CLAIMS

1. Two polypeptides comprising:

(a) a first non-naturally occurring polypeptide comprising a fragment or domain of an arthropod nuclear receptor protein; and

(b) a second non-naturally occurring polypeptide comprising a fragment or domain of an arthropod or a mammalian nuclear receptor protein,

wherein the first polypeptide is capable of binding an activating ligand, wherein the second polypeptide associates with the first polypeptide in the presence of the activating ligand, wherein each of the first and second polypeptides further comprises first and second heterologous polypeptide sequence, such that activating ligand induced association of the first and second polypeptides results in an activated functional, biological or cell signal transduction condition, wherein the functional, biological, or cell signal transduction condition is not transcription.

2. The first and second polypeptide of claim 1, wherein one or both nuclear receptor protein fragments or domains comprise an arthropod nuclear receptor amino acid sequence.

3. The first and second polypeptide of claims 1 or 2, wherein one or both nuclear receptor protein fragments or domains comprise a Group H nuclear receptor amino acid sequence.

4. The first and second polypeptide of any one of claims 1 to 3, wherein the nuclear receptor amino acid sequence of the first polypeptide comprises an ecdysone receptor (EcR) ligand binding domain, polypeptide fragment, or substitution mutant thereof.

5. The first and second polypeptide of any one of claims 1 to 4, wherein the second polypeptide nuclear receptor protein fragment or domain comprises a mammalian nuclear receptor amino acid sequence.

6. The first and second polypeptide of claim 5, wherein the mammalian nuclear receptor protein fragment or domain comprises a retinoid X receptor (RXR) nuclear receptor polypeptide fragment, or substitution mutant thereof.

7. The first and second polypeptide of any one of claim 1 to 6, wherein the second polypeptide nuclear receptor protein fragment or domain comprises a chimera of invertebrate and mammalian nuclear receptor amino acid sequences, or substitution mutants thereof.

8. The first and second polypeptide of claim 7, wherein the second polypeptide nuclear receptor protein fragment or domain comprises a chimera of invertebrate ultraspiracle protein (USP) and mammalian RXR nuclear receptor amino acid sequences, or substitution mutants thereof.

9. A ligand inducible polypeptide coupling (LIPC) system comprising:

a) A first non-naturally occurring polypeptide comprising a fragment or domain of an arthropod nuclear receptor protein, and

b) A second non-naturally occurring polypeptide comprising a fragment or domain of an arthropod and/or mammalian nuclear receptor protein,

wherein the first and second polypeptides comprise additional heterologous sequences capable of producing an activated functional, biological or cell signal transduction condition following contact with an activating ligand, wherein the functional, biological, or cell signal transduction condition is not transcription.

10. The LIPC system of claim 9, wherein one or both nuclear receptor protein fragments or domains comprise a Group H nuclear receptor amino acid sequence.

11. The LIPC system of claim 9 or 10, wherein the first polypeptide comprises an ecdysone receptor (EcR) ligand binding domain, polypeptide fragment, or substitution mutant thereof.

12. The LIPC system of any one of claims 9 to 11, wherein the second polypeptide comprises a mammalian nuclear receptor amino acid sequence.

13. The LIPC system of claim 12, wherein the second polypeptide comprises a RXR nuclear receptor polypeptide fragment, or substitution mutant thereof.

14. The LIPC system of any one of claim 9 to 13, wherein the second polypeptide comprises a chimera of invertebrate and mammalian nuclear receptor amino acid sequences, or substitution mutants thereof.

15. The LIPC system of claim 14, wherein the second polypeptide comprises a chimera of invertebrate USP (RXR homologue) and mammalian RXR nuclear receptor amino acid sequences, or substitution mutants thereof.

16. The first and second polypeptides in any one of claims 1 to 8, or the LIPC system of any one of claims 9-15, wherein at least one of the nuclear receptor protein fragments are derived from an ecdysone receptor polypeptide selected from the group consisting of a spruce budworm *Choristoneura fumiferana* EcR ("CfEcR") LBD, a beetle *Tenebrio molitor* EcR ("TmEcR") LBD, a *Manduca sexta* EcR ("MsEcR") LBD, a *Heliothies virescens* EcR ("HvEcR") LBD, a midge *Chironomus tentans* EcR ("CfEcR") LBD, a silk moth *Bombyx mori* EcR ("BmEcR") LBD, a fruit fly *Drosophila melanogaster* EcR ("DmEcR") LBD, a mosquito *Aedes aegypti* EcR ("AaEcR") LBD, a blowfly *Lucilia capitata* EcR ("LcEcR") LBD, a blowfly *Lucilia cuprina* EcR ("LucEcR") LBD, a Mediterranean fruit fly *Ceratitis capitata* EcR ("CcEcR") LBD, a locust *Locusta migratoria* EcR ("LmEcR") LBD, an aphid *Myzus persicae* EcR ("MpEcR") LBD, a fiddler crab *Celuca pugilator* EcR ("CpEcR") LBD, a whitefly *Bamecia argentifoli* EcR (BaEcR) LBD, a leafhopper *Nephotetix cincticeps* EcR (NcEcR) LBD, and an ixodid tick *Amblyomma americanum* EcR ("AmaEcR") LBD.

17. The first and second polypeptides in any one of claims 1 to 8, or the LIPC system of any one of claims 9-15, wherein at least one of the nuclear receptor protein fragments are derived from an ecdysone receptor polypeptide encoded by a polynucleotide comprising a nucleic acid sequence of SEQ ID NO: 1 (CfEcR-DEF), SEQ ID NO: 2 (CfEcR-CDEF), SEQ ID NO: 3

(DmEcR-DEF), SEQ ID NO: 4 (TmEcR-DEF) SEQ ID NO: 5 (AmaEcR-DEF), or a polynucleotide sequence having at least 90% sequence identity to any of SEQ ID NOs: 1-5.

18. The first and second polypeptides or the LIPC system of claims 16-17, wherein at least one of the ecdysone receptor polypeptides comprises a polypeptide sequence of SEQ ID NO: 6 (CfEcR-DEF), SEQ ID NO: 7 (DmEcR-DEF), SEQ ID NO: 8 (CfEcR-CDEF), SEQ ID NO: 9 (TmEcR-DEF), SEQ ID NO: 10 (AmaEcR-DEF), or a polypeptide sequence having at least 90% sequence identity to any of SEQ ID NOs: 6-10.

19. The first and second polypeptides or the LIPC system of any one of claims 16-18, wherein the ecdysone receptor polypeptide sequence comprises about or at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 substitution mutations relative to the corresponding wild-type ecdysone receptor polypeptide.

20. The first and second polypeptides or the LIPC system of any one of claims 16-19, wherein the ecdysone receptor polypeptide is encoded by a polynucleotide comprising a codon mutation that results in a substitution of an amino acid residue, wherein the amino acid residue is at a position equivalent to or analogous to a) amino acid residue 20, 21, 48, 51, 52, 55, 58, 59, 61, 62, 92, 93, 95, 96, 107, 109, 110, 120, 123, 125, 175, 218, 219, 223, 230, 234, or 238 of SEQ ID NO: 17, b) amino acid residues 95 and 110 of SEQ ID NO: 17, c) amino acid residues 218 and 219 of SEQ ID NO: 17, d) amino acid residues 107 and 175 of SEQ ID NO: 17, e) amino acid residues 127 and 175 of SEQ ID NO: 17, f) amino acid residues 107 and 127 of SEQ ID NO: 17, g) amino acid residues 107, 127 and 175 of SEQ ID NO: 17, h) amino acid residues 52, 107 and 175 of SEQ ID NO: 17, i) amino acid residues 96, 107 and 175 of SEQ ID NO: l7, j) amino acid residues 107, 110 and 175 of SEQ ID NO: l7, k) amino acid residue 107, 121, 213, or 217 of SEQ ID NO: 18, or l) amino acid residue 91 or 105 of SEQ ID NO: 19.

21. The first and second polypeptides or the LIPC system of any one of claims 16-20, wherein the substitution mutation is selected from the group consisting of a) E20A, Q21A, F48A, I51A, T52A, T52V, T52I, T52L, T55A, T58A, V59A, L61A, I62A, M92A, M93A, R95A, V96A, V96T, V96D, V96M, V107I, F109A, A110P, A110S, A110M, A110L, Y120A, A123F, M125A,

R175E, M218A, C219A, L223A, L230A, L234A, W238A, R95A/A110P, M218A/C219A, V107I/R175E, Y127E/R175E, V107I/Y127E, V107I/Y127E/R175E, T52V/V107I/R175E, V96A/V107I/R175E, T52A/V107I/R175E, V96T/V107I/R175E, or V107I/A110P/R175E substitution mutation of SEQ ID NO: 17, b) A107P, G121R, G121L, N213A, C217A, or C217S substitution mutation of SEQ ID NO: 18, and c) G91A or A105P substitution mutation of SEQ ID NO: 19.

22. The first and second polypeptides or the LIPC system of any one of claims 16-21, wherein the retinoid X receptor polypeptide comprises a polypeptide selected from the group consisting of a vertebrate retinoid X receptor polypeptide, an invertebrate retinoid X receptor polypeptide (USP), and a chimeric retinoid X polypeptide comprising polypeptide fragments from a vertebrate and invertebrate RXR.

23. The first and second polypeptides or the LIPC system of claim 22, wherein the chimeric retinoid X receptor polypeptide comprises at least two different retinoid X receptor polypeptide fragments selected from the group consisting of a vertebrate species retinoid X receptor polypeptide fragment, an invertebrate species retinoid X receptor polypeptide fragment, and a non-Dipteran/non-Lepidopteran invertebrate species retinoid X receptor polypeptide fragment.

24. The first and second polypeptides or the LIPC system of claim 23, wherein the chimeric retinoid X receptor polypeptide comprises a retinoid X receptor polypeptide comprising at least one retinoid X receptor polypeptide fragment selected from the group consisting of an EF-domain helix 1, an EF-domain helix 2, an EF-domain helix 3, an EF-domain helix 4, an EF-domain helix 5, an EF-domain helix 6, an EF-domain helix 7, an EF-domain helix 8, an EF-domain helix 9, an EF-domain helix 10, an EF-domain helix 11, an EF-domain helix 12, an F-domain, and an EF-domain β-pleated sheet, wherein the retinoid X receptor polypeptide fragment is from a different species retinoid X receptor polypeptide or a different isoform retinoid X receptor polypeptide than the second retinoid X receptor polypeptide fragment.

25. The first and second polypeptides or the LIPC system of claim 22, wherein the chimeric retinoid X receptor polypeptide is encoded by a polynucleotide comprising a nucleic acid

sequence of a) SEQ ID NO: 11, b) nucleotides 1-348 of SEQ ID NO: 12 and nucleotides 268-630 of SEQ ID NO: 13, c) nucleotides 1-408 of SEQ ID NO: 12 and nucleotides 337-630 of SEQ ID NO: 13, d) nucleotides 1-465 of SEQ ID NO: 12 and nucleotides 403-630 of SEQ ID NO: 13, e) nucleotides 1-555 of SEQ ID NO: 12 and nucleotides 490-630 of SEQ ID NO: 13, f) nucleotides 1-624 of SEQ ID NO: 12 and nucleotides 547-630 of SEQ ID NO: 13, g) nucleotides 1-645 of SEQ ID NO: 12 and nucleotides 601-630 of SEQ ID NO: 13, and h) nucleotides 1-717 of SEQ ID NO: 12 and/or nucleotides 613-630 of SEQ ID NO: 13, or a polynucleotide having at least 90% sequence identity to any of (a) to (h).

26. The first and second polypeptides or the LIPC system of claim 22, wherein the chimeric retinoid X polypeptide comprises a polypeptide sequence of a) SEQ ID NO: 14, b) amino acids 1-116 of SEQ ID NO: 15 and amino acids 90-210 of SEQ ID NO: 16, c) amino acids 1-136 of SEQ ID NO: 15 and amino acids 113-210 of SEQ ID NO: 16, d) amino acids 1-155 of SEQ ID NO: 15 and amino acids 135-210 of SEQ ID NO: 16, e) amino acids 1-185 of SEQ ID NO: 15 and amino acids 164-210 of SEQ ID NO: 16, f) amino acids 1-208 of SEQ ID NO: 15 and amino acids 183-210 of SEQ ID NO: 16, g) amino acids 1-215 of SEQ ID NO: 15 and amino acids 201-210 of SEQ ID NO: 16, and h) amino acids 1-239 of SEQ ID NO: 15 or amino acids 205-210 of SEQ ID NO: 16, or a polypeptide sequence having at least 90% sequence identity to any of (a) to (h).

27. The first and second polypeptides or the LIPC system of any one of claims 1-26, wherein one or both additional heterologous sequences comprise a transmembrane domain.

28. The first and second polypeptides or the LIPC system of claim 27, wherein at least one of the transmembrane domains is a single-pass type I transmembrane domain.

29. A first polynucleotide comprising a nucleotide sequence encoding the first polypeptide and a second polynucleotide comprising a nucleotide sequence encoding the second polypeptide in any one of claims 1 to 28.

30. A vector comprising the polynucleotides of claim 29.

31. The vector of claim 30, wherein said vector is an expression vector.

32. A host cell comprising the vector of claim 30 or 31.

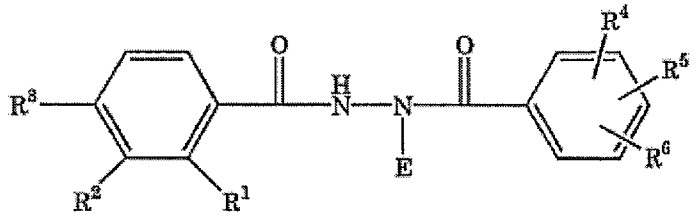
33. The host cell of claim 32, wherein the host cell is a mammalian T-cell.

34. The host cell of claim 32, wherein the host cell is a human T-cell.

35. A method of inducing cell signal transduction comprising introducing the first and second polypeptides or the LIPC system of any one claims 1-28, the polynucleotides of claim 29, or the vector of claim 30 or 31 into a host cell and contacting the host cell with an activating ligand.

36. The first and second polypeptides or the LIPC system of any one claims 1-28, the polynucleotides of claim 29, the vector of claim 30 or 31, or the method of claim 35, wherein the activating ligand is

a) a compound of the formula:



wherein:

E is a (C_4-C_6)alkyl containing a tertiary carbon or a cyano(C_3-C5)alkyl containing a tertiary carbon; R^1 is H, Me, Et, i-Pr, F, formyl, CF_3, CHF_2, $CHCl_2$, CH_2F, CH_2Cl, CH_2OH, CH_2OMe, CH_2CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OH, OMe, OEt, cyclopropyl, CF_2CF_3, CH=CHCN, allyl, azido, SCN, or $SCHF_2$;

R^2 is H, Me, Et, n-Pr, i-Pr, formyl, CF_3, CHF_2, $CHCl_2$, CH_2F, CH_2Cl, CH_2OH, CH_2OMe, CH_2CN, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, Ac, F, Cl, OH, OMe, OEt, O-n-Pr, OAc, NMe_2, NEt_2, SMe, SEt, $SOCF_3$, OCF_2CF_2H, COEt, cyclopropyl, CF_2CF_3, CH=CHCN, allyl,

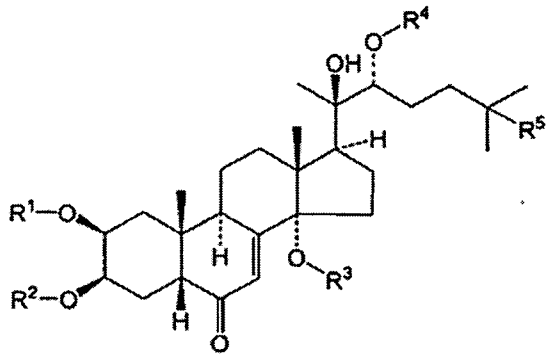
azido, OCF_3, $OCHF_2$, O-i-Pr, SCN, $SCHF_2$, SOMe, NH-CN, or joined with R^3 and the phenyl carbons to which R^2 and R^3 are attached to form an ethylenedioxy, a dihydrofuryl ring with the oxygen adjacent to a phenyl carbon, or a dihydropyryl ring with the oxygen adjacent to a phenyl carbon;

R^3 is H, Et, or joined with R^2 and the phenyl carbons to which R^2 and R^3 are attached to form an ethylenedioxy, a dihydrofuryl ring with the oxygen adjacent to a phenyl carbon, or a dihydropyryl ring with the oxygen adjacent to a phenyl carbon;

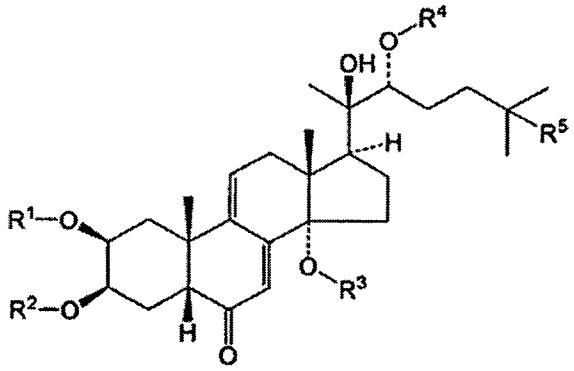
R^4, R^5, and R^6 are independently H, Me, Et, F, Cl, Br, formyl, CF_3, CHF_2, $CHC1_2$, CH_2F, CH_2Cl, CH_2OH, CN, C≡CH, 1-propynyl, 2-propynyl, vinyl, OMe, OEt, SMe, or Set; or

b) an ecdysone, 20-hydroxyecdysone, ponasterone A , muristerone A, an oxysterol, a 22(R) hydroxycholesterol, 24(S) hydroxycholesterol, 25-epoxycholesterol, T0901317, 5-alpha-6-alpha-epoxycholesterol-3-sulfate, 7-ketocholesterol-3-sulfate, farnesol, a bile acid, a 1,1- biphosphonate ester, or a Juvenile hormone III.

37. The first and second polypeptides or the LIPC system of any one claims 1-28, the polynucleotides of claim 29, the vector of claim 30 or 31, or the method of claim 35, wherein the activating ligand is a compound of the formula:



or



wherein R^1, R^2, R^3, and R^4 are: a) H, (C_1-C_6)alkyl; (C_1-C_6)haloalkyl; (C_1-C_6)cyanoalkyl; (C_1-C_6)hydroxyalkyl; (C_1-C_4)alkoxy(C_1-C_6)alkyl; (C_2-C_6)alkenyl optionally substituted with halo, cyano, hydroxyl, or (C_1-C_4)alkyl; (C_2-C_6)alkynyl optionally substituted with halo, cyano, hydroxyl, or (C_1-C_4)alkyl; (C_3-C_5)cycloalkyl optionally substituted with halo, cyano, hydroxyl, or (C_1-C_4)alkyl; or b) unsubstituted or substituted benzyl wherein the substituents are independently 1 to 5 H, halo, nitro, cyano, hydroxyl, (C_1-C_6)alkyl, or (Ci-C_6)alkoxy; and

R^5 is H; OH; F; Cl; or (C_1-C_6)alkoxy;

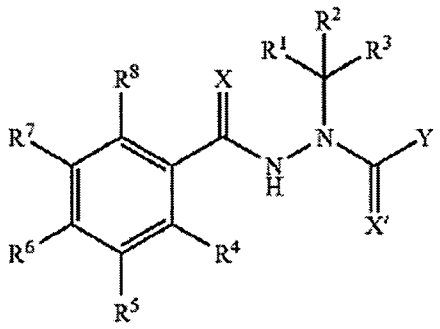
provided that: when R^1, R^2, R^3, and R^4 are isopropyl, then R^5 is not hydroxyl; when R^5 is H, hydroxyl, methoxy, or fluoro, then at least one of R^1, R^2, R^3, and R^4 is not H; when only one of R^1, R^2, R^3, and R^4 is methyl, and R^5 is H or hydroxyl, then the remainder of R^1, R^2, R^3, and R^4 are not H;

when both R^4 and one of R^1, R^2, and R^3 are methyl, then R^5 is neither H nor hydroxyl;

when R^1, R^2, R^3, and R^4 are all methyl, then R^5 is not hydroxyl;

when R^1, R^2, and R^3 are all H and R^5 is hydroxyl, then R^4 is not ethyl, n-propyl, n-butyl, allyl, or benzyl.

38. The first and second polypeptides or the LIPC system in any one claims 1-28, the polynucleotides of claim 29, the vector of claim 30 or 31, or the method of claim 35, wherein the activating ligand is a compound of the formula:



wherein X and X′ are independently O or S;

Y is:

(a) substituted or unsubstituted phenyl wherein the substitutents are independently 1-5H, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_2-C_4)alkenyl, halo (F, Cl, Br, I), (C_1-C_4)haloalkyl, hydroxy, amino, cyano, or nitro; or

(b) substituted or unsubstituted 2-pyridyl, 3-pyridyl, or 4-pyridyl, wherein the substitutents are independently 1-4H, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_2-C_4)alkenyl, halo (F, Cl, Br, I), (C_1-C_4)haloalkyl, hydroxy, amino, cyano, or nitro;

R^1 and R^2 are independently: H; cyano; cyano-substituted or unsubstituted (C_1-C_7) branched or straight-chain alkyl; cyano-substituted or unsubstituted (C_2-C_7) branched or straight-chain alkenyl; cyano-substituted or unsubstituted (C_3-C_7) branched or straight-chain alkenylalkyl; or together the valences of R^1 and R^2 form a (C_1-C_7) cyano-substituted or unsubstituted alkylidene group (R^aR^bC=) wherein the sum of non-substituent carbons in R^a and R^b is 0-6;

R^3 is H, methyl, ethyl, n-propyl, isopropyl, or cyano;

R^4, R^7, and R^8 are independently: H, (C_1-C_4)alkyl, (C_1-C_4)alkoxy, (C_2-C_4)alkenyl, halo (F, Cl, Br, I), (C_1-C_4)haloalkyl, hydroxy, amino, cyano, or nitro; and

R^5 and R^6 are independently: H, (C_1-C_4)alkyl, (C_2-C_4)alkenyl, (C_3-C_4)alkenylalkyl, halo (F, Cl, Br, I), C_1-C_4 haloalkyl, (C_1-C_4)alkoxy, hydroxy, amino, cyano, nitro, or together as a linkage of the type (—$OCHR^9CHR^{10}O$—) form a ring with the phenyl carbons to which they are attached; wherein R^9 and R^{10} are independently: H, halo, (C_1-C_3)alkyl, (C_2-C_3)alkenyl, (C_1-C_3)alkoxy(C_1-C_3)alkyl, benzoyloxy(C_1-C_3)alkyl, hydroxy(C_1-C_3)alkyl, halo(C_1-C_3)alkyl, formyl, formyl(C_1-C_3)alkyl, cyano, cyano(C_1-C_3)alkyl, carboxy, carboxy(C_1-C_3)alkyl, (C_1-C_3)alkoxycarbonyl(C_1-C_3)alkyl, (C_1-C_3)alkylcarbonyl(C_1-C_3)alkyl, (C_1-C_3)alkanoyloxy(C_1-C_3)alkyl, amino(C_1-C_3)alkyl, (C_1-C_3)alkylamino(C_1-C_3)alkyl (—$(CH_2)_nR^cR^e$), oximo (—

CH=NOH), oximo(C_1-C_3)alkyl, (C_1-C_3)alkoximo (—C=NOR^d), alkoximo(C_1-C_3)alkyl, (C_1-C_3)carboxamido (—C(O)NR^eR^f), (C_1-C_3)carboxamido(C_1-C_3)alkyl, (C_1-C_3)semicarbazido (—C=NNHC(O)NR^eR^f), semicarbazido(C_1-C_3)alkyl, aminocarbonyloxy (—OC(O)NHR^g), aminocarbonyloxy(C_1-C_3)alkyl, pentafluorophenyloxycarbonyl, pentafluorophenyloxycarbonyl(C_1-C_3)alkyl, p-toluenesulfonyl oxy(C_1-C_3)alkyl, arylsulfonyl oxy(C_1-C_3)alkyl, (C_1-C_3)thio(C_1-C_3)alkyl, (C_1-C_3)alkylsulfoxido(C_1-C_3)alkyl, (C_1-C_3)alkylsulfonyl(C_1-C_3)alkyl, or (C_1-C_5)trisubstituted-siloxy(C_1-C_3)alkyl (—$(CH_2)_nSiOR^dR^eR^g$); wherein n=1-3, R^c and R^d represent straight or branched hydrocarbon chains of the indicated length, R^e, R^f represent H or straight or branched hydrocarbon chains of the indicated length, R^g represents (C_1-C_3)alkyl or aryl optionally substituted with halo or (C_1-C_3)alkyl, and R^c, R^d, R^e, R^f, and R^g are independent of one another;

provided that

i) when R^9 and R^{10} are both H, or

ii) when either R^9 or R^{10} are halo, (C_1-C_3)alkyl, (C_1-C_3)alkoxy(C_1-C_3)alkyl, or benzoyloxy(C_1-C_3)alkyl, or

iii) when R^5 and R^6 do not together form a linkage of the type (—$OCHR^9CHR^{10}O$—),

then the number of carbon atoms, excluding those of cyano substitution, for either or both of groups R^1 or R^2 is greater than 4, and the number of carbon atoms, excluding those of cyano substitution, for the sum of groups R^1, R^2, and R^3 is 10, 11, or 12.

39. A method of measuring ligand-induced cell signal transduction comprising:

a) introducing the first and second polypeptides or the LIPC system of any one claims 1-28, the polynucleotides of claim 29, or the vector of claim 30 or 31 into a host cell;

b) contacting the host cell with an activating ligand; and,

c) quantitating the absolute or relative amount of ligand-induced biological activity or polypeptide oligomerization.