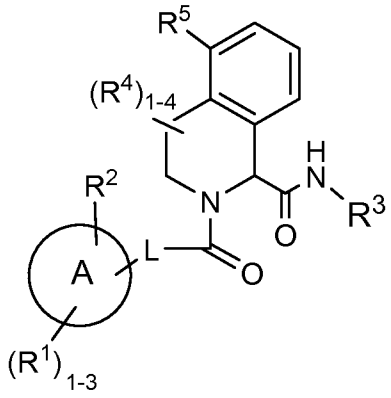
WHAT IS CLAIMED IS:

1. A compound according to formula (I):



(I)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein:

ring A is C3-io carbocycle;

L is selected from the group consisting of: a bond, -CHR^{10}CHR^{10}-, -CR^{10}=CR^{10}-, and -C≡C-;

R^1, at each occurrence, is selected from the group consisting of: H, halo, C$_{1-2}$ alkyl, -0(C$_{1-4}$ alkyl), CN, -CH$_2$NH$_2$, and -C(=NH)NH$_2$;

R^2 is selected from the group consisting of: H, halo, CN, OH, C$_{1-6}$ alkyl, C$_{1-4}$ alkoxy, C^haloalkyl, C^haloalkoxy, CO(C$_{1-4}$ alkyl), CONH$_2$, C0$_2$H and a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected fromN, NH, N(Ci_4 alkyl), O, and S(0)$_p$, wherein said heterocycle is substituted with 1-2 R^{2a};

R^{2a}, at each occurrence, is selected from the group consisting of: H, halo, C$_{1.4}$ alkyl, C0$_2$H, -C0$_2$(Ci_$_4$ alkyl), -CONH$_2$, -CH$_2$OH, -CH$_2$OCi_$_4$alkyl, and -CH$_2$NH$_2$;

R^3 is selected from the group consisting of: C$_{1-6}$ alkyl substituted with 1-3 R^{3a}, C$_{3.10}$ carbocycle substituted with 1-3 R^{3a}, and 5-10 membered heterocycle containing carbon atoms and 1-4 heteroatoms selected from the group consisting of N, NR^7, O, and S(0)$_p$; wherein said heterocycle is substituted with 1-3 R^{3a};

R^{3a}, at each occurrence, is selected from the group consisting of: H, halo, C$_{1.4}$ alkyl, -OH, C$_{1-4}$ alkoxy, -CN, -NH$_2$, ,-NH(C$_{1-4}$ alkyl), -N(C$_{1-4}$ alkyl)$_2$, -C0$_2$H, -CH$_2$C0$_2$H, -C0$_2$(C$_{1-4}$ alkyl), -C02-C$_{1-4}$ alkylene-0(C$_{1-4}$ alkyl), -C02-C$_{1-4}$ alkylene-

$N(C_{1-4}$ alkyl$)_2$, -CC^-C^ alkylene-O-C^ alkylene-$N(C_{1-4}$ alkyl$)_2$, -CO^C^ alkylene-0-C_{1-4} alkylene-OCC^ alkyl), $-CONH_2$, -$CONH(C_{1-6}$ alkyl), -$CON(C_{1-4}$ alkyl$)_2$, -CONH-C^ alkylene-$C0_2(C_{1-4}$ alkyl), -CONHCO^^ alkyl, -CONH-C^ alkylene-$NHCO(C_{1-4}$ alkyl), -CONH-C^ alkylene-$CONH_2$, -NHCOC^ alkyl, $-NHC0_2(C_{1-4}$ alkyl), R^c, -CONHRc , and $-C0_2R^c$;

R^4, at each occurrence, is selected from the group consisting of: H, halo, and C_{1-4} alkyl;

R^5 is selected from the group consisting of: halo, C_{1-4} alkyl substituted with 0-2 R^b, C_{2-4} alkenyl substituted with 0-2 R^b, -OH, -CN, $-NH_2$, $-N(C_{1-4}$ alkyl$)_2$, $-OCO(C_{1-4}$ alkyl), -0-C_{1-4} alkylene-CKC^ alkyl), -0-C_{1-4} alkylene-$N(C_{1-4}$ alkyl$)_2$, $-C0_2H$, -$C0_2(C_{1-4}$ alkyl), $-CONH_2$, $-(CH_2)_2CONH_2$, $-CONR^9(C_{1-4}$ alkyl), $-CON(C_{1-4}$ alkyl$)_2$, -$CONR^9$-C!-4 alkylene-0(C_{1-4} alkyl), $-CONR^9$-C_{1-4} alkylene-$N(C_{1-4}$ alkyl$)_2$, $-CONR^9$-C1-4 alkylene-$C0_2(C_{1-4}$ alkyl), $-NR^9COC_{1-4}$ alkyl, $-NR^9C0_2Ci_{-4}$ alkyl, $-NR^9CONH(C!_{-4}$ alkyl), $-NR^9CONR^9$-C!-4 alkylene-$C0_2C_{1-4}$ alkyl, $-NR^9$-C_{1-4} alkylene-$N(C_{1-4}$ alkyl$)_2$, -$NR^9S0_2(C!_{-4}$ alkyl), -$S(C_{1-4}$ alkyl), $-S0_2(Ci_{-4}$ alkyl), $-S0_2NH_2$, R^8, C_{2-4} alkenylene-R^8, $-OR^8$, $-COR^8$, C_{2-4} alkenylene-COR^8, $-CONR^9R^8$, $-NR^9COR^8$, $-NR^9C0_2R^8$, and -$NR^9CONR^9R^8$;

R^7, at each occurrence, is selected from the group consisting of: H, C_{1-4} alkyl, COCi.4 alkyl, $C0_2(C_{1-4}$ alkyl), $C0_2$Bn, -CONH-C^ alkylene-$C0_2C_{1-4}$ alkyl, phenyl, benzyl, and -$CO2_{-C1-4}$ alkylene-aryl;

R^8, at each occurrence, is selected from the group consisting of: $-(CH_2)_n$-C3-10 carbocycle and $-(CH_2)_n$-5- to 10-membered heterocycle containing carbon atoms and 1-4 heteroatoms selected from the group consisting of: N, NR^a, O, and $S(0)_p$; wherein said carbocycle or heterocycle is substituted with 0-3 R^b;

R^9, at each occurrence, is selected from the group consisting of: H and Ci_{-4}alkyl;

R^{10}, at each occurrence, is selected from the group consisting of: H, halo, OH, and Ci-4 alkyl;

R^a is selected from the group consisting of: H, C_{1-4} alkyl, $-(CH_2)_nOH$, $CO(C_{1-4}$ alkyl), $COCF_3$, $CO_2(C_{1-4}$ alkyl), $-CONH_2$, -CONH-C_{1-4} alkylene-$CO_2(C_{1-4}$ alkyl), C_{1-4} alkylene-$CO_2(C_{1-4}$ alkyl), R^c, CO_2R^c, and $CONHR^c$;

R^b is selected from the group consisting of: =O, halo, C_{1-4} alkyl, C_{1-4} alkoxy, OCF_3, NH_2, NO_2, $N(C_{1-4}$ alkyl)$_2$, $CO(C_{1-4}$ alkyl), $CO(C_{1-4}$ haloalkyl), $CO_2(C_{1-4}$ alkyl), $CONH_2$, $-CONH(C_{1-4}$ alkyl), $-CON(C_{1-4}$ alkyl)$_2$, -CONH-C_{1-4} alkylene-O(C_{1-4} alkyl), -CONH-C_{1-4} alkylene-N(C_{1-4} alkyl)$_2$, -CONH-C_{1-4} alkylene-N(C_{1-4} alkyl)$_2$-C_{1-4} alkylene-O-P(O)(OH)$_2$, $-NHCO_2(C_{1-4}$ alkyl), -Rc, COR^c, CO_2R^c, and $CONHR^c$;

R^c is, independently at each occurrence, selected from the group consisting of: $-(CH_2)_n$-C_{3-6} cycloalkyl, $-(CH_2)_n$-phenyl, and $-(CH_2)_n$-5- to 6- membered heterocycle containing carbon atoms and 1-4 heteroatoms selected from the group consisting of: N, NH, N(C_{1-4} alkyl), O, and S(O)$_p$; wherein each ring moiety is substituted with 0-2 R^d;

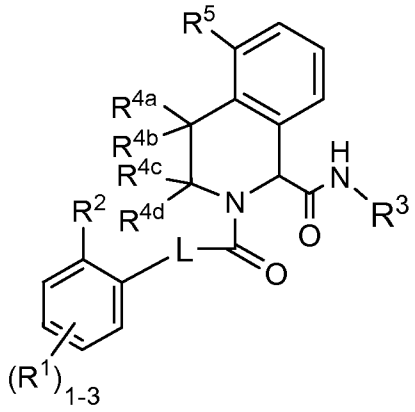
R^d is selected from the group consisting of: =O, halo, -OH, C_{1-4} alkyl, NH_2, NH(C_{1-4} alkyl), N(C_{1-4} alkyl)$_2$, C_{1-4} alkoxy, and -NHCO(C_{1-4} alkyl), and heterocycle containing carbon atoms and 1-4 heteroatoms selected from the group consisting of: N, NH, N(C_{1-4} alkyl), O, and S(O)$_p$;

n, at each occurrence, is selected from 0, 1, 2, 3, and 4;

p, at each occurrence, is selected from 0, 1, and 2;

provided when R^5 is heterocycle, the point of attachment of the heterocycle to the fused phenyl ring is not on a nitrogen atom.

2. The compound of claim 1 having formula (II):



(II)

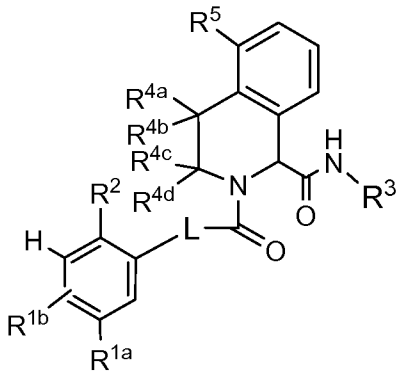
or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein:

R^1, at each occurrence, is selected from the group consisting of: H, halo, C_{1-2} alkyl, -0 (C_{1-4} alkyl), and -C(=NH)NH_2;

R^{4a}, R^{4b}, R^{4c}, and R^{4d} are independently selected from the group consisting of: H, F, and C_{1}.4 alkyl;

R^5 is selected from the group consisting of: halo, C_{1}.4 alkyl substituted with 0-2 R^b, C_{2-4} alkenyl substituted with 0-2 R^b, -OH, -CN, -N(C_{1-4} alkyl)$_2$, -0-C_{1-4} alkylene-0(C_{1-4} alkyl), -0-C_{1-4} alkylene-N(C_{1-4} alkyl)$_2$, -C0$_2$H, -C0$_2$($C_{1\cdot4}$ alkyl), -CON(C_{1-4} alkyl)$_2$, -CONR^C^ alkylene-0(C_{1-4} alkyl), -CONR^9-C_{1-4} alkylene-C0$_2$($C_{1\cdot4}$ alkyl), -NR^{9}COC$_{1-4}$ alkyl, NR^{9}C0$_2$Ci$_{-4}$ alkyl, -NR^{9}CONR^9-C!$_{-4}$ alkylene-C0$_2$C$_{1\cdot4}$ alkyl, -NHS0$_2$(C!$_{\cdot4}$ alkyl), R^8, $C_{2\cdot4}$ alkenylene-R^8, -OR^8, -COR^8, $C_{2\cdot4}$ alkenylene-COR^8, -CONR^{9}R^8, -NR^{9}COR^8, and -NR^{9}CONR^{9}R^8.

3. The compound of claim 2 having formula (III):



(III)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein:

R^{1a} is selected from the group consisting of: H, halo, C_{1-2} alkyl, and methoxy;

R^{1b} is selected from the group consisting of: H and halo;

R^2 is selected from the group consisting of: H, F, CN, OH, $C_{1.4}$ alkoxy, $-CHF_2$, $-CF_3$, $-CH_2NH_2$, $-OCHF_2$, $-CO(C!._4$ alkyl), $-CONH_2$, -COOH, triazole substituted with R^{2a}, and tetrazole substituted with R^{2a};

R^3 is selected from the group consisting of: phenyl substituted with 1-2 R^{3a}, $_{C3-6}$ cycloalkyl substituted with 1-2 R^{3a}, and heterocycle substituted with 1-2 R^{3a}; wherein said heterocycle is selected from the group consisting of: piperidinyl, pyridyl, indolyl, and indazolyl;

R^{3a}, at each occurrence, is selected from the group consisting of: H, halo, -OH, $-0(C_{1-4}$ alkyl), -CN, $-C0_2H$, $-CONH_2$, $-C0_2(C_{1\cdot4}$ alkyl), $-C0_2-C_{1\cdot4}$ alkylene-OCC^ alkyl), $-C0_2-C_{1\cdot4}$ alkylene-$N(C_{1-4}$ alkyl)$_2$, $-C0_2-C_{1\cdot4}$ alkylene-O-C^ alkylene-$N(C_{1-4}$ alkyl)$_2$, -CO^C^ alkylene-O-C^ alkylene-OCC^ alkyl), -NHCO^C^ alkyl), R^c, and $-C0_2R^c$;

R^5 is selected from the group consisting of: R^8, C_{2-4} alkenylene-R^8, $-OR^8$, COR^8, C_{2-4} alkenylene-COR^8, $-CONHR^8$, and $NHCONHR^8$;

R^8, at each occurrence, is selected from the group consisting of: $-(CH_2)_n-C_{3-6}$ cycloalkyl, $-(CH_2)_n$-phenyl and $-(CH_2)_n$-5- to 10-membered heterocycle containing carbon atoms and 1-4 heteroatoms selected from the group consisting of: N, NR^a, O, and $S(0)_p$; wherein said cycloalkyl, phenyl and heterocycle are substituted with 0-3 R^b;

R^a, at each occurrence, is selected from the group consisting of: H, $C_{1.4}$ alkyl, $-(CH_2)_nOH$, $CO(C_{1-4}$ alkyl), COCF3, $C0_2(C_{1-4}$ alkyl), -CONH-$C_{1.4}$ alkylene-$C0_2(C_{1\cdot4}$ alkyl), C_{1-4} alkylene-$C0_2(C_{1\cdot4}$ alkyl), R^c, and $C0_2R^c$;

R^b, at each occurrence, is selected from the group consisting of: halo, $C_{1.4}$ alkyl, C_{1-4} alkoxy, OCF3, NH_2, $N0_2$, $C0_2(C_{1\cdot4}$ alkyl), $CONH_2$, $-CONH(C_{1-4}$ alkyl), $-CON(C_{1-4}$ alkyl)$_2$, -CONH-C^ alkylene-$0(C_{1-4}$ alkyl), -CONH-C^ alkylene-$N(C_{1-4}$ alkyl)$_2$, -CONH-C^ alkylene-$C0_2(C_{1\cdot4}$ alkyl), -CONH-C^ alkylene-N^C^ alkyl)$_2$-Ci.4 alkylene-0-P(0)(OH) $_2$, $-NHC0_2(C_{1-4}$ alkyl), R^c, COR^c, and $CONHR^c$; and

R^c, at each occurrence, is selected from the group consisting of: $-(CH_2)_n$-C3-6 cycloalkyl, $-(CH_2)_n$-phenyl, and $-(CH_2)_n$-5- to 6- membered heterocycle containing carbon atoms and 1-4 heteroatoms selected from the group consisting of: N, NH, O, and $S(0)_p$; wherein each ring moiety is substituted with 0-2 R^d.

4. The compound of claim 3, wherein:

R^{1a} is CI;

R^{1b} is selected from the group consisting of: H and F;

R^2 is selected from the group consisting of: H, F, CF_3, COC^ alkyl, and tetrazolyl;

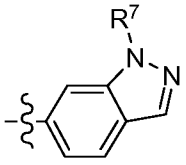
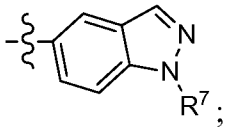
R^3 is selected from the group consisting of: phenyl substituted with 1-2 R^{3a}, C_{3-6} cycloalkyl substituted with 1-2 R^{3a}, and indazolyl substituted with 1-2 R^{3a};

R^{3a}, at each occurrence, is selected from the group consisting of: H, halo, -OH, -0(C_{1-4} alkyl), -CN, -C0 2H, -CON¾ -C0 2(C_{1-4} alkyl), -C0 2-$(CH_2)_{1-4}$-0(C_{1-4} alkyl), -C0 2-$(CH_2)_{1-4}$-N(C_{1-4} alkyl)$_2$, -C0 2-$(CH_2)_{1-4}$-0-$(CH_2)_{1-4}$-N(C_{1-4} alkyl)$_2$, -C0 2-$(CH_2)_{1-4}$-0-$(CH_2)_{1-4}$-0(C_{1-4} alkyl), -NHC0 2(C_{1-4} alkyl), Rc, and -C0 2Rc; and

R^8, at each occurrence, is selected from the group consisting of: phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, morpholine, thiamorpholine, $-(CH2)_{0-2}$-piperidine, tetrahydroquinoline, piperazine, pyridine, benzodioxolyl, pyrazolyl, and indazolyl.

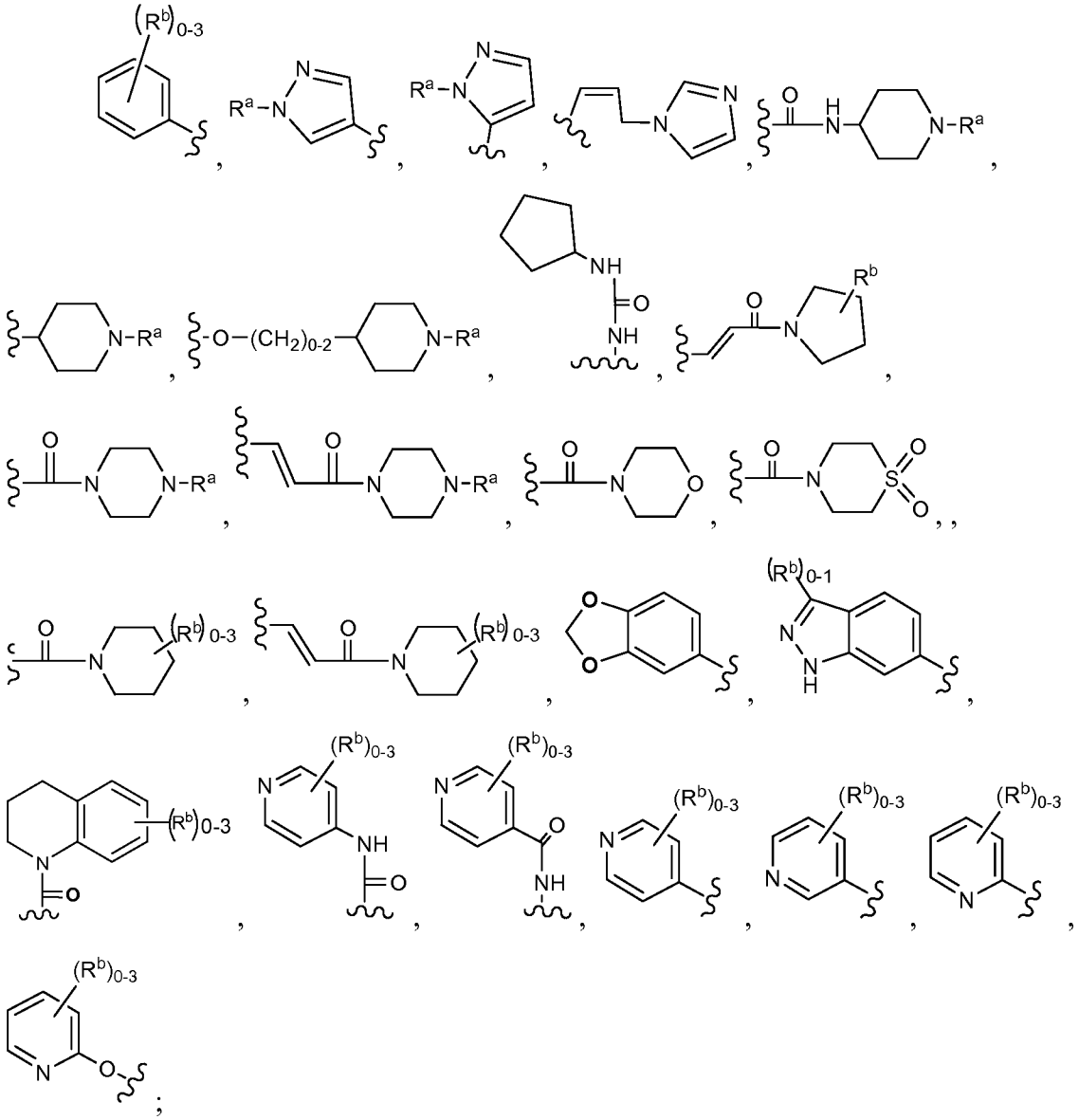
5. The compound of claim 4, wherein:

R^2 is selected from the group consisting of: H, F, CF_3, C(0)Me, and tetrazolyl;

R^3 is selected from the group consisting of: phenyl substituted with 1-2 R^{3a}, C_{3-6} cycloalkyl substituted with 1-2 R^{3a}, pyridyl substituted with 1-2 R^{3a},  , and  ;

R^{3a}, at each occurrence, is selected from the group consisting of: F, -OH, -OMe, -OEt, -CN, -CO_2H, -$CONH_2$, -CO_2Me, -CO_2Et, -CO_2(*t*-butyl), -$CO_2(CH_2)_2OMe$, -$CO_2(CH_2)_2N(C_{1-4}\ alkyl)_2$, -$CO_2(CH_2)_20(CH_2)_2N(C_{1-4}\ alkyl)_2$, -$CO_2(CH_2)_20(CH_2)_2OMe$, -$NHCO_2Me$, R^c, and -CO_2R^c;

R^5, at each occurrence, is selected from the group consisting of:



;

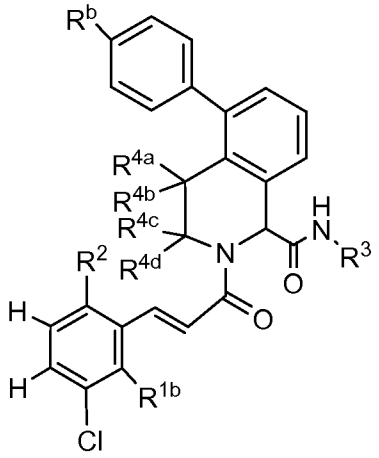
R^a is selected from the group consisting of: H, Me, Et, -$(CH_2)_3OH$, $COCF_3$, COMe, CO_2Me, CO_2Et, CO_2(*t*-butyl), -$CONH(CH_2)_2CO_2(C_{1-4}\ alkyl)$, R^c, and CO_2R^c;

R^b is, independently at each occurrence, selected from the group consisting of: Me, Et, Cl, OMe, OCF_3, NO_2, NH_2, $N(Me)_2$, CO_2Me, CO_2Et, $CONH_2$, -$CONH(C_{1-4}$ alkyl), -$CON(C_{1-4}\ alkyl)_2$, -$CONH(CH_2)_{1-2}0(C_{1-4}\ alkyl)$, -$CONH(CH_2)_{1-2}N(C_{1-4}$

alkyl)$_2$, -CONH(CH$_2$)$_{1-2}$N$^+$(C$_{1-4}$ alkyl)$_2$(CH$_2$)$_{1-2}$-0-P(0)(OH) $_2$, -NHCO^C^ alkyl), -R^c, CORc, CONHR^c; and

R^c is, independently at each occurrence, selected from the group consisting of: -(CH$_2$)$_n$-C$_{3-6}$ cycloalkyl, -(CH$_2$)$_n$-phenyl, and -(CH$_2$)$_{0-2}$-morpholine, methylpiperazine, pyrrolidine optionally substituted with =0, and pyrazole.

6. The compound of claim 5 having formula (IV):

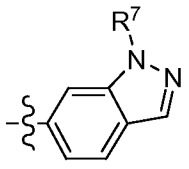
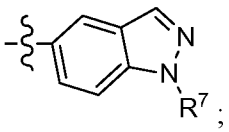


(IV)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein:

R^{1b} is H and F;

R^2 is selected from the group consisting of: H, F, CF$_3$, C(0)Me, and tetrazole;

R^3 is independently selected from the group consisting of: phenyl substituted with 1-2 R^{3a}, cyclohexyl substituted with 1-3 R^{3a},  , and  ;

R^{3a} is, independently at each occurrence, selected from the group consisting of: F and -C0 $_2$H;

R^7 is selected from the group consisting of: H and C$_{1-4}$ alkyl;

R^b is, independently at each occurrence, selected from the group consisting of: CI, OMe, **OCF3,** N0 $_2$, CONH$_2$, -CONHMe, -CONHEt, -CON(Me)$_2$, -CON(Et)$_2$, -CONH(CH$_2$)$_{1-2}$0(C $_{1-4}$ alkyl), -CONH(CH$_2$)$_{1-2}$N(C $_{1-4}$ alkyl)$_2$, -CONH(CH$_2$)$_{1-2}$N$^+$(C $_{1-4}$ alkyl)$_2$(CH$_2$)$_{1-2}$-0-P(0)(OH) $_2$, NHC0 $_2$Me, NHC0 $_2$Et, and COR^c; and

R^c is, independently at each occurrence, selected from the group consisting of:

-$(CH_2)_n$-C_{3-6} cycloalkyl, -$(CH_2)_n$-phenyl, and -$(CH_2)_{0-2}$-morpholine, methylpiperazine, pyrrolidine optionally substituted with =0, and pyrazole.

7. The compound of claim 2, wherein:

R^2 is selected from the group consisting of: H, F, CF_3, C(0)Me, and tetrazolyl;

R^3 is selected from the group consisting of: phenyl substituted with 1-2 R^{3a} and pyridyl substituted with 1-2 R^{3a};

R^5 is selected from the group consisting of: halo, $C_{1.4}$ alkyl substituted with 0-2 R^b, C_{2-4} alkenyl substituted with 0-2 R^b, -OH, -N(C_{1-4} alkyl)$_2$, -*0-Ci_4* alkylene-CKC^ alkyl), -0-C_{1-4} alkylene-NCC^ alkyl)$_2$, and -NHSO^C^ alkyl);

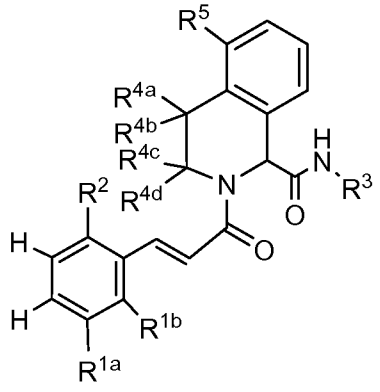
R^{3a}, at each occurrence, is selected from the group consisting of: F and -$C0_2H$;

R^b, at each occurrence, is selected from the group consisting of: $CONH_2$, $C0_2$(C_{1-4} alkyl), R^c, and COR^c;

R^c, at each occurrence, is selected from the group consisting of: imidazole, methylpiperazine, pyrrolidine substituted with 0-2 R^d, and piperidine substituted with 0-2 R^d; and

R^d, at each occurrence, is selected from the group consisting of: NH_2 and pyrrolidine.

8. The compound of claim 2 having formula (V):

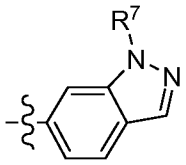
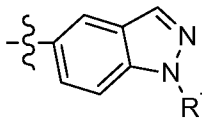


(V)

or a stereoisomer, tautomer, pharmaceutically acceptable salt thereof, wherein:

R^{1b} is selected from the group consisting of: H and F;

R^3 is selected from the group consisting of: phenyl substituted with 1-2 R^{3a},


, and

;

R^{3a}, at each occurrence, is selected from the group consisting of: H, halo, CN, $C0_2H$, $-C0_2(Ci\_4$ alkyl), $-C0_2(CH_2)i\_20(C_{1\cdot4}$ alkyl), $-C0_2(CH_2)i\_2CON(C_{1\cdot4}$ alkyl)$_2$, $-CONH_2$, $-CONH(C_{1-4}$ alkyl), $-NHCO^C^$ alkyl), $-C0_2(C_{3\cdot6}$ cycloalkyl), $-C0_2(CH_2)i_2$Ph, and $-C0_2(CH_2)i_2$triazole.

R^{4a}, R^{4b}, R^{4c}, and R^{4d} are independently selected from the group consisting of: H and methyl;

R^5 is selected from the group consisting of: halo, C_1.4 alkyl substituted with 0-2 R^b, C_{2-4} alkenyl substituted with 0-2 R^b, -OH, -CN, $-N(C_{1-4}$ alkyl)$_2$, -0-C_{1-4} alkylene-0(C_{1-4} alkyl), -0-C_{1-4} alkylene-N(C_{1-4} alkyl)$_2$,$-C0_2H$, $-C0_2(C_{1\cdot4}$ alkyl), $-CONR^9(C_{1-4}$ alkyl)$_2$, $-CONR^9$-C_{1-4} alkylene-0(C_{1-4} alkyl), $-CONR^9$-C_{1-4} alkylene-N(C_{1-4} alkyl)$_2$, $-CON(C_{1-4}$ alkyl)$_2$, $-CONR^9$-C_{1-4} alkylene-$C0_2(C_{1\cdot4}$ alkyl), $-NR^OC^$ alkyl, $NR^9C0_2Ci\_4$ alkyl, $-NR^9CONR^9$-C!$\_4$ alkylene-$C0_2C_{1\cdot4}$ alkyl, $-NR^9S0_2(C!\_4$ alkyl), R^8, $C_{2\cdot4}$ alkenylene-R^8, $-OR^8$, $-COR^8$, $-C0_2R^8$, $C_{2\cdot4}$ alkenylene-COR^8, $-CONR^9R^8$, $-NR^9COR^8$, and $-NR^9CONR^9R^8$;

R^7, at each occurrence, is selected from the group consisting of: H and methyl;

R^8, at each occurrence, is selected from the group consisting of: $C3_{-6}$ cycloalkyl, phenyl and 5- to 10-membered heterocycle containing carbon atoms and 1-4 heteroatoms selected from the group consisting of: N, NR^a, O, and $S(0)_p$; wherein said cycloalkyl, phenyl and heterocycle are substituted with 0-3 R^b;

R^a, at each occurrence, is selected from the group consisting of: H, c_{1}.4 alkyl, $-(CH_2)_nOH$, $CO(C_{1-4}$ alkyl), COCF3, $C0_2(C_{1-4}$ alkyl), -CONH-C^ alkylene-$C0_2(C_{1\cdot4}$ alkyl), R^c, and $C0_2R^c$;

R^b, at each occurrence, is selected from the group consisting of: halo, C_{1-4} alkoxy, OCF3, NH_2, $N0_2$, $C0_2(C_{1\cdot4}$ alkyl), $CONH_2$, $-CONH(C_{1-4}$ alkyl), $-CON(C_{1-4}$ alkyl)$_2$, -CONH-C!.4 alkylene-O^!^ alkyl), -CONH-C!.4 alkylene-N(C_{1-4}

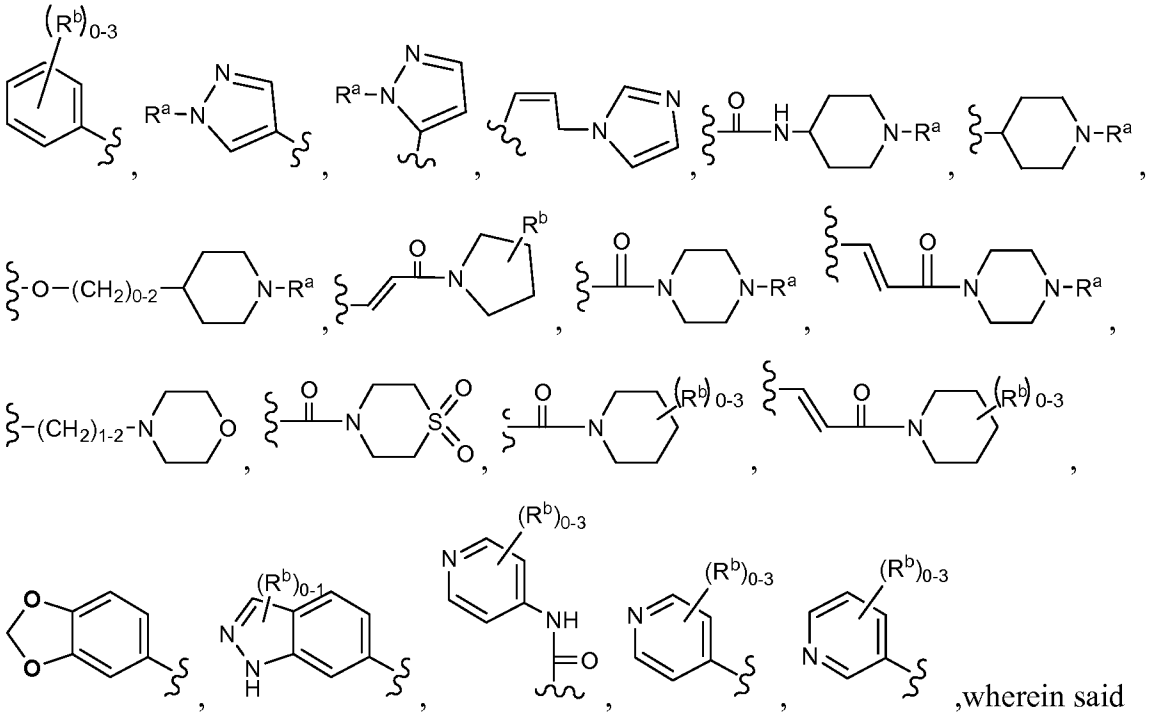
alkyl)$_2$, -CONH-C$_{1-4}$ alkylene-C0 $_2$(C$_{1\cdot4}$ alkyl), -CONH-C^ alkylene-lSr(C$_{1-4}$ alkyl)$_2$-C$_{1-4}$ alkylene-0-P(0)(OH) $_2$, -NHC0 $_2$(C$_{1\cdot4}$ alkyl), R^c, COR^c, and CONHR^c;

R^c, at each occurrence, is selected from the group consisting of: -(CH$_2$)$_n$-C$_{3\cdot6}$ cycloalkyl, -(CH$_2$)$_n$-phenyl, and -(CH$_2$)$_n$-5- to 6- membered heterocycle containing carbon atoms and 1-4 heteroatoms selected from the group consisting of: N, NR^C, O, and S; wherein each ring moiety is substituted with 0-2 R^d; and

R^d, at each occurrence, is selected from the group consisting of: =0, N(C$_{1\text{-}}$4 alkyl)$_2$, heterocycle containing carbon atoms and 1-4 heteroatoms selected from the group consisting of: N, NH, N(C$_{1\cdot4}$ alkyl), O, and S.

9. The compound of claim 8, wherein:

R^5 is selected from the group consisting of: C$_{1\text{-}}$4 alkyl substituted with 0-2 R^b, C$_{2\text{-}}$4 alkenyl substituted with 0-2 R^b, -N(Me)$_2$, -0(CH $_2$)$_2$N(Me)$_2$, 0(CH $_2$)$_2$OMe , CONH(CH$_2$)$_2$N(Me)$_2$, -NHS0 $_2$Me,



,wherein said ring moieties are substituted with 0-3 R^b;

R^{3a}, at each occurrence, is selected from the group consisting of: F, CN, C0 $_2$H, C0 $_2$Me, C0 $_2$Et , C0 $_2$(/-Bu), andNHC0 $_2$Me;

R^a, at each occurrence, is selected from the group consisting of:

H, methyl, -$(CH_2)_{0-3}$OH, COMe, $COCF_3$, $C0_2Me$, R^c, and $C0_2R^c$;

R^b, at each occurrence, is selected from the group consisting of: H Cl, OMe, OCF3, NO2, NH_2, -$N(Me)_2$, -$C0_2Me$, -$C0_2Et$, $CONH_2$, -CONHMe, -CONHEt, -$CON(Me)_2$, -$CONH(CH_2)_2OMe$, -$CONH(CH_2)_2N(Me)_2$, -$CONH(CH_2)_2N^+(Me)_2CH_2$-OP(0)$(OH)_2$, -$NHC0_2Et$, -$NHC0_2Me$, R^c, COR^c, and $CONHR^c$;

R^c, at each occurrence, is selected from the group consisting of: -$(CH_2)_0$-iphenyl, pyrrolidine substituted with 0-2 R^d, pyrazole, imidazole, -$(CH_2)_{0-2}$morpholine, piperidine substituted with 0-2 R^d, methylpiperidine, and methylpiperazine; and

R^d, at each occurrence, is selected from the group consisting of: =0, pyrrolidine, and$N(Me)_2$.

10. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

11. A method of treating a thromboembolic or an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt or solvate form thereof.

12. A method of treating a thromboembolic disorder according to claim 11, wherein the thromboembolic disorder is selected from the group consisting of arterial cardiovascular thromboembolic disorders, venous cardiovascular thromboembolic disorders, and thromboembolic disorders in the chambers of the heart.

13. A method of treating a thromboembolic disorder according to claim 11, wherein the thromboembolic disorder is selected from unstable angina, an acute coronary syndrome, atrial fibrillation, first myocardial infarction, recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, peripheral occlusive arterial disease, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary arterial thrombosis, cerebral arterial thrombosis, cerebral embolism, kidney embolism, pulmonary embolism, and thrombosis resulting from (a)

prosthetic valves or other implants, (b) indwelling catheters, (c) stents, (d) cardiopulmonary bypass, (e) hemodialysis, or (f) other procedures in which blood is exposed to an artificial surface that promotes thrombosis.

SUBSTITUTED TETRAHYDROISOQUINOLINE COMPOUNDS AS FACTOR XIA INHIBITORS

FIELD OF THE INVENTION

[0001] The present invention provides novel substituted tetrahydroisoquinoline (THQ) compounds, and their analogues thereof, which are inhibitors of factor XIa or plasma kallikrein, compositions containing them, and methods of using them, for example, for the treatment or prophylaxis of thromboembolic disorders.

BACKGROUND OF THE INVENTION

[0002] Thromboembolic diseases remain the leading cause of death in developed countries despite the availability of anticoagulants such as warfarin (COUMADIN®), heparin, low molecular weight heparins (LMWH), and synthetic pentasaccharides and antiplatelet agents such as aspirin and clopidogrel (PLAVIX®). The oral anticoagulant warfarin, inhibits the post-translational maturation of coagulation factors VII, IX, X and prothrombin, and has proven effective in both venous and arterial thrombosis. However, its usage is limited due to its narrow therapeutic index, slow onset of therapeutic effect, numerous dietary and drug interactions, and a need for monitoring and dose adjustment. Thus discovering and developing safe and efficacious oral anticoagulants for the prevention and treatment of a wide range of thromboembolic disorders has become increasingly important.

[0003] One approach is to inhibit thrombin generation by targeting the inhibition of coagulation factor XIa (FXIa). Factor XIa is a plasma serine protease involved in the regulation of blood coagulation, which is initiated *in vivo* by the binding of tissue factor (TF) to factor VII (FVII) to generate factor Vila (FVIIa). The resulting TF:FVIIa complex activates factor IX (FIX) and factor X (FX) that leads to the production of factor Xa (FXa). The generated FXa catalyzes the transformation of prothrombin into small amounts of thrombin before this pathway is shut down by tissue factor pathway inhibitor (TFPI). The process of coagulation is then further propagated via the feedback activation of Factors V, VIII and XI by catalytic amounts of thrombin. (Gailani, D. et al., *Arterioscler. Thromb. Vase. Biol.*, 27:2507-2513 (2007).) The resulting burst of thrombin converts fibrinogen to fibrin that polymerizes to form the structural framework of a blood

clot, and activates platelets, which are a key cellular component of coagulation (Hoffman, M., *Blood Reviews,* 17:S1-S5 (2003)). Therefore, factor XIa plays a key role in propagating this amplification loop and is thus an attractive target for anti-thrombotic therapy.

SUMMARY OF THE INVENTION

[0004] The present invention provides novel substituted tetrahydroisoquinoline compounds, and their analogues thereof, including stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, which are useful as selective inhibitors of serine protease enzymes, especially factor XIa and/or plasma kallikrein.

[0005] The present invention also provides processes and intermediates for making the compounds of the present invention.

[0006] The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

[0007] The compounds of the invention may be used in the treatment and/or prophylaxis of thromboembolic disorders.

[0008] The compounds of the present invention may be used in therapy.

[0009] The compounds of the present invention may be used for the manufacture of a medicament for the treatment and/or prophylaxis of a thromboembolic disorder.

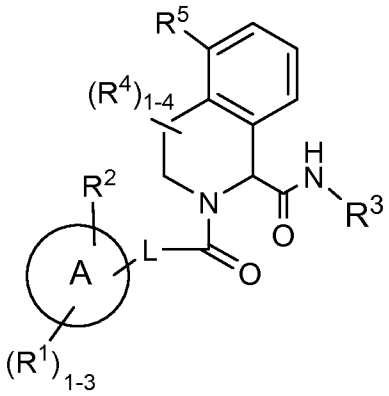
[0010] The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more, preferably one to two, other agent(s).

[0011] These and other features of the invention will be set forth in expanded form as the disclosure continues.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOUNDS OF THE INVENTION

[0012] In a first aspect, the present invention provides compounds of Formula (I):



(I)

or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof, wherein:

ring A is C3-6 carbocycle;

L is selected from the group consisting of: $-CHR^{10}CHR^{10}-$, $-CR^{10}=CR^{10}-$, $-C\equiv C-$, $-CHR^{10}NH-$, $-NHCHR^{10}-$, $-SCH_2-$, $-CH_2S-$, $-SO_2CH_2-$, $-CH_2SO_2-$, $-NHCH_2-$, and $-CH_2NH-$;

R^1, at each occurrence, is selected from the group consisting of: H, halo, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, OH, SH, CHF_2, CF_3, OCF_3, CN, NH_2, COC^ alkyl, $CO_2(C_{1.4}$ alkyl), $-CH_2CO_2H$, $-CH_2CO_2(C_{1.4}$ alkyl), $-CH_2NH_2$, $-CONH_2$, -CONHCC^ alkyl), $-NHCO(C_{1-4}$ alkyl), $-NHCO_2(C_{1.4}$ alkyl), $-NHSO_2(C_{1-4}$ alkyl), $-SO_2NH_2$, and $-C(=NH)NH_2$;

R^2 is selected from the group consisting of: H, halo, CN, OH, C_{1-6} alkyl, C_{1-4} alkoxy, C^haloalkyl, C^haloalkoxy, $CO(C!_{-4}$ alkyl), $CONH_2$, CO_2H, CH_2NH_2, and a 5- to 7-membered heterocycle comprising carbon atoms and 1-4 heteroatoms selected from N, NR^C, O, and $S(0)_p$, wherein said heterocycle is substituted with 0-2 R^{2a};

R^{2a}, at each occurrence, is selected from the group consisting of: H, halo, $C_{1}.4$ alkyl, $-CH_2OH$, C_{1-4} alkoxy, OH, CF_3, OCF3, CN, NH_2, CO_2H, $CO_2(C_{1-4}$ alkyl), $CO(C_{1-4}$ alkyl), $-CONH_2$, $-CH_2OH$, $-CH_2OCi_{-4}$alkyl, $-CH_2NH_2-$, CONH(Ci_4 alkyl), $-CON(C!_{-4}$ alkyl)$_2$, $-SO_2(Ci._4$ alkyl), $-SO_2NH_2$, $-SO_2NH(Ci._4$ alkyl), and -S02N(C_{1-4} alkyl)$_2$;

R^3 is selected from the group consisting of: C_{1-6} alkyl substituted with 1-3 R^{3a}, -$(CH_2)_n$-C3. 10 carbocycle substituted with 0-3 R^{3a} or -$(CH_2)_n$-5-10 membered heterocycle containing carbon atoms and 1-4 heteroatoms selected from the group consisting of N, NR^7, O, and S(0) $_p$; wherein said heterocycle is substituted with 0-3 R^{3a};

R^{3a}, at each occurrence, is selected from the group consisting of: H, halo, C_{1-}4 alkyl, -OH, C_{1-4} alkoxy, -CN, -NH_2, ,-NH(C_{1-4} alkyl), -N(C_{1-4} alkyl)$_2$, -C0 $_2$H, -CH_2C0 $_2$H, -C0 $_2$(C_{1-4} alkyl), -C0 $_2$-C_{1-4} alkylene-0(C_{1-4} alkyl), -C0 $_2$-C_{1-4} alkylene-N(C_{1-4} alkyl)$_2$, -C0 $_2$-C_{1-4} alkylene-O-C^ alkylene-N(C_{1-4} alkyl)$_2$, -C0 $_2$-C_{1-4} alkylene-0-C_{1-4} alkylene-0(C_{1-4} alkyl), -$CONH_2$, -CONH(C_{1-6} alkyl), -CON(C_{1-4} alkyl)$_2$, -CONH-C_{1-4} alkylene-C0 $_2$(C_{1-4} alkyl), -CONHC0 $_2$$C_{1-4}$ alkyl, -CONH-C^ alkylene-NHCO(C_{1-4} alkyl), -CONH-C_{1-4} alkylene-$CONH_2$, -NHCOC_{1-4} alkyl, -NHC0 $_2$(C_{1-4} alkyl), R^c, -CONHR^c, and -C0 $_2$$R^c$;

R^4, at each occurrence, is selected from the group consisting of: H, halo and C_{1}.4 alkyl;

R^5, at each occurrence, is selected from the group consisting of: halo, C_{1}.4 alkyl substituted with 0-2 R^e, C_{2-4} alkenyl substituted with 0-2 R^e, C_{2-4} alkynyl substituted with 0-2 Rb OH, CN, NH_2, -N(C_{1-4} alkyl)$_2$, N0 $_2$, C_{1-4} alkoxy, -OCO(C_{1-4} alkyl), -O-C^ 4 alkylene-0(C_{1-4} alkyl), -0-C_{1-4} alkylene-NCC^ alkyl)$_2$, -C0 $_2$H, -C0 $_2$(C_{1-4} alkyl), -$CONH_2$, -(CH_2)$_2$$CONH_2$, -CONR^9($C_{1-4}$ alkyl), -CONR^9-C_{1-4} alkylene-0(C_{1-4} alkyl), -CON(C_{1-4} alkyl)$_2$, -CONR^9-C_{1-4} alkylene-N(C_{1-4} alkyl)$_2$, -CON(C_{1-4} alkyl)-C_{1-4} alkylene-0(C_{1-4} alkyl), -CONR^9-C_{1-4} alkylene-C0 $_2$(C_{1-4} alkyl), -NR^{9}COC$_{1-4}$ alkyl, -NR^{9}C0 $_2$$C_{1-4}$ alkyl, -NR^{9}CONH(C_{1-4} alkyl), -NR^{9}CONR^9-C_{1-4} alkylene-C0 $_2$$C_{1-4}$ alkyl, -NR^9-Ci_4 alkylene-N(C_{1-4} alkyl)$_2$, R^8, -OR^8, -O-C1.4 alkylene-R^8, -COR^8, -C0 $_2$$R^8$, -CONR^{9}R^8, -NR^{9}COR^8, -NR^{9}C0 $_2$R^8, and -NR^{9}CON R^{9}R^8;

R^7, at each occurrence, is selected from the group consisting of: H, C_{1}.4 alkyl, COC$_{1-4}$ alkyl, C0 $_2$(C_{1-4} alkyl), C0 $_2$Bn, -CONH-C_{1-4} alkylene-C0 $_2$$C_{1-4}$ alkyl, phenyl, benzyl, and -C0 $_2$-Ci.4 alkylene-aryl;

R^8, at each occurrence, is selected from the group consisting of: