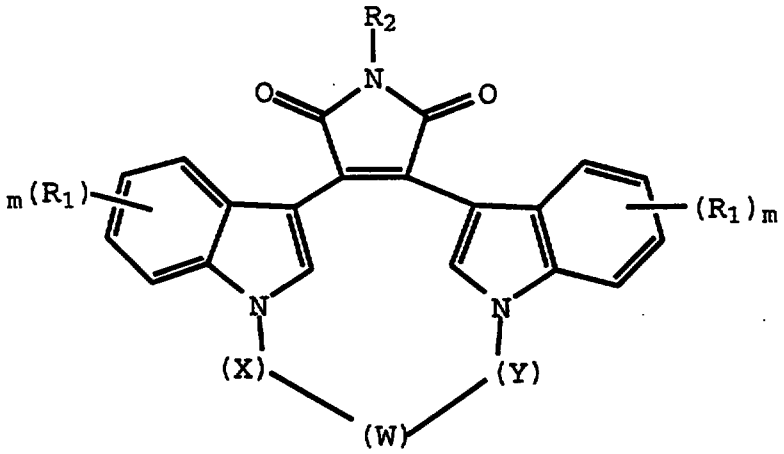
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X-8951A FOR

Abstract

This invention provides novel bis-indolemaleimide macrocycle derivatives of the formula:



The invention further provides the preparation, pharmaceutical formulations and the methods of use for inhibiting Protein Kinase C in mammals.

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R_2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R_3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -COO(C_1-C_4 alkyl), -CONR$_4$R$_5$, -(C=NH)NH_2, -SO(C_1-C_4 alkyl), -SO_2(NR$_4$R$_5$), or -SO_2(C_1-C_4 alkyl);

R_4 and R_5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

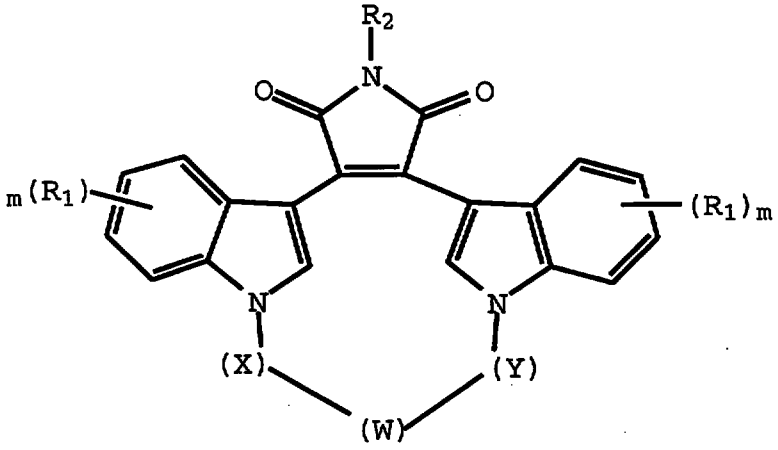
AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5;

substantially as hereinbefore described with reference to any one of the examples.

16. A compound of the formula:



wherein:

W is -O-, -S-, -SO-, -SO_2-, -CO-, C_2-C_6 alkylene, substituted alkylene, C_2-C_6 alkenylene, -aryl-, -aryl$(CH_2)_m$O-, -heterocycle-, -heterocycle-$(CH_2)_m$O-, -fused bicyclic-, -fused bicyclic-$(CH_2)_m$O-, -NR$_3$-, -NOR$_3$-, -CONH-, or -NHCO-;

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X and Y are independently C_1-C_4 alkylene, substituted alkylene, or together X, Y, and W combine to form $-(CH_2)_n$-AA-;

R_1 is independently hydrogen, halo, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, haloalkyl, nitro, NR_4R_5, or -NHCO(C_1-C_4 alkyl);

R_2 is hydrogen, CH_3CO-, NH_2, or hydroxy;

R_3 is hydrogen, $(CH_2)_m$aryl, C_1-C_4 alkyl, -COO(C_1-C_4 alkyl), $-CONR_4R_5$, $-(C=NH)NH_2$, -SO(C_1-C_4 alkyl), $-SO_2(NR_4R_5)$, or $-SO_2$(C_1-C_4 alkyl);

R_4 and R_5 are independently hydrogen, C_1-C_4 alkyl, phenyl, benzyl, or combine to the nitrogen to which they are bonded to form a saturated or unsaturated 5 or 6 member ring;

AA is an amino acid residue;

m is independently 0, 1, 2, or 3; and

n is independently 2, 3, 4, or 5;

substantially as hereinbefore described with reference to any of the examples.

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