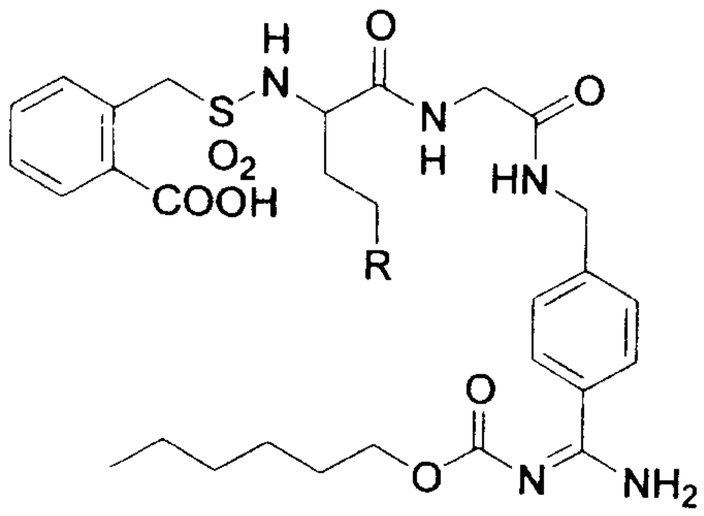


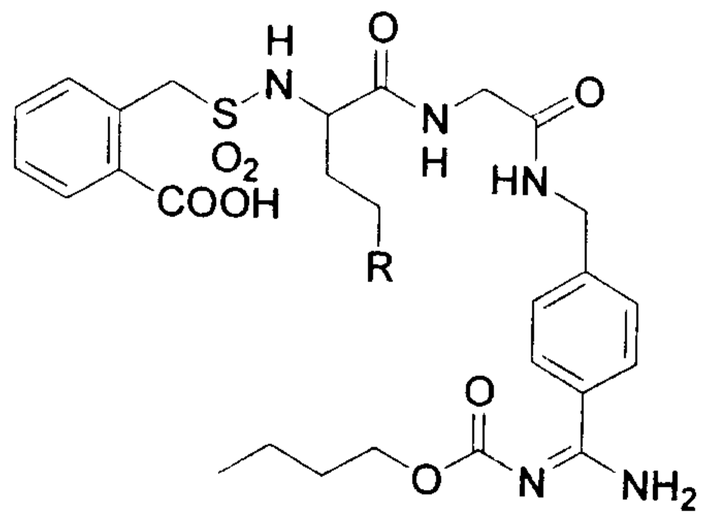


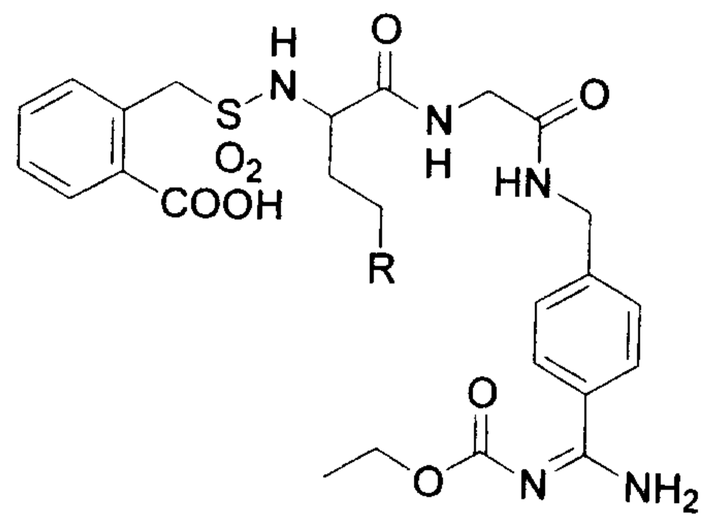


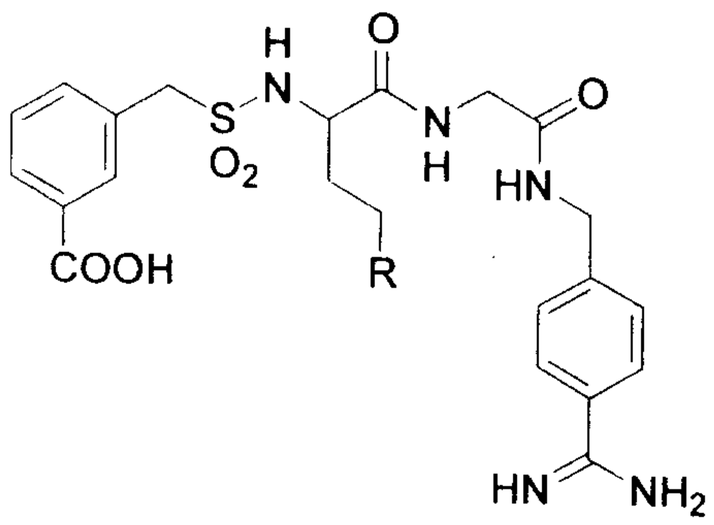


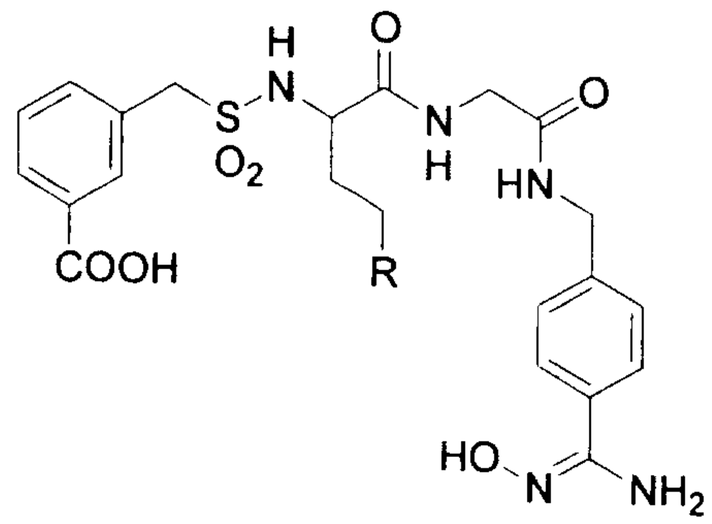


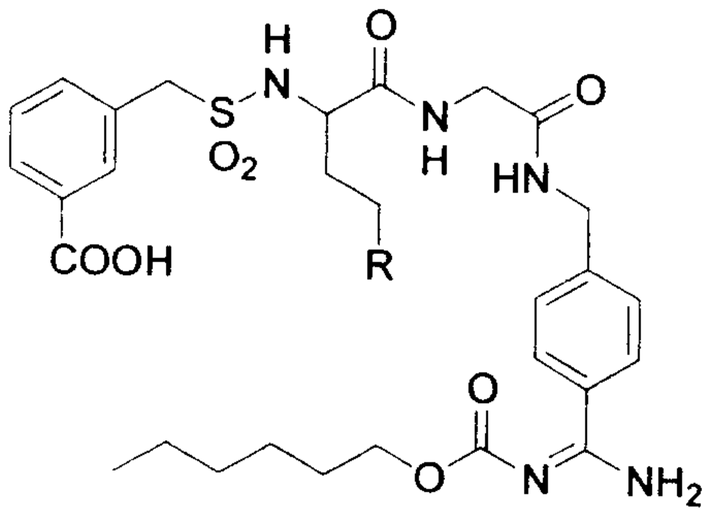


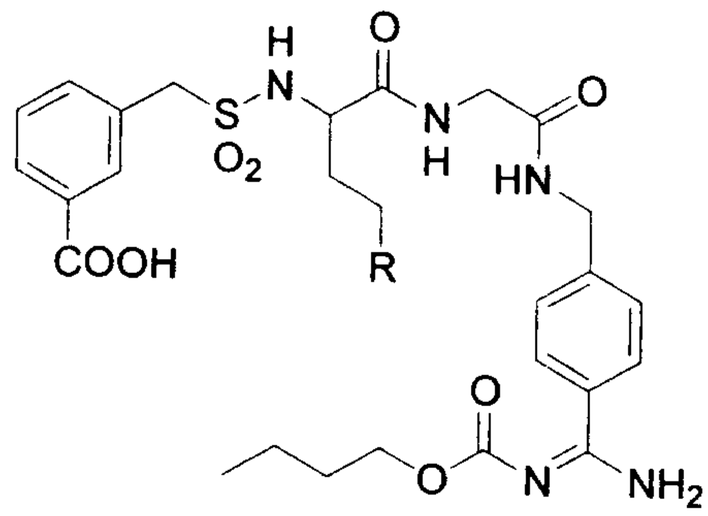


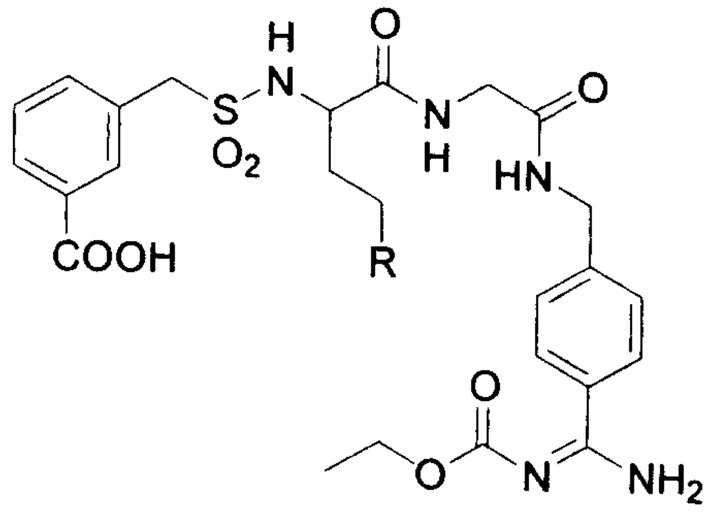


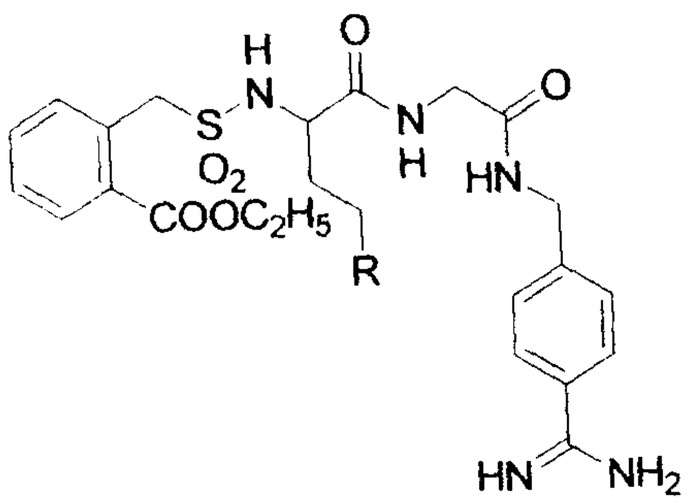


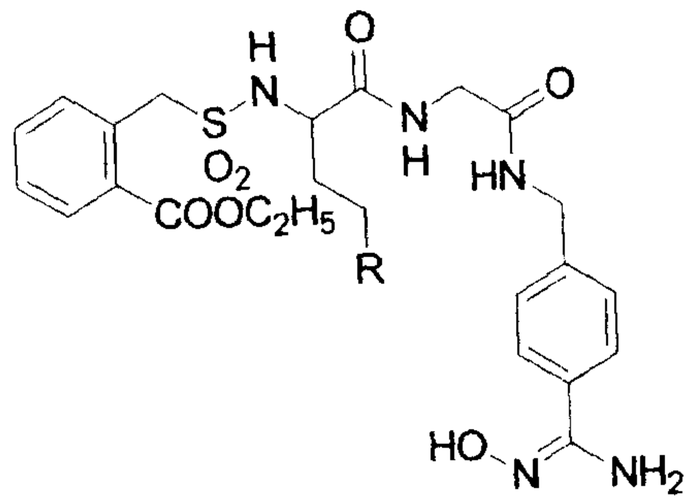


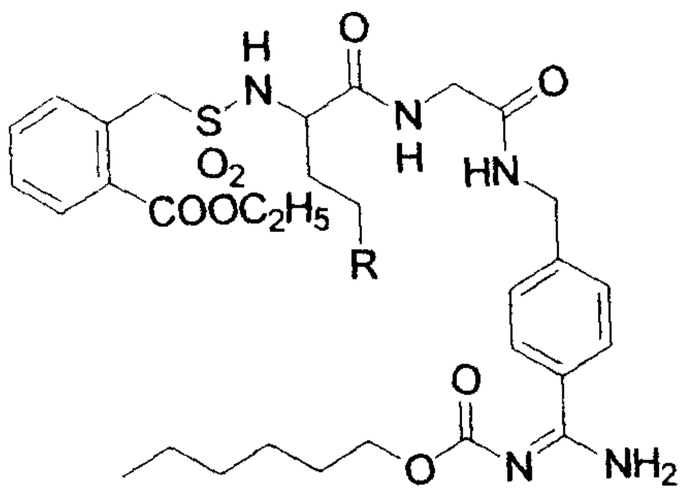


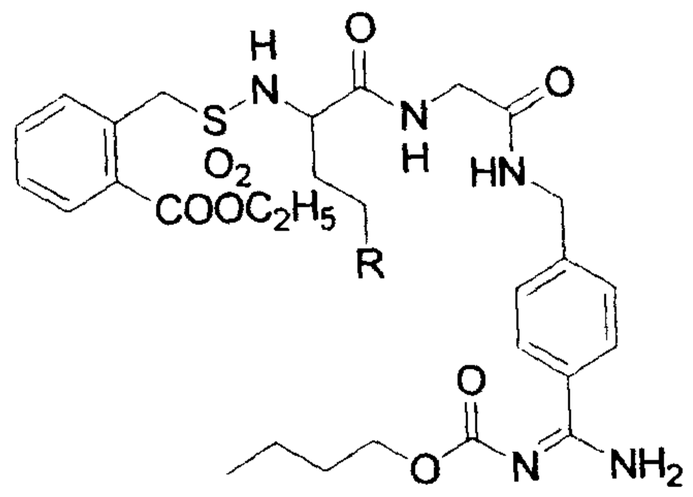


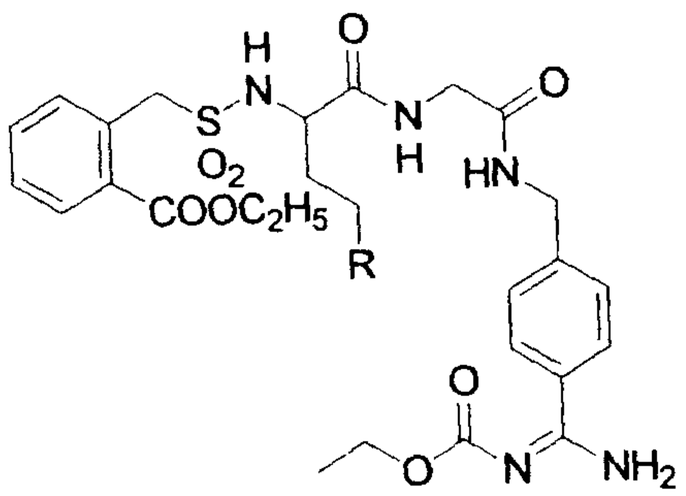


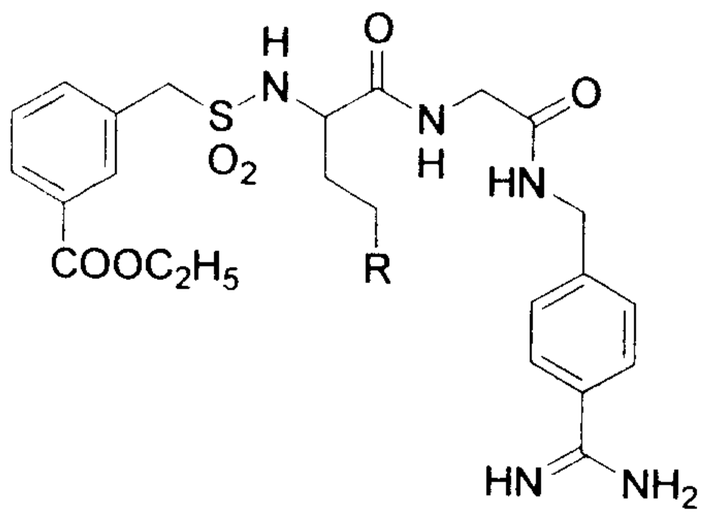


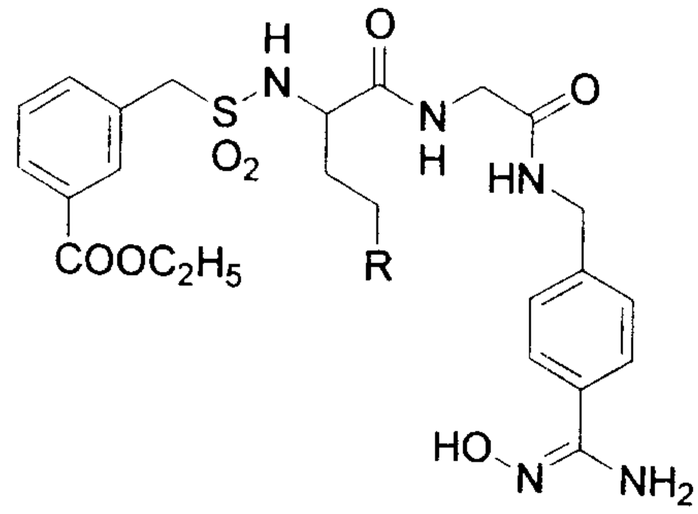


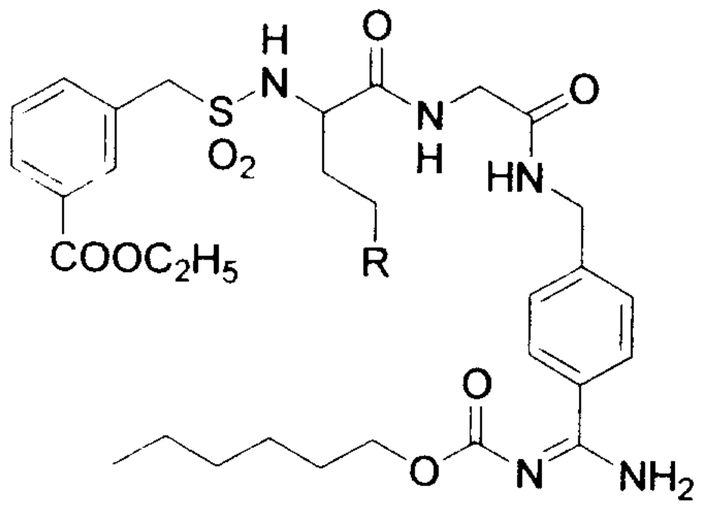


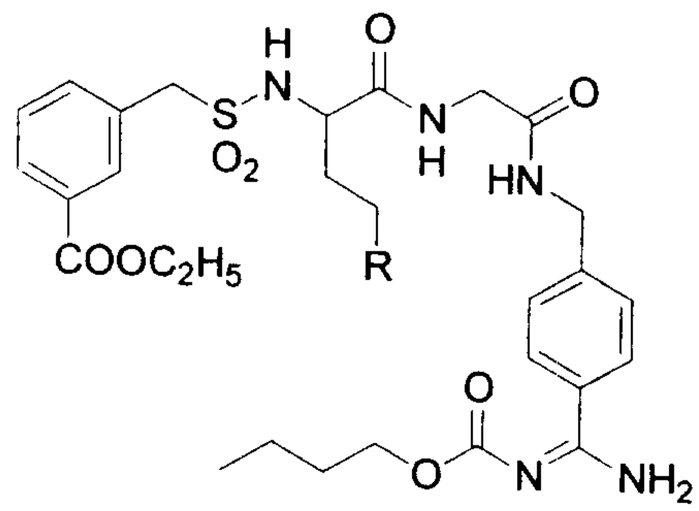


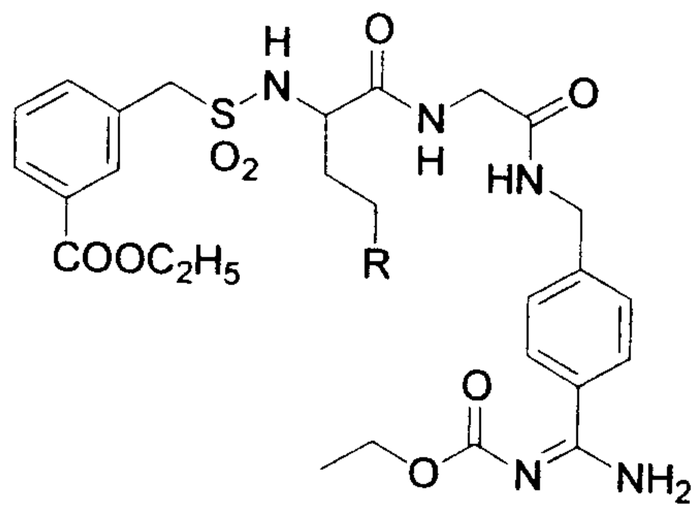


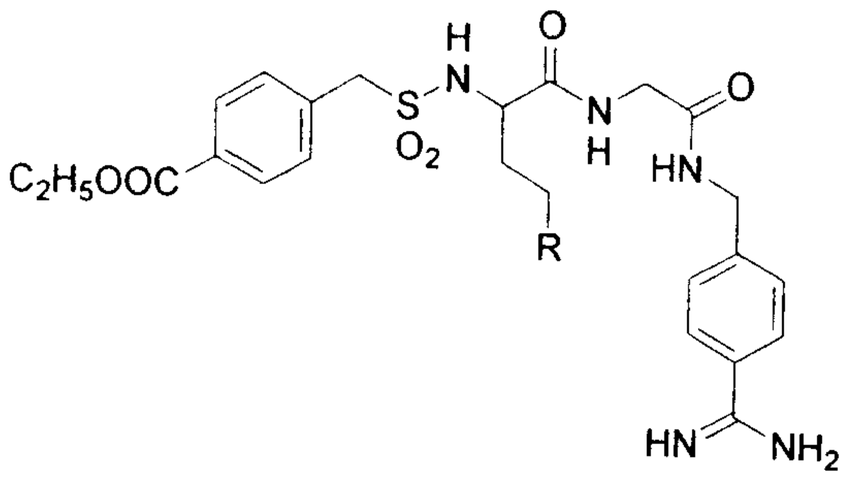


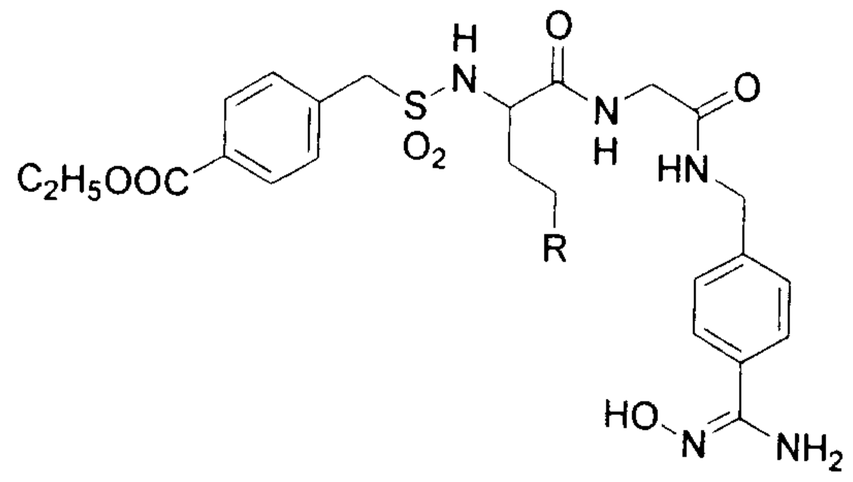


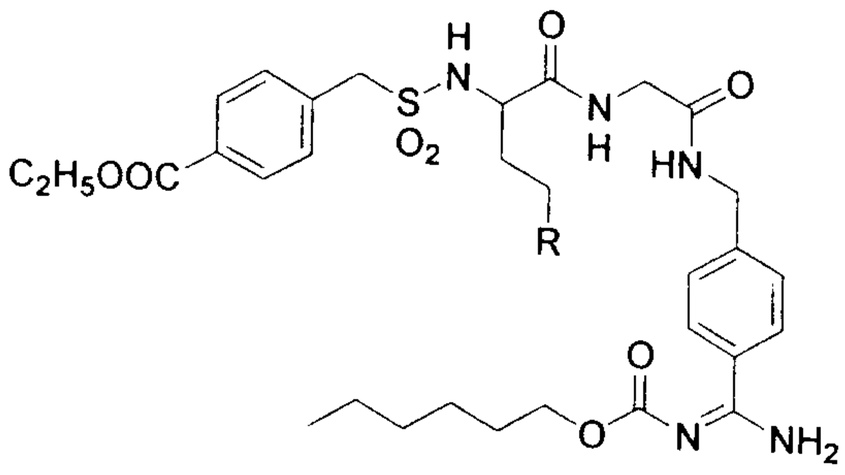


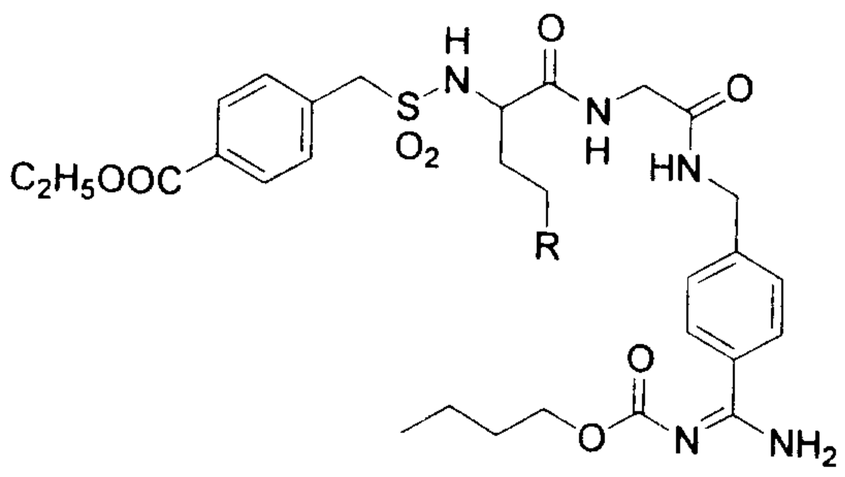


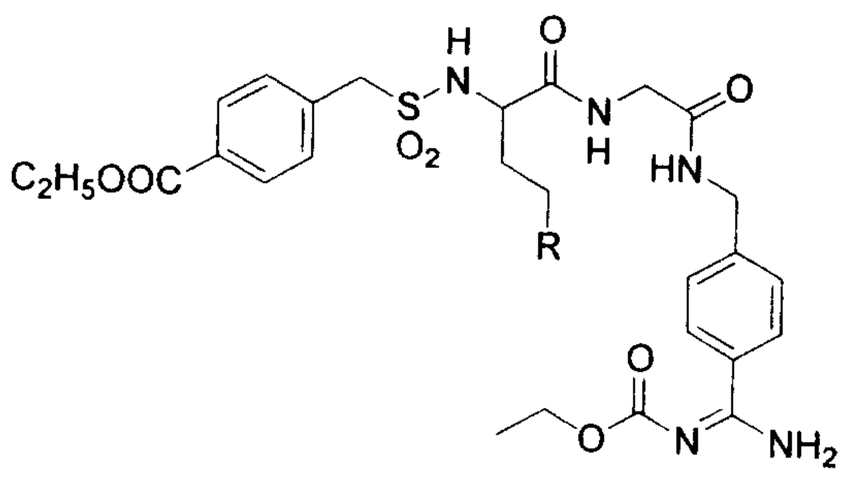


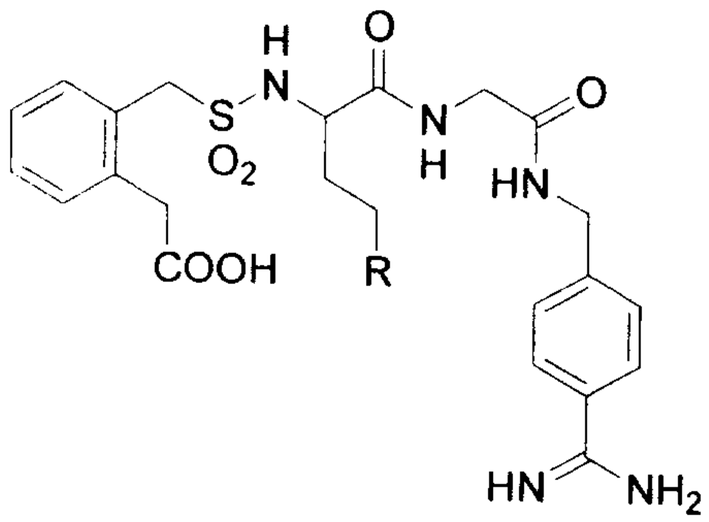


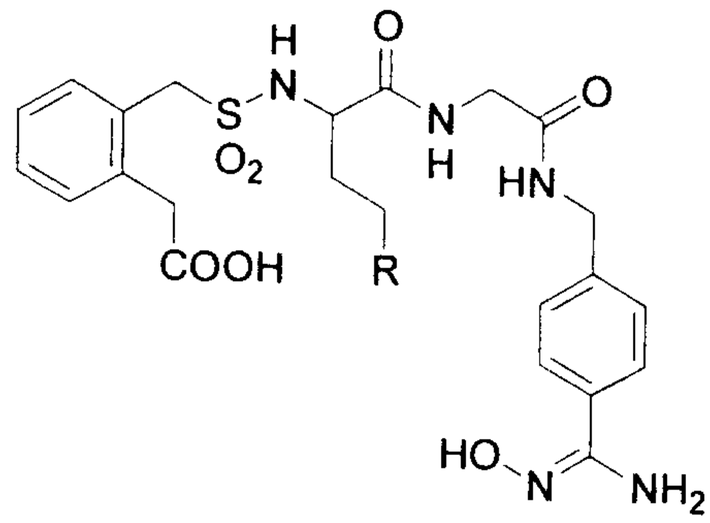


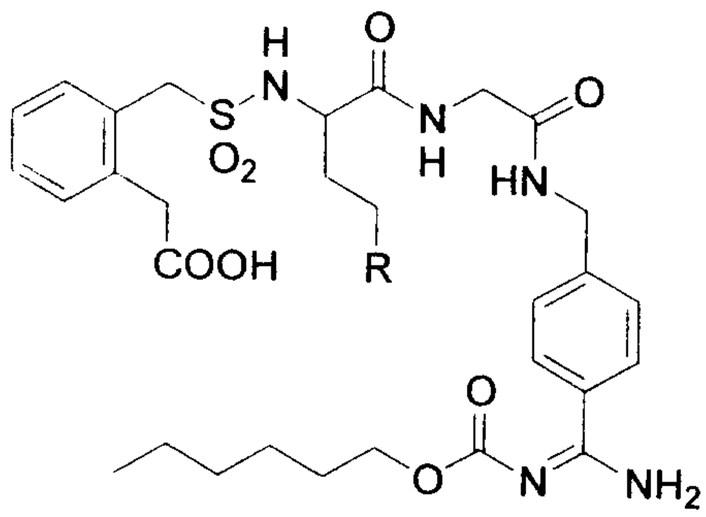


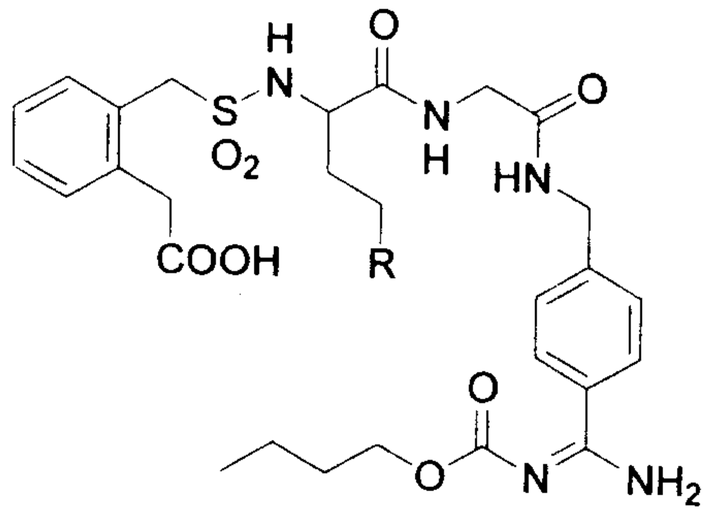


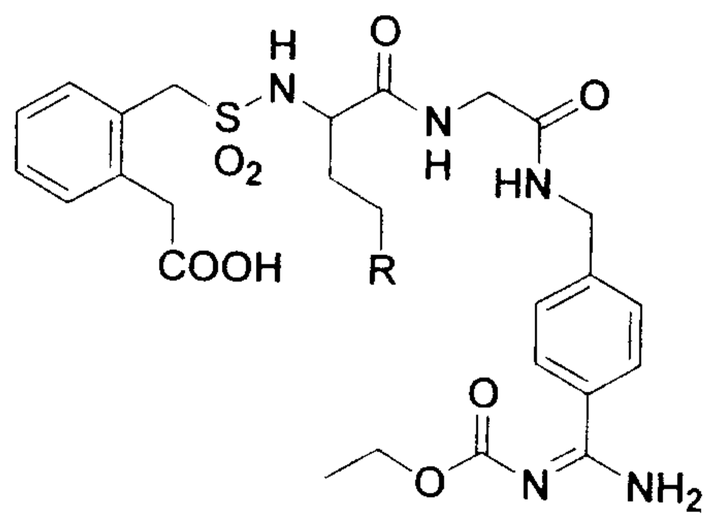


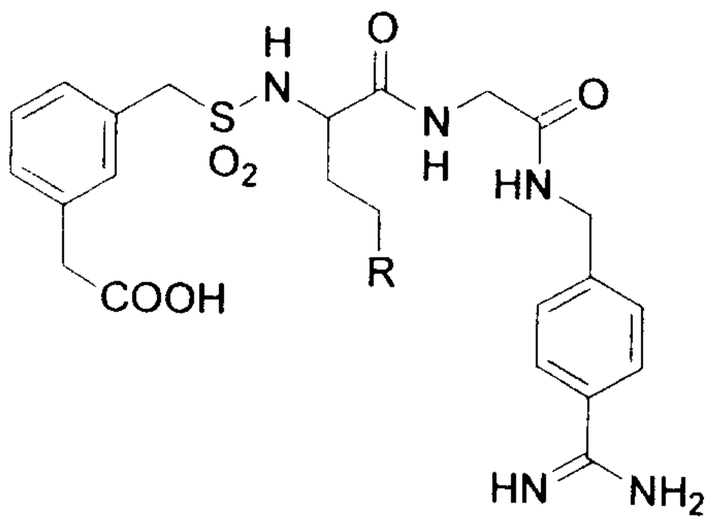


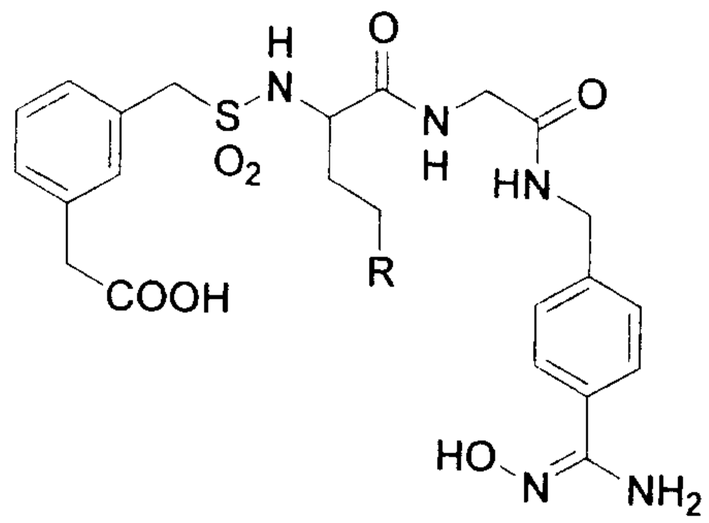


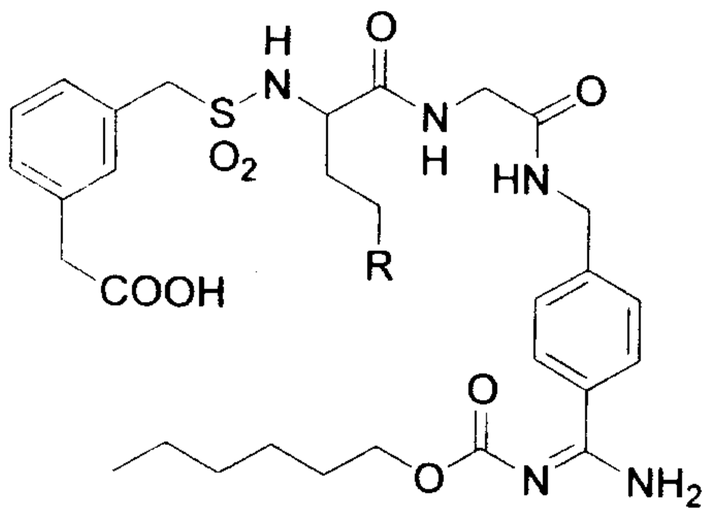


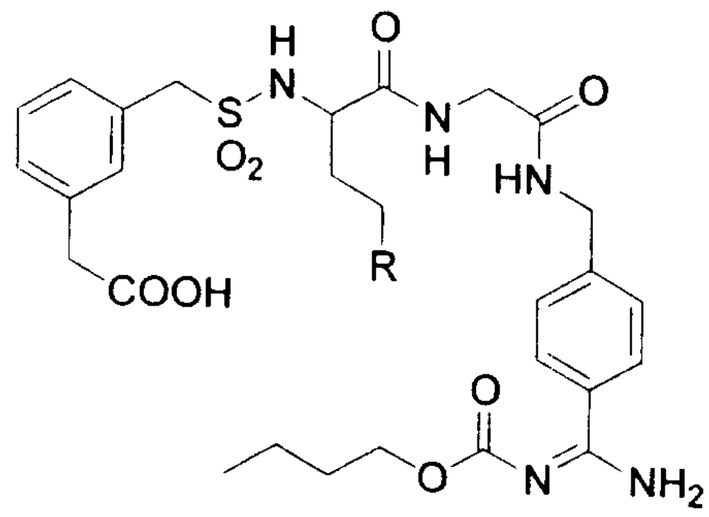


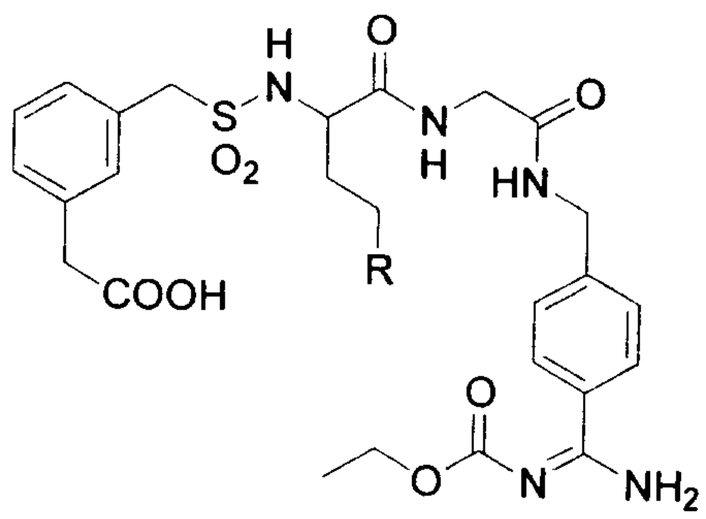


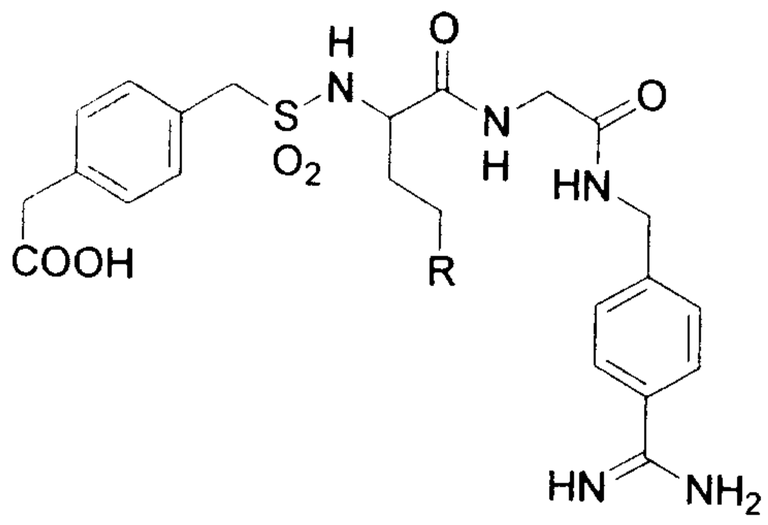


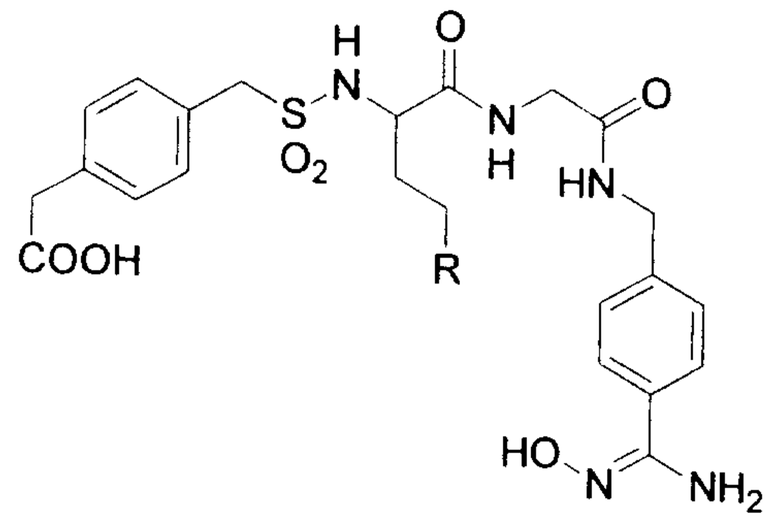


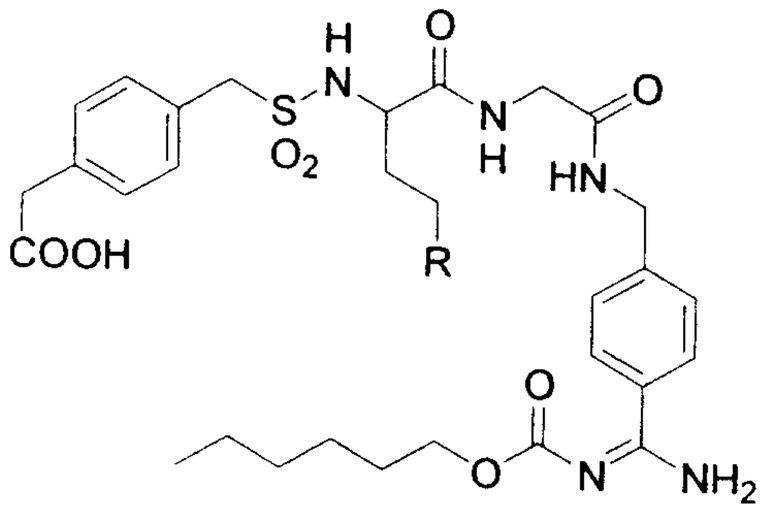


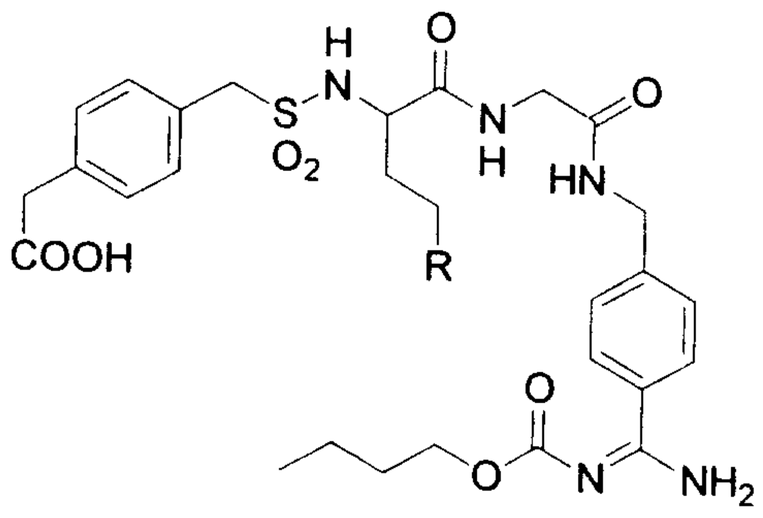


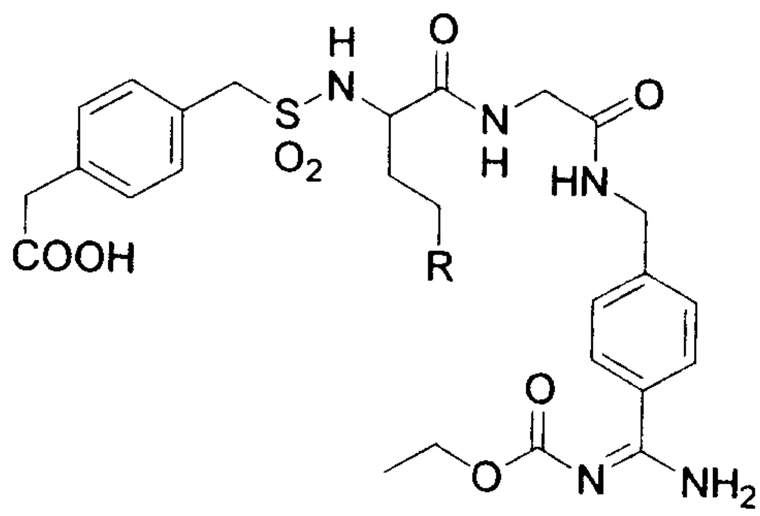


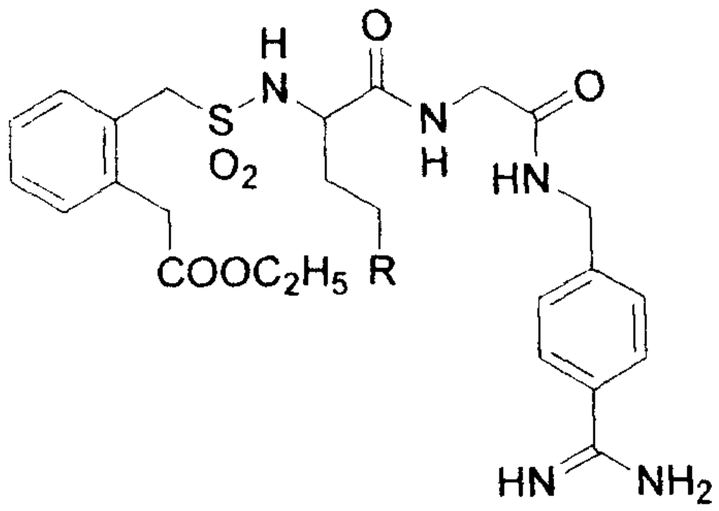


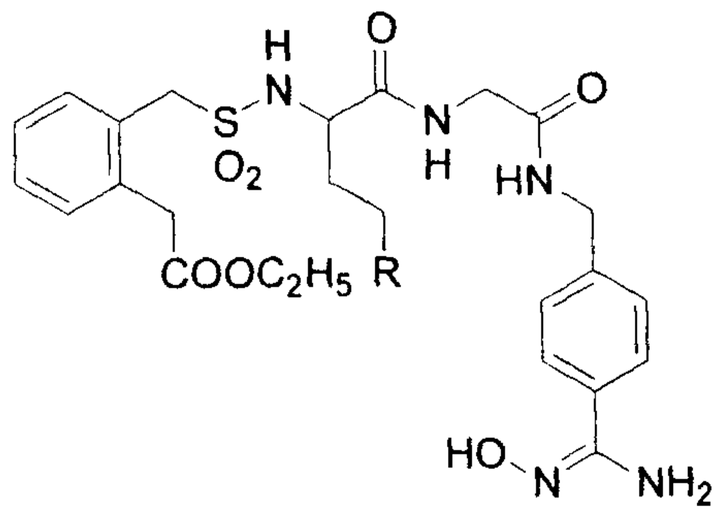


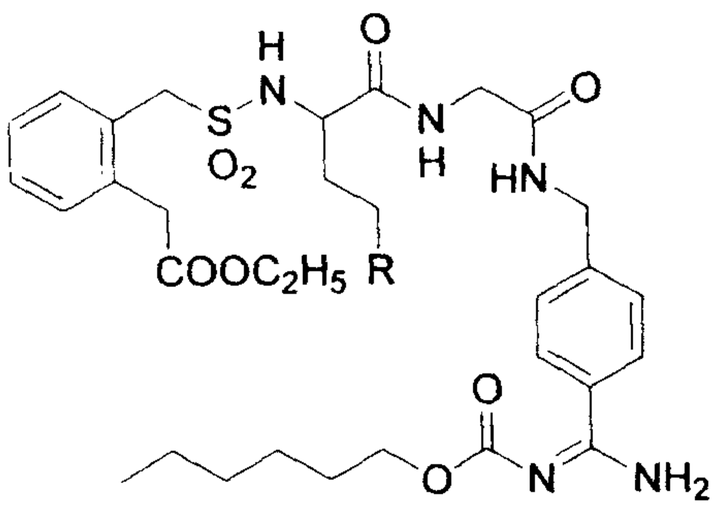


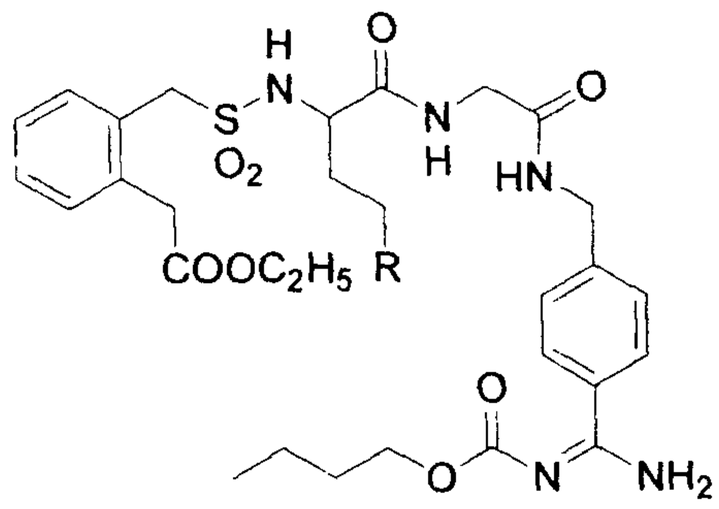


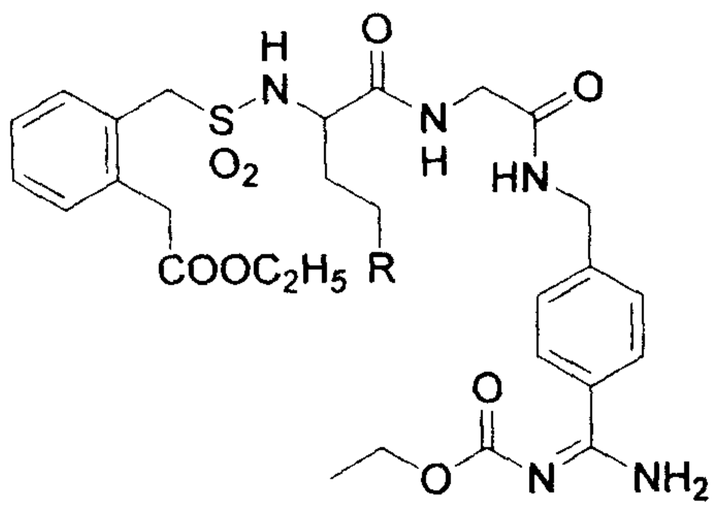


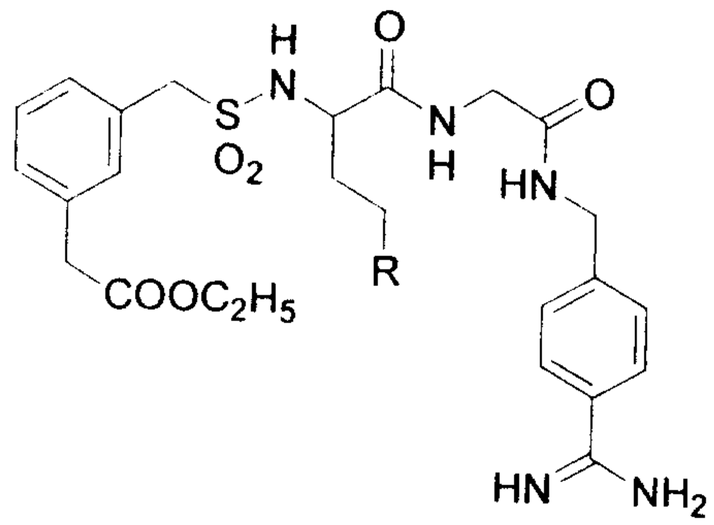


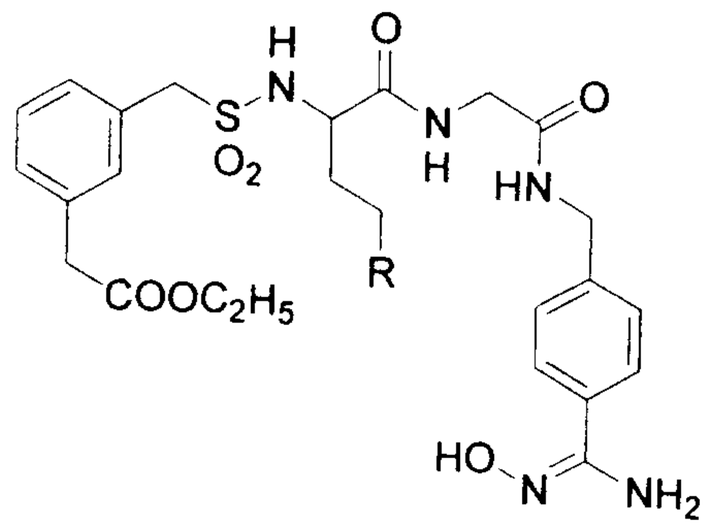


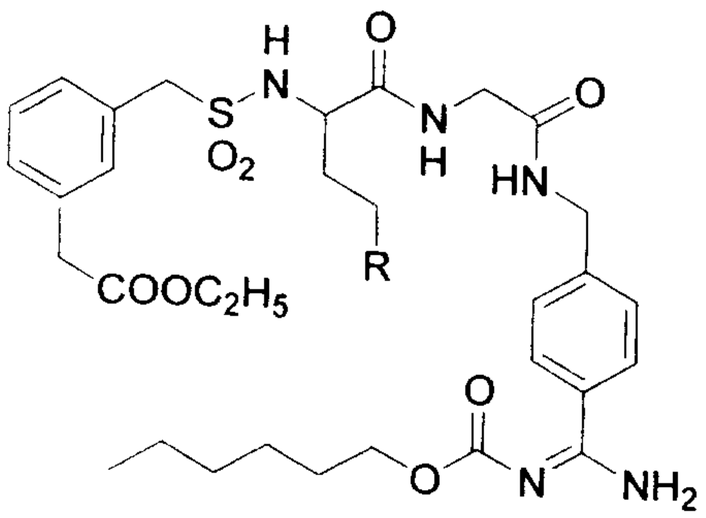


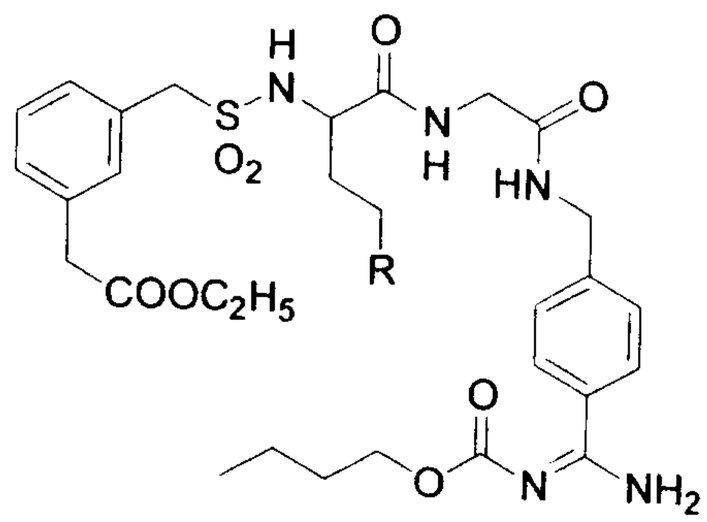


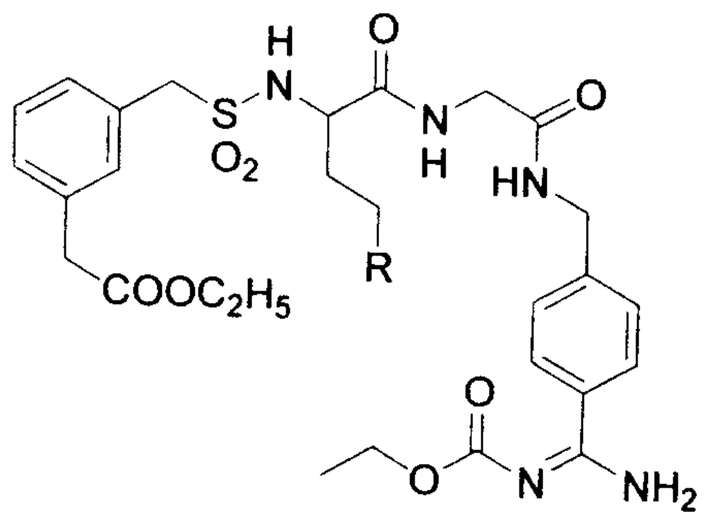


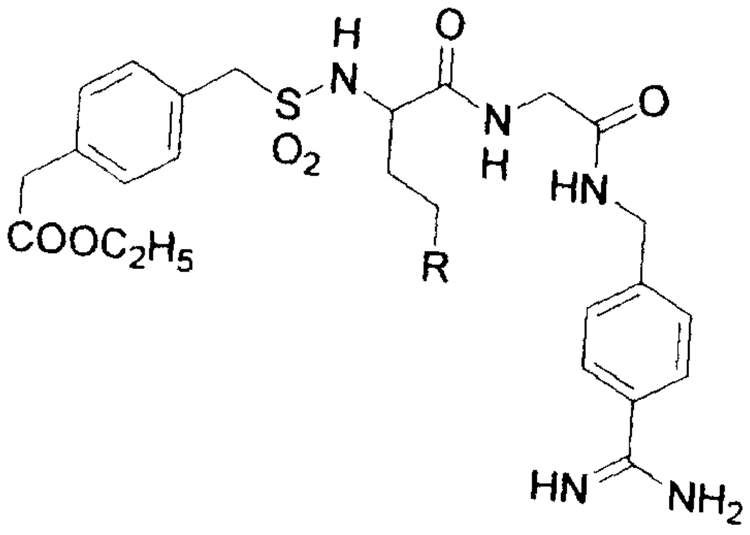


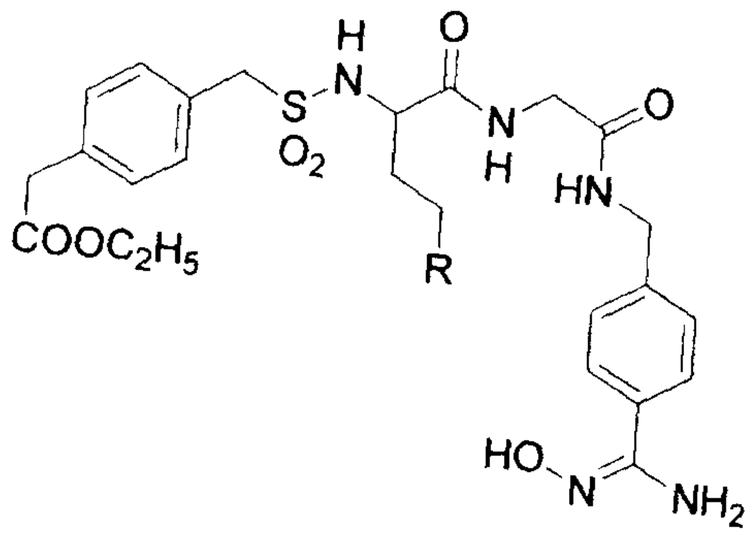


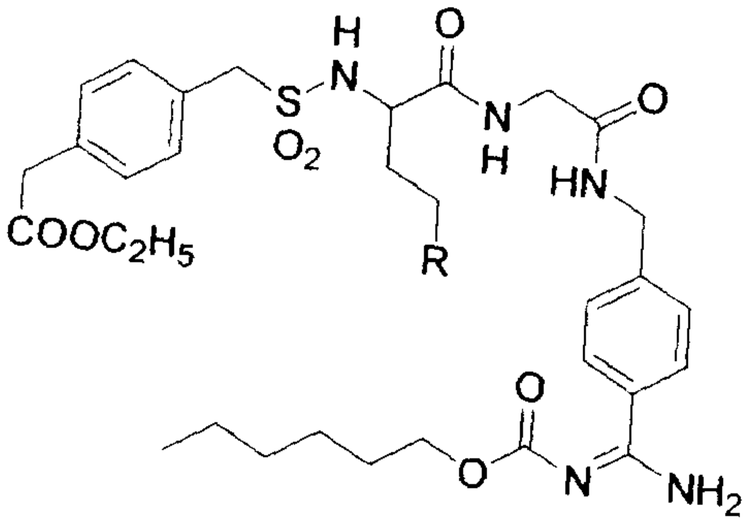


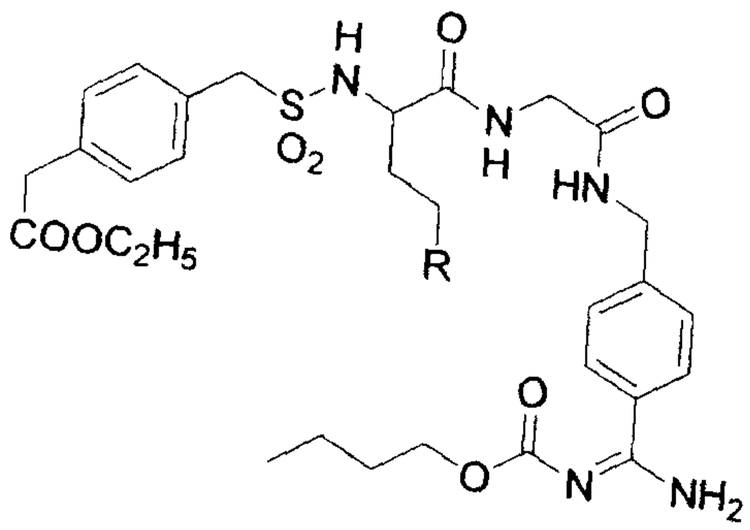


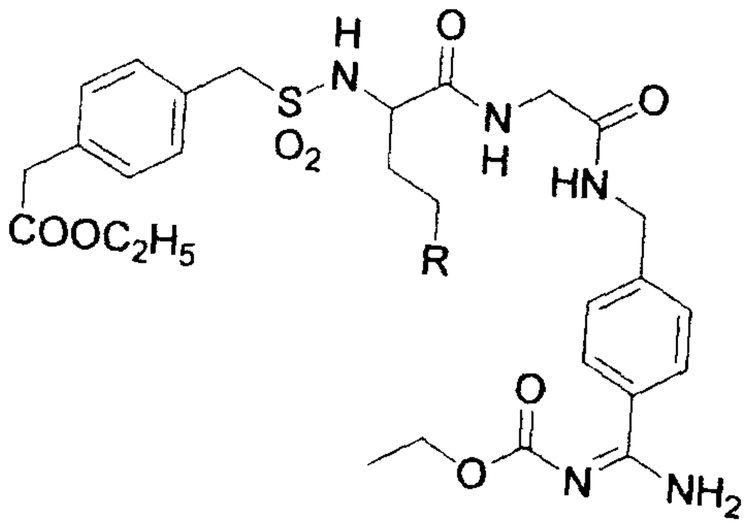


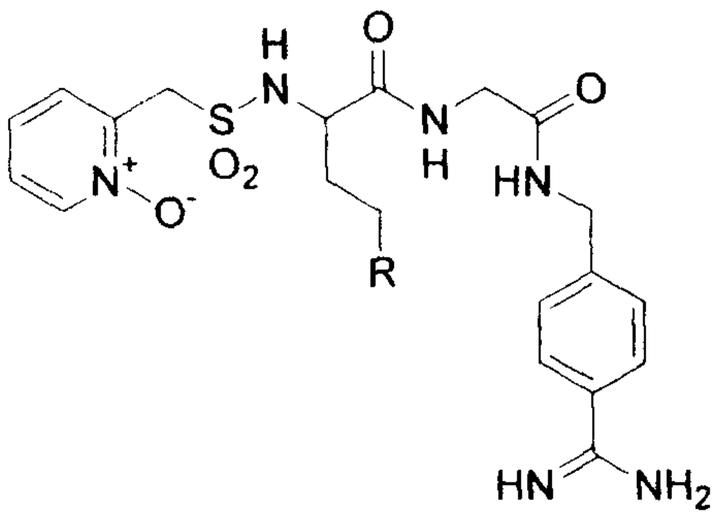


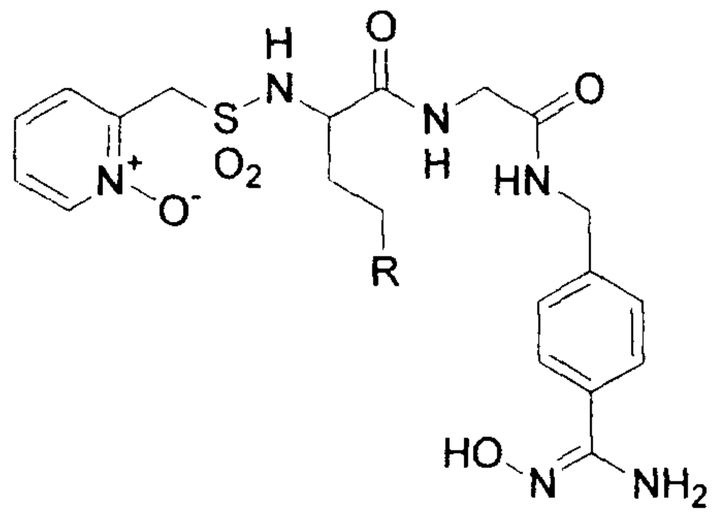


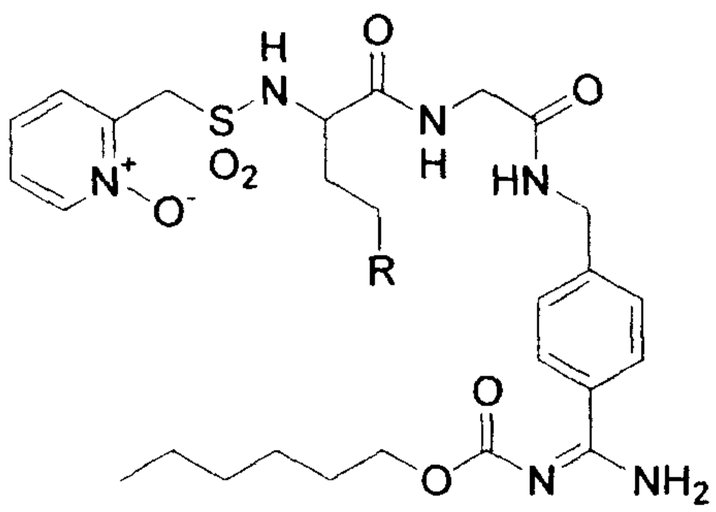


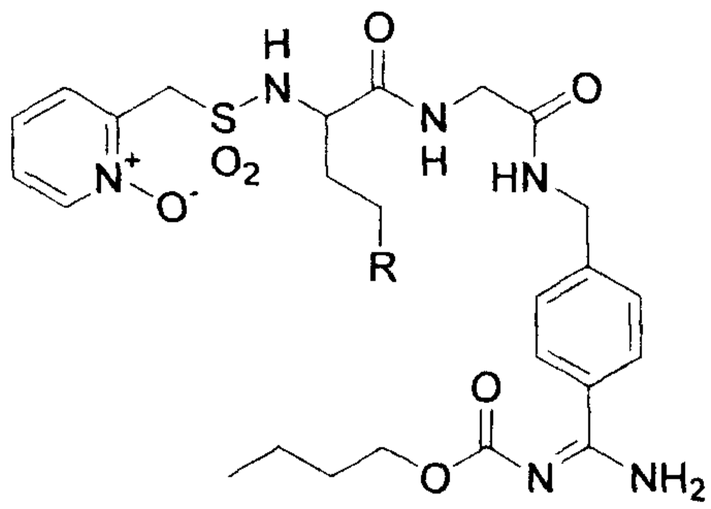


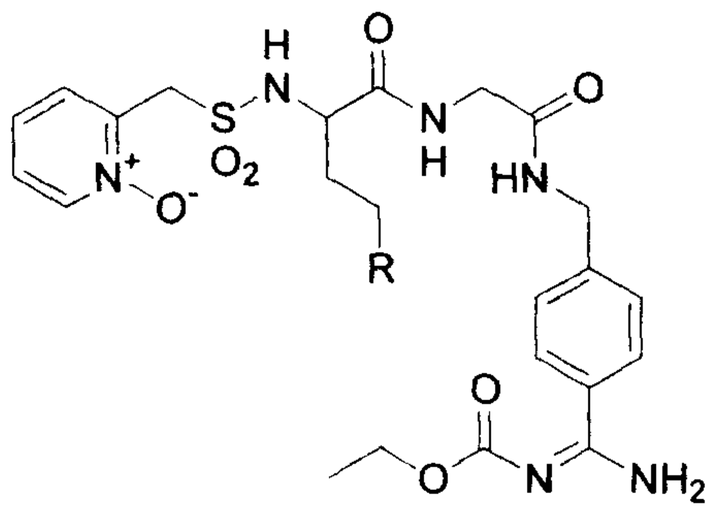


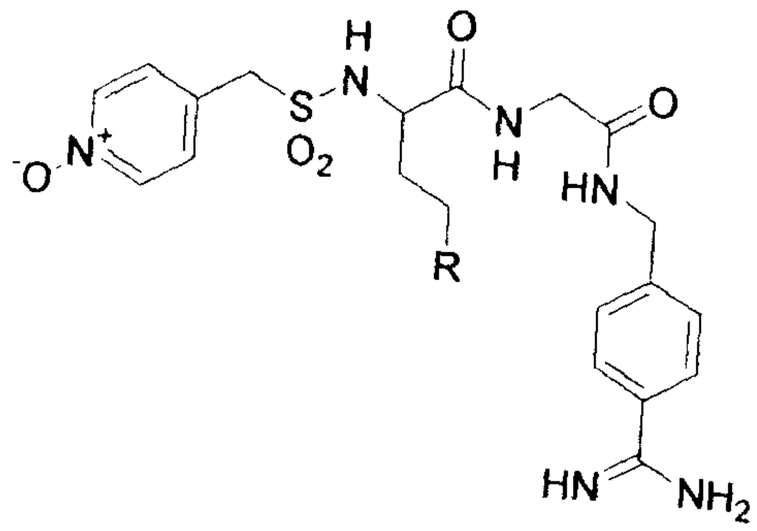


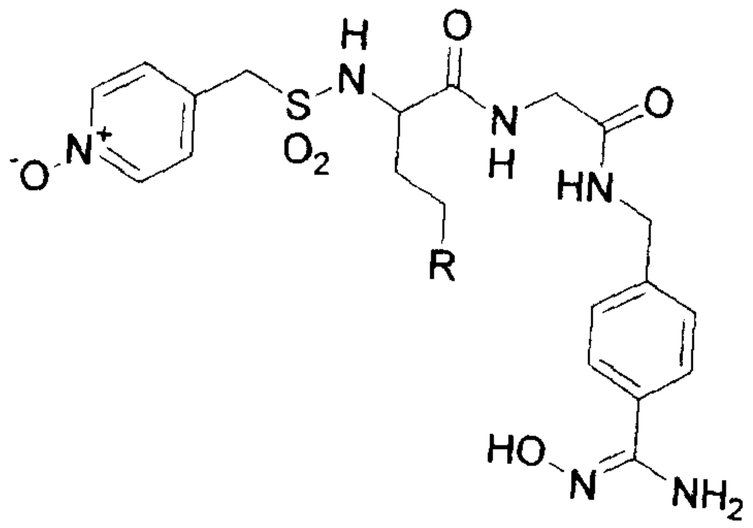


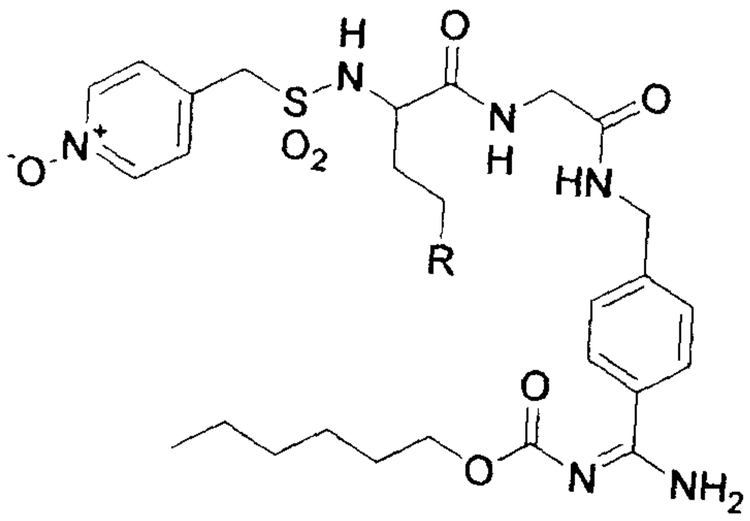


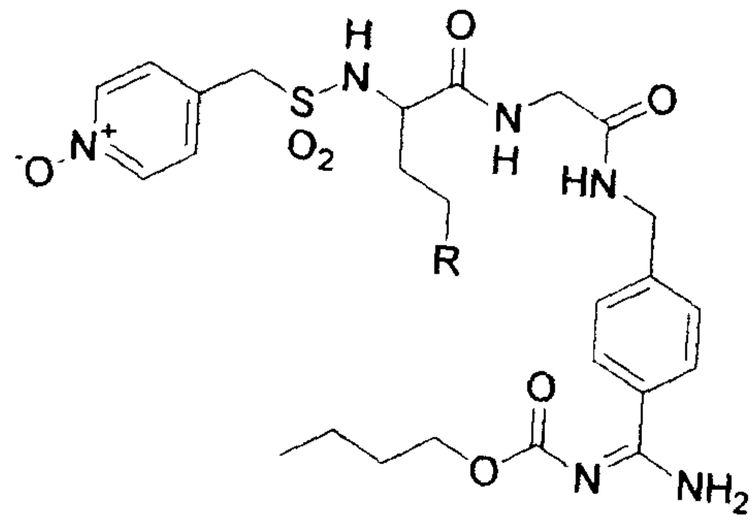


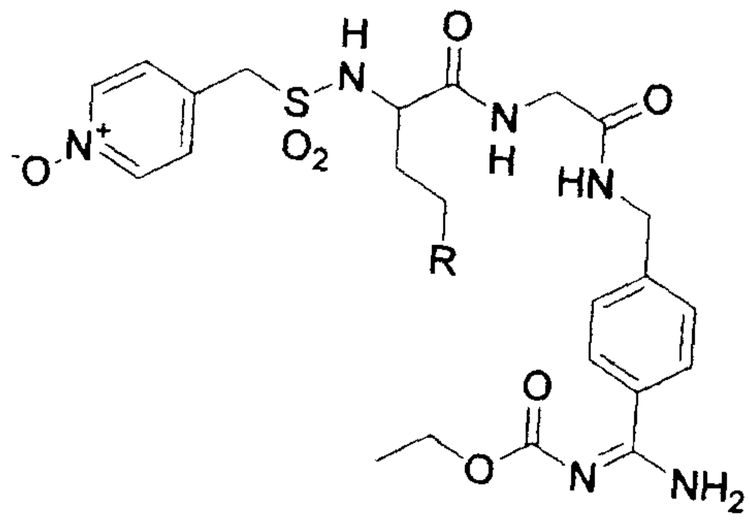


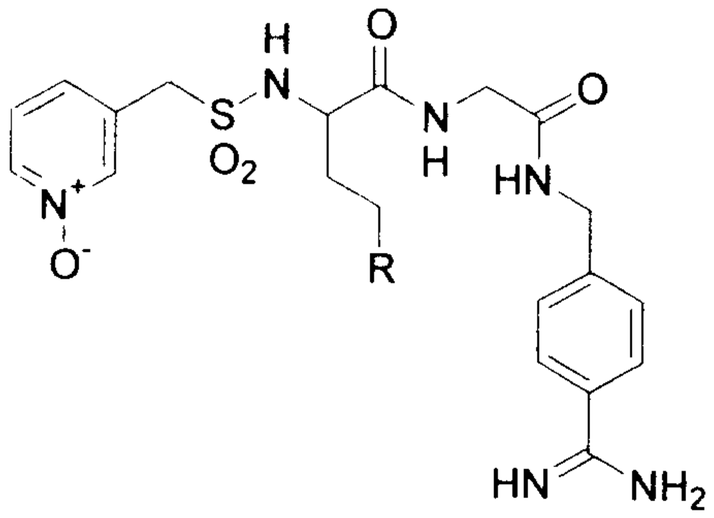


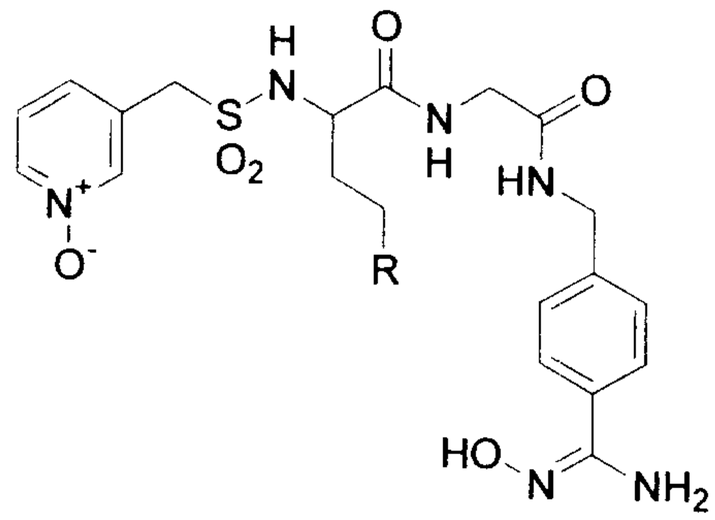


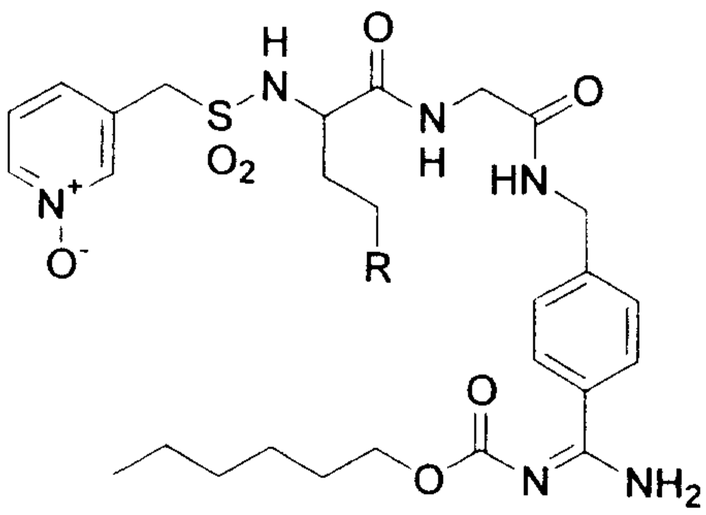


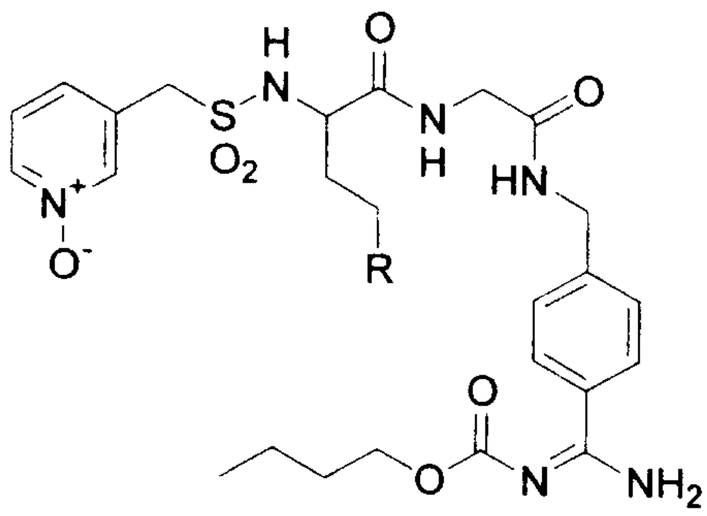


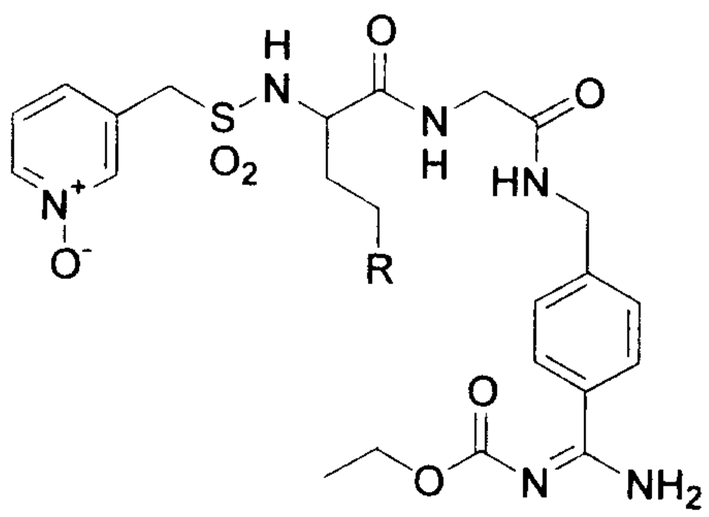


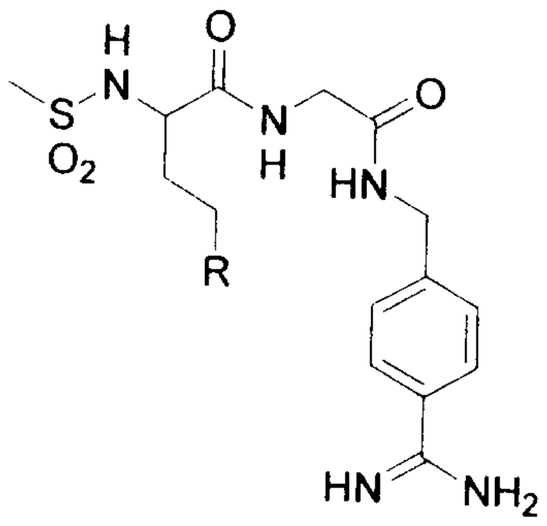


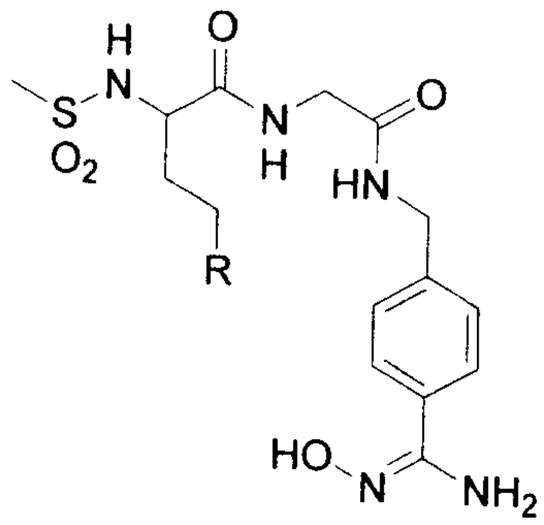


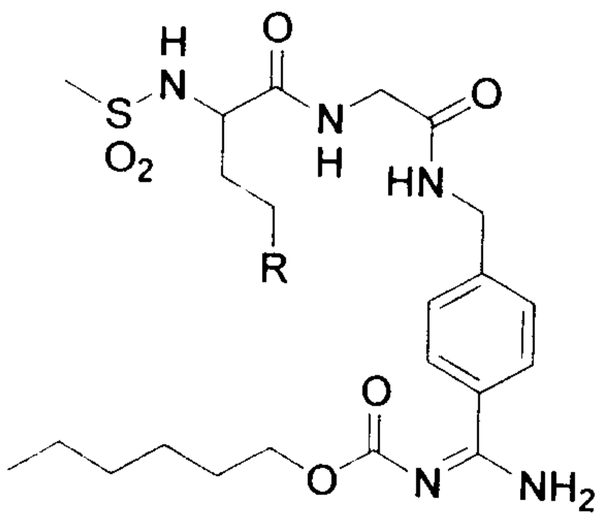


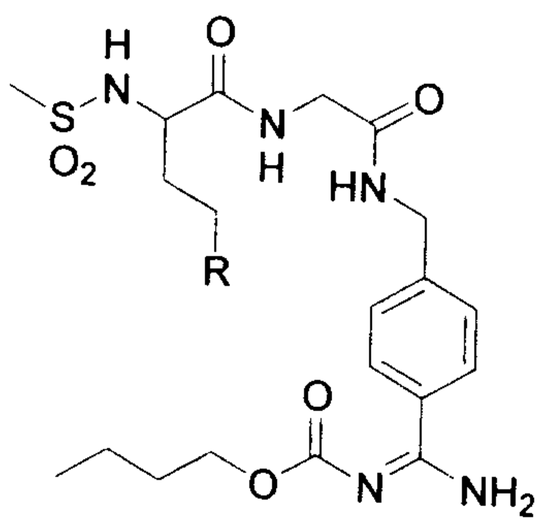


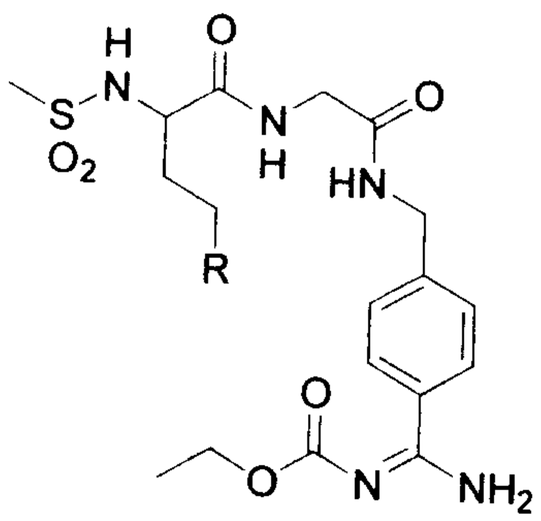


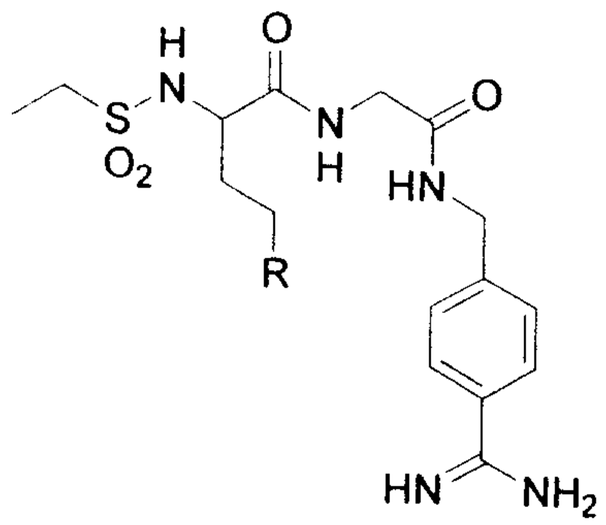


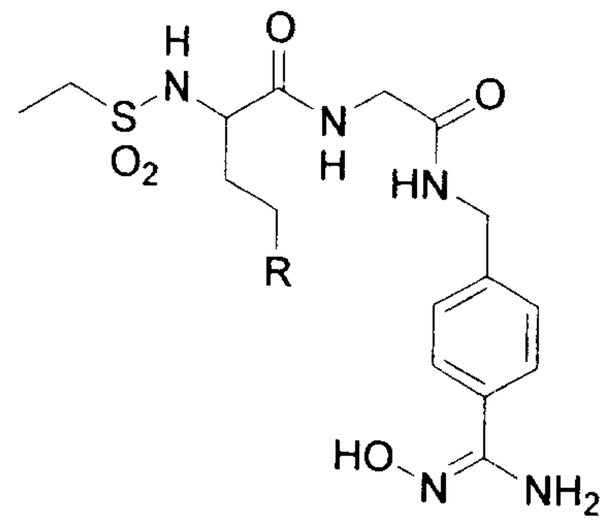


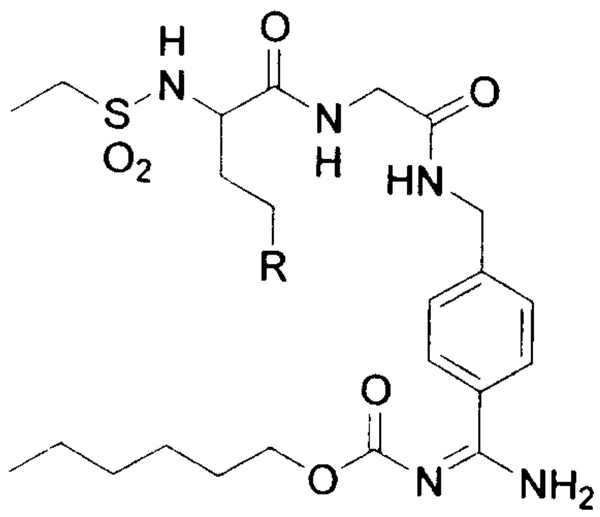


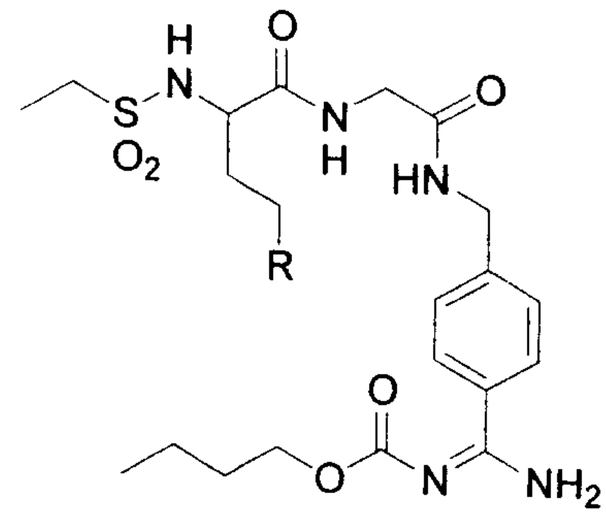


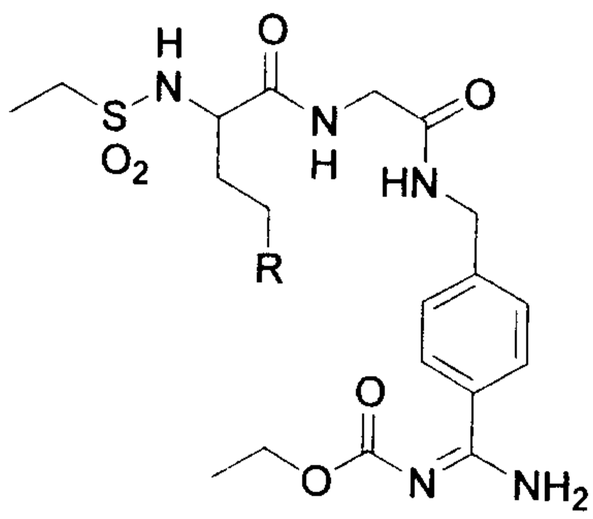


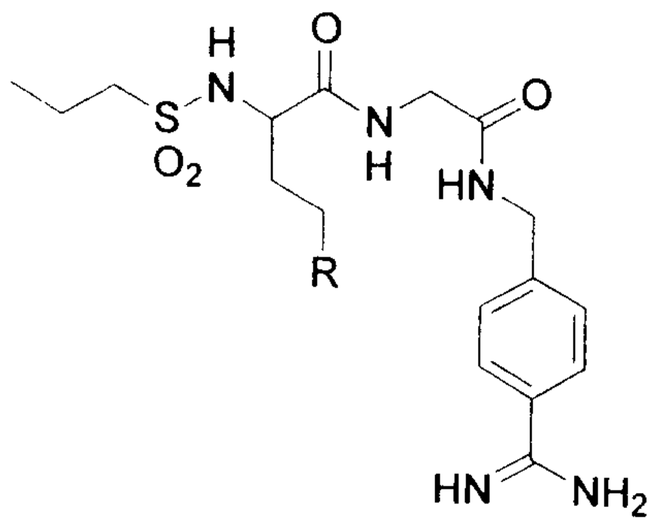


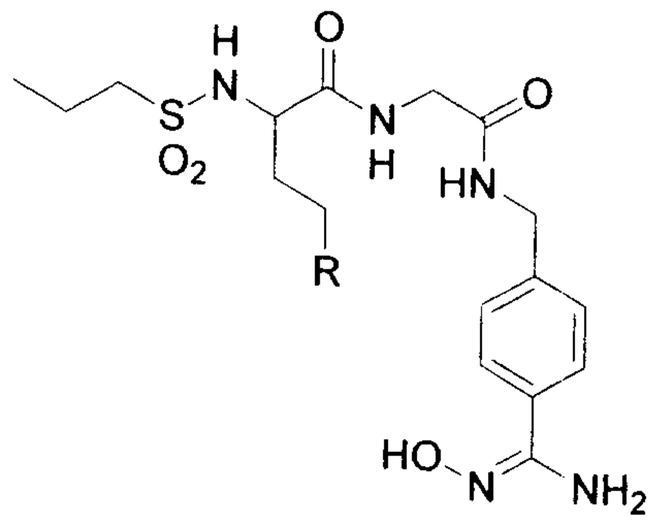


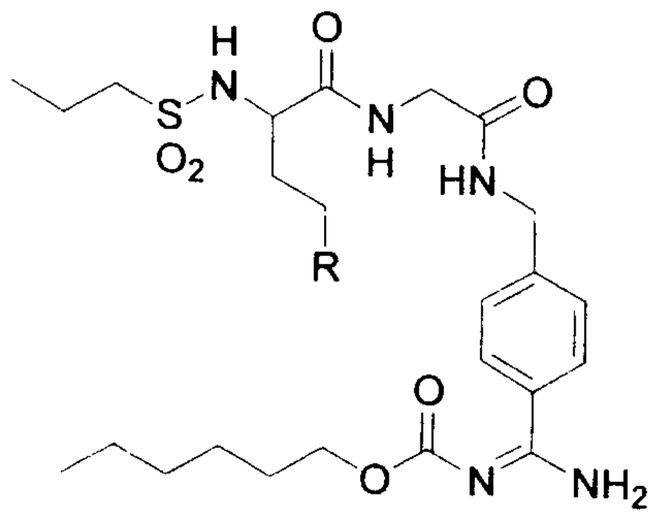


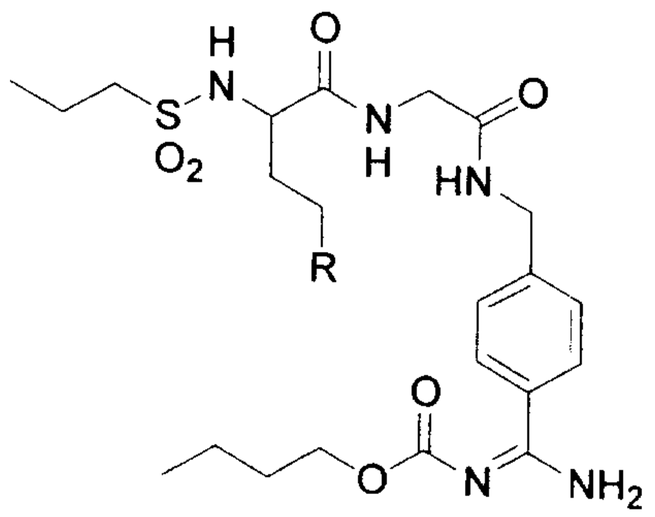


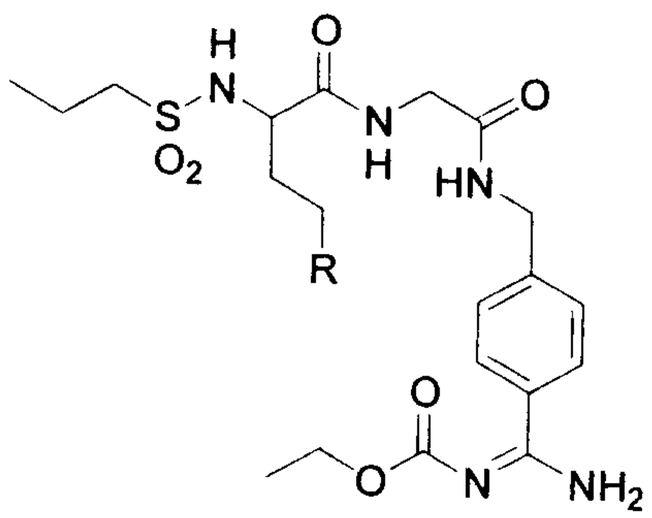


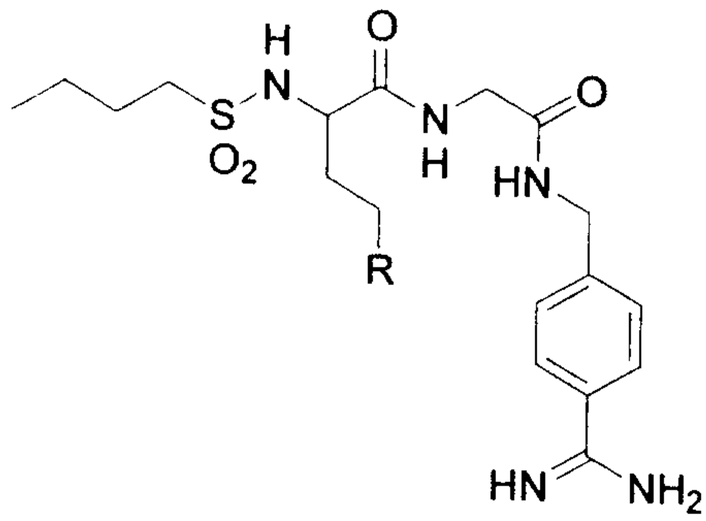


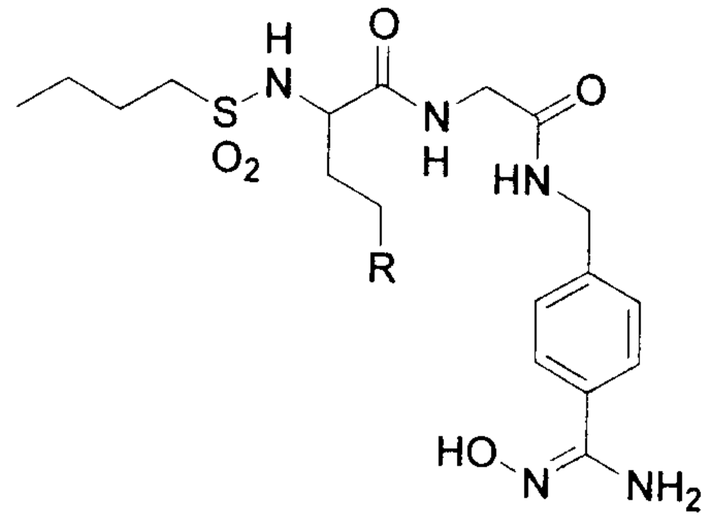


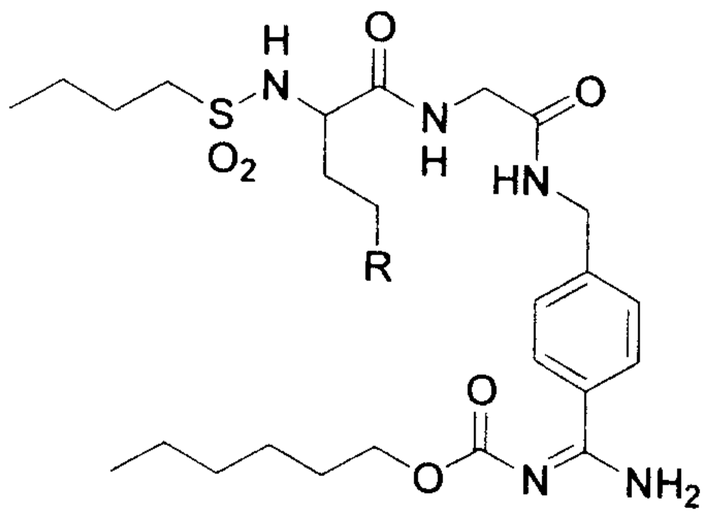


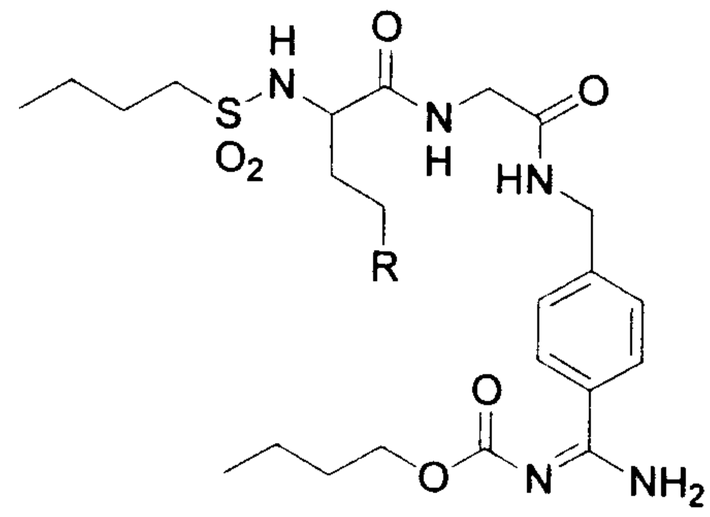


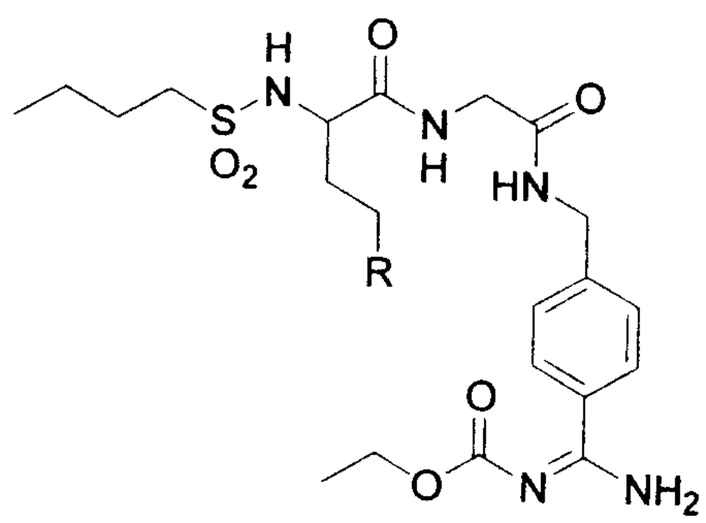


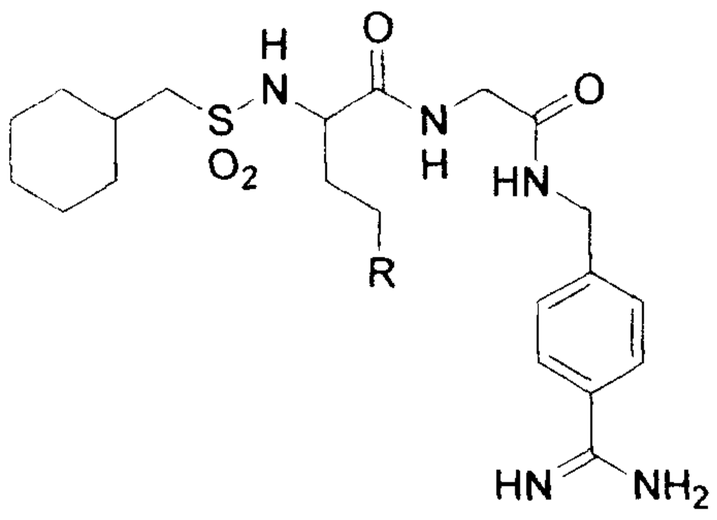


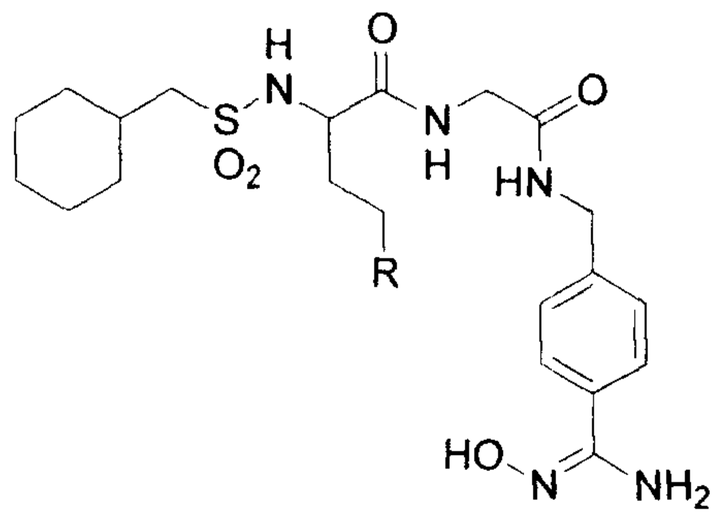


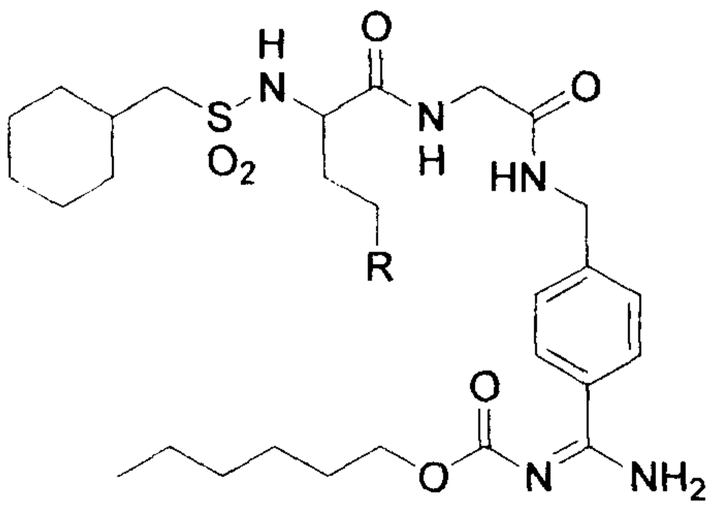


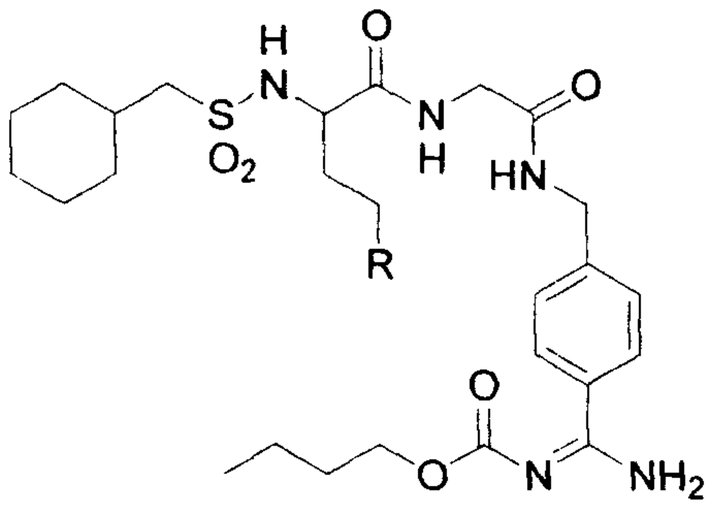


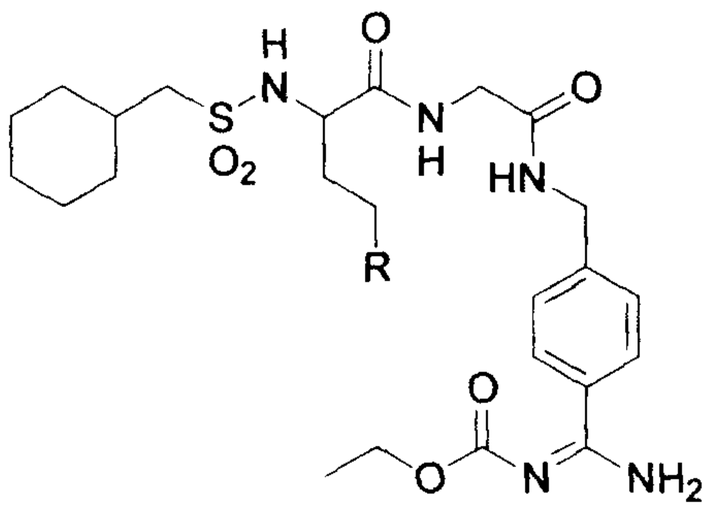




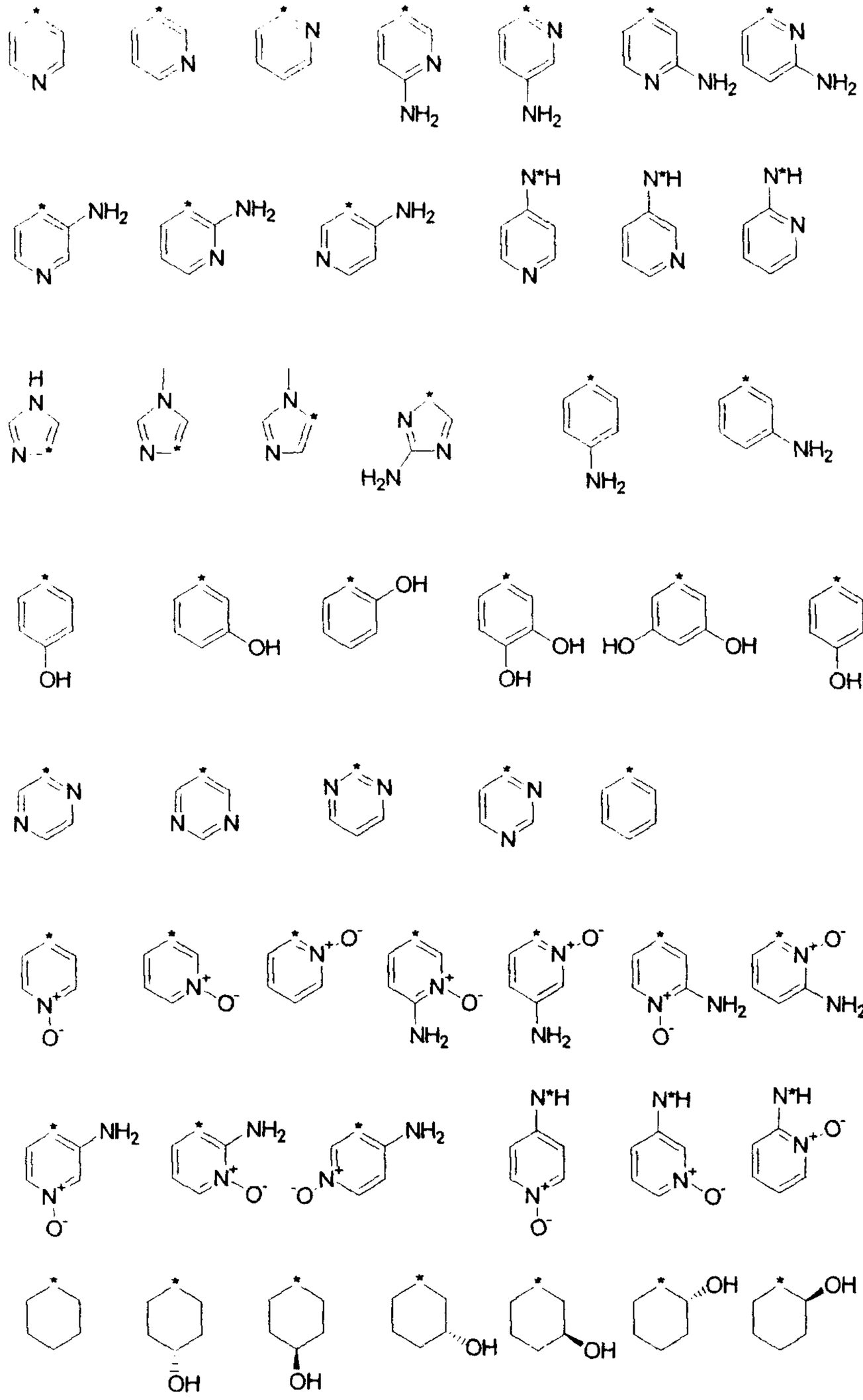








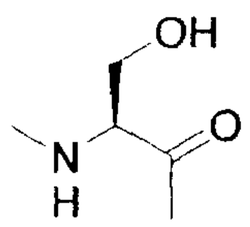
where the radical R is selected from the radicals



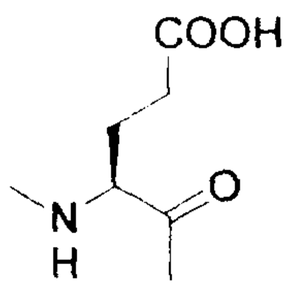
where the linkage of the group R to the Cγ carbon atom of the radical P_2 originates from the atom labeled with an asterisk, and the amino acid on which the radical R is located may be present in both the D and the L configuration, but particularly preferably in the D configuration.

10. The compound as claimed in at least one of claims 1 to 8, characterized in that the compound is selected from a structure as claimed in claim 9, where, in the structures mentioned, the glycine residue with the structural element

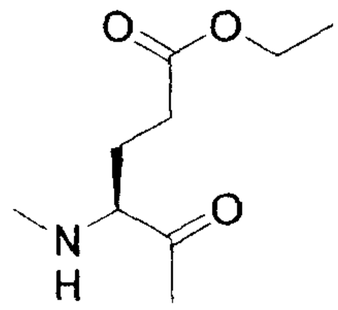
is in each case replaced by a serine residue with the structural element



or by a glutamic acid residue with the structural element



or by a glutamine γ-ethyl ester with the structural element



11. The compound as claimed in at least one of claims 1 to 10, characterized in that the compounds are in the form of salts, preferably with mineral acids or with suitable organic acids, preferably with hydrochloric acid, sulfuric acid, acetic acid, formic acid, methylsulfonic acid, succinic acid, malic acid or trifluoroacetic acid, especially in the form of their hydrochlorides, sulfates or acetates.

12. A method for preparing a compound as claimed in at least one of claims 1 to 11, characterized in that the appropriate amino acids are coupled sequentially onto an amidinobenzylamine which is protected on the amidino group, with the N-terminal amino acid either already carrying the R_5 radical or the latter subsequently being linked thereto.

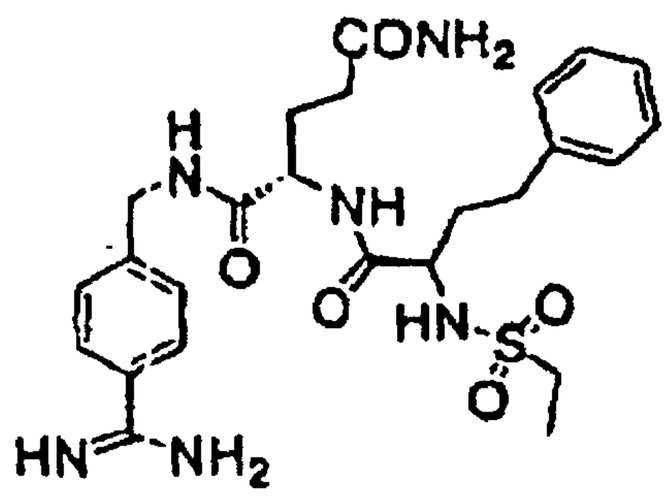
13. A medicament comprising a compound as claimed in at least one of claims 1 to 11 and pharmaceutically suitable excipients and/or additives.

14. The medicament as claimed in claim 13, where the medicament is employed in the form of a tablet, of a coated tablet, of a capsule, of a pellet, suppository, of a solution, in particular of a solution for injection or infusion, of eyedrops, nose and ear drops, of a syrup, of a capsule, of an emulsion or suspension, of a pessary, stick, aerosol, dusting powder, of a paste, cream or ointment.

15. The use of a compound as claimed in at least one of claims 1 to 11 or of a medicament as claimed in claim 13 or 14 as factor Xa inhibitor for the therapy or prophylaxis of a cardiovascular disorder or of a thromboembolic event, in particular in oral, subcutaneous, intravenous or transdermal form.

16. The compound as claimed in any of claims 1 to 7, where Z is an amino group.

17. The compound as claimed in any of claims 1 to 7 or 16, where R_2 is a $-(CH_2)_aCONHR_{7*}$ or $-(CH_2)_aCONHR_{7**}$ group, where a = 1, 2 or 3 and R_{7**} is an aryl radical or a heteroaryl radical having 1-2 heteroatoms selected from N, S or O, with the proviso that the compound is not



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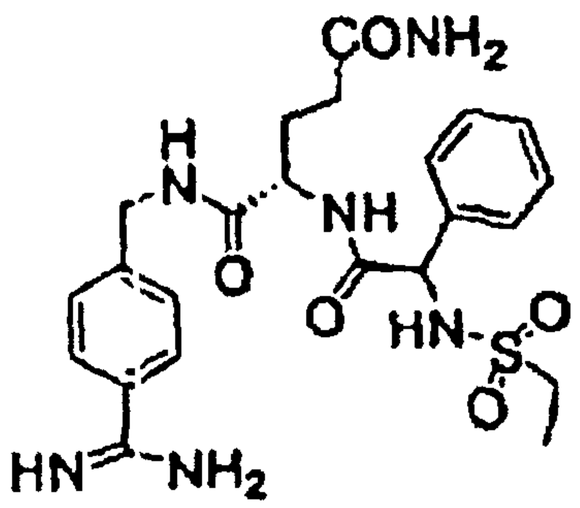

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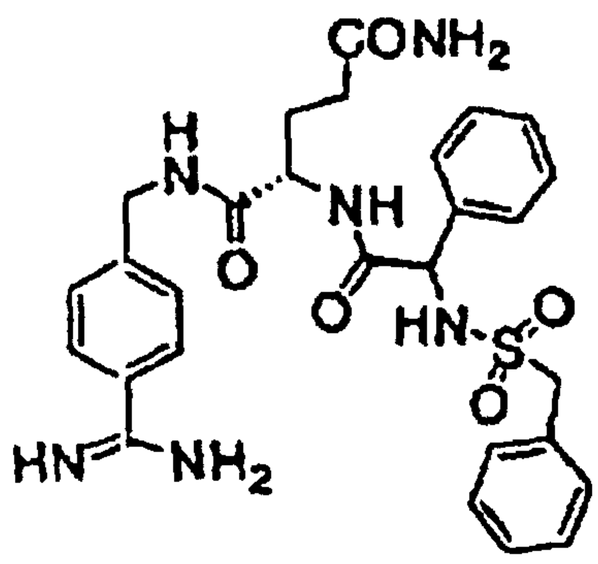


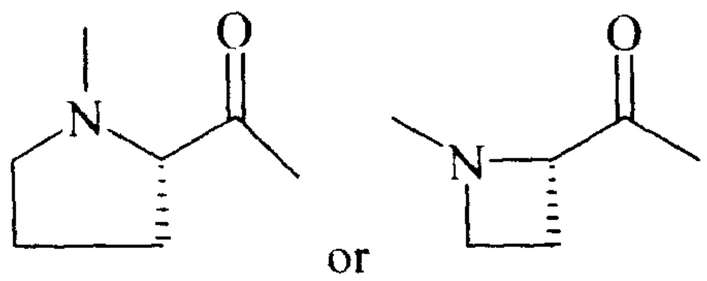
18. The compound as claimed in any of claims 1 to 7 or 16, where R_1 is a $-(CH_2)_aCONHR_{7*}$ or $-(CH_2)_aCONHR_{7**}$ group, where a = 1, 2 or 3 and R_{7**} is an aryl radical or a heteroaryl radical having 1-2 heteroatoms selected from N, S or O, and the heteroaryl radical is substituted by at least one of the following: halogen, methyl, ethyl, amino, $-CH_2NH_2$, nitro, -OH, -COOH, $-CH_2COOH$.

19. The compound as claimed in any of claims 1 to 7 or 16, where R_2 is a $-(CH_2)_n-NH_2$ group with n = 1, 2, 3, 4 or 5, preferably 1 or 4.

20. The compound as claimed in any of claims 1 to 7, 16 to 19, where R_5 R_9 is H.

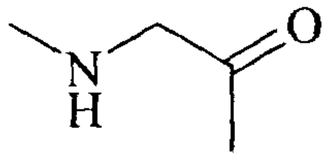
21. The compound as claimed in any of claims 1 to 7, 16 to 20, where R_4 is a $-CH_2-SR_8$ or $-CH_2CH_2-SR_8$ group.

22. The compound as claimed in any of claims 1 to 7, 16 to 21, where P_1 is a

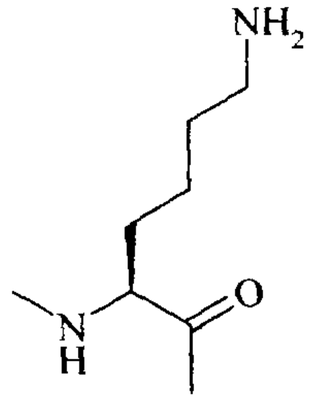


and where the radical R_4 is a $-CH_2-CH_2-R_8$ radical, where R_8 is a heteroaryl radical having 4-6 ring atoms, which has 1 or 2 heteroatoms, preferably N, and which may be substituted by one or more $-NH_2$ and/or $-OH$ groups, or P_2 in the structure A of the general formula I is derived from a homotyrosine, indanylglycine or 4-pyridylhomoalanine, or R_8 is a pyridyl N-oxide radical.

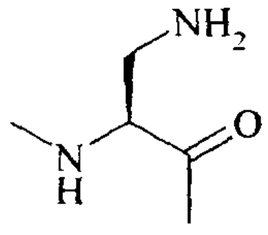
23. The compound as claimed in claim 10, characterized in that in the structures mentioned the glycine residue with the structural element



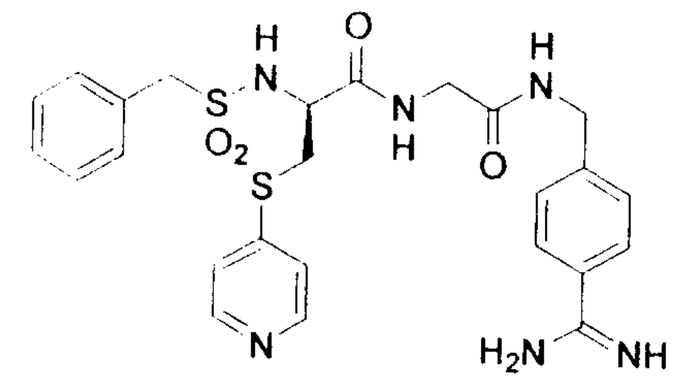
is in each case replaced by a lysyl radical with the structural element

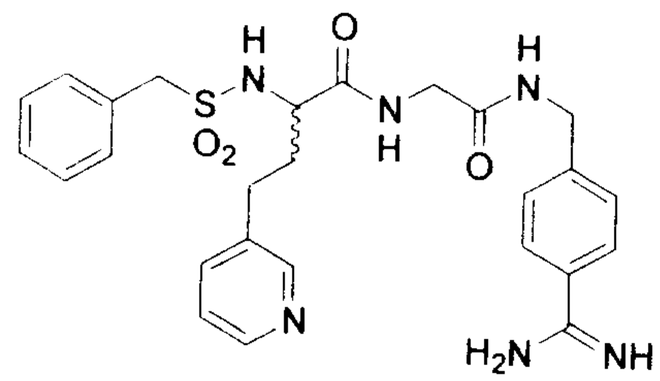


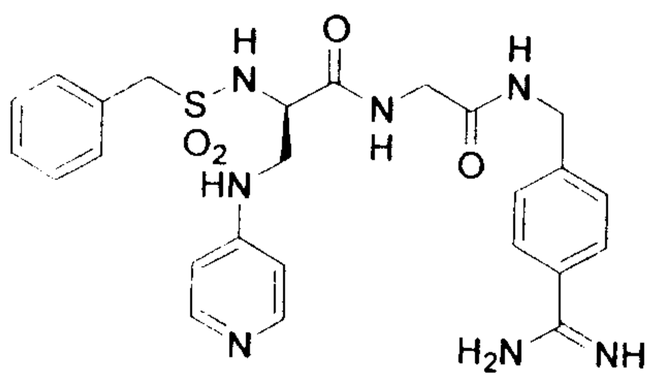
or is replaced by an α,β-diaminopropionic acid residue with the structural element

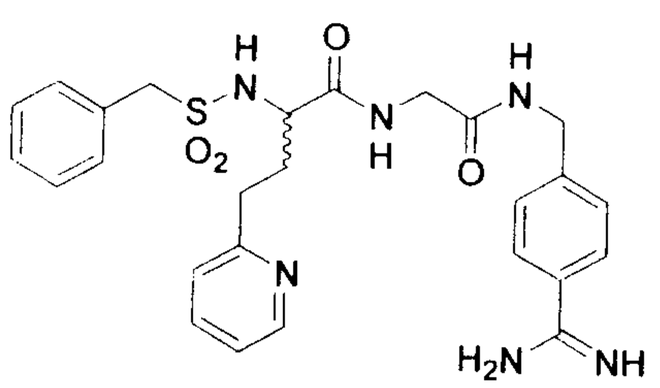


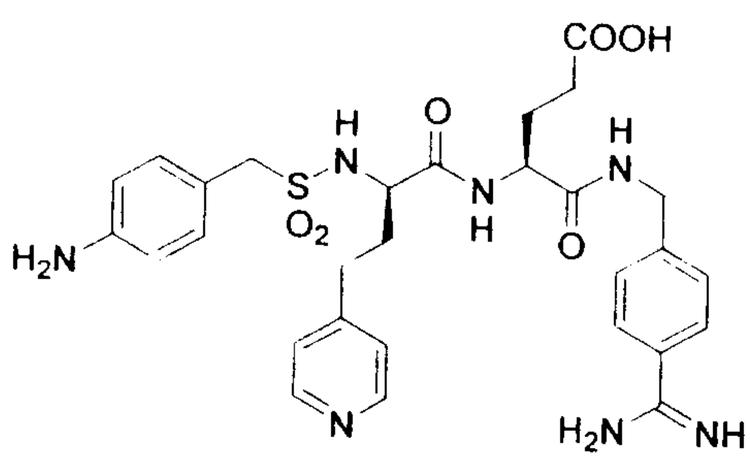
24. The compounds as claimed in any of claims 1 to 7, characterized in that the compound is selected from the following structures:

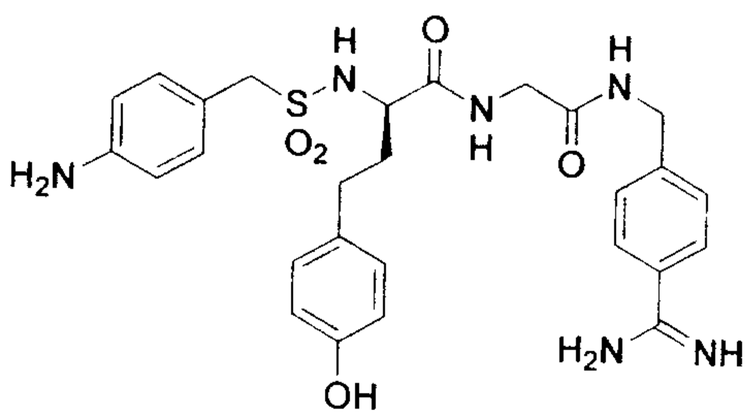


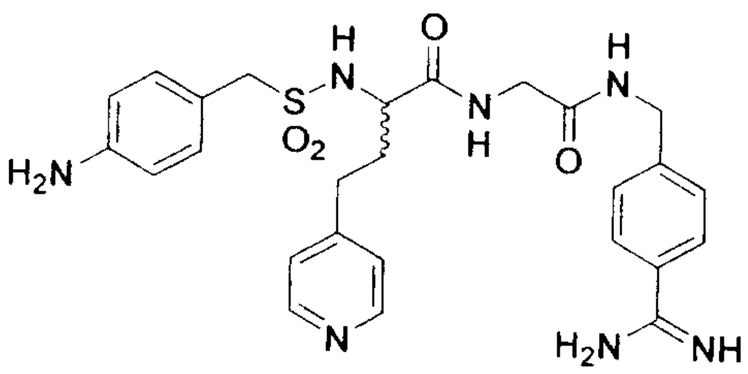


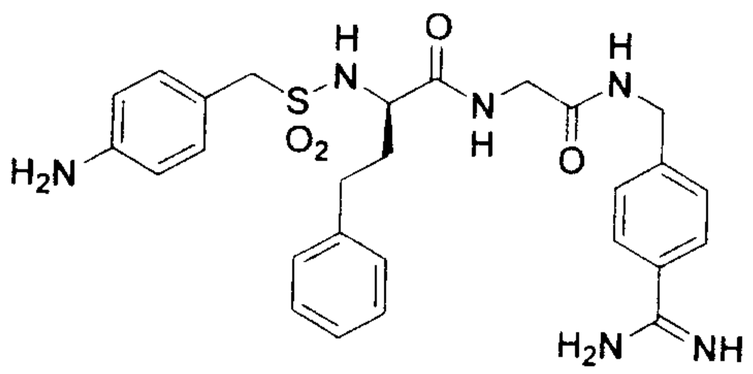


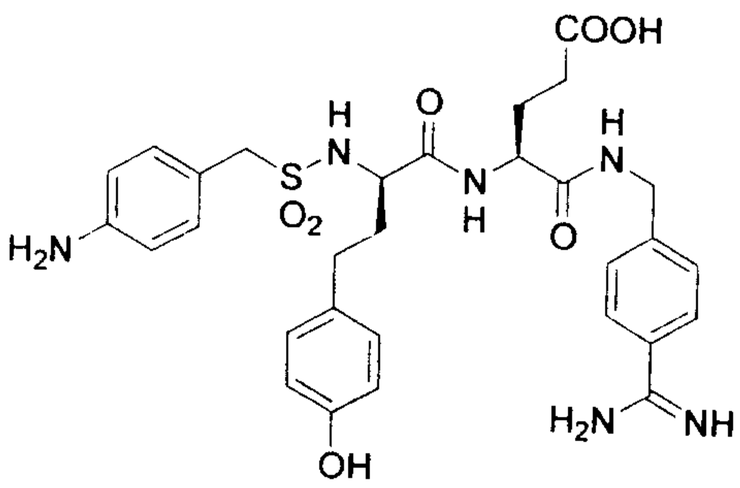


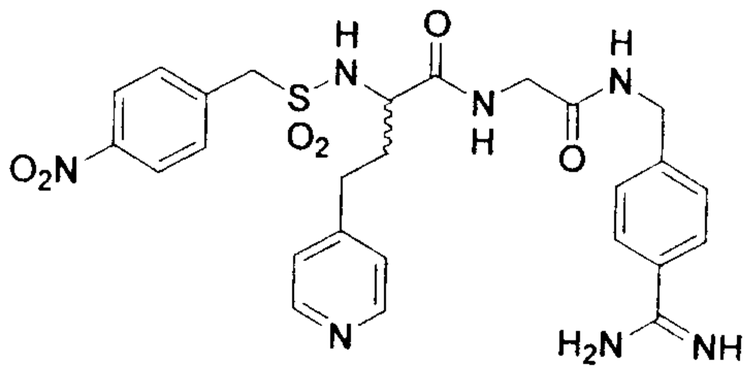


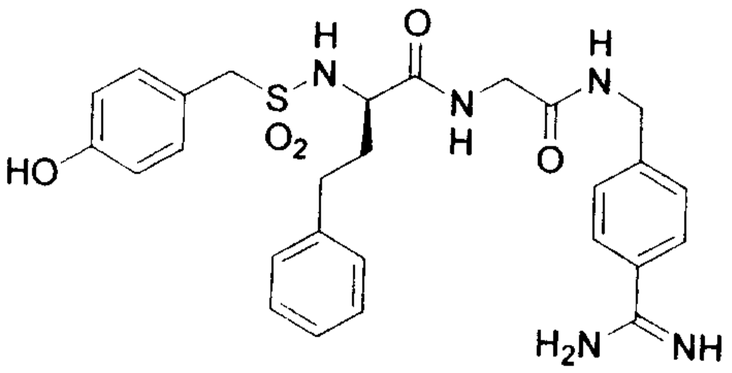


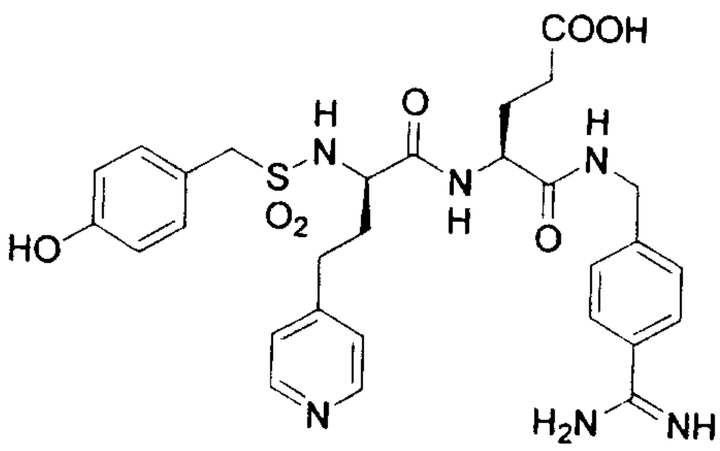


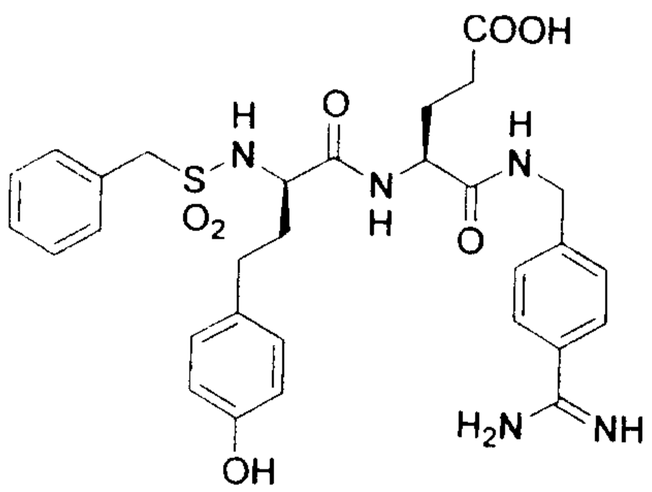


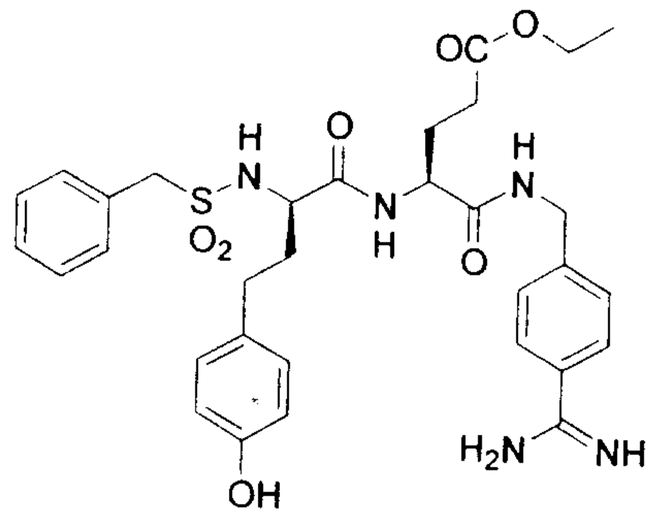


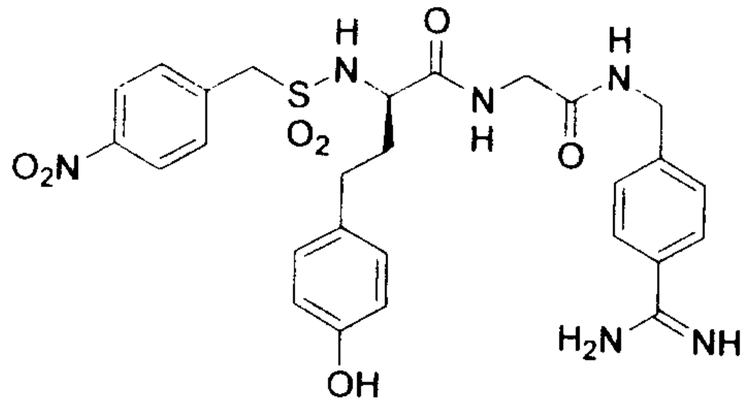


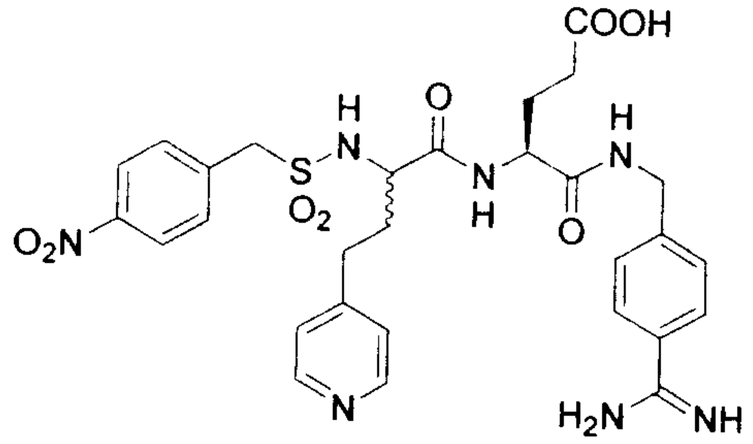


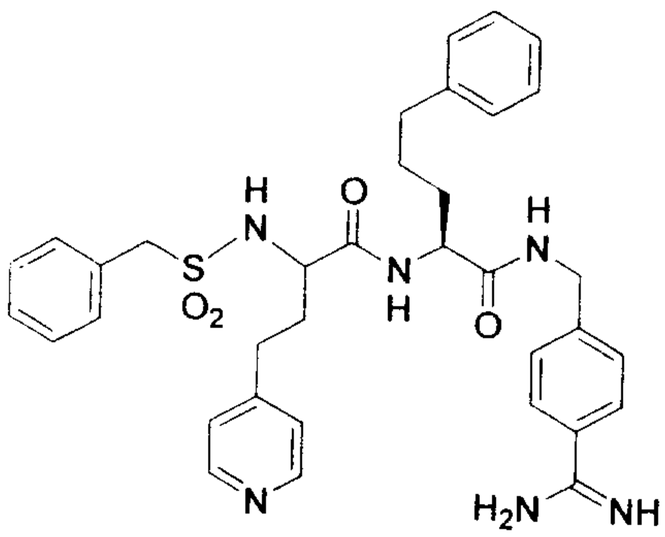


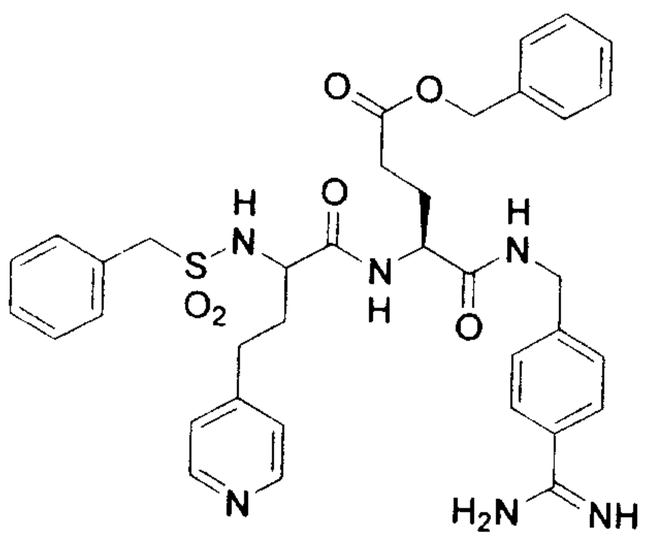


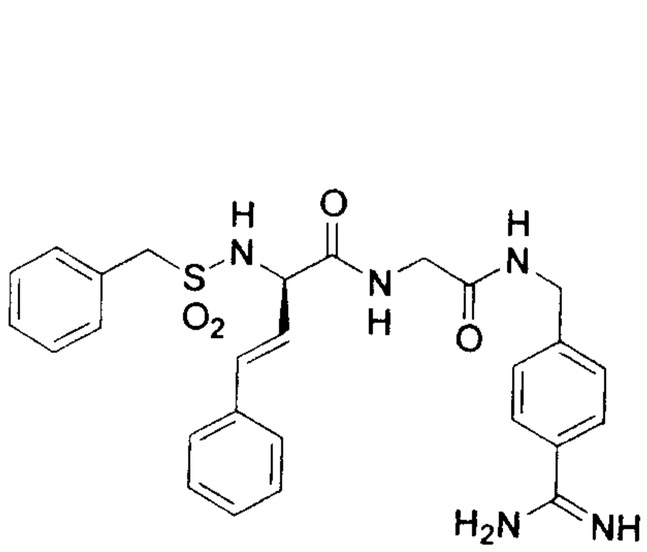


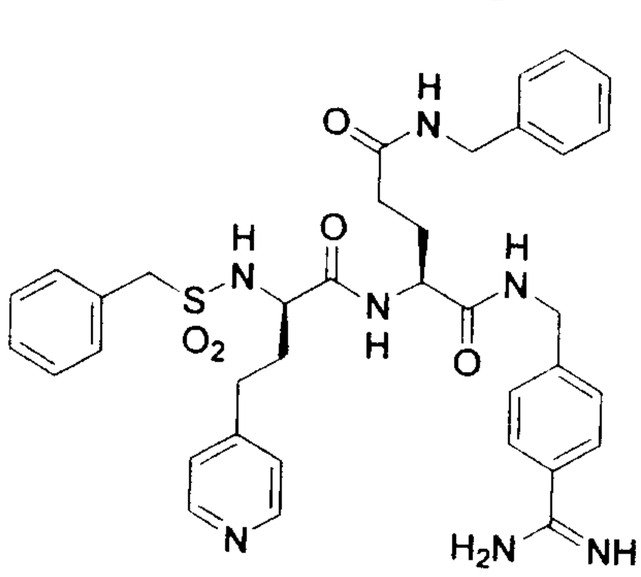


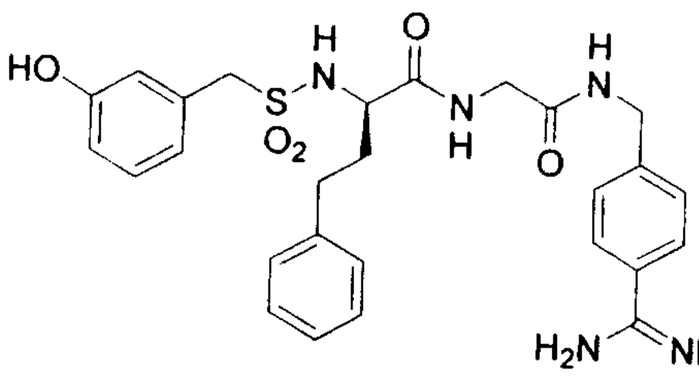


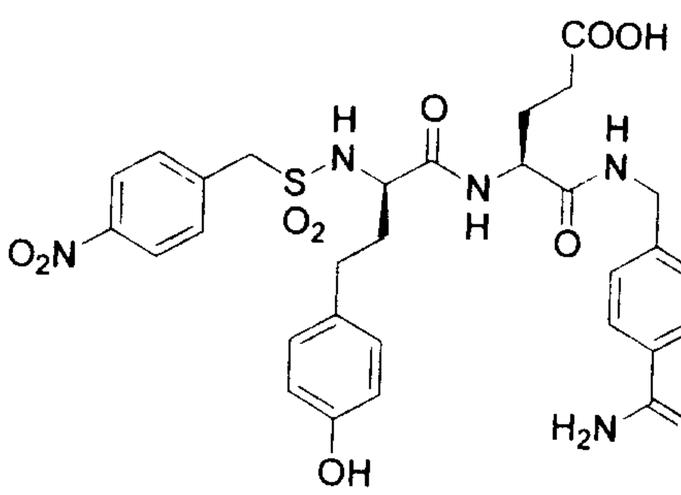












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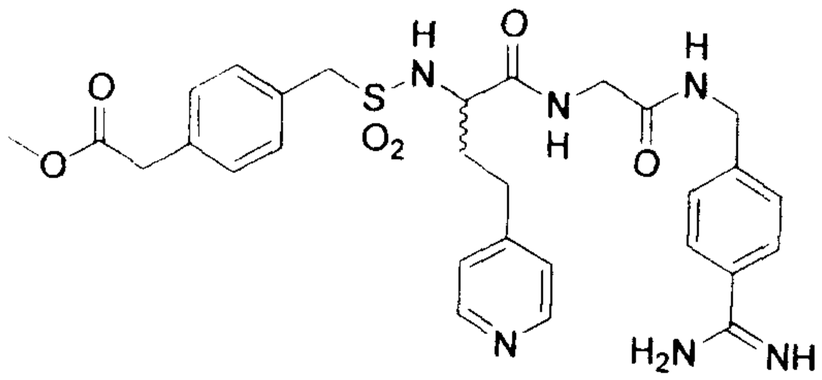
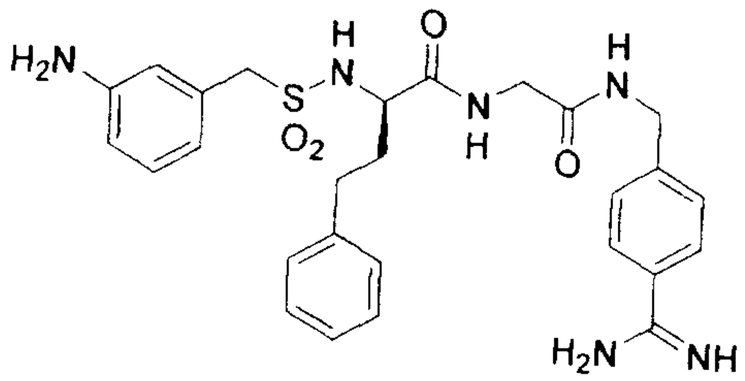
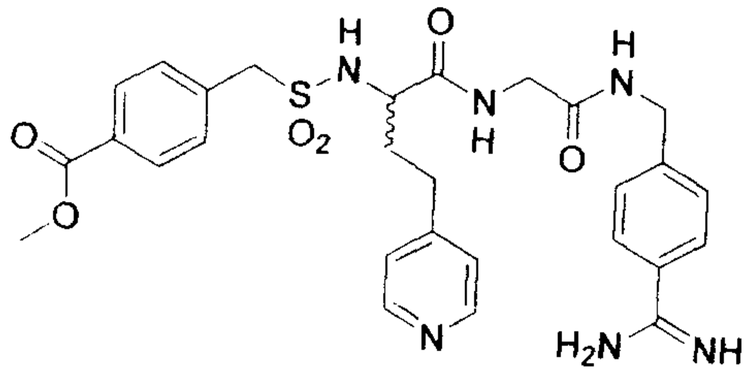
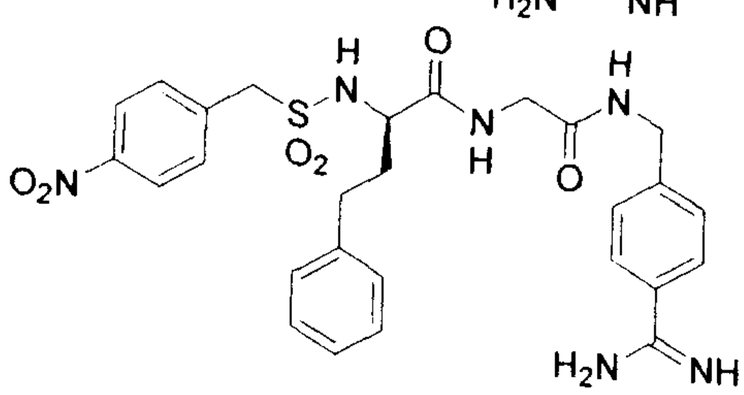
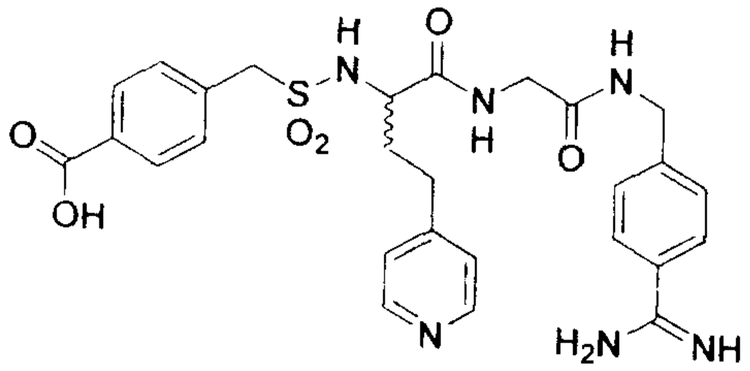
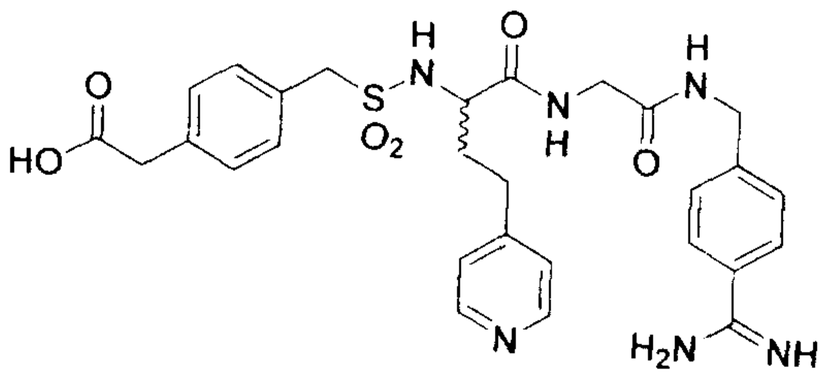


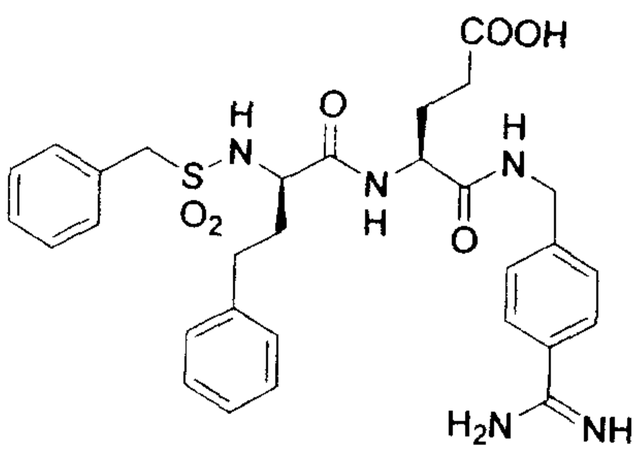


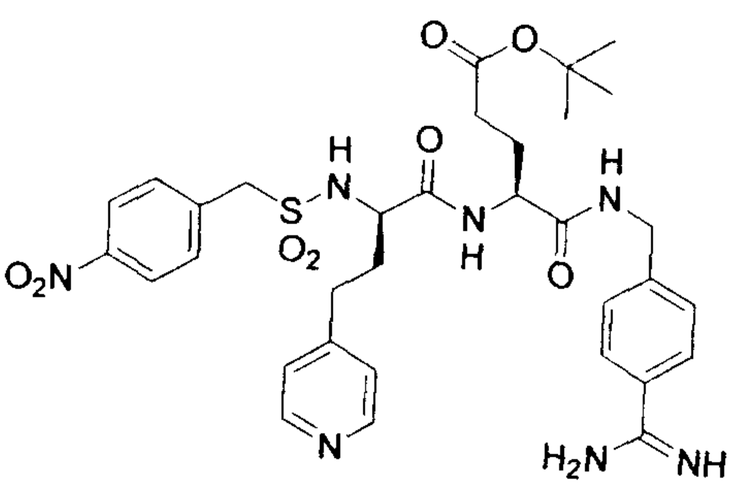


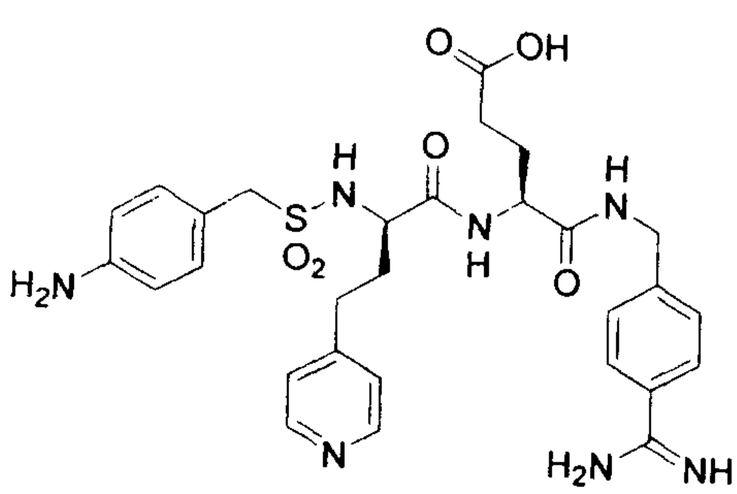


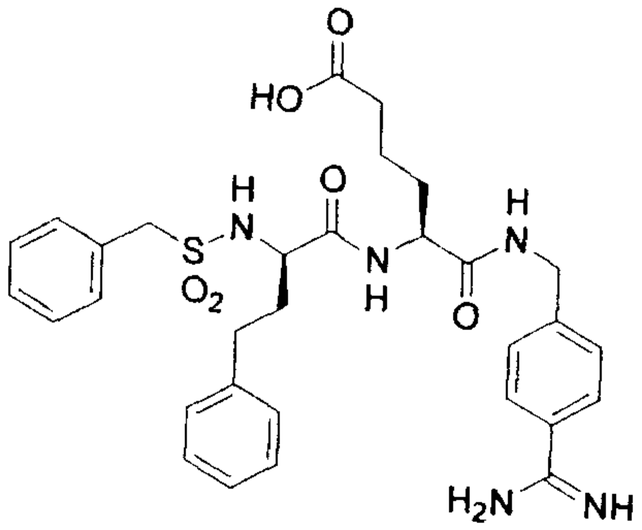


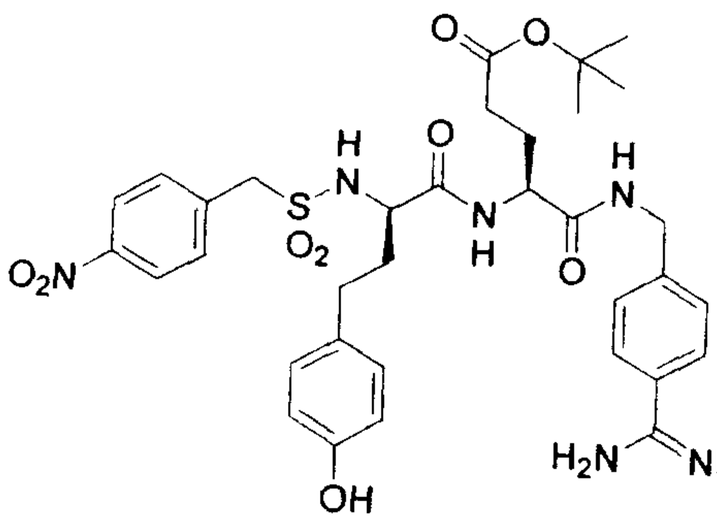


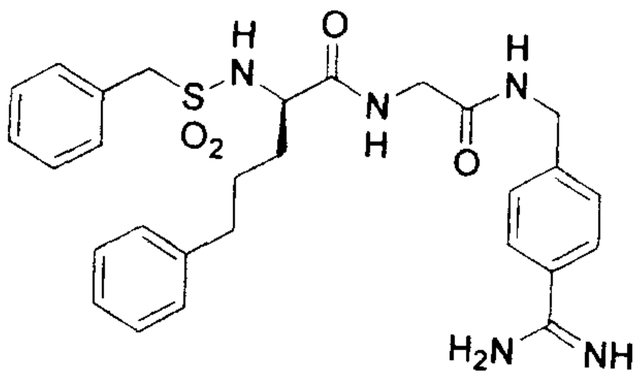


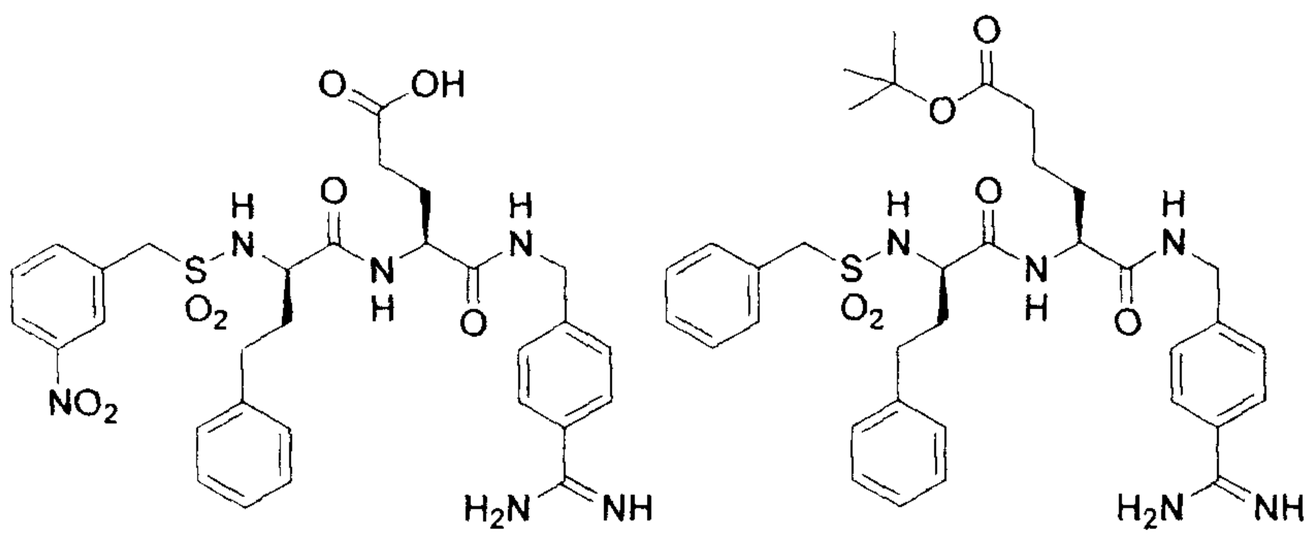


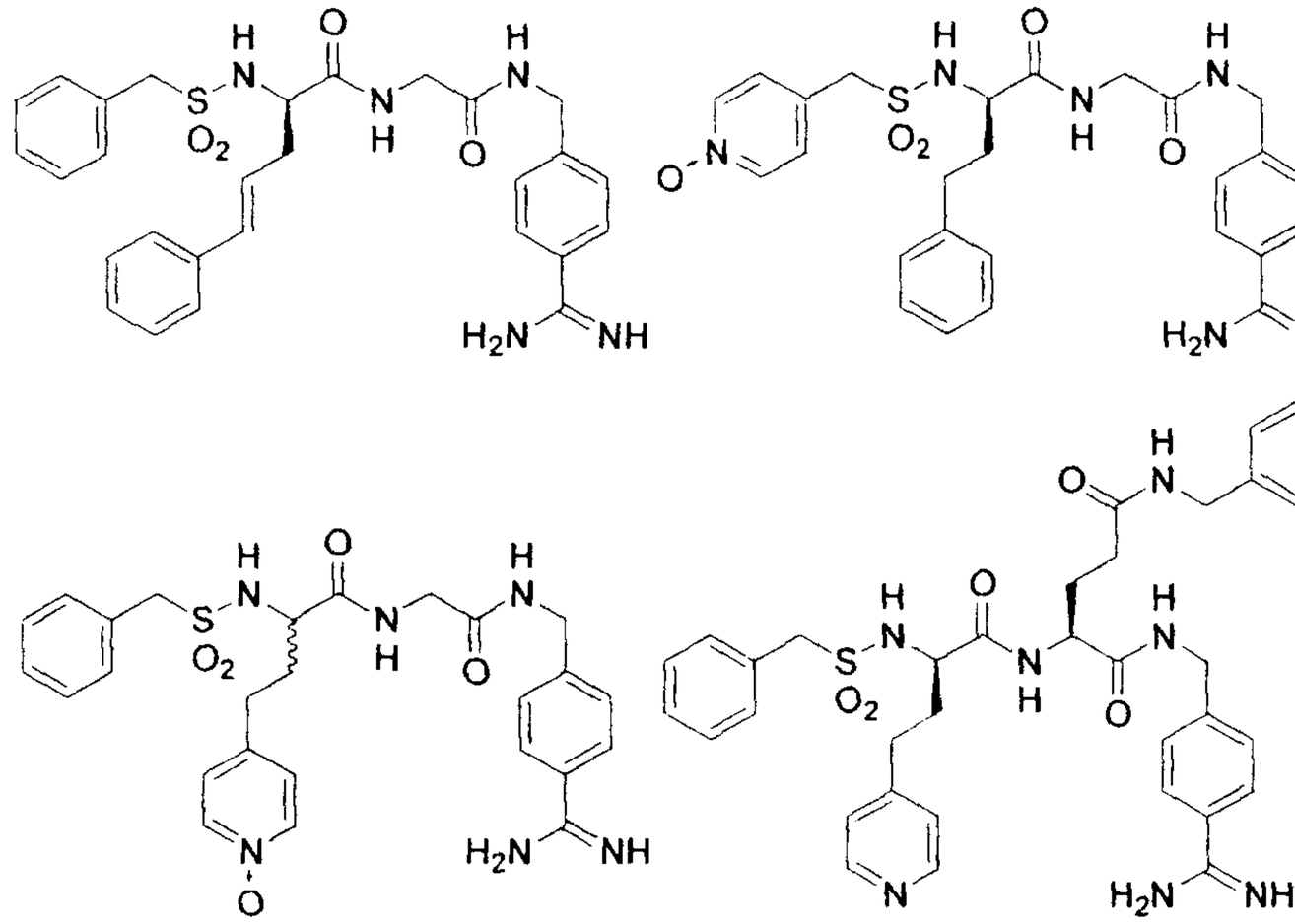


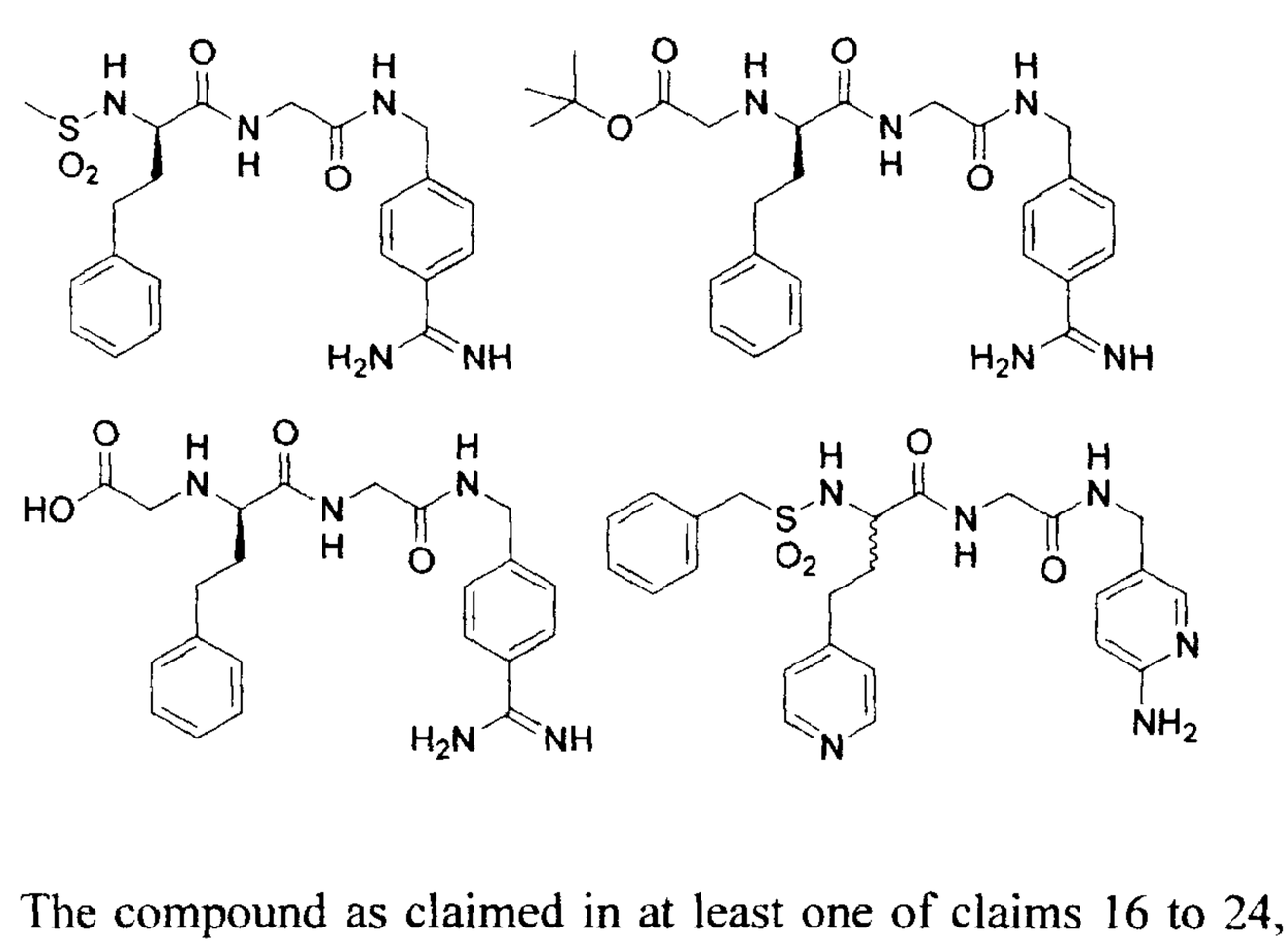


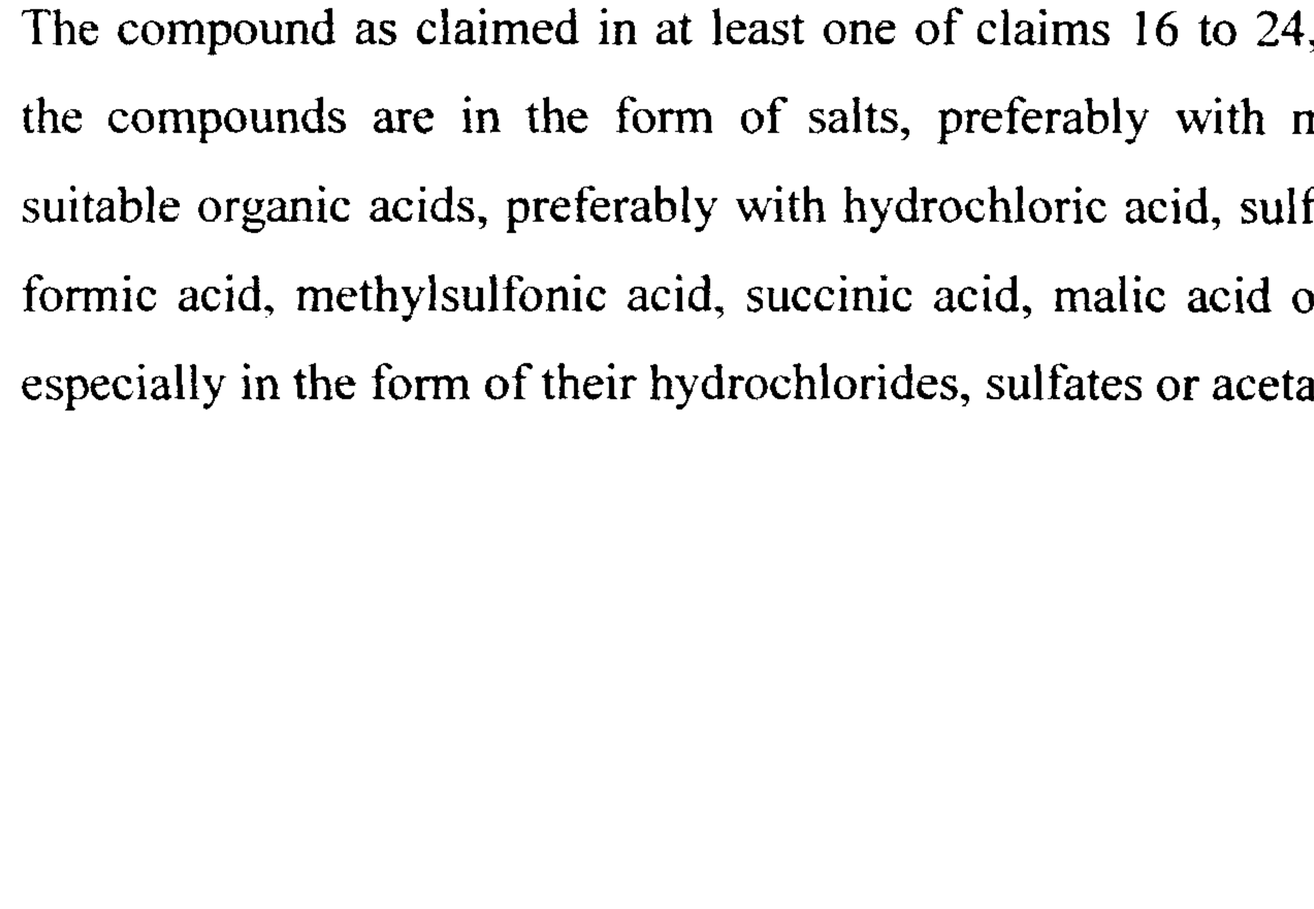












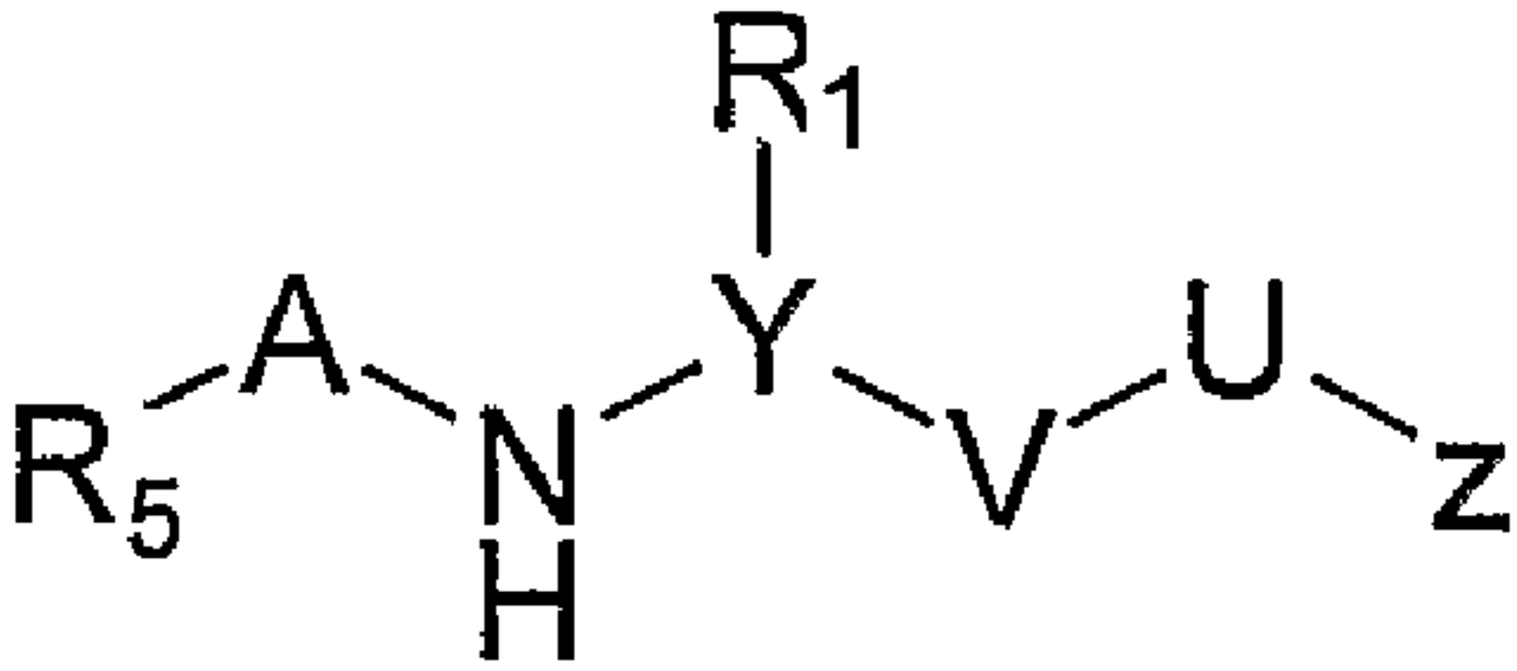
25. The compound as claimed in at least one of claims 16 to 24, characterized in that the compounds are in the form of salts, preferably with mineral acids or with suitable organic acids, preferably with hydrochloric acid, sulfuric acid, acetic acid, formic acid, methylsulfonic acid, succinic acid, malic acid or trifluoroacetic acid, especially in the form of their hydrochlorides, sulfates or acetates.

26. A method for preparing a compound as claimed in at least one of claims 16 to 25, characterized in that the appropriate amino acids are coupled sequentially onto an amidinobenzylamine which is protected on the amidino group, with the N-terminal amino acid either already carrying the R_5 radical or the latter subsequently being linked thereto.

27. A medicament comprising a compound as claimed in at least one of claims 16 to 25 and pharmaceutically suitable excipients and/or additives.

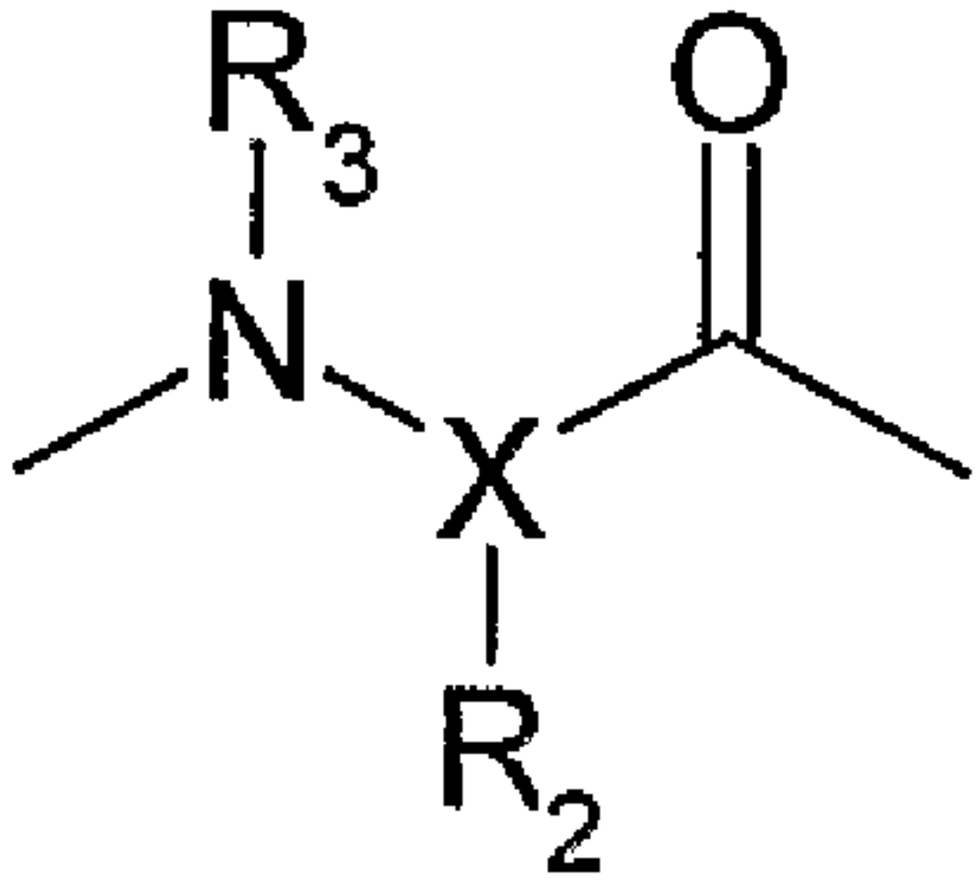
28. The medicament as claimed in claim 27, where the medicament is employed in the form of a tablet, of a coated tablet, of a capsule, of a pellet, suppository, of a solution, in particular of a solution for injection or infusion, of eyedrops, nose and ear drops, of a syrup, of a capsule, of an emulsion or suspension, of a pessary, stick, aerosol, dusting powder, of a paste, cream or ointment.

29. The use of a compound as claimed in at least one of claims 16 to 26 or of a medicament as claimed in claim 27 or 28 as factor Xa inhibitor for the therapy or prophylaxis of a cardiovascular disorder or of a thromboembolic event, in particular in oral, subcutaneous, intravenous or transdermal form.



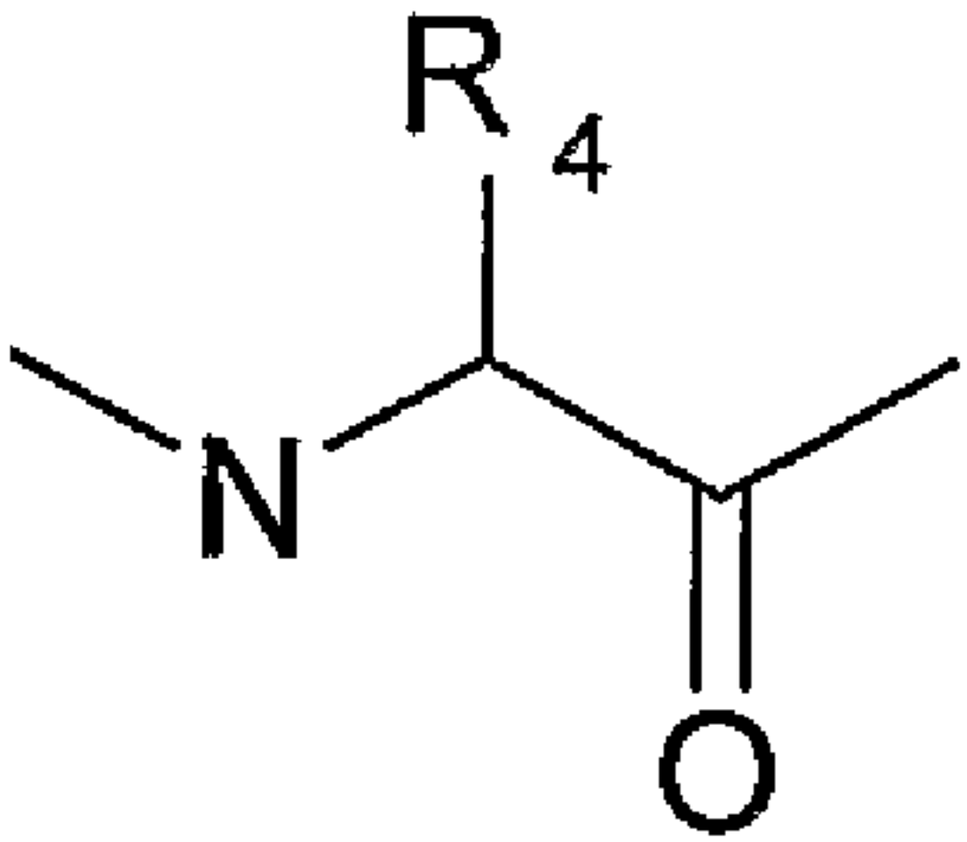
(I)

$P_1 =$



(A)

$P_2 =$



(B)