SUBSTITUTED IMIDAZO RING SYSTEMS AND METHODS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Application Serial No. 60/524961, filed on November 25, 2003, and to U.S. Provisional Application Serial No. 60/580139, filed on June 16, 2004, both of which are incorporated by reference herein in their entirety.

BACKGROUND

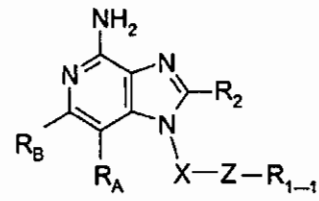
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed and 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*] quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-c]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders.

There continues to be interest in the imidazoquinoline ring system, and other ring systems, and there is a continuing need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formula (I):



I-1

wherein: Z is -C(O)-, -C(O)O-, or -C(-Q-R_{1-3})$_2$-; and

wherein: X, R_A, R_B, R_2, R_{1-1}, Q, and R_{1-3} are as defined below.

The compounds of Formula I-1 are useful as immune response modifiers due to their ability to induce cytokine biosynthesis (e.g., induces the synthesis of at least one cytokine) and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the treatment of a variety of conditions such as viral diseases and tumors that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions containing an effective amount of a compound of Formula I-1 and methods of inducing cytokine biosynthesis in an animal, treating a viral infection and/or treating a neoplastic disease in an animal by administering an effective amount of a compound of Formula I-1 to the animal.

In addition, methods of synthesizing compounds of Formula I-1 and intermediates useful in the synthesis of these compounds are provided.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

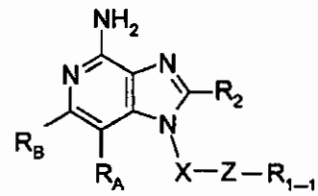
The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention.

The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the application, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

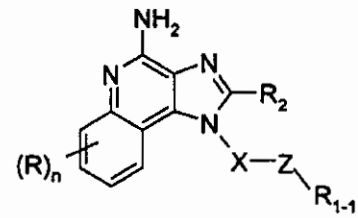
DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formula (I-1):

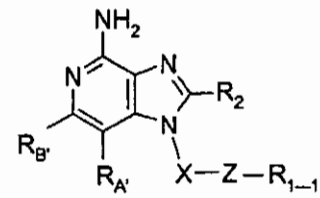


I-1

wherein: Z is -C(O)-, -C(O)O-, or -C(-Q-R_{1-3})$_2$-; and as well as more specific compounds of Formulas (I-2, I-3, and I-4), which represent different core ring structures:

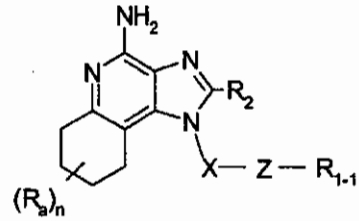


I-2



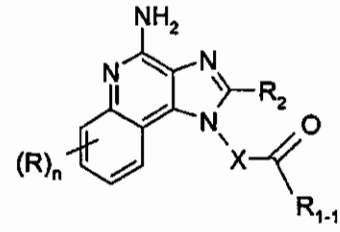
I-3

and

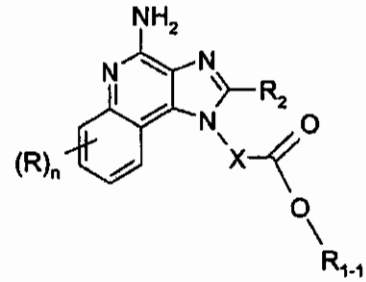


I-4

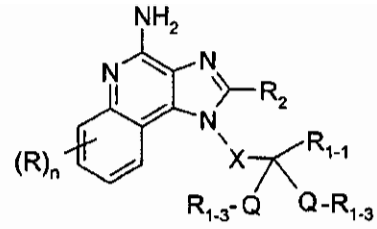
wherein: Z is -C(O)-, -C(O)O-, or -C(-Q-R_{1-3})$_2$-; and more specific compounds of the following Formulas (Ia, Ib, Id, and Ie):



Ia

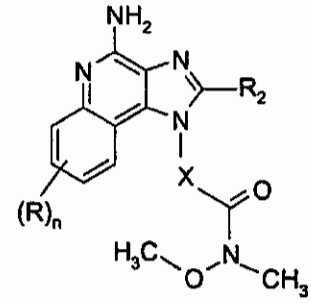


Ib



Id

and

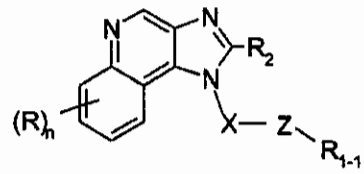


Ie

wherein: X, R, R_a, R_A, R_B, $R_{A'}$, $R_{B'}$, R_2, R_3, R_{1-1}, Q, R_{1-3}, and n are as defined below;

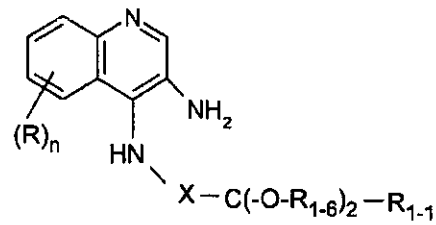
and pharmaceutically acceptable salts thereof.

The present invention also provides compounds of the following Formulas (II, III, and IV):



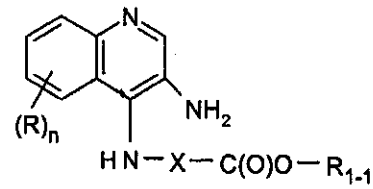
II

wherein: Z is -C(O)-, -C(O)O-, or -C(-Q-R_{1-3})$_2$-;



III

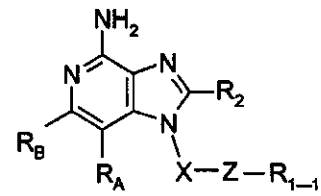
and



IV

wherein: X, R, R_2, R_{1-1}, R_{1-6}, Q, R_{1-3}, and n are as defined below; and pharmaceutically acceptable salts thereof.

In one embodiment, there is provided a compound of the Formula (I-1):



I-1

wherein:

X is alkylene optionally interrupted by one or more -O- groups;

Z is -C(O)-, -C(O)O-, or $-C(-Q-R_{1-3})_2-$;

R_{1-1} is selected from the group consisting of:

hydrogen,

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

$-NH-SO_2-R_{1-4}$,

$-NH-C(O)-R_{1-4}$,

$-NH-C(O)-NH_2$,

$-NH-C(O)-NH-R_{1-4}$, and

$-N_3$;

with the proviso that if Z is -C(O)-, then R_{1-1} may also be $-N(CH_3)(OCH_3)$;

with the further proviso that if Z is -C(O)O-, then R_{1-1} is not hydrogen;

with the further proviso that if Z is -C(O)O-, then X does not include -O- groups;

Q is O or S;

R_{1-3} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,
cyano,
nitro,
alkoxy,
dialkylamino,
alkylthio,
haloalkyl,
haloalkoxy,
alkyl,
$-NH-SO_2-R_{1-4}$,
$-NH-C(O)-R_{1-4}$,
$-NH-C(O)-NH_2$,
$-NH-C(O)-NH-R_{1-4}$, and
$-N_3$;

or the R_{1-3} groups can join together to form a ring system comprising a saturated or unsaturated 5-, 6-, or 7-membered ring;

R_{1-4} is selected from the group consisting of:

alkyl,
aryl,
alkylene-aryl,
heteroaryl,
alkylene-heteroaryl, and
alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,
cyano,
nitro,
alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl, and

$-N_3$; and

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y'-R_4$, and

$-X'-R_5$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, and heteroarylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, or heteroarylene, and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

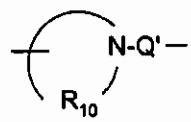
$-O-C(O)-O-$,

$-N(R_8)-Q'-$,

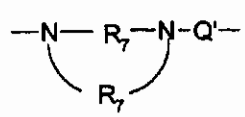
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

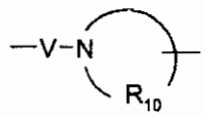
$-C(R_6)-N(OR_9)-$,



,



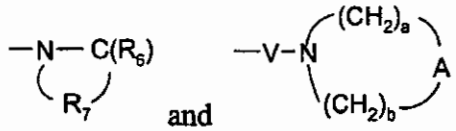
, and



,

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, and alkylheteroarylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, and alkylheteroarylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, and alkynyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is a C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q' is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, and $-S(O)_2-N(R_8)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or R_A and R_B taken together form either a fused aryl ring that is unsubstituted or substituted by one or more R groups, or a fused 5 to 7 membered saturated ring that is unsubstituted or substituted by one or more R_a groups;

R is selected from the group consisting of:

fluoro,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

R_a is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

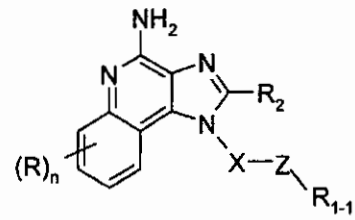
alkoxy,

alkylthio, and

$-N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.

In one embodiment, there is provided a compound of the Formula (I-2):



I-2

wherein:

X is alkylene optionally interrupted by one or more -O- groups;

n is an integer from 0 to 4;

Z is -C(O)-, -C(O)O-, or $-C(-Q-R_{1-3})_2-$;

R_{1-1} is selected from the group consisting of:

hydrogen,

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

$-NH-SO_2-R_{1-4}$,

$-NH-C(O)-R_{1-4}$,

-NH-C(O)-NH_2,

-NH-C(O)-NH-R_{1-4}, and

-N_3;

with the proviso that if Z is -C(O)-, then R_{1-1} may also be -$N(CH_3)(OCH_3)$;

with the further proviso that if Z is -C(O)O-, then R_{1-1} is not hydrogen;

with the further proviso that if Z is -C(O)O-, then X does not include -O- groups;

Q is O or S;

R_{1-3} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl; and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

-NH-SO_2-R_{1-4},

-NH-C(O)-R_{1-4},

-NH-C(O)-NH_2,

-NH-C(O)-NH-R_{1-4}, and

$-N_3$;

or the R_{1-3} groups can join together to form a ring system comprising a saturated or unsaturated 5-, 6-, or 7-membered ring;

R_{1-4} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl, and

$-N_3$; and

R is selected from the group consisting of:

fluoro,

alkyl,

haloalkyl,

alkoxy, and

$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y'-R_4$, and

$-X'-R_5$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, and heteroarylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, or heteroarylene, and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

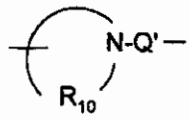
$-O-C(O)-O-$,

$-N(R_8)-Q'-$,

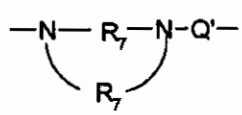
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

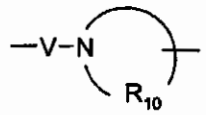
$-C(R_6)-N(OR_9)-$,



,



, and

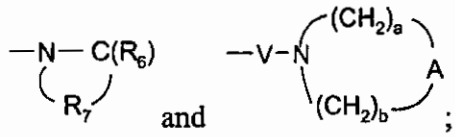


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, and alkylheteroarylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, and alkylheteroarylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy,

arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, and alkynyl, oxo;

R_5 is selected from the group consisting of:



and ;

R_6 is selected from the group consisting of =O and =S;

R_7 is a C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

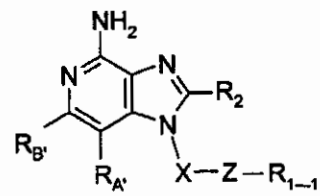
Q' is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, and $-S(O)_2-N(R_8)$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound of the Formula (I-3):



I-3

wherein:

X is alkylene optionally interrupted by one or more -O- groups;

Z is -C(O)-, -C(O)O-, or -C(-Q-R_{1-3})$_2$-;

R_{1-1} is selected from the group consisting of:

hydrogen,

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

-NH-SO_2-R_{1-4},

-NH-C(O)-R_{1-4},

-NH-C(O)-NH_2,

-NH-C(O)-NH-R_{1-4}, and

-N_3;

with the proviso that if Z is -C(O)-, then R_{1-1} may also be -N(CH_3)(OCH_3);

with the further proviso that if Z is -C(O)O-, then R_{1-1} is not hydrogen;

with the further proviso that if Z is -C(O)O-, then X does not include -O- groups;

Q is O or S;

R_{1-3} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

$-NH-SO_2-R_{1-4}$,

$-NH-C(O)-R_{1-4}$,

$-NH-C(O)-NH_2$,

$-NH-C(O)-NH-R_{1-4}$, and

$-N_3$;

or the R_{1-3} groups can join together to form a ring system comprising a saturated or unsaturated 5-, 6-, or 7-membered ring;

R_{1-4} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl, and

$-N_3$; and

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y'-R_4$, and

$-X'-R_5$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, and heteroarylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, or heteroarylene, and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

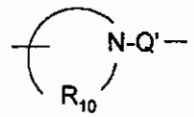
$-O-C(O)-O-$,

$-N(R_8)-Q'-$,

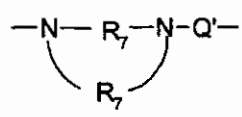
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

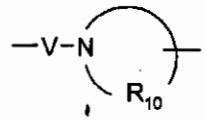
$-C(R_6)-N(OR_9)-$,



,



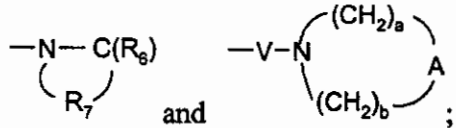
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, and alkylheteroarylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, and alkylheteroarylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, and alkynyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is a C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q' is selected from the group consisting of a bond, $-C(R_6)-$,

$-C(R_6)-C(R_6)-$, $-S(O)_2-$, and $-S(O)_2-N(R_8)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

$R_{A'}$ and $R_{B'}$ are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

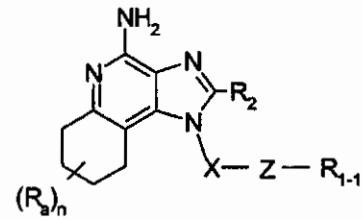
alkoxy,

alkylthio, and

$-N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound of the Formula (I-4):



(I-4)

wherein:

X is alkylene optionally interrupted by one or more -O- groups;

n is an integer from 0 to 4;

Z is $-C(O)-$, $-C(O)O-$, or $-C(-Q-R_{1-3})_2-$;

R_{1-1} is selected from the group consisting of:

hydrogen,

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

$-NH-SO_2-R_{1-4}$,

$-NH-C(O)-R_{1-4}$,

$-NH-C(O)-NH_2$,

$-NH-C(O)-NH-R_{1-4}$, and

$-N_3$;

with the proviso that if Z is -C(O)-, then R_{1-1} may also be $-N(CH_3)(OCH_3)$;

with the further proviso that if Z is -C(O)O-, then R_{1-1} is not hydrogen;

with the further proviso that if Z is -C(O)O-, then X does not include -O- groups;

Q is O or S;

R_{1-3} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,
cyano,
nitro,
alkoxy,
dialkylamino,
alkylthio,
haloalkyl,
haloalkoxy,
alkyl,
-NH-SO_2-R_{1-4},
-NH-C(O)-R_{1-4},
-NH-C(O)-NH_2,
-NH-C(O)-NH-R_{1-4}, and
-N_3;

or the R_{1-3} groups can join together to form a ring system comprising a saturated or unsaturated 5-, 6-, or 7-membered ring;

R_{1-4} is selected from the group consisting of:

alkyl,
aryl,
alkylene-aryl,
heteroaryl,
alkylene-heteroaryl, and
alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,
cyano,
nitro,
alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl, and

$-N_3$; and

R_a is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y'-R_4$, and

$-X'-R_5$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, and heteroarylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, or heteroarylene, and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

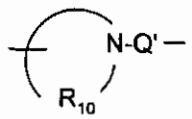
$-O-C(O)-O-$,

$-N(R_8)-Q'-$,

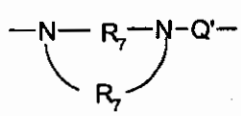
-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

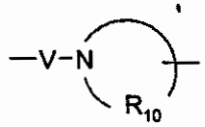
-$C(R_6)$-$N(OR_9)$-,



,



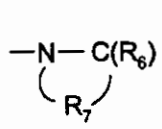
, and



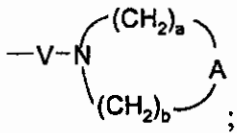
;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, and alkylheteroarylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, and alkylheteroarylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, and alkynyl, oxo;

R_5 is selected from the group consisting of:



and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is a C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, -CH_2-, and -$N(R_4)$-;

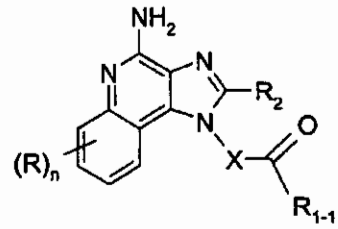
Q' is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, and -$S(O)_2$-$N(R_8)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, and -$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound of the Formula (Ia):



Ia

wherein:

X is alkylene optionally interrupted by one or more -O- groups;

n is an integer from 0 to 4;

R_{1-1} is selected from the group consisting of:

hydrogen,

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl,

-$N(CH_3)(OCH_3)$, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,
nitro,
alkoxy,
dialkylamino,
alkylthio,
haloalkyl,
haloalkoxy,
alkyl,
-NH-SO_2-R_{1-4},
-NH-C(O)-R_{1-4},
-NH-C(O)-NH_2,
-NH-C(O)-NH-R_{1-4}, and
-N_3;

R_{1-4} is selected from the group consisting of:

alkyl,
aryl,
alkylene-aryl,
heteroaryl,
alkylene-heteroaryl, and
alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,
cyano,
nitro,
alkoxy,
dialkylamino,
alkylthio,
haloalkyl,
haloalkoxy,
alkyl, and
-N_3;

R is selected from the group consisting of:

fluoro,

alkyl,

haloalkyl,

alkoxy, and

$N(R_9)_2$; and

R_2 is selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

heteroaryl,

heterocyclyl,

alkylene-Y-alkyl,

alkylene-Y-alkenyl,

alkylene-Y-aryl, and

alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

hydroxy,

halogen,

$-N(R_3)_2$,

$-C(O)-C_{1-10}$alkyl,

$-C(O)-O-C_{1-10}$alkyl,

$-N(R_3)-C(O)-C_{1-10}$alkyl,

$-N_3$,

aryl,

heteroaryl,

heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

wherein:

Y is –O– or $-S(O)_{0-2}-$; and

R_3 is selected from the group consisting of:

hydrogen,

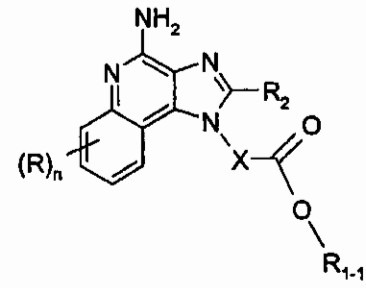
C_{1-10}alkyl, and

C_{2-10}alkenyl, and

R_9 is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound of the Formula (Ib):



Ib

wherein:

X is alkylene;

n is an integer from 0 to 4;

R_{1-1} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

-NH-SO_2-R_{1-4},

-NH-C(O)-R_{1-4},

-NH-C(O)-NH_2,

-NH-C(O)-NH-R_{1-4}, and

-N_3;

R_{1-4} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl, and

-N_3;

R is selected from the group consisting of:

fluoro,

alkyl,

alkoxy,

haloalkyl, and

$-N(R_9)_2$, and

R_2 is selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

heteroaryl,

heterocyclyl,

alkylene-Y-alkyl,

alkylene-Y-alkenyl,

alkylene-Y-aryl, and

alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

hydroxy,

halogen,

$-N(R_3)_2$,

$-C(O)-C_{1-10}$alkyl,

$-C(O)-O-C_{1-10}$alkyl,

$-N(R_3)-C(O)-C_{1-10}$alkyl,

$-N_3$,

aryl,

heteroaryl,

heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

wherein:

Y is –O– or $-S(O)_{0-2}-$; and

R_3 is selected from the group consisting of:

hydrogen,

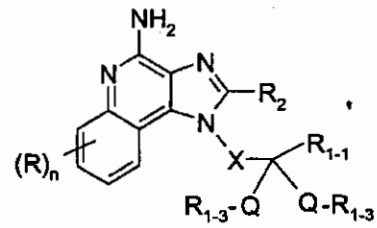
C_{1-10}alkyl, and

C_{2-10}alkenyl; and

R_9 is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides a compound of the Formula (Id):



Id

wherein:

X is alkylene optionally interrupted by one or more -O- groups;

n is an integer from 0 to 4;

R_{1-1} is selected from the group consisting of:

hydrogen,

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

-NH-SO_2-R_{1-4},

-NH-C(O)-R_{1-4},

-NH-C(O)-NH_2,

-NH-C(O)-NH-R_{1-4}, and

-N_3;

Q is O or S;

R_{1-3} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

-NH-SO_2-R_{1-4},

-NH-C(O)-R_{1-4},

-NH-C(O)-NH_2,

-NH-C(O)-NH-R_{1-4}, and

-N_3;

or the R_{1-3} groups can join together to form a ring system comprising a saturated or unsaturated 5-, 6-, or 7-membered ring;

R_{1-4} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl, and

$-N_3$;

R is selected from the group consisting of:

fluoro,

alkyl,

alkoxy,

haloalkyl, and

$-N(R_9)_2$, and

R_2 is selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

heteroaryl,

heterocyclyl,

alkylene-Y-alkyl,

alkylene-Y-alkenyl,

alkylene-Y-aryl, and

alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

hydroxy,

halogen,

$-N(R_3)_2$,

$-C(O)-C_{1-10}$alkyl,

$-C(O)-O-C_{1-10}$alkyl,

$-N(R_3)-C(O)-C_{1-10}$alkyl,

$-N_3$,

aryl,

heteroaryl,

heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

wherein:

Y is –O– or $-S(O)_{0-2}-$; and

R_3 is selected from the group consisting of:

hydrogen,

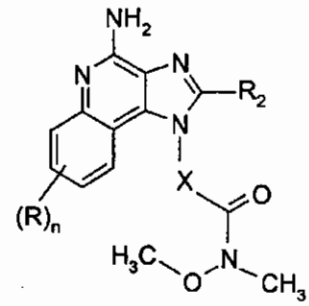
C_{1-10}alkyl, and

C_{2-10}alkenyl; and

R_9 is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound of the Formula (Ie):



Ie

wherein:

X is alkylene optionally interrupted by one or more -O- groups;

n is an integer from 0 to 4;

R is selected from the group consisting of:

fluoro,

alkyl,

alkoxy,

haloalkyl, and

$-N(R_9)_2$, and

R_2 is selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

heteroaryl,

heterocyclyl,

alkylene-Y-alkyl,

alkylene-Y-alkenyl,

alkylene-Y-aryl, and

alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

hydroxy,

halogen,

-$N(R_3)_2$,

-C(O)-C_{1-10}alkyl,

-C(O)-O-C_{1-10}alkyl,

-$N(R_3)$-C(O)-C_{1-10}alkyl,

-N_3,

aryl,

heteroaryl,

heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

wherein:

Y is –O– or –$S(O)_{0-2}$-; and

R_3 is selected from the group consisting of:

hydrogen,

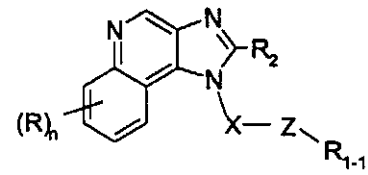
C_{1-10}alkyl, and

C_{2-10}alkenyl; and

R_9 is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound of the Formula (II):



II

wherein:

X is alkylene optionally interrupted by one or more -O- groups;

n is an integer from 0 to 4;

Z is -C(O)-, -C(O)O-, or -$C(-Q-R_{1-3})_2$-;

R_{1-1} is selected from the group consisting of:

hydrogen,

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

$-NH-SO_2-R_{1-4}$,

$-NH-C(O)-R_{1-4}$,

$-NH-C(O)-NH_2$,

$-NH-C(O)-NH-R_{1-4}$, and

$-N_3$;

with the proviso that if Z is -C(O)-, then R_{1-1} may also be $-N(CH_3)(OCH_3)$;

with the further proviso that if Z is -C(O)O-, then R_{1-1} is not hydrogen;

with the further proviso that if Z is -C(O)O-, then X does not include -O- groups;

Q is O or S;

R_{1-3} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

-NH-SO_2-R_{1-4},

-NH-C(O)-R_{1-4},

-NH-C(O)-NH_2,

-NH-C(O)-NH-R_{1-4}, and

-N_3;

or the R_{1-3} groups can join together to form a ring system comprising a saturated or unsaturated 5-, 6-, or 7-membered ring;

R_{1-4} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl, and

$-N_3$;

R is selected from the group consisting of:

fluoro,

alkyl,

alkoxy,

haloalkyl, and

$-N(R_9)_2$;

R_2 is selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

heteroaryl,

heterocyclyl,

alkylene-Y-alkyl,

alkylene-Y-alkenyl,

alkylene-Y-aryl, and

alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

hydroxy,

halogen,

$-N(R_3)_2$,

$-C(O)-C_{1-10}$alkyl,

$-C(O)-O-C_{1-10}$alkyl,

-$N(R_3)$-C(O)-C_{1-10}alkyl,

-N_3,

aryl,

heteroaryl,

heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

wherein:

Y is –O– or –$S(O)_{0-2}$–; and

R_3 is selected from the group consisting of:

hydrogen,

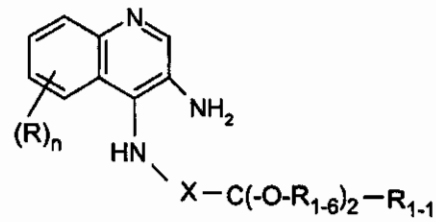
C_{1-10}alkyl, and

C_{2-10}alkenyl, and

R_9 is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound of the Formula (III):



III

wherein:

X is alkylene optionally interrupted by one or more -O- groups;

n is an integer from 0 to 4;

R_{1-1} is selected from the group consisting of:

hydrogen,

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

$-NH-SO_2-R_{1-4}$,

$-NH-C(O)-R_{1-4}$,

$-NH-C(O)-NH_2$,

$-NH-C(O)-NH-R_{1-4}$, and

$-N_3$;

R_{1-6} is alkyl or the R_{1-6} groups can join together to form a ring system comprising a saturated 5- or 6-membered ring;

R_{1-4} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl, and

$-N_3$;

R is selected from the group consisting of:

fluoro,

alkyl,

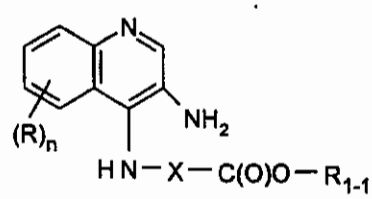
alkoxy,

haloalkyl, and

$-N(R_9)_2$; and

R_9 is selected from the group consisting of hydrogen and alkyl; or a pharmaceutically acceptable salt thereof.

In another embodiment, there is provided a compound of the Formula (IV):



IV

wherein:

X is alkylene;

n is an integer from 0 to 4;

R_{1-1} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,
cyano,
nitro,
alkoxy,
dialkylamino,
alkylthio,
haloalkyl,
haloalkoxy,
alkyl,
-NH-SO_2-R_{1-4},
-NH-C(O)-R_{1-4},
-NH-C(O)-NH_2,
-NH-C(O)-NH-R_{1-4}, and
-N_3;

R_{1-4} is selected from the group consisting of:

alkyl,
aryl,
alkylene-aryl,
heteroaryl,
alkylene-heteroaryl, and
alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,
cyano,
nitro,
alkoxy,
dialkylamino,
alkylthio,

haloalkyl,

haloalkoxy,

alkyl, and

$-N_3$;

R is selected from the group consisting of:

fluoro,

alkyl,

alkoxy,

haloalkyl, and

$-N(R_9)_2$; and

R_9 is selected from the group consisting of hydrogen and alkyl;

or a pharmaceutically acceptable salt thereof.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "alkenylene," and "alkynylene" are the divalent forms of the "alkyl," "alkenyl," and "alkynyl" groups defined above. The terms, "alkylenyl," "alkenylenyl," and "alkynylenyl" are use when "alkylene," "alkenylene," and "alkynylene," respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other

groups that include the prefix "halo-." Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, and the like. When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. The terms, "arylenyl," "heteroarylenyl," and "heterocyclylenyl" are used when "arylene," "heteroarylene," and "heterocyclylene," respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula $-N(R_3)_2$ each R_3 group is independently selected. In a further example, when more than one R_{1-3} group is present and each R_{1-3} group contains one or more R_{1-4} groups, then each R_{1-3} group is independently selected, and each R_{1-4} group is independently selected.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

For any of the compounds presented herein, each one of the following variables (e.g., Z, X, Y, Y', R_A, R_B, R_2, R_{1-1} , Q, R_{1-3}, n, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments, A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}$-, $-CH_2$-, and $-N(R_4)$-.

For certain embodiments, Q is -O- or -S-. For certain embodiments, Q is -O-.

For certain embodiments, Q' is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, and $-S(O)_2-N(R_8)$-.

For certain embodiments, V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, and $-S(O)_2$-.

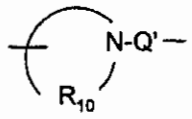
For certain embodiments, X is alkylene optionally interrupted by one or more -O- groups. For certain embodiments, X is a C_{1-6} alkylene or

$-(CH_2)_{2-4}-O-(CH_2)_{1-3}-$. For certain embodiments, X is alkylene. For certain embodiments, X is selected from the group consisting of $-(CH_2)_{1-6}-$, $-CH_2-C(CH_3)_2-$, $-(CH_2)_2-O-CH_2-$, $-(CH_2)_3-O-CH_2-$, and $-CH_2-C(CH_3)_2-CH_2-$. For certain embodiments, X is selected from the group consisting of $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $-CH_2C(CH_3)_2-$, $-CH_2C(CH_3)_2CH_2-$, and $-(CH_2)_2OCH_2-$.

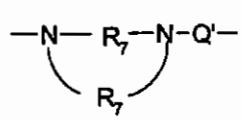
For certain embodiments, X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, and heteroarylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, or heteroarylene, and optionally interrupted by one or more -O- groups.

For certain embodiments, Y is -O- or $-S(O)_{0-2}-$.

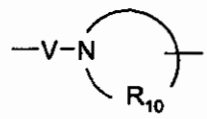
For certain embodiments, Y' is selected from the group consisting of $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q'-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$,



,



, and



.

For certain embodiments, Z is -C(O)-, -C(O)O-, or $-C(-Q-R_{1-3})_2-$. For certain embodiments, Z is -C(O)-. For certain embodiments, Z is -C(O)O-. For certain embodiments, Z is $-C(-Q-R_{1-3})_2-$.

For certain embodiments, R is selected from the group consisting of fluoro, alkyl, alkoxy, haloalkyl, and $-N(R_9)_2$. In certain of these embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_A and R_B are each independently selected from the group consisting of: hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. For certain embodiments, R_A and R_B are each independently selected from the group consisting of hydrogen and alkyl. For certain embodiments, R_A and R_B are both methyl.

For certain alternative embodiments, R_A and R_B form a fused aryl ring that is unsubstituted or substituted by one or more R groups.

For certain alternative embodiments, R_A and R_B form a fused 5 to 7 membered saturated ring, which is unsubstituted or substituted by one or more R_a groups.

For certain embodiments, R_a is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$.

For certain embodiments, $R_{A'}$ and $R_{B'}$ are each independently selected from the group consisting of: hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. For certain embodiments, $R_{A'}$ and $R_{B'}$ are independently selected from the group consisting of hydrogen and alkyl. For certain embodiments, $R_{A'}$ and $R_{B'}$ are both methyl.

For certain embodiments, R_{1-1} is selected from the group consisting of hydrogen, alkyl, aryl, alkylene-aryl, heteroaryl, alkylene-heteroaryl, and alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of halogen, cyano, nitro, alkoxy, dialkylamino, alkylthio, haloalkyl, haloalkoxy, alkyl, $-NH-SO_2-R_{1-4}$, $-NH-C(O)-R_{1-4}$, $-NH-C(O)-NH_2$, $-NH-C(O)-NH-R_{1-4}$, and $-N_3$.

For certain embodiments, R_{1-1} is selected from the group consisting of aryl, alkyl, and $-N(CH_3)OCH_3$. For certain embodiments, R_{1-1} is selected from the group consisting of aryl, alkyl, and hydrogen. For certain embodiments, R_{1-1} is selected from the group consisting of alkyl and aryl. For certain embodiments, R_{1-1} is selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, cyclopentyl, *n*-hexyl, cyclohexyl, phenyl, 4-chlorophenyl and 2,4-dichlorophenyl.

For certain embodiments, R_{1-3} is selected from the group consisting of alkyl, aryl, alkylene-aryl, heteroaryl, alkylene-heteroaryl, and alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of halogen, cyano, nitro, alkoxy, dialkylamino, alkylthio, haloalkyl, haloalkoxy, alkyl, $-NH-SO_2-R_{1-4}$, $-NH-C(O)-R_{1-4}$, $-NH-C(O)-NH_2$, $-NH-C(O)-NH-R_{1-4}$, and $-N_3$. For certain embodiments, the R_{1-3} groups can join together to form a ring system. The ring system includes a 5-, 6-, or 7-membered ring. One of skill in the art would understand that the size and components of the ring system are not limiting as

long as they do not destroy the immunomodulator activity of the compound (i.e., it is non-interfering). Typically, this means that the 5-, 6-, or 7-membered ring is unsubstituted or is optionally fused to one or two saturated or unsaturated 5-, 6-, or 7-membered rings or is substituted by one or more substituents selected from the group consisting of aryl, heteroaryl, halogen, haloalkyl, alkylene-O-alkyl, and substituted aryl. For certain embodiments, R_{1-3} is alkyl, or the R_{1-3} groups join to form a 5-membered ring.

For certain embodiments, R_{1-4} is selected from the group consisting of alkyl, aryl, alkylene-aryl, heteroaryl, alkylene-heteroaryl, and alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of halogen, cyano, nitro, alkoxy, dialkylamino, alkylthio, haloalkyl, haloalkoxy, alkyl, and $-N_3$.

For certain embodiments, R_{1-6} is alkyl or the R_{1-6} groups can join together to form a ring system comprising a saturated 5- or 6-membered ring.

For certain embodiments, R_2 is selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, alkylene-Y-alkyl, alkylene-Y- alkenyl, alkylene-Y-aryl, and alkyl or alkenyl substituted by one or more substituents selected from the group consisting of hydroxy, halogen, $-N(R_3)_2$, $-C(O)-C_{1-10}$alkyl, $-C(O)-O-C_{1-10}$alkyl, $-N(R_3)-C(O)-C_{1-10}$alkyl, $-N_3$, aryl, heteroaryl, heterocyclyl, -C(O)-aryl, and -C(O)-heteroaryl. In certain of these embodiments,Y is –O– or $-S(O)_{0-2}-$; and R_3 is selected from the group consisting of hydrogen, C_{1-10}alkyl, and C_{2-10}alkenyl.

For certain embodiments, R_2 is selected from the group consisting of hydrogen, alkyl, hydroxyalkyl, and alkoxyalkyl. For certain embodiments, R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkyl. For certain embodiments, R_2 is selected from the group consisting of hydrogen, hydroxymethyl, methyl, ethyl, *n*-propyl, *n*-butyl, ethoxymethyl, and 2-methoxyethyl.

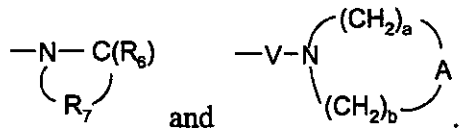
For certain embodiments, particularly embodiments of Formula I-1, R_2 is selected from the group consisting of: $-R_4$, $-X'-R_4$, $-X'-Y'-R_4$, and $-X'-R_5$.

For certain embodiments, R_3 is selected from the group consisting of hydrogen, C_{1-10}alkyl, and C_{2-10}alkenyl.

For certain embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, and alkylheteroarylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, and alkylheteroarylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, and alkynyl, oxo.

For certain embodiments, R_4 is alkyl which may be unsubstituted or substituted by hydroxy or alkoxy.

For certain embodiments, R_5 is selected from the group consisting of:



and

.

For certain embodiments, R_6 is selected from the group consisting of =O and =S.

For certain embodiments, R_7 is a C_{2-7} alkylene.

For certain embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl. For certain embodiments, R_8 is H or CH_3.

For certain embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_{10} is C_{3-8} alkylene.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

For certain embodiments, n is an integer fom 0 to 4. For certain embodiments, n is 0.

For certain embodiments, particularly embodiments of Formula (I-1): if Z is -C(O)-, then R_{1-1} may also be -N(CH_3)(OCH_3); if Z is -C(O)O-, then R_{1-1} is not hydrogen; and if Z is -C(O)O-, then X does not include -O- groups.

For certain embodiments, particularly embodiments of Formula (I-2): if Z is -C(O)-, then R_{1-1} may also be -N(CH_3)(OCH_3); if Z is -C(O)O-, then R_{1-1} is not hydrogen; and if Z is -C(O)O-, then X does not include -O- groups.
wherein:

For certain embodiments, particularly embodiments of Formula (I-3): if Z is -C(O)-, then R_{1-1} may also be -N(CH_3)(OCH_3); if Z is -C(O)O-, then R_{1-1} is not hydrogen; and if Z is -C(O)O-, then X does not include -O- groups.

For certain embodiments, particularly embodiments of Formula (I-4): if Z is -C(O)-, then R_{1-1} may also be -N(CH_3)(OCH_3); if Z is -C(O)O-, then R_{1-1} is not hydrogen; and if Z is -C(O)O-, then X does not include -O- groups.

For certain embodiments, particularly embodiments of Formula (II): if Z is -C(O)-, then R_{1-1} may also be -N(CH_3)(OCH_3); if Z is -C(O)O-, then R_{1-1} is not hydrogen; and if Z is -C(O)O-, then X does not include -O- groups.

For certain embodiments, Z is -C(O)- and preferably R_{1-1} is selected from the group consisting of aryl, alkyl, and -N(CH_3)OCH_3. For certain other embodiments, R_{1-1} is selected from the group consisting of methyl, ethyl, *n*-propyl, isopropyl, cyclopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, cyclopentyl, *n*-hexyl, cyclohexyl, phenyl, 4-chlorophenyl and 2,4-dichlorophenyl.

For certain embodiments, Z is -C(O)O- and preferably R_{1-1} is selected from the group consisting of alkyl and aryl.

For certain embodiments, Z is -C(-Q-R_{1-3})$_2$- and preferably R_{1-1} is selected from the group consisting of alkyl, aryl, and hydrogen. For certain of these embodiments, Q is -O-.

For certain embodiments, Z is -C(-Q-R_{1-3})$_2$- and preferably the 5-, 6-, or 7-membered ring formed by the joining of the R_{1-3} groups is optionally fused to one or two saturated or unsaturated 5-, 6-, or 7-membered rings or is substituted by one or more substituents selected from the group consisting of aryl,

heteroaryl, halogen, haloalkyl, alkylene-O-alkyl, and substituted aryl. For certain of these embodiments, R_{1-3} is alkyl, or the R_{1-3} groups join to form a 5-membered ring.

Preparation of the Compounds

Compounds of the invention can be prepared according to the routes shown herein where R_{1-1}, R_{1-3}, R_{1-6}, R_2, R, Q, X, and n are as defined above except that R_{1-1} is other than $-N(CH_3)(OCH_3)$. In Reaction Schemes 1a, 1b, 2b, 4, and 6, R is not hydroxy, R_{1-1} is not hydrogen, and R_{1-1} and R_2 do not contain substituents that one skilled in the art would recognize as being reactive with Grignard reagents. These substituents include, for example, ketone, ester, hydroxy, and cyano (i.e., nitrile) groups as well as groups containing -NH-.

Ketones of the present invention of Formula Ia can be prepared by one of two routes where the ketone group is derived from an alcohol intermediate, as shown in Reaction Schemes 1a and 1b. Alternatively, ketones of the present invention can be prepared by routes where the ketone group is derived from a ketal or acetal intermediate as shown in Reaction Schemes 2a and 2b. In another alternative embodiment, they can be prepared by a route where the ketone group is derived from an ester intermediate, as shown in Reaction Scheme 4.

Ketals or acetals of the present invention of Formula XXI can be prepared by the route shown in Reaction Scheme 2a, which also outlines the preparation of compounds of Formula III. Ketals or acetals of the present invention of Formula Id can be prepared by the route shown in Reaction Scheme 3.

Esters of the present invention of Formula Ib can be prepared as shown in Reaction Scheme 5 starting with a compound of Formula XXV, the preparation of which is shown in Reaction Scheme 4.

Weinreb amides of the present invention of Formula Ie can be prepared by a route where the amide group is derived from an ester intermediate, as shown in Reaction Scheme 4.

Reaction Scheme 1a

In step (1) of Reaction Scheme 1a, a 4-chloro-3-nitroquinoline of Formula VI is treated with an amino alcohol in the presence of triethylamine in a suitable solvent such as dichloromethane, wherein the amino alcohol is of the general formula H_2N-X-CH_2-OH and X is as defined herein. Numerous amino alcohols of the formula H_2N-X-CH_2-OH are commercially available; others can be readily synthesized using well-known methods. Many 4-chloro-3-nitroquinolines of Formula VI are known or can be prepared using known synthetic methods, see for example, U.S. Patent Nos. 4,689,338; 5,175,296; 5,367,076; and 5,389,640; and the references cited therein.

The resultant compound of Formula VII can be reduced in step (2) of Reaction Scheme 1a using a variety of methods to provide a quinoline-3,4-diamine of Formula VIII. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as toluene or ethanol. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

Alternatively, step (2) can be carried out using a one- or two-phase sodium dithionite reduction. The reaction is conveniently carried out using the conditions described by Park, K. K.; Oh, C. H.; and Joung, W. K.; *Tetrahedron Lett.* **1993**, *34*, 7445-7446 by adding sodium dithionite to a compound of Formula VII in a mixture of dichloromethane and water at ambient temperature in the presence of potassium carbonate and ethyl viologen dibromide. The product can be isolated using conventional methods.

In step (3) of Reaction Scheme Ia, a quinoline-3,4-diamine of Formula VIII is treated with a carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula IX. Suitable carboxylic acid equivalents include orthoesters of Formula R_2C(O-alkyl)$_3$, 1,1-dialkoxyalkyl alkanoates of Formula R_2C(O-alkyl)$_2$(O-C(O)-alkyl), and acid chlorides of Formula R_2C(O)Cl. The selection of the carboxylic acid equivalent is determined by the desired substituent at R_2. For example, triethyl orthoformate will provide a compound where R_2 is hydrogen, and trimethyl orthovalerate will provide a compound

where R_2 is a butyl group. The reaction is conveniently carried out by adding the carboxylic acid equivalent to a quinoline-3,4-diamine of Formula VIII in a suitable solvent such as toluene or xylenes. Optionally, catalytic pyridine hydrochloride or pyridium *p*-toluenesulfonate can be added. The reaction is carried out at a temperature high enough to drive off alcohol or water formed during the reaction. Conveniently, a Dean-Stark trap can be used to collect the volatiles.

Optionally, the alcohol group on the compound of Formula VII can be protected with a suitable alcohol protecting group prior to step (2), and this protecting group can be removed prior to step (4). Suitable protecting groups include the *tert*-butyldimethylsilyl group, which can be introduced and removed using conventional methods.

In step (4) of Reaction Scheme 1a, the alcohol-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula IX is oxidized to an aldehyde-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula X using conventional methods, for example, Swern conditions. The Swern oxidation is conveniently carried out by adding the compound of Formula IX followed by triethylamine to a mixture of oxalyl chloride and dimethylsulfoxide in a suitable solvent, such as dichloromethane. The reaction can be carried out at sub-ambient temperatures, such as -78°C, and the product can be isolated using conventional methods.

The aldehyde-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula X is then treated with a Grignard reagent in step (5) of Reaction Scheme 1a. The Grignard reagent is of the formula R_{1-1}MgHalide to form a compound of Formula XI. Several of these reagents are commercially available; others can be prepared using known synthetic methods. The reaction is conveniently carried out by adding a solution of the Grignard reagent to a solution of the compound of Formula X in a suitable solvent such as tetrahydrofuran. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

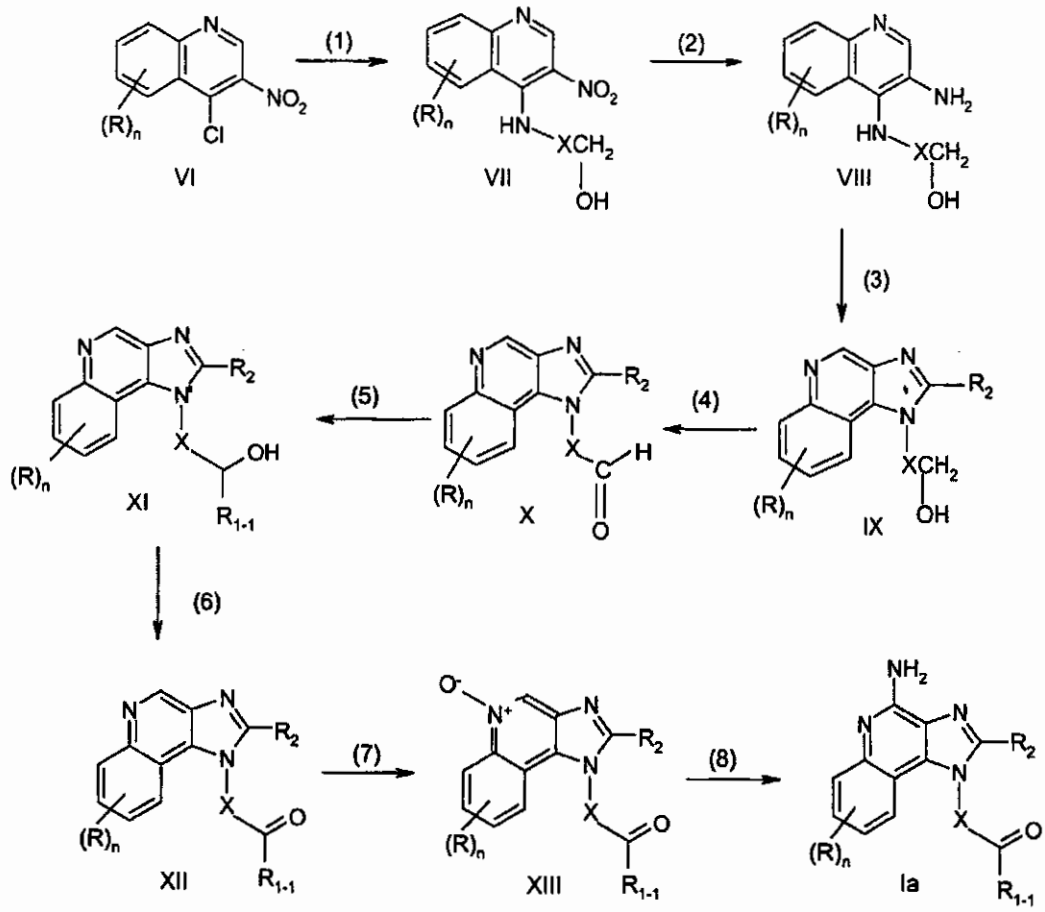
In step (6) of Reaction Scheme 1a, an alcohol-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XI is oxidized to a ketone of Formula XII

using conventional methods. The reaction is conveniently carried out under Swern conditions, described in step (4) above.

In step (7) of Reaction Scheme 1a, a ketone-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XII is oxidized to provide an *N*-oxide of Formula XIII using a conventional oxidizing agent capable of forming such compounds. For example, the reaction can be conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XII in a solvent, such as chloroform or dichloromethane, at ambient temperature.

In step (8) of Reaction Scheme 1a, the *N*-oxide of Formula XIII is aminated to provide a ketone-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula Ia. Step (8) involves the activation of an *N*-oxide of Formula XIII by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula XIII in a suitable solvent, such as dichloromethane or chloroform, and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature. The resultant ketone-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amines of Formula Ia or pharmaceutically acceptable salt thereof can be isolated from the reaction mixture using conventional methods.

Reaction Scheme 1a

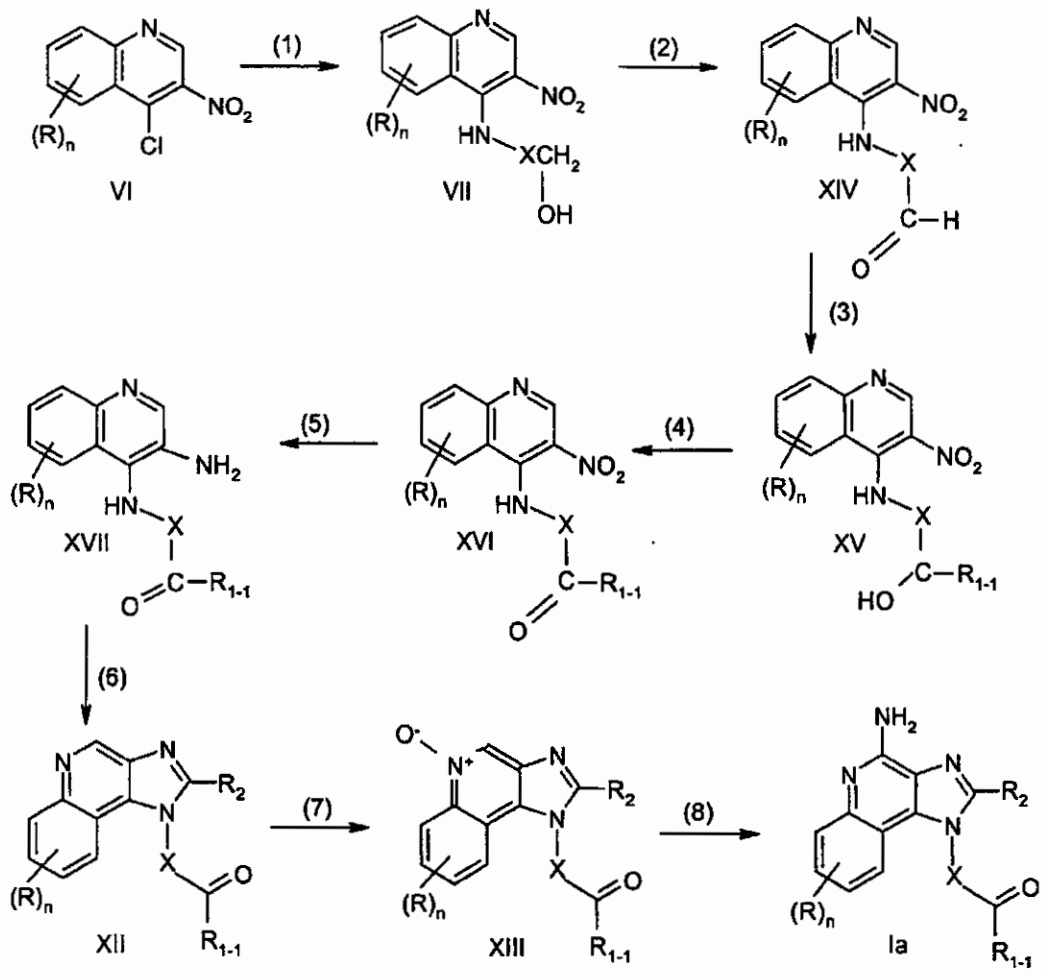


Reaction Scheme 1b

In Reaction Scheme 1b, the reactions are very similar to those of Reaction Scheme 1a but in a different order. In step (1) of Reaction Scheme 1b, a 4-chloro-3-nitroquinoline of Formula VI is treated with an amino alcohol as in step (1) of Reaction Scheme 1a. In step (2), the resultant compound of Formula VII is oxidized using conventional methods as in step (4) of Reaction Scheme 1a to form an aldehyde of Formula XIV. In step (3), the resultant aldehyde of Formula XIV is treated with a Grignard reagent as in step (5) of Reaction Scheme 1a to form a compound of Formula XV. In step (4), the compound of Formula XV is oxidized as in step (6) of Reaction Scheme 1a to form a compound of Formula XVI. In step (5), the compound of Formula XVI is reduced as in step (2) of Reaction Scheme 1a to form a ketone-substituted quinoline-3,4-diamine of Formula XVII. In step (6), the quinoline-3,4-diamine

of Formula XVII is cyclized using, for example, an ortho ester, as in step (3) in Reaction Scheme 1a to form a ketone-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XII. In step (7), the compound of Formula XII is oxidized to the *N*-oxide as in step (7) of Reaction Scheme 1a to form a compound of Formula XIII. In step (8), the *N*-oxide of Formula XIII can be aminated as in step (8) of Reaction Scheme 1a to provide the ketone-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula Ia.

Reaction Scheme 1b



Reaction Scheme 2a

Ketones of the invention of Formula Ia and ketals and acetals of the invention of Formula XXI can be prepared according to Reaction Scheme 2a. In step (1) of Reaction Scheme 2a, a 4-chloro-3-nitroquinoline of Formula VI is

reacted with a compound of the formula H_2N-X-C(R_{1-1})(O-R_{1-6})$_2$, such as an amino ketal of this formula, wherein R_{1-1} is methyl and R_{1-6} is ethylene, in the presence of triethylamine in a suitable solvent, such as chloroform or dichloromethane. Compounds of the formula H_2N-X-C(R_{1-1})(O-R_{1-6})$_2$ can be commercially obtained or readily synthesized using conventional methods. For example, see C.J. Stewart et al., *J. Liebigs Ann. der Chem.*, **1978**, 57-65 and PCT Publication WO 01/51486.

Ketals of Formula $H_2NCH_2C(CH_3)_2CH_2C(O\text{-}R_{1-6})_2CH_3$ can be prepared according to referenced methods by the reaction of nitromethane and mesityl oxide, conversion of the resulting ketone to a ketal, and reduction of the nitro group to an amine.

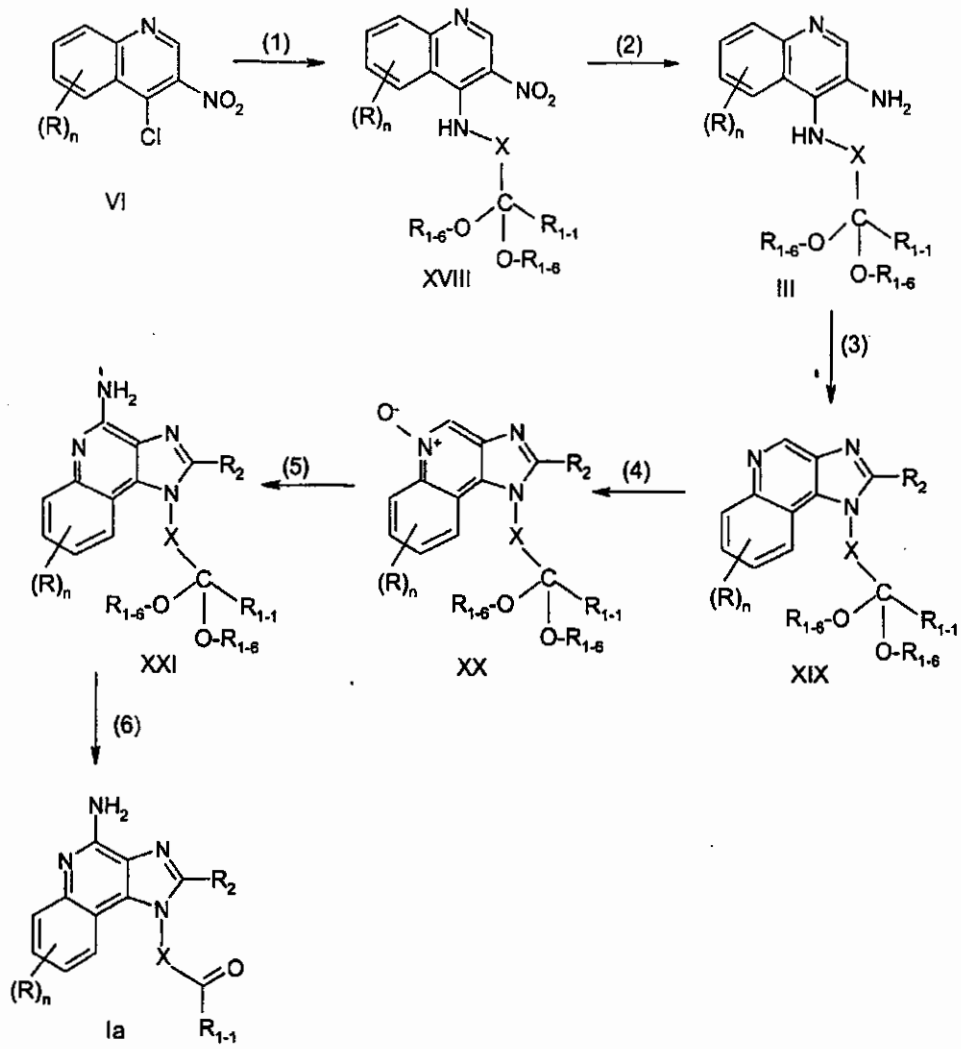
The resultant compound of Formula XVIII can be reduced using a variety of methods in step (2) of Reaction Scheme 2a to form a ketal- or acetal-substituted quinoline-3,4-diamine of Formula III. The reduction can be carried out as described for step (2) of Reaction Scheme 1a.

In step (3) of Reaction Scheme 2a, the quinoline-3,4-diamine of Formula III is treated with a carboxylic acid equivalent to form a ketal- or acetal-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XIX. The reaction can be carried out as described for step (3) of Reaction Scheme 1a.

In step (4) of Reaction Scheme 2a, the 1*H*-imidazo[4,5-*c*]quinoline of Formula XIX can be converted to the *N*-oxide of Formula XX using the method outlined in step (7) of Reaction Scheme 1a. In step (5), the *N*-oxide of Formula XX can be aminated to the compound (e.g., ketal) of Formula XXI (a subset of the compounds of Formula Id) as described in step (8) of Reaction Scheme 1a. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (6), compounds of Formula XXI can be converted to ketones of Formula Ia by acid-catalyzed hydrolysis. The reaction is conveniently carried out by adding a strong acid, such as hydrochloric acid, to a ketal of Formula XXI. The reaction may be carried out at ambient temperature in a suitable solvent such as water. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme 2a



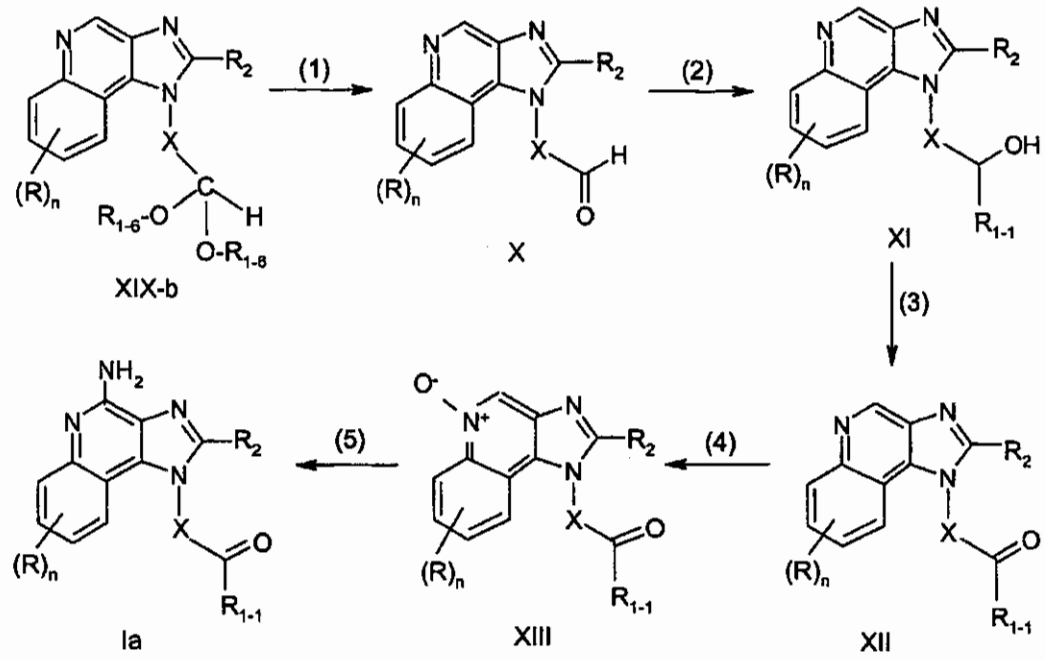
Reaction Scheme 2b

Compounds of Formula Ia can also be prepared according to Reaction Scheme 2b. In step (1) of Reaction Scheme 2b, an acetal of Formula XIX-b, which is a subset of Formula XIX where R_{1-1} is hydrogen, undergoes acid-catalyzed hydrolysis to provide an aldehyde of Formula X. The reaction can be carried out as described for step (6) of Reaction Scheme 2a.

In step (2) of Reaction Scheme 2b, an aldehyde of Formula X reacts with a Grignard reagent of Formula R_{1-1}MgHalide. The reaction can be carried out as described in step (5) of Reaction Scheme 1a to provide an alcohol of Formula XI.

In steps (3) through (5) of Reaction Scheme 2b, an alcohol of Formula XI is oxidized using conventional methods to a ketone-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XII, which is converted to a *N*-oxide of Formula XIII. The compound of Formula XIII is then aminated to provide a ketone-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula Ia. Steps (3), (4), and (5) of Reaction Scheme 2b can be carried out as described for steps (6), (7), and (8) of Reaction Scheme 1a.

Reaction Scheme 2b



Reaction Scheme 3

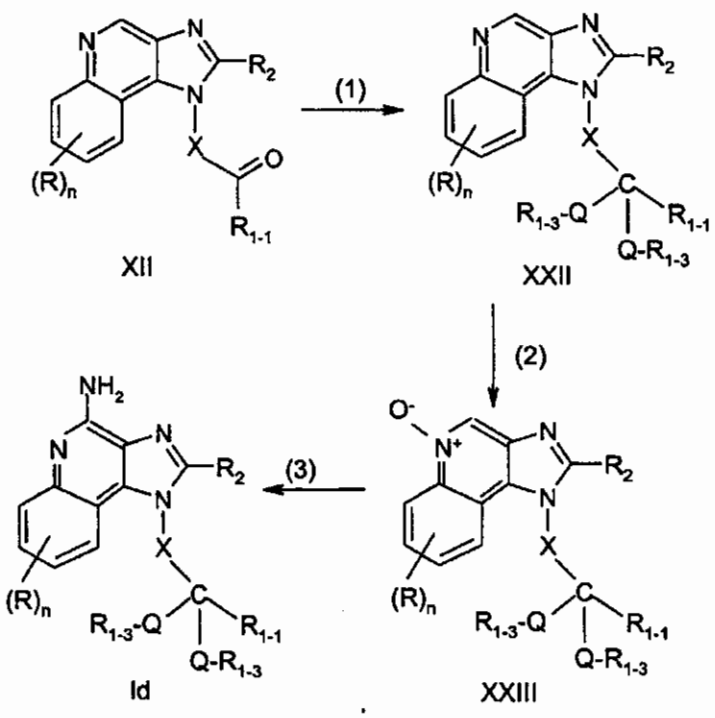
Ketals and acetals of the invention can be prepared according to Reaction Scheme 3. Step (1) of Reaction Scheme 3 involves the conversion of a ketone or aldehyde of Formula XII to a ketal or acetal of Formula XIX by reaction with a compound of Formula H-Q-R_{1-3} or H-Q-R_{1-3}-Q-H. The reaction can be carried out by treating a ketone or aldehyde of Formula XII with a compound of Formula H-Q-R_{1-3}-Q-H or two equivalents of a compound of Formula H-Q-R_{1-3} in the presence of an acid catalyst. Conditions for this reaction are well known to one skilled in the art. See, for example, Greene, T. W.; Wuts, P. G. M.

Protective Groups in Organic Synthesis; John Wiley & Sons, Inc.: New York, 2nd Ed, 1991, p. 178.

In step (2) of Reaction Scheme 3, a compound of Formula XXII is oxidized to a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXIII, which is then aminated to a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula Id. Steps (2) and (3) of Reaction Scheme 3 can be carried out as steps (7) and (8) of Reaction Scheme 1a. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Alternatively, ketones of Formula Ia can be converted to ketals of Formula Id by the reaction described in step (1) of Reaction Scheme 3.

Reaction Scheme 3



Reaction Scheme 4

Compounds of Formula Ia and Formula Ie can be prepared according to Reaction Scheme 4. In step (1) of Reaction Scheme 4, a 4-chloro-3-nitroquinoline of Formula VI is reacted with a compound of the formula H_2N-X-C(O)(O-R_{1-1}) - HCl to form a compound of Formula XXIV. This reaction is

conveniently carried out in the presence of triethylamine in a suitable solvent, such as dichloromethane. Compounds of the formula H_2N-X-C(O)(O- R_{1-1}) - HCl can be commercially obtained or readily synthesized using conventional methods. For example, the amino ester wherein R_{1-1} is ethyl and X is propylene or dodecylene can be synthesized according to the procedure of C. Temple et al., *J. Med. Chem.*, **1988**, *31*, 697-700.

In steps (2) and (3) of Reaction Scheme 4, a compound of Formula XXIV is reduced to form a quinoline-3,4-diamine of Formula IV, which can be cyclized with a carboxylic acid equivalent to form a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXV. Steps (2) and (3) of Reaction Scheme 4 can be carried out as described for steps (2) and (3) of Reaction Scheme 1a.

In step (4), the ester group of a 1*H*-imidazo[4,5-*c*]quinoline Formula XXV is converted to a Weinreb amide to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVI. The transformation can be carried out by base-promoted hydrolysis of the ester to form a carboxylic acid, conversion to an acid chloride using conventional methods, and finally treating the acid chloride with *N,O*-dimethylhydroxylamine hydrochloride to form a Weinreb amide of Formula XXVI. The base-promoted hydrolysis is conveniently carried out by adding sodium hydroxide to an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline Formula XXV in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods. The conversion of the resulting carboxylic acid to an acid chloride is conveniently carried out by slowly adding oxalyl chloride to a solution of the carboxylic acid in a suitable solvent such as dichloromethane. The reaction can be carried out at a sub-ambient temperature, such as 0°C. The resulting acid chloride can then be treated with *N,O*-dimethylhydroxylamine hydrochloride followed by triethylamine in a suitable solvent such as dichloromethane. The reaction can be run at ambient temperature, and the product of Formula XXVI can be isolated using conventional methods.

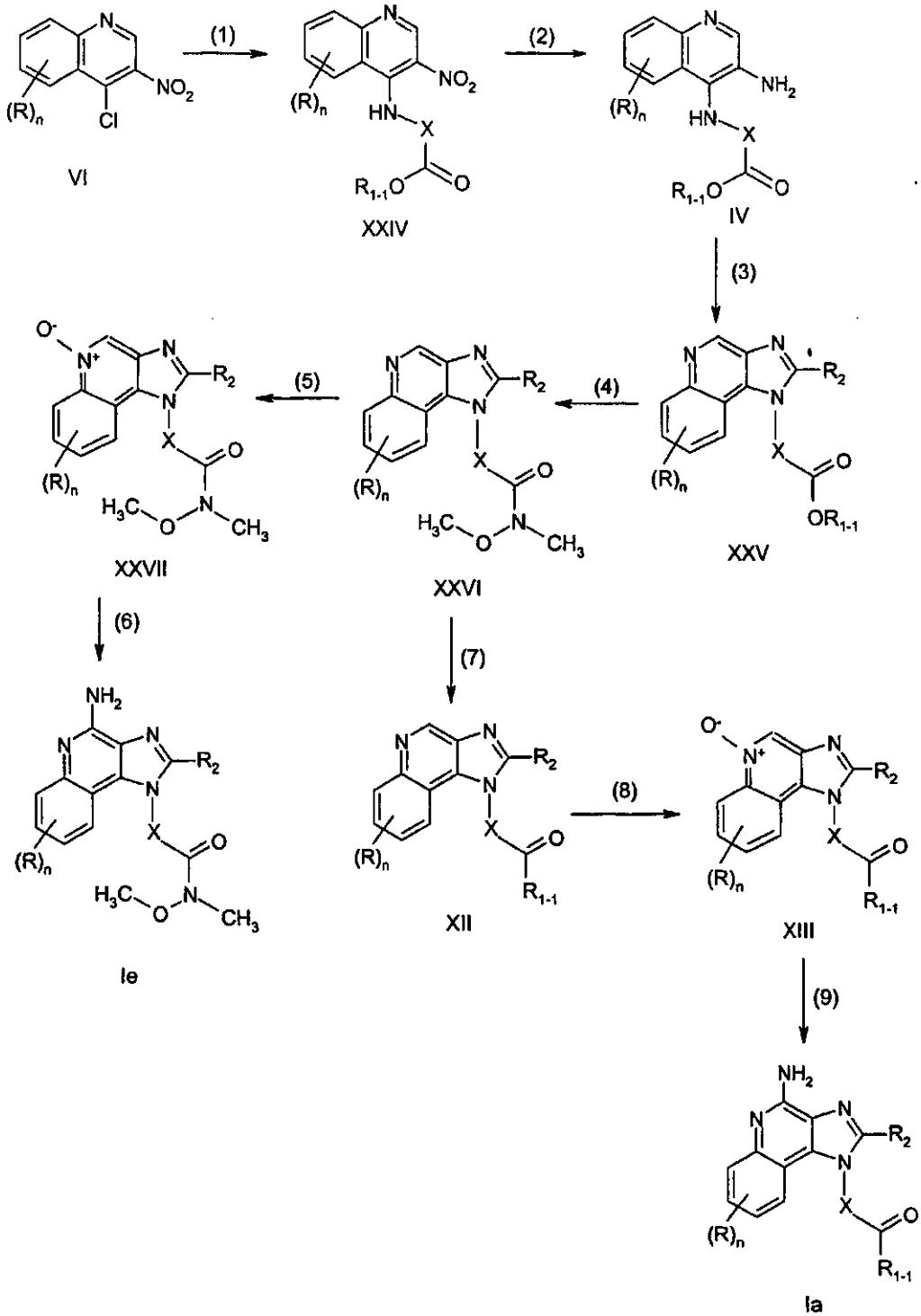
Alternatively, step (4) can be carried out in one step by treating an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline Formula XXV with an aluminum reagent made from trimethylaluminum and *N,O*-dimethylhydroxylamine

hydrochloride. The reaction is conveniently carried out by adding a solution of an ester-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XXV in a suitable solvent such as dichloromethane to a pre-reacted mixture of trimethylaluminum and *N*,*O*-dimethylhydroxylamine hydrochloride in a suitable solvent such as dichloromethane. The reaction can then be heated at an elevated temperature, for example, the reflux temperature of the solvent. The product can be isolated using conventional methods.

In steps (5) and (6) of Reaction Scheme 4, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVI is converted to a *N*-oxide of Formula XXVII, which is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula Ie. Steps (5) and (6) of Reaction Scheme 4 can be carried out as described for steps (7) and (8) of Reaction Scheme 1a. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Compounds of Formula Ia are available using an alternative route shown in Reaction Scheme 4 steps (7), (8), and (9). The Weinreb amide of Formula XXVI is treated with a Grignard reagent of Formula R_{1-1}MgHalide in step (7) to form a ketone of Formula XII. The Grignard reaction can be carried out as described in step (5) of Reaction Scheme 1a. In step (8), the ketone-substituted 1*H*-imidazo[4,5-*c*]quinoline of Formula XII is oxidized to an *N*-oxide of Formula XIII as described in step (7) of Reaction Scheme 1a. In step (9), the *N*-oxide of Formula XIII is aminated as described in step (8) of Reaction Scheme 1a to provide the ketone-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula Ia.

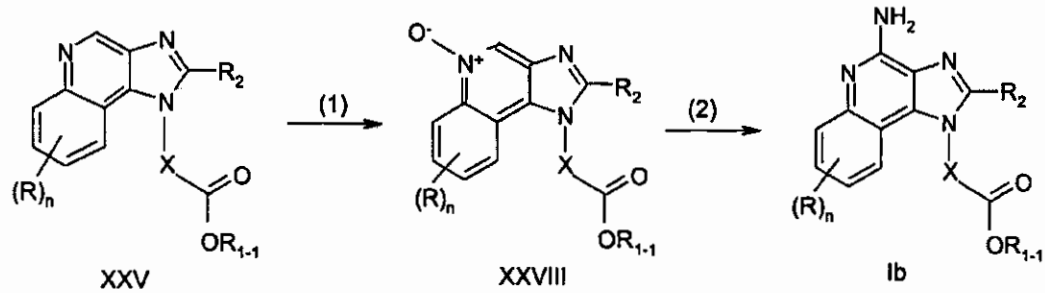
Reaction Scheme 4



Reaction Scheme 5

In Reaction Scheme 5, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXV, prepared as described in steps (1) through (3) of Reaction Scheme 5, is converted to a compound of Formula Ib. In step (1), the 1*H*-imidazo[4,5-*c*]quinoline of Formula XXV is oxidized to an *N*-oxide as in step (7) of Reaction Scheme 1a to form a compound of Formula XXVIII. In step (2), the *N*-oxide of Formula XXVIII is aminated as in step (8) of Reaction Scheme 1a to provide the ester-substituted 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula Ib. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme 5



Reaction Scheme 6

Ketones of Formula I-3b can be prepared according to Reaction Scheme 6, where R_{1-1}, R_2, $R_{A'}$, $R_{B'}$, and X are as defined above and Ph is phenyl. In step (1) of Reaction Scheme 6, a 2,4-dichloro-3-nitropyridine of Formula XXX is reacted with an amino ester of the Formula H_2N-X-C(O)-O-alkyl or a hydrochloride salt thereof to form a 2-chloro-3-nitropyridine of Formula XXXI. The reaction is conveniently carried out by combining an amino ester of Formula H_2N-X-C(O)-O-alkyl - HCl and a 2,4-dichloro-3-nitropyridine of Formula XXX in the presence of a base such as triethylamine in an inert solvent such as *N,N*-dimethylformamide (DMF). The reaction can be carried out at ambient temperature, and the product can be isolated from the reaction mixture using conventional methods. Many 2,4-dichloro-3-nitropyridines of the Formula XXX are known and can be readily prepared using known synthetic methods. (See,

for example, Dellaria et al, U.S. Pat. No. 6,525,064 and the references cited therein.)

In step (2) of Reaction Scheme 6, a 2-chloro-3-nitropyridine of Formula XXXI is reacted with an alkali metal azide to provide an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula XXXII. The reaction can be carried out by combining the compound of Formula XXXI with an alkali metal azide, for example, sodium azide, in a suitable solvent such as acetonitrile/water, preferably 90/10 acetonitrile/water, in the presence of cerium III chloride, preferably cerium III chloride heptahydrate. Optionally, the reaction can be carried out with heating, for example, at the reflux temperature. Alternatively, the reaction can be carried out by combining the compound of Formula XXXI with an alkali metal azide, for example, sodium azide, in a suitable solvent such as DMF and heating, for example to about 50-60 °C, optionally in the presence of ammonium chloride. The product can be isolated from the reaction mixture using conventional methods.

In step (3) of Reaction Scheme 6, an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula XXXVI is reduced to provide a tetrazolo[1,5-*a*]pyridine-7,8-diamine of Formula XXXIII. The reduction can be carried out by hydrogenation using a conventional heterogeneous hydrogenation catalyst, for example, platinum on carbon or palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as acetonitrile or ethyl acetate. The product can be isolated from the reaction mixture using conventional methods. Alternatively, the reduction can be carried out using the one- to two-phase sodium dithionite reduction described in step (2) of Reaction Scheme 1a.

In step (4) of Reaction Scheme 6, a tetrazolo[1,5-*a*]pyridine-7,8-diamine of Formula XXXIII is reacted with a carboxylic acid equivalent to provide a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XXXIV. The reaction can be carried out as described in step (3) of Reaction Scheme 1a, and the product can be isolated from the reaction mixture using conventional methods.

In step (5) of Reaction Scheme 6, the ester group of the 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XXXIV is converted to a Weinreb amide

to provide a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XXXV. The conversion can be carried out as described in step (4) of Reaction Scheme 4, and the product can be isolated from the reaction mixture using conventional methods.

In step (6) of Reaction Scheme 6, the Weinreb amide of Formula XXXV is treated with a Grignard reagent of Formula R_{1-1}MgHalide to form a ketone of Formula XXXVI. The Grignard reaction can be carried out as described in step (5) of Reaction Scheme 1a, and the product can be isolated from the reaction mixture using conventional methods.

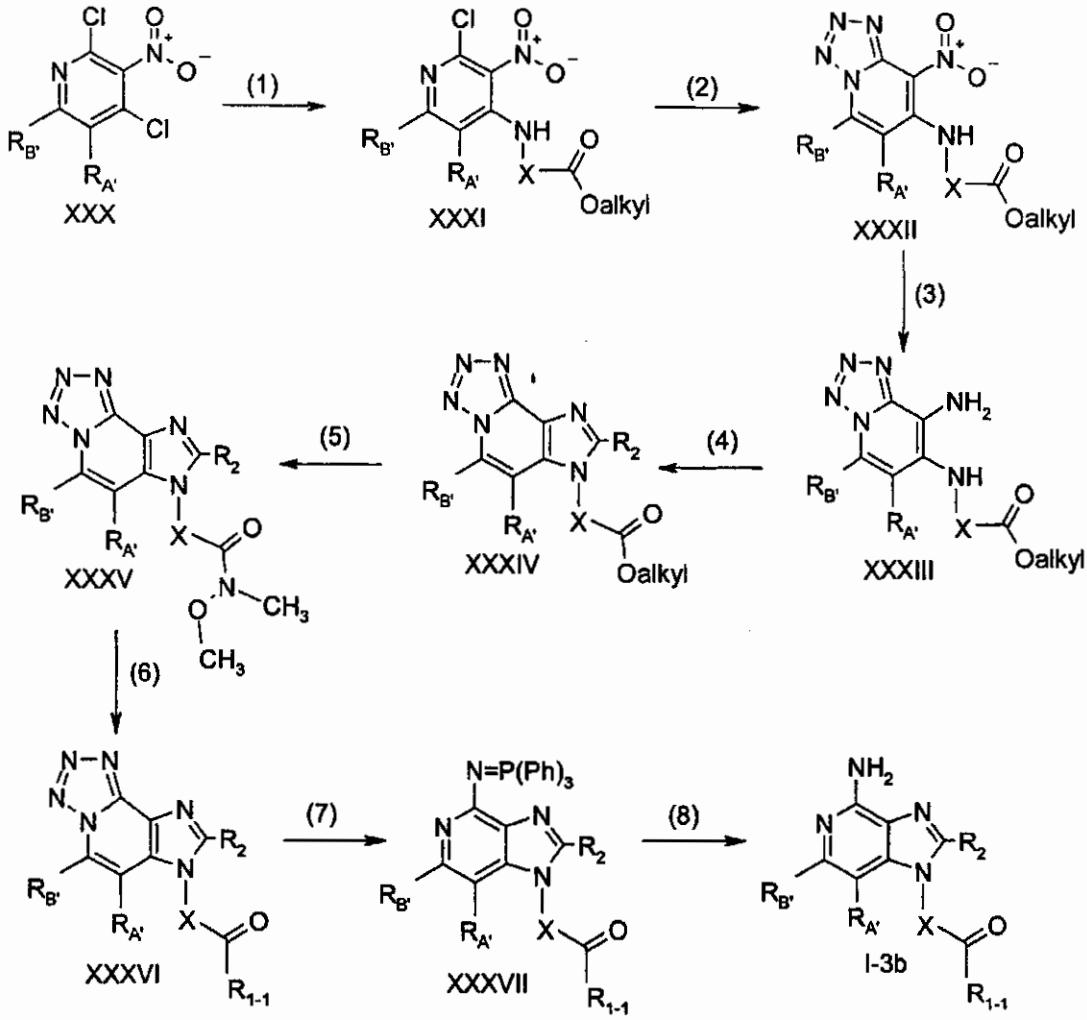
In step (7) of Reaction Scheme 6, a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XXXVI is reacted with triphenylphosphine to form an *N*-triphenylphosphinyl intermediate of Formula XXXVII. The reaction with triphenylphosphine can be run in a suitable solvent such as toluene or 1,2-dichlorobenzene under an atmosphere of nitrogen with heating, for example at the reflux temperature. The product can be isolated from the reaction mixture using conventional methods.

In step (8) of Reaction Scheme 6, an *N*-triphenylphosphinyl intermediate of Formula XXXVII is hydrolyzed to provide a ketone substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula I-3b. The hydrolysis can be carried out by general methods well known to those skilled in the art, for example, by heating in a lower alkanol in the presence of an acid. The product can be isolated from the reaction mixture using conventional methods as the compound of Formula I-3b or as a pharmaceutically acceptable salt thereof.

Esters of Formula I-3 (Z is -C(O)O-) can be prepared by omitting steps (5) and (6).

Weinreb amides of Formula I-3 (Z is -C(O)- and R_{1-1} is $-N(CH_3)(OCH_3)$) can be prepared from esters of Formula I-3 using the method of step (5).

Reaction Scheme 6



Reaction Scheme 7

Ketones of Formula I-4b can be prepared according to Reaction Scheme 7, wherein R_b is alkyl, alkoxy, or $-N(R_9)_2$ and R_{2b}, $R_{1\text{-}1b}$, and X_b are subsets of R_2, $R_{1\text{-}1}$, and X as defined above that do not include those substituents that one skilled in the art would recognize as being susceptible to reduction under the acidic hydrogenation conditions of the reaction. These susceptible groups include, for example, alkenyl, alkynyl, and aryl groups and groups bearing nitro substituents.

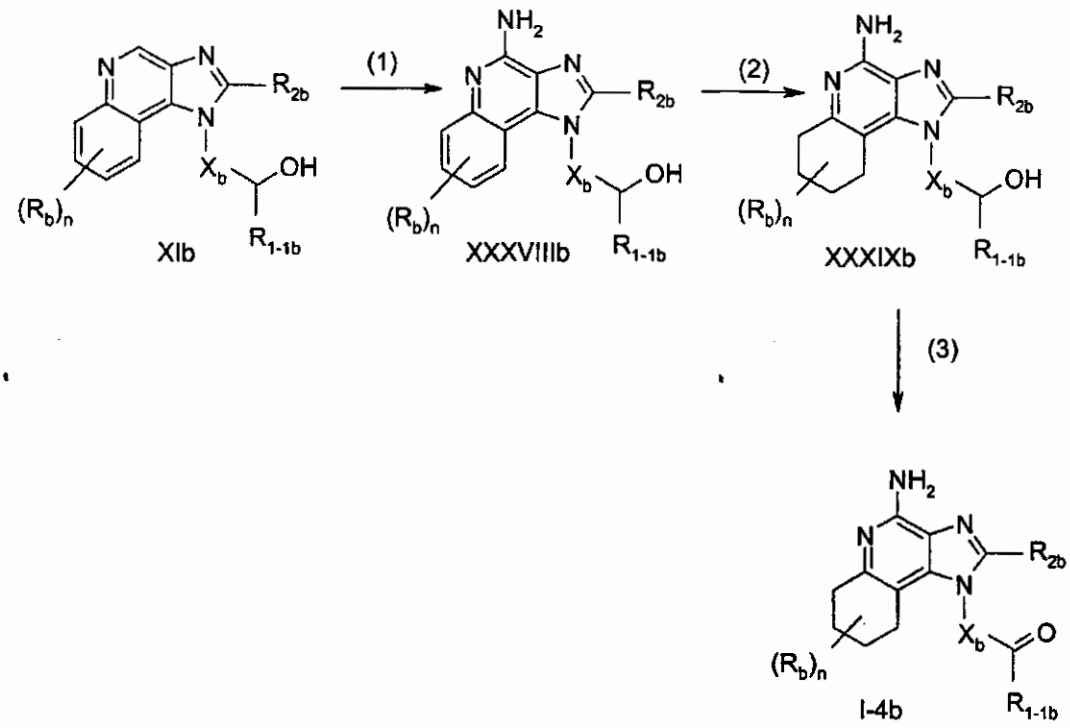
In step (1) of Reaction Scheme 7, a 1*H*-imidazo[4,5-*c*]quinoline of Formula XIb is converted to a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula

XXXVIIIb. The conversion can be carried out as described in steps (7) and (8) of Reaction Scheme 1a, and the product can be isolated from the reaction mixture using conventional methods.

In step (2) of Reaction Scheme 7, a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXVIIIb is reduced to a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXIXb. The reaction is conveniently carried out under hetereogeneous hydrogenation conditions by adding platinum (IV) oxide to a solution of the compound of Formula XXXVIIIb in trifluoroacetic acid and placing the reaction under hydrogen pressure. The reaction can be carried out on a Parr apparatus at ambient temperature. The product can be isolated from the reaction mixture using conventional methods.

In step (3) of Reaction Scheme 7, the alcohol-substituted 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXIXb is oxidized to a ketone-substituted 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula I-4b. The oxidation can be carried out as described in step (4) of Reaction Scheme 1a. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme 7



Compounds of the invention can also be prepared using variations of the synthetic routes shown in Reaction Schemes 1 through 7 that would be apparent to one of skill in the art. For example, the ketones of Formulas Ia, I-3b, and I-4b can be converted to ketals using the method described in step (1) of Reaction Scheme (3). Compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt of the invention as described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical

and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce the production of certain cytokines in experiments performed according to the test set forth below. These results indicate that the compounds or salts are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease,

and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts of the invention can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which compounds or salts identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g.,

SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to myelogeous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, compounds or salts of the present invention may be useful as a vaccine adjuvant for use in conjunction with any material that raises either

humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens, toxoids, toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Compounds or salts of the present invention may be particularly helpful in individuals having compromised immune function. For example, compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An amount of a compound or salt effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or

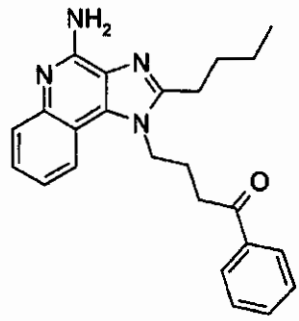
inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

EXAMPLES

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

Example 1

4-(4-Amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-one



Step 1:

To a stirred mixture of 4-chloro-3-nitroquinoline (100.0 g, 479 mmol) and triethylamine (72.8 g, 719 mmol) in dichloromethane (700 mL) was added dropwise 4-amino-1-butanol (42.7 g, 479 mmol). After the addition was complete, water (500 mL) was added to the reaction mixture to cause the product to precipitate. More water (2 L) was added, and the mixture was stirred

overnight and then filtered. The organic solution was dried over sodium sulfate, concentrated under reduced pressure, and combined with the product isolated by filtration to provide 4-(3-nitroquinolin-4-ylamino)butan-1-ol (113 g) as a bright yellow solid.

Step 2:

To a stirred solution of 4-(3-nitroquinolin-4-ylamino)butan-1-ol (70.0 g, 268 mmol) and triethylamine (54.2 g, 536 mmol) in chloroform (900 mL) was added *tert*-butyldimethylsilyl chloride (TBDMSCl, 60.6 g, 402 mmol). After 3.5 hours, additional triethylamine (19.0 g, 188 mmol) and TBDMSCl (20.2 g, 134 mmol) were added and the mixture stirred overnight. After the addition of additional TBDMSCl (4.0 g, 27 mmol), the reaction was complete as judged by thin layer chromatography (TLC). Chloroform (900 mL) was added and the mixture washed successively with 360 mL each of a 0.10 N hydrochloric acid solution, a saturated aqueous sodium bicarbonate solution, and brine; dried over sodium sulfate; filtered; and solvent evaporated to leave a mixture of [4-(*tert*-butyldimethylsilanyloxy)butyl](3-nitro-quinolin-4-yl)amine and *tert*-butyldimethylsilanol (117 g total, about 65:35 mol:mol) which was used in the next step without further purification.

Step 3:

The mixture of [4-(*tert*-butyldimethylsilanyloxy)butyl](3-nitro-quinolin-4-yl)amine and *tert*-butyldimethylsilanol (110 g) from the previous step was dissolved in toluene (880 mL) and placed in a Parr hydrogenation vessel along with 5% platinum on carbon catalyst (3.0 g). The vessel was pressurized to 50 psi (3.4×10^5 Pa) hydrogen and shaken on the Parr apparatus for 1.5 hours, occasionally adding additional hydrogen to maintain a pressure of 50 psi (3.4×10^5 Pa). After 3 hours, the reaction mixture was filtered through CELITE filter agent and concentrated under reduced pressure to provide N^4-[4-(*tert*-butyldimethylsilanyloxy)butyl]quinoline-3,4-diamine as a dark oil that was used directly in the next step without further purification.

Step 4:

A solution of N^4-[4-(*tert*-butyldimethylsilanyloxy)butyl]quinoline-3,4-diamine (62.9 g, 182 mmol) and trimethyl orthovalerate (45.2 g, 278 mmol) in

toluene (200 mL) was heated at reflux for 2 hours and then concentrated under reduced pressure to provide 2-butyl-1-[4-(*tert*-butyldimethylsilanyloxy)butyl]-1*H*-imidazo[4,5-*c*]quinoline as an oil that was used directly in the next step without further purification.

Step 5:

The 2-butyl-1-[4-(*tert*-butyldimethylsilanyloxy)butyl]-1*H*-imidazo[4,5-*c*]quinoline from the previous step and tetrabutylammonium fluoride (142 mL of a 1 M solution in tetrahydrofuran) were dissolved in tetrahydrofuran (THF) (400 mL) and stirred for 1 hour, then concentrated under reduced pressure to provide 4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol (20.0 g) as a light brown solid after chromatography on silica gel (elution with 10% methanol in dichloromethane).

Step 6:

A solution of dimethyl sulfoxide (DMSO, 7.88 g, 101 mmol) in dichloromethane (130 mL) was cooled in a dry ice/acetone bath and stirred. Oxalyl chloride (9.40 g, 74 mmol) was added dropwise, followed by a solution of 4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol (20.0 g, 67.3 mmol) in dichloromethane (320 mL). After five minutes triethylamine (20.42 g, 202 mmol) was added, and the mixture was allowed to warm to room temperature. After the addition of chloroform (500 mL), the mixture was washed successively with a saturated ammonium chloride solution (200 mL) and a saturated aqueous sodium bicarbonate solution (200 mL), dried over sodium sulfate, filtered, and concentrated to a dark solid. This solid was slurried in diethyl ether until a fine solid resulted. The product was filtered and dried to provide 4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyraldehyde (17.9 g) as a light brown solid.

Step 7:

To a stirred solution of 4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyraldehyde (8.0 g, 27.1 mmol) in anhydrous THF (270 mL) was added dropwise a solution of phenylmagnesium bromide (27.08 mL of a 1 M solution in THF). After 30 minutes, the solution was quenched with saturated ammonium chloride (100 mL), diluted with ethyl acetate (300 mL), and the layers separated. The organic solution was washed successively with a saturated aqueous sodium

bicarbonate solution (100 mL) and brine (100 mL), dried over sodium sulfate, filtered, and concentrated to a light orange oil. Chromatography on silica gel (elution with 5% methanol in dichloromethane) provided 4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-ol (4.3 g) as a light orange, gummy solid.

Step 8:

A solution of DMSO (1.35 g, 17.3 mmol) in dichloromethane (22 mL) was cooled in a dry ice/acetone bath and stirred. Oxalyl chloride (1.61 g, 12.7 mmol) was added dropwise, followed by a solution of 4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-ol (4.3 g, 11.5 mmol) in dichloromethane (55 mL). After five minutes, triethylamine (3.49 g, 34.5 mmol) was added, and the mixture was allowed to warm to room temperature. After the addition of chloroform (300 mL), the mixture was washed successively with a saturated ammonium chloride solution (100 mL) and a saturated aqueous sodium bicarbonate solution (100 mL), dried over sodium sulfate, filtered, and concentrated to provide 4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-one (4.15 g) as an off-white solid.

Step 9:

To a stirred solution of 4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-one (4.15 g, 11.2 mmol) in chloroform (56 mL) was added 3-chloroperoxybenzoic acid (m-CPBA, approximately 77% purity, 2.75 g, 12.3 mmol) portionwise over a several minute period. After 1 hour, the reaction was not complete as judged by TLC, so an additional charge of m-CPBA (1.0 g) was added. After stirring for 30 minutes, the mixture was diluted with chloroform (200 mL), washed successively with a saturated aqueous sodium bicarbonate solution (2 x 100 mL) and brine (100 mL), dried over sodium sulfate, filtered, and concentrated to provide 4-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-one as a dark oil that was used directly in the next step without further purification.

Step 10:

To a vigorously stirred mixture of the 4-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-one from the previous step in

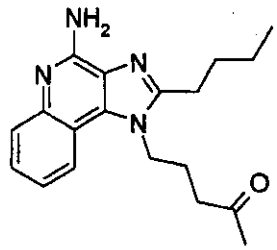
dichloromethane (49 mL) and ammonium hydroxide (16 mL) was added *p*-toluenesulfonyl chloride (2.34 g, 12.3 mmol) portionwise over several minutes. After 15 minutes the reaction mixture was diluted with chloroform (200 mL) and saturated aqueous sodium bicarbonate solution (100 mL). The layers were separated and the organic phase was washed again with a saturated aqueous sodium bicarbonate solution (100 mL). The aqueous portions were then back extracted with chloroform (50 mL). The organics were combined, dried over sodium sulfate, filtered, and concentrated to a dark yellow solid. The dark yellow solid was slurried in diethyl ether and filtered to form a fine off-white solid. This solid was recrystallized from *N,N*-dimethylformamide (DMF) and water to afford 4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-one as an off-white fluffy solid, mp 178-180 °C.

MS (APCI) m/z 387 $(M + H)^+$;

Anal. calcd for $C_{24}H_{26}N_4O$: C, 74.58; H, 6.78; N, 14.50. Found: C, 74.45; H, 6.77; N, 14.47.

Example 2

5-(4-Amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one



Steps 1- 6 were carried out as described above for the Preparation of Example 1.

Step 7:

The general method described in Step 7 of Example 1 was used to react 4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyraldehyde (8.5 g, 28.8 mmol) with methylmagnesium bromide (20.6 mL of a 1.4 M solution in toluene/THF, 28.8 mmol) to provide 5-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-ol (3.54 g) as an off-white solid after chromatography on silica gel (elution with 5% methanol in dichloromethane).

Step 8:

The general method described in Step 8 of Example 1 was used to oxidize 5-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-ol (3.54 g, 11.4 mmol) with DMSO (1.33 g, 17.1 mmol), oxalyl chloride (1.59 g, 12.5 mmol), and triethylamine (3.45 g, 34.1 mmol) to provide 5-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one (2.15 g) as a dark solid.

Steps 9 and 10:

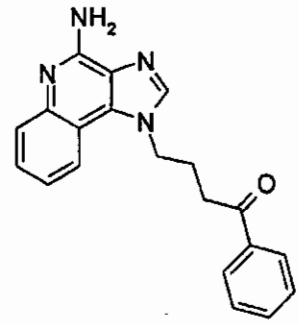
The general method described in Steps 9 and 10 of Example 1 was used to aminate 5-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one (2.15 g, 6.95 mmol) by reaction with m-CPBA (1.71 g, 7.64 mmol) to provide 5-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one followed by reaction with *p*-toluenesulfonyl chloride (1.46 g, 7.64 mmol) and ammonium hydroxide solution (10 mL) to provide 5-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one as an off-white solid, mp 173-176 °C.

MS (APCI) m/z 325 $(M + H)^+$;

Anal. calcd for $C_{19}H_{24}N_4O$: C, 70.34; H, 7.46; N, 17.27. Found: C, 70.24; H, 7.37; N, 17.25.

Example 3

4-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-one



Steps 1-3 were carried out as described above for the Preparation of Example 1.

Step 4:

A mixture of N^4-[4-(*tert*-butyldimethylsilanyloxy)butyl]quinoline-3,4-diamine (101 g, 293 mmol) and triethyl orthoformate (43.4 g, 293 mmol) in toluene (200 mL) was heated at reflux for 2 hours and then concentrated under

reduced pressure to provide 1-[4-(*tert*-butyldimethylsilanyloxy)butyl]-1*H*-imidazo[4,5-*c*]quinoline as an oil that was used directly in the next step without further purification.

Step 5:

The 1-[4-(*tert*-butyldimethylsilanyloxy)butyl]-1*H*-imidazo[4,5-*c*]quinoline (46.0 g, 129 mmol) from the previous step and tetrabutylammonium fluoride (142 mL of a 1 M solution in THF) were dissolved in THF (400 mL) and stirred for 1 hour, then concentrated under reduced pressure to provide 4-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol (20.0 g) as a light brown solid after chromatography on silica gel (elution with 10% methanol in dichloromethane).

Step 6:

The general method described in Step 6 of Example 1 was used to oxidize 4-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol (20.0 g, 82.9 mmol) with DMSO (48.6 g, 620 mmol), oxalyl chloride (58.0 g, 456 mmol), and triethylamine (126 g, 1.25 mol) to provide 4-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyraldehyde (10.0 g) as a light orange oil after chromatography on silica gel (elution with 10% methanol in dichloromethane) followed by brief treatment with trifluoroacetic acid (0.10 g, 1 mmol) in a mixture of THF (50 mL) and water (20 mL).

Step 7:

The general method described in Step 7 of Example 1 was used to react 4-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyraldehyde (7.94 g, 33.2 mmol) with phenylmagnesium bromide (33.2 mL of a 1 M solution in THF, 33.2 mmol) to provide 4-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-ol (7.2 g) as an off-white solid that was used directly in the next step without further purification.

Step 8:

By the general method described in Step 6 of Example 1, 4-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-ol) (7.2 g, 22.7mmol) was oxidized with DMSO (2.70 g, 34.0 mmol), oxalyl chloride (3.20 g, 25.0 mmol), and triethylamine (6.90 g, 68.1 mmol) to provide 4-(1*H*-imidazo[4,5-*c*]quinolin-

1-yl)-1-phenylbutan-1-one (4.08 g) as a light yellow solid after chromatography on silica gel (elution with 10% methanol in dichloromethane).

Step 9:

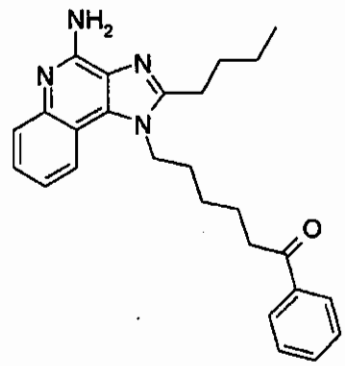
The general method described in Steps 9 and 10 of Example 1 was used to aminate 4-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-one (4.08 g, 12.9 mmol) by reaction with m-CPBA (3.20 g, 14.2 mmol) to provide 4-(5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-one followed by reaction with *p*-toluenesulfonyl chloride (2.71 g, 14.2 mmol) and ammonium hydroxide solution (22 mL) to provide 4-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylbutan-1-one) as white needles, mp 209-211 °C.

MS (APCI) m/z 331 $(M + H)^+$;

Anal. calcd for $C_{20}H_{18}N_4O$: C, 72.71; H, 5.49; N, 16.96. Found: C, 72.60; H, 5.39; N, 16.98.

Example 4

6-(4-Amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylhexan-1-one



Step 1:

To a stirred mixture of 4-chloro-3-nitroquinoline (50.0 g, 240 mmol) and triethylamine (36.4 g, 360 mmol) in dichloromethane (370 mL) was added 6-amino-1-hexanol (28.1 g, 240 mmol) portionwise over a ten-minute period. The mixture was heated at reflux for 35 minutes, cooled, and diluted with chloroform (300 mL). The solution was washed successively with water (200 mL), a saturated aqueous sodium bicarbonate solution (200 mL), and brine (200 mL); dried over sodium sulfate; filtered; and concentrated to a bright yellow solid, 6-

(3-nitroquinolin-4-ylamino)hexan-1-ol (68.3 g), that was used directly in the next step without further purification.

Step 2:

The alcohol from Step 1, 6-(3-nitro-quinolin-4-ylamino)hexan-1-ol (10.0 g, 34.6 mmol), was oxidized by the general method described in Step 6 of Example 1 with DMSO (4.05 g, 51.8 mmol), oxalyl chloride (4.83 g, 38.0 mmol), and triethylamine (10.5 g, 104 mmol) to provide 6-(3-nitroquinolin-4-ylamino)hexanal (9.9 g) as a bright yellow solid that was used directly in the next step without further purification.

Step 3:

By the general method described in Step 7 of Example 1, 6-(3-nitroquinolin-4-ylamino)hexanal (9.9 g, 34.5 mmol) was reacted with phenylmagnesium bromide (36.2 mL of a 1 M solution in THF, 36.2 mmol) to provide 6-(3-nitroquinolin-4-ylamino)-1-phenylhexan-1-ol (4.4 g) as a bright yellow solid after chromatography on silica gel (elution with ethyl acetate and hexane, 1:1, volume:volume).

Step 4:

By the general method described in Step 6 of Example 1, 6-(3-nitroquinolin-4-ylamino)-1-phenylhexan-1-ol (4.0 g, 11 mmol) was oxidized with DMSO (1.28 g, 16.4 mmol), oxalyl chloride (1.53 g, 12.0 mmol), and triethylamine (3.32 g, 32.8 mmol) to provide 6-(3-nitroquinolin-4-ylamino)-1-phenylhexan-1-one (2.27 g) as light orange crystals after recrystallization from ethyl acetate.

Step 5:

A mixture of 6-(3-nitroquinolin-4-ylamino)-1-phenylhexan-1-one (2.27 g, 6.25 mmol) and 5% platinum on carbon catalyst (0.50 g) in toluene (60 mL) was hydrogenated on a Parr shaker at 50 psi (3.4×10^5 Pa) for 3 hours. After filtration through CELITE filter agent and concentration under reduced pressure, 6-(3-aminoquinolin-4-ylamino)-1-phenylhexan-1-one (2.09 g) was obtained as a dark yellow oil that was used directly in the next step without further purification.

Step 6:

A solution of 6-(3-aminoquinolin-4-ylamino)-1-phenylhexan-1-one (2.09 g, 6.25 mmol) and trimethyl orthovalerate (1.52 g, 9.37 mmol) in toluene (50 mL) was heated at reflux under a Dean-Stark trap for 2 hours, then concentrated under reduced pressure to provide 6-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylhexan-1-one (2.19 g) as a dark red oil that was used directly in the next step without further purification.

Steps 7 and 8:

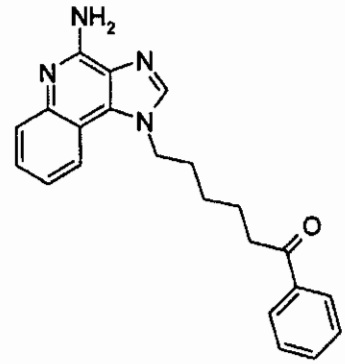
The general method described in Steps 9 and 10 of Example 1 was used to aminate 6-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylhexan-1-one (2.19 g, 5.48 mmol) by reaction with m-CPBA (1.35 g, 6.03 mmol) to provide 6-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylhexan-1-one followed by reaction with *p*-toluenesulfonyl chloride (1.15 g, 6.03 mmol) and ammonium hydroxide solution (9 mL) to provide 6-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylhexan-1-one (0.50 g) as a white solid after chromatography on silica gel (elution with 10% methanol in dichloromethane) and recrystallization from ethanol, mp 149-151 °C.

MS (APCI) m/z 415 $(M + H)^+$;

Anal. calcd for $C_{26}H_{30}N_4O$: C, 75.33; H, 7.29; N, 13.52. Found: C, 75.14; H, 7.13; N, 13.48.

Example 5

6-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylhexan-1-one



Step 1:

By the general method described in Step 6 of Example 4, a solution of 6-(3-aminoquinolin-4-ylamino)-1-phenylhexan-1-one (2.76 g, 8.25 mmol),

trimethyl orthoformate (1.5 g, 9.9 mmol), and pyridine hydrochloride (95 mg, 0.83 mmol) in toluene (26 mL) was heated at reflux under a Dean-Stark trap for 2 hours, then concentrated under reduced pressure to provide 6-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylhexan-1-one as a dark oil that was used directly in the next step without further purification.

Step 2:

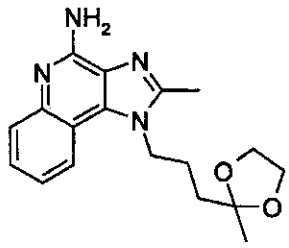
The general method described in Steps 9 and 10 of Example 1 was used to aminate 6-(1*H*-imidazo[4,5-c]quinolin-1-yl)-1-phenylhexan-1-one (2.0 g, 5.8 mmol) by reaction with m-CPBA (1.44 g, 6.41 mmol) to provide 6-(5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylhexan-1-one followed by reaction with *p*-toluenesulfonyl chloride (1.22 g, 6.41 mmol) and ammonium hydroxide solution (10 mL) to provide 6-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenylhexan-1-one (0.29 g) as an off-white solid after chromatography on silica gel (elution with 5% methanol in dichloromethane) and recrystallization from dichloroethane, mp 163-165 °C.

MS (APCI) m/z 359 $(M + H)^+$;

Anal. calcd for $C_{22}H_{22}N_4O$: C, 73.72; H, 6.19; N, 15.63. Found: C, 73.66; H, 5.88; N, 15.55.

Example 6

2-Methyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Step 1:

The general method described in Step 1 of Example 1 was used to react 4-chloro-3-nitroquinoline (45.0 g, 216 mmol), 3-(2-methyl-[1,3]dioxolan-2-yl)propylamine (37.0 g, 255 mmol, prepared as described in PCT Publication WO 01/51486) and triethylamine (37.0 g, 366 mmol) in dichloromethane for 15

hours to provide [3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-(3-nitroquinolin-4-yl)amine (44.1 g) as a yellow solid after recrystallization from a toluene/hexane mixture.

Step 2:

The product from the previous step, [3-(2-methyl-[1,3]dioxolan-2-yl)propyl](3-nitro-quinolin-4-yl)amine (29.5 g, 93.0 mmol), was stirred with sodium dithionite (67.0 g, approximately 85% pure), potassium carbonate (51.4 g, 372 mmol), and ethyl viologen dibromide (0.37 g, 1 mmol) in a mixture of dichloromethane and water (375 mL each) for 15 hours. The layers were then separated, and the organic phase was washed successively with a saturated aqueous sodium bicarbonate solution and water (250 mL each), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide N^4-[3-(2-methyl-[1,3]dioxolan-2-yl)-propyl]quinoline-3,4-diamine (26.0 g) as a dark solid that was used directly in the next step without further purification.

Step 3:

A solution of N^4-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]quinoline-3,4-diamine (6.20 g, 21.6 mmol), triethyl orthoacetate (3.10 g,, 25.8 mmol) and pyridinium *p*- toluenesulfonate (0.18 g, 0.71 mmol) in toluene (250 mL) was heated at reflux under a Dean-Stark trap for 2 hours, periodically draining off the distillate and adding fresh toluene to the reaction mixture. The solution was concentrated under reduced pressure, and the residue was taken up in dichloromethane (150 mL), washed successively with a saturated aqueous sodium bicarbonate solution and water (100 mL each), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide 2-methyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinoline (6.70 g) as a dark oil that was used directly in the next step without further purification.

Step 4:

The general method described in Steps 9 and 10 of Example 1 was used to aminate 2-methyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinoline (6.70 g, 21.5 mmol) by reaction with m-CPBA (9.4 g) to provide 2-

methyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-5-oxido-1*H*-imidazo[4,5-*c*]quinoline followed by reaction with *p*-toluenesulfonyl chloride (7.20 g, 37.8 mmol) and ammonium hydroxide solution (100 mL) to provide 2-methyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine (3.9 g) as an off-white solid after recrystallization from toluene, mp 193-195 °C.

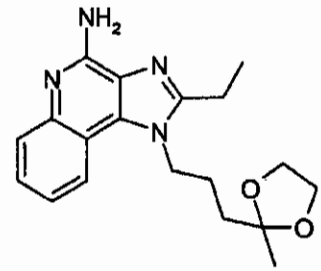
MS (APCI) *m/z* 327 $(M + H)^+$;

Anal. calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.17. Found: C, 66.07; H, 6.58; N, 16.91.

Examples 7, 8, 9, and 10 were prepared by the general method described above for Example 6, wherein the orthoester or acid chloride described below was substituted for triethyl orthoacetate in Step 3 of the synthesis.

Example 7

2-Ethyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine



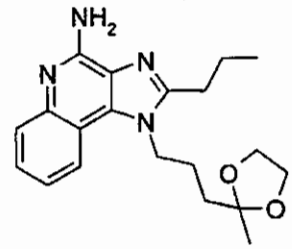
By utilizing triethyl orthopropionate in Step 3 of Example 6, 2-ethyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine was prepared, mp 195-196.5 °C.

MS (APCI) *m/z* 341 $(M + H)^+$;

Anal. calcd for $C_{19}H_{24}N_4O_2$: C, 67.04; H, 7.11; N, 16.46. Found C, 66.77; H, 7.20; N, 16.41.

Example 8

1-[3-(2-Methyl-[1,3]dioxolan-2-yl)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



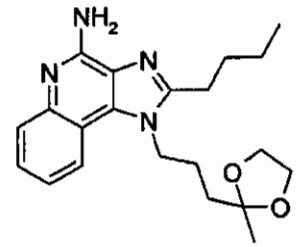
By utilizing trimethyl orthobutyrate in Step 3 of Example 6, 1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine was prepared, mp 184-186 °C.

MS (APCI) m/z = 355 $(M+H)^+$;

Anal. calcd for $C_{20}H_{26}N_4O_2$: C, 67.77; H, 7.39; N, 15.81. Found C, 67.55; H, 7.45; N, 15.74.

Example 9

2-Butyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine



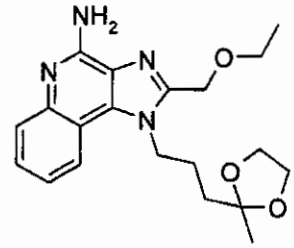
By utilizing trimethyl orthovalerate in Step 3 of Example 6, 2-butyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine was prepared, mp 169-171.5 °C.

MS (APCI) m/z = 369 $(M+H)^+$;

Anal. calcd for $C_{21}H_{28}N_4O_2 \cdot 0.9\ H_2O$: C, 68.17; H, 7.67; N, 15.14. Found C, 67.84; H, 7.69; N, 14.99.

Example 10

2-Ethoxymethyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine



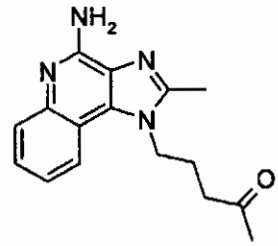
By utilizing ethoxyacetyl chloride (1.1 equivalents) and triethylamine (1.1 equivalents) instead of triethyl orthoacetate and pyridinium *p*-toluenesulfonate in Step 3 of Example 6, 2-ethoxymethyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine was prepared, mp 150-152 °C.

MS (APCI) *m/z* 371 $(M + H)^+$;

Anal. calcd for $C_{20}H_{26}N_4O_3$: C, 64.84; H, 7.07; N, 15.12. Found: C, 64.65; H, 7.13; N, 15.01.

Example 11

5-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one



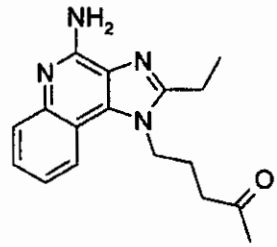
Concentrated hydrochloric acid (3 mL) was added to 2-methyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1.0 g, 2.7 mmol), and the mixture stirred for a few minutes until everything was in solution. Water (5 mL) was then added and the solution stirred for one hour at room temperature. After the addition of dichloromethane (75 mL) and water (25 mL), the solution was made basic by the slow addition of potassium carbonate (10.0 g). The layers were separated, and the organic layer was washed with a saturated aqueous sodium bicarbonate solution (25 mL), dried over potassium

carbonate, filtered, and concentrated under reduced pressure to provide 5-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one, mp 194-196 °C.
MS (APCI) *m/z* 283 $(M + H)^+$;
Anal. calcd for $C_{16}H_{18}N_4O \cdot 0.44\ H_2O$: C, 66.20; H, 6.56; N, 19.30. Found: C, 66.23; H, 6.52; N, 19.35.

Examples 12, 13, 14 were prepared by the general method described above for Example 11 by acid-catalyzed hydrolysis of the appropriate ketal.

Example 12

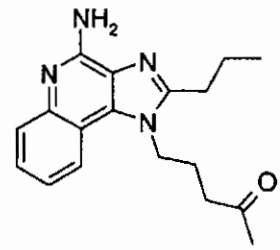
5-(4-Amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one



2-Ethyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine was hydrolyzed to 5-(4-amino-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one, mp 206-208 °C.
MS (APCI) m/z = 297 $(M+H)^+$;
Anal. calcd for $C_{17}H_{20}N_4O$: C, 68.90; H, 6.80; N, 18.9. Found C, 68.66; H, 6.84; N, 18.62.

Example 13

5-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one



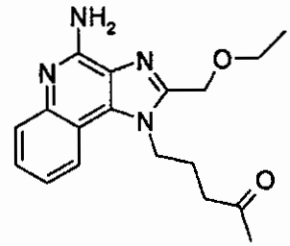
1-[3-(2-Methyl-[1,3]dioxolan-2-yl)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine was hydrolyzed to 5-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one, mp 176-177 °C.

MS (APCI) m/z = 311 $(M+H)^+$;

Anal. calcd for $C_{18}H_{22}N_4O \cdot 0.0125\ CH_2Cl_2$: C, 69.46; H, 7.13; N, 17.99. Found C, 69.12; H, 7.15; N, 17.71.

Example 14

5-(4-Amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one



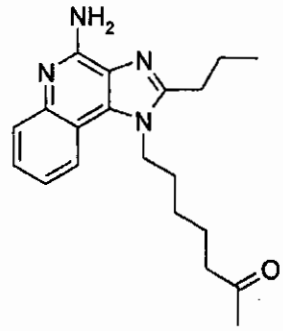
2-Ethoxymethyl-1-[3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine was hydrolyzed to 5-(4-amino-2-ethoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentan-2-one, mp 173-175 °C.

MS (APCI) *m/z* 327 $(M + H)^+$;

Anal. calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.17. Found: C, 66.05; H, 6.94; N, 16.89.

Example 15

7-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)heptan-2-one



Step 1:

Ethyl 6-aminocaproate hydrochloride was prepared from 6-aminocaproic acid, thionyl chloride, and ethanol by the general method of C. Temple, Jr., R.D. Elliott, and J.A. Montgomery, *J. Med. Chem.*, **1988**, *31*, 697-700. The general method described in Step 1 of Example 1 was used to react 4-chloro-3-nitroquinoline (41.7 g, 200 mmol), ethyl 6-aminocaproate hydrochloride (46.9 g, 240 mmol) and triethylamine (50.6 g, 500 mmol) in dichloromethane for 15 hours to provide ethyl 6-(3-nitroquinolin-4-ylamino)hexanoate (60.6 g) as a yellow solid.

Step 2:

A Parr hydrogenation vessel was charged with ethyl 6-(3-nitroquinolin-4-ylamino)hexanoate (14.4 g, 43.2 mmol), 10% palladium on carbon catalyst (1.0 g), and ethanol (250 mL); placed on a Parr shaker; and the system pressurized to 40 psi (2.7×10^5 Pa) hydrogen. After shaking for 15 hours, the reaction mixture was filtered through CELITE filter agent and concentrated under reduced pressure to provide ethyl 6-(3-aminoquinolin-4-ylamino)hexanoate as a dark oil (9.8 g) that was used directly in the next step without further purification. This step was repeated several times to provide material for the subsequent step.

Step 3:

A solution of ethyl 6-(3-aminoquinolin-4-ylamino)hexanoate (34.3 g, 114 mmol), trimethyl orthobutyrate (19.5 g, 131 mmol), and pyridinium *p*-toluenesulfonate (1.0 g, 4.0 mmol) in toluene (250 mL) was heated at reflux under a Dean-Stark trap for 5 hours, periodically draining off the distillate and

adding fresh toluene to the reaction mixture. The solution was concentrated under reduced pressure, and the residue was taken up in dichloromethane (150 mL), washed successively with a saturated aqueous sodium bicarbonate solution and water (100 mL each), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (36.0 g) as a dark oil that was used directly in the next step without further purification.

Step 4:

To a solution of ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (39.0 g, 110 mmol) in ethanol (100 mL) was added a solution of sodium hydroxide (5.73 g, 143 mmol) in water (100 mL). After stirring at room temperature overnight, the volatiles were removed under reduced pressure, the residue taken up in water (200 mL), the solution washed with dichloromethane (3 x 75 mL) and then acidified to about pH 6. The aqueous mixture was extracted with dichloromethane (3 x 75 mL), and then the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoic acid (31.0 g) as a solid that was used directly in the next step without further purification.

Step 5:

To a solution of 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoic acid (31.0 g, 95.3 mmol) in dichloromethane (200 mL) in an ice bath was added oxalyl chloride (21.9 g, 172 mmol) dropwise over a 30 minute period. The reaction mixture was then stirred for one hour at room temperature then concentrated under reduced pressure, and dichloromethane (400 mL) and *N*,*O*-dimethylhydroxylamine hydrochloride (18.6 g, 190 mmol) were added to the residue followed by the dropwise addition of triethylamine (38.5 g, 380 mmol). After stirring at room temperature overnight, the reaction mixture was washed successively with a saturated aqueous sodium bicarbonate solution and brine (100 mL each), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide *N*-methoxy-*N*-methyl-6-(2-propyl-1*H*-imidazo[4,5-

c]quinolin-1-yl)hexanamide (28.0 g) as a dark oil that was used directly in the next step without further purification.

Step 6:

To a solution of *N*-methoxy-*N*-methyl-6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide (22.0 g, 59.7 mmol) in chloroform (20 mL) and THF (200 mL) in an ice bath was added dropwise a solution of methylmagnesium bromide (40 mL of a 3 M solution in diethyl ether, 120 mmol). After 1 hour another charge of methylmagnesium bromide (40 mL of a 3 M solution in diethyl ether, 120 mmol) was added, the reaction mixture stirred at room temperature for 1 more hour and then quenched by the addition of a 10% solution of hydrochloric acid (about 10 mL). The mixture was concentrated under reduced pressure, the residue taken up in dichloromethane (200 mL), and the solution washed successively with a saturated aqueous sodium bicarbonate solution and brine (100 mL each), dried over potassium carbonate, and filtered. The solution was concentrated under reduced pressure and chromatographed on silica gel (elution with 3% methanol in dichloromethane) to provide 7-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)heptan-2-one (12.6 g) as an oil that was used directly in the next step without further purification.

Step 7:

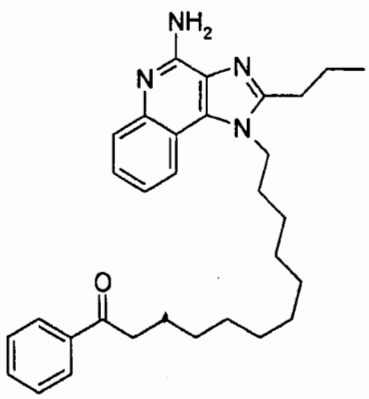
The general method described in Steps 9 and 10 of Example 1 was used to aminate 7-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)heptan-2-one (5.0 g, 15.5 mmol) by reaction with m-CPBA (8.0 g) to provide 7-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)heptan-2-one followed by reaction with *p*-toluenesulfonyl chloride (4.42 g, 23.2 mmol) and ammonium hydroxide solution (50 mL) to provide 7-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)heptan-2-one) as an off-white solid after recrystallization from a mixture of acetonitrile, ethyl acetate, and hexane, mp 161-163 °C.

MS (APCI) m/z = 339 $(M+H)^+$;

Anal. calcd for $C_{20}H_{26}N_4O$: C, 70.98; H, 7.74; N, 16.55. Found C, 70.62; H, 7.91; N, 16.37.

Example 16

12-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenyldodecan-1-one hydrochloride



Step 1:

Ethyl 12-aminododecanoate hydrochloride was prepared from 12-aminododecanoic acid, thionyl chloride, and ethanol by the general method of C. Temple, Jr., R.D. Elliott, and J.A. Montgomery, *J. Med. Chem.*, **1988**, *31*, 697-700. The general method described in Step 1 of Example 15 was used to react 4-chloro-3-nitroquinoline (15.5 g, 74.4 mmol), ethyl 12-aminododecanoate hydrochloride (25.0 g, 89.3 mmol), and triethylamine (18.8 g, 186 mmol) in dichloromethane for 15 hours to provide ethyl 12-(3-nitroquinolin-4-ylamino)dodecanoate (30.0 g) as a yellow solid that was used directly in the next step without further purification.

Step 2:

The general method described in Step 2 of Example 15 was used to reduce ethyl 12-(3-nitroquinolin-4-ylamino)dodecanoate (30.0 g, 77.0 mmol) to provide ethyl 12-(3-aminoquinolin-4-ylamino)dodecanoate (30.4 g) as a solid that was used directly in the next step without further purification.

Step 3:

The general method described in Step 3 of Example 15 was used to cyclize ethyl 12-(3-aminoquinolin-4-ylamino)dodecanoate (30.4 g, 78.8 mmol) by reaction with trimethyl orthobutyrate (13.4 g, 90.6 mmol) to provide ethyl 12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanoate (32.1 g) as a solid that was used directly in the next step without further purification.

Steps 4 and 5:

The general method described in Step 4 of Example 15 was used to provide 12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanoic acid (33.6 g) which was converted to *N*-methoxy-*N*-methyl-12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanamide (36.8 g) by the general method described in Step 5 of Example 15.

Step 6:

The general method described in Step 6 of Example 15 was used to react *N*-methoxy-*N*-methyl-12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanamide (6.0 g, 13.3 mmol) with phenylmagnesium bromide (26.5 mmol, 26.5 mL of a 1 M solution in THF) to provide 1-phenyl-12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecan-1-one (6.0 g).

Step 7:

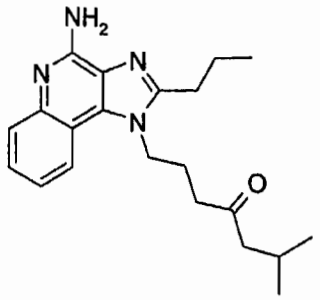
The general method described in Steps 9 and 10 of Example 1 was used to aminate 1-phenyl-12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecan-1-one (6.0 g, 12.8 mmol) by reaction with m-CPBA (8.18 g) to provide 12-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenyldodecan-1-one followed by reaction with *p*-toluenesulfonyl chloride (3.65 g, 19.2 mmol) and ammonium hydroxide solution (40 mL). The product was dissolved a mixture of ethanol and diethyl ether, and a solution of hydrogen chloride (1 equivalent of a 1.0 M solution in diethyl ether) was added. A precipitate formed, and the solvents were removed under reduced pressure. The resulting solid was recrystallized from a mixture of isopropanol and hexane to provide 12-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-1-phenyldodecan-1-one hydrochloride as an off-white solid, mp 195-196° C.

MS (APCI) m/z = 485 $(M+H)^+$;

Anal. calcd for $C_{31}H_{40}N_4O \cdot 1.20\ HCl \cdot 0.17\ H_2O$: C, 70.05; H, 7.87; N, 10.52. Found C, 69.97; H, 7.70; N, 10.46.

Example 17

1-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-6-methylheptan-4-one



Step 1:

The general method described in Step 1 of Example 15 was used to react 4-chloro-3-nitroquinoline (49.6 g, 238 mmol), ethyl 4-aminobutyrate hydrochloride (43.8 g, 262 mmol), and triethylamine (36.1 g, 357 mmol) in dichloromethane for 15 hours to provide ethyl 4-(3-nitroquinolin-4-ylamino)butyrate (63.8 g) as a yellow solid that was used directly in the next step without further purification.

Step 2:

The general method described in Step 2 of Example 6 was used to reduce ethyl 4-(3-nitroquinolin-4-ylamino)butyrate (37.0 g, 122 mmol) to provide ethyl 4-(3-aminoquinolin-4-ylamino)butyrate (24.9 g) as a dark oil that was used directly in the next step without further purification.

Step 3:

The general method described in Step 3 of Example 15 was used to cyclize ethyl 4-(3-aminoquinolin-4-ylamino)butyrate (18.0 g, 65.9 mmol) by reaction with trimethyl orthobutyrate (10.4 g, 70.2 mmol) to provide ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate (14.2 g) as a solid after chromatography on silica gel (elution with 5% methanol in dichloromethane).

Step 4:

A solution of trimethylaluminum in toluene (80 mL of a 2 M solution, 160 mmol) was added dropwise to a stirred suspension of *N,O*-dimethylhydroxylamine hydrochloride (15.6 g, 160 mmol) in dichloromethane (150 mL) at 0°C. After 15 minutes, the reaction flask was removed from bath and the solution stirred for 15 minutes at room temperature. The flask was then

cooled in ice bath, and a solution of ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate (34.7 g, 107 mmol) in dichloromethane (100 mL) was added rapidly dropwise. After 15 minutes, the ice bath was removed and the solution heated at reflux to cause considerable gas evolution. After 20 hours, a 10 % solution of hydrochloric acid in water (15 mL) was added slowly, followed by a saturated solution of sodium bicarbonate in water (50 mL). The layers were separated, and the aqueous mixture was extracted with dichloromethane (2 x 50 mL). The combined organic solutions were washed successively with a 5% solution of sodium hydroxide in water (2 x 50 mL) and a saturated solution of sodium bicarbonate in water (1x 50 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to provide *N*-methoxy-*N*-methyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide (35.9 g) as a dark oil that was used directly in the next step without further purification.

Step 5:

To a stirred solution of *N*-methoxy-*N*-methyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide (4.80 g, 14.1 mmol) in THF (100 mL) in a dry ice/isopropanol bath was added a solution of isobutylmagnesium chloride (28 mL of a 2 M solution in diethyl ether, 56 mmol) over a period of several minutes. When addition was complete, the reaction flask was removed from the cold bath and the mixture stirred for 4 hours at room temperature. A 10% solution of hydrochloric acid in water (3 mL) was added slowly, followed by a saturated solution of sodium bicarbonate in water (15 mL) and dichloromethane (100 mL). The layers were separated, the aqueous phase extracted with dichloromethane (1 x 75 mL), and the combined organics dried over potassium carbonate, filtered, and concentrated under reduced pressure. After chromatography on silica gel (elution with 5% methanol in dichloromethane) 6-methyl-1-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)heptan-4-one (2.40 g) was obtained as an oil.

Step 6:

The general method described in Steps 9 and 10 of Example 1 was used to aminate 6-methyl-1-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)heptan-4-one (2.40 g, 7.10 mmol) by reaction with m-CPBA (3.9 g) to provide 6-methyl-1-(5-

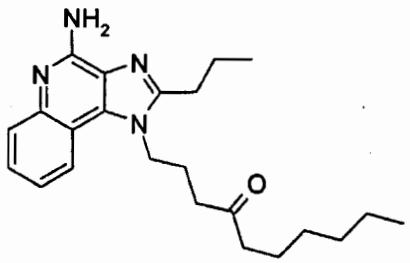
oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)heptan-4-one followed by reaction with *p*-toluenesulfonyl chloride (2.0 g, 10.5 mmol) and ammonium hydroxide solution (75 mL) to provide 1-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-6-methylheptan-4-one as tan crystals after recrystallization from aqueous methanol, mp 136-138 °C.

MS (APCI) *m/z* 353 $(M + H)^+$;

Anal. calcd for $C_{21}H_{28}N_4O$: C, 71.56; H, 8.01; N, 15.90. Found: C, 71.33; H, 8.09; N, 15.69.

Example 18

1-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)decan-4-one



Steps 1 through 4:

The general method described in Steps 1 through 4 of Example 17 was used to prepare *N*-methoxy-*N*-methyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide.

Step 5:

The general method described in Step 5 of Example 17 was used to react *N*-methoxy-*N*-methyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide (6.10 g, 17.9 mmol) with *n*-hexylmagnesium bromide (13.5 mL of a 2 M solution in diethyl ether, 27 mmol) to provide 1-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)decan-4-one (6.10 g) as a yellow oil that was used directly in the next step without further purification.

Step 6:

The general method described in Steps 9 and 10 of Example 1 was used to aminate 1-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)decan-4-one (6.10 g, 17.2 mmol) by reaction with m-CPBA (8.50 g) to provide 1-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)decan-4-one followed by reaction with *p*-

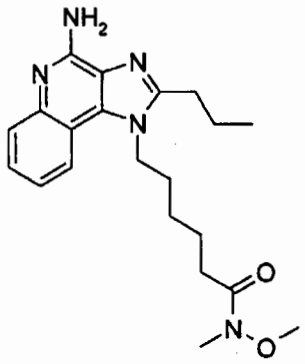
toluenesulfonyl chloride (4.90 g, 25.8 mmol) and ammonium hydroxide solution (100 mL) to provide 1-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)decan-4-one) as a white solid after recrystallization from aqueous methanol, mp 111-113 °C.

MS (APCI) *m/z* 381 $(M + H)^+$;

Anal. calcd for $C_{23}H_{32}N_4O$: C, 72.59; H, 8.48; N, 14.72. Found: C, 72.53; H, 8.59; N, 14.63.

Example 19

6-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methoxy-*N*-methylhexanamide



Steps 1 through 5:

The method described in Steps 1 through 5 of Example 15 was used to prepare *N*-methoxy-*N*-methyl-6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide.

Step 6:

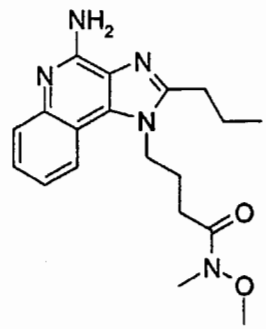
The general method described in Steps 9 and 10 of Example 1 was used to aminate *N*-methoxy-*N*-methyl-6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide (4.01 g, 10.9 mmol) by reaction with m-CPBA (6.13 g) to provide *N*-methoxy-*N*-methyl-6-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanamide followed by reaction with *p*-toluenesulfonyl chloride (2.53 g, 13.3 mmol) and ammonium hydroxide solution (40 mL) to provide 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methoxy-*N*-methylhexanamide) as an off-white solid after recrystallization from a mixture of ethyl acetate and hexane, mp 134-135°C.

MS (APCI) m/z = 384 $(M+H)^+$;

Anal. calcd for $C_{21}H_{29}N_5O_2 \cdot 0.023\ C_4H_8O_2$: C, 65.71; H, 7.63; N, 18.17. Found C, 65.44; H, 7.77; N, 17.88.

Example 20

4-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methoxy-*N*-methylbutyramide



Steps 1 through 4:

The method of Steps 1 through 4 of Example 17 was used to prepare *N*-methoxy-*N*-methyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide.

Step 5:

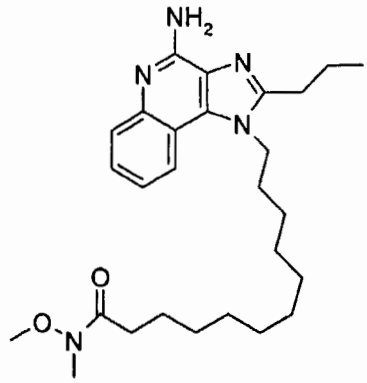
The general method described in Steps 9 and 10 of Example 1 was used to aminate *N*-methoxy-*N*-methyl-4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide (7.4 g, 21.7 mmol) by reaction with m-CPBA (9.50 g) to provide *N*-methoxy-*N*-methyl-4-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyramide followed by reaction with *p*-toluenesulfonyl chloride (7.20 g, 37.8 mmol) and ammonium hydroxide solution (200 mL) to provide 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methoxy-*N*-methyl-butyramide as white crystals after recrystallization from aqueous methanol, mp 163-165 °C.

MS (APCI) *m/z* 356 $(M + H)^+$;

Anal. calcd for $C_{19}H_{25}N_5O_2$: C, 64.20; H, 7.09; N, 19.70. Found: C, 64.10; H, 6.91; N, 19.57.

Example 21

12-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methoxy-*N*-methyldodecanamide hydrochloride



Steps 1 through 5:

The method of Steps 1 through 5 of Example 16 was used to prepare *N*-methoxy-*N*-methyl-12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanamide.

Step 6:

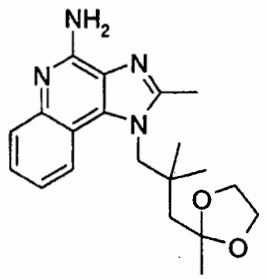
The general methods described in Steps 9 and 10 of Example 1 and Step 7 of Example 16 was used to aminate *N*-methoxy-*N*-methyl-12-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanamide (4.01 g, 8.86 mmol) by reaction with m-CPBA (6.13 g) to provide *N*-methoxy-*N*-methyl-12-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)dodecanamide followed by reaction with *p*-toluenesulfonyl chloride (2.53 g, 13.3 mmol) and ammonium hydroxide solution (40 mL) to provide 2-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methoxy-*N*-methyldodecanamide hydrochloride as an off-white solid after recrystallizationof the hydrochloride salt from isopropanol, mp 156-158 °C.

MS (APCI) m/z = 468 $(M+H)^+$;

Anal. calcd for $C_{27}H_{41}N_5O_2 \cdot 1.20$ HCl: C, 63.41; H, 8.31; N, 13.69. Found C, 63.44; H, 8.24; N, 13.74.

Example 22

1-[2,2-Dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Step 1:

A mixture of nitromethane (36.3 g, 0.59 mol), mesityl oxide (53.0 g, 0.54 mol), and 1,5-diazabicyclo[5.4.0]undec7-ene (DBU, 1.5 g, 10 mmol) was allowed to stand at room temperature for 14 days. Dichloromethane (150 mL) was then added, and the solution was washed with a 10% hydrochloric acid solution (3 x 35 mL), dried over potassium carbonate, and filtered. The dichloromethane solution of 4,4-dimethyl-5-nitropentan-2-one was used directly in the next step without further purification.

Step 2:

A stirred solution of 1,2-bis(trimethylsilyloxy)ethane (26.5 g, 128 mmol) in dichloromethane (50 mL) was cooled in a dry ice/isopropanol bath, and trimethylsilyl trifluoromethanesulfonate (2.2 g, 1.0 mmol) was added, followed by the dichloromethane solution of 4,4-dimethyl-5-nitropentan-2-one (50 mL, 19.0 g, 119 mmol) from the previous step. After 30 minutes, the cooling bath was removed and the solution was allowed to warm to room temperature. The solution was filtered through a plug of potassium carbonate and concentrated under reduced pressure to provide 2-(2,2-dimethyl-3-nitropropyl)-2-methyl-[1,3]dioxolane (23.5 g) as a dark oil that was used directly in the next step without further purification.

Step 3:

A Parr hydrogenation vessel was charged with 2-(2,2-dimethyl-3-nitropropyl)-2-methyl-[1,3]dioxolane (23.1 g, 113 mmol), 5% platinum on carbon catalyst (3.0 g) and ethanol (250 mL); placed on a Parr shaker; and the

system pressurized to 50 psi (3.4 x 10^5 Pa) hydrogen. After shaking for 24 hours, the reaction mixture was filtered through CELITE filter agent and concentrated under reduced pressure to provide 2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propylamine (19.8 g) as an oil that was used directly in the next step without further purification.

Step 4:

The general method described in Step 1 of Example 1 was used to react 4-chloro-3-nitroquinoline (21.8 g, 104 mmol), 2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propylamine (19.8 g, 114 mmol) and triethylamine (15.2 g, 150 mmol) in dichloromethane for 75 hours to provide [2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-(3-nitroquinolin-4-yl)amine (35.9 g) as a yellow solid that was used directly in the next step without further purification.

Step 5:

The general method described in Step 2 of Example 6 was used to reduce [2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-(3-nitroquinolin-4-yl)amine (35.9 g, 104 mmol) to provide N^4-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]quinoline-3,4-diamine (25.2 g) as a dark oil that was used directly in the next step without further purification.

Step 6:

The general method described in Step 3 of Example 6 was used to cyclize N^4-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]quinoline-3,4-diamine (8.0 g, 25.4 mmol) by reaction with trimethyl orthoacetate (3.6 g, 30 mmol) to provide 1-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-2-methyl-1*H*-imidazo[4,5-*c*]quinoline (5.80 g) as a solid after chromatography on silica gel (elution with a solution of 7% methanol in dichloromethane that contained about 5 mL of ammonium hydroxide solution per liter of eluent).

Step 7:

The general method described in Steps 9 and 10 of Example 1 was used to aminate 1-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-2-methyl-1*H*-imidazo[4,5-*c*]quinoline (5.80 g, 17.1 mmol) by reaction with m-CPBA (7.5 g) to provide 1-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-2-methyl-5-oxido-1*H*-imidazo[4,5-*c*]quinoline followed by reaction with *p*-

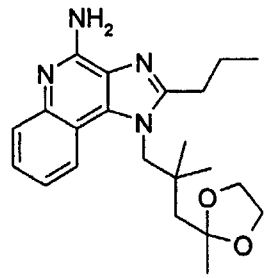
toluenesulfonyl chloride (5.7 g, 30 mmol) and ammonium hydroxide solution (150 mL) to provide 1-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a light brown solid after recrystallization from a mixture of acetonitrile, methanol, and water, mp 209-211 °C.

MS (APCI) *m/z* 355 $(M + H)^+$;

Anal. calcd for $C_{20}H_{26}N_4O_2$: C, 67.77; H, 7.39; N, 15.81. Found: C, 67.68; H, 7.62; N, 15.87.

Example 23

1-[2,2-Dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Steps 1 – 5 were the same as described for Example 22.

Step 6:

The general method described in Step 6 of Example 22 was used to cyclize N^4-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]quinoline-3,4-diamine (9.1 g, 28.9 mmol) by reaction with trimethyl orthobutyrate (4.4 g, 30 mmol) to provide 1-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinoline (3.10 g) as a solid after chromatography on silica gel (elution with a solution of 7% methanol in dichloromethane that contained about 5 mL of ammonium hydroxide solution per liter of eluent).

Step 7:

The general method described in Steps 9 and 10 of Example 1 was used to aminate 1-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinoline (3.10 g, 8.44 mmol) by reaction with m-CPBA (3.70 g) to provide 1-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-5-oxido-2-

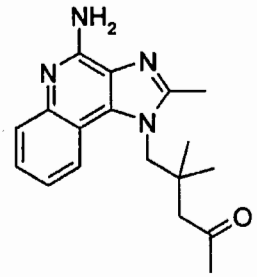
propyl-1*H*-imidazo[4,5-*c*]quinoline followed by reaction with *p*-toluenesulfonyl chloride (2.80 g, 14.7 mmol) and ammonium hydroxide solution (100 mL) to provide 1-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as off-white needles after recrystallization from aqueous methanol, mp 186-188 °C.

MS (APCI) *m/z* 383 $(M + H)^+$;

Anal. calcd for $C_{22}H_{30}N_4O_2$: C, 69.08; H, 7.91; N, 14.65. Found: C, 69.03; H, 8.15; N, 14.60.

Example 24

5-(4-Amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-4,4-dimethylpentan-2-one



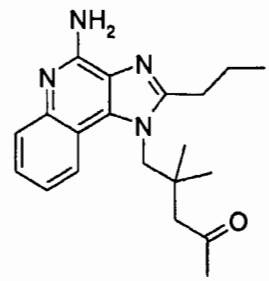
By the general method of Example 11, 1-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine was hydrolyzed with aqueous hydrochloric acid to provide 5-(4-amino-2-methyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-4,4-dimethylpentan-2-one as a light brown solid after recrystallization from aqueous acetonitrile, mp 223-225 °C.

MS (APCI) *m/z* 311 $(M + H)^+$;

Anal. calcd for $C_{18}H_{22}N_4O$: C, 69.65; H, 7.14; N, 18.05. Found: C, 69.64; H, 7.42; N, 18.04.

Example 25

5-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-4,4-dimethylpentan-2-one



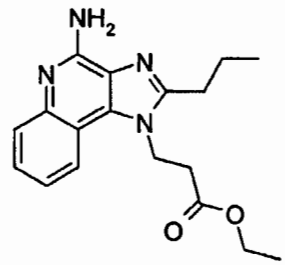
By the general method of Example 11, 1-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine was hydrolyzed with aqueous hydrochloric acid to provide 5-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-4,4-dimethylpentan-2-one as a light brown solid after recrystallization from aqueous acetonitrile, mp 178-180 °C.

MS (APCI) *m/z* 339 $(M + H)^+$;

Anal. calcd for $C_{20}H_{26}N_4O$: C, 70.97; H, 7.74; N, 16.55. Found: C, 70.80; H, 7.89; N, 16.66.

Example 26

Ethyl 3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate



Step 1:

The general method described in Step 1 of Example 1 was used to react 4-chloro-3-nitroquinoline (45.3 g, 217 mmol), *β*-alanine ethyl ester hydrochloride (40.0 g, 240 mmol), and triethylamine (54.8 g, 542 mmol) in dichloromethane for 15 hours to provide ethyl 3-(3-nitroquinolin-4-ylamino)propionate (62.0 g) as a yellow solid.

Step 2:

The general method described in Step 2 of Example 6 was used to reduce ethyl 3-(3-nitroquinolin-4-ylamino)propionate to provide ethyl 3-(3-aminoquinolin-4-ylamino)propionate (40.2 g) as a dark oil that was used directly in the next step without further purification.

Step 3:

The general method described in Step 3 of Example 15 was used to cyclize ethyl 3-(3-aminoquinolin-4-ylamino)propionate (11.0 g, 42.4 mmol) by reaction with trimethyl orthobutyrate (7.22 g, 48.7 mmol) to provide ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (10.6 g) as a dark oil that was used directly in the next step without further purification.

Step 4:

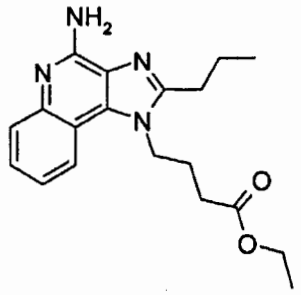
The general method described in Steps 9 and 10 of Example 1 was used to aminate ethyl 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate (3.30 g, 10.6 mmol) by reaction with m-CPBA (4.63 g) to provide ethyl 3-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propionate followed by reaction with *p*-toluenesulfonyl chloride (3.53 g, 18.6 mmol) and ammonium hydroxide solution (50 mL) to provide ethyl 3-(4-amino-2-propyl-1*H*-imidazo[4,5-c]quinolin-1-yl)propionate as an off-white solid after recrystallization from aqueous methanol, mp 156-157 °C.

MS (APCI) m/z = 327 $(M+H)^+$;

Anal. calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.16. Found C, 65.98; H, 6.96; N, 17.29.

Example 27

Ethyl 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate



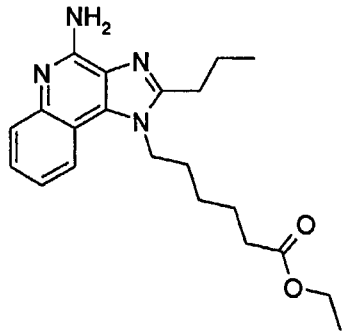
The general method described in Steps 9 and 10 of Example 1 was used to aminate ethyl 4-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate (8.20 g, 25.2 mmol, available from Step 3 of Example 17) by reaction with m-CPBA (14.1 g) to provide ethyl 4-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate followed by reaction with *p*-toluenesulfonyl chloride (8.40 g, 44.1 mmol) and ammonium hydroxide solution (150 mL) to provide ethyl 4-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyrate as an off-white solid after recrystallization from aqueous methanol, mp 154-156 °C.

MS (APCI) m/z = 341 $(M+H)^+$;

Anal. calcd for $C_{19}H_{24}N_4O_2$: C, 67.04; H, 7.11; N, 16.46. Found C, 66.68; H, 6.87; N, 16.51.

Example 28

Ethyl 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate



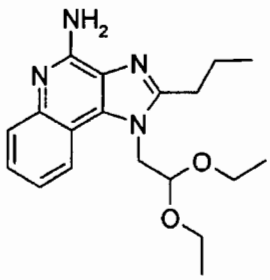
The general method described in Steps 9 and 10 of Example 1 was used to aminate ethyl 6-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate (6.30 g, 17.8 mmol, available from Step 3 of Example 15) by reaction with m-CPBA (13.1 g) to provide ethyl 6-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate followed by reaction with *p*-toluenesulfonyl chloride (4.58 g, 24.0 mmol) and ammonium hydroxide solution (60 mL) to provide ethyl 6-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)hexanoate as a tan solid after recrystallization from aqueous methanol, mp 112-113 °C.

MS (APCI) m/z = 369 $(M+H)^+$;

Anal. calcd for $C_{21}H_{28}N_4O_2 \cdot 1.0\ H_2O$: C, 67.77; H, 7.69; N, 15.05. Found C, 67.39; H, 7.73; N, 14.79.

Example 29

1-(2,2-Diethoxyethyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Step 1:

The general method described in Step 1 of Example 1 was used to react 4-chloro-3-nitroquinoline (20.9 g, 100 mmol), aminoacetaldehyde diethyl acetal (14.4 g, 110 mmol), and triethylamine (12.6 g, 125 mmol) in dichloromethane for 15 hours to provide (2,2-diethoxyethyl)-(3-nitroquinolin-4-yl)amine (29.7 g) as a yellow solid.

Step 2:

The general method described in Step 2 of Example 6 was used to reduce (2,2-diethoxyethyl)-(3-nitroquinolin-4-yl)amine to provide N^4-(2,2-diethoxyethyl)quinoline-3,4-diamine (26.5 g) as a dark oil that was used directly in the next step without further purification.

Step 3:

The general method described in Step 3 of Example 15 was used to cyclize N^4-(2,2-diethoxyethyl)quinoline-3,4-diamine (26.5 g, 96.2 mmol) by reaction with trimethyl orthobutyrate (15.9 g, 107 mmol) to provide 1-(2,2-diethoxyethyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline (25.4 g) as a dark oil that was used directly in the next step without further purification.

Step 4:

The general method described in Steps 9 and 10 of Example 1 was used to aminate 1-(2,2-diethoxyethyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline (4.50 g, 13.7 mmol) by reaction with m-CPBA (6.0 g) to provide 1-(2,2-diethoxyethyl)-5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinoline followed by reaction with *p*-toluenesulfonyl chloride (4.60 g, 24.1 mmol) and ammonium hydroxide solution

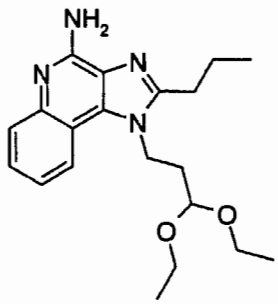
(130 mL) to provide 1-(2,2-diethoxyethyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off-white solid after recrystallization from aqueous methanol, mp 148-150 °C.

MS (APCI) m/z = 343 $(M+H)^+$;

Anal. calcd for $C_{19}H_{26}N_4O_2$: C, 66.64; H, 7.65; N, 16.36. Found C, 66.62; H, 7.80; N, 16.43

Example 30

1-(3,3-Diethoxypropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Step 1:

The general method described in Step 1 of Example 1 was used to react 4-chloro-3-nitroquinoline (20.3 g, 97.1 mmol), 1-amino-3,3-diethoxypropane (25.0 g, 116 mmol) and triethylamine (33.8 g, 333 mmol) in dichloromethane for 15 hours to provide (3,3-diethoxypropyl)-(3-nitroquinolin-4-yl)amine (30.5 g) as a yellow solid.

Step 2:

The general method described in Step 2 of Example 6 was used to reduce (3,3-diethoxypropyl)-(3-nitroquinolin-4-yl)amine to provide N^4-(3,3-diethoxypropyl)quinoline-3,4-diamine (20.7 g) as a dark oil that was used directly in the next step without further purification.

Step 3:

The general method described in Step 3 of Example 15 was used to cyclize N^4-(3,3-diethoxypropyl)quinoline-3,4-diamine (20.7 g, 71.5 mmol) by reaction with trimethyl orthobutyrate (13.2 g, 89.4 mmol) to provide 1-(3,3-diethoxypropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline (22.3 g) as a dark oil that was used directly in the next step without further purification.

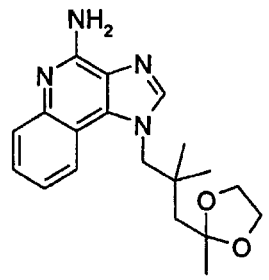
Step 4:

The general method described in Steps 9 and 10 of Example 1 was used to aminate 1-(3,3-diethoxyproyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinoline (4.50 g, 13.2 mmol) by reaction with m-CPBA (5.3 g) to provide 1-(3,3-diethoxypropyl)-5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinoline followed by reaction with *p*-toluenesulfonyl chloride (4.89 g, 25.7 mmol) and ammonium hydroxide solution (40 mL) to provide 1-(3,3-diethoxypropyl)-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as grey needles after recrystallization from methanol, mp 148-150 °C. MS (APCI) m/z = 357 $(M+H)^+$;

Anal. calcd for $C_{20}H_{28}N_4O_2$: C, 67.39; H, 7.92; N, 15.72. Found C, 67.24; H, 8.05; N, 15.70.

Example 31

1-[2,2-Dimethyl-3-(2-methyl[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Steps 1 – 5 were the same as described for Example 22.

Step 6:

The general method described in Step 6 of Example 22 was used to cyclize N^4-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]quinoline-3,4-diamine (8.1 g, 25.7 mmol) by reaction with trimethyl orthoformate (3.3 g, 10 mmol) to provide 1-[2,2-dimethyl-3-(2-methyl[1,3]dioxolan-2-yl)propyl]-1H-imidazo[4,5-c]quinoline (8.8 g) as an oil that was used directly in the next step without further purification.

Step 7:

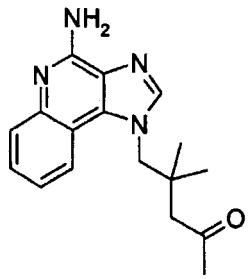
The general method described in Steps 9 and 10 of Example 1 was used to aminate 1-[2,2-dimethyl-3-(2-methyl[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinoline (8.8 g, 27 mmol) by reaction with m-CPBA (11.8 g) to provide 1-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-5-oxido-1*H*-imidazo[4,5-*c*]quinoline followed by reaction with *p*-toluenesulfonyl chloride (9.1 g, 48 mmol) and ammonium hydroxide solution (100 mL) to provide 1-[2,2-dimethyl-3-(2-methyl[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a light brown solid after chromatography on silica gel (elution with a solution of 7% methanol in dichloromethane that contained about 5 mL of ammonium hydroxide solution per liter of eluent) and recrystallization from aqueous methanol, mp 153-155 °C.

MS (APCI) *m/z* 341 $(M + H)^+$;

Anal. calcd for $C_{19}H_{24}N_4O_2$: C, 67.04; H, 7.11; N, 16.46. Found: C, 66.76; H, 7.39; N, 16.41.

Example 32

5-(4-Amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-4,4-dimethylpentan-2-one



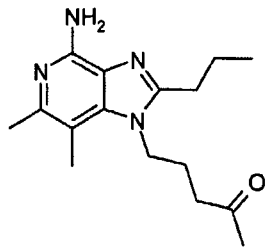
By the general method of Example 11, 1-[2,2-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)propyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine was hydrolyzed with aqueous hydrochloric acid to provide 5-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-4,4-dimethylpentan-2-one as a light yellow solid after recrystallization from aqueous methanol, mp 214-216 °C.

MS (APCI) *m/z* 297 $(M + H)^+$;

Anal. calcd for $C_{18}H_{22}N_4O$: C, 68.89; H, 6.80; N, 18.90. Found: C, 68.91; H, 6.85; N, 19.12.

Example 33

5-(4-Amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)pentan-2-one



Step 1:

2,4-Dichloro-5,6-dimethyl-3-nitropyridine (135.0 g, 0.488 mol) and ethyl 4-aminobutyrate hydrochloride (114.0 g, 0.683 mol) were triturated in *N,N*-dimethylformamide (675 mL) (DMF) at 0 °C. Triethylamine (272.6 mL, 1.95 mol) was added to generate a brown slurry. After 15 minutes, the reaction mixture was allowed to warm to ambient temperature and the reaction was stirred overnight. Analysis by ^{1}H NMR indicated the reaction was incomplete. An additional amount of triethylamine (102.2 mL, 0.73 mol) and ethyl 4-aminobutyrate hydrochloride (35.28 g, 0.159 mol) in DMF (200 mL) were added to the reaction mixture and allowed to stir over an additional 24 hours. Half of the reaction mixture was added to separate flasks and deionized water (3 L) was added to each flask and were stirred for 1 hour. The resulting precipitate in each flask was harvested by filtration and dried under reduced pressure. The crude product was recrystallized from ethyl acetate and filtered to yield 86.20 g of ethyl 4-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]butyrate as a yellow granular solid.

Step 2:

Ethyl 4-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]butyrate (86.2 g, 0.276 mol), sodium azide (35.49 g, 0.552 mol), and cerium chloride heptahydrate(50.86 g, 0.138 mol) were triturated in a 9:1 mixture of acetonitrile:water (1012 mL). The reaction mixture was stirred and heated to reflux for 18 hours. The reaction was filtered and the yellow filtrate was concentrated under reduced pressure to yield 90.94 g of crude product. The material was triturated at 95 °C with 360 mL ethyl acetate and filtered. The filtrate produced pale yellow crystals at ambient temperature to afford 64.3 g of

ethyl 4-[(5,6-dimethyl-8-nitrotetrazolo[1,5-*a*]pyridin-7-yl)amino]butyrate as a yellow solid.

Step 3:

Ethyl 4-[(5,6-dimethyl-8-nitrotetrazolo[1,5-*a*]pyridin-7-yl)amino]butyrate (64.3 g, 0.198 mol) was mixed with acetonitrile (2 L) and catalytic 10% palladium on carbon was added. The mixture was placed on a hydrogenator for 72 hours and filtered through a layer of CELITE filter aid. The filtrate was concentrated under reduced pressure to yield 58.2 g of ethyl 4-[(8-amino-5,6-dimethyltetrazolo[1,5-*a*]pyridin-7-yl)amino]butyrate.

Step4:

Pyridinium chloride (8.57 g, 74 mmol) and ortho-*n*-butyric acid trimethyl ester (34.6 mL, 217 mmol) were sequentially added to ethyl 4-[(8-amino-5,6-dimethyltetrazolo[1,5-*a*]pyridin-7-yl)amino]butyrate (58.2 g, 198 mmol) triturated in toluene (1165 mL) and heated to reflux for 0.5 hours. The reaction mixture was concentrated under reduced pressure and partitioned between dichloromethane and saturated aqueous sodium carbonate. The organic layer was isolated, concentrated under reduced pressure, and 52.99 g of ethyl 4-(5,6-dimethyl-8-propyl-1*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridin-7-yl)butyrate solid was recrystallized from ethyl acetate and used without additional purification.

Step 5:

Ethyl 4-(5,6-dimethyl-8-propyl-1*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridin-7-yl)butyrate (52.99 g, 0.153 mol) was slurried in ethanol (550 mL) and treated with a 50% sodium hydroxide solution for 0.5 hours. The reaction was concentrated under reduced pressure, maintained overnight, and dissolved in water (250 mL). The pH was adjusted to 5 and the resulting white precipitate was filtered. The residue was triturated at ambient temperature with methanol (1 L) and concentrated under reduced pressure to afford 4-(5,6-dimethyl-8-propyl-1*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridin-7-yl)butyric acid which was used without any further purification.

Step 6:

Five drops of *N,N*- dimethylformamide (DMF) were added to 4-(5,6-dimethyl-8-propyl-1*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridin-7-yl)butyric acid

(36.22 g, 113.8 mmol) and dichloromethane (725 mL). Oxalyl chloride (29.8 mL, 341.3 mmol) was added dropwise to the reaction mixture. After 10 minutes, the reaction mixture was concentrated under reduced pressure to afford 4-(5,6-dimethyl-8-propyl-1*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridin-7-yl)butyryl chloride.

Step 7:

4-(5,6-Dimethyl-8-propyl-1*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridin-7-yl)butyryl chloride (38.39 g, 114 mmol) was triturated with chloroform (768 mL) and cooled to 0 °C. *N,O*-Dimethylhydroxylamine hydrochloride (16.68 g, 171 mmol) and triethylamine (47.7 mL, 342 mmol, dropwise addition) were sequentially added to the reaction mixture and stirred for 0.5 hours. The reaction mixture was stirred for 10 additional minutes after addition of saturated aqueous sodium bicarbonate solution (400 mL). The organic phase was isolated, dried over sodium sulfate, and concentrated under reduced pressure to afford 40.01 g of 4-(5,6-dimethyl-8-propyl-1*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridin-7-yl)-*N*-methoxy-N-methylbutyramide as a yellow oil.

Step 8:

Methylmagnesium iodide (5.5 mL, 41.5 mmol) was added slowly dropwise to a triturated mixture of 4-(5,6-dimethyl-8-propyl-1*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridin-7-yl)-*N*-methoxy-N-methylbutyramide (10.0 g, 27.7 mmol) and tetrahydrofuran (125 mL) at 0 °C. The reaction was warmed to ambient temperature and ^{1}H NMR indicated the reaction was incomplete after stirring overnight. An additional amount of methyl magnesium iodide (5.5 mL, 41.5 mmol) was added at 18 and 21.75 hours after the initial addition. A final addition of methyl magnesium iodide (3.6 mL, 27 mmol) was added at 23 hours after the initial addition and allowed to react for one additional hour. Addition of 1N aqueous hydrogen chloride solution (35 mL) followed to generate a yellow-orange slurry and the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane (200 mL), washed with saturated aqueous sodium bicarbonate (100 mL), dried over sodium sulfate and concentrated under reduced pressure to afford 8.15 g of 5-(5,6-dimethyl-8-

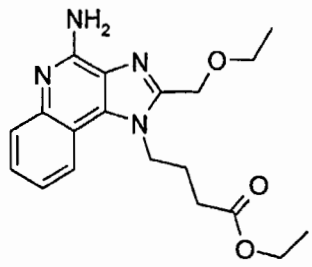
propyl-1*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridin-7-yl)pentan-2-one without any further purification.

Step 9:

Triphenylphosphine (13.5 g, 51.5 mmol) was added to a mixture of 5-(5,6-dimethyl-8-propyl-1*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridin-7-yl)pentan-2-one (8.15 g, 25.8 mmol) and 1,2-dichlorobenzene (163 mL) and heated to 133 °C for 13.5 hours. The reaction temperature was incrementally increased to 140 °C over an additional 1.5 hours. Additional triphenylphosphine (3.39 g, 12.9 mmol) was then added and the reaction was heated for one additional hour. The resulting dark brown solution was cooled to ambient temperature and concentrated under reduced pressure. The resulting residue was dissolved in methanol (150 mL) and 1 N aqueous hydrochloric acid (75 mL) was added to create a slurry. The reaction was stirred at 40 °C for an hour, upon which the resulting mixture was filtered, concentrated under reduced pressure, dissolved in dichloromethane (100 mL) and washed with 1 N aqueous hydrochloric acid. The aqueous layer was adjusted to pH 14 with saturated aqueous sodium bicarbonate and 50% sodium hydroxide solutions and the product was extracted into chloroform (250 mL). The organic layer was dried with sodium sulfate and concentrated under reduced pressure to produce 4.61 g of a brown solid material. The material was recrystallized from acetonitrile to yield 2.53 g of isolated material. A portion of the material (1.22 g) was purified by column chromatography on a BIOTAGE HORIZON High-Performance Flash Chromatography instrument (eluting with chloroform/methanol/ammonium hydroxide (80/18/2):chloroform ranging in ratios from 0:100 to 40:60) to provide 0.81 g of 5-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)pentan-2-one as an off-white powder, mp 148.5-149.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 5.58 (s, 2H), 4.16 (t, J = 8.1 Hz, 2H), 2.77 (t, J = 8.1 Hz, 2H), 2.58 (t, J = 6.9 Hz, 2H), 2.37 (s, 3H), 2.30 (s, 3H), 2.10 (s, 3H), 1.80 (m, J = 7.5 Hz, 4H), 1.00 (t, J = 7.5 Hz, 3H; MS (APCI) *m/z* 289 $(M + H)^+$; Anal. calcd for $C_{20}H_{26}N_6O_2$: C, 66.64; H, 8.39; N, 19.43. Found: C, 66.40; H, 8.63; N, 1944.

Example 34

Ethyl 4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanoate



Step 1:

A solution of ethoxyacetyl chloride (7.00 g, 57.1 mmol) in dichloromethane (10 mL) was added dropwise to a stirred solution of ethyl 4-(3-aminoquinolin-4-ylamino)butyrate (prepared as described in Steps 1-2 of Example 17, 12.5 g, 45.7 mmol) in dichloromethane (100 mL) at room temperature. After 1.5 hours, the reaction mixture was concentrated under reduced pressure to afford a solid to which was added ethanol (100 mL) and triethylamine (17.4 mL, 125 mmol). The solution was left at room temperature for 5 days, then was heated at reflux for 2 hours. The solution was concentrated under reduced pressure. The residue was partitioned between dichloromethane (150 mL) and water (50 mL). The organic layer was washed with water (50 mL) and saturated aqueous sodium bicarbonate (50 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to yield 15.4 g of ethyl 4-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanoate as a brown oil that was used in the next step without purification.

Step 2:

To a stirred solution of ethyl 4-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanoate (15.4 g, 45.1 mmol) in dichloromethane (150 mL) at 0 °C was added mCPBA (approximately 77% purity, 19.7 g, 87.9 mmol) in portions. The reaction mixture was stirred at room temperature for 1.5 hours, then concentrated ammonium hydroxide (50 mL) was added. *p*-Toluenesulfonyl chloride was added in portions to the mixture, which was stirred for 1 hour then filtered. The filtrate was transferred to a separatory funnel, saturated aqueous sodium bicarbonate (50 mL) was added and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 50 mL). The organic

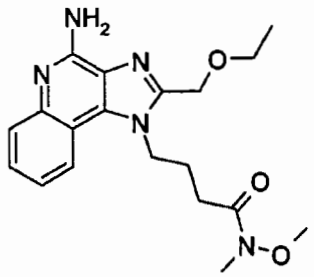
layers were combined, washed with 5% aqueous sodium hydroxide (2 x 75 mL), dried over potassium carbonate, filtered, and concentrated under reduced pressure to yield a brown solid that was slurried in ethyl acetate (50 mL) and filtered. The filtrate was concentrated under reduced pressure and the solid was recrystallized from ethanol/water four times, then was dissolved in dichloromethane (100 mL). The solution was washed with saturated aqueous sodium bicarbonate (2 x 50 mL), then was concentrated under reduced pressure to yield a solid that was recrystallized from ethanol/water three times. The crystals were dried in a vacuum oven at 70 °C to provide ethyl 4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanoate as pale yellow crystals, mp 129-131 °C.

MS (APCI) *m/z* 357 ($M + H^+$);

Anal. calcd for $C_{19}H_{24}N_4O_3$: C, 64.03; H, 6.79; N, 15.72. Found: C, 63.76; H, 6.89; N, 15.49.

Example 35

4-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-methoxy-*N*-methylbutanamide



Step 1:

A solution of trimethylaluminum in toluene (2 M, 35 mL, 70 mmol) was added to a stirred suspension of *N,O*-dimethylhydroxylamine hydrochloride (6.81 g, 69.9 mmol) in dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred for 15 minutes at °0 C, then at room temperature for 15 minutes before cooling to °0 C again. A solution of ethyl 4-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butanoate (prepared as described in Step 1 of Example 34) in dichloromethane (50 mL) was added. After 15 minutes, the

reaction mixture was allowed to warm to room temperature, then was heated at reflux for 2 days. The reaction mixture was allowed to cool to room temperature and dichloromethane (150 mL) was added. Methanol (10 mL) followed by 10% aqueous hydrochloric acid (10 mL) were added slowly. To the mixture was added saturated aqueous sodium bicarbonate. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with dichloromethane. The organic layers were combined, washed with saturated aqueous sodium bicarbonate, dried over potassium carbonate, filtered, and concentrated under reduced pressure to yield 13.9 g of an oil that was used without purification in the next step.

Step 2:

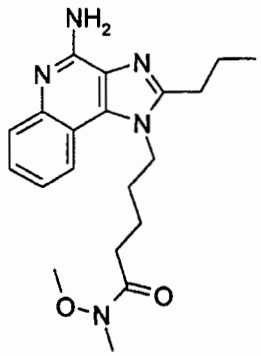
The material from Step 1 (13.9 g) was treated according to the general conditions described in Step 2 of Example 34. The crude product was slurried in ethyl acetate and filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, elution with a 7% methanol in dichloromethane solution containing 0.4% concentrated ammonium hydroxide by volume) to afford an oil that was triturated with ethyl acetate. A solid formed that was isolated by filtration and recrystallized twice from methanol/water. The crystals were dried overnight in a vacuum oven at 70 °C to provide 1.59 g of 4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-*N*-methoxy-*N*-methylbutanamide as a pale yellow solid, mp 163-165 °C.

MS (APCI) *m/z* 372 ($M + H^+$);

Anal. calcd for $C_{19}H_{25}N_5O_3$: C, 61.44; H, 6.78; N, 18.85. Found: C, 61.48; H, 6.82; N, 18.68.

Example 36

5-(4-Amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methoxy-*N*-methylpentanamide



Step 1:

Potassium carbonate (66.23 g, 0.479 mol), triethylamine (167 mL, 1.20 mol), and ethyl 5-aminovalerate hydrochloride (104 g, 0.575 mol) were added to a mixture of 4-chloro-3-nitroquinoline (100 g, 0.470 mol) in chloroform (1 L). The reaction mixture was stirred at room temperature for 4 hours, then water (200 mL) was added. The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 151 g of ethyl 5-[(3-nitroquinolin-4-yl)amino]pentanoate.

Step 2:

The general method described in Step 2 of Example 6 was used to reduce ethyl 5-[(3-nitroquinolin-4-yl)amino]pentanoate (151 g, 0.476 mol) to 131.5 g of crude ethyl 5-[(3-aminoquinolin-4-yl)amino]pentanoate, which was used in the next step without purification.

Step 3:

The general method described in Step 3 of Example 6 was used to convert crude ethyl 5-[(3-aminoquinolin-4-yl)amino]pentanoate (26.3 g, 91.5 mmol) into 28 g of crude ethyl 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoate, using trimethyl orthobutyrate in lieu of triethyl orthoacetate.

Step 4:

A solution of sodium hydroxide (2.23 g, 55.9 mmol) in water (100 mL) was added to a solution of ethyl 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoate (14.6 g, 43.0 mmol) in ethanol (100 mL). The reaction mixture was stirred at room temperature overnight, then the ethanol was removed under reduced pressure. The remaining aqueous solution was washed with dichloromethane and adjusted to pH 5 with 10% aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (2 x). The later organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to yield 11.5 g of 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoic acid as yellow solid.

Step 5

Oxalyl chloride (2.62 mL, 30.1 mmol) was added to a solution of 5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanoic acid (5.21 g, 16.7 mmol) in dichloromethane (50 mL) at room temperature. The reaction was stirred for 1 hour, then the volatiles were removed under reduced pressure. Dichloromethane (50 mL) was added to the residue, followed by *N,O*-dimethylhydroxylamine hydrochloride (3.26 g, 33.5 mmol) and *N,N*-dimethylformamide (2 mL). The reaction mixture was stirred at room temperature overnight, then was concentrated under reduced pressure. The residue was diluted with dichloromethane and an ammonium hydroxide solution. The mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 5.5 g of crude *N*-methoxy-*N*-methyl-5-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)pentanamide as a brown oil that was used without purification in the next step.

Step 6:

The material from Step 5 was treated according to a modification of the procedure described in Step 2 of Example 34. The reaction mixture was worked up by separating the layers using a separatory funnel. The organic layer was washed with saturated aqueous sodium bicarbonate and brine, dried over

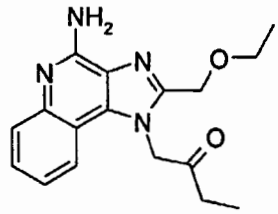
magnesium sulfate, filtered, and concentrated under reduced pressure. The crude 5-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methoxy-*N*-methylpentanamide was purified by flash chromatography (silica gel, eluted with 10% methanol in dichloromethane) to provide a solid. Acetone was added to the solid and the mixture was sonicated. The solid was isolated by filtration and dried at 80 °C in a vacuum oven to provide 5-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)-*N*-methoxy-*N*-methylpentanamide as beige needles, mp 150-151 °C.

MS (APCI) *m/z* 370.1($M+H^+$);

Anal. calcd for $C_{20}H_{27}N_5O_2 \cdot 0.15\ H_2O$: C, 64.51; H, 7.40; N, 18.81. Found: C, 64.16; H, 7.40; N, 18.81.

Example 37

1-[4-Amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butan-2-one



Step 1:

1-(Aminomethyl)cyclopropanol was prepared using the method of I. L. Lysenko and O. G. Kulinkovich, *Russ. J. Org. Chem., 37*, pp. 1238-1243 (2001). A solution of 4-chloro-3-nitroquinoline (7.28 g, 34.9 mmol) in dichloromethane (30 mL) was added dropwise to a 0 °C stirred suspension of 1-(aminomethyl)cyclopropanol (36.7 mmol) and triethylamine (6.30 mL, 45.4 mmol) in dichloromethane (120 mL). The mixture was stirred at room temperature for 3 days, then was concentrated under reduced pressure. The residue was suspended in water (150 mL) and was stirred for 3 hours. The solid was isolated by filtration, washed with water (50 mL), and dried in a vacuum oven at 75 °C to afford 8.99 g of 1-{[(3-nitroquinolin-4-yl)amino]methyl}cyclopropanol as a yellow solid.

Step 2:

A mixture of 1-{[(3-nitroquinolin-4-yl)amino]methyl}cyclopropanol (4.00 g, 15.4 mmol) and 5% platinum on carbon (400 mg) in ethyl acetate (80 mL) and methanol (8 mL) was hydrogenated on a Parr apparatus at 35 psi (2.4 x 10^5 Pa) of hydrogen at room temperature for 3 hours. The mixture was filtered through CELITE filter agent, which was rinsed with 10% methanol/ethyl acetate. The filtrate was concentrated to an orange oil that was used directly in the next step.

Step 3:

The material from Step 2 was dissolved in dichloromethane (70 mL). The solution was cooled to 0 °C and ethoxyacetyl chloride (1.7 mL, 16.9 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 hour, then the solvent was removed under reduced pressure. The residue was used directly in the next step.

Step 4:

The material from Step 3 was dissolved in ethanol (70 mL) and 2 M aqueous sodium hydroxide (15 mL, 30.8 mmol) was added. The reaction mixture was heated at 60 °C for 1 hour, then was stirred at room temperature overnight. The volatiles were removed under reduced pressure and to the resulting residue was added dichloromethane (70 mL) and water (50 mL). The mixture was adjusted to pH 7 with 1 M HCl. The layers were separated and the aqueous layer was extracted with dichloromethane (25 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to afford 4.23 g of crude 1-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butan-2-one a tan solid.

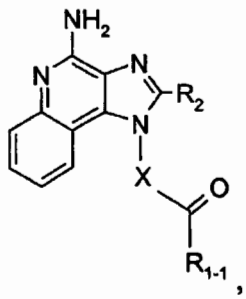
Step 5:

mCPBA (2.11 g, 8.57 mmol) was added to a solution of 1-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butan-2-one (1.96 g, 6.59 mmol) in chloroform (30 mL) at room temperature. The reaction mixture was stirred for 1 hour, then was cooled to 0 °C. Concentrated ammonium hydroxide (10 mL) and p-toluenesulfonyl chloride (1.38 g, 7.25 mmol) were added. The mixture was stirred at 0 °C for 1 hour, then was filtered. The filtrate was diluted

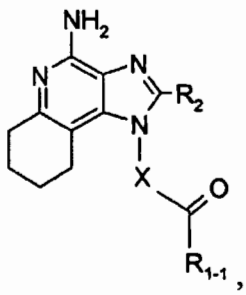
with dichloromethane (50 mL) and saturated aqueous sodium bicarbonate (50 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (25 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to yield a brown solid. The solid was purified by chromatography on a HORIZON High-Performance Flash Chromatography (HPFC) instrument (available from Biotage, Inc, Charlottesville, Virginia, USA) (silica gel, gradient elution with 0-35% of a solution comprised of 80% CHCl3, 18% MeOH, and 2% conc. NH_4OH (CMA) in chloroform) to afford a tan solid that was recrystallized from chloroform/hexanes. The crystals were isolated by filtration and dried in a vacuum oven at 80 °C to afford 0.718 g of 1-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butan-2-one as pale pink needles, mp 187-188 °C.
MS (APCI) *m/z* 313 $(M + H)^+$;
Anal. calcd for $C_{17}H_{20}N_4O_2$: C, 65.37; H, 6.45; N, 17.94. Found: C, 65.22; H, 6.19; N, 17.71.

Exemplary Compounds

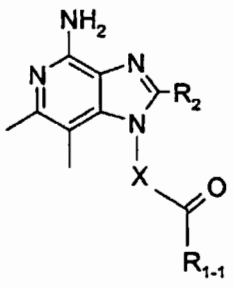
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (I-2a, I-4a, and I-3a) wherein X, R_2, and R_{1-1} are defined immediately below in the table. In this table, for each ring system, each line represents one specific compound.



I-2a



I-4a



I-3a

R_2	X	R_{1-1}
H (hydrogen)	$-CH_2-$	methyl
H	$-CH_2-$	ethyl
H	$-CH_2-$	*n*-propyl
H	$-CH_2-$	isopropyl
H	$-CH_2-$	cyclopropyl
H	$-CH_2-$	*n*-butyl
H	$-CH_2-$	*sec*-butyl
H	$-CH_2-$	isobutyl
H	$-CH_2-$	*tert*-butyl
H	$-CH_2-$	*n*-pentyl
H	$-CH_2-$	cyclopentyl
H	$-CH_2-$	*n*-hexyl
H	$-CH_2-$	cyclohexyl
H	$-CH_2-$	phenyl
H	$-CH_2-$	4-chlorophenyl
H	$-CH_2-$	2,4-dichlorophenyl
H	$-(CH_2)_2-$	methyl
H	$-(CH_2)_2-$	ethyl
H	$-(CH_2)_2-$	*n*-propyl
H	$-(CH_2)_2-$	isopropyl
H	$-(CH_2)_2-$	cyclopropyl
H	$-(CH_2)_2-$	*n*-butyl
H	$-(CH_2)_2-$	*sec*-butyl
H	$-(CH_2)_2-$	isobutyl
H	$-(CH_2)_2-$	*tert*-butyl
H	$-(CH_2)_2-$	*n*-pentyl
H	$-(CH_2)_2-$	cyclopentyl
H	$-(CH_2)_2-$	*n*-hexyl
H	$-(CH_2)_2-$	cyclohexyl
H	$-(CH_2)_2-$	phenyl
H	$-(CH_2)_2-$	4-chlorophenyl
H	$-(CH_2)_2-$	2,4-dichlorophenyl
H	$-(CH_2)_3-$	methyl
H	$-(CH_2)_3-$	ethyl
H	$-(CH_2)_3-$	*n*-propyl
H	$-(CH_2)_3-$	isopropyl
H	$-(CH_2)_3-$	cyclopropyl
H	$-(CH_2)_3-$	*n*-butyl
H	$-(CH_2)_3-$	*sec*-butyl
H	$-(CH_2)_3-$	isobutyl
H	$-(CH_2)_3-$	*tert*-butyl
H	$-(CH_2)_3-$	*n*-pentyl
H	$-(CH_2)_3-$	cyclopentyl
H	$-(CH_2)_3-$	*n*-hexyl

H	$-(CH_2)_3-$	cyclohexyl
H	$-(CH_2)_3-$	phenyl
H	$-(CH_2)_3-$	4-chlorophenyl
H	$-(CH_2)_3-$	2,4-dichlorophenyl
H	$-(CH_2)_4-$	methyl
H	$-(CH_2)_4-$	ethyl
H	$-(CH_2)_4-$	*n*-propyl
H	$-(CH_2)_4-$	isopropyl
H	$-(CH_2)_4-$	cyclopropyl
H	$-(CH_2)_4-$	*n*-butyl
H	$-(CH_2)_4-$	*sec*-butyl
H	$-(CH_2)_4-$	isobutyl
H	$-(CH_2)_4-$	*tert*-butyl
H	$-(CH_2)_4-$	*n*-pentyl
H	$-(CH_2)_4-$	cyclopentyl
H	$-(CH_2)_4-$	*n*-hexyl
H	$-(CH_2)_4-$	cyclohexyl
H	$-(CH_2)_4-$	phenyl
H	$-(CH_2)_4-$	4-chlorophenyl
H	$-(CH_2)_4-$	2,4-dichlorophenyl
H	$-(CH_2)_5-$	methyl
H	$-(CH_2)_5-$	ethyl
H	$-(CH_2)_5-$	*n*-propyl
H	$-(CH_2)_5-$	isopropyl
H	$-(CH_2)_5-$	cyclopropyl
H	$-(CH_2)_5-$	*n*-butyl
H	$-(CH_2)_5-$	*sec*-butyl
H	$-(CH_2)_5-$	isobutyl
H	$-(CH_2)_5-$	*tert*-butyl
H	$-(CH_2)_5-$	*n*-pentyl
H	$-(CH_2)_5-$	cyclopentyl
H	$-(CH_2)_5-$	*n*-hexyl
H	$-(CH_2)_5-$	cyclohexyl
H	$-(CH_2)_5-$	phenyl
H	$-(CH_2)_5-$	4-chlorophenyl
H	$-(CH_2)_5-$	2,4-dichlorophenyl
H	$-(CH_2)_6-$	methyl
H	$-(CH_2)_6-$	ethyl
H	$-(CH_2)_6-$	*n*-propyl
H	$-(CH_2)_6-$	isopropyl
H	$-(CH_2)_6-$	cyclopropyl
H	$-(CH_2)_6-$	*n*-butyl
H	$-(CH_2)_6-$	*sec*-butyl
H	$-(CH_2)_6-$	isobutyl
H	$-(CH_2)_6-$	*tert*-butyl
H	$-(CH_2)_6-$	*n*-pentyl

H	$-(CH_2)_6-$	cyclopentyl
H	$-(CH_2)_6-$	*n*-hexyl
H	$-(CH_2)_6-$	cyclohexyl
H	$-(CH_2)_6-$	phenyl
H	$-(CH_2)_6-$	4-chlorophenyl
H	$-(CH_2)_6-$	2,4-dichlorophenyl
H	$-CH_2C(CH_3)_2-$	methyl
H	$-CH_2C(CH_3)_2-$	ethyl
H	$-CH_2C(CH_3)_2-$	*n*-propyl
H	$-CH_2C(CH_3)_2-$	isopropyl
H	$-CH_2C(CH_3)_2-$	cyclopropyl
H	$-CH_2C(CH_3)_2-$	*n*-butyl
H	$-CH_2C(CH_3)_2-$	*sec*-butyl
H	$-CH_2C(CH_3)_2-$	isobutyl
H	$-CH_2C(CH_3)_2-$	*tert*-butyl
H	$-CH_2C(CH_3)_2-$	*n*-pentyl
H	$-CH_2C(CH_3)_2-$	cyclopentyl
H	$-CH_2C(CH_3)_2-$	*n*-hexyl
H	$-CH_2C(CH_3)_2-$	cyclohexyl
H	$-CH_2C(CH_3)_2-$	phenyl
H	$-CH_2C(CH_3)_2-$	4-chlorophenyl
H	$-CH_2C(CH_3)_2-$	2,4-dichlorophenyl
H	$-CH_2C(CH_3)_2CH_2-$	methyl
H	$-CH_2C(CH_3)_2CH_2-$	ethyl
H	$-CH_2C(CH_3)_2CH_2-$	*n*-propyl
H	$-CH_2C(CH_3)_2CH_2-$	isopropyl
H	$-CH_2C(CH_3)_2CH_2-$	cyclopropyl
H	$-CH_2C(CH_3)_2CH_2-$	*n*-butyl
H	$-CH_2C(CH_3)_2CH_2-$	*sec*-butyl
H	$-CH_2C(CH_3)_2CH_2-$	isobutyl
H	$-CH_2C(CH_3)_2CH_2-$	*tert*-butyl
H	$-CH_2C(CH_3)_2CH_2-$	*n*-pentyl
H	$-CH_2C(CH_3)_2CH_2-$	cyclopentyl
H	$-CH_2C(CH_3)_2CH_2-$	*n*-hexyl
H	$-CH_2C(CH_3)_2CH_2-$	cyclohexyl
H	$-CH_2C(CH_3)_2CH_2-$	phenyl
H	$-CH_2C(CH_3)_2CH_2-$	4-chlorophenyl
H	$-CH_2C(CH_3)_2CH_2-$	2,4-dichlorophenyl
H	$-(CH_2)_2OCH_2-$	methyl
H	$-(CH_2)_2OCH_2-$	ethyl
H	$-(CH_2)_2OCH_2-$	*n*-propyl
H	$-(CH_2)_2OCH_2-$	isopropyl
H	$-(CH_2)_2OCH_2-$	cyclopropyl
H	$-(CH_2)_2OCH_2-$	*n*-butyl
H	$-(CH_2)_2OCH_2-$	*sec*-butyl
H	$-(CH_2)_2OCH_2-$	isobutyl

H	$-(CH_2)_2OCH_2-$	*tert*-butyl
H	$-(CH_2)_2OCH_2-$	*n*-pentyl
H	$-(CH_2)_2OCH_2-$	cyclopentyl
H	$-(CH_2)_2OCH_2-$	*n*-hexyl
H	$-(CH_2)_2OCH_2-$	cyclohexyl
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H	$-(CH_2)_2OCH_2-$	4-chlorophenyl
H	$-(CH_2)_2OCH_2-$	2,4-dichlorophenyl
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H	$-(CH_2)_3OCH_2-$	*n*-propyl
H	$-(CH_2)_3OCH_2-$	isopropyl
H	$-(CH_2)_3OCH_2-$	cyclopropyl
H	$-(CH_2)_3OCH_2-$	*n*-butyl
H	$-(CH_2)_3OCH_2-$	*sec*-butyl
H	$-(CH_2)_3OCH_2-$	isobutyl
H	$-(CH_2)_3OCH_2-$	*tert*-butyl
H	$-(CH_2)_3OCH_2-$	*n*-pentyl
H	$-(CH_2)_3OCH_2-$	cyclopentyl
H	$-(CH_2)_3OCH_2-$	*n*-hexyl
H	$-(CH_2)_3OCH_2-$	cyclohexyl
H	$-(CH_2)_3OCH_2-$	phenyl
H	$-(CH_2)_3OCH_2-$	4-chlorophenyl
H	$-(CH_2)_3OCH_2-$	2,4-dichlorophenyl
$-CH_2OH$	$-CH_2-$	methyl
$-CH_2OH$	$-CH_2-$	ethyl
$-CH_2OH$	$-CH_2-$	*n*-propyl
$-CH_2OH$	$-CH_2-$	isopropyl
$-CH_2OH$	$-CH_2-$	cyclopropyl
$-CH_2OH$	$-CH_2-$	*n*-butyl
$-CH_2OH$	$-CH_2-$	*sec*-butyl
$-CH_2OH$	$-CH_2-$	isobutyl
$-CH_2OH$	$-CH_2-$	*tert*-butyl
$-CH_2OH$	$-CH_2-$	*n*-pentyl
$-CH_2OH$	$-CH_2-$	cyclopentyl
$-CH_2OH$	$-CH_2-$	*n*-hexyl
$-CH_2OH$	$-CH_2-$	cyclohexyl
$-CH_2OH$	$-CH_2-$	phenyl
$-CH_2OH$	$-CH_2-$	4-chlorophenyl
$-CH_2OH$	$-CH_2-$	2,4-dichlorophenyl
$-CH_2OH$	$-(CH_2)_2-$	methyl
$-CH_2OH$	$-(CH_2)_2-$	ethyl
$-CH_2OH$	$-(CH_2)_2-$	*n*-propyl
$-CH_2OH$	$-(CH_2)_2-$	isopropyl
$-CH_2OH$	$-(CH_2)_2-$	cyclopropyl
$-CH_2OH$	$-(CH_2)_2-$	*n*-butyl

$-CH_2OH$	$-(CH_2)_2-$	*sec*-butyl
$-CH_2OH$	$-(CH_2)_2-$	isobutyl
$-CH_2OH$	$-(CH_2)_2-$	*tert*-butyl
$-CH_2OH$	$-(CH_2)_2-$	*n*-pentyl
$-CH_2OH$	$-(CH_2)_2-$	cyclopentyl
$-CH_2OH$	$-(CH_2)_2-$	*n*-hexyl
$-CH_2OH$	$-(CH_2)_2-$	cyclohexyl
$-CH_2OH$	$-(CH_2)_2-$	phenyl
$-CH_2OH$	$-(CH_2)_2-$	4-chlorophenyl
$-CH_2OH$	$-(CH_2)_2-$	2,4-dichlorophenyl
$-CH_2OH$	$-(CH_2)_3-$	methyl
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$-CH_2OH$	$-(CH_2)_3-$	*sec*-butyl
$-CH_2OH$	$-(CH_2)_3-$	isobutyl
$-CH_2OH$	$-(CH_2)_3-$	*tert*-butyl
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$-CH_2OH$	$-(CH_2)_4-$	*n*-propyl
$-CH_2OH$	$-(CH_2)_4-$	isopropyl
$-CH_2OH$	$-(CH_2)_4-$	cyclopropyl
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$-CH_2OH$	$-(CH_2)_4-$	*sec*-butyl
$-CH_2OH$	$-(CH_2)_4-$	isobutyl
$-CH_2OH$	$-(CH_2)_4-$	*tert*-butyl
$-CH_2OH$	$-(CH_2)_4-$	*n*-pentyl
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$-CH_2OH$	$-(CH_2)_5-$	ethyl
$-CH_2OH$	$-(CH_2)_5-$	*n*-propyl
$-CH_2OH$	$-(CH_2)_5-$	isopropyl

$-CH_2OH$	$-(CH_2)_5-$	cyclopropyl
$-CH_2OH$	$-(CH_2)_5-$	*n*-butyl
$-CH_2OH$	$-(CH_2)_5-$	*sec*-butyl
$-CH_2OH$	$-(CH_2)_5-$	isobutyl
$-CH_2OH$	$-(CH_2)_5-$	*tert*-butyl
$-CH_2OH$	$-(CH_2)_5-$	*n*-pentyl
$-CH_2OH$	$-(CH_2)_5-$	cyclopentyl
$-CH_2OH$	$-(CH_2)_5-$	*n*-hexyl
$-CH_2OH$	$-(CH_2)_5-$	cyclohexyl
$-CH_2OH$	$-(CH_2)_5-$	phenyl
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$-CH_2OH$	$-(CH_2)_5-$	2,4-dichlorophenyl
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$-CH_2OH$	$-(CH_2)_6-$	ethyl
$-CH_2OH$	$-(CH_2)_6-$	*n*-propyl
$-CH_2OH$	$-(CH_2)_6-$	isopropyl
$-CH_2OH$	$-(CH_2)_6-$	cyclopropyl
$-CH_2OH$	$-(CH_2)_6-$	*n*-butyl
$-CH_2OH$	$-(CH_2)_6-$	*sec*-butyl
$-CH_2OH$	$-(CH_2)_6-$	isobutyl
$-CH_2OH$	$-(CH_2)_6-$	*tert*-butyl
$-CH_2OH$	$-(CH_2)_6-$	*n*-pentyl
$-CH_2OH$	$-(CH_2)_6-$	cyclopentyl
$-CH_2OH$	$-(CH_2)_6-$	*n*-hexyl
$-CH_2OH$	$-(CH_2)_6-$	cyclohexyl
$-CH_2OH$	$-(CH_2)_6-$	phenyl
$-CH_2OH$	$-(CH_2)_6-$	4-chlorophenyl
$-CH_2OH$	$-(CH_2)_6-$	2,4-dichlorophenyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	methyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	ethyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	*n*-propyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	isopropyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	cyclopropyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	*n*-butyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	*sec*-butyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	isobutyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	*tert*-butyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	*n*-pentyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	cyclopentyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	*n*-hexyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	cyclohexyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	phenyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	4-chlorophenyl
$-CH_2OH$	$-CH_2C(CH_3)_2-$	2,4-dichlorophenyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	methyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	ethyl

$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	*n*-propyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	isopropyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	cyclopropyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	*n*-butyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	*sec*-butyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	isobutyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	*tert*-butyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	*n*-pentyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	cyclopentyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	*n*-hexyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	cyclohexyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	phenyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	4-chlorophenyl
$-CH_2OH$	$-CH_2C(CH_3)_2CH_2-$	2,4-dichlorophenyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	methyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	ethyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	*n*-propyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	isopropyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	cyclopropyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	*n*-butyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	*sec*-butyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	isobutyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	*tert*-butyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	*n*-pentyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	cyclopentyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	*n*-hexyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	cyclohexyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	phenyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	4-chlorophenyl
$-CH_2OH$	$-(CH_2)_2OCH_2-$	2,4-dichlorophenyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	methyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	ethyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	*n*-propyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	isopropyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	cyclopropyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	*n*-butyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	*sec*-butyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	isobutyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	*tert*-butyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	*n*-pentyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	cyclopentyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	*n*-hexyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	cyclohexyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	phenyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	4-chlorophenyl
$-CH_2OH$	$-(CH_2)_3OCH_2-$	2,4-dichlorophenyl

$-CH_3$ (methyl)	$-CH_2-$	methyl
$-CH_3$	$-CH_2-$	ethyl
$-CH_3$	$-CH_2-$	*n*-propyl
$-CH_3$	$-CH_2-$	isopropyl
$-CH_3$	$-CH_2-$	cyclopropyl
$-CH_3$	$-CH_2-$	*n*-butyl
$-CH_3$	$-CH_2-$	*sec*-butyl
$-CH_3$	$-CH_2-$	isobutyl
$-CH_3$	$-CH_2-$	*tert*-butyl
$-CH_3$	$-CH_2-$	*n*-pentyl
$-CH_3$	$-CH_2-$	cyclopentyl
$-CH_3$	$-CH_2-$	*n*-hexyl
$-CH_3$	$-CH_2-$	cyclohexyl
$-CH_3$	$-CH_2-$	phenyl
$-CH_3$	$-CH_2-$	4-chlorophenyl
$-CH_3$	$-CH_2-$	2,4-dichlorophenyl
$-CH_3$	$-(CH_2)_2-$	methyl
$-CH_3$	$-(CH_2)_2-$	ethyl
$-CH_3$	$-(CH_2)_2-$	*n*-propyl
$-CH_3$	$-(CH_2)_2-$	isopropyl
$-CH_3$	$-(CH_2)_2-$	cyclopropyl
$-CH_3$	$-(CH_2)_2-$	*n*-butyl
$-CH_3$	$-(CH_2)_2-$	*sec*-butyl
$-CH_3$	$-(CH_2)_2-$	isobutyl
$-CH_3$	$-(CH_2)_2-$	*tert*-butyl
$-CH_3$	$-(CH_2)_2-$	*n*-pentyl
$-CH_3$	$-(CH_2)_2-$	cyclopentyl
$-CH_3$	$-(CH_2)_2-$	*n*-hexyl
$-CH_3$	$-(CH_2)_2-$	cyclohexyl
$-CH_3$	$-(CH_2)_2-$	phenyl
$-CH_3$	$-(CH_2)_2-$	4-chlorophenyl
$-CH_3$	$-(CH_2)_2-$	2,4-dichlorophenyl
$-CH_3$	$-(CH_2)_3-$	methyl
$-CH_3$	$-(CH_2)_3-$	ethyl
$-CH_3$	$-(CH_2)_3-$	*n*-propyl
$-CH_3$	$-(CH_2)_3-$	isopropyl
$-CH_3$	$-(CH_2)_3-$	cyclopropyl
$-CH_3$	$-(CH_2)_3-$	*n*-butyl
$-CH_3$	$-(CH_2)_3-$	*sec*-butyl
$-CH_3$	$-(CH_2)_3-$	isobutyl
$-CH_3$	$-(CH_2)_3-$	*tert*-butyl
$-CH_3$	$-(CH_2)_3-$	*n*-pentyl
$-CH_3$	$-(CH_2)_3-$	cyclopentyl
$-CH_3$	$-(CH_2)_3-$	*n*-hexyl
$-CH_3$	$-(CH_2)_3-$	cyclohexyl
$-CH_3$	$-(CH_2)_3-$	phenyl

$-CH_3$	$-(CH_2)_3-$	4-chlorophenyl
$-CH_3$	$-(CH_2)_3-$	2,4-dichlorophenyl
$-CH_3$	$-(CH_2)_4-$	methyl
$-CH_3$	$-(CH_2)_4-$	ethyl
$-CH_3$	$-(CH_2)_4-$	*n*-propyl
$-CH_3$	$-(CH_2)_4-$	isopropyl
$-CH_3$	$-(CH_2)_4-$	cyclopropyl
$-CH_3$	$-(CH_2)_4-$	*n*-butyl
$-CH_3$	$-(CH_2)_4-$	*sec*-butyl
$-CH_3$	$-(CH_2)_4-$	isobutyl
$-CH_3$	$-(CH_2)_4-$	*tert*-butyl
$-CH_3$	$-(CH_2)_4-$	*n*-pentyl
$-CH_3$	$-(CH_2)_4-$	cyclopentyl
$-CH_3$	$-(CH_2)_4-$	*n*-hexyl
$-CH_3$	$-(CH_2)_4-$	cyclohexyl
$-CH_3$	$-(CH_2)_4-$	phenyl
$-CH_3$	$-(CH_2)_4-$	4-chlorophenyl
$-CH_3$	$-(CH_2)_4-$	2,4-dichlorophenyl
$-CH_3$	$-(CH_2)_5-$	methyl
$-CH_3$	$-(CH_2)_5-$	ethyl
$-CH_3$	$-(CH_2)_5-$	*n*-propyl
$-CH_3$	$-(CH_2)_5-$	isopropyl
$-CH_3$	$-(CH_2)_5-$	cyclopropyl
$-CH_3$	$-(CH_2)_5-$	*n*-butyl
$-CH_3$	$-(CH_2)_5-$	*sec*-butyl
$-CH_3$	$-(CH_2)_5-$	isobutyl
$-CH_3$	$-(CH_2)_5-$	*tert*-butyl
$-CH_3$	$-(CH_2)_5-$	*n*-pentyl
$-CH_3$	$-(CH_2)_5-$	cyclopentyl
$-CH_3$	$-(CH_2)_5-$	*n*-hexyl
$-CH_3$	$-(CH_2)_5-$	cyclohexyl
$-CH_3$	$-(CH_2)_5-$	phenyl
$-CH_3$	$-(CH_2)_5-$	4-chlorophenyl
$-CH_3$	$-(CH_2)_5-$	2,4-dichlorophenyl
$-CH_3$	$-(CH_2)_6-$	methyl
$-CH_3$	$-(CH_2)_6-$	ethyl
$-CH_3$	$-(CH_2)_6-$	*n*-propyl
$-CH_3$	$-(CH_2)_6-$	isopropyl
$-CH_3$	$-(CH_2)_6-$	cyclopropyl
$-CH_3$	$-(CH_2)_6-$	*n*-butyl
$-CH_3$	$-(CH_2)_6-$	*sec*-butyl
$-CH_3$	$-(CH_2)_6-$	isobutyl
$-CH_3$	$-(CH_2)_6-$	*tert*-butyl
$-CH_3$	$-(CH_2)_6-$	*n*-pentyl
$-CH_3$	$-(CH_2)_6-$	cyclopentyl
$-CH_3$	$-(CH_2)_6-$	*n*-hexyl

$-CH_3$	$-(CH_2)_6-$	cyclohexyl
$-CH_3$	$-(CH_2)_6-$	phenyl
$-CH_3$	$-(CH_2)_6-$	4-chlorophenyl
$-CH_3$	$-(CH_2)_6-$	2,4-dichlorophenyl
$-CH_3$	$-CH_2C(CH_3)_2-$	methyl
$-CH_3$	$-CH_2C(CH_3)_2-$	ethyl
$-CH_3$	$-CH_2C(CH_3)_2-$	*n*-propyl
$-CH_3$	$-CH_2C(CH_3)_2-$	isopropyl
$-CH_3$	$-CH_2C(CH_3)_2-$	cyclopropyl
$-CH_3$	$-CH_2C(CH_3)_2-$	*n*-butyl
$-CH_3$	$-CH_2C(CH_3)_2-$	*sec*-butyl
$-CH_3$	$-CH_2C(CH_3)_2-$	isobutyl
$-CH_3$	$-CH_2C(CH_3)_2-$	*tert*-butyl
$-CH_3$	$-CH_2C(CH_3)_2-$	*n*-pentyl
$-CH_3$	$-CH_2C(CH_3)_2-$	cyclopentyl
$-CH_3$	$-CH_2C(CH_3)_2-$	*n*-hexyl
$-CH_3$	$-CH_2C(CH_3)_2-$	cyclohexyl
$-CH_3$	$-CH_2C(CH_3)_2-$	phenyl
$-CH_3$	$-CH_2C(CH_3)_2-$	4-chlorophenyl
$-CH_3$	$-CH_2C(CH_3)_2-$	2,4-dichlorophenyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	methyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	ethyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-propyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	isopropyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclopropyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-butyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	*sec*-butyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	isobutyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	*tert*-butyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-pentyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclopentyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-hexyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclohexyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	phenyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	4-chlorophenyl
$-CH_3$	$-CH_2C(CH_3)_2CH_2-$	2,4-dichlorophenyl
$-CH_3$	$-(CH_2)_2OCH_2-$	methyl
$-CH_3$	$-(CH_2)_2OCH_2-$	ethyl
$-CH_3$	$-(CH_2)_2OCH_2-$	*n*-propyl
$-CH_3$	$-(CH_2)_2OCH_2-$	isopropyl
$-CH_3$	$-(CH_2)_2OCH_2-$	cyclopropyl
$-CH_3$	$-(CH_2)_2OCH_2-$	*n*-butyl
$-CH_3$	$-(CH_2)_2OCH_2-$	*sec*-butyl
$-CH_3$	$-(CH_2)_2OCH_2-$	isobutyl
$-CH_3$	$-(CH_2)_2OCH_2-$	*tert*-butyl
$-CH_3$	$-(CH_2)_2OCH_2-$	*n*-pentyl

$-CH_3$	$-(CH_2)_2OCH_2-$	cyclopentyl
$-CH_3$	$-(CH_2)_2OCH_2-$	*n*-hexyl
$-CH_3$	$-(CH_2)_2OCH_2-$	cyclohexyl
$-CH_3$	$-(CH_2)_2OCH_2-$	phenyl
$-CH_3$	$-(CH_2)_2OCH_2-$	4-chlorophenyl
$-CH_3$	$-(CH_2)_2OCH_2-$	2,4-dichlorophenyl
$-CH_3$	$-(CH_2)_3OCH_2-$	methyl
$-CH_3$	$-(CH_2)_3OCH_2-$	ethyl
$-CH_3$	$-(CH_2)_3OCH_2-$	*n*-propyl
$-CH_3$	$-(CH_2)_3OCH_2-$	isopropyl
$-CH_3$	$-(CH_2)_3OCH_2-$	cyclopropyl
$-CH_3$	$-(CH_2)_3OCH_2-$	*n*-butyl
$-CH_3$	$-(CH_2)_3OCH_2-$	*sec*-butyl
$-CH_3$	$-(CH_2)_3OCH_2-$	isobutyl
$-CH_3$	$-(CH_2)_3OCH_2-$	*tert*-butyl
$-CH_3$	$-(CH_2)_3OCH_2-$	*n*-pentyl
$-CH_3$	$-(CH_2)_3OCH_2-$	cyclopentyl
$-CH_3$	$-(CH_2)_3OCH_2-$	*n*-hexyl
$-CH_3$	$-(CH_2)_3OCH_2-$	cyclohexyl
$-CH_3$	$-(CH_2)_3OCH_2-$	phenyl
$-CH_3$	$-(CH_2)_3OCH_2-$	4-chlorophenyl
$-CH_3$	$-(CH_2)_3OCH_2-$	2,4-dichlorophenyl
$-CH_2CH_3$ (ethyl)	$-CH_2-$	methyl
$-CH_2CH_3$	$-CH_2-$	ethyl
$-CH_2CH_3$	$-CH_2-$	*n*-propyl
$-CH_2CH_3$	$-CH_2-$	isopropyl
$-CH_2CH_3$	$-CH_2-$	cyclopropyl
$-CH_2CH_3$	$-CH_2-$	*n*-butyl
$-CH_2CH_3$	$-CH_2-$	*sec*-butyl
$-CH_2CH_3$	$-CH_2-$	isobutyl
$-CH_2CH_3$	$-CH_2-$	*tert*-butyl
$-CH_2CH_3$	$-CH_2-$	*n*-pentyl
$-CH_2CH_3$	$-CH_2-$	cyclopentyl
$-CH_2CH_3$	$-CH_2-$	*n*-hexyl
$-CH_2CH_3$	$-CH_2-$	cyclohexyl
$-CH_2CH_3$	$-CH_2-$	phenyl
$-CH_2CH_3$	$-CH_2-$	4-chlorophenyl
$-CH_2CH_3$	$-CH_2-$	2,4-dichlorophenyl
$-CH_2CH_3$	$-(CH_2)_2-$	methyl
$-CH_2CH_3$	$-(CH_2)_2-$	ethyl
$-CH_2CH_3$	$-(CH_2)_2-$	*n*-propyl
$-CH_2CH_3$	$-(CH_2)_2-$	isopropyl
$-CH_2CH_3$	$-(CH_2)_2-$	cyclopropyl
$-CH_2CH_3$	$-(CH_2)_2-$	*n*-butyl
$-CH_2CH_3$	$-(CH_2)_2-$	*sec*-butyl
$-CH_2CH_3$	$-(CH_2)_2-$	isobutyl

$-CH_2CH_3$	$-(CH_2)_2-$	*tert*-butyl
$-CH_2CH_3$	$-(CH_2)_2-$	*n*-pentyl
$-CH_2CH_3$	$-(CH_2)_2-$	cyclopentyl
$-CH_2CH_3$	$-(CH_2)_2-$	*n*-hexyl
$-CH_2CH_3$	$-(CH_2)_2-$	cyclohexyl
$-CH_2CH_3$	$-(CH_2)_2-$	phenyl
$-CH_2CH_3$	$-(CH_2)_2-$	4-chlorophenyl
$-CH_2CH_3$	$-(CH_2)_2-$	2,4-dichlorophenyl
$-CH_2CH_3$	$-(CH_2)_3-$	methyl
$-CH_2CH_3$	$-(CH_2)_3-$	ethyl
$-CH_2CH_3$	$-(CH_2)_3-$	*n*-propyl
$-CH_2CH_3$	$-(CH_2)_3-$	isopropyl
$-CH_2CH_3$	$-(CH_2)_3-$	cyclopropyl
$-CH_2CH_3$	$-(CH_2)_3-$	*n*-butyl
$-CH_2CH_3$	$-(CH_2)_3-$	*sec*-butyl
$-CH_2CH_3$	$-(CH_2)_3-$	isobutyl
$-CH_2CH_3$	$-(CH_2)_3-$	*tert*-butyl
$-CH_2CH_3$	$-(CH_2)_3-$	*n*-pentyl
$-CH_2CH_3$	$-(CH_2)_3-$	cyclopentyl
$-CH_2CH_3$	$-(CH_2)_3-$	*n*-hexyl
$-CH_2CH_3$	$-(CH_2)_3-$	cyclohexyl
$-CH_2CH_3$	$-(CH_2)_3-$	phenyl
$-CH_2CH_3$	$-(CH_2)_3-$	4-chlorophenyl
$-CH_2CH_3$	$-(CH_2)_3-$	2,4-dichlorophenyl
$-CH_2CH_3$	$-(CH_2)_4-$	methyl
$-CH_2CH_3$	$-(CH_2)_4-$	ethyl
$-CH_2CH_3$	$-(CH_2)_4-$	*n*-propyl
$-CH_2CH_3$	$-(CH_2)_4-$	isopropyl
$-CH_2CH_3$	$-(CH_2)_4-$	cyclopropyl
$-CH_2CH_3$	$-(CH_2)_4-$	*n*-butyl
$-CH_2CH_3$	$-(CH_2)_4-$	*sec*-butyl
$-CH_2CH_3$	$-(CH_2)_4-$	isobutyl
$-CH_2CH_3$	$-(CH_2)_4-$	*tert*-butyl
$-CH_2CH_3$	$-(CH_2)_4-$	*n*-pentyl
$-CH_2CH_3$	$-(CH_2)_4-$	cyclopentyl
$-CH_2CH_3$	$-(CH_2)_4-$	*n*-hexyl
$-CH_2CH_3$	$-(CH_2)_4-$	cyclohexyl
$-CH_2CH_3$	$-(CH_2)_4-$	phenyl
$-CH_2CH_3$	$-(CH_2)_4-$	4-chlorophenyl
$-CH_2CH_3$	$-(CH_2)_4-$	2,4-dichlorophenyl
$-CH_2CH_3$	$-(CH_2)_5-$	methyl
$-CH_2CH_3$	$-(CH_2)_5-$	ethyl
$-CH_2CH_3$	$-(CH_2)_5-$	*n*-propyl
$-CH_2CH_3$	$-(CH_2)_5-$	isopropyl
$-CH_2CH_3$	$-(CH_2)_5-$	cyclopropyl
$-CH_2CH_3$	$-(CH_2)_5-$	*n*-butyl

$-CH_2CH_3$	$-(CH_2)_5-$	*sec*-butyl
$-CH_2CH_3$	$-(CH_2)_5-$	isobutyl
$-CH_2CH_3$	$-(CH_2)_5-$	*tert*-butyl
$-CH_2CH_3$	$-(CH_2)_5-$	*n*-pentyl
$-CH_2CH_3$	$-(CH_2)_5-$	cyclopentyl
$-CH_2CH_3$	$-(CH_2)_5-$	*n*-hexyl
$-CH_2CH_3$	$-(CH_2)_5-$	cyclohexyl
$-CH_2CH_3$	$-(CH_2)_5-$	phenyl
$-CH_2CH_3$	$-(CH_2)_5-$	4-chlorophenyl
$-CH_2CH_3$	$-(CH_2)_5-$	2,4-dichlorophenyl
$-CH_2CH_3$	$-(CH_2)_6-$	methyl
$-CH_2CH_3$	$-(CH_2)_6-$	ethyl
$-CH_2CH_3$	$-(CH_2)_6-$	*n*-propyl
$-CH_2CH_3$	$-(CH_2)_6-$	isopropyl
$-CH_2CH_3$	$-(CH_2)_6-$	cyclopropyl
$-CH_2CH_3$	$-(CH_2)_6-$	*n*-butyl
$-CH_2CH_3$	$-(CH_2)_6-$	*sec*-butyl
$-CH_2CH_3$	$-(CH_2)_6-$	isobutyl
$-CH_2CH_3$	$-(CH_2)_6-$	*tert*-butyl
$-CH_2CH_3$	$-(CH_2)_6-$	*n*-pentyl
$-CH_2CH_3$	$-(CH_2)_6-$	cyclopentyl
$-CH_2CH_3$	$-(CH_2)_6-$	*n*-hexyl
$-CH_2CH_3$	$-(CH_2)_6-$	cyclohexyl
$-CH_2CH_3$	$-(CH_2)_6-$	phenyl
$-CH_2CH_3$	$-(CH_2)_6-$	4-chlorophenyl
$-CH_2CH_3$	$-(CH_2)_6-$	2,4-dichlorophenyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	methyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	ethyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-propyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	isopropyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	cyclopropyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-butyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	*sec*-butyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	isobutyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	*tert*-butyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-pentyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	cyclopentyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-hexyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	cyclohexyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	phenyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	4-chlorophenyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2-$	2,4-dichlorophenyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	methyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	ethyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-propyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	isopropyl

$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclopropyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-butyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*sec*-butyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	isobutyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*tert*-butyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-pentyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclopentyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-hexyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclohexyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	phenyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	4-chlorophenyl
$-CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	2,4-dichlorophenyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	methyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	ethyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-propyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	isopropyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	cyclopropyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-butyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	*sec*-butyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	isobutyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	*tert*-butyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-pentyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	cyclopentyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-hexyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	cyclohexyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	phenyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	4-chlorophenyl
$-CH_2CH_3$	$-(CH_2)_2OCH_2-$	2,4-dichlorophenyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	methyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	ethyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-propyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	isopropyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	cyclopropyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-butyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	*sec*-butyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	isobutyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	*tert*-butyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-pentyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	cyclopentyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-hexyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	cyclohexyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	phenyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	4-chlorophenyl
$-CH_2CH_3$	$-(CH_2)_3OCH_2-$	2,4-dichlorophenyl
$-CH_2CH_2CH_3$ (n-propyl)	$-CH_2-$	methyl
$-CH_2CH_2CH_3$	$-CH_2-$	ethyl

$-CH_2CH_2CH_3$	$-CH_2-$	*n*-propyl
$-CH_2CH_2CH_3$	$-CH_2-$	isopropyl
$-CH_2CH_2CH_3$	$-CH_2-$	cyclopropyl
$-CH_2CH_2CH_3$	$-CH_2-$	*n*-butyl
$-CH_2CH_2CH_3$	$-CH_2-$	*sec*-butyl
$-CH_2CH_2CH_3$	$-CH_2-$	isobutyl
$-CH_2CH_2CH_3$	$-CH_2-$	*tert*-butyl
$-CH_2CH_2CH_3$	$-CH_2-$	*n*-pentyl
$-CH_2CH_2CH_3$	$-CH_2-$	cyclopentyl
$-CH_2CH_2CH_3$	$-CH_2-$	*n*-hexyl
$-CH_2CH_2CH_3$	$-CH_2-$	cyclohexyl
$-CH_2CH_2CH_3$	$-CH_2-$	phenyl
$-CH_2CH_2CH_3$	$-CH_2-$	4-chlorophenyl
$-CH_2CH_2CH_3$	$-CH_2-$	2,4-dichlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	methyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	ethyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	*n*-propyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	isopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	cyclopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	*n*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	*sec*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	isobutyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	*tert*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	*n*-pentyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	cyclopentyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	*n*-hexyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	cyclohexyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	phenyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	4-chlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_2-$	2,4-dichlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	methyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	ethyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	*n*-propyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	isopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	cyclopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	*n*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	*sec*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	isobutyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	*tert*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	*n*-pentyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	cyclopentyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	*n*-hexyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	cyclohexyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	phenyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	4-chlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_3-$	2,4-dichlorophenyl

$-CH_2CH_2CH_3$	$-(CH_2)_4-$	methyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	ethyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	*n*-propyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	isopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	cyclopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	*n*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	*sec*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	isobutyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	*tert*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	*n*-pentyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	cyclopentyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	*n*-hexyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	cyclohexyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	phenyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	4-chlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_4-$	2,4-dichlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	methyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	ethyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	*n*-propyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	isopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	cyclopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	*n*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	*sec*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	isobutyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	*tert*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	*n*-pentyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	cyclopentyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	*n*-hexyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	cyclohexyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	phenyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	4-chlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_5-$	2,4-dichlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	methyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	ethyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	*n*-propyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	isopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	cyclopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	*n*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	*sec*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	isobutyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	*tert*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	*n*-pentyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	cyclopentyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	*n*-hexyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	cyclohexyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	phenyl

$-CH_2CH_2CH_3$	$-(CH_2)_6-$	4-chlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_6-$	2,4-dichlorophenyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	methyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	ethyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-propyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	isopropyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	cyclopropyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-butyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	*sec*-butyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	isobutyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	*tert*-butyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-pentyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	cyclopentyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-hexyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	cyclohexyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	phenyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	4-chlorophenyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	2,4-dichlorophenyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	methyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	ethyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-propyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	isopropyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclopropyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-butyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*sec*-butyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	isobutyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*tert*-butyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-pentyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclopentyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-hexyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclohexyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	phenyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	4-chlorophenyl
$-CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	2,4-dichlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	methyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	ethyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-propyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	isopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	cyclopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	*sec*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	isobutyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	*tert*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-pentyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	cyclopentyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-hexyl

$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	cyclohexyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	phenyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	4-chlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	2,4-dichlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	methyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	ethyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-propyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	isopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	cyclopropyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	*sec*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	isobutyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	*tert*-butyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-pentyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	cyclopentyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-hexyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	cyclohexyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	phenyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	4-chlorophenyl
$-CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	2,4-dichlorophenyl
$-CH_2CH_2CH_2CH_3$ (n-butyl)	$-CH_2-$	methyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	ethyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	*n*-propyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	isopropyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	cyclopropyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	*n*-butyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	*sec*-butyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	isobutyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	*tert*-butyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	*n*-pentyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	cyclopentyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	*n*-hexyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	cyclohexyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	phenyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	4-chlorophenyl
$-CH_2CH_2CH_2CH_3$	$-CH_2-$	2,4-dichlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	methyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	ethyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	*n*-propyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	isopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	cyclopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	*n*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	*sec*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	isobutyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	*tert*-butyl

$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	*n*-pentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	cyclopentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	*n*-hexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	cyclohexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	phenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	4-chlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2-$	2,4-dichlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	methyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	ethyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	*n*-propyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	isopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	cyclopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	*n*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	*sec*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	isobutyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	*tert*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	*n*-pentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	cyclopentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	*n*-hexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	cyclohexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	phenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	4-chlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3-$	2,4-dichlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	methyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	ethyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	*n*-propyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	isopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	cyclopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	*n*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	*sec*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	isobutyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	*tert*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	*n*-pentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	cyclopentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	*n*-hexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	cyclohexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	phenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	4-chlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_4-$	2,4-dichlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	methyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	ethyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	*n*-propyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	isopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	cyclopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	*n*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	*sec*-butyl

$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	isobutyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	*tert*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	*n*-pentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	cyclopentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	*n*-hexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	cyclohexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	phenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	4-chlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_5-$	2,4-dichlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	methyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	ethyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	*n*-propyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	isopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	cyclopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	*n*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	*sec*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	isobutyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	*tert*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	*n*-pentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	cyclopentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	*n*-hexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	cyclohexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	phenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	4-chlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_6-$	2,4-dichlorophenyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	methyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	ethyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-propyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	isopropyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	cyclopropyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-butyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	*sec*-butyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	isobutyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	*tert*-butyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-pentyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	cyclopentyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-hexyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	cyclohexyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	phenyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	4-chlorophenyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2-$	2,4-dichlorophenyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	methyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	ethyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-propyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	isopropyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclopropyl

$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-butyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*sec*-butyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	isobutyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*tert*-butyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-pentyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclopentyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-hexyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclohexyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	phenyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	4-chlorophenyl
$-CH_2CH_2CH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	2,4-dichlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	methyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	ethyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-propyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	isopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	cyclopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	*sec*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	isobutyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	*tert*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-pentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	cyclopentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-hexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	cyclohexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	phenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	4-chlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_2OCH_2-$	2,4-dichlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	methyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	ethyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-propyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	isopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	cyclopropyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	*sec*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	isobutyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	*tert*-butyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-pentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	cyclopentyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-hexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	cyclohexyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	phenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	4-chlorophenyl
$-CH_2CH_2CH_2CH_3$	$-(CH_2)_3OCH_2-$	2,4-dichlorophenyl
$-CH_2OCH_2CH_3$ (ethoxymethyl)	$-CH_2-$	methyl
$-CH_2OCH_2CH_3$	$-CH_2-$	ethyl

$-CH_2OCH_2CH_3$	$-CH_2-$	*n*-propyl
$-CH_2OCH_2CH_3$	$-CH_2-$	isopropyl
$-CH_2OCH_2CH_3$	$-CH_2-$	cyclopropyl
$-CH_2OCH_2CH_3$	$-CH_2-$	*n*-butyl
$-CH_2OCH_2CH_3$	$-CH_2-$	*sec*-butyl
$-CH_2OCH_2CH_3$	$-CH_2-$	isobutyl
$-CH_2OCH_2CH_3$	$-CH_2-$	*tert*-butyl
$-CH_2OCH_2CH_3$	$-CH_2-$	*n*-pentyl
$-CH_2OCH_2CH_3$	$-CH_2-$	cyclopentyl
$-CH_2OCH_2CH_3$	$-CH_2-$	*n*-hexyl
$-CH_2OCH_2CH_3$	$-CH_2-$	cyclohexyl
$-CH_2OCH_2CH_3$	$-CH_2-$	phenyl
$-CH_2OCH_2CH_3$	$-CH_2-$	4-chlorophenyl
$-CH_2OCH_2CH_3$	$-CH_2-$	2,4-dichlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	methyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	ethyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	*n*-propyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	isopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	cyclopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	*n*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	*sec*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	isobutyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	*tert*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	*n*-pentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	cyclopentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	*n*-hexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	cyclohexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	phenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	4-chlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2-$	2,4-dichlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	methyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	ethyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	*n*-propyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	isopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	cyclopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	*n*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	*sec*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	isobutyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	*tert*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	*n*-pentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	cyclopentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	*n*-hexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	cyclohexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	phenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	4-chlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3-$	2,4-dichlorophenyl

$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	methyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	ethyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	*n*-propyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	isopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	cyclopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	*n*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	*sec*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	isobutyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	*tert*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	*n*-pentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	cyclopentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	*n*-hexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	cyclohexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	phenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	4-chlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_4-$	2,4-dichlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	methyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	ethyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	*n*-propyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	isopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	cyclopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	*n*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	*sec*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	isobutyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	*tert*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	*n*-pentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	cyclopentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	*n*-hexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	cyclohexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	phenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	4-chlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_5-$	2,4-dichlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	methyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	ethyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	*n*-propyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	isopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	cyclopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	*n*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	*sec*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	isobutyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	*tert*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	*n*-pentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	cyclopentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	*n*-hexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	cyclohexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	phenyl

$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	4-chlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_6-$	2,4-dichlorophenyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	methyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	ethyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-propyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	isopropyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	cyclopropyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-butyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	*sec*-butyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	isobutyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	*tert*-butyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-pentyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	cyclopentyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	*n*-hexyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	cyclohexyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	phenyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	4-chlorophenyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2-$	2,4-dichlorophenyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	methyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	ethyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-propyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	isopropyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclopropyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-butyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*sec*-butyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	isobutyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*tert*-butyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-pentyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclopentyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-hexyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclohexyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	phenyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	4-chlorophenyl
$-CH_2OCH_2CH_3$	$-CH_2C(CH_3)_2CH_2-$	2,4-dichlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	methyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	ethyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-propyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	isopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	cyclopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	*sec*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	isobutyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	*tert*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-pentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	cyclopentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	*n*-hexyl

$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	cyclohexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	phenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	4-chlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_2OCH_2-$	2,4-dichlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	methyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	ethyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-propyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	isopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	cyclopropyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	*sec*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	isobutyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	*tert*-butyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-pentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	cyclopentyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	*n*-hexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	cyclohexyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	phenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	4-chlorophenyl
$-CH_2OCH_2CH_3$	$-(CH_2)_3OCH_2-$	2,4-dichlorophenyl
$-CH_2CH_2OCH_3$ (2-methoxyethyl)	$-CH_2-$	methyl
$-CH_2CH_2OCH_3$	$-CH_2-$	ethyl
$-CH_2CH_2OCH_3$	$-CH_2-$	*n*-propyl
$-CH_2CH_2OCH_3$	$-CH_2-$	isopropyl
$-CH_2CH_2OCH_3$	$-CH_2-$	cyclopropyl
$-CH_2CH_2OCH_3$	$-CH_2-$	*n*-butyl
$-CH_2CH_2OCH_3$	$-CH_2-$	*sec*-butyl
$-CH_2CH_2OCH_3$	$-CH_2-$	isobutyl
$-CH_2CH_2OCH_3$	$-CH_2-$	*tert*-butyl
$-CH_2CH_2OCH_3$	$-CH_2-$	*n*-pentyl
$-CH_2CH_2OCH_3$	$-CH_2-$	cyclopentyl
$-CH_2CH_2OCH_3$	$-CH_2-$	*n*-hexyl
$-CH_2CH_2OCH_3$	$-CH_2-$	cyclohexyl
$-CH_2CH_2OCH_3$	$-CH_2-$	phenyl
$-CH_2CH_2OCH_3$	$-CH_2-$	4-chlorophenyl
$-CH_2CH_2OCH_3$	$-CH_2-$	2,4-dichlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	methyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	ethyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	*n*-propyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	isopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	cyclopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	*n*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	*sec*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	isobutyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	*tert*-butyl

$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	*n*-pentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	cyclopentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	*n*-hexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	cyclohexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	phenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	4-chlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2-$	2,4-dichlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	methyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	ethyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	*n*-propyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	isopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	cyclopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	*n*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	*sec*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	isobutyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	*tert*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	*n*-pentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	cyclopentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	*n*-hexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	cyclohexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	phenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	4-chlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3-$	2,4-dichlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	methyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	ethyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	*n*-propyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	isopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	cyclopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	*n*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	*sec*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	isobutyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	*tert*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	*n*-pentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	cyclopentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	*n*-hexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	cyclohexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	phenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	4-chlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_4-$	2,4-dichlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	methyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	ethyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	*n*-propyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	isopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	cyclopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	*n*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	*sec*-butyl

$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	isobutyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	*tert*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	*n*-pentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	cyclopentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	*n*-hexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	cyclohexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	phenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	4-chlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_5-$	2,4-dichlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	methyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	ethyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	*n*-propyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	isopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	cyclopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	*n*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	*sec*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	isobutyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	*tert*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	*n*-pentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	cyclopentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	*n*-hexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	cyclohexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	phenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	4-chlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_6-$	2,4-dichlorophenyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	methyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	ethyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	*n*-propyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	isopropyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	cyclopropyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	*n*-butyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	*sec*-butyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	isobutyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	*tert*-butyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	*n*-pentyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	cyclopentyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	*n*-hexyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	cyclohexyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	phenyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	4-chlorophenyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2-$	2,4-dichlorophenyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	methyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	ethyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-propyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	isopropyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclopropyl

$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-butyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	*sec*-butyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	isobutyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	*tert*-butyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-pentyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclopentyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	*n*-hexyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	cyclohexyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	phenyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	4-chlorophenyl
$-CH_2CH_2OCH_3$	$-CH_2C(CH_3)_2CH_2-$	2,4-dichlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	methyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	ethyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	*n*-propyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	isopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	cyclopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	*n*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	*sec*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	isobutyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	*tert*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	*n*-pentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	cyclopentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	*n*-hexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	cyclohexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	phenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	4-chlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_2OCH_2-$	2,4-dichlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	methyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	ethyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	*n*-propyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	isopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	cyclopropyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	*n*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	*sec*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	isobutyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	*tert*-butyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	*n*-pentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	cyclopentyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	*n*-hexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	cyclohexyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	phenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	4-chlorophenyl
$-CH_2CH_2OCH_3$	$-(CH_2)_3OCH_2-$	2,4-dichlorophenyl

CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention have been found to induce cytokine biosynthesis when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, *58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μM). The final

concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

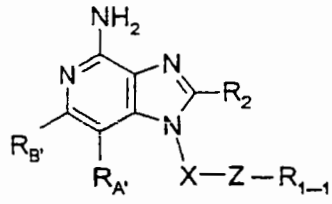
Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

What is claimed is:

1. A compound of the Formula (I-3):



I-3

wherein:

X is alkylene optionally interrupted by one or more -O- groups;

Z is -C(O)-, -C(O)O-, or -C(-Q-R_{1-3})$_2$-;

R_{1-1} is selected from the group consisting of:

hydrogen,

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

-NH-SO_2-R_{1-4},

-NH-C(O)-R_{1-4},

-NH-C(O)-NH_2,

-NH-C(O)-NH-R_{1-4}, and

-N_3;

with the proviso that if Z is -C(O)-, then R_{1-1} may also be -N(CH_3)(OCH_3);

with the further proviso that if Z is -C(O)O-, then R_{1-1} is not hydrogen;

with the further proviso that if Z is -C(O)O-, then X does not include -O- groups;

Q is O or S;

R_{1-3} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl,

-NH-SO_2-R_{1-4},

-NH-C(O)-R_{1-4},

-NH-C(O)-NH_2,

-NH-C(O)-NH-R_{1-4}, and

-N_3;

or the R_{1-3} groups can join together to form a ring system comprising a saturated or unsaturated 5-, 6-, or 7-membered ring;

R_{1-4} is selected from the group consisting of:

alkyl,

aryl,

alkylene-aryl,

heteroaryl,

alkylene-heteroaryl, and

alkyl, aryl, alkylene-aryl, heteroaryl, or alkylene-heteroaryl substituted by one or more substituents selected from the group consisting of:

halogen,

cyano,

nitro,

alkoxy,

dialkylamino,

alkylthio,

haloalkyl,

haloalkoxy,

alkyl, and

-N_3; and

R_2 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y'-R_4, and

$-X'-R_5$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, and heteroarylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene or heteroarylene, and optionally interrupted by one or more -O- groups;

Y' is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

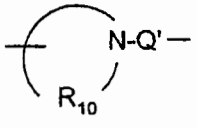
$-O-C(O)-O-$,

$-N(R_8)-Q'-$,

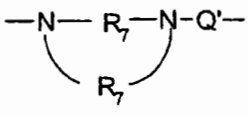
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

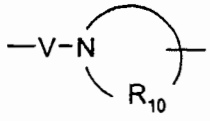
$-C(R_6)-N(OR_9)-$,



,



, and

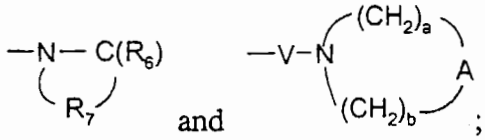


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, and alkylheteroarylenyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, and alkylheteroarylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy,

arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, and alkynyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is a C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, $-CH_2-$, and $-N(R_4)-$;

Q' is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, and $-S(O)_2-N(R_8)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

$R_{A'}$ and $R_{B'}$ are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1 wherein R_A and R_B are independently selected from the group consisting of hydrogen and alkyl.

3. The compound or salt of claim 2 wherein R_A and R_B are both methyl.