Objectives

- Observe and assess the effect of oral administration of **27** on animal wellbeing.
- Quantify levels of **27** in tissues (plasma, tumor, liver, spleen and brain) to assess the compound bioaccumulation and distribution.

Method

B16F10 cells (25 x 10^5 cells/mouse) were injected subcutaneously into the right flank of female BALB/c mice aged 7-8 weeks. Mice (n =10) were divided into 2 groups and given daily oral suspension of **27** (treated group), or vehicle (control group) for 15 days. The treated group was orally given a suspension of **27** at 900 mg/kg. The control group was given the vehicle suspension (SEDDS). Measurements performed on days 0, 9 and 15 only. Tissues (plasma, tumor, liver, spleen and brain) were harvested within 3 hours of final treatment. Biopsies of tumor tissues for histopathology were obtained subsequently.

Tissue samples from the tumors of both treated and control mice were fixed with formalin. Histopathological examination of these tumor samples was performed by Lore Laboratory, CA, USA.

Concentrations of **27** in different tissues were determined using LC/MS/MS spectrometry.

Results

Mice showed no signs of toxic effect at 900 mg/kg of **27**. Concentration of **27** in different tissues are determined as shown in table 1 and presented graphically as shown in Figure 15 A and B.

Table 8. Measurement of compound 27 in mice tissues using mass spectrometry

	Concentration of compound 27 in tissues				
Animal	Plasma (ng/mL)	Tumor (µg/mg)	Liver (µg/mg)	Spleen (µg/mg)	Brain (µg/mg)
Control 1	0.0	NA	0	0	0

Control 2	0.0	0	0	NA	0
Control 3	0.0	0	0	0	0
Treated 1	0.0	0	12.6	2	156
Treated 2	0.0	NA	10.2	0	77
Treated 3	8.4	0	1.0	0	35
Treated 4	0.4	0	0.0	0	170
Treated 5	0.0	11.6	0.0	0	48
P-Value control vs treated	0.22	0.54	0.36	0.65	0.004

NA = not acquired

Figure 15. Concentrations of 27 in different tissue samples isolated from treated mice. Mice were orally administration of 900 mg/kg of **27** in SEDDS suspension or vehicle (control) daily for 15 days.

It was found that concentration of compound **27** was variously distributed in different tissues as shown in Figure 15. Low plasma level of compound **27** can be explained as the compound being bound to plasma proteins such as albumin.

Histochemical analysis of the tumor samples.

Preliminary investigation revealed that two out of five biopsies samples from five mice treated with **27** displayed melanomas as detailed below.

Treated 1.

It was found that the lesion was located deep in the dermis and panniculus. There was a sheet of pleomorphic round cells with occasional pigmented cytoplasm. These cells were predominantly degenerated or necrotic with adjacent areas of lytic necrosis (Figure 16). Mixed inflammatory cells were noticed at the periphery.

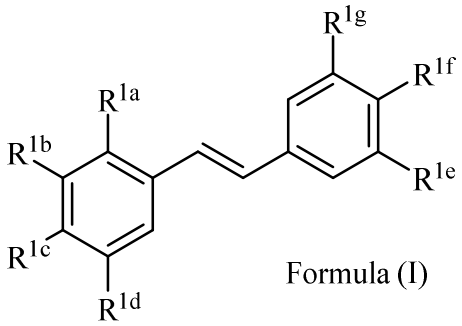
Treated 2.

It was found that the lesion was located in the superficial and mid dermis. There was a sheet of pleomorphic round cells with occasional pigmented cytoplasm surrounded by lytic necrosis (Figure 16). Mixed inflammatory cells were noticed at the periphery.

Histochemical analysis of tumor samples from treated 1 and 2 mice.

CLAIMS:

1. A process of synthesising a compound of formula (I):



Formula (I)

wherein:

R^{1a} is independently allyl, crotyl, prenyl, geranyl, farnesyl, benzyl, 2-alkenyl or 2-alkynyl;

R^{1b} is independently CF_3, OH, OR^2, NO_2, NHEt, NMe_2, NMeEt, NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;

R^{1c} is independently H, alkyl, alkenyl, alkynyl, alkanedienyl, prenyl, geranyl, farnesyl, or benzyl;

R^{1d} is independently CF_3, OH,OR^2, NHR^3, NO_2, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;

R^{1e} is independently H, C_1-C_6 alkyl, OH, OR^2, NO_2, NMe_2, NHR^3 or $NMeR^3$, NHC(O)H, SR^2;

R^{1f} is independently H, OH, OR^2, NO_2, NHR^3, $NHC{=}NH(NH_2)$, $COOR^2$, COOH;

R^{1g} is independently H, alkyl, CF_3,OH or OR^2;

and no more than one of R^{1e}, R^{1f} or R^{1g} can be H;

or R^{1e} and R^{1f} form a five or six-membered heterocyclic ring containing a carbonyl group or $(CO)CH_2$ group when R^{1e} is independently OH, NH_2 or NHMe and R^{1f} is NH_2, such that the nitrogen of R^{1f} is bridged with the carbonyl group or $(CO)CH_2$ group to the oxygen or nitrogen of R^{1e};

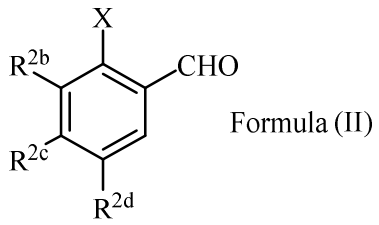
R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl, $COCOOR^4$ or an O-protecting group when R^2 is attached to an O;

R^3 is independently H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOH, CH_2COOR^2, $CO(CH_2)_nNH_2$, $CONH_2$, $CO(CH_2)_nCOOH$ or $COCOOR^4$, where n is 0, 1 or 2;

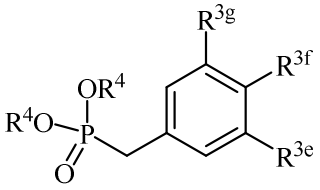
R^4 is C_1-C_6 alkyl; and

the process comprising:

i) a step of coupling a compound of formula (II) (Module A) with a compound of formula (III) (Module B) to afford a compound of formula (IV) (Module C):

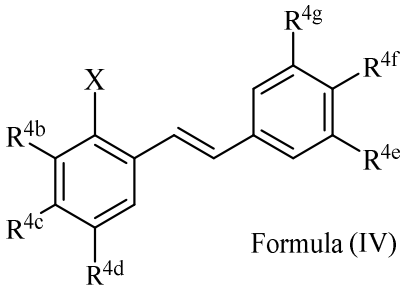


Formula (II)



Formula (III)

Module A **Module B**



Formula (IV)

Module C

wherein,

in Formula II (Module A):

R^{2b} is independently CF_3, OH,OR^2, NO_2, NMe_2, NHEt, NMeEt, NHR^3 or $NMeR^3$;

R^{2c} is independently H, alkyl, alkenyl, alkynyl, alkanedienyl, prenyl, geranyl, farnesyl, or benzyl;

R^{2d} is independently CF_3, OH or OR^2, NO_2,NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;

X is a halide or a hydroxyl group, wherein the halide is selected from the group consisting of F, Cl, Br, I, and At;

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl, or O-protecting group when R^2 is attached to an O; and

R^3 is independently H, OH, CH_3, (CO)H, COMe, SO_2Me, $COCH_2NH_2$, or CH_2COOR^2; and

in Formula III (Module B):

R^{3e} is independently H, C_1-C_6 alkyl, OH, OR^2, NO_2, NHMe, NMe_2, NHR^3 or $NMeR^3$, SR^2;

R^{3f} is independently H, OH, OR^2, NO_2, NHR^3, $NHC{=}NH(NH_2)$, COOH or $COOR^2$;

R^{3g} is independently H, alkyl, CF_3, OH or OR^2;

and no more than one of R^{3e}, R^{3f} or R^{3g} can be H;

or R^{3e} and R^{3f} form a five or six-membered heterocyclic ring containing a carbonyl group or $(CO)CH_2$ group when R^{3e} is OH, NH_2 or NHMe and R^{3f} is NH_2, such that the nitrogen of R^{3f} is bridged with the carbonyl group or $(CO)CH_2$ group to the oxygen or nitrogen of R^{3e};

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or O-protecting group when R^2 is attached to an O,

R^3 is independently H, CH_3, OH, (CO)H, COMe, SO_2Me, $COCH_2NH_2$, CH_2COOH or CH_2COOR^2; and

in Formula IV (Module C):

R^{4b} is independently CF_3, OH or OR^2, NO_2, NMe_2, NHEt, NMeEt, NHR^3 or $NMeR^3$;

R^{4c} is independently H, alkyl, alkenyl, alkynyl, alkanedienyl, prenyl, geranyl, farnesyl, or benzyl;

R^{4d} is independently CF_3, OH, OR^2, OR^3, NO_2 or NHR^3, $NMeR^3$, $NHC=NH(NH_2)$ or $COOR^2$;

R^{4e} is independently H, C_1-C_6 alkyl, OH, OR^2, NO_2, NMe_2, NHR^3 or $NMeR^3$ NHC(O)H or SR^2;

R^{4f} is independently H, OH, OR^2, NO_2, NHR^3, $NHC=NH(NH_2)$, COOH or $COOR^2$;

R^{4g} is independently H, alkyl, CF_3, OH or OR^2;

and no more than one of R^{4e}, R^{4f} or R^{4g} can be H;

or R^{4e} and R^{4f} form a five or six-membered heterocyclic ring containing a carbonyl group or $(CO)CH_2$ group when R^{4e} is OH, NH_2 or NHMe and R^{4f} is NH_2, such that the nitrogen of R^{4f} is bridged with the carbonyl group or $(CO)CH_2$ group to the oxygen or nitrogen of R^{4e};

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or O-protecting group when R^2 is attached to an O;

R^3 is independently H,CH_3, OH, (CO)H, COMe, SO_2Me, $COCH_2NH_2$, CH_2COOH or CH_2COOR^2; and

X is a halide or a hydroxyl group, wherein the halide is selected from the group consisting of F, Cl, Br, I, and At;

wherein the O-protecting group is selected from the group consisting of COMe, *t*-$BuSi(CH_3)_2$, 2-(trimethylsilyl)ethoxy]methyl (SEM), $CH(OEt)CH_3$, tetrahydropyranyl, or $C(OEt)(CH_3)_2$.

2. The process of claim 1, wherein ~~when~~ X in formula (II) and (IV) is a halide~~.~~

~~3. The process of claim 1, wherein X in formula (II) and (IV) is hydroxyl.~~

~~4. The process of claim 2,~~ and wherein the ~~compound~~ halide of formula (IV) undergoes a coupling reaction with one of the following:

a) a R^{1a}-substituted boronic acid compound or ester, preferably a R^{1a}-substituted boronic acid pinacol ester;

b) a R^{1a}-substituted trifluoroborate compound , preferably a potassium R^{1a}-substituted trifluoroborate; or

c) a R^{1a}-substituted organostannane compound, preferably a R^{1a}-substituted tributylstannane;

to form the compound of formula (I),

wherein R^{1a} is selected from the group consisting of allyl, crotyl, prenyl, geranyl, farnesyl, benzyl, 2-alkenyl or 2-alkynyl.;

or

~~5. The process of claim 3~~ wherein X in formula (II) and (IV) is hydroxyl and wherein the hydroxyl group is converted to a triflate (trifluoromethylsulfonate) group to form a triflate of formula (IV), and the triflate of formula (IV) undergoes a coupling reaction with one of the following:

a) a R^{1a}-substituted boronic acid compound or ester, preferably a R^{1a}-substituted boronic acid pinacol ester;;

b) a R^{1a}-substituted trifluoroborate compound, preferably a potassium R^{1a}-substituted trifluoroborate; or

c) a R^{1a}-substituted organostannane compound, preferably a R^{1a}-substituted tributylstannane

to form the compound of formula (I),

wherein R^{1a} is selected from the group consisting of allyl, crotyl, prenyl, geranyl, farnesyl, benzyl, 2-alkenyl or 2-alkynyl.

~~6. The process of claim 4 or 5 , wherein the R^{1a}-substituted boronic acid compound is a R^{1a}-substituted boronic acid pinacol ester.~~

~~7. The process of claim 4 or 5 wherein the R^{1a}-substituted organostannane compound is a R^{1a}-substituted tributylstannane.~~

~~8. The process of claim 4 or 5 wherein the R^{1a}-substituted trifluoroborate compound is potassium R^{1a}-substituted trifluoroborate.~~

~~9. The process of any one of claims 4 - 8 wherein R^{1a} is selected from the group consisting of allyl, crotyl, prenyl, benzyl or 2-alkenyl.~~

~~10. The process of any one of claims 4 - 9, wherein R^{1a} is a prenyl group selected from the group consisting of $CH_2CH=C(CH_3)_2$, $CH=CHCH(CH_3)_2$ and $CH=CHC(CH_3)=CH_2$.~~

~~11. The process of any one of claims 4 to 6 wherein the R^{1a} substituted boronic acid compound is selected from the group comprising 3-methylbut-2-enylboronic acid pinacol ester, crotylboronic acid pinacol ester, allylboronic acid pinacol ester and benzylboronic acid pinacol ester.~~

~~12~~3. The process of any one of claims ~~4 to 10~~1-2, wherein the coupling reaction is catalysed by a palladium compound~~.~~.

~~13. The process of any one of claims 4 to 12, wherein the coupling reaction is catalysed by a palladium compound~~ including~~selected from the group consisting of~~ tetrakis(triphenylphosphine)palladium(0) and 1,1′-bis(diphenylphosphino) ferrocene]dichloropalladium(II)~~.~~

~~14. The process of any one of claims 4 to 13, wherein the coupling reaction is catalysed by the palladium catalyst~~ , optionally in the presence of a base~~.~~

~~15. The process of claim 14, wherein the base is~~ selected from ~~the group consisting of~~ alkali metal carbonates including potassium carbonate (K_2CO_3); hydrogen carbonates; calcium carbonate; magnesium carbonate; and alkylamines including triethylamine~~.~~ .

~~16. The process of any one of claims 4 to 5 and 6, wherein the compound of formula (IV) undergoes a coupling reaction with a R^{1a} substituted boronic acid pinacol ester catalysed by tetrakis(triphenylphosphine)palladium(0) in the presence of a base , preferably potassium carbonate, wherein R^{1a} is selected from a prenyl, crotyl, allyl or benzyl group.~~

~~17. The process of any one of claims 4 to 5 and 7, wherein the compound of formula (IV) undergoes a coupling reaction with a R^{1a} substituted tributylstannane catalysed by~~

~~[1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) wherein R^{1a} is selected from a prenyl, crotyl, allyl or benzyl group.~~

~~184~~. The process of any one of claims 1-~~173~~, wherein

in Formula (I):

R^{1a} is independently allyl, crotyl, prenyl, benzyl, or 2-alkenyl;

R^{1b} is independently OH, OR^2 or NHC(O)Me;

R^{1c} is H;

R^{1d} is independently OH, NHR^3, NHC(O)H or NO_2;

R^{1e} is independently OH, OR^2, NMe_2, NHR^3, $NMeR^3$, NHC(O)H or SR^2;

R^{1f} is independently H, OH, NO_2, OR^2, NHR^3, NHC=NH(NH_2), or COOH;

R^{1g} is independently H, alkyl, OH or OR^2;

and no more than one of R^{1e}, R^{1f} or R^{1g} can be H;

or R^{1e} and R^{1f} form a five or six-membered heterocyclic ring containing a carbonyl group when R^{1e} is OH, NH_2 or NHMe and R^{1f} is NH_2, such that the nitrogen of R^{1f} is bridged with the carbonyl group to the oxygen or nitrogen of R^{1e};

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl or an O-protecting group when R^2 is attached to an O, wherein the O-protecting group is selected from the group consisting of COMe, *t*-BuSi(CH_3)$_2$, 2-(trimethylsilyl)ethoxymethyl (SEM), CH(OEt)CH_3, tetrahydropyranyl, or C(OEt)(CH_3)$_2$.;

R^3 is independently H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CO(CH_2)$_n$$NH_2$, CH_2COOR^2, CO(CH_2)$_n$COOH or $COCOOR^4$, where n is 0, 1 or 2; and

R^4 is C_1-C_6 alkyl;

in Formula II (Module A):

R^{2b} is OH or OR^2;

R^{2c} is H;

R^{2d} is independently OH or OR^2, NO_2, NHR^3 or $COOR^2$;

X is a halide or a hydroxyl group, wherein the halide is selected from the group consisting of F, Cl, Br, I, and At;

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl, or an O-protecting group;

R^3 is independently H, OH, CH_3, (CO)H, COMe, SO_2Me, $COCH_2NH_2$, or CH_2COOR^2; and

in Formula III (Module B):

R^{3e} is independently OH, OR^2, NO_2, NHMe, NMe_2, NHR^3 $NMeR^3$ or SR^2;

R^{3f} is independently H, OH, OR^2, NO_2, NHR^3, NHC=NH(NH_2), COOH or $COOR^2$;

R^{3g} is independently H, alkyl, OH or OR^2;

and no more than one of R^{3e}, R^{3f} or R^{3g} can be H;

or R^{3e} and R^{3f} form a five or six-membered heterocyclic ring containing a carbonyl group or $(CO)CH_2$ group when R^{3e} is OH, NH_2 or NHMe and R^{3f} is NH_2, such that the nitrogen of R^{3f} is bridged with the carbonyl group or $(CO)CH_2$ group to the oxygen or nitrogen of R^{3e};

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or an O-protecting group when R^2 is attached to an O;

R^3 is independently H, CH_3, OH, (CO)H, COMe, SO_2Me, $COCH_2NH_2$, CH_2COOH or CH_2COOR^2; and

in Formula IV (Module C):

R^{4b} is OH or OR^2, NHC(O)Me;

R^{4c} is H;

R^{4d} is independently OH or OR^2, NO_2 or NHR^3, $NMeR^3$;

R^{4e} is independently OH, OR^2, NO_2, NMe_2, NHR^3 or $NMeR^3$, NHC(O)H or SR^2;

R^{4f} is independently H, OH, OR^2, NO_2, NHR^3, NHC=NH(NH_2), COOH or $COOR^2$;

R^{4g} is independently H, alkyl, CF_3, OH or OR^2;

and no more than one of R^{4e}, R^{4f} or R^{4g} can be H;

or R^{4e} and R^{4f} form a five or six-membered heterocyclic ring containing a carbonyl group or $(CO)CH_2$ group when R^{4e} is OH, NH_2 or NHMe and R^{4f} is

NH_2, such that the nitrogen of R^{4f} is bridged with the carbonyl group or $(CO)CH_2$ group to the oxygen or nitrogen of R^{4e};

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or an O-protecting group when R^2 is attached to an O;

R^3 is independently H, CH_3, OH, (CO)H, COMe, SO_2Me, $COCH_2NH_2$, CH_2COOH or CH_2COOR^2; and

X is a halide or a hydroxyl group, wherein the halide is selected from the group consisting of F, Cl, Br, I, and At.

~~19~~5. The process of any one of claims 1-~~17~~ 3 wherein

in Formula (I):

R^{1a} is independently crotyl, prenyl, benzyl, 2-alkenyl;

R^{1b} is independently CF_3, or OR^2 or NHC(O)Me;

R^{1c} is H;

R^{1d} is independently OH, NHR^3 or NO_2;

R^{1e} is independently OR^2, NHR^3 or $NMeR^3$ or SR^2;

R^{1f} is independently H, OH, NO_2, NHR^3, $NHC{=}NH(NH_2)$ or COOH;

R^{1g} is independently H, alkyl, OH or OR^2;

or R^{1e} and R^{1f} form a five or six-membered heterocyclic ring containing a carbonyl group when R^{1e} is OH, NH_2 or NHMe and R^{1f} is NH_2, such that the nitrogen of R^{1f} is bridged with the carbonyl group to the oxygen or nitrogen of R^{1e};

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl,

R^3 is independently H, Me, (CO)H, (CO)Me, SO_2Me, CH_2COOR^2, $COCH_2NH_2$ or $CO(CH_2)_nCOOH$ where n = 0, 1 or 2; and

in Formula II (Module A):

R^{2b} is independently CF_3, OH, OR^2, NO_2, NMe_2, NHEt, NMeEt, NHR^3 or $NMeR^3$;

R^{2c} is independently H, alkyl, alkenyl, alkynyl, alkanedienyl, prenyl, geranyl, farnesyl, or benzyl;

R^{2d} is independently CF_3, OH or OR^2, NO_2, NHR^3 , $NMeR^3$, NHC=NH(NH_2) or $COOR^2$;

X is a halide or a hydroxyl group, wherein the halide is selected from the group consisting of F, Cl, Br, I, and At;

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl, or an O-protecting group;

R^3 is independently H, OH, CH_3, (CO)H, COMe, SO_2Me, $COCH_2NH_2$, or CH_2COOR^2; and

in Formula III:

R^{3e} is independently OH, OR^2, NO_2, NHR^3 or $NMeR^3$, (CO)H, NHC(O)H or SR^2;

R^{3f} is independently H, OH, OR^2, NO_2, NHR^3;

R^{3g} is independently H, alkyl, OH or OR^2;

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or O-protecting group when R^2 is protecting an O, wherein the O-protecting group is selected from the group consisting of COMe, *t*-$BuSi(CH_3)_2$, 2-(trimethylsilyl)ethoxymethyl (SEM), $CH(OEt)CH_3$, tetrahydropyranyl, or $C(OEt)(CH_3)_2$; and

R^3 is independently H, CH_3, (CO)H, COMe, SO_2Me, CH_2COOR^2, or $COCH_2NH_2$; and

in Formula IV:

R^{4b} is independently CF_3, OH, OR^2 or NHC(O)Me;

R^{4c} is H;

R^{4d} is independently OH, NH_2 or NH(CO)H;

R^{4e} is independently OH, OR^2, NO_2, NHR^3, $NMeR^3$ or SR^2;

R^{4f} is independently H, OH, OR^2, NO_2 or NHR^3;

R^{4g} is independently H, alkyl, OH or OR^2;

R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or O-protecting group when R^2 is attached to an O, wherein the O-protecting group

is selected from the group consisting of COMe, *t*-BuSi(CH_3)$_2$, 2-(trimethylsilyl)ethoxymethyl (SEM), CH(OEt)CH_3, tetrahydropyranyl, or C(OEt)(CH_3)$_2$;

R^3 is independently H, (CO)H, COMe, SO_2Me, or CH_2COOR^2; and

X is a halide or a hydroxyl group, wherein the halide is selected from the group consisting of F, Cl, Br, I, and At.

~~20~~6. The process of any one of claims 1-~~17~~ 3 wherein

in formula (I):

R^{1a} is independently allyl, crotyl, prenyl, benzyl;

R^{1b} is independently OR^2 or NHC(O)Me;

R^{1c} is H;

R^{1d} is independently OH, NH_2, NHC(O)H;

R^{1e} is independently OH, OR^2, NO_2, NHR^3 or $NMeR^3$, (CO)H, SMe;

R^{1f} is independently H, OH, OR^2, NO_2, NHR^3, NHC=NH(NH_2), COOH;

R^{1g} is H, alkyl, OH, OR^2;

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or an O-protecting group when R^2 is attached to an O, wherein the O-protecting group is selected from the group consisting of COMe, *t*-BuSi(CH_3)$_2$, 2-(trimethylsilyl)ethoxymethyl (SEM), CH(OEt)CH_3, tetrahydropyranyl, or C(OEt)(CH_3)$_2$;

R^3 is independently H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOR^2, $COCH_2NH_2$, $CO(CH_2)_nCOOH$ where n is 0, 1 or 2; and

in Formula II:

R^{2b} is independently CF_3, OH or OR^2;

R^{2c} is H,

R^{2d} is independently OH or NH_2 or NHC(O)H;

X is a halide or a hydroxyl group, wherein the halide is selected from the group consisting of F, Cl, Br, I, and At;

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or O-protecting group when R^2 is attached to an O, wherein the

O-protecting group is selected from the group consisting of (CO)Me, *t*-BuSi(CH_3)$_2$, 2-(trimethylsilyl)ethoxymethyl (SEM), CH(OEt)CH_3, tetrahydropyranyl, or C(OEt)(CH_3)$_2$; and

in Formula III:

R^{3e} is independently OH, OR^2, NO_2, NHR^3, $NMeR^3$ or SR^2;

R^{3f} is independently H, OH, OR^2, NO_2 or NHR^3;

R^{3g} is independently H, alkyl, OH or OR^2;

R^2 is independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or O-protecting group when R^2 is protecting an O, wherein the O-protecting group is selected from the group consisting of (CO)Me, *t*-BuSi(CH_3)$_2$, 2-(trimethylsilyl)ethoxymethyl (SEM), CH(OEt)CH_3, tetrahydropyranyl, or C(OEt)(CH_3)$_2$; and

R^3 is independently H, CH_3, (CO)H, (CO)Me, SO_2Me, CH_2COOR^2 or, $COCH_2NH_2$; and

in Formula IV:

R^{4b} is independently CF_3, OH or OR^2;

R^{4c} is H;

R^{4d} is independently OH, NH_2, or NH(CO)H;

R^{4e} is independently OH, OR^2, NO_2, NHR^3 or $NMeR^3$ or SR^2;

R^{4f} is independently H, OH, OR^2, NO_2 or NHR^3;

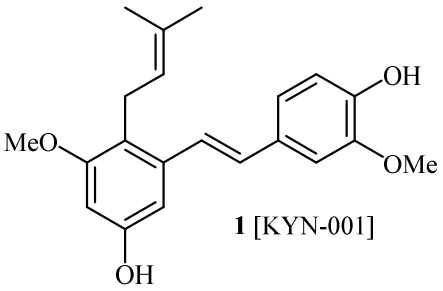
R^{4g} is independently H, alkyl, OH or OR^2;

R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or O-protecting group when R^2 is attached to an O, wherein the O-protecting group is selected from the group consisting of (CO)Me, *t*-BuSi(CH_3)$_2$, 2-(trimethylsilyl)ethoxymethyl (SEM), CH(OEt)CH_3, tetrahydropyranyl, or C(OEt)(CH_3)$_2$;

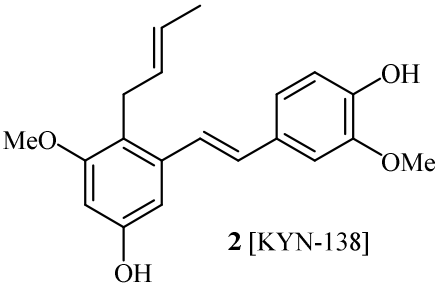
R^3 is independently H, (CO)H, (CO)Me, SO_2Me, or CH_2COOR^2; and

X is a halide(Hal) or a hydroxyl group, wherein the halide is selected from the group consisting of F, Cl, Br, I, and At.

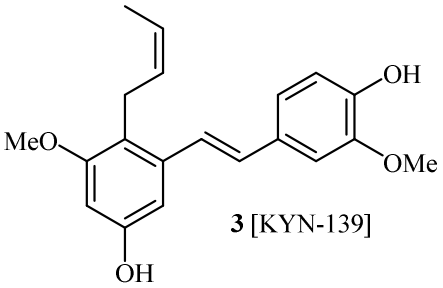
~~21~~7. The process of any one of claims 1-~~17~~ 3 wherein the compound according to formula (I) is selected from the group consisting of:



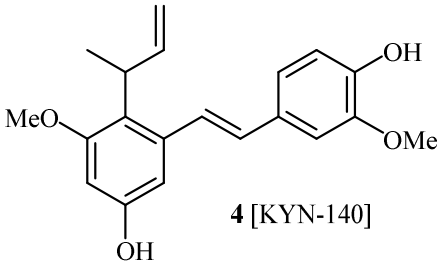
1 [KYN-001]



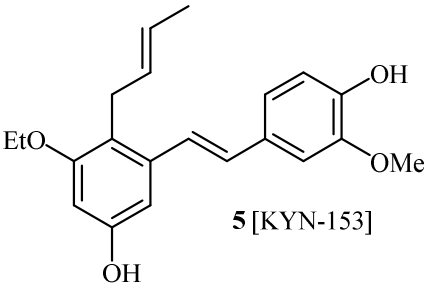
2 [KYN-138]



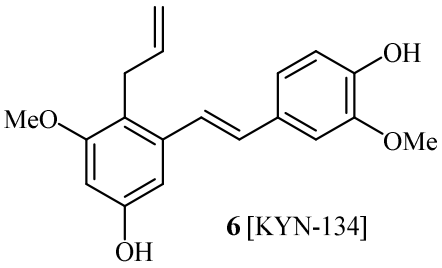
3 [KYN-139]



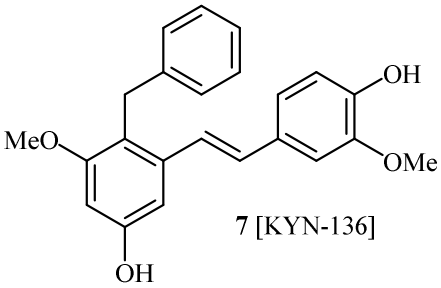
4 [KYN-140]



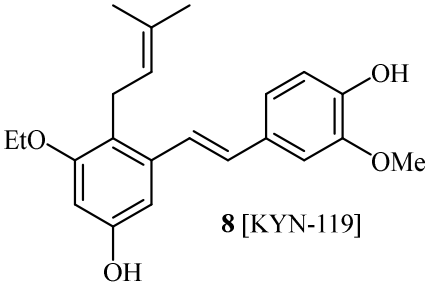
5 [KYN-153]



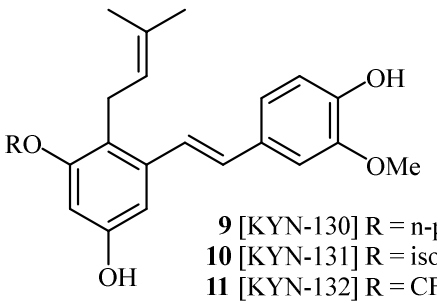
6 [KYN-134]



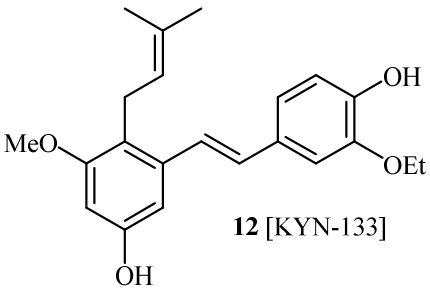
7 [KYN-136]



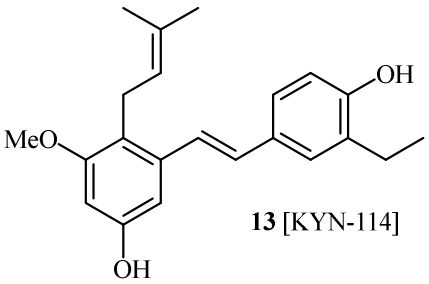
8 [KYN-119]



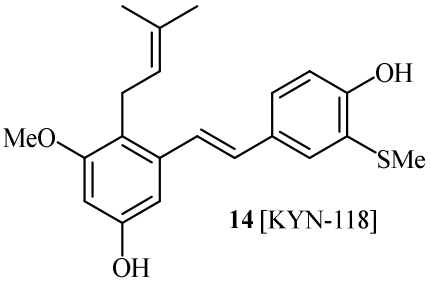
9 [KYN-130] R = n-propyl
10 [KYN-131] R = iso-propyl
11 [KYN-132] R = CF_3



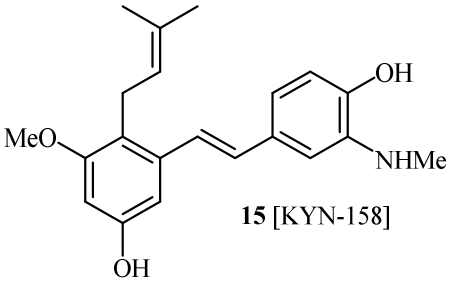
12 [KYN-133]



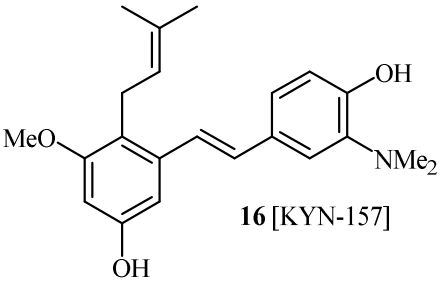
13 [KYN-114]



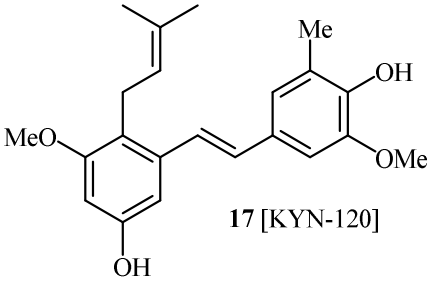
14 [KYN-118]



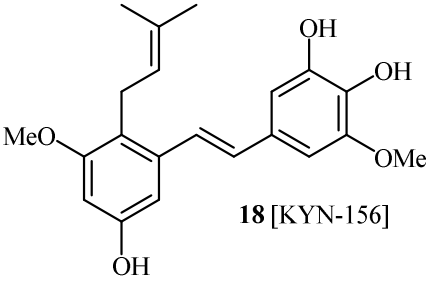
15 [KYN-158]



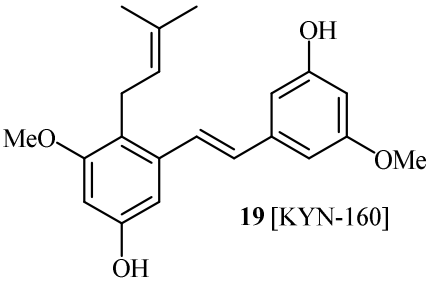
16 [KYN-157]



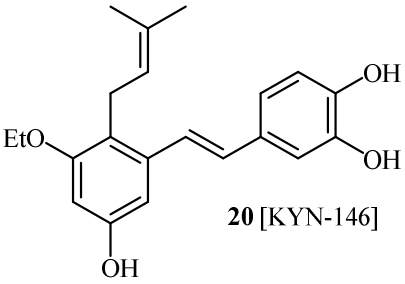
17 [KYN-120]



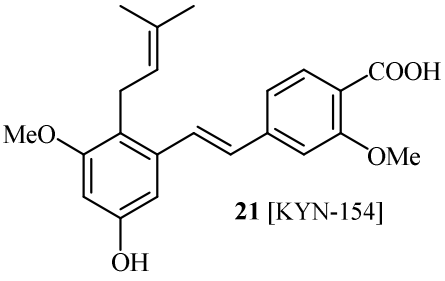
18 [KYN-156]



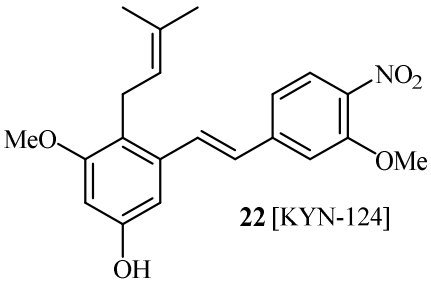
19 [KYN-160]



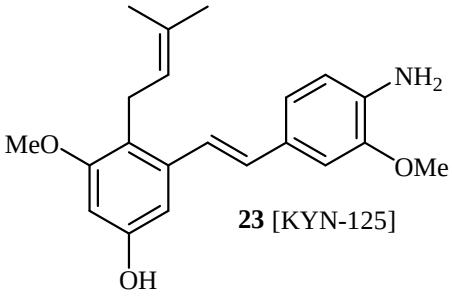
20 [KYN-146]



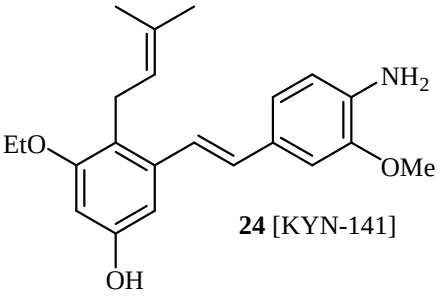
21 [KYN-154]



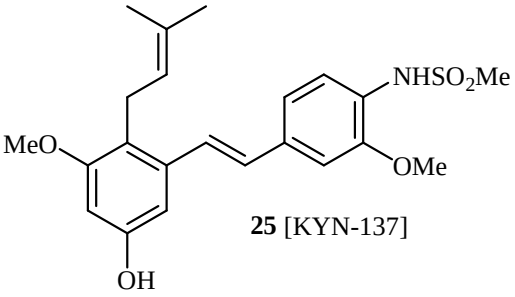
22 [KYN-124]



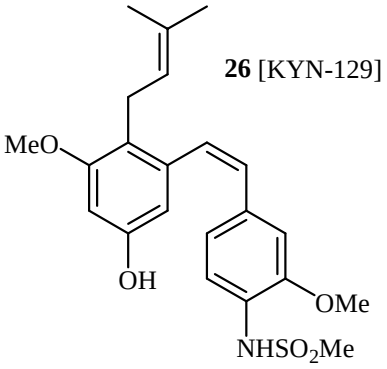
23 [KYN-125]



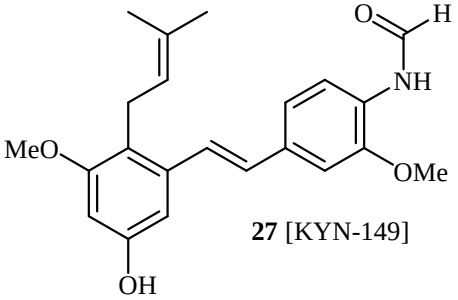
24 [KYN-141]



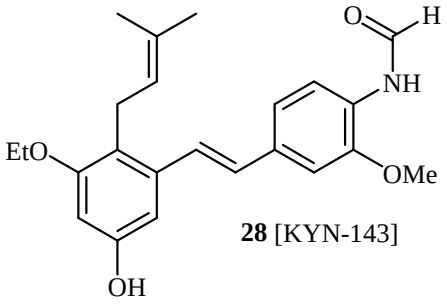
25 [KYN-137]



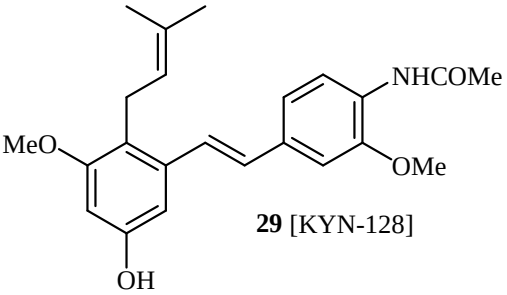
26 [KYN-129]



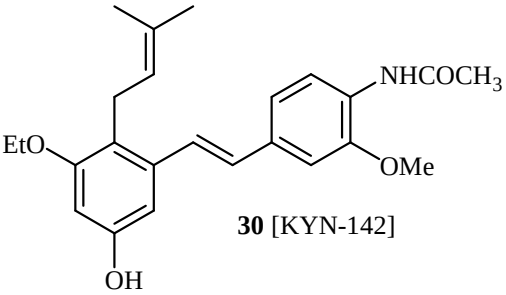
27 [KYN-149]



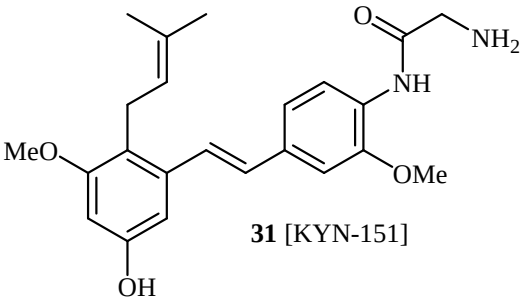
28 [KYN-143]



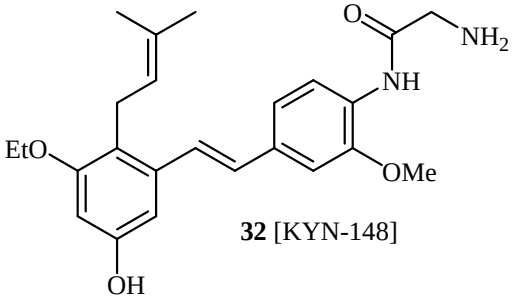
29 [KYN-128]



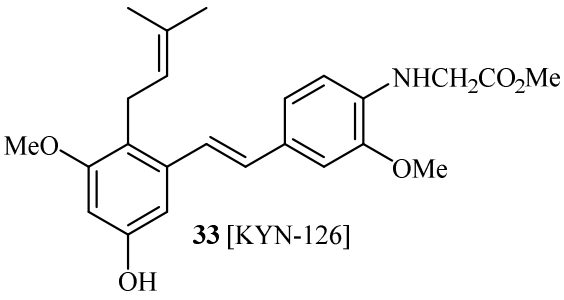
30 [KYN-142]



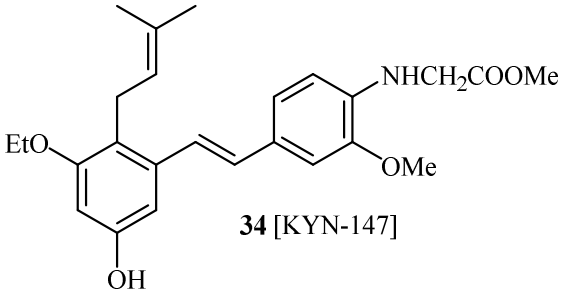
31 [KYN-151]



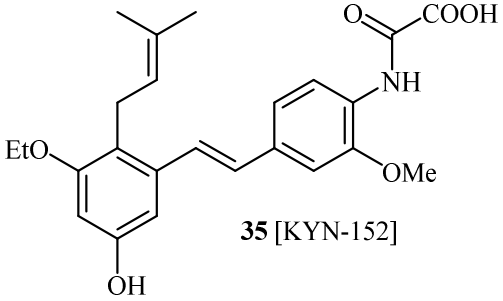
32 [KYN-148]



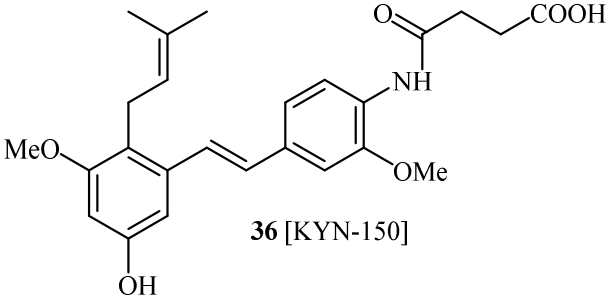
33 [KYN-126]



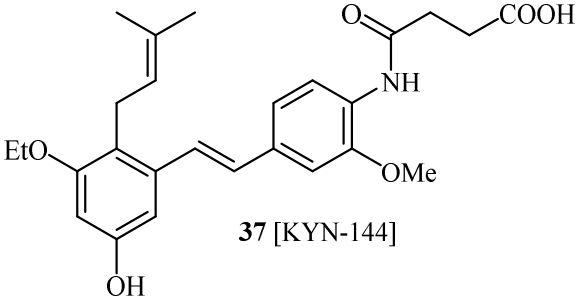
34 [KYN-147]



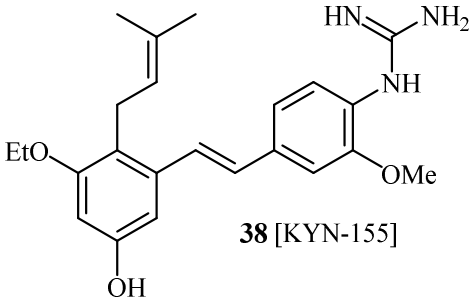
35 [KYN-152]



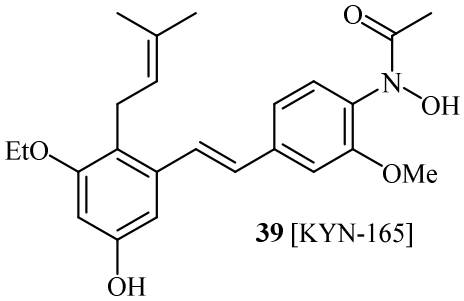
36 [KYN-150]



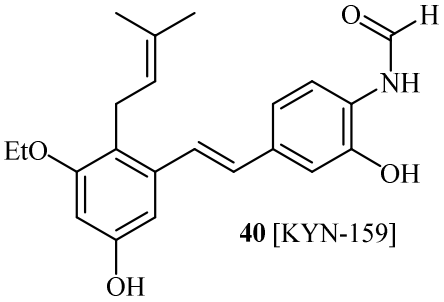
37 [KYN-144]



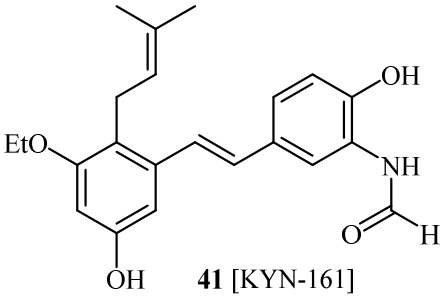
38 [KYN-155]



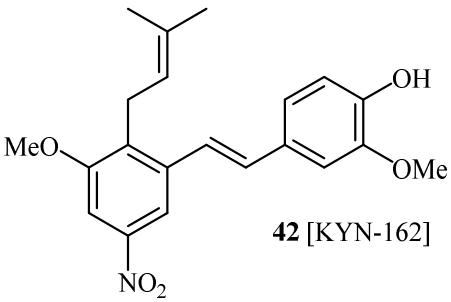
39 [KYN-165]



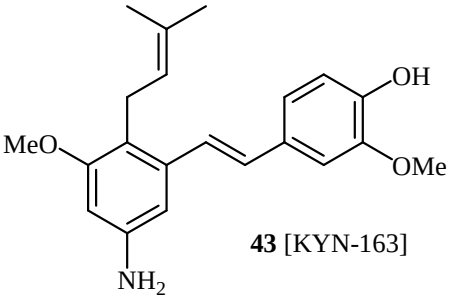
40 [KYN-159]



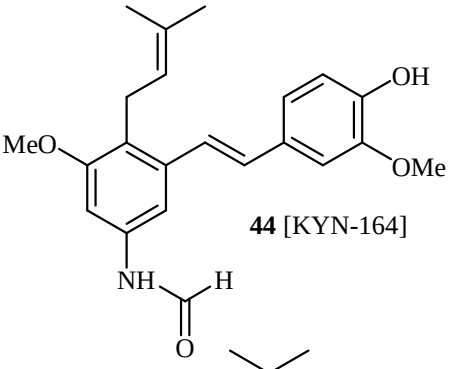
41 [KYN-161]



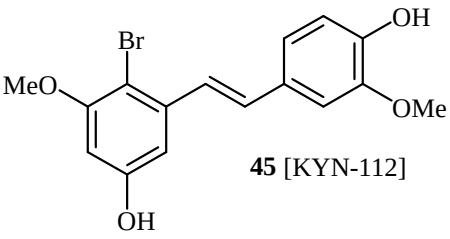
42 [KYN-162]



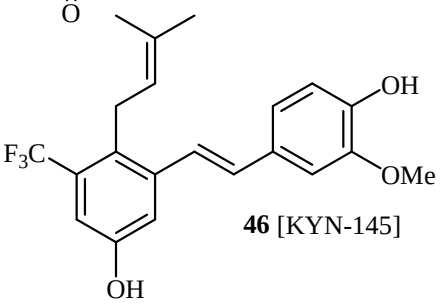
43 [KYN-163]



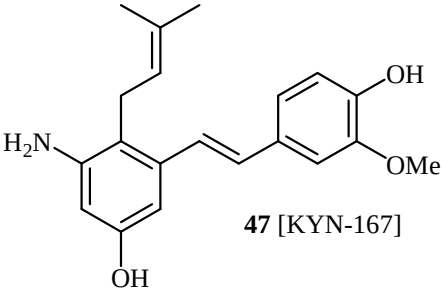
44 [KYN-164]



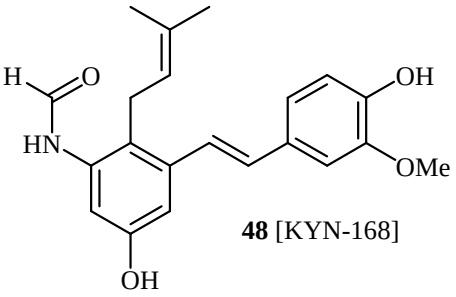
45 [KYN-112]



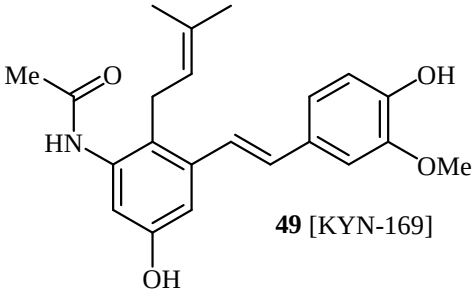
46 [KYN-145]



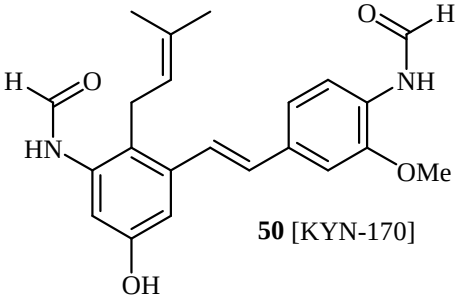
47 [KYN-167]



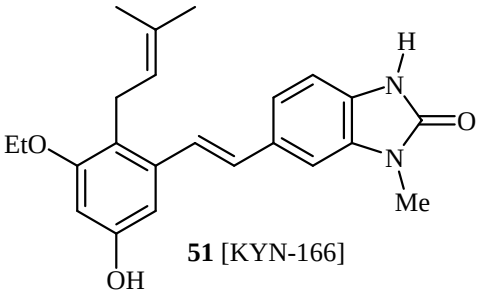
48 [KYN-168]



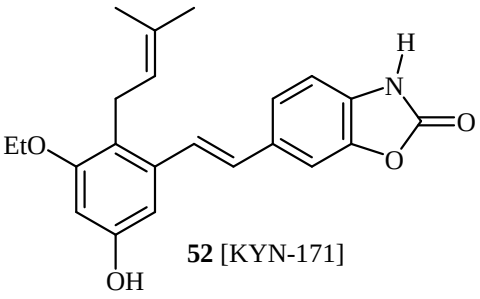
49 [KYN-169]



50 [KYN-170]



51 [KYN-166]



52 [KYN-171]

~~22~~8. The process of any one of claims 1-~~17~~3,

wherein in formula (I):

R^{1a} is allyl, crotyl, prenyl, benzyl, or 2-alkenyl;

R^{1b} is OR^2 or NHC(O)H,

R^{1c} is H;

R^{1d} is OH;

R^{1e} is OR^2;

R^{1f} is NO_2, NHR^3 or NHC=NH(NH_2);

R^{1g} is H;

R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl;

R^3 is H, (CO)H, (CO)Me, SO_2Me, CH_2COOR^2, $COCH_2NH_2$ or $CO(CH_2)_nCOOH$ (where n = 0, 1 or 2);

in Formula (II):

R^{2b} is CF_3, OH or OR^2;

R^{2c} is H,

R^{2d} is OH or NH_2, NH(CO)H~~;~~;

Hal is a halide selected from the group consisting of F, Cl, Br, I, and At;

R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or O-protecting group when R^2 is attached to an O, wherein the O-protecting group is selected from the group consisting of COMe, *t*-BuSi(CH_3)$_2$, 2-(trimethylsilyl)ethoxymethyl (SEM), CH(OEt)CH_3, tetrahydropyranyl, or C(OEt)(CH_3)$_2$; and

in Formula (III):

R^{3e} is OH, OR^2;

R^{3f} is, NO_2, NHR^3, NHC=NH(NH_2);

R^{3g} is H;

R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl~~,~~; and

R^3 is H, (CO)H, COMe, SO_2Me or CH_2COOR^2 , $COCH_2NH_2$, $CO(CH_2)_nCOOH$ (where n = 0, 1 or 2); and

in Formula (IV):

R^{4b} is, OR^2, NHC(O)Me;

R^{4c} is H;

R^{4d} is OH;

R^{4e} is OR^2;

R^{4f} is, NO_2, NHR^3, NHC=NH(NH_2);

R^{4g} is H;

R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl~~,~~;

R^3 is H, (CO)H, COMe, SO_2Me, or CH_2COOR^2, $COCH_2NH_2$, $CO(CH_2)_nCOOH$ (where n = 0, 1 or 2); and

Hal is a halide selected from the group consisting of F, Cl, Br, I, and At;

wherein formula IV is coupled with a R^{1a} boronic pinacol ester selected from the group consisting of 3-methylbut-2-enylboronic acid pinacol ester, crotylboronic acid pinacol ester, allylboronic acid pinacol ester and benzylboronic acid pinacol ester, catalysed by a palladium catalyst in the presence of a base, to produce the compound of formula (I).

~~23. The process of claim 21 wherein~~

~~in formula (I):~~

~~R^{1a} is crotyl, prenyl;~~

~~R^{1b} is OR^2;~~

~~R^{1c} is H;~~

~~R^{1d} is OH;~~

~~R^{1e} is OR^2;~~

~~R^{1f} is NO_2, NHR^3, NHC=NH(NH_2);~~

~~R^{1g} is H;~~

~~R^2 is methyl, ethyl;~~

~~R^3 is H, (CO)H, (CO)Me, SO_2Me, CH_2COOR^2, $COCH_2NH_2$, $CO(CH_2)_nCOOH$ (where n = 0, 1 or 2);~~

~~in Formula (II):~~

~~R^{2b} is OH or OR^2;~~

~~R^{2c} is H;~~

~~R^{2d} is OH;~~

~~Hal is Br;~~

~~R^{2} is methyl, ethyl; and~~

~~in Formula (III):~~

~~R^{3e} is OH, OR^{2};~~

~~R^{3f} is, NO_2, NHR^{3}, $NHC{=}NH(NH_2)$;~~

~~R^{3g} is H;~~

~~R^{2} is methyl, ethyl; and~~

~~R^{3} is H, (CO)H, (CO)Me, SO_2Me or CH_2COOR^{2}, $COCH_2NH_2$;~~

~~$CO(CH_2)_nCOOH$ (where n = 0, 1 or 2); and~~

~~in Formula (IV):~~

~~R^{4b} is OR^{2};~~

~~R^{4c} is H;~~

~~R^{4d} is OH;~~

~~R^{4e} is OR^{2};~~

~~R^{4f} is NO_2, NHR^{3}, $NHC{=}NH(NH_2)$;~~

~~R^{4g} is H;~~

~~R^{2} is methyl, ethyl;~~

~~R^{3} is H, (CO)H, (CO)Me, SO_2Me, or CH_2COOR^{2}, $COCH_2NH_2$,~~

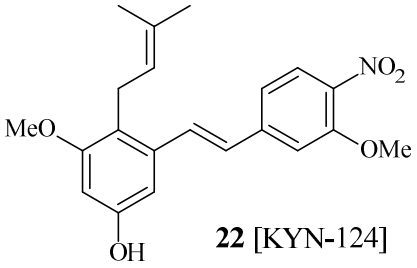
~~$CO(CH_2)_nCOOH$; and~~

~~Halide is Br;~~

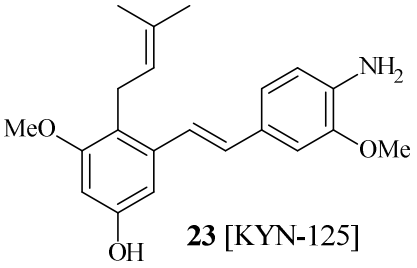
~~wherein formula (IV) is coupled with a R^{1a} boronic pinacol ester selected from the group consisting of 3-methylbut-2-enylboronic acid pinacol ester, crotylboronic acid pinacol ester, allylboronic acid pinacol ester and benzylboronic acid pinacol ester, catalysed by a palladium catalyst in the presence of a base, to produce the compound of formula (I).~~

~~24,~~9. The process of claim~~s 21 or 22~~7 , wherein the compound according to formula (I) are selected for the group consisting of:

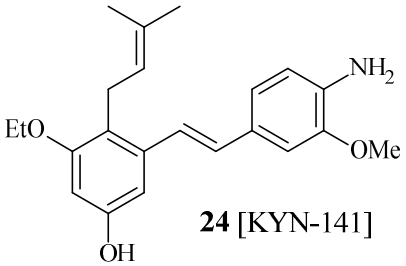
~~compounds~~ Compounds 22, 23, 24, 25, 27, 28 , 29, 30, 31, 33, 34, 35, 36, 37, 38, 39, 40, 50 as shown below:



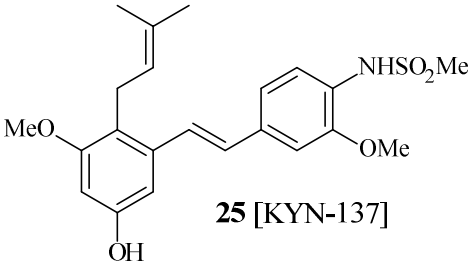
22 [KYN-124]



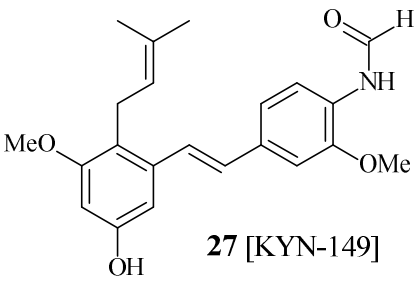
23 [KYN-125]



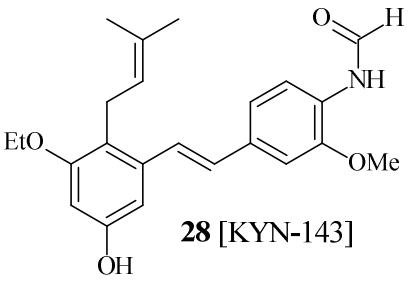
24 [KYN-141]



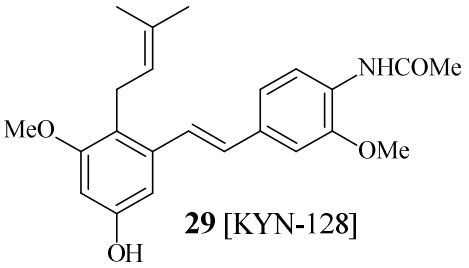
25 [KYN-137]



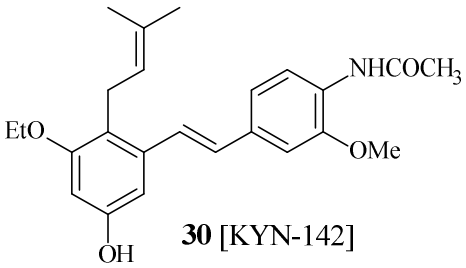
27 [KYN-149]



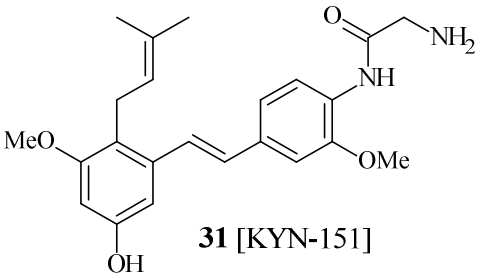
28 [KYN-143]



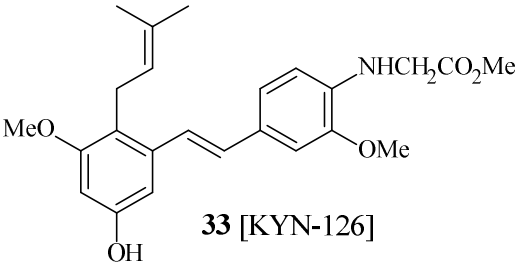
29 [KYN-128]



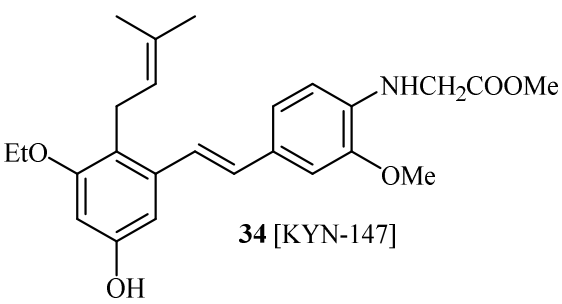
30 [KYN-142]



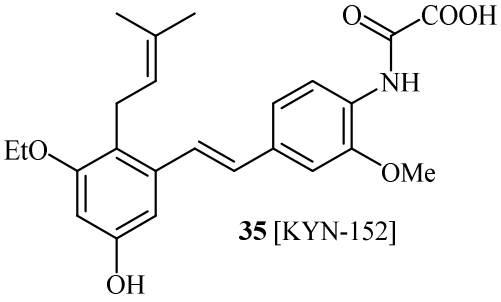
31 [KYN-151]



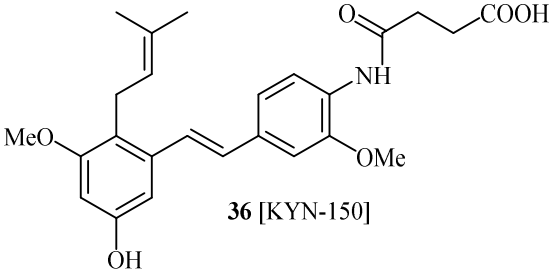
33 [KYN-126]



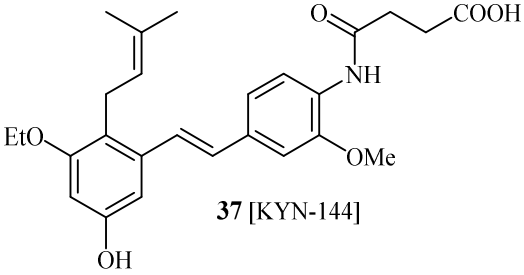
34 [KYN-147]



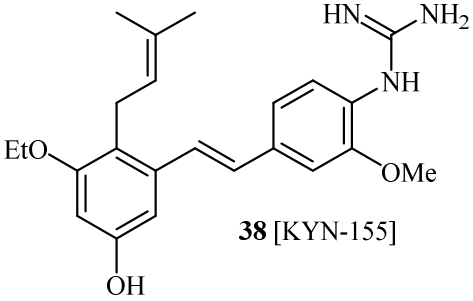
35 [KYN-152]



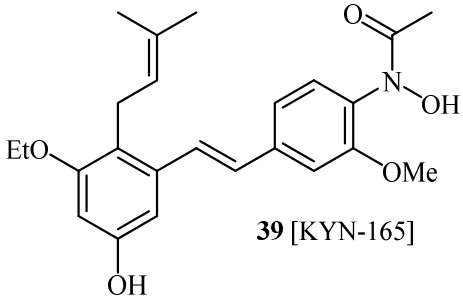
36 [KYN-150]



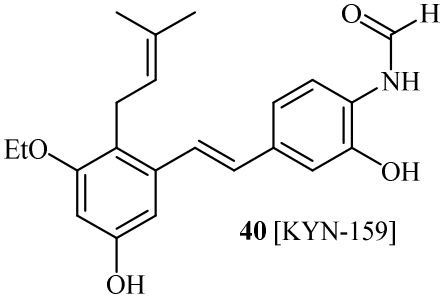
37 [KYN-144]



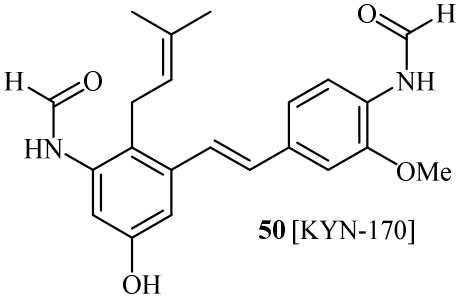
38 [KYN-155]



39 [KYN-165]



40 [KYN-159]



50 [KYN-170]

~~25~~10. The process of any one of claims 1-~~17~~ 3 wherein the compound of formula (IV) or (I) undergo one or more further reactions, selected form one or more of the following:

-reaction with one or more $–NH_2$, NO_2 and/or -OH substituents on formula (IV) or formula (I);

-conversion of an –OH substituents to methoxyoxoacetamido (-$NHC(O)C(O)OCH_3$) substituents by reaction of the compound containing the

OH substituent with methyl chlorooxoacetate in the presence of a base, such as triethylamine;

-conversion of one or more $–NH_2$ substituents to methyl oxalate substituents by reaction of the compound containing the NH_2 substituent with methyl chlorooxoacetate in the presence of a base, such as triethylamine;

-Hydrolysis of one or more methoxyoxoacetamido substituents to a -NHC(O)C(O)OH substituents by reaction of the compound containing the N methoxyoxoacetamido substituent with a base, for example LiOH;

-Hydrolysis of one or more methyl oxalate substituents to - OH substituents by reaction of the compound containing the methyl oxalate substituent with a base, for example LiOH;

-Conversion of one or more $–NH_2$ substituents to guanidine (-NHC(NH)NH_2) substituents by reaction of the compound containing the NH_2 substituent with cyanamide in the presence of an acid, such as p-toluenesulfonic acid;

-Conversion of one or more $–NH_2$ substituents to formamide (-NHC(O)H) substituents by reaction of the compound containing the NH_2 substituent with ethyl formate;

-Conversion of one or more $–NH_2$ substituents to an acetamido (-NHC(O)CH_3) substituents by reaction of the compound containing the NH_2 substituent with acetic anhydride in the presence of a base such as DIPEA (diisopropylethylamine);

-Conversion of one or more $–NH_2$ substituents to an amide derivative (-NHC(O)CH_2CH_2C(O)OH) substituents by reaction of the compound containing the NH_2 substituent with succinic anhydride in the presence of a base such as DIPEA (diisopropylethylamine);

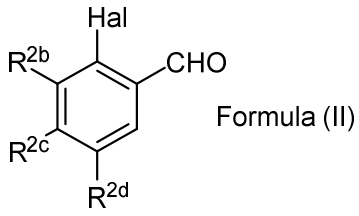
-Conversion of one or more $–NH_2$ substituents to methyl amine substituents (-NHMe) by reaction of the compound containing the NH_2 substituent with formaldehyde in the presence of triacetoxyborohydride;

-Conversion of one or more –OH substituents to acetate ($-OC(O)CH_3$) substituents by reaction of the compound containing the -OH substituent with acetic anhydride in the presence of a base such as DIPEA (diisopropylethylamine);

-Hydrolysis of one or more acetate substituents may to form - OH substituents by reaction of the compound containing the acetate substituent with a base, for example, LiOH;

-Reduction of one or more $–NO_2$ substituents to amine substituents by, for example, reaction of the compound containing the NO_2 substituent with Zn in the presence of ammonium chloride.

~~26~~11. The process according to any one of claims 1-~~25~~ 10 wherein the compound according to formula (II) is



Formula (II)

A

wherein

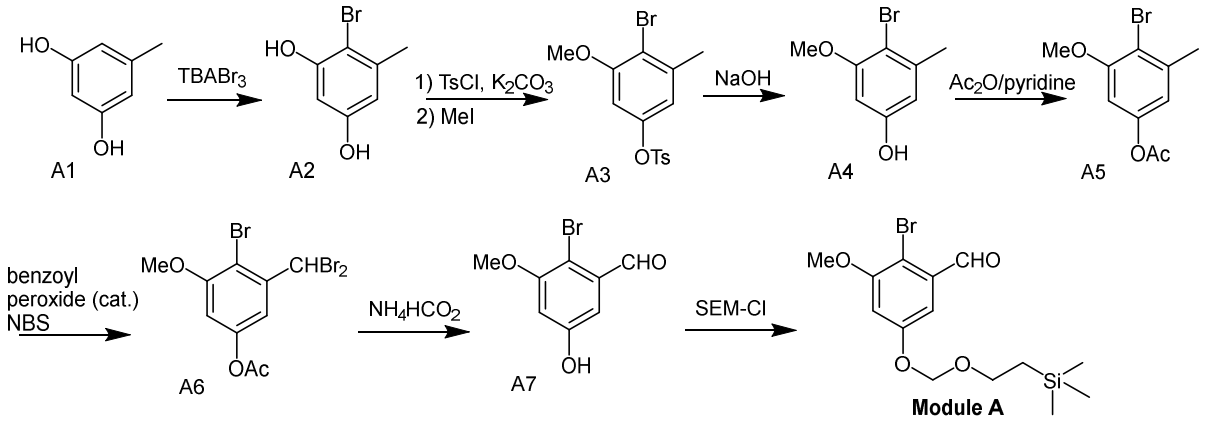
R^{2b}= OMe;

R^{2d}=OH or OSEM;

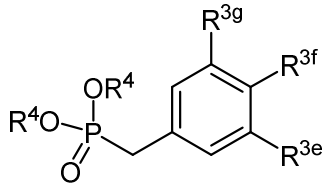
R^{2c}=H; and

Hal is Br.

~~27~~12. The process according to claim ~~26~~ 11 wherein the compound according to formula (II) is Module A and is prepared according to the following process:



~~28~~13. The process according to any one of claims 1-~~25~~ 10 wherein the compound according to formula (III) is



Formula (III)

B

wherein

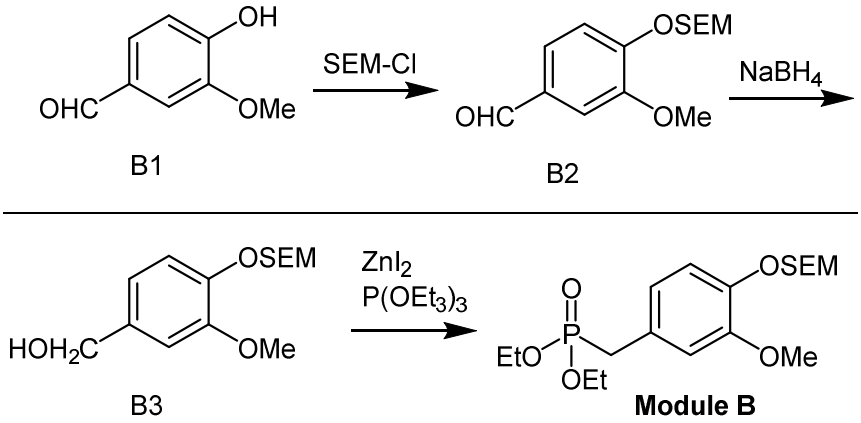
R^{3g}=H;

R^{3f}=OSEM;

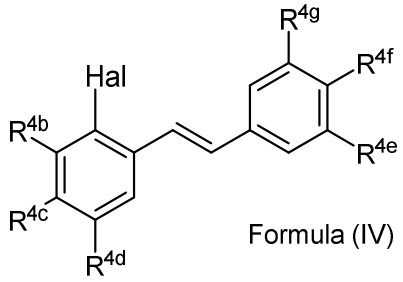
R^{3e}=OMe; and

R^4=Et~~.~~.

~~29. The process according to claim 28 wherein the compound according to formula (III) is Module B and is prepared according to the following process:~~



~~30~~14. The process according to any one of claims 1-~~25~~ 10 wherein the compound according to formula (IV) is



wherein

R^{4b}=OMe;

R^{4c}=H;

R^{4d}=OSEM or OH;

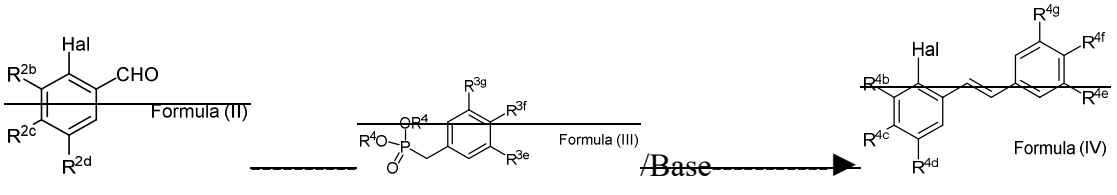
R^{4g}=H;

R^{4e}=OMe;

R^{4f}=OSEM; and

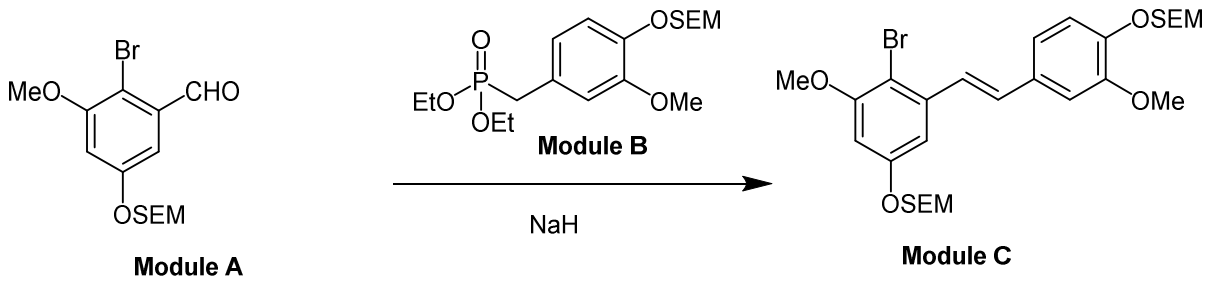
Hal =Br.

~~31. The process according to any one of claims 1-25 wherein the compound according to formula (IV) is prepared according to the following process:~~



~~wherein the base is selected from the group consisting of NaH.~~

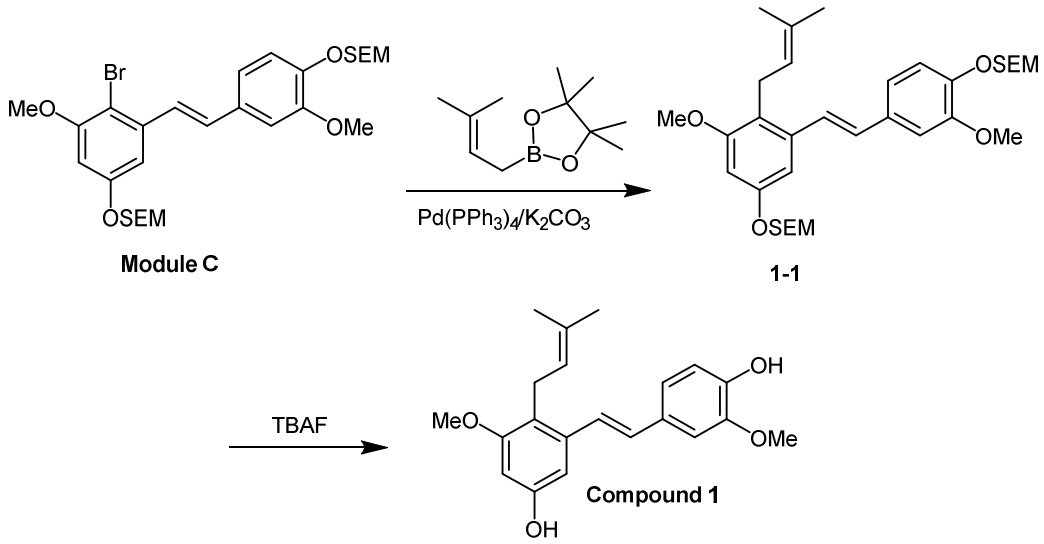
~~32~~15. The process of claim ~~30~~ 14 wherein formula(II) is Module A, formula (III) is Module B and formula (IV) is Module C according to the following:



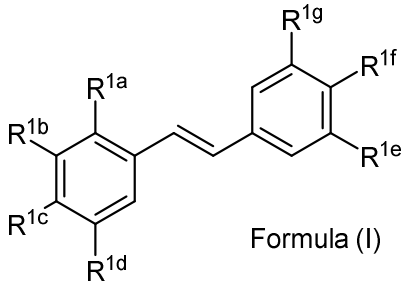
~~33. The process of claim 32~~ optionally wherein:

i) Module C is coupled with 3-methylbut-2-enylboronic acid pinacol ester in the presence of tetrakis(triphenylphosphine)palladium(0) and potassium carbonate to afford compound 1.1; and

ii) compound 1.1 is treated with tetrabutylammonium fluoride to afford compound 1, according to the following:



~~34~~16. A compound according to formula (I)



Formula (I)

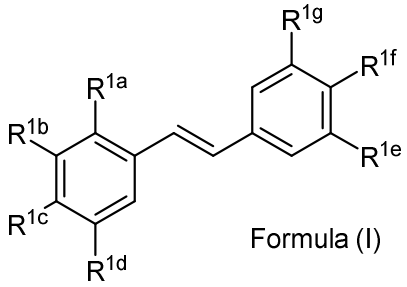
prepared by a process according to any one of claims 1-~~33~~15,

wherein:

R^{1a} is Hal, allyl, crotyl, prenyl, geranyl, farnesyl, benzyl, 2-alkenyl, 2-alkynyl;
R^{1b} is CF_3, OH or OR^2, NO_2, NHEt, NMe_2, NMeEt, NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;
R^{1c} is H, alkyl, alkenyl, alkynyl, alkanedienyl, prenyl, geranyl, farnesyl, or benzyl;
R^{1d} is CF_3, OH or OR^2, NHR^3, NO_2, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;
R^{1e} is H, C_1-C_6 alkyl, OH, OR^2, NO_2, NMe_2, NHR^3 or $NMeR^3$, SR^2;
R^{1f} is H, OH, OR^2, NO_2, NHR^3, $NHC{=}NH(NH_2)$, $COOR^2$, COOH;
R^{1g} is H, alkyl, CF_3, OH or OR^2;
R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl, $COCOOR^4$ or O-protecting group, wherein the O-protecting group is selected from the group consisting of COMe, *t*-$BuSi(CH_3)_2$, 2-(trimethylsilyl)ethoxymethyl (SEM) acetal, $CH(OEt)CH_3$, tetrahydropyranyl, or $C(OEt)(CH_3)_2$;
R^3 is H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOH, CH_2COOR^2, $CO(CH_2)_nNH_2$, $CONH_2$, $CO(CH_2)_nCOOH$ or $COCOOR^4$ (where n = 0, 1 or 2);
R^4 is C_1-C_6 alkyl; and
Hal is a halide selected from the group consisting of F, Cl, Br, I, and At;
only one of R^{1e}, R^{1f} or R^{1g} can be H; and
R^{1e} and R^{1f} are joined to form a five or six-membered heterocyclic ring containing a carbonyl or $(CO)CH_2$ group when R^{1e} is OH, NH_2 or NHMe and

R^{1f} is NH_2, such that the nitrogen of R^{1f} is bridged via the carbonyl or $(CO)CH_2$ group to the oxygen or nitrogen of R^{1e}.

~~35~~17. A compound according to formula (I)



Formula (I)

wherein:

R^{1a} is allyl, crotyl, prenyl, geranyl, farnesyl, benzyl, 2-alkenyl, 2-alkynyl;
R^{1b} is CF_3, OH, OR^2, NO_2, NHEt, NMe_2, NMeEt, NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;
R^{1c} is H, alkyl, alkenyl, alkynyl, alkanedienyl, prenyl, geranyl, farnesyl, or benzyl;
R^{1d} is CF_3, OH or OR^2, NO_2, NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;
R^{1e} is H, C_1-C_6 alkyl, OH, OR^2, NO_2, NMe_2, NHR^3 or $NMeR^3$, SR^2~~;~~
R^{1f} is H, OH, OR^2, NO_2, NHR^3, $NHC{=}NH(NH_2)$, $COOR^2$, COOH;
R^{1g} is H, alkyl, CF_3, OH or OR^2;
R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl, $COCOOR^4$or O-protecting group, wherein the O-protecting group is selected from the group consisting of COMe, *t*-$BuSi(CH_3)_2$, 2-(trimethylsilyl)ethoxymethyl (SEM) acetal, $CH(OEt)CH_3$, tetrahydropyranyl, or $C(OEt)(CH_3)_2$;
R^3 is H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOH, CH_2COOR^2, $CO(CH_2)_nNH_2$, $CONH_2$, $CO(CH_2)_nCOOH$ or $COCOOR^4$ (where n = 0, 1 or 2);
R^4 is C_1-C_6 alkyl; and
only one of R^{1e}, R^{1f} or R^{1g} can be H; and

R^{1e} and R^{1f} are joined to form a five or six-membered heterocyclic ring containing a carbonyl or $(CO)CH_2$ group when R^{1e} is OH, NH_2 or NHMe and R^{1f} is NH_2, such that the nitrogen of R^{1f} is bridged via the carbonyl or $(CO)CH_2$ group to the oxygen or nitrogen of R^{1e};

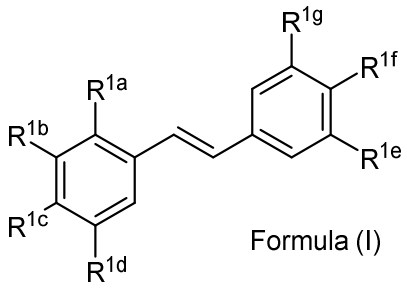
provided that:

i) when R^{1a} or R^{1c} is prenyl, R^{1d} is OH, R^{1f} is OH, R^{1g} is H and R^{1e} is OH, OMe or OEt, then R^{1b} cannot be OR where R =methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, or benzyl;

ii) R^{1b} and R^{1d} are not the same.

iii) when R^{1b} is OH, R^{1d} is OMe, R^{1f} is OMe, R^{1g} is H and R^{1e} is OH, then R^{1a} cannot be prenyl.

~~36~~18. -A compound according to formula (I)



Formula (I)

wherein:

R^{1a} is allyl, crotyl, prenyl, geranyl, farnesyl, benzyl, 2-alkenyl, 2-alkynyl;

R^{1b} is CF_3, OR^2, NO_2, NHEt, NMe_2, NMeEt, NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;

R^{1c} is H, alkyl, alkenyl, alkynyl, alkanedienyl, prenyl, geranyl, farnesyl, or benzyl;

R^{1d} is CF_3, OH, NO_2, NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;

R^{1e} is H, C_1-C_6 alkyl, OH, OR^2, NO_2, NMe_2, NHR^3 or $NMeR^3$, SR^2;

R^{1f} is H, OH, OR^2, NO_2, NHR^3, $NHC{=}NH(NH_2)$, $COOR^2$, COOH;

R^{1g} is H, alkyl, CF_3, OH or OR^2;

R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl, $COCOOR^4$or O-protecting group, wherein the O-protecting group is selected from the group consisting of COMe, *t*-$BuSi(CH_3)_2$, 2-(trimethylsilyl)ethoxymethyl (SEM) acetal, $CH(OEt)CH_3$, tetrahydropyranyl, or $C(OEt)(CH_3)_2$;

R^3 is H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOH, CH_2COOR^2, $CO(CH_2)_nNH_2$, $CONH_2$, $CO(CH_2)_nCOOH$ or $COCOOR^4$ (where n = 0, 1 or 2);

R^4 is C_1-C_6 alkyl;

only one of R^{1e}, R^{1f} or R^{1g} can be H, and

R^{1e} and R^{1f} are joined to form a five or six-membered heterocyclic ring containing a carbonyl or $(CO)CH_2$ group when R^{1e} is OH, NH_2 or NHMe and R^{1f} is NH_2, such that the nitrogen of R^{1f} is bridged via the carbonyl or $(CO)CH_2$ group to the oxygen or nitrogen of R^{1e};

provided that:

when R^{1a} or R^{1c} is prenyl, R^{1d} is OH, R^{1f} is OH, R^{1g} is H and R^{1e} is OH, OMe or OEt, then R^{1b} cannot be OR where R =methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, or benzyl.

~~37. A compound of formula (I) according to claim 35 or 36 wherein:~~

~~R^{1a} is allyl, prenyl or benzyl;~~

~~R^{1b} is CF_3 or OR^2;~~

~~R^{1c} is H;~~

~~R^{1d} is OH, NH_2 or N(CO)H;~~

~~R^{1e} is OH, OR^2, NO_2, NHR^3 or $NMeR^3$, (CO)H or SMe;~~

~~R^{1f} is H, OH, OR^2, NO_2, NHR^3, NHC=NH(NH_2) or COOH;~~

~~R^{1g} is H, alkyl, OH;~~

~~R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl or t-butyl; and~~

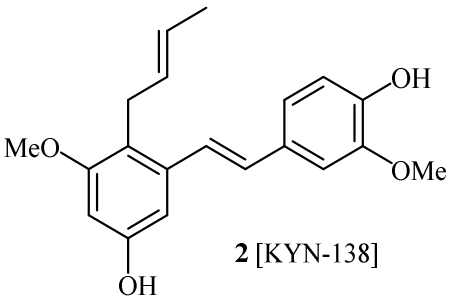
~~R^3 is H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOR^2, $COCH_2NH_2$ or $CO(CH_2)_nCOOH$ (where n = 0, 1 or 2).~~

~~provided that:~~

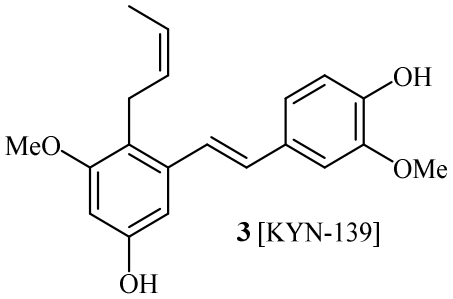
~~when R^{1a} or R^{1c} is prenyl, R^{1d} is OH, R^{1f} is OH, R^{1g} is H and R^{1e} is OH, OMe or OEt, then R^{1b} cannot be OR where R =methyl, ethyl, isopropyl,propyl, butyl, isobutyl, *t*-butyl, or benzyl.~~

~~38~~19. A compound according to any one of claims ~~35~~ 17 or 18~~to 37~~ wherein formula (I) is a compound selected from the group consisting of:

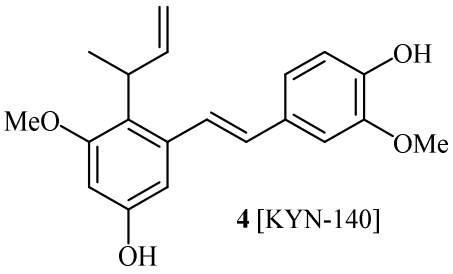
Compounds KYN 154, 132, 145, 138, 139, 140, 153, 134, 136, 124, 125, 126, 128, 129, 137, 149, 150, 151, 141, 147, 143, 142, 144, 148, 152, 155, 114, 118, 158, 157, 120, 156, 160, 159, 161, S16(163), S17(164) as shown below:



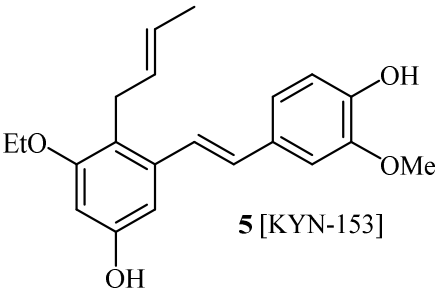
2 [KYN-138]



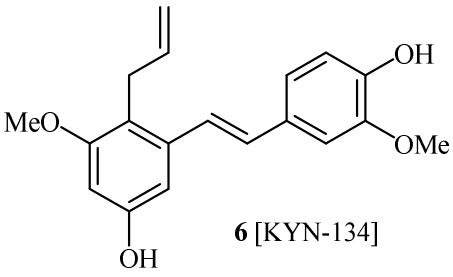
3 [KYN-139]



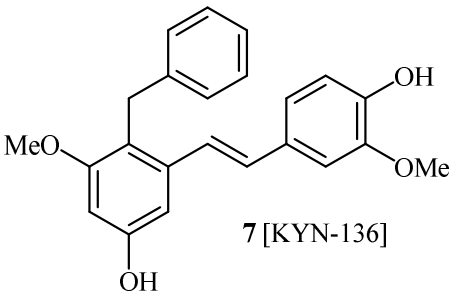
4 [KYN-140]



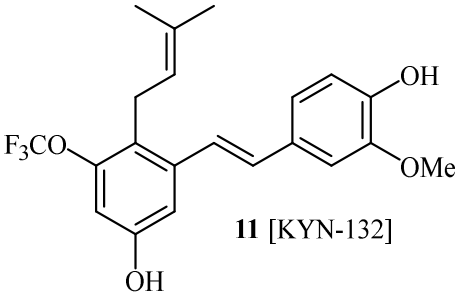
5 [KYN-153]



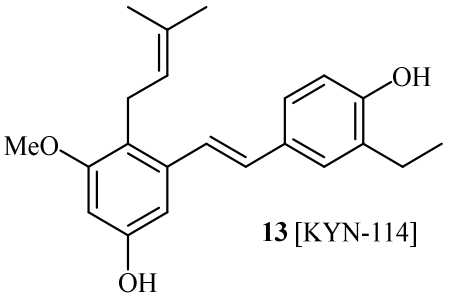
6 [KYN-134]



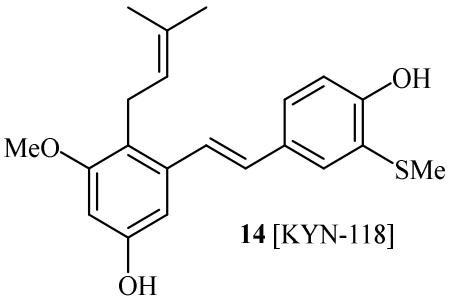
7 [KYN-136]



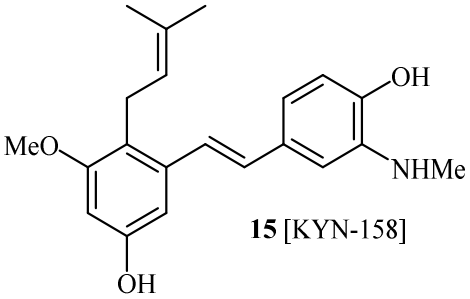
11 [KYN-132]



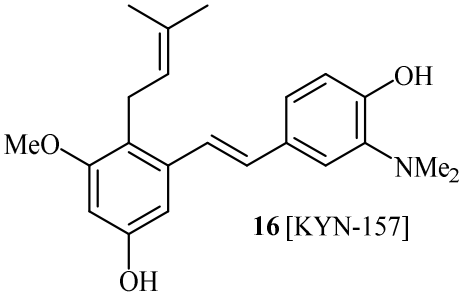
13 [KYN-114]



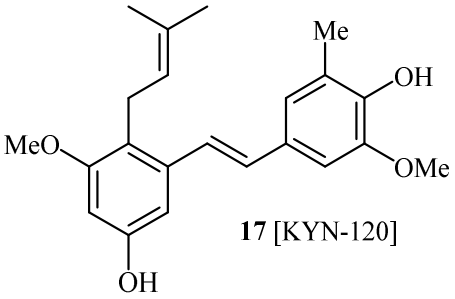
14 [KYN-118]



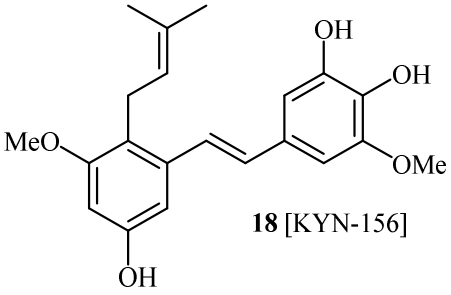
15 [KYN-158]



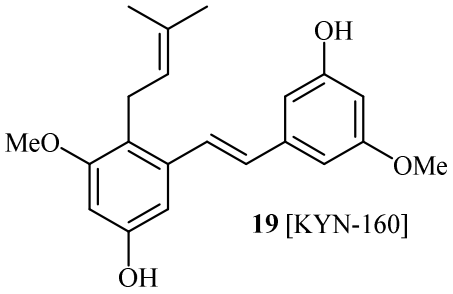
16 [KYN-157]



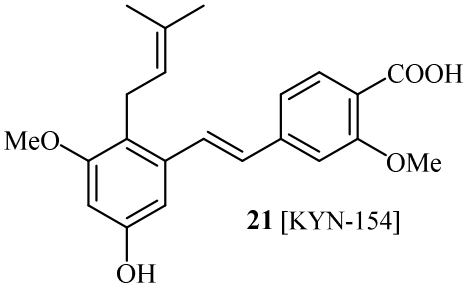
17 [KYN-120]



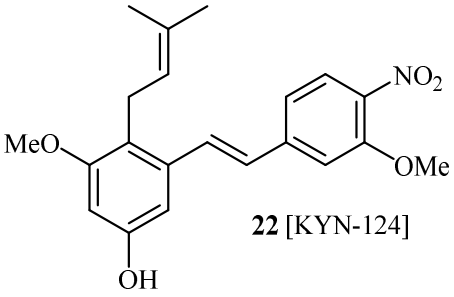
18 [KYN-156]



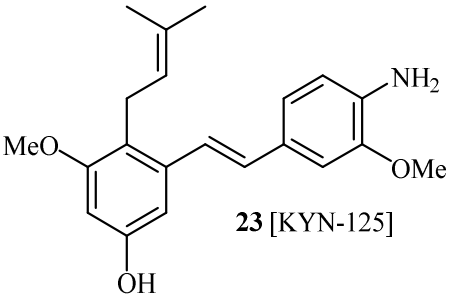
19 [KYN-160]



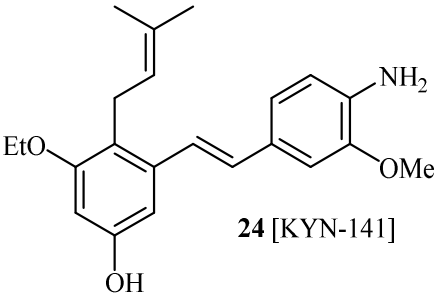
21 [KYN-154]



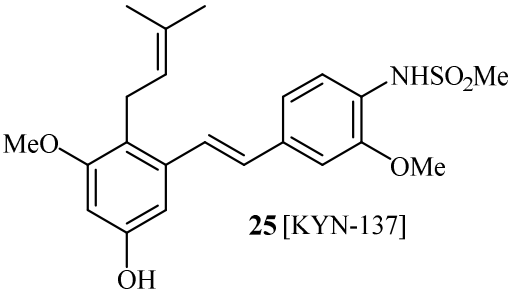
22 [KYN-124]



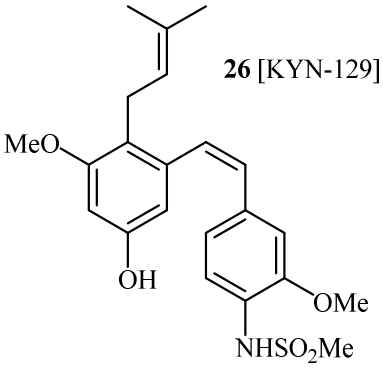
23 [KYN-125]



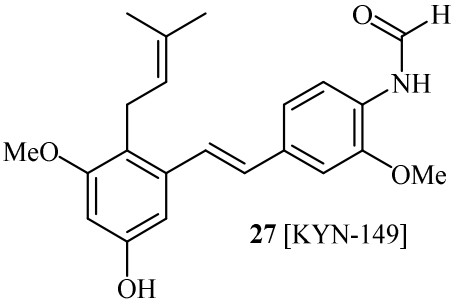
24 [KYN-141]



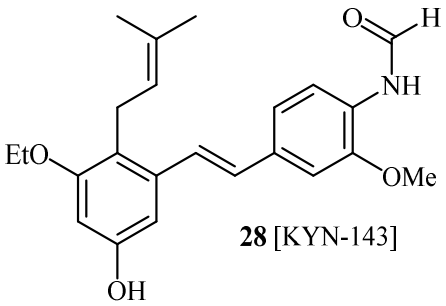
25 [KYN-137]



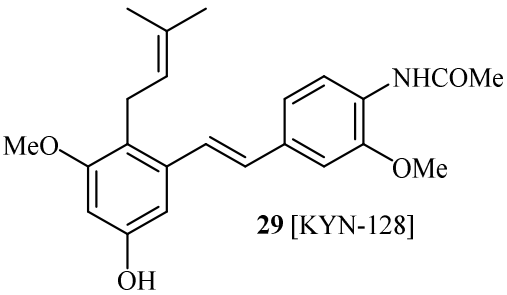
26 [KYN-129]



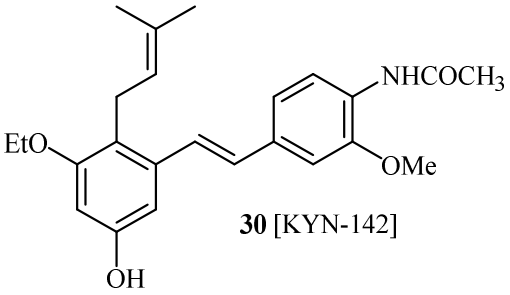
27 [KYN-149]



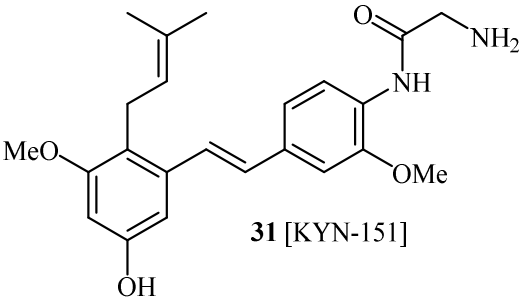
28 [KYN-143]



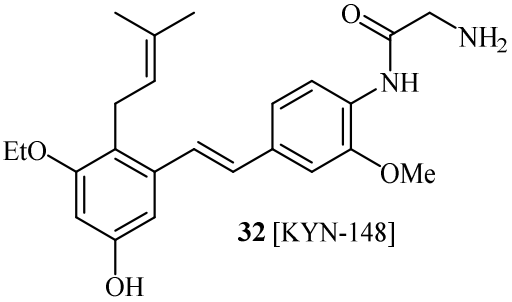
29 [KYN-128]



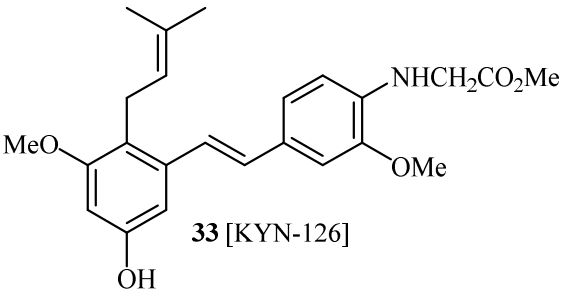
30 [KYN-142]



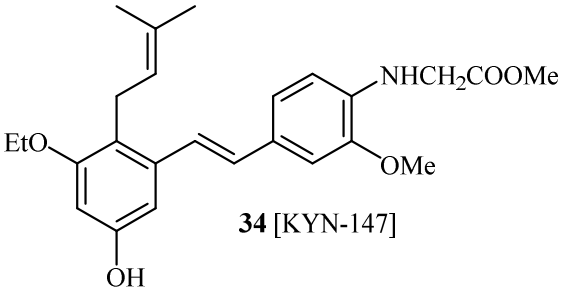
31 [KYN-151]



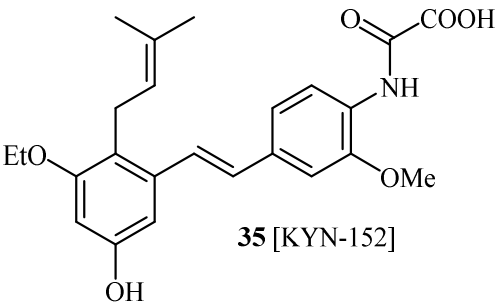
32 [KYN-148]



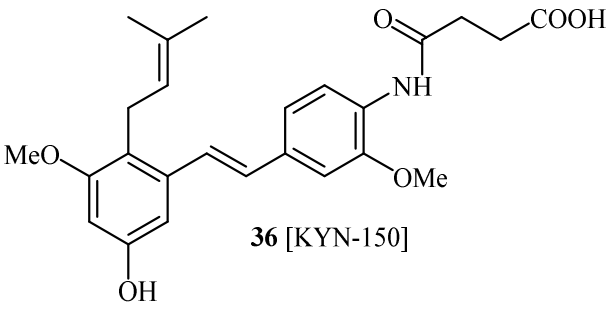
33 [KYN-126]



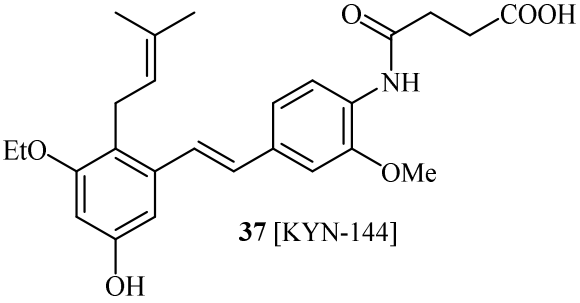
34 [KYN-147]



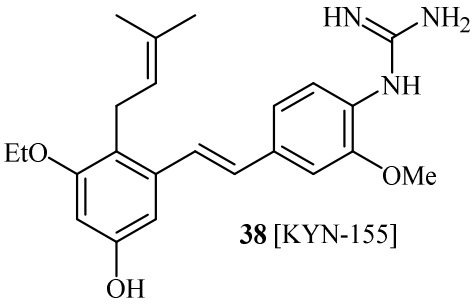
35 [KYN-152]



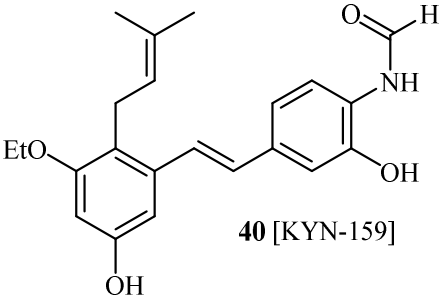
36 [KYN-150]



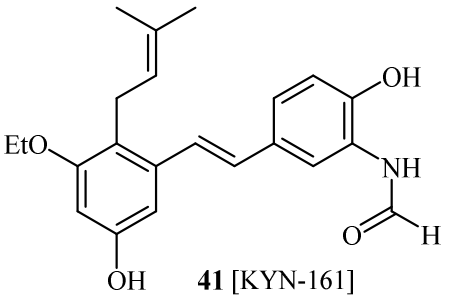
37 [KYN-144]



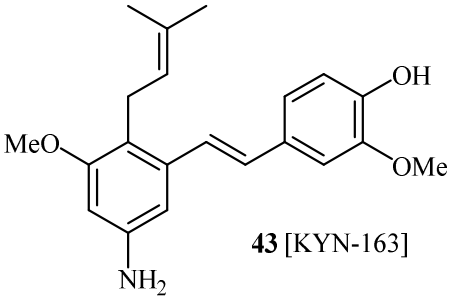
38 [KYN-155]



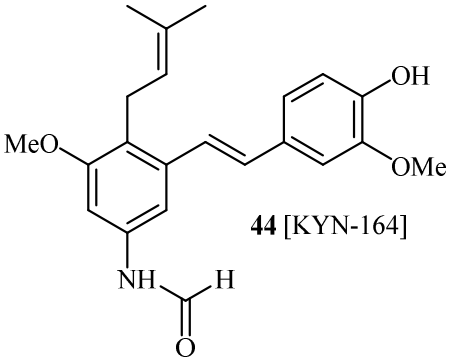
40 [KYN-159]



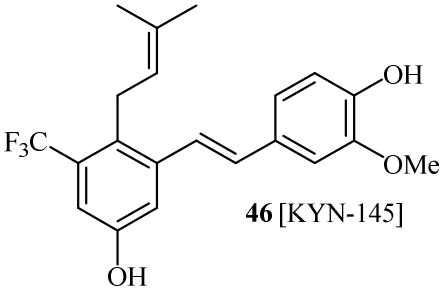
41 [KYN-161]



43 [KYN-163]

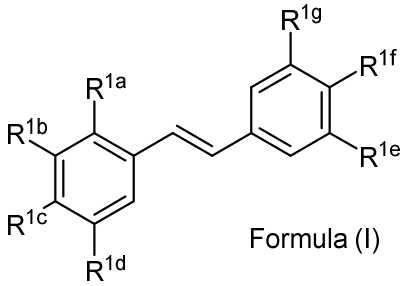


44 [KYN-164]



46 [KYN-145]

~~39~~20. A compound according to formula (I)



Formula (I)

wherein:

R^{1a} is allyl, crotyl, prenyl, farnesyl, benzyl or 2-alkynyl;

R^{1b} is CF_3, OR^2, NO_2, NHEt, NMe_2, NMeEt, NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;

R^{1c} is H, alkyl, alkenyl, alkynyl, alkanedienyl, prenyl, geranyl, farnesyl, or benzyl;

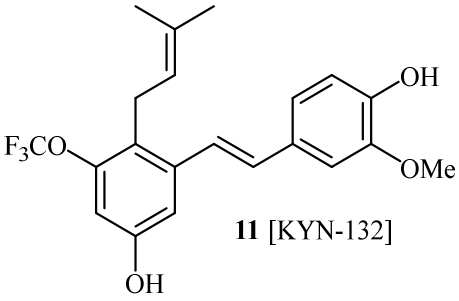
R^{1d} is CF_3, OH, NO_2, NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;

R^{1e} is H, C_1-C_6 alkyl, OH, OR^2, NO_2, NMe_2, NHR^3 or $NMeR^3$ or SR^2;
R^{1f} is H, OH, OR^2, NO_2, NHR^3, $NHC{=}NH(NH_2)$, $COOR^2$ or COOH;
R^{1g} is H, alkyl, CF_3, OH or OR^2;
wherein at least one of R^{1b} or R^{1d} is CF_3, NO_2, NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;
R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl, $COCOOR^4$or O-protecting group, wherein the O-protecting group is selected from the group consisting of COMe, *t*-$BuSi(CH_3)_2$, 2-(trimethylsilyl)ethoxymethyl (SEM) acetal, $CH(OEt)CH_3$, tetrahydropyranyl, or $C(OEt)(CH_3)_2$;
R^3 is H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOH, CH_2COOR^2, $CO(CH_2)_nNH_2$, $CONH_2$, $CO(CH_2)_nCOOH$ or $COCOOR^4$ (where n = 0, 1 or 2);
R^4 is C_1-C_6 alkyl;
only one of R^{1e}, R^{1f} or R^{1g} can be H, and

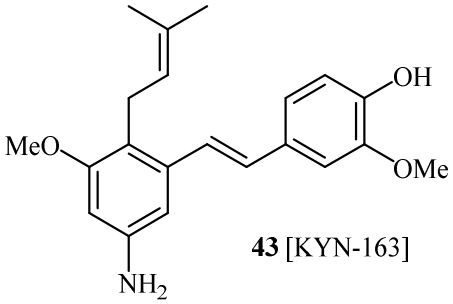
R^{1e} and R^{1f} are joined to form a five or six-membered heterocyclic ring containing a carbonyl or $(CO)CH_2$ group when R^{1e} is OH, NH_2 or NHMe and R^{1f} is NH_2, such that the nitrogen of R^{1f} is bridged via the carbonyl or $(CO)CH_2$ group to the oxygen or nitrogen of R^{1e}.

~~40~~21. A compound according to claim ~~39~~ 20 wherein formula (I) is a compound selected from the group consisting of:

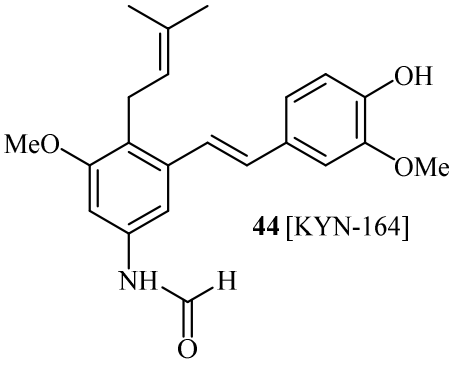
KYN-132, 145, S16(163), S17(164) as shown below:



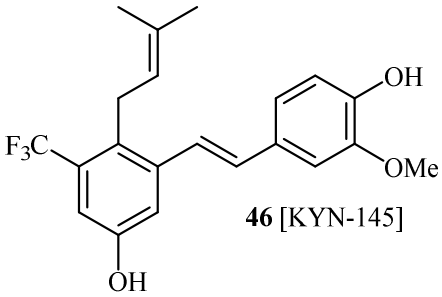
11 [KYN-132]



43 [KYN-163]

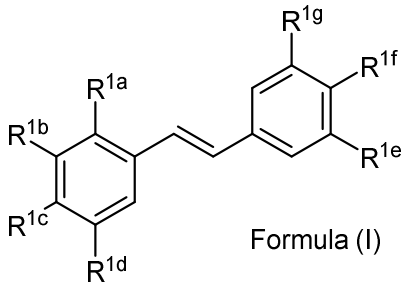


44 [KYN-164]



46 [KYN-145]

~~41.~~22 A compound of formula (I)



Formula (I)

wherein:

R^{1a} is Hal, allyl, crotyl, prenyl, geranyl, farnesyl, benzyl, 2-alkenyl or 2-alkynyl,;

R^{1b} is CF_3, OH or OR^2, NO_2, NHMe, NHEt, NMe_2, NMeEt, NHR^3 or $NMeR^3$, $NHC{=}NH(NH_2)$ or COOR2, NHR3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;

R^{1c} is H, alkyl, alkenyl, alkynyl, alkanedienyl, prenyl, geranyl, farnesyl, or benzyl;

R^{1d} is CF_3, OH or OR^2, NHR^3, NO_2, NH_2, NHMe, $NHC{=}NH(NH_2)$ or $COOR^2$;

R^{1e} is OH or OR^2;

R^{1f} is NO_2, NHR^3, $NHC{=}NH(NH_2)$, $COOR^2$, COOH, $NHSO_2Me$, $NHC(O)(CH_2)COOH$, NHC(O)COOH, $NHC(O)(CH_2)NNH_2$, $NHC(O)CH_2NH_2$, $NHCH_2COOMe$, NHC(O)H, $NHC(O)CH_3$, $NHC(O)(CH_2)_2COOH$ or $NHC(NH)NH_2$;

R^{1g} is H;

R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or O-protecting group, wherein the O-protecting group is selected from the group consisting of COMe, *t*-$BuSi(CH_3)_2$, 2-(trimethylsilyl)ethoxymethyl (SEM) acetal, $CH(OEt)CH_3$, tetrahydropyranyl, or $C(OEt)(CH_3)_2$;

R^3 is H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOH, CH_2COOR^2, $COCH_2NH_2$, $CONH_2$, $CO(CH_2)_nCOOH$ or $CO(CH_2)_nCOOR^4$ (where n = 0, 1 or 2);

R^4 is C1-C6 alkyl;

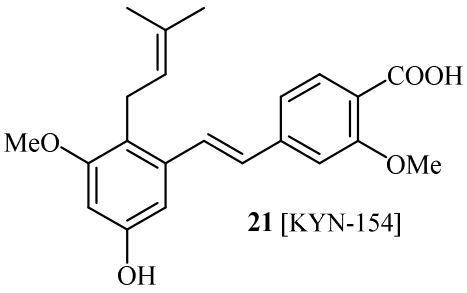
Hal is a halide selected from the group consisting of F, Cl, Br, I, and At;

only one of R^{1e}, R^{1f} or R^{1g} can be H, and

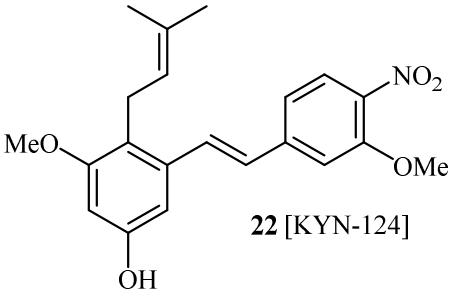
R^{1e} and R^{1f} are joined to form a five or six-membered heterocyclic ring containing a carbonyl or $(CO)CH_2$ group when R^{1e} is OH, NH_2 or NHMe and R^{1f} is NH_2, such that the nitrogen of R^{1f} is bridged via the carbonyl or $(CO)CH_2$ group to the oxygen or nitrogen of R^{1e}.

~~42~~23. A compound according to claim ~~41~~ 22 wherein formula (I) is a compound selected from the group consisting of:

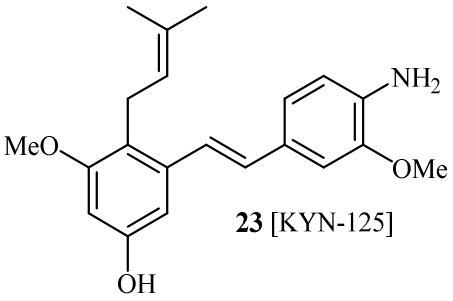
Compounds KYN-154, 124, 125, 126, 128, 129, 137, 149, 150, 151, 141, 147, 143, 142, 144, 148, 152, 155, 159 as shown below:



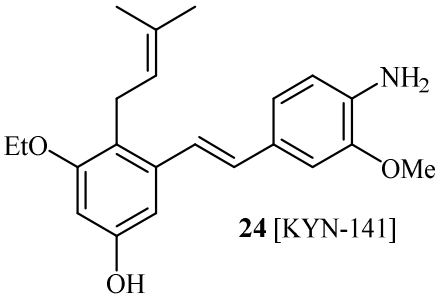
21 [KYN-154]



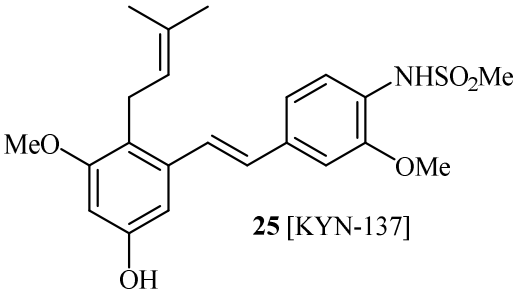
22 [KYN-124]



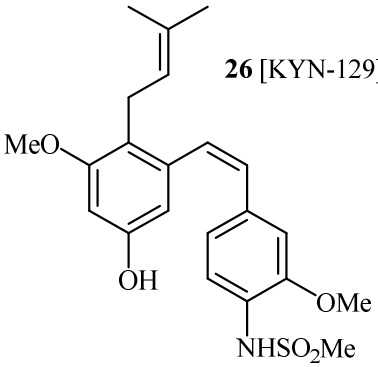
23 [KYN-125]



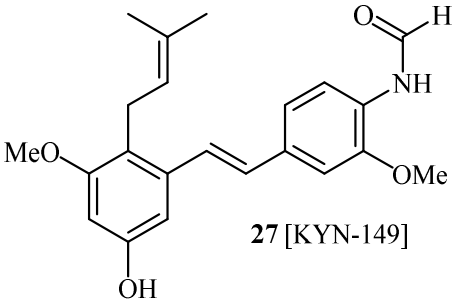
24 [KYN-141]



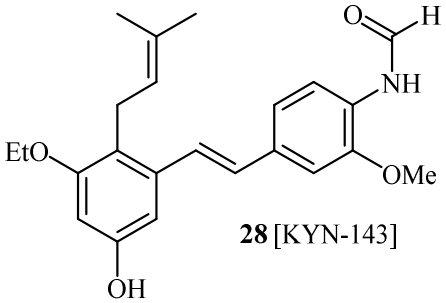
25 [KYN-137]



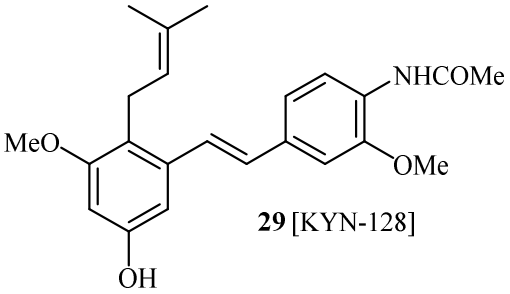
26 [KYN-129]



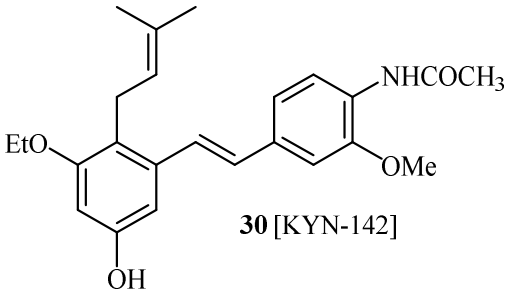
27 [KYN-149]



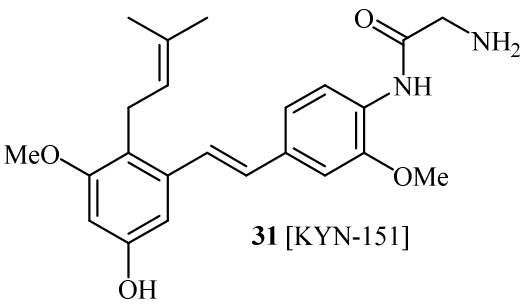
28 [KYN-143]



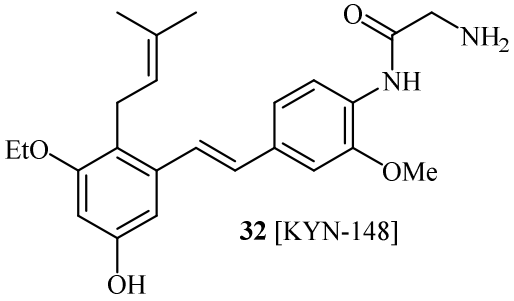
29 [KYN-128]



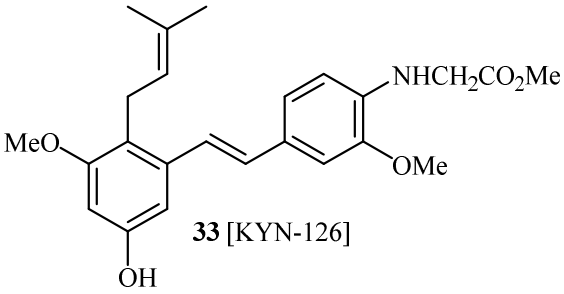
30 [KYN-142]



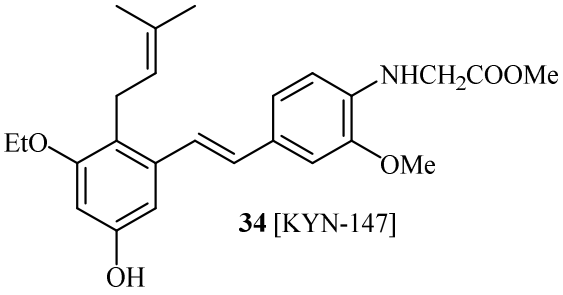
31 [KYN-151]



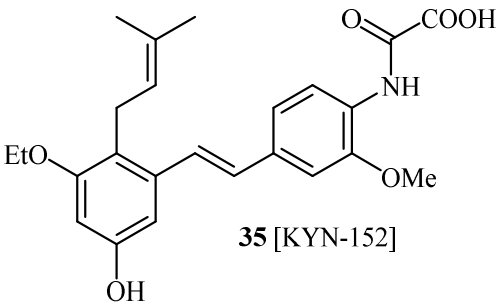
32 [KYN-148]



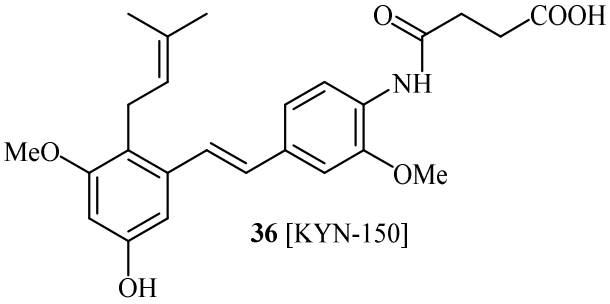
33 [KYN-126]



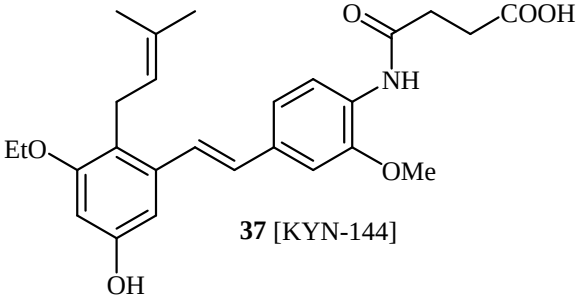
34 [KYN-147]



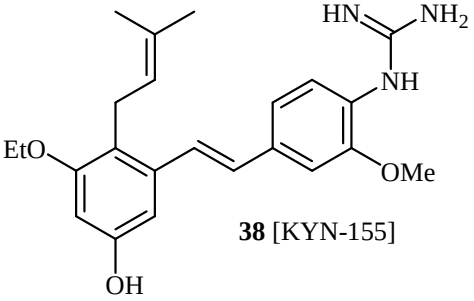
35 [KYN-152]



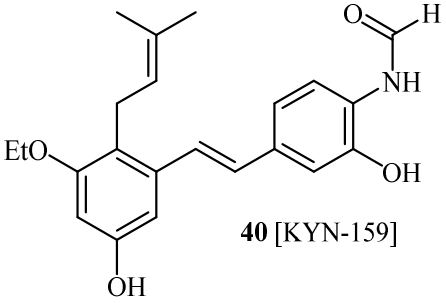
36 [KYN-150]



37 [KYN-144]

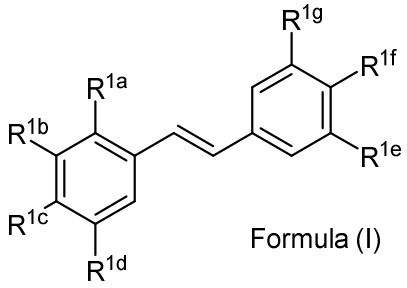


38 [KYN-155]



40 [KYN-159]

~~43~~24. A compound according to formula (I)



Formula (I)

wherein:

R^{1a} is Hal, allyl, crotyl, prenyl, geranyl, farnesyl, benzyl, 2-alkenyl or 2-alkynyl;

R^{1b} is CF_3, OH or OR^2, NO_2, NHMe, NHEt, NMe_2, NMeEt, NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or COOR2, NHR3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;

R^{1c} is H, alkyl, alkenyl, alkynyl, alkanedienyl, prenyl, geranyl, farnesyl, or benzyl;

R^{1d} is CF_3, OH or OR^2, NHR^3, NO_2, NH_2, NHMe, $NHC{=}NH(NH_2)$ or $COOR^2$;

R^{1e} is C_1-C_6 alkyl, NO_2, NH_2, NHMe, NMe_2, NHR^3 or $NMeR^3$ or SR^2;

R^{1f} is OH or, OR^2;

R^{1g} is H;

R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl or O-protecting group, wherein the O-protecting group is selected from the group consisting of COMe, *t*-$BuSi(CH_3)_2$, 2-(trimethylsilyl)ethoxymethyl (SEM) acetal, $CH(OEt)CH_3$, tetrahydropyranyl, or $C(OEt)(CH_3)_2$;

R^3 is H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOH, CH_2COOR^2, $COCH_2NH_2$, $CONH_2$ or $CO(CH_2)_nCOOH$ (where n = 0, 1 or 2); and

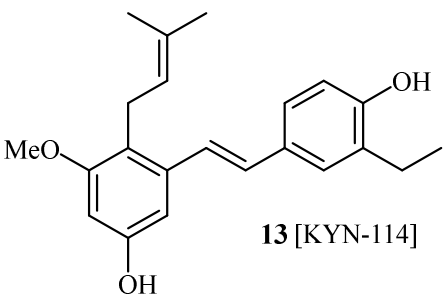
Hal is a halide selected from the group consisting of F, Cl, Br, I, and At;

only one of R^{1e}, R^{1f} or R^{1g} can be H, and

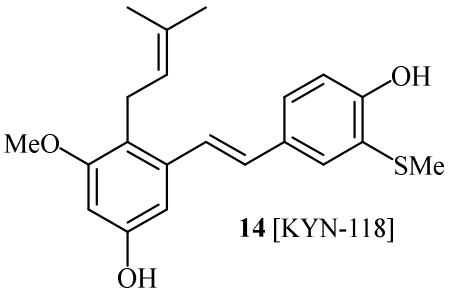
R^{1e} and R^{1f} are joined to form a five or six-membered heterocyclic ring containing a carbonyl or $(CO)CH_2$ group when R^{1e} is OH, NH_2 or NHMe and R^{1f} is NH_2, such that the nitrogen of R^{1f} is bridged via the carbonyl or $(CO)CH_2$ group to the oxygen or nitrogen of R^{1e}.

~~44~~25. A compound according to claim ~~43~~ 24 wherein formula (I) is a compound selected from the group consisting of:

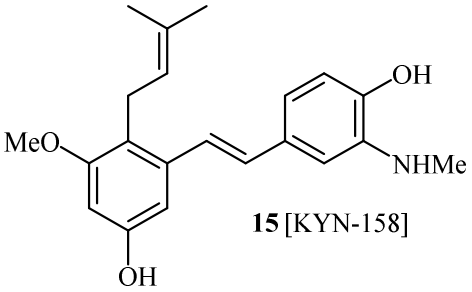
Compounds KYN-114, 118, 158, 157, 161 as shown below:



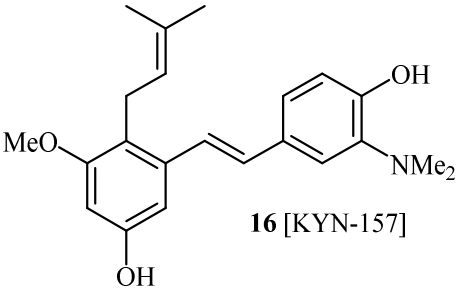
13 [KYN-114]



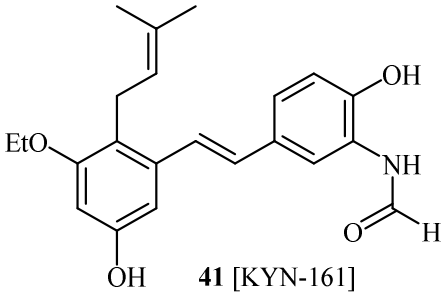
14 [KYN-118]



15 [KYN-158]

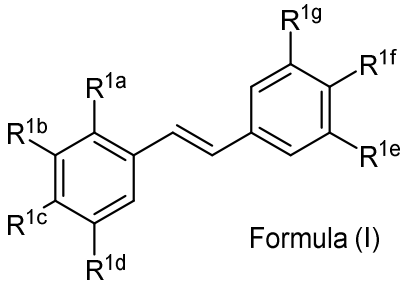


16 [KYN-157]



41 [KYN-161]

~~45~~26. A compound according to formula (I)



Formula (I)

wherein:

R^{1a} is allyl, crotyl, farnesyl, benzyl or 2-alkynyl;

R^{1b} is CF_3, OR^2, NO_2, NHMe, NHEt, NMe_2, NMeEt, NHR^3 or $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;

R^{1c} is H, alkyl, alkenyl, alkynyl, alkanedienyl, geranyl, farnesyl, or benzyl;

R^{1d} is CF_3, OH, NHR^3, NO_2, NH_2, NHMe, $NHC{=}NH(NH_2)$ or $COOR^2$;

R^{1e} is H, OH, OR^2, NO_2, NH_2, NHMe, NMe_2, NHR^3 or $NMeR^3$, SR^2;

R^{1f} is H, OH, OR^2, NO_2, NH_2, NHMe, NHR^3, $NHC{=}NH(NH_2)$, $COOR^2$ or COOH;

R^{1g} is H, alkyl, CF_3, OH or OR^2;

R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl, C(O)C(O)OR^4 or O-protecting group, wherein the O-protecting group is selected from the group consisting of COMe, *t*-$BuSi(CH_3)_2$, 2-(trimethylsilyl)ethoxymethyl (SEM) acetal, $CH(OEt)CH_3$, tetrahydropyranyl, or $C(OEt)(CH_3)_2$;

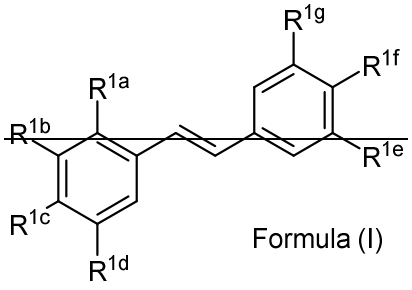
R^3 is H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOH, CH_2COOR^2, $COCH_2NH_2$, $CONH_2$ or $CO(CH_2)_nCOOH$ (where n = 0, 1 or 2);

R^4 is C1-C6 alkyl;

only one of R^{1e}, R^{1f} or R^{1g} can be H, and

R^{1e} and R^{1f} are joined to form a five or six-membered heterocyclic ring containing a carbonyl or $(CO)CH_2$ group when R^{1e} is OH, NH_2 or NHMe and R^{1f} is NH_2, such that the nitrogen of R^{1f} is bridged via the carbonyl or $(CO)CH_2$ group to the oxygen or nitrogen of R^{1e}.

~~46. A compound of formula (I),~~



Formula (I)

~~wherein:~~

~~R^{1a} is allyl, crotyl, farnesyl, benzyl , or 2-alkynyl;~~

~~R^{1b} is CF_3 or OR^2;~~

~~R^{1c} is H;~~

~~R^{1d} is OH, NH_2 or NH(CO)H;~~

~~R^{1e} is OR^2, R^4, NO_2, NH_2, NHMe, NMe_2 or SR^2;~~

~~R^{1f} is OH, OR^2, NO_2, NH_2, NHMe, NHR^3, NHC=NH(NH_2), $COOR^2$ or $^-$COOH;~~

~~R^{1g} is H;~~

~~R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl, C(O)C(O)OR^4 or O-protecting group, wherein the protecting group is selected from the group consisting of COMe, *t*-BuSi(CH_3)$_2$, 2-(trimethylsilyl)ethoxymethyl (SEM) acetal, CH(OEt)CH_3, tetrahydropyranyl, or C(OEt)(CH_3)$_2$;~~

~~R^3 is H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOH, CH_2COOR^2, $COCH_2NH_2$, $CONH_2$ or $CO(CH_2)_n$COOH (where n = 0, 1 or 2);~~

~~R^4 is C1-C6 alkyl;~~

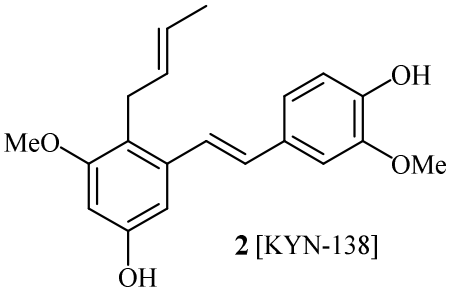
~~Hal is a halide selected from the group consisting of F, Cl, Br, I, and At;~~

~~only one of R^{1e}, R^{1f} or R^{1g} can be H, and~~

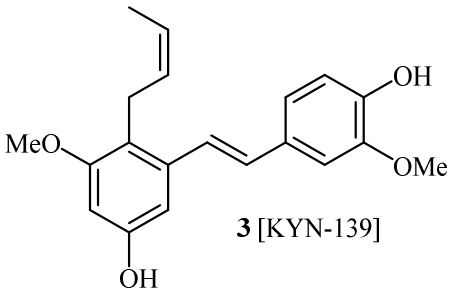
~~R^{1e} and R^{1f} are joined to form a five or six-membered heterocyclic ring containing a carbonyl or (CO)CH_2 group when R^{1e} is OH, NH_2 or NHMe and R^{1f} is NH_2, such that the nitrogen of R^{1f} is bridged via the carbonyl or (CO)CH_2 group to the oxygen or nitrogen of R^{1e}.~~

~~47~~27. A compound according to claim ~~45 or 46~~ 26 wherein formula (I) is a compound selected from the group consisting of:

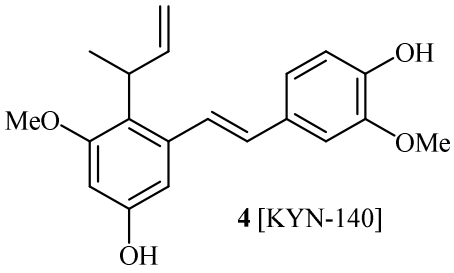
KYN-138, 139, 140, 153, 134, 136 as shown below:



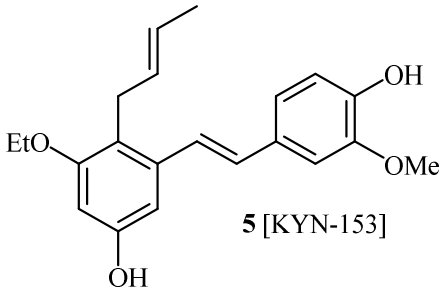
2 [KYN-138]



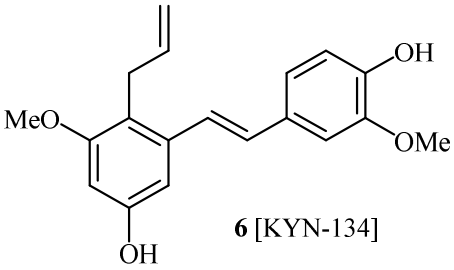
3 [KYN-139]



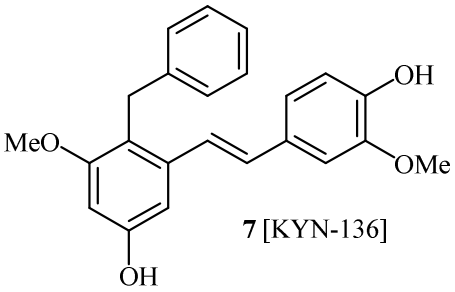
4 [KYN-140]



5 [KYN-153]



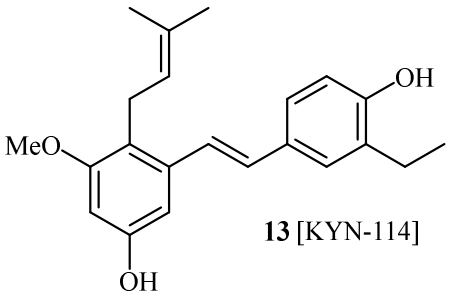
6 [KYN-134]



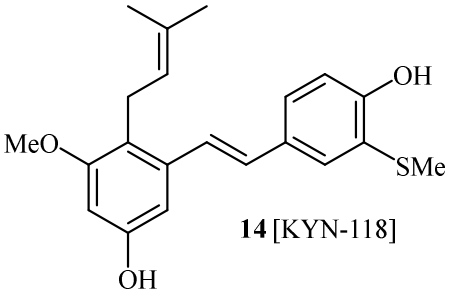
7 [KYN-136]

5

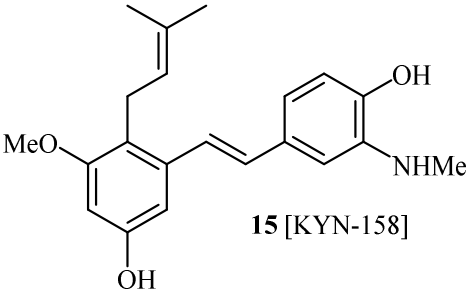
~~48~~28. A compound of formula (I) according to claim ~~34~~ 16 or ~~35~~ 17 wherein the compound is selected from the group consisting of:



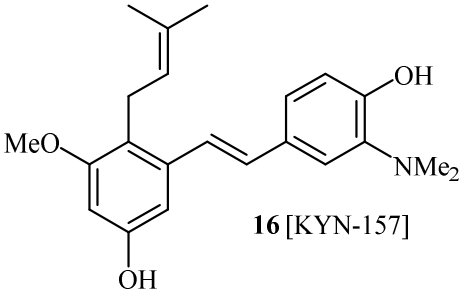
13 [KYN-114]



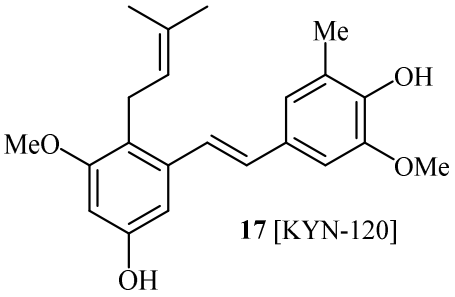
14 [KYN-118]



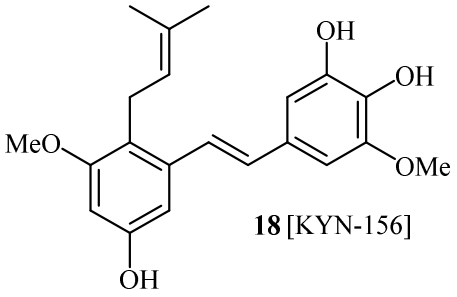
15 [KYN-158]



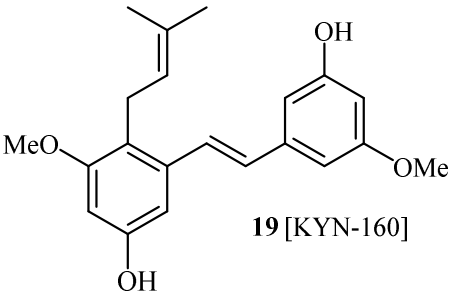
16 [KYN-157]



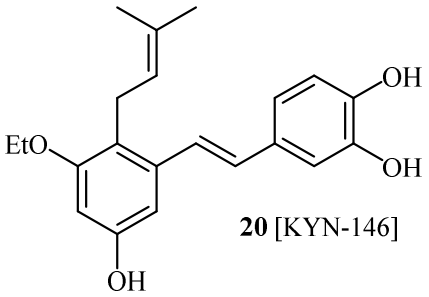
17 [KYN-120]



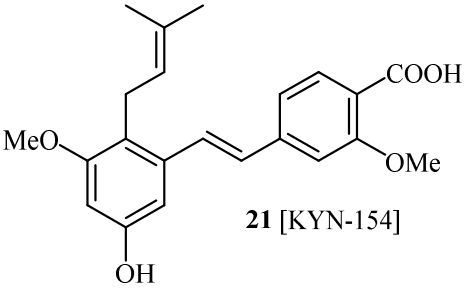
18 [KYN-156]



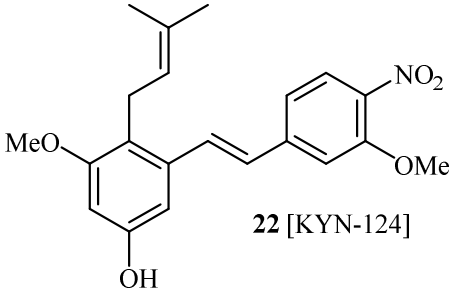
19 [KYN-160]



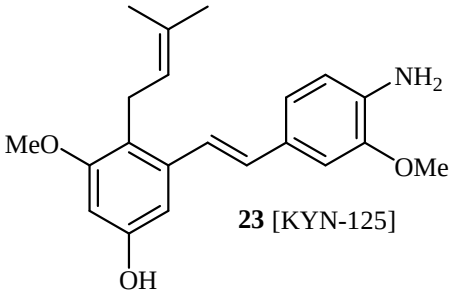
20 [KYN-146]



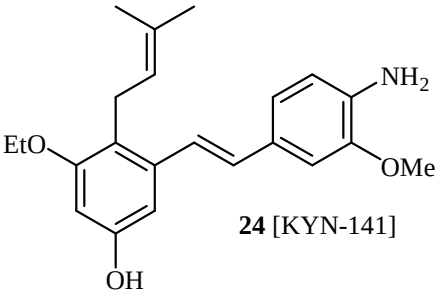
21 [KYN-154]



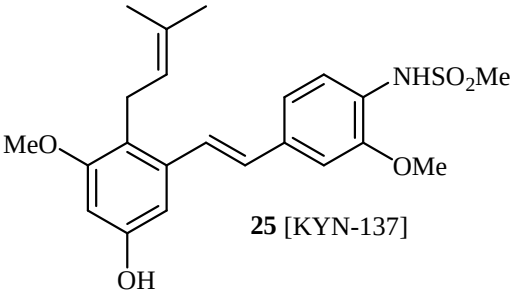
22 [KYN-124]



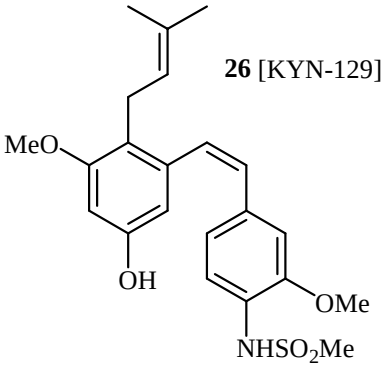
23 [KYN-125]



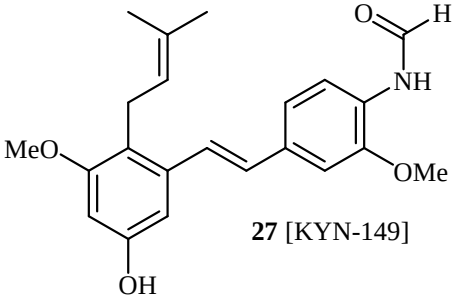
24 [KYN-141]



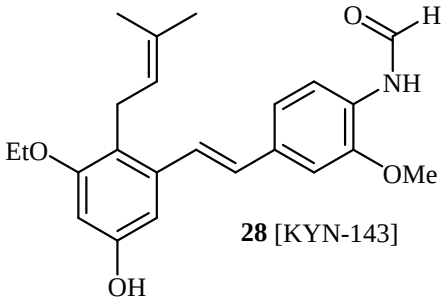
25 [KYN-137]



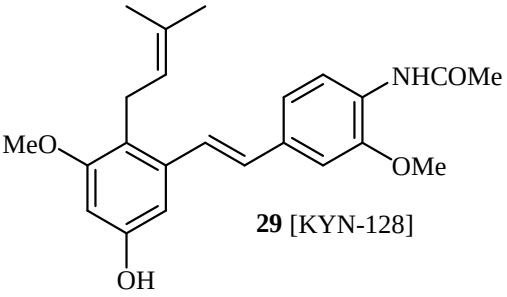
26 [KYN-129]



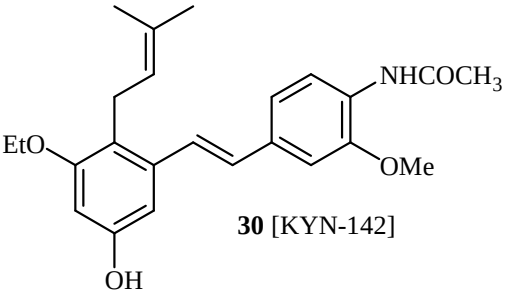
27 [KYN-149]



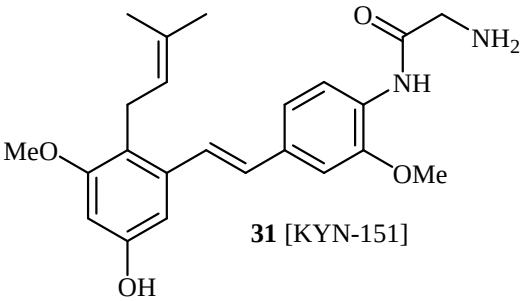
28 [KYN-143]



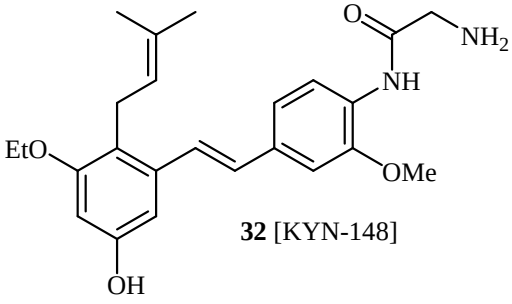
29 [KYN-128]



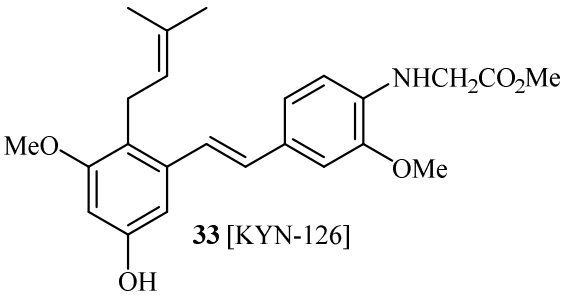
30 [KYN-142]



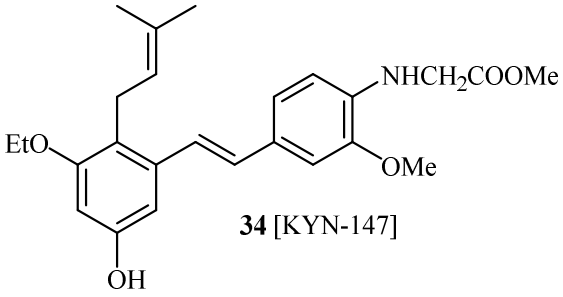
31 [KYN-151]



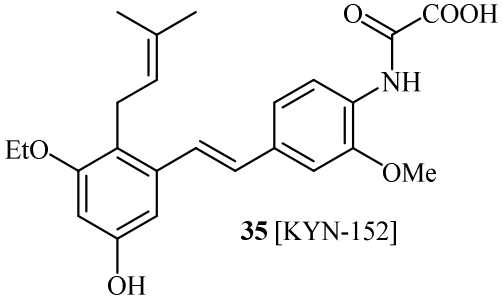
32 [KYN-148]



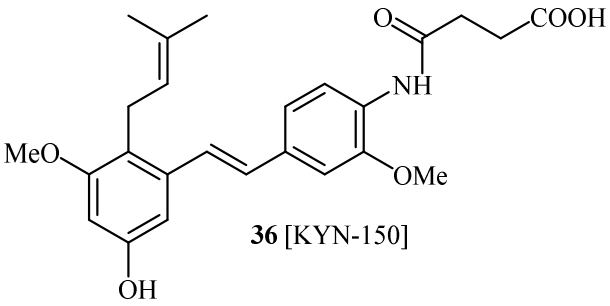
33 [KYN-126]



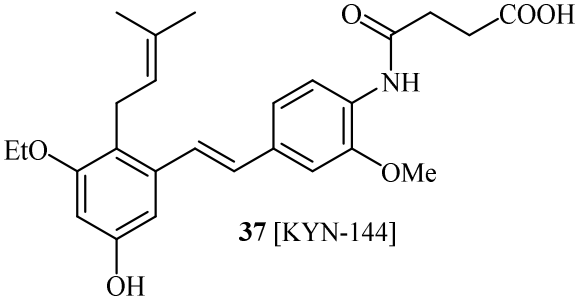
34 [KYN-147]



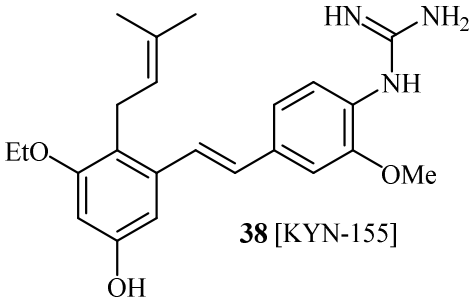
35 [KYN-152]



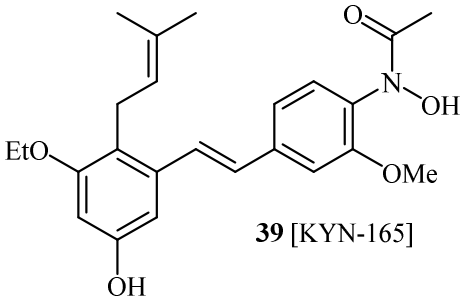
36 [KYN-150]



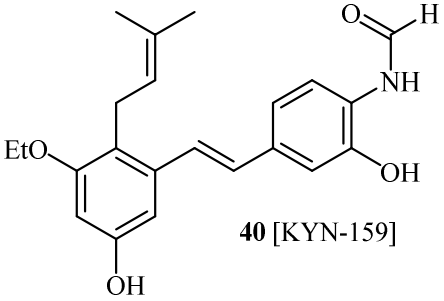
37 [KYN-144]



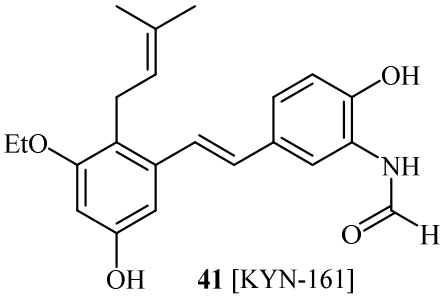
38 [KYN-155]



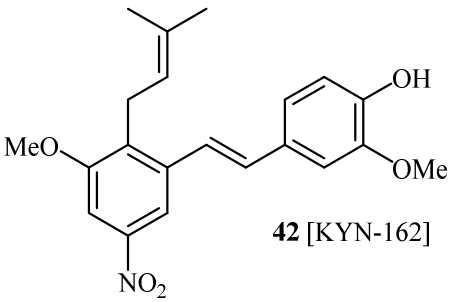
39 [KYN-165]



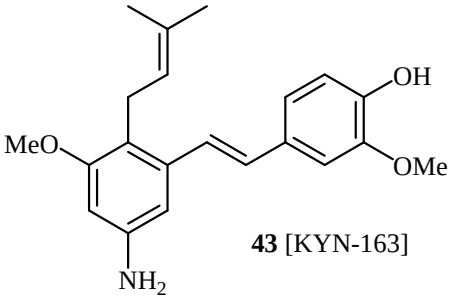
40 [KYN-159]



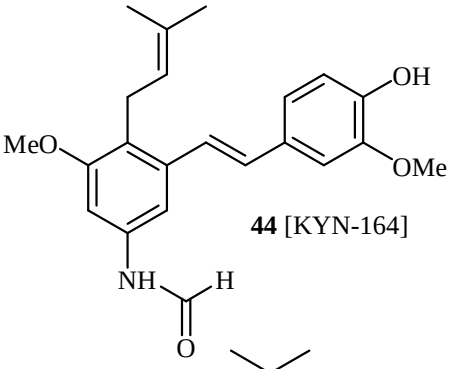
41 [KYN-161]



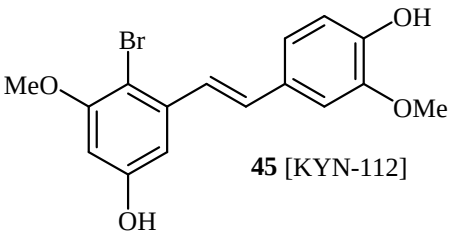
42 [KYN-162]



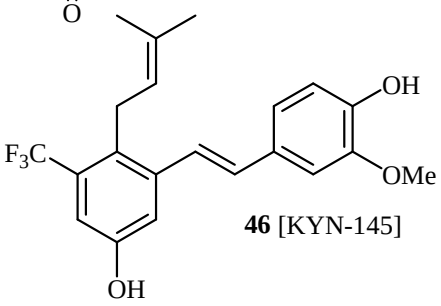
43 [KYN-163]



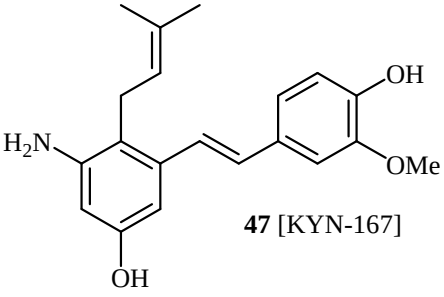
44 [KYN-164]



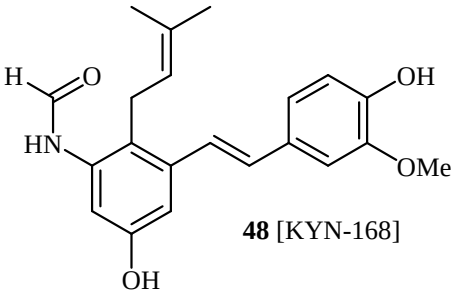
45 [KYN-112]



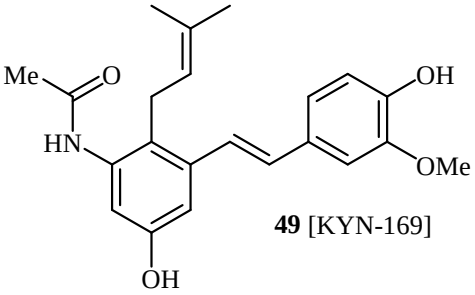
46 [KYN-145]



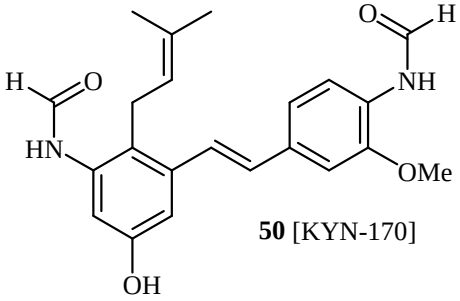
47 [KYN-167]



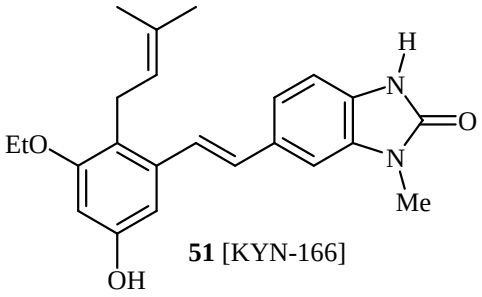
48 [KYN-168]



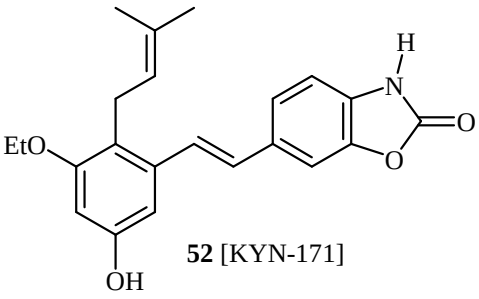
49 [KYN-169]



50 [KYN-170]



51 [KYN-166]



52 [KYN-171]

~~49~~29. A compound of formula (I) according to any one of claims ~~34~~16, ~~35~~17, ~~36~~18, ~~37~~, ~~39~~or -20 ~~or 41~~ wherein:

R^{1a} is prenyl;

R^{1b} is OR^2;

R^{1c} is H;

R^{1d} is OH;

R^{1e} is OR^2;

R^{1f} is NHR^3, ~~or~~ NHC=NH(NH_2) or~~;~~ OH ,

R^{1g} is H, alkyl or OH;

R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl; and

R^3 is H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOR^2, $COCH_2NH_2$ or $CO(CH_2)_nCOOH$ (where n = 0, 1 or 2).

~~50. A compound of formula (I) according to any one of claims 34, 35, 36, 37 or 39~~

~~wherein:~~

~~R^{1a} is prenyl;~~

~~R^{1b} is OR^2;~~

~~R^{1c} is H;~~

~~R^{1d} is OH:~~

~~R^{1e} is OR^2;~~

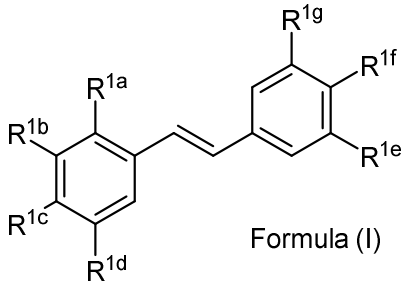
~~R^{1f} is OH,;~~

~~R^{1g} is alkyl or OH;~~

~~R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl;~~

~~alkyl is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, or t-butyl.~~

~~51~~30. A compound according to formula (I)



Formula (I)

wherein:

R^{1a} is Hal, allyl, crotyl, prenyl, geranyl, farnesyl, benzyl, 2-alkenyl or 2-alkynyl;
R^{1b} is CF_3, OH or OR^2, NO_2, NHEt, NMe_2, NMeEt, NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;
R^{1c} is H, alkyl, alkenyl, alkynyl, alkanedienyl, prenyl, geranyl, farnesyl, or benzyl;
R^{1d} is CF_3, OH or OR^2, NO_2, NHR^3, $NMeR^3$, $NHC{=}NH(NH_2)$ or $COOR^2$;
R^{1e} is H, C_1-C_6 alkyl, OH, OR^2, NO_2, NMe_2, NHR^3, $NMeR^3$ or SR^2;
R^{1f} is H, OH, OR^2, NO_2, NHR^3, $NHC{=}NH(NH_2)$, $COOR^2$ or COOH;
R^{1g} is H, alkyl, CF_3, OH or OR^2;
R^2 is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, trifluoromethyl, $COCOOR^4$or O-protecting group, wherein the O-protecting group is selected from the group consisting of COMe, *t*-$BuSi(CH_3)_2$, 2-(trimethylsilyl)ethoxymethyl (SEM) acetal, $CH(OEt)CH_3$, tetrahydropyranyl, or $C(OEt)(CH_3)_2$;
R^3 is H, CH_3, OH, (CO)H, (CO)Me, SO_2Me, CH_2COOH, CH_2COOR^2, $CO(CH_2)_nNH_2$, $CONH_2$, $CO(CH_2)_nCOOH$ or $COCOOR^4$ (where n = 0, 1 or 2);
R^4 is C_1-C_6 alkyl; and
Hal is a halide selected from the group consisting of F, Cl, Br, I, and At;
only one of R^{1e}, R^{1f} or R^{1g} can be H; and

wherein at least one of R^{1e} or R^{1f} is – NHC(O)H.

~~52. The compound of claim 51 wherein at least one of R^{1b} or R^{1d} is an EtO.~~

~~53~~31. A ~~method~~ compound according to any one of claims 16-30 or a pharmaceutically acceptable salt, solvate or pharmaceutical composition including said compound for use in the treat~~ing~~ment of cancer or a skin disease or disorder~~comprising administering a therapeutically effective amount of a compound according to any one of claims 34-52 or a pharmaceutically acceptable salt, solvate or pharmaceutical composition including said compounds to a patient in need.~~

~~54. A method for treating skin diseases and disorders comprising administering a therapeutically effective amount of a compound according to any one of claims 34-52 or a pharmaceutically acceptable salt, solvate or pharmaceutical composition including said compounds to a patient in need .~~

~~55. The method of claim 54 wherein the skin diseases and disorders is~~ including atopic dermatitis ~~and~~ and psoriasis.

32. Use of a compound according to any one of claims 16-30 or a pharmaceutically acceptable salt, solvate or pharmaceutical composition including said compound in the preparation of a medicament for treating cancer or a skin disease or disorder.