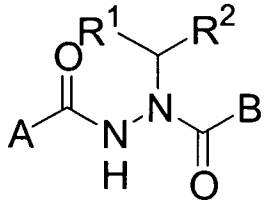
WHAT IS CLAIMED IS:

1. A compound of Formula I



Formula I

wherein

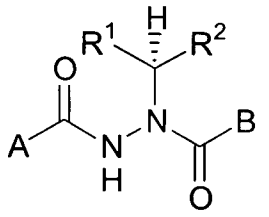
A is alkoxy, arylalkyloxy or aryloxy;

B is optionally substituted aryl or optionally substituted heteroaryl; and

R^1 and R^2 are independently optionally substituted alkyl, arylalkyl, hydroxyalkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl;

or a pharmaceutically acceptable salt, hydrate, crystalline form or amorphous form thereof.

2. An enantiomerically enriched compound of Formula II



Formula II

wherein

A is alkoxy, arylalkyloxy, aryloxy, arylalkyl, optionally substituted aryl or optionally substituted heteroaryl;

B is optionally substituted aryl or optionally substituted heteroaryl; and

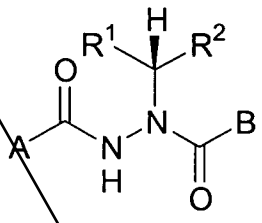
R^1 and R^2 are independently optionally substituted alkyl, arylalkyl, hydroxyalkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl;

with the proviso that R^1 does not equal R^2;

wherein the absolute configuration at the asymmetric carbon atom bearing R^1 and R^2 is predominantly *S;*

or a pharmaceutically acceptable salt, hydrate, crystalline form or amorphous form thereof.

3. An enantiomerically enriched compound of Formula III



Formula III

wherein

A is alkoxy, arylalkyloxy, aryloxy, arylalkyl, optionally substituted aryl or optionally substituted heteroaryl;

B is optionally substituted aryl or optionally substituted heteroaryl; and

R^1 and R^2 are independently optionally substituted alkyl, arylalkyl, hydroxyalkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl;

with the proviso that R^1 does not equal R^2;

wherein the absolute configuration at the asymmetric carbon atom bearing R^1 and R^2 is predominantly *R;*

or a pharmaceutically acceptable salt, hydrate, crystalline form or amorphous form thereof.

4. The compound of claim 2 or 3 having an enantiomeric excess of at least 50%.

5. The compound of claim 4 having an enantiomeric excess of at least 75%.

6. The compound of claim 5 having an enantiomeric excess of at least 85%.

7. The compound of claim 6 having an enantiomeric excess of at least 95%.

8. The compound of claim 2 or 3 wherein

A is $-OC(CH_3)_3$, $-OCH_2Ph$, optionally substituted aryl or optionally substituted heteroaryl;

B is optionally substituted aryl;

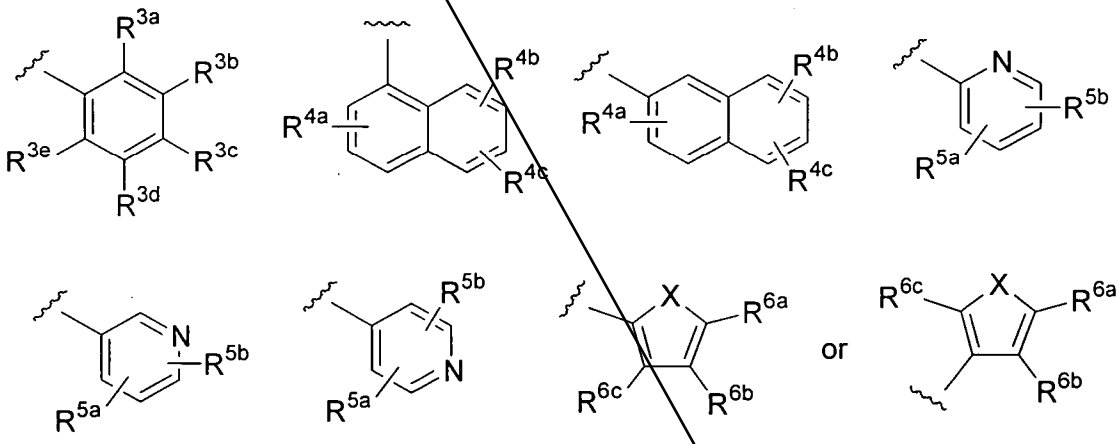
R^1 is optionally substituted (C_1-C_6)alkyl, hydroxy(C_1-C_4)alkyl or optionally substituted (C_2-C_6)alkenyl; and

R^2 is optionally substituted (C_1-C_6)alkyl, aryl(C_1-C_4)alkyl, optionally substituted (C_3-C_7)cycloalkyl or optionally substituted aryl.

9. The compound of claim 8 wherein A is optionally substituted aryl or optionally substituted heteroaryl.

10. The compound of claim 9 wherein

A is



R^{3a}, R^{3b}, R^{3c}, R^{3d} and R^{3e} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido, sulfonamido, $-COR^c$, $-SO_2R^d$, $-N(R^e)COR^f$, $-N(R^e)SO_2R^g$ or $-N(R^e)C=N(R^h)$-amino; or

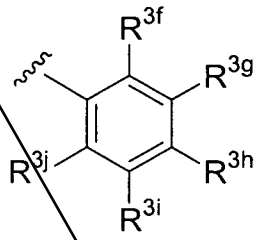
R^{3a} and R^{3b} taken together with the carbon atoms to which they are attached form a five, six or seven membered fused cycloalkyl or heterocycle ring; or

R^{3b} and R^{3c} taken together with the carbon atoms to which they are attached form a five, six or seven membered fused cycloalkyl or heterocycle ring;

R^{4a}, R^{4b}, R^{4c}, R^{5a}, R^{5b}, R^{6a}, R^{6b} and R^{6c} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido, sulfonamido, $-COR^c$, $-SO_2R^d$, $-N(R^e)COR^f$, $-N(R^e)SO_2R^g$ or $-N(R^e)C=N(R^h)$-amino;

X is O or S;

B is



R^{3f}, R^{3g}, R^{3h}, R^{3i} and R^{3j} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido, sulfonamido, $-COR^c$, $-SO_2R^d$, $-N(R^e)COR^f$, $-N(R^e)SO_2R^g$ or $-N(R^e)C=N(R^h)$-amino; or

R^{3f} and R^{3g} taken together with the carbon atoms to which they are attached form a five, six or seven membered fused cycloalkyl or heterocycle ring; or

R^{3g} and R^{3h} taken together with the carbon atoms to which they are attached form a five, six or seven membered fused cycloalkyl or heterocycle ring;

wherein

R^c is hydrogen, hydroxy, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl, optionally substituted heteroaryl, alkoxy, aryloxy or arylalkyloxy;

R^d is haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl,

optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl;

R^e is hydrogen, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl;

R^f is hydrogen, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl, optionally substituted heteroaryl, alkoxy, aryloxy, arylalkyloxy or amino;

R^g is haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl, optionally substituted heteroaryl or amino; and

R^h is hydrogen, alkyl, aryl, cyano or nitro.

11. The compound of claim 10 wherein

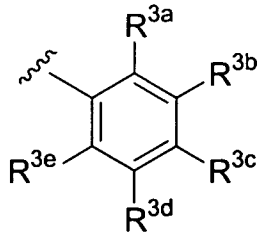
R^1 is $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl or $(C_2\text{-}C_4)$alkenyl; and

R^2 is optionally substituted $(C_1\text{-}C_6)$alkyl;

wherein the absolute configuration at the asymmetric carbon atom bearing R^1 and R^2 is predominantly *R*.

12. The compound of claim 11 wherein

A is



R^{3a}, R^{3b}, R^{3c}, R^{3d} and R^{3e} are independently selected from hydrogen, halo, $(C_1\text{-}C_4)$alkyl or $(C_1\text{-}C_4)$alkoxy; and

R^{3f}, R^{3g}, R^{3h}, R^{3i} and R^{3j} are independently selected from hydrogen, halo, (C_1-C_4)alkyl or (C_1-C_4)alkoxy.

13. The compound of claim 8 having an enantiomeric excess of at least 50%.

14. The compound of claim 13 having an enantiomeric excess of at least 75%.

15. The compound of claim 14 having an enantiomeric excess of at least 85%.

16. The compound of claim 15 having an enantiomeric excess of at least 95%.

17. The compound of claim 3 selected from:

(R)-N'-(1-*tert*-Butyl-butyl)-N'-(3,5-dimethyl-benzoyl)-hydrazinecarboxylic acid benzyl ester;

(R)-N'-(1-*tert*-Butyl-butyl)-N'-(3,5-dimethyl-benzoyl)-hydrazinecarboxylic acid *tert*-butyl ester;

(R)-N'-(1-*tert*-Butyl-4-hydroxy-butyl)-N'-(3,5-dimethyl-benzoyl)-hydrazinecarboxylic acid benzyl ester;

(*R*)- N'-(1-*tert*-Butyl-4-hydroxy-butyl)-N'-(3,5-dimethyl-benzoyl)-hydrazine carboxylic acid benzyl ester;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-ethyl-3-methoxy-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N'-benzoyl-N-(1-*tert*-butyl-butyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-methyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-methoxy-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-fluoro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-chloro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N'-(2-bromo-benzoyl)-N-(1-*tert*-butyl-butyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3-methyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3-methoxy-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3-chloro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(4-methyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(4-ethyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(4-methoxy-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(4-chloro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2,6-difluoro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2,6-dichloro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3,4-dimethoxy-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3,5-difluoro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3,5-dimethoxy-4-methyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(4-methyl-benzo[1,3]dioxole-5-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(5-ethyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(naphthalene-1-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(naphthalene-2-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(thiophene-2-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2,5-dimethyl-furan-3-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-chloro-pyridine-3-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(6-chloro-pyridine-3-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide;

(*R*)-3,5-Dimethoxy-4-methyl-benzoic acid N-(1-tert-butyl-butyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide; or

(*R*)-3,5-Dimethyl-benzoic acid N'-(4-ethyl-benzoyl)-N-(1-phenethyl-but-3-enyl)-hydrazide.

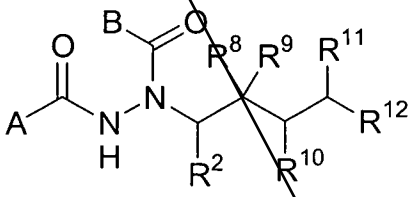
18. *(R)*-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-ethyl-3-methoxy-benzoyl)-hydrazide having an enantiomeric excess of at least 95% or a pharmaceutically acceptable salt, hydrate, crystalline form or amorphous form thereof.

19. *(R)*-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-ethyl-3-methoxy-benzoyl)-hydrazide having an enantiomeric excess of at least 99% or a pharmaceutically acceptable salt, hydrate, crystalline form or amorphous form thereof.

20. A pharmaceutical composition comprising the compound of any one of claims 1-17.

21. A pharmaceutical composition comprising the compound of claim 18 or 19.

22. A process for preparing a compound of Formula IV



Formula IV

wherein

A is arylalkyl, optionally substituted aryl or optionally substituted heteroaryl;

B is optionally substituted aryl or optionally substituted heteroaryl;

R^2 is independently optionally substituted alkyl, arylalkyl, hydroxyalkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl;

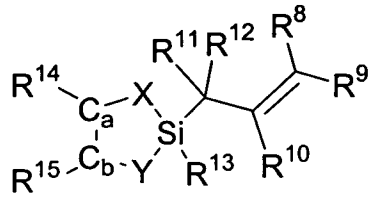
with the proviso that R^2 does not equal $-CR^8R^9CHR^{10}CR^{11}R^{12}$; and

R^8, R^9, R^{10}, R^{11} and R^{12} are independently selected from hydrogen, alkyl, cycloalkyl, heterocycle, aryl or heteroaryl;

wherein the asymmetric carbon atom to which R^2 is attached is enantiomerically enriched in either the *R* or *S* isomer;

comprising:

a) reacting a compound of Formula V



Formula V

with a compound of Formula VI

$R^2HC=N-NH-CO_2R^7$ Formula VI

wherein

X and Y are independently O or NR wherein R is alkyl or aryl;

C_a and C_b are independently an asymmetric carbon atom of the *S* configuration or an asymmetric carbon atom of the *R* configuration;

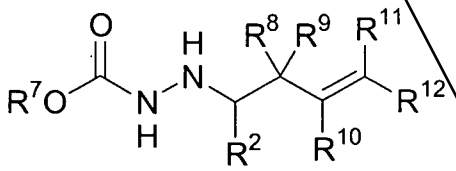
R^{14} and R^{15} are independently alkyl or aryl;

R^{13} is halo, hydrogen, alkyl, alkoxy or OSO_2CF_3;

R^7 is alkyl, arylalkyl or aryl; and

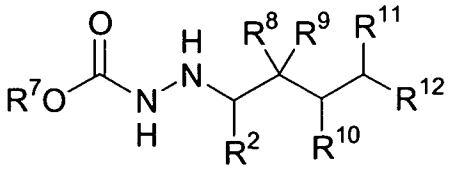
R^2, R^8, R^9, R^{10}, R^{11} and R^{12} have the same meanings noted above;

to form a compound of Formula VII;



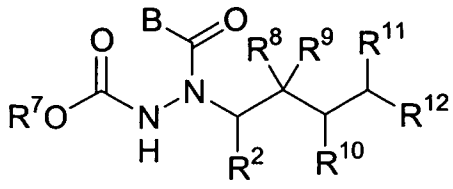
Formula VII

b) reducing the compound of Formula VII to form a compound of Formula VIII;



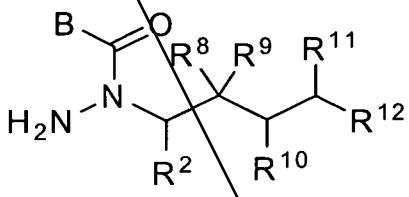
Formula VIII

c) reacting the compound of Formula VIII with a compound of Formula B-CO-LG where LG is a leaving group to form a compound of Formula IX;



Formula IX

d) removing the R^7CO_2- group of the compound of Formula IX to form a compound of Formula X; and



Formula X

e) reacting the compound of Formula X with a compound of Formula A-CO-LG where LG is a leaving group, to form a compound of Formula IV.

23. The process of claim 22 wherein R^8, R^9, R^{10}, R^{11} and R^{12} are hydrogen.

24. The process of claim 23 wherein

X is NR and R is methyl;

Y is O;

R^{14} is methyl;

R^{15} is phenyl; and

each of C_a and C_b is of the *R* configuration.

25. The process of claim 24 wherein

X is NR and R is methyl;

Y is O;

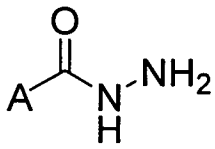
R^{14} is methyl;

R^{15} is phenyl; and

each of C_a and C_b is of the *S* configuration.

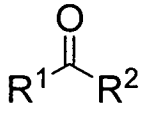
26. A process for preparing a compound of claim 2 or 3 comprising:

a) reacting an acyl hydrazine of Formula XI



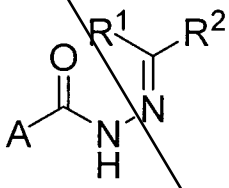
Formula XI

with a ketone of Formula XII



Formula XII

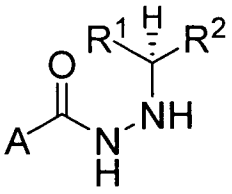
to form a compound of Formula XIII;



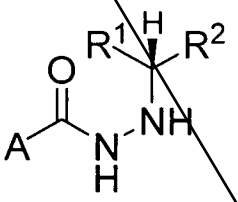
Formula XIII

wherein R^1 does not equal R^2;

b) reducing the compound of Formula XIII in the presence of a chiral catalyst to form a compound of Formula *S*-XIV or *R*-XIV; and



Formula *S*-XIV



Formula *R*-XIV

c) reacting the compound of Formula *S*-XIV or *R*-XIV with a compound of formula B-CO-LG where LG is a leaving group to form a compound of claim 2 or 3.

27. The process of claim 25 or 26 wherein B is 3,5-di-methylphenyl.

28. The process of claim 25 or 26 wherein A is 2-ethyl-3-methoxyphenyl.

29. The process of claim 25 or 26 wherein R^2 is *tert*-butyl.

30. A method of modulating the expression of a gene of interest in a host cell, wherein the host cell comprises a first recombinant gene expression cassette comprising a first polynucleotide encoding a first polypeptide comprising:

i) a DNA-binding domain; and

ii) a Group H nuclear receptor ligand binding domain;

and a second recombinant gene expression cassette comprising:

i) a response element capable of binding to said DNA binding domain;

ii) a promoter; and

iii) said gene of interest;

the method comprising contacting said host cell with a compound of any one of claims 1-3; wherein the expression of the gene of interest is modulated.

31. A method for regulating endogenous or heterologous gene expression in a transgenic subject comprising contacting a ligand with an ecdysone receptor complex within the cells of said subject, wherein said cells further contain a DNA binding sequence for said ecdysone receptor complex when in combination with said ligand and wherein formation of an ecdysone receptor complex-ligand-DNA binding sequence complex induces expression of the gene, and wherein said ligand is a compound of any one of claims 1-3; wherein endogenous or heterologous gene expression in a transgenic subject is regulated.

32. The method of claim 31, wherein said ecdysone receptor complex is a chimeric ecdysone receptor complex and said DNA binding sequence further comprises a promoter.

33. The method of claim 31 wherein the subject is a plant.

34. The method of claim 31 wherein the subject is an animal.

35. The method of claim 31 wherein the subject is a mammal.

36. The method of claim 34 wherein the subject is a human.

37. The method of claim 31, wherein said cells are autologous cells.

38. The method of claim 37, wherein said autologous cells contain said ecdysone receptor complex and the DNA binding sequence for the ecdysone complex, and said cells are implanted into said subject to make it transgenic.

39. The method of claim 38, wherein said implanted is by injection.

40. The method of claim 39, wherein said injection is into a tumor.

41. The method of claim 31, wherein said ligand is administered to said transgenic subject as part of a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

42. The method of claim 41, wherein said pharmaceutical composition is administered orally.

43. The method of claim 41, wherein said pharmaceutically acceptable carrier comprises a lipophilic solvent.

44. A method of regulating transgene expression in a transgenic subject, wherein said transgenic subject comprises a recombinant ecdysone receptor complex capable of regulating transgene expression; the method comprising administering to said subject an effective amount of a compound of any one of claims 1-3.

45. A method of modulating the expression of a gene in a host cell comprising the steps of:

(a) introducing into the host cell a gene expression modulation system comprising:

(i) a first recombinant gene expression cassette that is capable of being expressed in a host cell, said first recombinant gene expression cassette comprising a polynucleotide sequence that encodes a first hybrid polypeptide comprising:

(a) a DNA-binding domain that recognizes a response element associated with a gene whose expression is to be modulated; and

(b) an ecdysone receptor ligand binding domain;

(ii) a second recombinant gene expression cassette that is capable of being expressed in the host cell, said second recombinant gene expression cassette comprising a polynucleotide sequence that encodes a second hybrid polypeptide comprising:

(a) a transactivation domain; and

(b) a chimeric retinoid X receptor ligand binding domain; and

(iii) a third recombinant gene expression cassette that is capable of being expressed in a host cell, said third recombinant gene expression cassette comprising a polynucleotide sequence comprising:

(a) a response element recognized by the DNA-binding domain of the first hybrid polypeptide;

(b) a promoter that is activated by the transactivation domain of the second hybrid polypeptide; and

(c) a gene whose expression is to be modulated; and

(b) introducing into the host cell a compound of any one of claims 1-3; wherein the expression of a gene in a host cell is modulated.

46. A method for producing a polypeptide comprising the steps of:

(a) selecting a host cell which is substantially insensitive to exposure to a compound of any one of claims 1-3;

(b) introducing into the host cell:

(i) a DNA construct comprising:

(a) an exogenous gene encoding the polypeptide; and

(b) a response element;

wherein the exogenous gene is under the control of the response element; and

(ii) an ecdysone receptor complex comprising:

a) a DNA binding domain that binds to the response element;

b) a binding domain for said compound; and

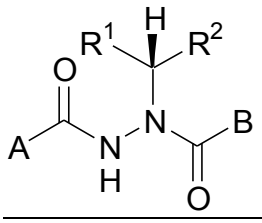
c) a transactivation domain; and

(c) exposing the cell to said compound; wherein a polypeptide is produced.

47. The method of any one of claims 31-44, wherein said ecdysone receptor complex or ecdysone receptor ligand binding domain comprises a mutation.

WHAT IS CLAIMED IS:

1. An enantiomerically enriched compound of Formula III



Formula III

or a pharmaceutically acceptable salt thereof, wherein:

A is alkoxy, arylalkyloxy, aryloxy, arylalkyl, optionally substituted aryl or optionally substituted heteroaryl;

B is optionally substituted aryl or optionally substituted heteroaryl; and

R^1 and R^2 are independently optionally substituted alkyl, arylalkyl, hydroxyalkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl;

with the proviso that R^1 does not equal R^2;

wherein the absolute configuration at the asymmetric carbon atom bearing R^1 and R^2 is predominantly *R*.

2. The compound of claim 1, wherein:

A is $-OC(CH_3)_3$, $-OCH_2Ph$, optionally substituted aryl or optionally substituted heteroaryl;

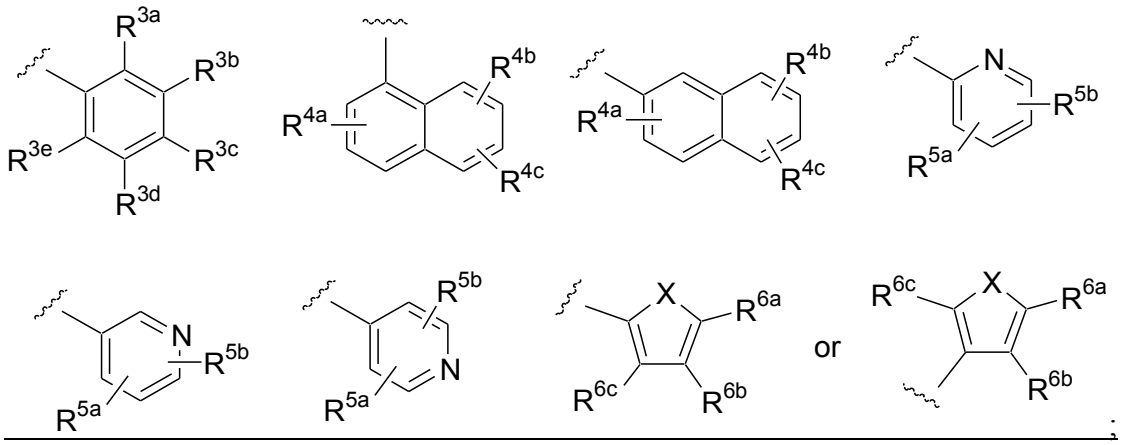
B is optionally substituted aryl;

R^1 is optionally substituted $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl or optionally substituted $(C_2\text{-}C_6)$alkenyl; and

R^2 is optionally substituted $(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_4)$alkyl, optionally substituted $(C_3\text{-}C_7)$cycloalkyl or optionally substituted aryl.

3. The compound of claim 2, wherein:

A is



;

R^{3a}, R^{3b}, R^{3c}, R^{3d} and R^{3e} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido, sulfonamido, $-COR^c$, $-SO_2R^d$, $-N(R^e)COR^f$, $-N(R^e)SO_2R^g$ or $-N(R^e)C=N(R^h)$-amino; or

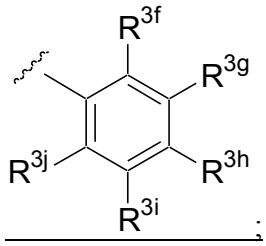
R^{3a} and R^{3b} taken together with the carbon atoms to which they are attached form a five, six or seven membered fused cycloalkyl or heterocycle ring; or

R^{3b} and R^{3c} taken together with the carbon atoms to which they are attached form a five, six or seven membered fused cycloalkyl or heterocycle ring;

R^{4a}, R^{4b}, R^{4c}, R^{5a}, R^{5b}, R^{6a}, R^{6b} and R^{6c} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido, sulfonamido, $-COR^c$, $-SO_2R^d$, $-N(R^e)COR^f$, $-N(R^e)SO_2R^g$ or $-N(R^e)C=N(R^h)$-amino;

X is O or S;

B is



;

R^{3f}, R^{3g}, R^{3h}, R^{3i} and R^{3j} are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, optionally substituted alkyl, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycle, alkoxy, aryloxy, arylalkyloxy, alkylthio, carboxamido, sulfonamido, $-COR^c$, $-SO_2R^d$, $-N(R^e)COR^f$, $-N(R^e)SO_2R^g$ or $-N(R^e)C=N(R^h)$-amino; or

R^{3f} and R^{3g} taken together with the carbon atoms to which they are attached form a five, six or seven membered fused cycloalkyl or heterocycle ring; or

R^{3g} and R^{3h} taken together with the carbon atoms to which they are attached form a five, six or seven membered fused cycloalkyl or heterocycle ring;

wherein:

R^c is hydrogen, hydroxy, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl, optionally substituted heteroaryl, alkoxy, aryloxy or arylalkyloxy;

R^d is haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl;

R^e is hydrogen, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted

alkynyl, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl;

R^f is hydrogen, haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl, optionally substituted heteroaryl, alkoxy, aryloxy, arylalkyloxy or amino;

R^g is haloalkyl, hydroxyalkyl, arylalkyl, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl, optionally substituted heteroaryl or amino; and

R^h is hydrogen, alkyl, aryl, cyano or nitro.

4. The compound of claim 3, wherein:

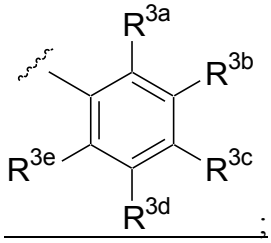
R^1 is $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_4)$alkyl or $(C_2\text{-}C_4)$alkenyl; and

R^2 is optionally substituted $(C_1\text{-}C_6)$alkyl;

wherein the absolute configuration at the asymmetric carbon atom bearing R^1 and R^2 is predominantly *R*.

5. The compound of claim 4, wherein:

A is



;

R^{3a}, R^{3b}, R^{3c}, R^{3d} and R^{3e} are independently selected from hydrogen, halo, $(C_1\text{-}C_4)$alkyl or $(C_1\text{-}C_4)$alkoxy; and

R^{3f}, R^{3g}, R^{3h}, R^{3i} and R^{3j} are independently selected from hydrogen, halo, (C_1-C_4)alkyl or (C_1-C_4)alkoxy.

6. The compound according to any one of claims 1 to 5, said compound having an enantiomeric excess of at least 95%.

7. The compound of claim 1, wherein said compound is selected from the group consisting of:

(R)-N'-(1-*tert*-Butyl-butyl)-N'-(3,5-dimethyl-benzoyl)-hydrazinecarboxylic acid benzyl ester;

(R)-N'-(1-*tert*-Butyl-butyl)-N'-(3,5-dimethyl-benzoyl)-hydrazinecarboxylic acid *tert*-butyl ester;

(R)-N'-(1-*tert*-Butyl-4-hydroxy-butyl)-N'-(3,5-dimethyl-benzoyl)-hydrazinecarboxylic acid benzyl ester;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-ethyl-3-methoxy-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N'-benzoyl-N-(1-*tert*-butyl-butyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-methyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-methoxy-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-fluoro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-chloro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N'-(2-bromo-benzoyl)-N-(1-*tert*-butyl-butyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3-methyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3-methoxy-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3-chloro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(4-methyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(4-ethyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(4-methoxy-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(4-chloro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2,6-difluoro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2,6-dichloro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3,4-dimethoxy-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3,5-difluoro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3,5-dimethoxy-4-methyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(4-methyl-benzo[1,3]dioxole-5-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(5-methyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(5-ethyl-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(naphthalene-1-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(naphthalene-2-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(thiophene-2-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2,5-dimethyl-furan-3-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-chloro-pyridine-3-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(6-chloro-pyridine-3-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide;

(*R*)-3,5-Dimethoxy-4-methyl-benzoic acid N-(1-tert-butyl-butyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide; and

(*R*)-3,5-Dimethyl-benzoic acid N'-(4-ethyl-benzoyl)-N-(1-phenethyl-but-3-enyl)-hydrazide.

8. The compound of claim 9, wherein said compound is selected from the group consisting of:

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-ethyl-3-methoxy-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N'-benzoyl-N-(1-*tert*-butyl-butyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-methyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-fluoro-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N'-(2-bromo-benzoyl)-N-(1-*tert*-butyl-butyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3-methyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(4-methyl-benzoyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-chloro-pyridine-3-carbonyl)-hydrazide;

(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(6-chloro-pyridine-3-carbonyl)-hydrazide; and

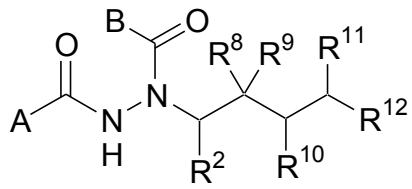
(R)-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(3-methoxy-2-methyl-benzoyl)-hydrazide.

9. A compound which is *(R)*-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-ethyl-3-methoxy-benzoyl)-hydrazide having an enantiomeric excess of at least 95% or a pharmaceutically acceptable salt thereof.

10. A compound which is *(R)*-3,5-Dimethyl-benzoic acid N-(1-*tert*-butyl-butyl)-N'-(2-ethyl-3-methoxy-benzoyl)-hydrazide having an enantiomeric excess of at least 99% or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising the compound according to any one of claims 1-10 and a pharmaceutically acceptable carrier and/or excipient.

12. A process for preparing a compound of Formula IV



Formula IV

wherein:

A is arylalkyl, optionally substituted aryl or optionally substituted heteroaryl;

B is optionally substituted aryl or optionally substituted heteroaryl;

R^2 is independently optionally substituted alkyl, arylalkyl, hydroxyalkyl, haloalkyl, optionally substituted cycloalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted heterocycle, optionally substituted aryl or optionally substituted heteroaryl;

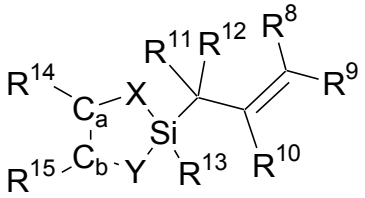
with the proviso that R^2 does not equal $-CR^8R^9CHR^{10}CR^{11}R^{12}$; and

R^8, R^9, R^{10}, R^{11} and R^{12} are independently selected from hydrogen, alkyl, cycloalkyl, heterocycle, aryl or heteroaryl;

wherein the asymmetric carbon atom to which R^2 is attached is enantiomerically enriched in either the *R* or *S* isomer;

said process comprising:

a) reacting a compound of Formula V



Formula V

with a compound of Formula VI

$R^2HC=N-NH-CO_2R^7$ Formula VI

wherein:

X and Y are independently O or NR wherein R is alkyl or aryl;

C_a and C_b are independently an asymmetric carbon atom of the *S* configuration or an asymmetric carbon atom of the *R* configuration;

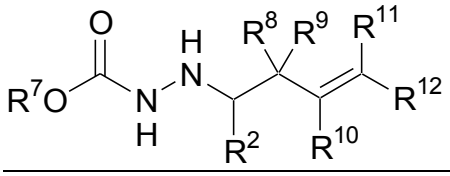
R^{14} and R^{15} are independently alkyl or aryl;

R^{13} is halo, hydrogen, alkyl, alkoxy or OSO_2CF_3;

R^7 is alkyl, arylalkyl or aryl; and

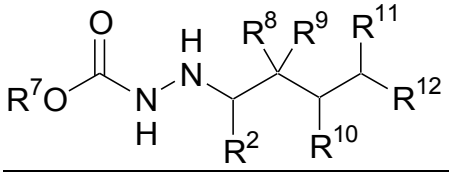
R^2, R^8, R^9, R^{10}, R^{11} and R^{12} have the same meanings noted above;

to form a compound of Formula VII;



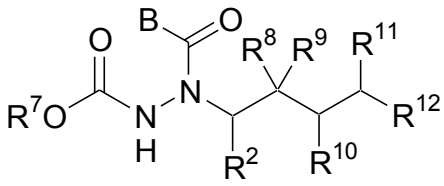
Formula VII

b) reducing the compound of Formula VII to form a compound of Formula VIII;



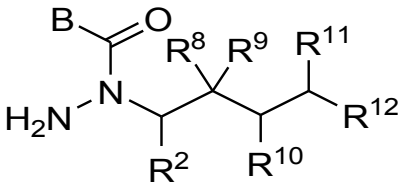
Formula VIII

c) reacting the compound of Formula VIII with a compound of Formula B-CO-LG where LG is a leaving group to form a compound of Formula IX;



Formula IX

d) removing the R^7CO_2- group of the compound of Formula IX to form a compound of Formula X; and



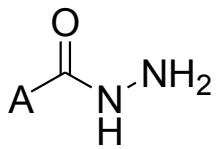
Formula X

e) reacting the compound of Formula X with a compound of Formula A-CO-LG where LG is a leaving group, to form a compound of Formula IV.

13. The process of claim 12, wherein R^8, R^9, R^{10}, R^{11} and R^{12} are hydrogen.

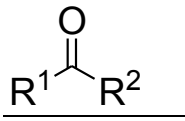
14. A process for preparing a compound of claim 1, said process comprising:

a) reacting an acyl hydrazine of Formula XI



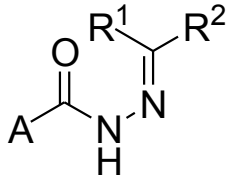
Formula XI

with a ketone of Formula XII



Formula XII

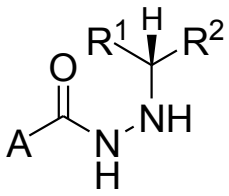
to form a compound of Formula XIII;



Formula XIII

wherein R^1 does not equal R^2;

b) reducing the compound of Formula XIII in the presence of a chiral catalyst to form a compound of Formula *R*-XIV; and



Formula *R*-XIV

c) reacting the compound of Formula *R*-XIV with a compound of formula B-CO-LG where LG is a leaving group to form a compound of claim 1.

15. The process of claim 13 or claim 14, wherein:

B is 3,5-di-methylphenyl;

A is 2-ethyl-3-methoxyphenyl; and

R^2 is *tert*-butyl.

16. An *in vitro* method of modulating the expression of a gene of interest in a host cell, said method comprising contacting the host cell with a compound according to any one of claims 1 to 10,

wherein the host cell comprises:

(a) a first recombinant gene expression cassette comprising a first polynucleotide encoding a first polypeptide comprising:

i) a DNA-binding domain; and

ii) a Group H nuclear receptor ligand binding domain; and

(b) a second recombinant gene expression cassette comprising:

i) a response element capable of binding to said DNA binding domain;

ii) a promoter; and

iii) said gene of interest.

17. A method for regulating endogenous or heterologous gene expression in a transgenic subject, said method comprising contacting a ligand with an ecdysone receptor complex within one or more cells of the transgenic subject, wherein said one or more cells further contain a DNA binding sequence for said ecdysone receptor complex when in combination with said ligand and wherein formation of an ecdysone receptor complex-ligand-DNA binding sequence complex induces expression of the gene, and wherein said ligand is a compound according to any one of claims 1-10.

18. The method of claim 17, wherein the subject is a plant or a human.

19. A method of regulating transgene expression in a transgenic subject, said method comprising administering to said subject an effective amount of a compound of any one of claims 1-10, wherein said transgenic subject comprises a recombinant ecdysone receptor complex capable of regulating transgene expression.

20. An *in vitro* method of modulating the expression of a gene in a host cell comprising the steps of:

(a) introducing into the host cell a gene expression modulation system comprising:

(i) a first recombinant gene expression cassette that is capable of being expressed in a host cell, said first recombinant gene expression cassette comprising a polynucleotide sequence that encodes a first hybrid polypeptide comprising:

(a) a DNA-binding domain that recognizes a response element associated with a gene whose expression is to be modulated; and

(b) an ecdysone receptor ligand binding domain;

(ii) a second recombinant gene expression cassette that is capable of being expressed in the host cell, said second recombinant gene expression cassette comprising a polynucleotide sequence that encodes a second hybrid polypeptide comprising:

(a) a transactivation domain; and

(b) a chimeric retinoid X receptor ligand binding domain; and

(iii) a third recombinant gene expression cassette that is capable of being expressed in a host cell, said third recombinant gene expression cassette comprising a polynucleotide sequence comprising:

(a) a response element recognized by the DNA-binding domain of the first hybrid polypeptide;

(b) a promoter that is activated by the transactivation domain of the second hybrid polypeptide; and

(c) a gene whose expression is to be modulated; and

(b) introducing into the host cell a compound of any one of claims 1-10.

21. A method of temporally controlling polypeptide production in a host cell, said method comprising exposing the host cell to a compound according to any one of claims 1-10.

22. The method of claim 21 comprising the steps of:

(c) selecting a host cell which is substantially insensitive to exposure to said compound; and

(d) introducing into the host cell:

(i) a DNA construct comprising:

(a) an exogenous gene encoding the polypeptide; and

(b) a response element;

wherein the exogenous gene is under the control of the response element; and

(ii) a DNA construct encoding an ecdysone receptor complex comprising:

a) a DNA binding domain that binds to the response element;

b) an ecdysone receptor ligand binding domain for said compound; and

c) a transactivation domain.

23. Use of a compound according to any one of claims 1-10 or a pharmaceutical composition according to claim 11 in preparation of a medicament for treatment of cancer or a genetic disorder.

24. The use according to claim 23, wherein at least one of said one or more exogenous genes is hIL-12.

25. A compound when prepared by the process according to any one of claims 12 to 15.