

THERAPEUTIC PEPTIDE DERIVATIVES

BACKGROUND OF THE INVENTION

This invention is a continuation-in-part of U.S. Ser. No. 104,194, filed Aug. 9, 1993 now abandoned.

This invention relates to therapeutic peptides.

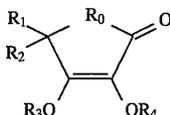
Several attempts have been made to prolong the activity of biologically active peptides. For example, peptides have been chemically modified by synthetically adding sugar moieties to increase the period during which the peptide is active (Sandoz, WO 88/02756; Sandoz, WO 89/09786; DE 3910667 A1, EPO 0 374 089 A2 (1990); and Breipohl, U.S. Pat. No. 4,861,755 (1989)). The addition of cationic anchors (EPO 0 363 589 A2 (1990)) and lipid moieties (Whittaker, WO 91/09837; Jung, U.S. Pat. No. 4,837,303 (1989)) has also been used to increase the lifetime of the peptide.

SUMMARY OF THE INVENTION

In general, the present invention provides derivatives of biologically active peptides which contain one or more substituents separately bonded to an amino group located on the N-terminal end or a side chain of the peptide moiety. In this modified form, the derivatives have more potent and prolonged biological activity than the corresponding unmodified peptide.

The peptide derivatives are advantageous in that they are inexpensive, highly biocompatible, lack deleterious side effects, and are compatible with different forms of therapeutic administration. In particular, many of the derivatives which have somatostatin as the peptide moiety have improved greatly improved potency and selectivity compared to unmodified somatostatin.

In one aspect, the invention features a peptide derivative containing a biologically active peptide moiety and at least one substituent attached to the peptide moiety; the substituent is selected from the group including Compounds I, II, and III, where Compound I is:



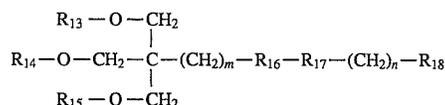
where:

R_0 is O, S, or NR_5 , where R_5 is H or (C_1-C_6) alkyl; each R_1 and R_2 , independently, is H, $(CH_2)_mOR_6$, or $CH(OR_7)CH_2OR_8$, where R_6 is H or (C_2-C_7) acyl, and each R_7 and R_8 , independently, is H, (C_2-C_7) acyl, or $C(R_9)(R_{10})$, where each R_9 and R_{10} , independently, is H or (C_1-C_6) alkyl;

or each R_1 and R_2 is $=CHCH_2OR_{11}$, wherein in R_{11} , each R_1 and R_2 , independently, is H or (C_2-C_7) acyl, and m is an integer between 1 and 5, inclusive; and

one of R_3 or R_4 is $(CH_2)_nR_{12}$ or $(CH_2)_nCH(OH)R_{12}$, where R_{12} is CO, CH_2 , or SO_2 , and n is an integer between 1 and 5, inclusive; and the remaining R_3 or R_4 is H, (C_1-C_6) hydroxyalkyl, or (C_2-C_7) acyl; and

Compound II is:



where:

each R_{13} , R_{14} and R_{15} , independently, is H or (C_2-C_{24}) acyl;

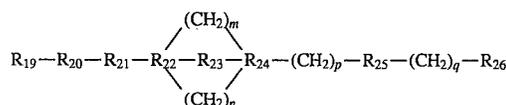
R_{16} is NH or absent;

R_{17} is CO, O, or absent;

R_{18} is CO, CH_2 , SO_2 , or absent; and

m is an integer between 1 and 5, inclusive; and n is an integer between 0 and 5, inclusive; and

Compound III is:



where:

R_{19} is H, NH_2 , an aromatic functional group, OH, (C_1-C_6) hydroxyalkyl, $H(R_{27})(R_{28})$, SO_3H , or absent where each R_{27} and R_{28} , independently, is H or (C_1-C_6) alkyl;

R_{20} is O or absent;

R_{21} is (C_1-C_6) alkyl or absent;

R_{22} is N, CH, O, or C;

$-R_{23}-$ is (C_1-C_6) alkyl or absent;

R_{24} is N, CH, or C;

R_{25} is NH, O, or absent;

R_{26} is SO_2 , CO, CH_2 , or absent;

m is an integer between 0 and 5, inclusive;

n is an integer between 0 and 5, inclusive;

p is an integer between 0 and 5, inclusive; and

q is an integer between 0 and 5, inclusive.

In Compounds I, II and III the peptide moiety is attached to each of the substituents by a $CO-N$, CH_2-N , or SO_2-N bond between the substituent and a nitrogen atom of the N-terminus or a side chain of said peptide moiety.

In preferred embodiments, $-R_{23}-$ is (C_1-C_6) alkyl; R_{22} is N, C or CH; and R_{24} is C. Alternatively, R_{22} is O; R_{19} , R_{20} , R_{21} , and $-R_{23}-$ are absent; and the sum of m and n is 3, 4, or 5.

In other preferred embodiments of the invention, the substituent is Compound I; in this embodiment, R_{12} is preferably CH_2 or SO_2 . Alternatively, the substituent may be Compound II, in which case R_{18} is preferably CH_2 or SO_2 ; R_{13} , R_{14} , and R_{15} are H; and R_{17} is absent. In particularly preferred embodiments, the substituent is $(HOCH_2)_3C-NH-(CH_2)_2-SO_2$ or $(HOCH_2)_3C-CH_2$.

In still other embodiments of the invention, the substituent is Compound III; preferably, in this embodiment, $-R_{23}-$ is absent and at least one of R_{22} and R_{24} is N. Alternatively, both R_{22} and R_{24} may be N.

In other embodiments, the substituent is one of:

