carbomethoxy-1(2H)-isoquinoline, however, the methods disclosed therein provided a mixture of the 6- and 7-nitro isoquinoline compounds.

[0006] Weidmann et al. (U.S. Patent No. 6,093,730) reported the synthesis of various substituted isoquinoline-3-carboxamides via chromatographic separation of the 4-hydroxy-3-carbomethoxy-1(2H)-isoquinoline isomers provided by the Caswell et al. synthesis, followed by hydrolysis of the methyl ester, activation of the corresponding acid to the acid halide, and condensation with glycine methyl ester.

[0007] Other methods for the preparation of substituted isoquinoline compounds have been reported in U.S. Patent 7,629,357 and U.S. Patent 7,928,120. U.S. Patent 7,928,120 teaches the preparation of substituted cyanoisoquinoline compounds from an optionally substituted 2-methylbenzoic acid ester via reaction with a halogenating reagent to provide the corresponding 2-(halomethyl)benzoic acid ester, followed by reaction with a N-protected glycine ester, and finally cyclization/aromatization using a base and optionally an oxidizing agent. Such methods have an advantage over the documents described hereinabove in that the disclosed process affords only a single isomer of the 5-, 6-, 7-, or 8-substituted isoquinoline compounds. However, only halo and cyano substituents at the 1-position of the isoquinoline are provided. U.S. Patent 7,629,357 discloses methods for the synthesis of various substituents at the 1-position of variously substituted isoquinoline compounds, including 1-methyl isoquinoline compounds. The 1-methyl isoquinoline compounds of U.S. Patent 7,629,357 are prepared by first reacting the corresponding 1,4-dihydroxyisoquinoline compound with phosphorous oxychloride or phosphorous oxybromide to afford the 1-chloro or 1-bromoisoquinoline compound, followed by methylation using either trimethylboroxine with tetrakis(triphenylphosphine)palladium or an excess of n-butyllithium followed by methyliodide.

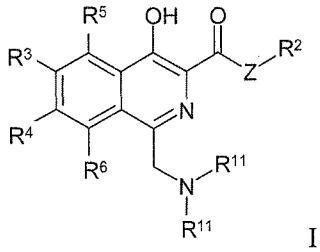
SUMMARY

[0008] The present disclosure~~invention~~ relates to methods for synthesizing variously substituted isoquinoline compounds, and the intermediate compounds achieved thereby, safely and efficiently on a large scale. Specifically, the methods disclosed herein provide the desired 5-, 6-, 7-, or 8-substituted isoquinoline compound as a single regioisomer without the need for chromatographic separation, and do not utilize reagents such as phosphorous oxychloride, phosphorous oxybromide, n-butyllithium or trimethylboroxine, which can be unsafe and/or costly when used in a large scale.

[0009] Also provided are novel intermediate compounds achieved by the methods. The compounds disclosed herein can be used as, or in the preparation of, isoquinoline compounds for inhibiting HIF hydroxylase activity, thereby increasing the stability and/or activity of hypoxia inducible factor (HIF). Such compounds are useful for the treatment of disorders associated with ischemia and hypoxia, and for

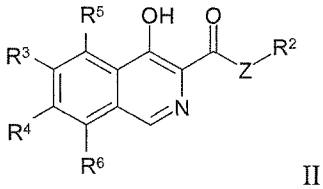
treatment of erythropoietin associated disorders, including *inter alia*, anemia (see, e.g., U.S. Patent No. 7,629,357).

[0010] In ~~one~~a first aspect, there is provided ~~present invention is directed to~~ a method of making a compound of formula I or a stereoisomer or mixture of stereoisomers thereof:



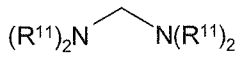
I

the method comprising contacting a compound of formula II:



II

with a compound of formula III:



III

under reaction conditions sufficient to produce a compound of formula I; wherein

Z is O, NR^1, or S;

R^1 is selected from the group consisting of hydrogen and alkyl;

R^2 is selected from the group consisting of hydrogen and alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxy, cyano, $-S(O)_n-N(R^8)-R^8$, $-NR^8C(O)NR^8R^8$, and $-X^1R^8$;

where X^1 is oxygen, $-S(O)_n-$, or $-NR^9-$;

n is 0, 1, or 2;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl provided that when X^1 is –SO- or $–SO_2$-, then R^8 is not hydrogen; and

R^9 is selected from the group consisting of hydrogen, alkyl, and aryl;

or R^3 and R^4 together with the carbon atoms pendent thereto, form a cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl and $–X^2R^{10}$;

where X^2 is oxygen, $-S(O)_n$-, or $–NR^{13}$-;

n is 0, 1, or 2;

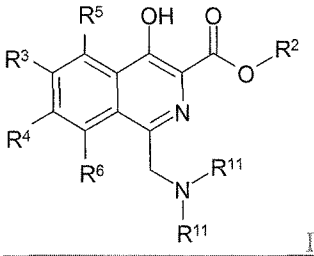
R^{10} is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl; and

R^{13} is selected from the group consisting of hydrogen, alkyl, and aryl;

or when X^2 is $–NR^{13}$-, then R^{10} and R^{13}, together with the nitrogen atom to which they are bound, can be joined to form a heterocyclyl or substituted heterocyclyl group; and

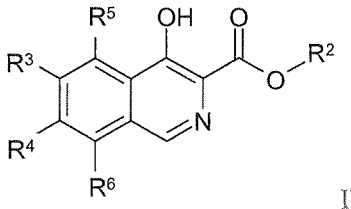
each R^{11} is independently selected from alkyl, benzyl or aryl, or two R^{11} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclyl or a heteroaryl.

[0010a] In a second aspect, there is provided a method of making a compound of formula IA or a stereoisomer or mixture of stereoisomers thereof:



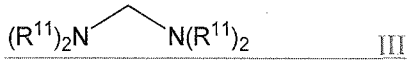
IA

comprising contacting a compound of formula IIA:



IIA

with a compound of formula III:



III

under reaction conditions sufficient to produce a compound of formula IA; wherein

R^2 is selected from the group consisting of hydrogen and alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxy, cyano, $-S(O)_n-N(R^8)-R^8$ where n is 0, 1, or 2, $-NR^8C(O)NR^8R^8$, $-X^1R^8$ where X^1 is oxygen, $-S(O)_n-$ or $-NR^9-$ where n is 0, 1, or 2, or R^3, R^4 together with the carbon atom pendent thereto, form a cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl and $-X^2R^{10}$ where X^2 is oxygen, $-S(O)_n-$ or $-NR^{13}-$ where n is 0, 1, or 2, or when X^2 is $-NR^{13}-$, then R^{13} and R^{10}, together with the nitrogen atom to which they are bound, can be joined to form a heterocyclyl or substituted heterocyclyl group;

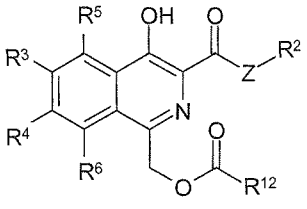
each R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl provided that when X^1 is $-SO-$ or $-SO_2-$, then R^8 is not hydrogen;

R^9 and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and aryl;

R^{10} is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl; and

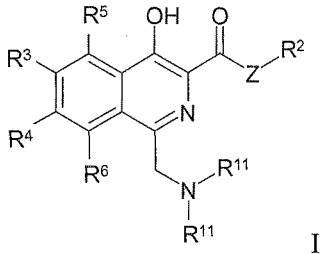
each R^{11} is independently selected from alkyl, benzyl or aryl, or two R^{11} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclyl or a heteroaryl.

[0011] In an~~other aspect~~embodiment, the present disclosure~~invention~~ is directed to a method of making a compound of formula IV or a stereoisomer or mixture of stereoisomers thereof:



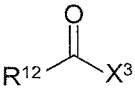
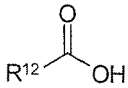
IV

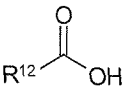
the method comprising contacting a compound of formula I:



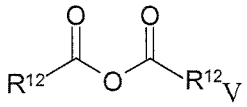
I

with one of the following:

(a) a compound of formula  followed by a compound of formula ;

(b) a compound of formula R^{12}-X^3 followed by a compound of formula ; or

(c) a compound of formula V:



V

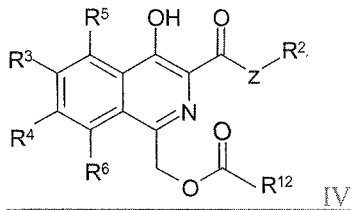
under reaction conditions sufficient to produce a compound of formula IV; wherein

X^3 is halo;

R^{12} is selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl, or when two R^{12} are present, two R^{12} together with the carbon atom to which they are attached form a 4-8 membered heterocyclyl; and

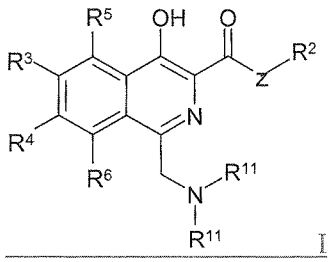
Z, R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^9, R^{10}, R^{11}, R^{13}, n, X^1 and X^2 are as defined for formula I above.

[0011a] In a third aspect, there is provided a method of making a compound of formula IV or a stereoisomer or mixture of stereoisomers thereof:

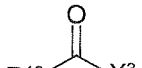
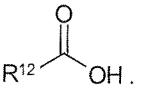
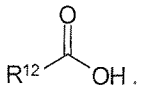


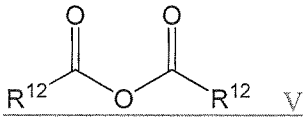
IV

comprising contacting a compound of formula I:



I

with a compound of formula  followed by a compound of formula ; a compound of formula R^{12}-X^3 followed by a compound of formula ; or a compound of formula V:



V

under reaction conditions sufficient to produce a compound of formula IV; wherein

Z is O, NR^1 or S;

R^1 is selected from the group consisting of hydrogen and alkyl;

R^2 is selected from the group consisting of hydrogen and alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxy, cyano, $-S(O)_n-N(R^8)-R^8$ where n is 0, 1, or 2, $-NR^8C(O)NR^8R^8$, $-X^1R^8$ where X^1 is oxygen, $-S(O)_n-$ or $-NR^9-$ where n is 0, 1, or 2, or R^3, R^4 together with the carbon atom pendent thereto, form a cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl and $-X^2R^{10}$ where X^2 is oxygen, $-S(O)_n-$ or $-NR^{13}-$ where n is 0, 1, or 2, or when X^2 is $-NR^{13}-$, then R^{13} and R^{10}, together with the nitrogen atom to which they are bound, can be joined to form a heterocyclyl or substituted heterocyclyl group;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl provided that when X^1 is –SO- or -SO_2-, then R^8 is not hydrogen;

R^9 and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and aryl;

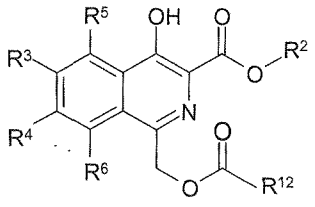
R^{10} is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl;

each R^{11} is independently selected from alkyl, benzyl or aryl, or two R^{11} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclyl or a heteroaryl;

each R^{12} is independently selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl, or when two R^{12} are present, two R^{12} together with the carbon atom to which they are attached form a 4-8 membered heterocyclyl; and

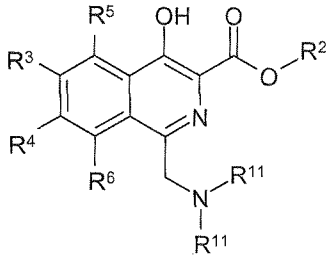
X^3 is halo.

[0011b] In a fourth aspect, there is provided a method of making a compound of formula IVA or a stereoisomer or mixture of stereoisomers thereof:



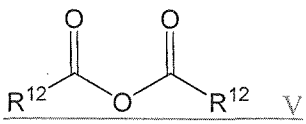
IVA

comprising contacting a compound of formula IA:



IA

with a compound of formula V:



V

under reaction conditions sufficient to produce a compound of formula IVA; wherein

R^2 is selected from the group consisting of hydrogen and alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxy, cyano, $-S(O)_n-N(R^8)-R^8$ where n is 0, 1, or 2, $-NR^8C(O)NR^8R^8$, $-X^1R^8$ where X^1 is oxygen, $-S(O)_n-$ or $-NR^9-$ where n is 0, 1, or 2, or R^3, R^4 together with the carbon atom pendent thereto, form a cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl and $-X^2R^{10}$ where X^2 is oxygen, $-S(O)_n-$ or $-NR^{13}-$ where n is 0, 1, or 2, or when X^2 is $-NR^{13}-$, then R^{13} and R^{10}, together with the nitrogen atom to which they are bound, can be joined to form a heterocyclyl or substituted heterocyclyl group;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl provided that when X^1 is $-SO-$ or $-SO_2-$, then R^8 is not hydrogen;

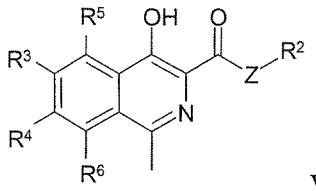
R^9 and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and aryl;

R^{10} is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl;

each R^{11} is independently selected from alkyl, benzyl or aryl, or two R^{11} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclyl or a heteroaryl; and

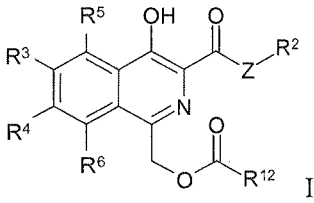
each R^{12} is independently selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl, or two R^{12} together with the carbon atom to which they are attached form a 4-8 membered heterocyclyl.

[0012] In an embodiment~~other aspect~~, the present disclosure~~invention~~ is directed to a method of making a compound of formula VI or a stereoisomer or mixture of stereoisomers thereof:



VI

the method comprising converting a compound of formula IV:



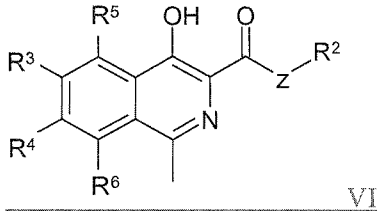
IV

under reaction conditions sufficient to produce a compound of formula VI; wherein

Z, R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^9, R^{10}, R^{11}, R^{13}, n, X^1 and X^2 are as defined for formula I above; and

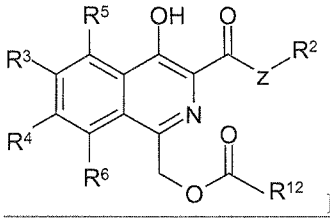
R^{12} is selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl.

[0012a] In a fifth aspect, there is provided a method of making a compound of formula VI or a stereoisomer or mixture of stereoisomers thereof:



VI

comprising converting a compound of formula IV:



IV

under reaction conditions sufficient to produce a compound of formula VI; wherein

Z is O, NR^1 or S;

R^1 is selected from the group consisting of hydrogen and alkyl;

R^2 is selected from the group consisting of hydrogen and alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxy, cyano, $-S(O)_n-N(R^8)-R^8$ where n is 0, 1, or 2, $-NR^8C(O)NR^8R^8$, $-X^1R^8$ where X^1 is oxygen, $-S(O)_n-$ or $-NR^9-$ where n

is 0, 1, or 2, or R^3, R^4 together with the carbon atom pendent thereto, form a cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl and $-X^2R^{10}$ where X^2 is oxygen, $-S(O)_n-$ or $-NR^{13}-$ where n is 0, 1, or 2, or when X^2 is $-NR^{13}-$, then R^{13} and R^{10}, together with the nitrogen atom to which they are bound, can be joined to form a heterocyclyl or substituted heterocyclyl group;

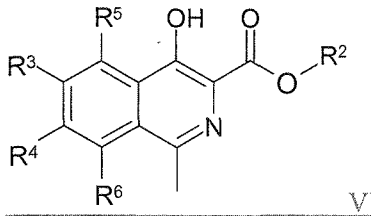
each R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl provided that when X^1 is –SO- or $-SO_2-$, then R^8 is not hydrogen;

R^9 and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and aryl; and

R^{10} is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl; and

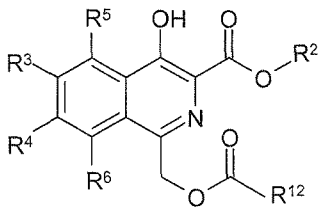
each R^{12} is independently selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl.

[0012b] In a sixth aspect, there is provided a method of making a compound of formula VIA or a stereoisomer or mixture of stereoisomers thereof:



VIA

comprising converting a compound of formula IVA:



IVA

under reaction conditions sufficient to produce a compound of formula VIA; wherein

R^2 is selected from the group consisting of hydrogen and alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxy, cyano, $-S(O)_n-N(R^8)-R^8$ where n is 0, 1, or 2, $-NR^8C(O)NR^8R^8$, $-X^1R^8$ where X^1 is oxygen, $-S(O)_n-$ or $-NR^9-$ where n is 0, 1, or 2, or R^3, R^4 together with the carbon atom pendent thereto, form a cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl and $-X^2R^{10}$ where X^2 is oxygen, $-S(O)_n-$ or $-NR^{13}-$ where n is 0, 1, or 2, or when X^2 is $-NR^{13}-$, then R^{13} and R^{10}, together with the nitrogen atom to which they are bound, can be joined to form a heterocyclyl or substituted heterocyclyl group;

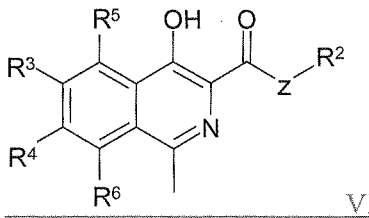
each R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl provided that when X^1 is –SO- or $-SO_2-$, then R^8 is not hydrogen;

R^9 and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and aryl; and

R^{10} is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl; and

each R^{12} is independently selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl.

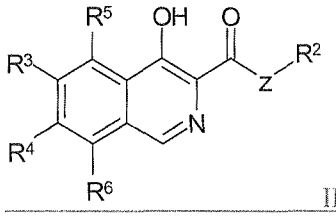
[0012c] In a seventh aspect, there is provided a method of making a compound of formula VI or a stereoisomer or mixture of stereoisomers thereof:



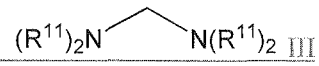
VI

the method comprising the steps of:

a) contacting a compound of formula II with a compound of formula III

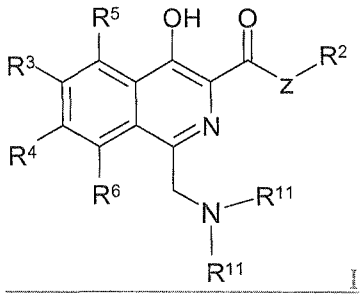


II

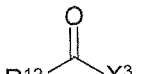
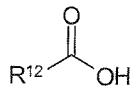
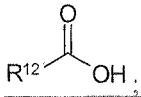


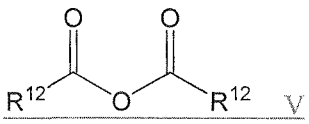
III

under reaction conditions sufficient to produce a compound of formula I:



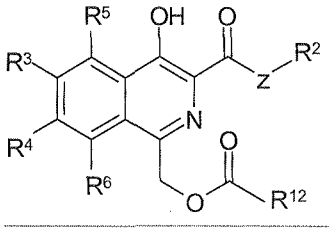
I

b) contacting a compound of formula I with a compound of formula  followed by a compound of formula  ; a compound of formula R^{12}-X^3 followed by a compound of formula  ; or a compound of formula V:



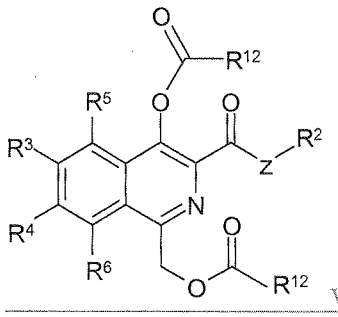
V

under reaction conditions sufficient to produce a compound of formula IV:



IV

c) optionally converting a compound of formula VII:



VII

under reaction conditions sufficient to produce a compound of formula IV; and

d) converting a compound of formula IV under reaction conditions sufficient to produce a compound of formula VI:

wherein

Z is O, NR^1 or S;

R^1 is selected from the group consisting of hydrogen and alkyl;

R^2 is selected from the group consisting of hydrogen and alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxy, cyano, $-S(O)_n-N(R^8)-R^8$ where n is 0, 1, or 2, $-NR^8C(O)NR^8R^8$, $-X^1R^8$ where X^1 is oxygen, $-S(O)_n-$ or $-NR^9-$ where n is 0, 1, or 2, or R^3, R^4 together with the carbon atom pendent thereto, form a cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl and $-X^2R^{10}$ where X^2 is oxygen, $-S(O)_n-$ or $-NR^{13}-$ where n is 0, 1, or 2, or when X^2 is $-NR^{13}-$, then R^{13} and R^{10}, together with the nitrogen atom to which they are bound, can be joined to form a heterocyclyl or substituted heterocyclyl group;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl provided that when X^1 is $-SO-$ or $-SO_2-$, then R^8 is not hydrogen;

R^9 and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and aryl; and

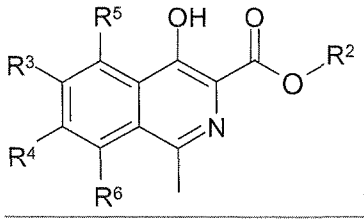
R^{10} is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl;

each R^{11} is independently selected from alkyl, benzyl or aryl, or two R^{11} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclyl or a heteroaryl;

each R^{12} is independently selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl, or when two R^{12} are present, two R^{12} together with the carbon atom to which they are attached form a 4-8 membered heterocyclyl; and

X^3 is halo.

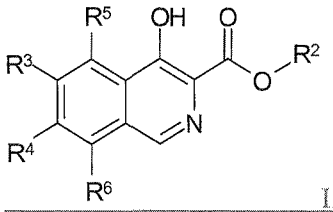
[0012d] In an eighth aspect, there is provided a method of making a compound of formula VIA or a stereoisomer or mixture of stereoisomers thereof:



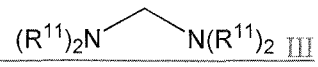
VIA

the method comprising the steps of:

a) contacting a compound of formula IIA with a compound of formula III

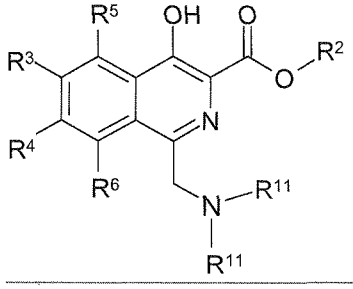


IIA



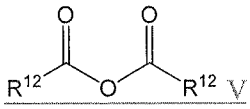
III

under reaction conditions sufficient to produce a compound of formula IA:



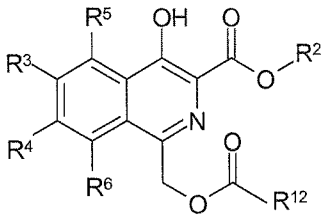
IA

b) contacting a compound of formula IA with a compound of formula V



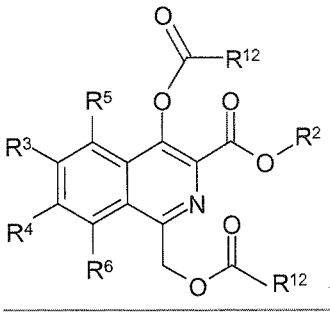
V

under reaction conditions sufficient to produce a compound of formula IVA:



IVA

c) optionally converting a compound of formula VIIA:



VIIA

under reaction conditions sufficient to produce a compound of formula IVA; and

d) converting a compound of formula IVA under reaction conditions sufficient to produce a compound of formula VIA;

wherein

R^2 is selected from the group consisting of hydrogen and alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxy, cyano, $-S(O)_n-N(R^8)-R^8$ where n is 0, 1, or 2, $-NR^8C(O)NR^8R^8$, $-X^1R^8$ where X^1 is oxygen, $-S(O)_n-$ or $-NR^9-$ where n is 0, 1, or 2, or R^3, R^4 together with the carbon atom pendent thereto, form a cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl and $-X^2R^{10}$ where X^2 is oxygen, $-S(O)_n-$ or $-NR^9-$ where n is 0, 1, or 2, or when X^2 is $-NR^{13}-$, then R^{13} and R^{10}, together with the nitrogen atom to which they are bound, can be joined to form a heterocyclyl or substituted heterocyclyl group;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl provided that when X^1 is $-SO-$ or $-SO_2-$, then R^8 is not hydrogen;

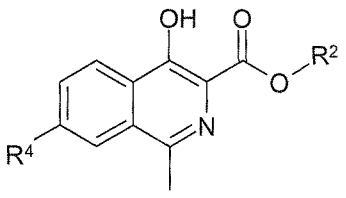
R^9 and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and aryl; and

R^{10} is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl;

each R^{11} is independently selected from alkyl, benzyl or aryl, or two R^{11} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclyl or a heteroaryl; and

each R^{12} is independently selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl, or two R^{12} together with the carbon atom to which they are attached form a 4-8 membered heterocyclyl.

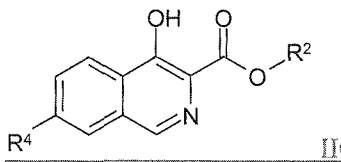
[0012e] In a ninth aspect, there is provided a method of making a compound of formula VIC or a stereoisomer or mixture of stereoisomers thereof:



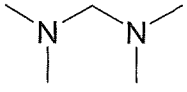
VIC

comprising the steps of:

a) contacting a compound of formula IIC with a compound of formula IIIA

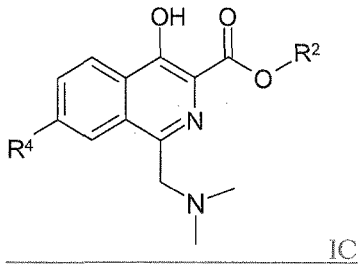


IIC



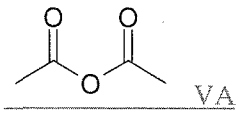
IIIA

under reaction conditions sufficient to produce a compound of formula IC:



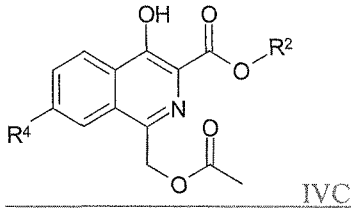
IC

b) contacting a compound of formula IC with a compound of formula VA



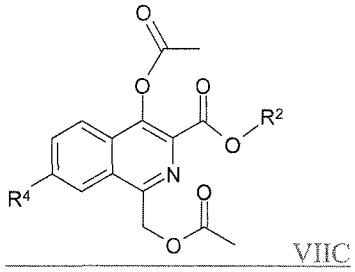
VA

under reaction conditions sufficient to produce a compound of formula IVC:



IVC

c) optionally converting a compound of formula VIIC:



VIIC

under reaction conditions sufficient to produce a compound of formula IVC; and

d) converting a compound of formula IVC under reaction conditions sufficient to produce a compound of formula VIC;

wherein

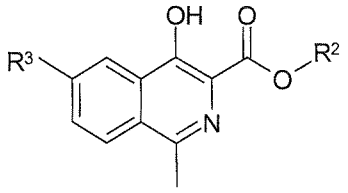
R^2 is selected from the group consisting of hydrogen and alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^4 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxy, cyano, $-S(O)_n-N(R^8)-R^8$ where n is 0, 1, or 2, $-NR^8C(O)NR^8R^8$, $-X^1R^8$ where X^1 is oxygen, $-S(O)_n-$ or $-NR^9-$ where n is 0, 1, or 2, or R^3, R^4 together with the carbon atom pendent thereto, form a cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl provided that when X^1 is –SO- or $-SO_2-$, then R^8 is not hydrogen; and

each R^9 is selected from the group consisting of hydrogen, alkyl, and aryl.

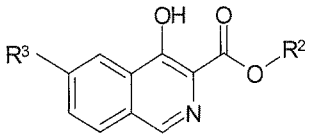
[0012f] In a tenth aspect, there is provided a method of making a compound of formula VID or a stereoisomer or mixture of stereoisomers thereof:



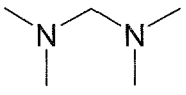
VID

comprising the steps of:

a) contacting a compound of formula IID with a compound of formula IIIA

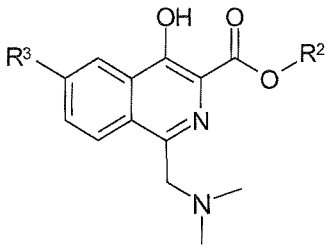


IID



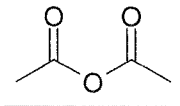
IIIA

under reaction conditions sufficient to produce a compound of formula ID:



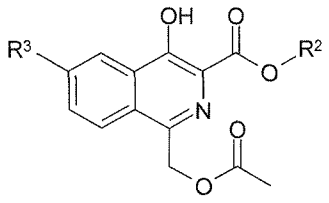
ID

b) contacting a compound of formula ID with a compound of formula VA



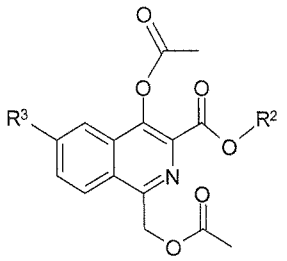
VA

under reaction conditions sufficient to produce a compound of formula IVD:



IVD

c) optionally converting a compound of formula VIID:



VIID

under reaction conditions sufficient to produce a compound of formula IVD; and

d) converting a compound of formula IVD under reaction conditions sufficient to produce a compound of formula VID;

wherein

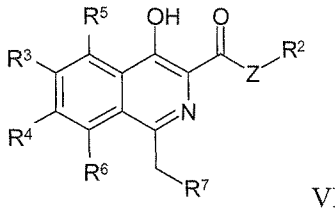
R^2 is selected from the group consisting of hydrogen and alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^3 is selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxy, cyano, $-S(O)_n-N(R^8)-R^8$ where n is 0, 1, or 2, $-NR^8C(O)NR^8R^8$, $-X^1R^8$ where X^1 is oxygen, $-S(O)_n-$ or $-NR^9-$ where n is 0, 1, or 2, or R^3, R^4 together with the carbon atom pendent thereto, form a cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl provided that when X^1 is –SO- or $-SO_2-$, then R^8 is not hydrogen; and

each R^9 is selected from the group consisting of hydrogen, alkyl, and aryl.

[0013] In ~~another aspect~~an embodiment, the disclosure~~invention~~ is directed to a compound of formula VIII:



VIII

wherein:

Z, R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^9, R^{10}, R^{11}, R^{13}, n, X^1 and X^2 are as defined for formula I above;

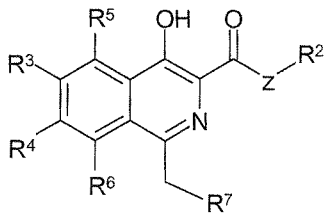
R^7 is $-N(R^{11})(R^{11})$ or $-OC(O)R^{12}$; and

R^{12} is selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl;

or a salt, ester, stereoisomer, or mixture of stereoisomers thereof;

provided that the compound is not 1-dimethylaminomethyl-4-hydroxy-7-phenylsulfanyl-isoquinoline-3-carboxylic acid butyl ester.

[0013a] In an eleventh aspect, there is provided a compound of formula VIII:



VIII

wherein:

Z is O, NR^1 or S;

R^1 is selected from the group consisting of hydrogen and alkyl;

R^2 is selected from the group consisting of hydrogen and alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxy, cyano, $-S(O)_n-N(R^8)-R^8$ where n is 0, 1, or 2, $-NR^8C(O)NR^8R^8$, $-X^1R^8$ where X^1 is oxygen, $-S(O)_n-$ or $-NR^9-$ where n is 0, 1, or 2, or R^3, R^4 together with the carbon atom pendent thereto, form a cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl and $-X^2R^{10}$ where X^2 is oxygen, $-S(O)_n-$ or $-NR^{13}-$ where n is 0, 1, or 2, or when X^2 is $-NR^{13}-$, then R^{13} and R^{10}, together with the nitrogen atom to which they are bound, can be joined to form a heterocyclyl or substituted heterocyclyl group;

R^7 is either $-N(R^{11})(R^{11})$ or $-OC(O)R^{12}$;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl provided that when X^1 is –SO- or $-SO_2-$, then R^8 is not hydrogen;

R^9 and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and aryl;

R^{10} is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl;

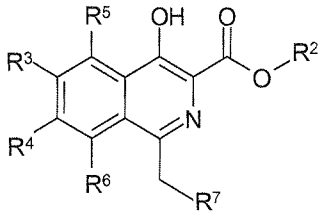
each R^{11} is independently selected from alkyl, benzyl or aryl, or two R^{11} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclyl or a heteroaryl; and

each R^{12} is independently selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl;

or a salt, ester, stereoisomer, or mixture of stereoisomers thereof;

provided that the compound is not 1-dimethylaminomethyl-4-hydroxy-7-phenylsulfanyl-isoquinoline-3-carboxylic acid butyl ester.

[0013b] In a twelfth aspect, there is provided a compound of formula VIIIA:



VIIIA

wherein:

R^2 is selected from the group consisting of hydrogen and alkyl which is unsubstituted or substituted with one or more substituents independently selected from the group consisting of cycloalkyl, heterocyclyl, aryl, and heteroaryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, halo, hydroxy, cyano, $-S(O)_n-N(R^8)-R^8$ where n is 0, 1, or 2, $-NR^8C(O)NR^8R^8$, $-X^1R^8$ where X^1 is oxygen, $-S(O)_n-$ or $-NR^9-$ where n is 0, 1, or 2, or R^3, R^4 together with the carbon atom pendent thereto, form a cycloalkyl, substituted cycloalkyl, heterocyclyl, substituted heterocyclyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

R^5 and R^6 are independently selected from the group consisting of hydrogen, halo, alkyl, substituted alkyl, alkoxy, substituted alkoxy, aryl, substituted aryl, heteroaryl, substituted heteroaryl and $-X^2R^{10}$ where X^2 is oxygen, $-S(O)_n-$ or $-NR^{13}-$ where n is 0, 1, or 2, or when X^2 is $-NR^{13}-$, then R^{13} and R^{10}, together with the nitrogen atom to which they are bound, can be joined to form a heterocyclyl or substituted heterocyclyl group;

R^7 is either $-N(R^{11})(R^{11})$ or $-OC(O)R^{12}$;

each R^8 is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl provided that when X^1 is –SO- or $-SO_2-$, then R^8 is not hydrogen;

R^9 and R^{13} are independently selected from the group consisting of hydrogen, alkyl, and aryl;

R^{10} is selected from the group consisting of alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl and substituted heterocyclyl;

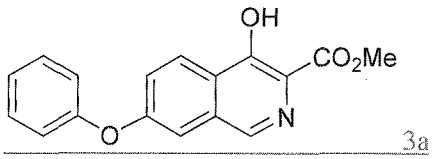
each R^{11} is independently selected from alkyl, benzyl or aryl, or two R^{11} together with the nitrogen atom to which they are attached form a 4-8 membered heterocyclyl or a heteroaryl; and

each R^{12} is independently selected from the group consisting of alkyl, aryl, heteroaryl, and heterocyclyl;

or a salt, ester, stereoisomer, or mixture of stereoisomers thereof;

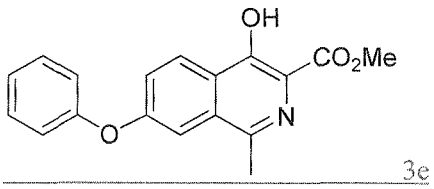
provided that the compound is not 1-dimethylaminomethyl-4-hydroxy-7-phenylsulfanyl-isoquinoline-3-carboxylic acid butyl ester.

[0013c] In a thirteenth aspect, there ir provided a compound that is 4-hydroxy-7-phenoxyisoquinoline-3-carboxylic acid methyl ester (3a):



3a

[0013d] In a fourteenth aspect, there is provided a compound that is methyl 4-hydroxy-1-methyl-7-phenoxyisoquinoline-3-carboxylate (3e):



3e

[0014] Additional embodiments of the invention are described throughout.

DETAILED DESCRIPTION

[0015] Before the compounds and methods are described, it is to be understood that the invention is not limited to the particular compounds, compositions, methodologies, protocols, cell lines, assays, and reagents described, as these may vary. It is also to be understood that the terminology used herein is intended to describe particular embodiments of the present invention, and is in no way intended to limit the scope of the present invention as set forth in the appended claims.