PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 401/14, A61K 31/47, C07D 409/14, 401/06
A1

(11) International Publication Number: **WO 00/47574**

(43) International Publication Date: 17 August 2000 (17.08.00)

(21) International Application Number: PCT/IB00/00121

(22) International Filing Date: 4 February 2000 (04.02.00)

(30) Priority Data:
60/119,702 11 February 1999 (11.02.99) US

(71) Applicant *(for all designated States except US)*: PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: YANG, Bingwei, Vera [US/US]; Pfizer Inc., Central Research Division, Eastern Point Road, Groton, CT 06340 (US).

(74) Agents: SPIEGEL, Allen, J. et al.; c/o Simpson, Alison, Urquhart–Dykes & Lord, 30 Welbeck Street, London W1M 7PG (GB).

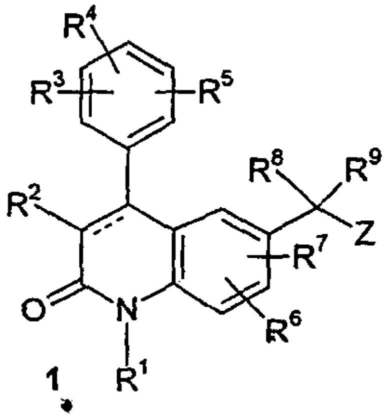
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: HETEROARYL–SUBSTITUTED QUINOLIN–2–ONE DERIVATIVES USEFUL AS ANTICANCER AGENTS

(57) Abstract

The present invention relates to compounds of formula (1) and pharmaceutically acceptable salts and solvates thereof wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, and Z are as defined herein. The invention also relates to pharmaceutical compositions comprising compounds of formula (1) and to methods of inhibiting abnormal cell growth, including cancer, in a mammal by administering compounds of formula (1) to the mammal. The invention also relates to intermediates and methods useful in synthesizing compounds of formula (1).



1

(1)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CU	Cuba
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakstan
LC	Saint Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	The former Yugoslav Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

HETEROARYL-SUBSTITUTED QUINOLIN-2-ONE DERIVATIVES USEFUL AS ANTICANCER AGENTS

Background of the Invention

This invention relates to a series of heteroaryl-substituted quinolin-2-one derivatives that are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals. This invention also relates to a method of using such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer.

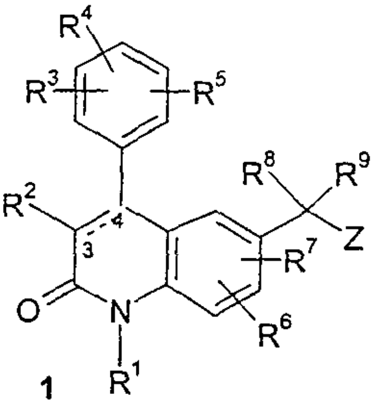
To acquire transforming potential, the precursor of the Ras oncoprotein must undergo farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, have therefore been suggested as agents to combat tumors in which Ras contributes to transformation. Mutated, oncogenic forms of Ras are frequently found in many human cancers, most notably in more than 50% of colon and pancreatic carcinomas (Kohl et al., Science, Vol. 260, 1834 to 1837, 1993). The compounds of the present invention exhibit activity as inhibitors of the enzyme farnesyl protein transferase and are therefore believed to be useful as anti-cancer and anti-tumor agents. Further, the compounds of the present invention may be active against any tumors that proliferate by virtue of farnesyl protein transferase.

Other compounds that are indicated as having activity inhibiting farnesyl protein transferase are referred to in International Publication Number WO 97/21701, entitled "Farnesyl Protein Transferase Inhibiting (Imidazol-5-yl)methyl-2-quinolinone Derivatives", which has an International Publication Date of June 19, 1997; in International Publication Number WO 97/16443, entitled "Farnesyl Transferase Inhibiting 2-Quinolone Derivatives", which has an International Publication Date of May 9, 1997; PCT/IB99/01393, filed August 5, 1999, entitled "2-Quinolone derivatives Useful as Anticancer Agents"; and PCT/IB99/01398, filed August 6, 1999, entitled "Alkynyl-Substituted Quinolin-2-one Derivatives Useful as Anticancer Agents"; all of which are incorporated herein by reference in their entireties.

The preceding Kohl et al. publication, as well as all other references discussed below in this application, are also hereby incorporated by reference in their entireties.

Summary of the Invention

The present invention relates to compounds of formula 1



1

or pharmaceutically acceptable salts or solvates thereof wherein:

the dashed line indicates an optional second bond connecting C-3 and C-4 of the quinolin-2-one ring;

R^1 is selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_qC(O)R^{12}$, $-(CR^{13}R^{14})_qC(O)OR^{15}$, $-(CR^{13}R^{14})_qOR^{12}$, $-(CR^{13}R^{14})_qCSO_2R^{15}$, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said cycloalkyl, aryl and heterocyclic R^1 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^1 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 4 R^6 groups;

R^2 is halo, cyano, $-C(O)OR^{15}$, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH{=}NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

R^8 is H, $-OR^{12}$, $-OC(O)R^{12}$, $-NR^{12}R^{13}$, $-N=CR^{12}R^{13}$, $-NR^{12}C(O)R^{13}$, cyano, $-C(O)OR^{13}$, $-SR^{12}$, or $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said heterocyclic R^8 groups are substituted by 1 to 4 R^6 groups;

R^9 is $-(CR^{13}R^{14})_t$(imidazolyl) or $-(CR^{13}R^{14})_t$(pyridinyl) wherein said imidazolyl or pyridinyl moiety is substituted by 1 or 2 R^6 substituents

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t$(C_3-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t$(C_6-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5 and each q is independently an integer from 1 to 5;

each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_q$ or $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of q or t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H.

Preferred compounds of formula 1 are those wherein Z is a 5 or 6 membered aromatic heterocyclic group substituted with from 1 to 4 R^6 substituents. More preferred compounds of formula 1 are those wherein Z is a pyridine or thiophene group substituted with from 1 to 4 R^6 substituents. Other preferred compounds of formula 1 are those wherein Z is a 5 or 6 membered aromatic heterocyclic group fused to a benzene group, substituted with from 1 to 4 R^6 substituents. Preferably, Z comprises from 1 to 3 heteroatoms selected from O, S and N.

Other preferred compounds of formula 1 are those wherein R^1 is H, C_1-C_6 alkyl, or cyclopropylmethyl.

Other preferred compounds of formula 1 are those wherein R^8 is $-NR^{12}R^{13}$, $-OR^{12}$, or $-(CR^{13}R^{14})t$ (4-10 membered heterocyclic) substituted with from 1 to 4 R^6 groups, wherein said 4-10 membered heterocyclic is selected from triazolyl, imidazolyl, pyrazolyl, and piperidinyl. More preferably, said heterocyclic is substituted with one R^6 group. Preferably, R^8 is hydroxy, amino, or triazolyl.

Other preferred compound of formula 1 are those wherein R^8 is H, $-OR^{12}$, $-OC(O)R^{12}$, $-NR^{12}R^{13}$, $-NR^{12}C(O)R^{13}$, cyano, $-C(O)OR^{13}$, $-SR^{12}$, or $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said heterocyclic R^8 groups are substituted by 1 to 4 R^6 groups.

Other preferred compounds of formula 1 are those wherein R^3, R^4, R^5 and R^6 are independently selected from H, halo, and C_1-C_6 alkoxy.

Preferred compounds of the invention include:

6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one (enantiomer A);

6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one (enantiomer B);

4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one;

6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one;

4-(3-chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one;

6-[amino-(5-chloro-pyridin-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one;

6-[amino-(5-chloro-pyridin-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one;

6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3,5-dichloro-phenyl)-1-methyl-1H-quinolin-2-one;

6-[amino-(5-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one;

6-[(5-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one;

amino-(5-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one;

6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one;

6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one;

6-[benzo[b]thiophen-2-yl-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one;

6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1H-quinolin-2-one;

(-)-6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one;

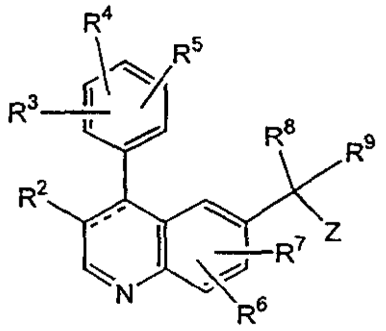
6-[amino-(6-methyl-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one;

6-[amino-(pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one;

(+)-4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one; and

pharmaceutically acceptable salts and solvates of the foregoing compounds.

The present invention also relates to compounds of the formula 12



12

wherein:

the dashed line indicates an optional second bond connecting C-3 and C-4 of the quinoline ring;

R^2 is halo, cyano, -C(O)OR^{15}, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -OR^{12}, -C(O)R^{12}, -C(O)OR^{12}, -NR^{13}C(O)OR^{15}, -OC(O)R^{12}, -NR^{13}SO$_2$R^{15}, -SO$_2$NR^{12}R^{13}, -NR^{13}C(O)R^{12}, -C(O)NR^{12}R^{13}, -NR^{12}R^{13}, -CH=NOR^{12}, -S(O)$_j$R^{12} wherein j is an integer from 0 to 2, -(CR^{13}R^{14})$_t$(C$_6$-C$_{10}$ aryl), -(CR^{13}R^{14})$_t$(4-10 membered heterocyclic), -(CR^{13}R^{14})$_t$(C$_3$-C$_{10}$ cycloalkyl), and -(CR^{13}R^{14})$_t$C≡CR^{16}; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

R^8 is H, $-OR^{12}$, $-OC(O)R^{12}$, $-NR^{12}R^{13}$, $-NR^{12}C(O)R^{13}$, cyano, $-C(O)OR^{13}$, $-SR^{12}$, or $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said heterocyclic R^8 groups are substituted by 1 to 4 R^6 groups;

R^9 is $-(CR^{13}R^{14})_t$(imidazolyl) or $-(CR^{13}R^{14})_t$(pyridinyl) wherein said imidazolyl or pyridinyl moiety is substituted by 1 or 2 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

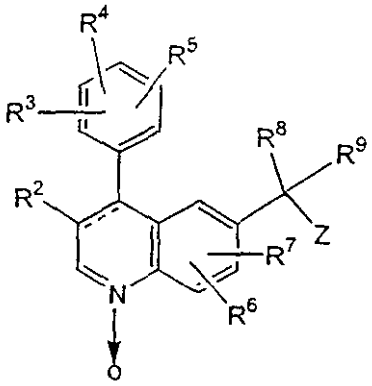
R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H.

Compounds of formula 12 are useful as intermediates for preparing compounds of formula 1. Compounds of formula 12 are also prodrugs of compounds of formula 1, and the present invention also includes pharmaceutically acceptable salts and solvates of compounds of formula 12.

The present invention also relates to compounds of the formula 6



6

wherein:

the dashed line indicates an optional second bond connecting C-3 and C-4 of the quinoline ring;

R^2 is halo, cyano, -C(O)OR^{15}, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -OR^{12}, -C(O)R^{12}, -C(O)OR^{12}, -NR^{13}C(O)OR^{15}, -OC(O)R^{12}, -NR^{13}SO$_2$R^{15}, -SO$_2$NR^{12}R^{13}, -NR^{13}C(O)R^{12}, -C(O)NR^{12}R^{13}, -NR^{12}R^{13}, -CH=NOR^{12}, -S(O)$_j$R^{12} wherein j is an integer from 0 to 2, -(CR^{13}R^{14})$_t$(C$_6$-C$_{10}$ aryl), -(CR^{13}R^{14})$_t$(4-10 membered heterocyclic), -(CR^{13}R^{14})$_t$(C$_3$-C$_{10}$ cycloalkyl), and -(CR^{13}R^{14})$_t$C≡CR^{16}; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -NR^{13}SO$_2$R^{15}, -SO$_2$NR^{12}R^{13}, -C(O)R^{12}, -C(O)OR^{12}, -OC(O)R^{12}, -NR^{13}C(O)OR^{15}, -NR^{13}C(O)R^{12}, -C(O)NR^{12}R^{13}, -NR^{12}R^{13}, -OR^{12}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -(CR^{13}R^{14})$_t$(C$_6$-C$_{10}$ aryl), and -(CR^{13}R^{14})$_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

R^8 is H, -OR^{12}, -OC(O)R^{12}, -NR^{12}R^{13}, -NR^{12}C(O)R^{13}, cyano, -C(O)OR^{13}, -SR^{12}, or -(CR^{13}R^{14})$_t$(4-10 membered heterocyclic), wherein said heterocyclic R^8 groups are substituted by 1 to 4 R^6 groups;

R^9 is -(CR^{13}R^{14})$_t$(imidazolyl) or -(CR^{13}R^{14})$_t$(pyridinyl) wherein said imidazolyl or pyridinyl moiety is substituted by 1 or 2 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, -(CR^{13}R^{14})$_t$(C$_3$-C$_{10}$ cycloalkyl), -(CR^{13}R^{14})$_t$(C$_6$-C$_{10}$ aryl), and -(CR^{13}R^{14})$_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

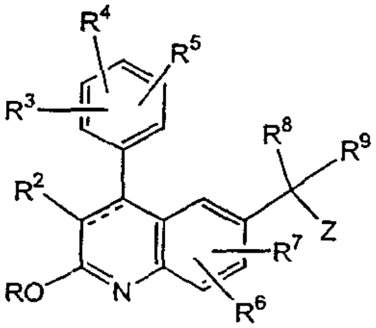
R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H.

Compounds of formula 6 are useful as intermediates for preparing compounds of formula 1. Compounds of formula 6 are furthermore prodrugs of compounds of formula 1, and the present invention also includes pharmaceutically acceptable salts and solvates of compounds of formula 6.

The invention also relates to compounds of the formula 2



2

wherein:

the dashed line indicates an optional second bond connecting C-3 and C-4 of the quinoline ring;

R is C_1-C_6 alkyl;

R^2 is halo, cyano, $-C(O)OR^{15}$, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$,

$-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH{=}NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

R^8 is H, $-OR^{12}$, $-OC(O)R^{12}$, $-NR^{12}R^{13}$, $-NR^{12}C(O)R^{13}$, cyano, $-C(O)OR^{13}$, $-SR^{12}$, or $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said heterocyclic R^8 groups are substituted by 1 to 4 R^6 groups;

R^9 is $-(CR^{13}R^{14})_t$(imidazolyl) or $-(CR^{13}R^{14})_t$(pyridinyl) wherein said imidazolyl or pyridinyl moiety is substituted by 1 or 2 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H. Compounds of formula 2 are useful as intermediates for preparing compounds of formula 1. Compounds of formula 2 are furthermore prodrugs of compounds of formula 1, and the present invention also includes pharmaceutically acceptable salts and solvates of compounds of formula 2.

This invention also relates to a method of inhibiting abnormal cell growth in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula 1, 2, 12, or 6, as defined above, or a pharmaceutically acceptable salt or solvate thereof, that is effective in inhibiting farnesyl protein transferase.

This invention also relates to a method of inhibiting abnormal cell growth in a mammal, including a human, comprising administering to said mammal an amount of a compound of the formula 1, 2, 12, or 6 as defined above, or a pharmaceutically acceptable salt or solvate thereof, that is effective in inhibiting abnormal cell growth.

The invention also relates to a method for the inhibition of abnormal cell growth in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of formula 1, 2, 12, or 6, or a pharmaceutically acceptable salt or solvate thereof, in combination with a chemotherapeutic. In one embodiment, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

This invention further relates to a method for inhibiting abnormal cell growth in a mammal which method comprises administering to the mammal an amount of a compound of formula 1, 2, 12, or 6, or a pharmaceutically acceptable salt or solvate thereof, in combination with radiation therapy, wherein the amount of the compound, salt, ot solvate of formula 1, 2, 12, or 6 is in combination with the radiation therapy effective in inhibiting abnormal cell growth in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described herein. The administration of the compound of the invention in this combination therapy can be determined as described herein.

It is believed that the compounds of formula 1, 2, 12, or 6 can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, this invention further relates to a method for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to the mammal an amount of a compound of formula 1, 2, 12, or 6, or a pharmaceutically acceptable salt or solvate thereof, which amount is effective in sensitizing abnormal cells to treatment with radiation. The amount of the compound, salt, or solvate in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein.

This invention also relates to a pharmaceutical composition for inhibiting abnormal cell growth in a mammal, including a human, comprising an amount of a compound of the formula 1, 2, 12, or 6 as defined above, or a pharmaceutically acceptable salt or solvate thereof, that is effective in inhibiting farnesyl protein transferase, and a pharmaceutically acceptable carrier.

This invention also relates to a pharmaceutical composition for inhibiting abnormal cell growth in a mammal, including a human, comprising an amount of a compound of the formula 1, 2, 12, or 6 as defined above, or a pharmaceutically acceptable salt or solvate thereof, that is effective in inhibiting abnormal cell growth, and a pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical composition for the inhibition of abnormal cell growth in a mammal which comprises a therapeutically effective amount of a compound of formula 1, 2, 12, or 6 or a pharmaceutically acceptable salt or solvate thereof, in combination with a chemotherapeutic, and a pharmaceutically acceptable carrier. In one embodiment, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

The invention also relates to a method of and a pharmaceutical composition for treating in a mammal a disease or condition selected from lung cancer, NSCLC (non small cell lung cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), pediatric malignancy, neoplasms of the central nervous system, (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas), Barrett's esophagus (pre-malignant syndrome), neoplastic cutaneous disease, psoriasis, mycoses fungoides, benign prostatic hypertrophy, human papilloma virus (HPV), and restinosis which comprise an amount of a compound of formula 1, 2, 12, or 6, or a pharmaceutically acceptable salt or solvate of such a compound, that is effective in inhibiting farnesyl protein transferase.

The invention also relates to a method of and pharmaceutical composition for treating in a mammal a disease or condition selected from lung cancer, NSCLC (non small cell lung cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), pediatric malignancy, neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas), Barrett's esophagus (pre-malignant syndrome), neoplastic cutaneous disease, psoriasis, mycoses fungoides, benign prostatic hypertrophy, human papilloma virus (HPV), and restinosis which comprise an amount of a compound of formula 1, 2, 12, or 6, or a pharmaceutically acceptable salt or solvate of such a compound, that is effective in treating said disease.

This invention also relates to a method of and to a pharmaceutical composition for inhibiting abnormal cell growth in a mammal which comprise an amount of a compound of formula 1, 2, 12, or 6, or a pharmaceutically acceptable salt or solvate thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents, which amounts are together effective in inhibiting abnormal cell growth.

Anti-angiogenesis agents, such as MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with a compound of formula 1, 2, 12, or 6, in the methods and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published

July 28, 1999), WO 90/05719 (published May 331, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Preferred MMP-2 and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (*i.e.* MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

Some specific examples of MMP inhibitors useful in the present invention are AG-3340, RO 32-3555, RS 13-0830, and the compounds recited in the following list:

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid;

3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid;

4-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide;

(R) 3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide;

(2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid;

3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-pyran-4-yl)-amino]-propionic acid;

3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide;

3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; and

(R) 3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide;

and pharmaceutically acceptable salts and solvates of said compounds.

Other anti-angiogenesis agents, including other COX-II inhibitors and other MMP inhibitors, can also be used in the present invention.

A compound of formula 1, 2, 12, or 6, can also be used with signal transduction inhibitors, such as agents that can inhibit EGFR (epidermal growth factor receptor) responses, such as EGFR antibodies, EGF antibodies, and molecules that are EGFR inhibitors; VEGF (vascular endothelial growth factor) inhibitors; and erbB2 receptor inhibitors, such as organic molecules or antibodies that bind to the erbB2 receptor, for example, HERCEPTIN™ (Genentech, Inc. of South San Francisco, California, USA).

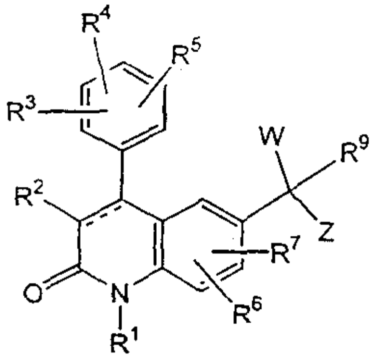
EGFR inhibitors are described in, for example in WO 95/19970 (published July 27, 1995), WO 98/14451 (published April 9, 1998), WO 98/02434 (published January 22, 1998), and United States Patent 5,747,498 (issued May 5, 1998), and such substances can be used in the present invention as described herein. EGFR-inhibiting agents include, but are not limited to, the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated of New York, New York, USA), the compounds ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc. of Annandale, New Jersey, USA), and OLX-103 (Merck & Co. of Whitehouse Station, New Jersey, USA), VRCTC-310 (Ventech Research) and EGF fusion toxin (Seragen Inc. of Hopkinton, Massachusettes). These and other EGFR-inhibiting agents can be used in the present invention.

VEGF inhibitors, for example SU-5416 and SU-6668 (Sugen Inc. of South San Francisco, California, USA), can also be combined with a compound of formula 1, 2, 12, or 6. VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613 (published August 17, 1995), WO 99/61422 (published December 2, 1999), United States Patent 5,834,504 (issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999), United States Patent 5,792,783 (issued August 11, 1998), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January 22, 1998), all of which are incorporated herein in their entireties by reference. Other examples of some specific VEGF inhibitors useful in the present invention are IM862 (Cytran Inc. of Kirkland, Washington, USA); anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, California; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California). These and other VEGF inhibitors can be used in the present invention as described herein.

ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Texas, USA) and 2B-1 (Chiron), can furthermore be combined with a compound of formula 1, 2, 12, or 6, for example those indicated in WO 98/02434 (published January 22, 1998), WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5,877,305 (issued March 2, 1999), which are all hereby incorporated herein in their entireties by reference. ErbB2 receptor inhibitors useful in the present invention are also described in United States Provisional Application No. 60/117,341, filed January 27, 1999, and in United States Provisional Application No. 60/117,346, filed January 27, 1999, both of which are incorporated in their entireties herein by reference. The erbB2 receptor inhibitor compounds and substance described in the aforementioned PCT applications, U.S. patents, and U.S. provisional applications, as well as other compounds and substances that inhibit the erbB2 receptor, can be used with a compound of formula 1, 2, 12, or 6, in accordance with the present invention.

A compound of formula 1, 2, 12, or 6, can also be used with other agents useful in treating abnormal cell growth or cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocite antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, for example the farnesyl protein transferase inhibitors described in the references cited in the "Background" section, *supra*. Specific CTLA4 antibodies that can be used in the present invention include those described in United States Provisional Application 60/113,647 (filed December 23, 1998) which is incorporated by reference in its entirety, however other CTLA4 antibodies can be used in the present invention.

The invention also relates to compounds of the formula 13



13

wherein:

the dashed line indicates an optional second bond connecting C-3 and C-4 of the quinolin-2-one ring;

W is selected from fluoro, chloro, bromo, and iodo;

R^1 is selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_qC(O)R^{12}$, $-(CR^{13}R^{14})_qC(O)OR^{15}$, $-(CR^{13}R^{14})_qOR^{12}$, $-(CR^{13}R^{14})_qCSO_2R^{15}$, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said cycloalkyl, aryl and heterocyclic R^1 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^1 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 4 R^6 groups;

R^2 is halo, cyano, $-C(O)OR^{15}$, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH=NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

R^9 is $-(CR^{13}R^{14})_t$(imidazolyl) or $-(CR^{13}R^{14})_t$(pyridinyl) wherein said imidazolyl or pyridinyl moiety is substituted by 1 or 2 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5 and each q is independently an integer from 1 to 5;

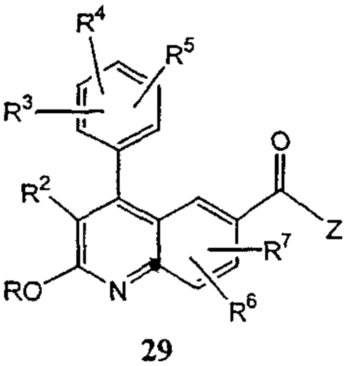
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_q$ or $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of q or t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H. Compounds of formula 13 are useful as intermediates for preparing compounds of formula 1.

The invention also relates to compounds of the formula 29



29

wherein:

R is C_1-C_6 alkyl;

R^2 is halo, cyano, $-C(O)OR^{15}$, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -OR^{12}, -$C(O)R^{12}$, -$C(O)OR^{12}$, -$NR^{13}C(O)OR^{15}$, -$OC(O)R^{12}$, -$NR^{13}SO_2R^{15}$, -$SO_2NR^{12}R^{13}$, -$NR^{13}C(O)R^{12}$, -$C(O)NR^{12}R^{13}$, -$NR^{12}R^{13}$, -$CH=NOR^{12}$, -$S(O)_jR^{12}$ wherein j is an integer from 0 to 2, -$(CR^{13}R^{14})_t(C_6$-C_{10} aryl), -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic), -$(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and -$(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$NR^{13}SO_2R^{15}$, -$SO_2NR^{12}R^{13}$, -$C(O)R^{12}$, -$C(O)OR^{12}$, -$OC(O)R^{12}$, -$NR^{13}C(O)OR^{15}$, -$NR^{13}C(O)R^{12}$, -$C(O)NR^{12}R^{13}$, -$NR^{12}R^{13}$, -OR^{12}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -$(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, -$(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), -$(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$NR^{13}C(O)R^{14}$, -$C(O)NR^{13}R^{14}$, -$NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

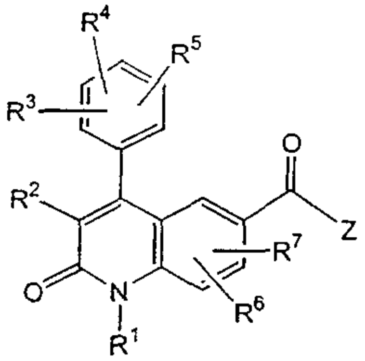
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as -$(CR^{13}R^{14})_t$ each is independently defined for each iteration t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and -$SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H. Compounds of formula 29 are useful as intermediates for preparing compounds of formula 1.

The invention also relates to compounds of the formula 30



30

wherein:

R^1 is selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_qC(O)R^{12}$, $-(CR^{13}R^{14})_qC(O)OR^{15}$, $-(CR^{13}R^{14})_qOR^{12}$, $-(CR^{13}R^{14})_qCSO_2R^{15}$, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said cycloalkyl, aryl and heterocyclic R^1 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^1 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 4 R^6 groups;

R^2 is halo, cyano, $-C(O)OR^{15}$, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH{=}NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5 and each q is independently an integer from 1 to 5;

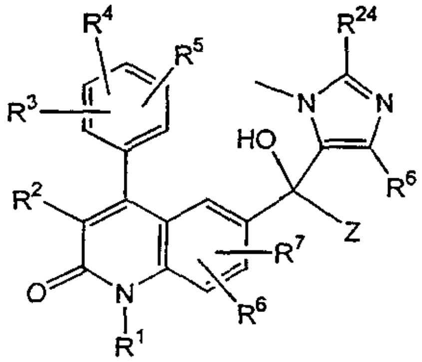
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_q$ or $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of q or t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H. Compounds of formula 30 are useful as intermediates for preparing compounds of formula 1.

The invention also relates to compounds of the formula 26



26

wherein:

R^{24} is selected from $-SR^{20}$ and $-SiR^{21}R^{22}R^{23}$, wherein R^{20} is selected from H and phenyl, and R^{21}, R^{22}, and R^{23} are independently selected from C_1-C_6 alkyl and phenyl;

R^1 is selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_qC(O)R^{12}$, $-(CR^{13}R^{14})_qC(O)OR^{15}$, $-(CR^{13}R^{14})_qOR^{12}$, $-(CR^{13}R^{14})_qCSO_2R^{15}$, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said cycloalkyl, aryl and heterocyclic R^1 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^1 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 4 R^6 groups;

R^2 is halo, cyano, $-C(O)OR^{15}$, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH{=}NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5 and each q is independently an integer from 1 to 5;

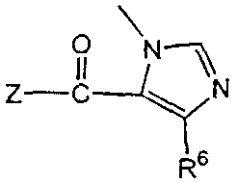
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_q$ or $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of q or t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H. Compounds of formula 26 are useful as intermediates for preparing compounds of formula 1.

The invention also relates to a method of synthesizing a compound of the formula



11a

wherein

R^6 is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH{=}NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

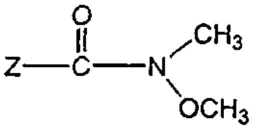
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H;

which method comprises reacting in an appropriate solvent in the presence of a suitable base a compound of the formula

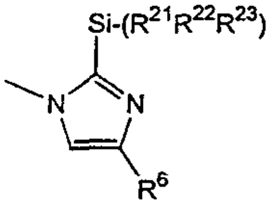


28

,

wherein Z is as defined above;

with a compound of the formula



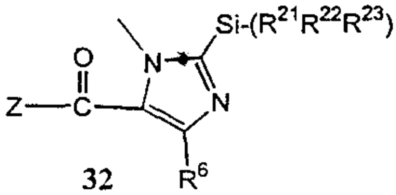
33

,

wherein R^6 is as defined above, and

R^{21}, R^{22}, and R^{23} are each independently selected from C_1-C_6 alkyl and phenyl;

thereby obtaining a compound of the formula

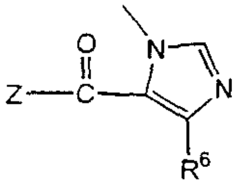


32

;

and reacting the compound of formula 32 so obtained in an appropriate solvent with acetic acid or with a fluoride reagent. Said method can be used in preparing compounds of formula 1.

The invention also relates to a method of synthesizing a compound of the formula



11a

wherein

R^6 is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -OR^{12}, -$C(O)R^{12}$, -$C(O)OR^{12}$, -$NR^{13}C(O)OR^{15}$, -$OC(O)R^{12}$, -$NR^{13}SO_2R^{15}$, -$SO_2NR^{12}R^{13}$, -$NR^{13}C(O)R^{12}$, -$C(O)NR^{12}R^{13}$, -$NR^{12}R^{13}$, -CH=NOR^{12}, -$S(O)_jR^{12}$ wherein j is an integer from 0 to 2, -$(CR^{13}R^{14})_t$(C_6-C_{10} aryl), -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic), -$(CR^{13}R^{14})_t$(C_3-C_{10} cycloalkyl), and -$(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$NR^{13}SO_2R^{15}$, -$SO_2NR^{12}R^{13}$, -$C(O)R^{12}$, -$C(O)OR^{12}$, -$OC(O)R^{12}$, -$NR^{13}C(O)OR^{15}$, -$NR^{13}C(O)R^{12}$, -$C(O)NR^{12}R^{13}$, -$NR^{12}R^{13}$, -OR^{12}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -$(CR^{13}R^{14})_t$(C_6-C_{10} aryl), and -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, -$(CR^{13}R^{14})_t$(C_3-C_{10} cycloalkyl), -$(CR^{13}R^{14})_t$(C_6-C_{10} aryl), and -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$NR^{13}C(O)R^{14}$, -$C(O)NR^{13}R^{14}$, -$NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

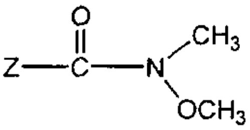
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as -$(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and -$SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H;

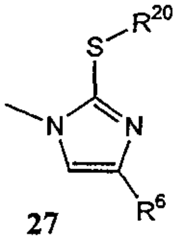
which method comprises reacting in an appropriate solvent in the presence of a suitable base a compound of the formula



28

wherein Z is as defined above;

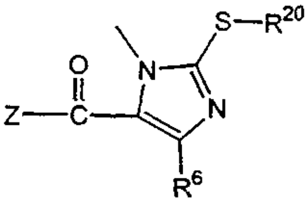
with a compound of the formula



27

wherein R^6 is as defined above and R^{20} is selected from H and phenyl;

thereby obtaining a compound of the formula



31

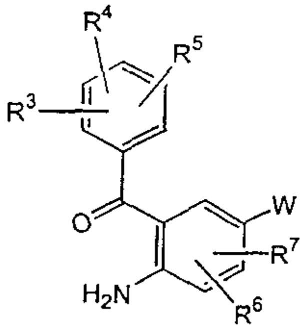
;

and removing from the compound of formula 31 so obtained the $-SR^{20}$ group, either:

a) reductively, with a nickel catalyst; or

b) oxidatively, with nitric acid or with aqueous hydrogen peroxide in acetic acid. Said method can be used in preparing compounds of formula 1.

The invention also relates to a method of synthesizing a compound of the formula



23

wherein

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH=NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

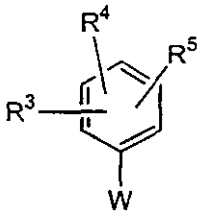
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

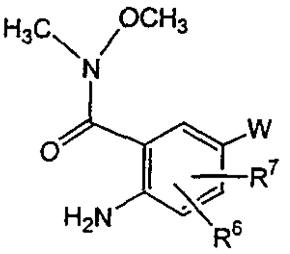
R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H;

which method comprises reacting, at a temperature of from about -78° C to about 0° C, in the presence of a suitable base and in an appropriate solvent a compound of formula



34

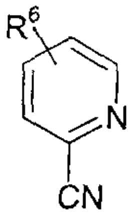
wherein W is an appropriate leaving group, and R^3, R^4 and R^5 are as defined above, with a compound of the formula



35

wherein R^6 and R^7 are as defined above. Said method can be used in preparing compounds of formula 1. In a preferred embodiment of the above-described method for synthesizing a compound of formula 23, the solvent in which the compound of formula 34 and the compound of formula 35 are reacted is ethyl ether.

The invention also pertains to a method of synthesizing a compound of the formula

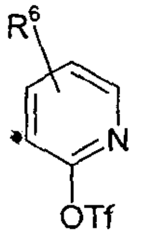


37

wherein R^6 is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH{=}NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

which method comprises

a) reacting with a metal cyanide, in the presence of a palladium catalyst and in an appropriate solvent, at a temperature of about 25° C to about 100° C, a compound of the formula

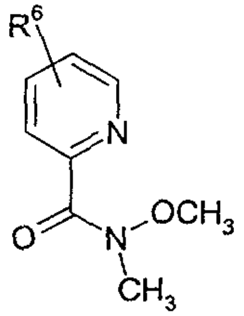


36

wherein Tf is $-SO_2$-CF_3 and R^6 is as defined above;

thereby obtaining a compound of the formula **37**. This method is useful in the preparation of compounds of formula **1**.

In one embodiment of the method described in the immediately preceding paragraph, a compound of the formula



28a

is further synthesized, wherein

R^6 is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH{=}NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

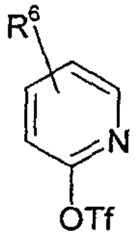
R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H;

which embodiment comprises

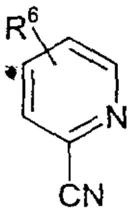
a) reacting with a metal cyanide, in the presence of a palladium catalyst and in an appropriate solvent, at a temperature of about 25° C to about 100° C, a compound of the formula



36

wherein Tf is $-SO_2-CF_3$ and R^6 is as defined above;

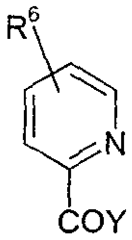
thereby obtaining a compound of the formula



37

b) treating the compound of formula 37 so obtained with either a suitable base or a suitable acid under hydrolysis conditions;

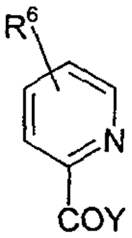
thereby obtaining a compound of the formula



38

wherein Y is OH;

c) converting the compound of formula 38 so obtained to a compound of the formula



38

wherein Y is -Cl or N1-imidazole; and

d) treating the compound of formula 38 obtained in (c) with N,O-dimethylhydroxyamine, in the presence of a suitable base and in an appropriate solvent, at a temperature of from about 0° C to about 40° C. Said embodiment can also be used in preparing compounds of formula 1.

"Abnormal cell growth", as used herein, refers to cell growth that is independent of normal regulatory mechanisms (e.g., loss of contact inhibition). This includes, but is not limited to, the abnormal growth of: (1) tumor cells (tumors), both benign and malignant, expressing an activated Ras oncogene; (2) tumor cells, both benign and malignant, in which the Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs.

Examples of such benign proliferative diseases are psoriasis, benign prostatic hypertrophy, human papilloma virus (HPV), and restinosis. "Abnormal cell growth" also refers to and includes the abnormal growth of cells, both benign and malignant, resulting from activity of the enzyme farnesyl protein transferase.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

The term "halo", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, and *t*-butyl.

The term "cycloalkyl", as used herein, unless otherwise indicated, includes cyclic alkyl moieties wherein alkyl is as defined above. Multicyclic, such as bicyclic and tricyclic, groups are included in this definition.

The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above.

The term "alkynyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above. Examples of alkynyl groups include, but are no limited to, ethynyl and 2-propynyl.

The term "alkoxy", as used herein, unless otherwise indicated, includes O-alkyl groups wherein alkyl is as defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "heterocyclic", as used herein, unless otherwise indicated, means aromatic and non-aromatic heterocyclic groups (including saturated heterocyclic groups) containing one or more heteroatoms each selected from O, S and N, wherein each ring of a heterocyclic group has from 4 to 10 atoms. Non-aromatic heterocyclic groups may include rings having only 4 atoms, but aromatic heterocyclic rings must have at least 5 atoms. Heterocyclic groups of this invention unless otherwise indicated may contain one ring or more than one ring, i.e. they may be monocyclic or multicyclic, for example bicyclic (which may comprise non-aromatic and/or aromatic rings). Preferably, bicyclic heterocyclic groups of this invention contain 6-9 members in their ring systems. Monocyclic heterocyclic groups of this invention preferably contain 5 or 6 members. Aromatic multicyclic heterocyclic groups include benzo-fused ring systems. The heterocyclic groups of this invention can also include ring systems substituted with one or more oxo moieties. An example of a 4 membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5 membered heterocyclic group is thiazolyl and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the compounds listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached).

Where R^{13} and R^{14} are as $(CR^{13}R^{14})_q$ or $(CR^{13}R^{14})_t$, each R^{13} and R^{14} is independently defined for each iteration of q or t in excess of 1. This means, for instance, that where q or t is 2 alkylene moieties of the type $-CH_2CH(CH_3)-$, and other asymmetrically branched groups, are included.

The term "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups that may be present in the compounds of formula 1. For example, pharmaceutically acceptable salts include sodium, calcium and potassium salts of carboxylic acid groups and hydrochloride salts of amino groups. Other pharmaceutically acceptable salts of amino groups are hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogen phosphate, acetate, succinate, citrate, tartrate, lactate, mandelate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts. The preparation of such salts is described below.

Certain compounds of formula 1 may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of formula 1, and mixtures thereof, are considered to be within the scope of the invention. With respect to the compounds of formula 1, the invention includes the use of a racemate, one or more enantiomeric forms, one or more diastereomeric forms, or mixtures thereof. The compounds of formula 1 may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

The subject invention also includes prodrugs of compounds of formula 1, which prodrugs are derivatives of compounds of formula 1, which compounds comprise free amino groups, said derivatives comprising amide, carbamide, or peptide derivations of said amino groups. Such prodrugs can comprise an amino acid residue, or a polypeptide chain of two or more, such as up to four, amino acid residues, that are covalently joined through peptide bonds. Amino acid residues useful in preparing prodrugs of the invention include the 20 naturally-occurring amino acids designated by three letter symbols, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Preferred amino acid residues are those with a non-polar group such as Ala, Val, Nval, Leu, Met, Gly, Pro, Phe, or a basic polar group such as Lys.

The subject invention also includes prodrugs of compounds of formula 1, which prodrugs are the compounds of formula 2, formula 12 and the compounds of formula 6 described herein.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula 1, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula 1 of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

Patients that can be treated with a compound of formula 1, 2, 6, or 12, or a pharmaceutically acceptable salt or solvate thereof, according to the methods of this invention include, for example, patients that have been diagnosed as having lung cancer, NSCLC (non small cell lung cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), pediatric malignancy, neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas), neoplastic cutaneous diseases (e.g. psoriasis, mycoses fungoides), or Barrett's esophagus (pre-malignant syndrome).

The compounds of formula 1, 2, 12, and 6, and their pharmaceutically acceptable salts and solvates can each independently also furthermore be used in a palliative neo-adjuvant/adjuvant therapy in alleviating the symptoms associated with the diseases recited in the preceding paragaph as well as the symptoms associated with abnormal cell growth. Such therapy can be a monotherapy or can be in a combination with chemotherapy and/or immunotherapy.

Patients that can be treated according to the methods of this invention also include patients suffering from abnormal cell growth, as defined above.

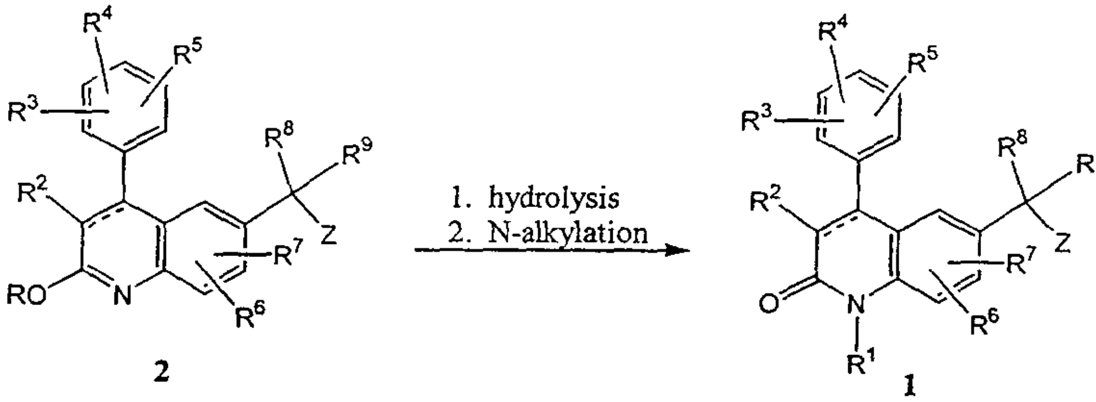
Detailed Description of the Invention

In the following Schemes and Examples, "Et" represents an ethyl moiety, and "Me" represents a methyl moiety. Hence, for example, "OEt" means ethanol. Also, "THF" means tetrahydrofuran, and "DMF" means dimethylformamide.

The compounds of formula **1** may be prepared as described below.

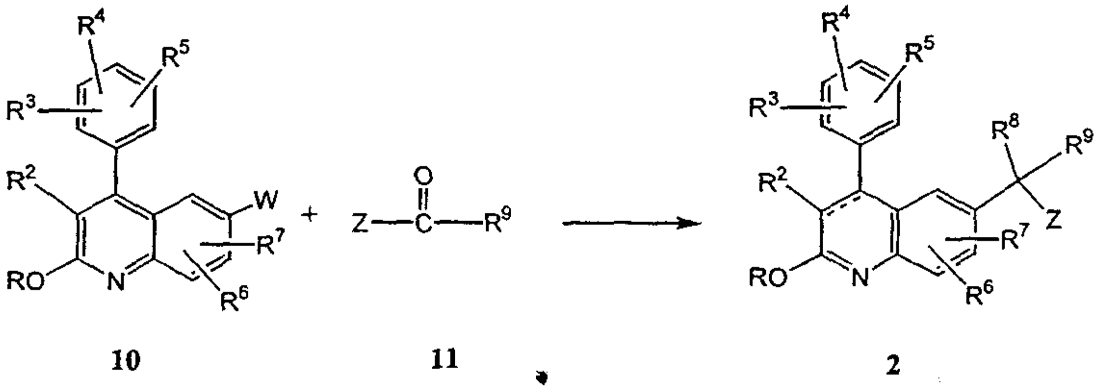
With reference to Scheme 1 below, the compounds of formula **1** may be prepared by hydrolysing an intermediate ether of formula **2**, wherein R is C_1-C_6 alkyl, according to methods familiar to those skilled in the art, such as by stirring the intermediate of formula **2** in an aqueous acid solution. An appropriate acid is, for example, hydrochloric acid. The resulting quinolinone of formula **1** wherein R^1 is hydrogen may be transformed into a quinolinone wherein R_1 has a meaning as defined above apart from hydrogen by *N*-alkylation methods familiar to those skilled in the art.

Scheme 1



With reference to Scheme 2 below, the intermediate of formula **2**, referred to above, may be prepared by reacting an intermediate of formula **10**, wherein W is an appropriate leaving group, such as halo, with an intermediate ketone of formula **11**. This reaction is done by converting the intermediate of formula **10** into a organometallic compound, by stirring it with a strong base such as butyl lithium, and subsequently adding the intermediate ketone of formula **11**. Although this reaction gives at first instance a hydroxy derivative (R^8 is hydroxy), said hydroxy derivative can be converted into other intermediates wherein R^8 has another definition by performing functional group transformations familiar to those skilled in the art.

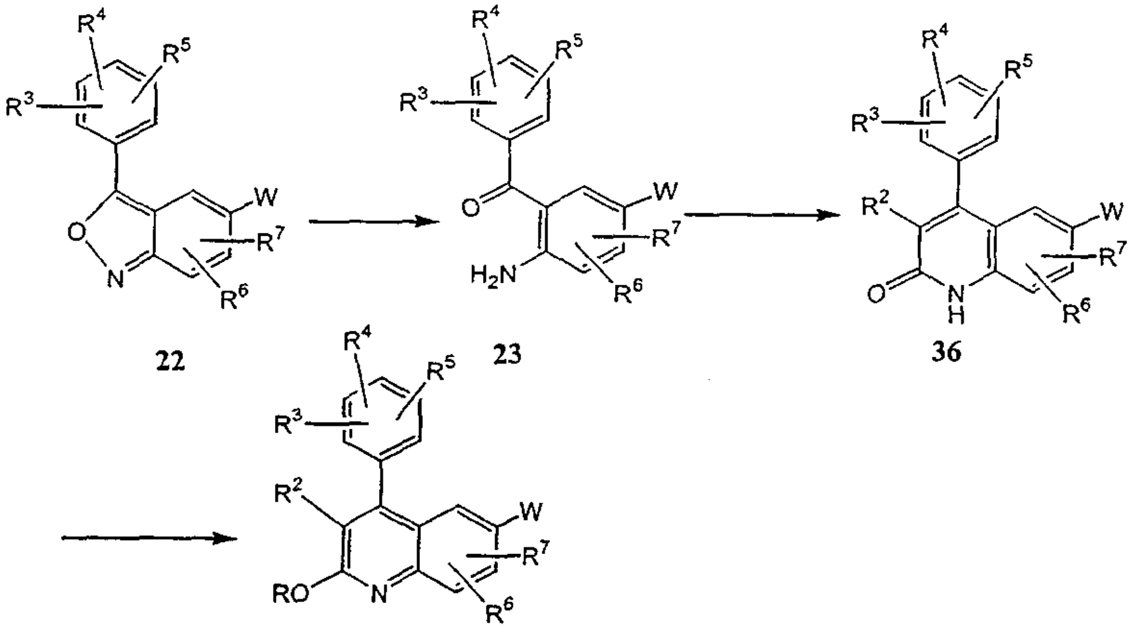
Scheme 2



With reference to Scheme 3 below, compounds of formula **36**, which are compounds of formula **1** wherein the dotted line is a bond and R^1 is hydrogen, can be prepared via ring opening of the isoxazole moiety of the intermediate of formula **22** by stirring it with an acid, such as $TiCl_3$, in the presence of water. Subsequent treatment of the resulting intermediate of formula **23** with a suitable reagent, such as R^2CH_2COCl or $R^2CH_2COOC_2H_5$, wherein R is as defined above, yields either directly a compound of formula **36** or an intermediate which can be converted to a compound of formula **36** by treatment with a base, such as potassium *tert*-

butoxide. The intermediate of formula **36** can be converted to intermediate of formula **10** by stirring it with an o-alkylation reagent, such as trimethyloxonium tetrafluoroborate (BF_4OMe_3) for a period of time, typically 4 to 15 hours, and subsequently adding a strong base such as sodium hydroxide in aqueous.

Scheme 3

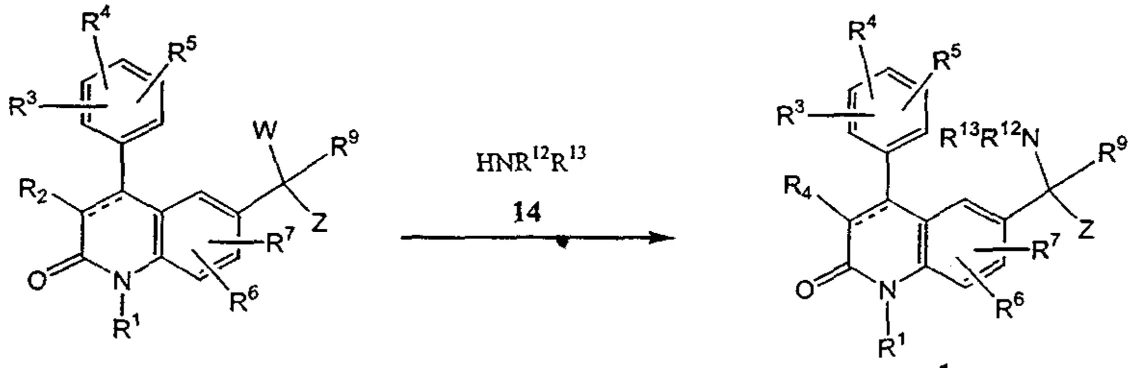


22 23 36

10

With reference to Scheme 4 below, compounds of formula **1** wherein R^8 is a radical of formula $-NR^{12}R^{13}$ wherein R^{12} and R^{13} are as described above (said compounds are represented below by formula **1(g)**), may be prepared by reacting an intermediate of formula **13**, wherein W is an appropriate leaving group, such as halo, with a reagent of formula **14**. Said reaction may be performed by stirring the reactants in an appropriate solvent, such as THF.

Scheme 4



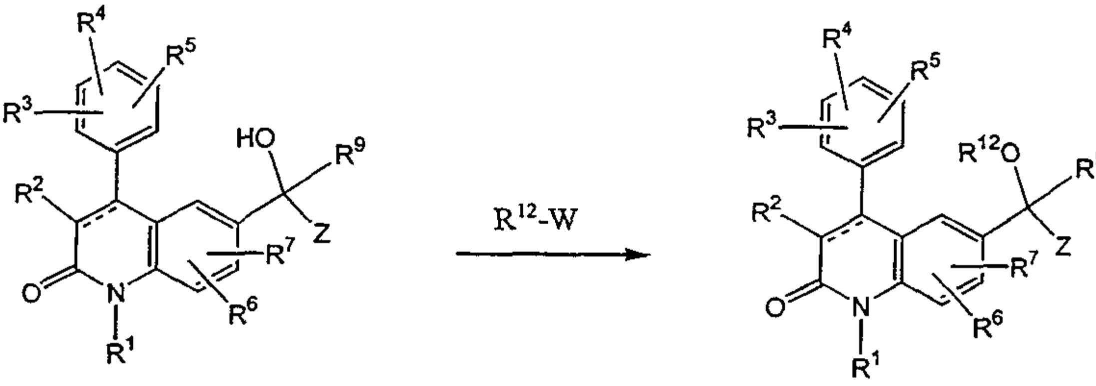
13

1g

Compounds of formula **1(g)**, or other embodiments of formula **1**, wherein the dotted line represents a bond can be converted into compounds wherein the dotted line does not represent a bond by hydrogenation methods familiar to those skilled in the art. Compounds wherein the dotted line does not represent a bond may be converted into compounds wherein the dotted line represents a bond by oxidation methods familiar to those skilled in the art.

With reference to Scheme 5 below, compounds of formula **1** wherein R^8 is hydroxy (said compounds being represented by formula **1(b)**) may be converted into compounds of formula **1(c)**, wherein R^{12} has the meaning described above except it is not hydrogen, by methods known to those skilled in the art, including O-alkylation or O-acylation reactions; such as by reacting the compound of formula **1(b)** with an alkylating reagent such as R^{12}-W, wherein R^{12} is as described above, in appropriate conditions, such as in a dipolar aprotic solvent, such as DMF, in the presence of a base, such as sodium hydride. W is a suitable leaving group, such as a halo group or a sulfonyl group.

Scheme 5



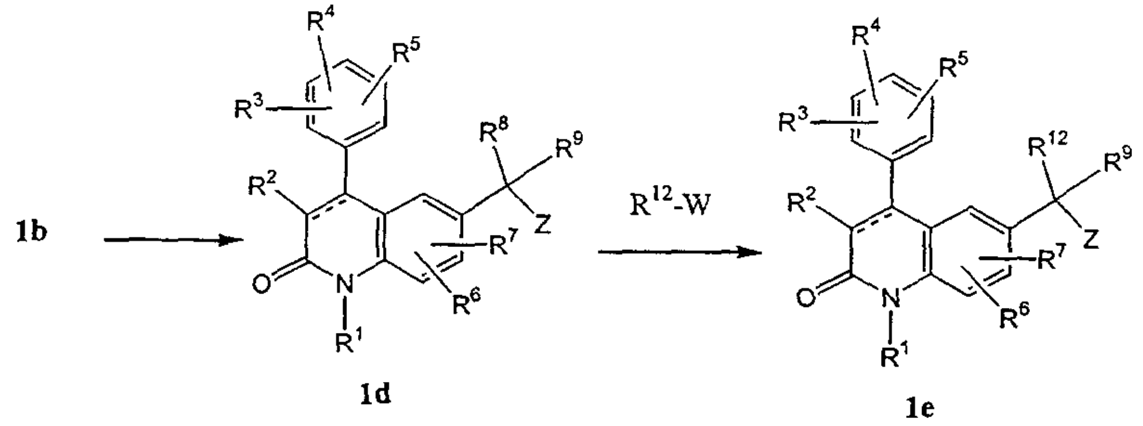
1b **1c**

As an alternative to the above reaction procedure, compounds of formula **1(c)** may also be prepared by reacting a compound of formula **1(b)** with a reagent of formula R^{12}-OH, wherein R^{12} is as described above, in acidic medium.

Compounds of formula **1(b)** may also be converted into compounds of formula **1(g)**, wherein R^{12} is hydrogen and R^{13} is replaced with C_1-C_6 alkylcarbonyl, by reacting compounds of formula **1(b)** in acidic medium, such as sulfuric acid, with C_1-C_6 alkyl-CN in a Ritter-type reaction. Further, compounds of formula **1(b)** may also be converted into compounds of formula **1(g)**, wherein R^{12} and R^{13} are hydrogen, by reacting a compound of formula **1(b)** with ammonium acetate and subsequent treatment with NH_3(aq.).

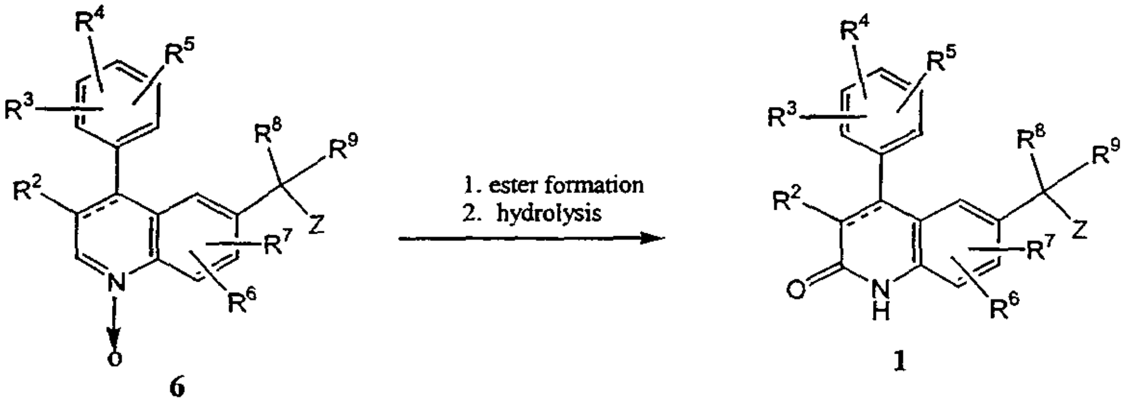
With reference to Scheme 6 below, compounds of formula **1(b)**, referred to above, may also be converted into compounds of formula **1(d)**, wherein R^8 is hydrogen, by submitting a compound of formula **1(b)** to appropriate reducing conditions, such as stirring in trifluoroacetic acid in the presence of an appropriate reducing agent, such as sodium borohydride, or, alternatively, stirring the compound of formula **1(b)** in acetic acid in the presence of formamide. Further, the compound of formula **1(d)** wherein R^8 is hydrogen may be converted into a compound of formula **1(e)** wherein R^{12} is C_1-C_{10} alkyl by reacting the compound of formula **1(d)** with a reagent of formula **5**, wherein W is an appropriate leaving group, in an appropriate solvent, such as diglyme, in the presence of a base, such as potassium *tert*-butoxide.

Scheme 6



With reference to Scheme 7 below, compounds of formula **1** may be prepared by reacting a nitrone of formula **6** with the anhydride of a carboxylic acid, such as acetic anhydride, thus forming the corresponding ester on the 2-position of the quinoline moiety. Said quinoline ester can be hydrolyzed *in situ* to the corresponding quinolinone using a base, such as potassium carbonate.

Scheme 7



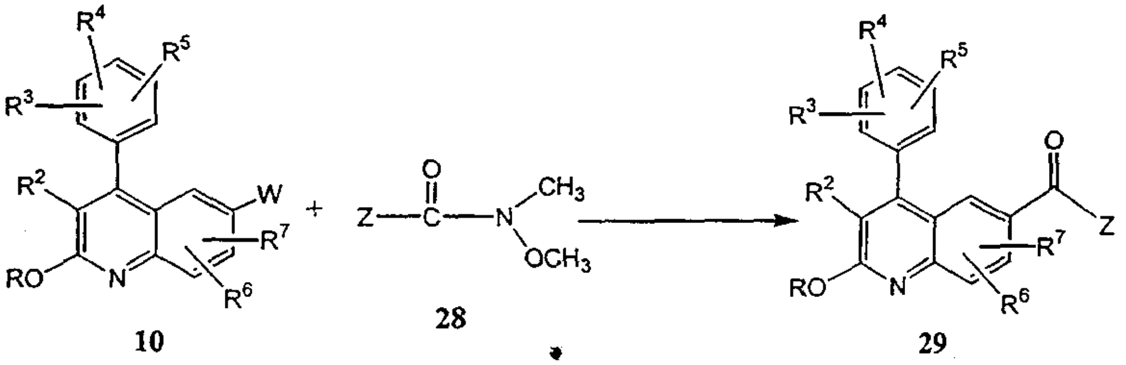
Alternatively, compounds of formula **1** can be prepared by reacting a nitrone of formula **6** with a sulfonyl containing electrophilic reagent, such as *p*-toluenesulfonylchloride, in the presence of a base, such as aqueous potassium carbonate. The reaction initially involves the formation of a 2-hydroxy-quinoline derivative which is subsequently tautomerized to the desired quinolinone derivative. The application of conditions of phase transfer catalysis, which are familiar to those skilled in the art, may enhance the rate of the reaction.

Compounds of formula **1** may also be prepared by an intramolecular photochemical rearrangement of compounds of formula **6**, referred to above. Said rearrangement can be carried out by dissolving the reagents in a reaction-inert solvent and irradiating at a wavelength of 366 nm. It is advantageous to use degassed solutions and to conduct the reaction under an inert atmosphere, such as oxygen-free argon or nitrogen gas, in order to minimize undesired side reactions or reduction of quantum yield.

The substituents of the compounds of formula **1** may be converted to other substituents falling within the scope of formula **1** via reactions or functional group transformations familiar to those skilled in the art. A number of such transformations are already described above. Other examples are hydrolysis of carboxylic esters to the corresponding carboxylic acid or alcohol; hydrolysis of amides to the corresponding carboxylic acids or amines; hydrolysis of nitriles to the corresponding amides; amino groups on imidazole or phenyl moieties may be replaced by hydrogen by diazotation reactions familiar to those skilled in the art, and subsequent replacement of the diazo-group by hydrogen; alcohols may be converted into esters and ethers; primary amines may be converted into secondary or tertiary amines; double bonds may be hydrogenated to the corresponding single bond.

With reference to Scheme 8 below, intermediates of formula **29**, wherein R is, as defined above, C_1-C_6 alkyl, may be prepared by reacting an intermediate of formula **10** with an intermediate of formula **28**, or a functional derivative thereof, under appropriate conditions. This reaction is done by converting the intermediate of formula **10** into an organometallic compound, by stirring it with a strong base such as butyl lithium, and subsequently adding the intermediate amide of formula **28**.

Scheme 8

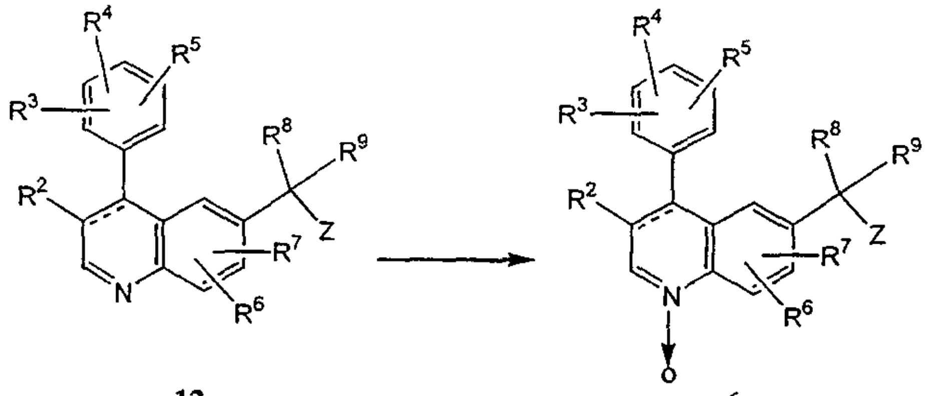


With reference to Scheme 9 below, the intermediate nitrones of formula **6** can be prepared by *N*-oxidizing a quinoline derivative of formula **12** with an appropriate oxidizing agent, such as m-chloro-peroxybenzoic acid or H_2O_2, in an appropriate solvent, such as dichloromethane.

Said *N*-oxidation may also be carried out on a precursor of a quinoline of forumula **12**.

The intermediate of formula **12** may be metabolized *in vivo* into compounds of formula **1** via intermediates of formula **6**. Hence, intermediates of formula **12** and **6** can act as prodrugs of compounds of formula 1. Also, the intermediates of formula 2 can be metabolized in vivo to compounds of formula 1. Hence, compounds of formula 2 are deemed "prodrugs" for puposes of the present invention. Such prodrugs are within the scope of the present invention.

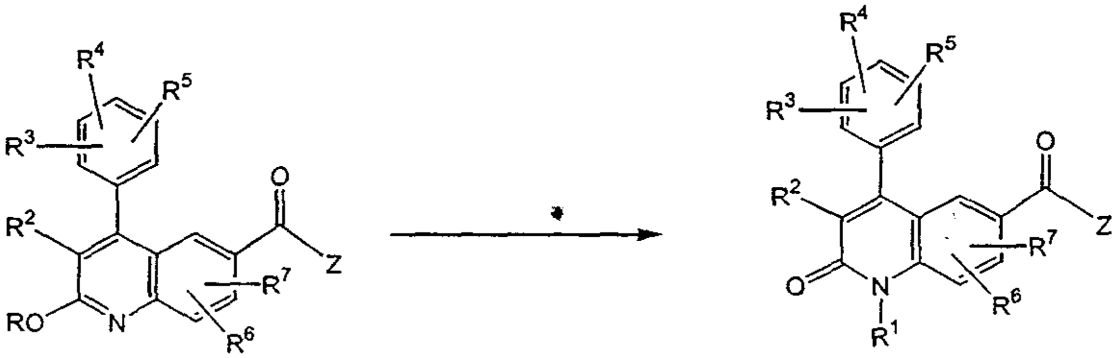
Scheme 9



12 **6**

With reference to Scheme 10 below, the compound of formula **30** can be prepared by hydrolysing an intermediate formula **29**, wherein R is C_1-C_6 alkyl, according to methods familiar to those skilled in the art, such as by stirring the intermediate of formula **29** in an aqueous acid solution or in an organic solvent with the presence of a Lewis acid. An appropriate acid is, for example, hydrochloric acid. An appropriate Lewis acid and the solvent are, for example, iodotrimethylsilane and dicholoromethane. The resulting quinolinone of formula **30** wherein R^1 is hydrogen may be transformed into a quinolinone wherein R^1 has a meaning as defined above apart from hydrogen by *N*-alkylation methods familiar to those skilled in the art.

Scheme 10

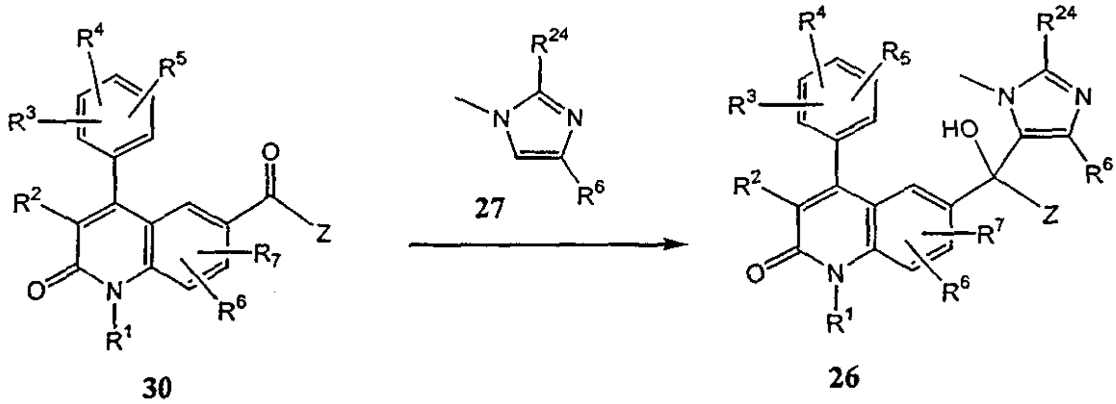


29 **30**

With reference to Scheme 11 below, the compound of formula **26** can be prepared by reacting a compound of formula **30** with an intermediate of formula **27**, where R^{24} is SR^{20} or $SiR^{21}R^{22}R^{23}$, R^{20} being H or phenyl, and R^{21}, R^{22}, and R^{23} being independently selected from

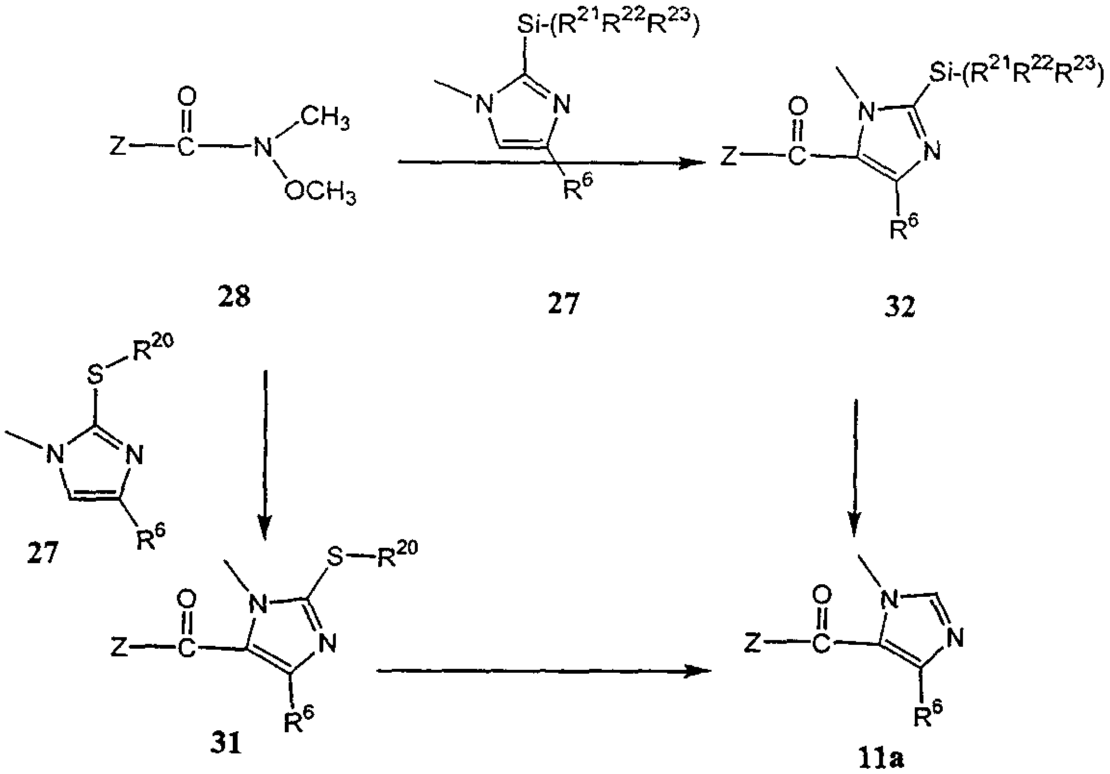
C_1-C_6 alkyl and phenyl. This reaction requires the presence of a suitable base, such as *tert*-butyl lithium (when R^{24} is SR^{20} and R^{20} = H) or lithium 2,2,6,6,-tetramethylpiperidine (when R^{24} is SR^{20} and R^{20} = phenyl), or *n*-butyl lithium (when R^{24} is $SiR^{21}R^{22}R^{23}$), in an appropriate solvent, such as THF. The -SR^{20} group can be reductively removed from the compound of formula **26** with a nickel catalyst such as RANEY™ nickel or oxidatively with nitric acid or aqueous hydrogen peroxide in acetic acid. When R^{24} is $SiR^{21}R^{22}R^{23}$, then R^{24} can be removed from the compound of formula **26** by reaction with acetic acid or a fluoride reagent such as tetrabutylammonia fluoride (TBAF) in a solvent such as tetrahydrofuran. Thus, a compound of formula **1** can be synthesized.

Scheme 11



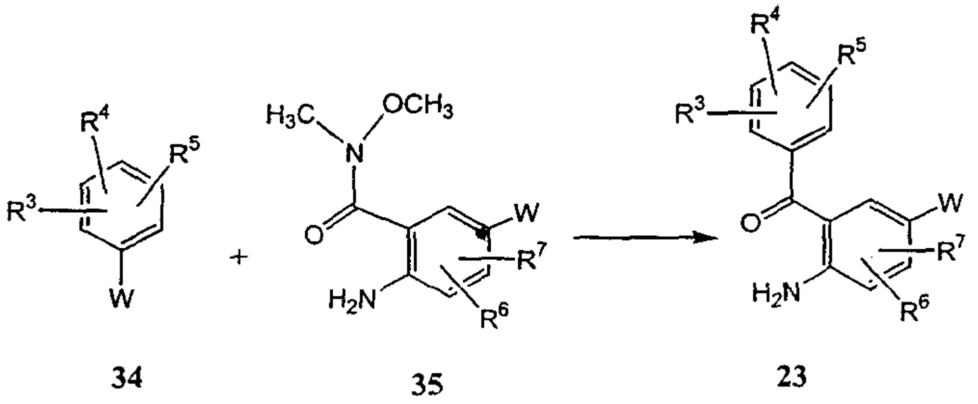
With reference to Scheme 12, intermediates of formula **11a**, which are compounds of formula 11 wherein R^9 is imidazole substituted with R^6, wherein R^6 is as defined above, can be prepared by reacting an intermediate of formula **28** with an intermediate of formula **27** where R^{21},R^{22}, R^{23} are C_1-C_6 alkyl or phenyl to generate an intermediate of formula **32**. This reaction requires the presence of a suitable base, such as *n*-butyl lithium, in an appropriate solvent, such as THF. The intermediate of formula **32** is reacted with acetic acid or a fluoride reagent such as TBAF in a solvent such as tetrahydrofuran to obtain the compound of formula **11a**. Alternatively, the compound of formula **11a** can be prepared by reacting a compound of formula **28** with an intermediate of formula **27** where R^{20} is H or phenyl. This reaction requires the presence of a suitable base, such as *tert*-butyl lithium (when R^{20} = H) or lithium 2,2,6,6,-tetramethylpiperidine (when R^{20} = phenyl), in an appropriate solvent, such as THF. The -SR^{20} group can be reductively removed from the compound of formula **31** with a nickel catalyst such as RANEY™ nickel or oxidatively with nitric acid or aqueous hydrogen peroxide in acetic acid.

Scheme 12



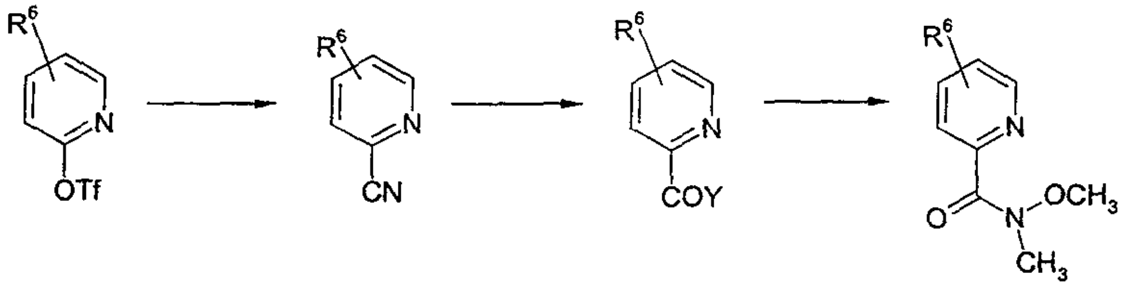
With reference to Scheme 13, intermediates of formula **23** may also be synthesized by reacting an intermediate of formula **34**, wherein W is an appropriate leaving group, such as halo, with an intermediate amide of formula **35**. This reaction requires the presence of a suitable base, such as *n*-butyl lithium, in an appropriate solvent, such as diethyl ether at a temperature of from about -78 to about zero degrees C.

Scheme 13



With reference to Scheme 14, intermediates of formula **28a**, which are compounds of formula **28** wherein Z is a pyridine substituted with R^6, can be prepared by reacting an intermediate of formula **36** with a metal cyanide, such as $Zn(CN)_2$ or NaCN, in the presence of a palladium catalyst such as tetrakis(triphenylphosphine)-palladium, in an appropriate solvent, such as THF or DMF, at a temperature of from about 25 to about 100 degrees C. Subsequent treatment of the resulting intermediate of formula 37 with either a base or acid under hydrolysis conditions familiar to those skilled in the art, yields a compound of formula **38a** which are compounds of formula **38** wherein Y is -OH. The intermediate of formula **38** can be converted to its activated form, intermediate **38b** which are compounds of formula **38** wherein Y is -Cl or N1-imidazole using methods familiar to those skilled in the art. Subsequent conversion to **28a** is furnished with N,O-dimethylhydroxyamine in the presence of a base, such as triethylamine, pyridine, or 4-dimethyaminopyridine, in an appropriate solvent, such as dichloromethane at a temperature of from about zero to about 40 degrees C. In Scheme **14**, "Tf" represents trifluoromethanesulfonyl, *i.e.*, $-SO_2-CF_3$.

Scheme 14



36 **37** **38** **28a**

The compounds of formula **1** and some of the intermediates described above may have one or more stereogenic centers in their structure. Such stereogenic centers may be present in a R or a S configuration. Oxime moieties, such as where R^3, R^4, R^5, R^6 or R^7 is $-CH=NOR^{12}$, may exist in E or Z configurations.

The compounds of formula **1** as prepared in the above processes are generally racemic mixtures of enantiomers which can be separated from one another following resolution procedures familiar to those skilled in the art. The racemic compounds of formula **1** may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomerics forms of the compounds of formula **1** involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs sterospecifically. Preferably if a specific stereoisomer is desired, said compound will be synthesized by stereospecfic methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula **1** that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of formula **1** from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon evaporation of the solvent, the desired solid salt is readily obtained. The desired acid addition salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid. Cationic salts of the compounds of formula **1** are similarly prepared except through reaction of a carboxy group with an appropriate cationic salt reagent, such as sodium, potassium, calcium, magnesium, ammonium, N,N'-dibenzylethylenediamine, N-methylglucamine (meglumine), ethanolamine, tromethamine, or diethanolamine.

The compounds of formula **1**, **12**, and **6** and their pharmaceutically acceptable salts and solvates (hereinafter referred to, collectively, as "the therapeutic compounds") can be administered orally, transdermally (e.g., through the use of a patch), parenterally or topically. Oral administration is preferred. In general, compounds of the formula 1, 12, and 6 and their pharmaceutically acceptable salts and solvates are most desirably administered in dosages ranging from about 1.0 mg up to about 500 mg per day, preferably from about 1 to about 100 mg per day in single or divided (i.e., multiple) doses. The therapeutic compounds will ordinarily be administered in daily dosages ranging from about 0.01 to about 10 mg per kg body weight per day, in single or divided doses. Variations may occur depending on the weight and condition of the person being treated and the particular route of administration chosen. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The therapeutic compounds may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by either of the two routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the novel therapeutic compounds of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a therapeutic compound in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

Additionally, it is also possible to administer the therapeutic compounds topically and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.

The therapeutic compounds may also be administered to a mammal other than a human. The dosage to be administered to a mammal will depend on the animal species and the disease or disorder being treated. The therapeutic compounds may be administered to animals in the form of a capsule, bolus, tablet or liquid drench. The therapeutic compounds may also be administered to animals by injection or as an implant. Such formulations are prepared in a conventional manner in accordance with standard veterinary practice. As an alternative the therapeutic compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

For the combination therapies and pharmaceutical compositions described herein, the effective amounts of the compound of the invention and of the chemotherapeutic or other agent useful for inhibiting abnormal cell growth (*e.g.*, other antiproliferative agent, anti-agiogenic, signal transduction inhibitor or immune-system enhancer) can be determined by those of ordinary skill in the art, based on the effective amounts for the compound described herein and those known or described for the chemotherapeutic or other agent. The formulations and routes of administration for such therapies and compositions can be based on the information described herein for compositions and therapies comprising the compound of the invention as the sole active agent and on information provided for the chemotherapeutic or other agent in combination therewith.

The compounds of formula 1 exhibit activity as Ras farnesylation inhibitors and are useful in the treatment of cancer and the inhibition of abnormal cell growth in mammals, including humans. The activity of the compounds of formula 1 as Ras farnesylation inhibitors may be determined by their ability, relative to a control, to inhibit Ras farnesyl transferase *in vitro*. An example of one such procedure is described below.

A crude preparation of human farnesyl transferase (FTase) comprising the cytosolic fraction of homogenized brain tissue is used for screening compounds in a 96-well assay format.

The cytosolic fraction is prepared by homogenizing approximately 40 grams of fresh tissue in 100 ml of sucrose/$MgCl_2$/EDTA buffer (using a Dounce homogenizer; 10-15 strokes), centrifuging the homogenates at 1000 g for 10 minutes at 4°C, re-centrifuging the supernatant at 17,000 g for 15 minutes at 4°C, and then collecting the resulting supernatant. This supernatant is diluted to contain a final concentration of 50 mM Tris HCl (pH 7.5), 5 mM DTT, 0.2 M KCl, 20 μM $ZnCl_2$, 1 mM PMSF and re-centrifuged at 178,000 g for 90 minutes at 4°C. The supernatant, termed "crude FTase" is assayed for protein concentration, aliquoted, and stored at -70°C.

The assay used to measure *in vitro* inhibition of human FTase is a modification of the method described by Amersham LifeScience for using their Farnesyl transferase (3H) Scintillation Proximity Assay (SPA) kit (TRKQ 7010). FTase enzyme activity is determined in a volume of 100 μl containing 50 mM N-(2-hydroxy ethyl) piperazine-N-(2-ethane sulfonic acid) (HEPES), pH 7.5, 30 mM $MgCl_2$, 20 mM KCl, 25 mM Na_2HPO_4, 5 mM dithiothreitol (DTT), 0.01% Triton X-100, 5% dimethyl sulfoxide (DMSO), 20 mg of crude FTase, 0.12 mM [3H]-farnesyl pyrophosphate ([3H]-FPP; 36000 dpm/pmole, Amersham LifeScience), and 0.2 μM of biotinylated Ras peptide KTKCVIS (Bt-KTKCVIS) that is N-terminally biotinylated at its alpha amino group and was synthesized and purified by HPLC in house. The reaction is initiated by addition of the enzyme and terminated by addition of EDTA (supplied as the STOP reagent in kit TRKQ 7010) following a 45 minute incubation at 37°C. Prenylated and unprenylated Bt-KTKCVIS is captured by adding 150 μl of steptavidin-coated SPA beads (TRKQ 7010) per well and incubating the reaction mixture for 30 minutes at room temperature. The amount of radioactivity bound to the SPA beads is determined using a MicroBeta 1450 plate counter. Under these assay conditions, the enzyme activity is linear with respect to the concentrations of the prenyl group acceptor, Bt-KTKCVIS, and crude FTase, and inhibition of Bt-KTKCVIS interaction with FTase can be detected. The enzyme activity is saturating with respect to the prenyl donor, FPP. The assay reaction time is also in the linear range.

The test compounds are routinely dissolved in 100% DMSO. Inhibition of farnesyl transferase activity is determined by calculating percent incorporation of tritiated-farnesyl in the presence of the test compound versus its incorporation in control wells (absence of inhibitor). IC_{50} values, that is, the concentration required to produce half maximal farnesylation of Bt-KTKCVIS, is determined from the dose-responses obtained.

All of the title compounds of formula 1 in the following Examples were assayed for their ability to inhibit the activity of human farnesyl transferase *in vitro* using the assay described above, and were found to have IC_{50} values for inhibiting farnesylation of the biotinylated KTKCVIS-peptide of about less than or equal to 500 nM.

The following Examples are provided to illustrate aspects of the subject invention. They are not intended, nor should they be construed, to limit the invention as more fully described herein and set forth in the claims.

EXAMPLE 1

4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one

1A. 5-Bromo-3-(3-chloro-phenyl)-benzo[c]isoxazole

To a solution of sodium hydroxide (19.8 g, 495 mmol) in methanol (36 ml) was added 3-choloroacetonitrile (17.5 ml, 149 mmol) at 0 °C under an atmosphere of dry N_2. The mixture was stirred at 0 °C for 30 minutes, 1-bromo-4-nitrobenzene (20 g, 99 mmol) was added as a solid at the same temperature. The solution was stirred at room temperature for 3 hours and then heated to reflux for one. The reaction mixture was cooled to ambient temperature and the MeOH was removed under vacuum. The resulting red oil was partitioned between ethyl acetate (EtOAc) and water. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under vacuum to give a tan solid. The solid was suspended in MeOH and the title compound of 1A was precipitated as a yellow solid (17.3 g , 55.9 mmol, 56.7% yield) which was used without further purification.

1B. (2-Amino-5-bromo-phenyl)-(3-chloro-phenyl)-methanone

To a solution of the title compound of example 1A (22.14 g, 78.1 mmol) in THF (300 ml) was added 276 mL of titanium(III) chloride (10 wt.% solution in 20-30 wt. % hydrochloric acid (HCl)). The reaction mixture was stirred for 1.5 hours. The reaction mixture was then poured into ice water. THF was removed from the resulting heterogeneous solution. The aqueous mixture was extracted with dichloromethane (DCM). The DCM layer was successively washed with aqueous saturated $NaHCO_3$ and brine. The DCM layer was dried over $MgSO_4$, filtered and concentrated under vacuum to give the title compoundof 1B as a bright yellow solid (21.86 g, 70.4 mmol, 98% yield). The solid was used without further purification.

1C. 6-Bromo-4-(3-chloro-phenyl)-1H-quinolin-2-one

The title compound of example 1B (21.86 g, 70.4 mmol) was suspended in anhydrous toluene (140 ml) under an atmosphere of dry N_2. To this solution was added sequentially 26.7 ml (282 mmol) of acetic anhydride (Ac_2O), 80 ml (56.3 mmol) of triethylamine (NEt_3) and 8.60 g (70.4 mmol) of 4-dimethylaminopyridine (DMAP). The reaction mixture was then heated to reflux and stirred at this temperature for 20 hours. The reaction mixture was cooled to ambient temperature and the precipitate was collected via suction filtration. The solid was washed with ethyl ether (Et_2O) and dried under vacuum to give the title compound of example 1C (21.57 g). The filtrate was evaporated and the residue was suspended in cold EtOAc to form a precipitate, providing additional 4.64 g of the title compound. A total of 20.21 g (60.4 mmol, 85.8% yield) of the tiltie compound of example 1C was obtain, which was used without further purification.

1D. 6-Bromo-4-(3-chloro-phenyl)-2-methoxy-quinoline

The title compound of example 1C (6.45 g, 19.4 mmol) was suspended in DCM (30 ml) under an atmosphere of dry N_2. To this suspension, was added trimethyloxonium tetrafluoroborate (BF4OMe3, 2.99 g, 20.2 mmol). The reaction mixture was stirred at ambient temperature for 15 hours. It was then cooled at 0 °C and a 10% aqueous NaOH solution (40 ml) was added. The reaction mixture was allowed to warm to room temperature and stirred for six hours after which time it was partitioned between DCM and water. The DCM layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give 6.11 g of the crude product. It was purified via chromatography with DCM as the eluent to afford the title compound of example 1D as a yellow solid, 5.23 g (15 mmol, 78% yield).

CI-MS: m/z 348/350.

1E. [4-(3-Chloro-phenyl)-2-methoxy-quinolin-6-yl]-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanol

To a solution of the title compound of example 1D (1.47 g, 348.6 mmol) in THF (10 ml) was added n-butyl lithium (2.5 M in hexane, 1.58 ml) dropwise at -78°C under an atmosphere of dry N_2. After stirring at -78°C for 30 minutes, a solution of (6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanone (582.7 mg, 2.64 mmol) in THF (10 ml) was added . The reaction mixture was allowed to warm to ambient temperature and stirred for 15 hours. To the mixture was added a saturated aqueous solution of ammonium chloride at 0°C. THF was removed from the resulting heterogeneous solution. The aqueous mixture was extracted with chloroform ($CHCl_3$). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to yield the crude product. It was chromatographed on silica gel with MeOH-$CHCl_3$-NH_4OH (2 : 98 : 0.2 to 5 : 95 : 0.5) as eluents to afford the title compound of example 1E as a yellow solid (943 mg, 1.92 mmol, 73 % yield).

CI-MS: m/z 491.1, 493.1 [M + 1].

1F. 4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one

To a solution of the title compound of example 1E (4.67 g, 9.53 mmol) in THF (340 ml) was added concentrated hydrogen chloride (HCl, 14 ml) dropwise. The mixture was heated at 60°C for 5 hours. After cooling to room temperature, THF was removed. The aqueous solution was adjusted to pH = ~9 with 40% aqueous NaOH and extracted with $CHCl_3$ several times. The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to yield the title compound of Example 1 as an off-white solid (2.46 g, 5.17 mmol, 54 % yield).

CI-MS: m/z 476.8.

EXAMPLE 2

4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one

To a solution of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol -4-yl)-methyl]-1H-quinolin-2-one (351 mg, 0.737 mmol) in THF (15 ml) was added a 40 % aqueous NaOH (2 ml), benzyltriethylammonium chloride (84 mg. 0.369 mmol) and a solution of methyl iodide (0.078 ml, 1.25 mmol) in THF (4 ml). The reaction mixture was stirred at ambient temperature for 4 hours after which time it was partitioned between $CHCl_3$ and water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel with MeOH-$CHCl_3$-NH_4OH (2 : 98 : 0.2 to 5 : 95 : 0.5) as eluents to afford the title compound as a white solid (200.3 mg, 0.408 mmol, 55 % yield).

CI-MS: m/z 491.1.

EXAMPLE 3

6-[Amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one

4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one (2 g, 4.08 mmol) was dissolved in 25 ml of thionyl chloride ($SOCl_2$) and stirred at room temperature under an atmosphere of dry N_2 for 2 hours. Thiony chloride was removed under reduced pressure. The crude chloride was taken up in toluene and concentrated under vacuum. The resulting solid was dissolved in THF (20 mL) and to this solution was bubbled ammonia gas (NH_3) for 30 minutes. The reaction mixture was stirred at ambient temperature under an atmosphere of NH_3 for 15 hours. After removal of THF, the product mixture was partitioned between $CHCl_3$ and water. The organic layer was washed, dried over $MgSO_4$ and concentrated under vacuum to give a brown solid. This was chromatographed on silica gel with $CHCl_3$ then MeOH-$CHCl_3$-NH_4OH (1 : 99 : 0.1) as eluents to afford the titled compound as a white solid (1.065 g, 2.02 mmol, 50 % yield).

C.I. m/z 490.2, 492.2 [M+1].

EXAMPLE 4 and EXAMPLE 5

Separation of the Enantiomers of 6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one

The title compound of Example 3, 6-[amino-(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethynyl-phenyl)-1-methyl-1H-quinolin-2-one (159 mg) was separated into its enantiomers and purified by high-performance liquid chromatography over CHIRALCEL™ OD (manufactured by Daicel Chemical Industries, LTD, Osaka, Japan) (2.2 cm x 25 cm, 10 μm; eluent: Hexane/ethanol/methanol/diethylamine 80/10/10/0.02; 25°C). Under these conditions, 28 mg of the faster eluting enantiomer A (Example 4) and 3 mg of the slower moving enantiomer B (Example 5) were obtained. Both enantiomers were >97% optically pure.

EXAMPLE 6

4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

To a solution of the title compound of example 1, 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one (100 mg, 0.210 mmol) in DMF (2 ml) were added NaCl (8 mg), cesium carbonate (Cs_2CO_3, 103 mg, 0.315 mmol) and (bromomethyl)cyclopropane (0.041 ml, 0.420 mmol). The reaction mixture was stirred at ambient temperature for 15 hours. Additional 0.041 ml) of (bromomethyl)cyclopropane and 100 mg of Cs_2CO were added. The reaction mixture was heated at 60°C for 1 hour after which time it was partitioned between $CHCl_3$ and water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel with MeOH-$CHCl_3$-NH_4OH (3 : 97 : 0) as eluents to afford the title compound as a white solid (25 mg, 22 % yield).

CI-MS: m/z 531.1, 533.1 [M+1].

EXAMPLE 7

6-[Amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one

The same procedure was used as that in example 3, except that 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (400 mg, 0.75 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one, to give title compound as a white solid, 137 mg (0.26 mmol, 34% yield).

C.I. m/z 530.1, 532.1 [M+1].

EXAMPLE 8

4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-isobutyl-1H-quinolin-2-one

Following the same procedure as described in Example 6, 1-bromo-2-methylpropane (0.041 ml, 0.42 mmol) was used in the place of (bromomethyl)cyclopropane . The alkylation of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (99.8 mg, 0.21 mmol afforded the title compound as a white solid, 20 mg (0.038 mmol, 18% yield).

C.I. m/z 533.1, 535.1[M+1].

EXAMPLE 9

4-(3-Chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one

Following the same procedure as that described in example 1E, 6-bromo-4-(3-chloro-phenyl)-2-methoxy-quinoline (2.89 g, 8.31 mmol) and (5-chloro-pyridin-2-yl)-(3-methyl-3H-imidazol-4-yl)-methanone (1.47 g, 6.65 mmol) generated 4.05 g of the crude [4-(3-chloro-phenyl)-2-methoxy-quinolin-6-yl]-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanol.

Following the same procedure as described in example 1F, the obtained [4-(3-chloro-phenyl)-2-methoxy-quinolin-6-yl]-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanol was treated with HCl in aqueous THF to yield the title compound, 1.02 g, (2.14 mmol, 26% yield).

C.I. m/z 477.1, 479.1[M+1].

EXAMPLE 10

4-(3-Chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one

The same procedure was used that described in example 2,except that 4-(3-chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one (230 mg, o.485 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol -4-yl)-methyl]-1H-quinolin-2-one to give the title compound as a white solid, 195 mg (0.40 mmol, 81% yield).

EXAMPLE 11

6-[Amino-(5-chloro-pyridin-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that described in example 3, 4-(3-chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (170 mg, 0.35 mmol) was used in the place of 4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one to give the title compound as a white solid, 69 mg (0.14 mmol, 40% yield).

C.I. m/z 490.0 [M+1].

EXAMPLE 12

4-(3-Chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

The same was used as that described in example 6, except that 4-(3-chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one (550 mg, 1.16 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one, to give the title compound, 57 mg, (0.11 mmol, 9% yield).

C.I. m/z 531.1 [M+1].

EXAMPLE 13

6-[Amino-(5-chloro-pyridin-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one

The same procedure was used as that in example 3, except that 4-(3-chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (258 mg, 0.486 mmol was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one, to give the title compound as a white solid, 112 mg (0.21 mmol, 43% yield).

C.I. m/z 530.0 [M+1].

EXAMPLE 14

4-(3-Chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-cyclopropylamino-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one

For the formation of the correspondent chloride, the same procedure was used as that in example 2, except that 4-(3-chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one (55 mg, 0.112 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one. The obtained chloride was dissolved in DMF (8 ml). To this solution were added potassium carbonate (K_2CO_3) and cyclopropylamine (0.049 ml, 0.786 mmol). The reaction mixture was stirred at ambient temperature for 15 hours after which time it was partitioned between $CHCl_3$ and water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel with MeOH-$CHCl_3$-NH_4OH (2 : 98 : 0.2 to 5 : 95 : 0.5) as eluents to afford the title compound as a white solid (19 mg, 0.036 mmol, 32 % yield).

C.I. m/z 529.9 [M+1].

EXAMPLE 15

4-(3-Chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-cyclopropylamino-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

The same procedure was used as that in example 14, except that 4-(3-Chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (52 mg, 0.098 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one to give the title compound as a white solid (24 mg, 0.042 mmol, 43 % yield).

C.I. m/z 569.9 [M+1].

EXAMPLE 16

6-[(6-Chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3,5-dichloro-phenyl)-1-methyl-1H-quinolin-2-one

16A. 6-Bromo-4-(3,5-dichloro-phenyl)-1H-quinolin-2-one

The same procedure was used as that in example 1C, except that (2-amino-5-bromo-phenyl)-(3,5-dichloro-phenyl)-methanone (1.50 g, 4.35 mmol) was used in the place of (2-amino-5-bromo-phenyl)-(3-chloro-phenyl)-methanone to give the title compound of **16A** as a white solid, 1.61 g (100 % yield).

16B. 6-Bromo-4-(3,5-dichloro-phenyl)-2-methoxy-quinoline

The same procedure was used as that in example 1D, except that 6-bromo-4-(3,5-dichloro-phenyl)-1H-quinolin-2-one (6.42 g, 17.4 mmol) was used in the place of 6-bromo-4-

(3-chloro-phenyl)-1H-quinolin-2-one to give the title compound of **16B** as a white solid, 3.47 g (52 % yield).

16C. [4-(3,5-Dichloro-phenyl)-2-methoxy-quinolin-6-yl]-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanol

Following the same procedure as described in example 1E, 6-bromo-4-(3,5-dichloro-phenyl)-2-methoxy-quinoline (1.88 g, 4.91 mmol) and (6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanone (0.94 g, 4.27 mmol) generated the title compound of **16C** as a yellow solid (0.885 g, 39.5 % yield).

16D. 4-(3,5-Dichloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one

Following the same procedure as described in example 1F, [4-(3,5-dichloro-phenyl)-2-methoxy-quinolin-6-yl]-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanol (886 mg, 1.68 mmol) was treated with HCl in aqueous THF to yield the title compound of **16D**. It was directly used for the next reaction without further purification.

16E. 6-[(6-Chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3,5-dichloro-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 2, except that 4-(3,5-dichloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one (~1.68 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one to give the title compound of 16E as a white solid, 388.6 mg (44 % yield for 16D and **16E**).

C.I. m/z 525.0, 527.0 [M+1].

EXAMPLE 17

6-[Amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3,5-dichloro-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 3, except that 6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3,5-dichloro-phenyl)-1-methyl-1H-quinolin-2-one (298.6 mg, 0.567 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one, to give the title compound as a white solid, 40 mg (0.076 mmol, 13% yield).

C.I. m/z 523.9, 526.0 [M+1].

EXAMPLE 18

4-(3-Chloro-phenyl)-6-[(5-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one

18A. [4-(3-Chloro-phenyl)-2-methoxy-quinolin-6-yl]-(5-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methanol

Following the same procedure as described in example 1E, 6-bromo-4-(3-chloro-phenyl)-2-methoxy-quinoline (1.0 g, 1.87 mmol) and (5-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methanone (170 mg, 3.44 mmol) generated the title compound of 18A as a yellow solid (919 mg, 65 % yield).

C.I. m/z 507.1 [M+1].

18B. 4-(3-Chloro-phenyl)-6-[(5-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one

Following the same procedure as described in example 1F, [4-(3-chloro-phenyl)-2-methoxy-quinolin-6-yl]-(5-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methanol (740 mg, 1.49 mmol) was treated with HCl in aqueous THF to yield the title compound of 18B as a yellow solid, 469.2 mg (0. 97 mmol, 65 % yield).

C.I. m/z 483.9 [M+1].

18C. 4-(3-Chloro-phenyl)-6-[(5-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 2, except that 4-(3-chloro-phenyl)-6-[(5-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one (76 mg, 0.157 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one to give the title compound as a white solid, 49 mg (0.10 mmol, 63 % yield)

C.I. m/z 497.9 [M+1].

EXAMPLE 19

6-[Amino-(5-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 3, except that 4-(3-chloro-phenyl)-6-[(5-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one (69 mg, 0.139 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one, to give the title compound as a white solid, 14 mg (0.028 mmol, 20 % yield).

C.I. m/z 523.9, 526.0 [M+1].

EXAMPLE 20

4-(3-Chloro-phenyl)-6-[(5-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

The same was used as that described in example 6, except that 4-(3-chloro-phenyl)-6-[(5-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one (75 mg, 0.155 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one, to give the title compound (15 mg, 20% yield).

C.I. m/z 536.2, 538.2 [M+1].

EXAMPLE 21

4-(3-Chloro-phenyl)-6-[(3-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one

21A. [4-(3-Chloro-phenyl)-2-methoxy-quinolin-6-yl]-(3-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methanol

Following the same procedure as described in example 1E, 6-bromo-4-(3-chloro-phenyl)-2-methoxy-quinoline (300 mg, 0.859 mmol) and (3-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methanone (230 mg1.032 mmol) generated the title compound of 21A as a yellow solid (218.5 mg, 51 % yield).

21B. 4-(3-Chloro-phenyl)-6-[(3-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one

Following the same procedure as described in example 1F, [4-(3-chloro-phenyl)-2-methoxy-quinolin-6-yl]-(3-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methanol (208 mg, 0.42 mmol) was treated with HCl in aqueous THF to yield the title compound of 21B as a yellow solid (164.7 mg, 81 % yield).

21C. 4-(3-Chloro-phenyl)-6-[(3-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 2, except that 4-(3-chloro-phenyl)-6-[(3-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one (164.7 mg, 0.342 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one to give the title compound as a white solid (70 mg, 41 % yield).

C.I. m/z [M+1].

EXAMPLE 22

6-[Amino-(3-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 3, except that 4-(3-chloro-phenyl)-6-[(3-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one (65 mg, 0.13 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one, to give the title compound as a white solid (4.7 mg, 7 % yield).

C.I. m/z 459.0 [M+1].

EXAMPLE 23

6-[(5-Chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1H-quinolin-2-one

23A. 6-Bromo-4-(3-ethoxy-phenyl)-2-methoxy-quinoline

To a suspension of 6-bromo-4-(3-ethoxy-phenyl)-1H-quinolin-2-one (7.4 g, 21.5 mmol) in 60 ml dichloroethane was added trimethyloxonium tetrafluoroborate (BF_4OMe_3, 3.66 g , 24.7 mmol). The resulting mixture was stirred at ambient temperature overnight. After cooling to 0 C, was added 60 ml of 10% aqueous NaOH dropwise. The reaction mixture was stirred for another six hours at ambient temperature. It was then partitioned between dichloromethane and water. The organic layer was washed brine, dried over $MgSO_4$, filtered and concentrated under vacuum to give an off-white solid. The solid was chromatographed on flash silica gel eluting with dichoromethane to yield the titled compound of **23A** as a white solid (4.48 g, 58% yield).

23B. (5-Chloro-thiophen-2-yl)-[4-(3-ethoxy-phenyl)-2-methoxy-quinolin-6-yl]-(3-methyl-3H-imidazol-4-yl)-methanol

Following the same procedure as that described in example 1E, 6-bromo-4-(3-ethoxy-phenyl)-2-methoxy-quinoline (800 mg, 2.23 mmol) and (5-chloro-thiophen-2-yl)-(3-*methyl-3H-imidazol-4-yl)-methanone (610 mg, 2.68 mmol) generated the title compound of* **23B** (810 mg, 72% yield).

23C. 6-[(5-Chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1H-quinolin-2-one

Following the same procedure as described in example 1F, (5-chloro-thiophen-2-yl)-[4-(3-ethoxy-phenyl)-2-methoxy-quinolin-6-yl]-(3-methyl-3H-imidazol-4-yl)-methanol (810 mg, 1.60 mmol) was treated with HCl in aqueous THF to yield the title compound (578 mg, 74 % yield).

C.I. m/z 492.1[M+1].

EXAMPLE 24

6-[(5-Chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 2, except that _6-[(5-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1H-quinolin-2-one (578.4 mg, 1.18 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one to give the title compound as a white solid (241 mg, 40.4 % yield).

C.I. m/z 506.2 [M+1].

EXAMPLE 25

Amino-(5-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 3, except that 6-[(5-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one (240 mg, 0.47 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one, to give the title compound as a white solid (196 mg, 82 % yield).

C.I. m/z 505.1, 507.2 [M+1].

EXAMPLE 26

6-[(6-Chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1H-quinolin-2-one

26A. (6-Chloro-pyridin-3-yl)-[4-(3-ethoxy-phenyl)-2-methoxy-quinolin-6-yl]-(3-methyl-3H-imidazol-4-yl)-methanol

Following the same procedure as that described in example 1E, 6-bromo-4-(3-ethoxy-phenyl)-2-methoxy-quinoline (2 g, 5.59 mmol) and (6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanone (1.48 g, 6.70 mmol) generated the title compound of **26A** (1.458 g, 52% yield).

26B. 6-[(6-Chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1H-quinolin-2-one

Following the same procedure as described in example 1F, (6-chloro-pyridin-3-yl)-[4-(3-ethoxy-phenyl)-2-methoxy-quinolin-6-yl]-(3-methyl-3H-imidazol-4-yl)-methanol (1.458 g, 2.92 mmol) was treated with HCl in aqueous THF to yield the title compound (1.21 g, 85 % yield).

C.I. m/z 487.2 [M+1].

EXAMPLE 27

6-[(6-Chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 2, except that 6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1H-quinolin-2-one (80.6 mg, 0.166 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one to give the title compound as a white solid (43 mg, 52 % yield).

C.I. m/z 501.2 [M+1].

EXAMPLE 28

6-[Amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 3, except that 6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one (20 mg, 0.04 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one, to give the title compound as a white solid (4.5 mg, 22.5 % yield).

C.I. m/z 501.2 [M+1].

EXAMPLE 29

6-[(6-Chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-isobutyl-1H-quinolin-2-one

The same procedure described in example 8, 6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1H-quinolin-2-one (50 mg, 0.103 mmol) and 1-bromo-2-methylpropane (0.022 ml, 0.206 mmol) generated the title compound as a white solid (24 mg, 40 % yield).

C.I. m/z 543.3 [M+1].

EXAMPLE 30

6-[(6-Chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-4-(3-ethoxy-phenyl)-1H-quinolin-2-one

The same procedure described in example 8, 6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1H-quinolin-2-one (50 mg, 0.103 mmol) and (bromomethyl)cyclopropane (0.020 ml, 0.206 mmol) generated the title compound as a white solid (4 mg, 7 % yield).

C.I. m/z 541.3 [M+1].

EXAMPLE 31

6-[(5-Chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-methoxy-phenyl)-1-methyl-1H-quinolin-2-one

31A. (5-Chloro-thiophen-2-yl)-[2-methoxy-4-(3-methoxy-phenyl)-quinolin-6-yl]-(3-methyl-3H-imidazol-4-yl)-methanol

Following the same procedure as that described in example 1E, 6-bromo-4-(3-methoxy-phenyl)-2-methoxy-quinoline (1g, 2.91 mmol) and (5-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methanone (0.78 g, 3.49 mmol) generated the title compound of **31A** (1.147 g, 80.2% yield).

C.I. m/z 492.1 [M+1].

31B. 6-[(5-Chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-methoxy-phenyl)-1H-quinolin-2-one

Following the same procedure as described in example 1F (5-chloro-thiophen-2-y)-[4-(3-methoxy-phenyl)-2-methoxy-quinolin-6-yl]-(3-methyl-3H-imidazol-4-yl)-methanol (1.14 g, 2.34 mmol) was treated with HCl in aqueous THF to yield the title compound of **31B** (1.12 g, 100 % yield).

C.I. m/z 478.1 [M+1].

31C. 6-[(5-Chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-methoxy-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 2, except that 6-[(5-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-methoxy-phenyl)-1H-quinolin-2-one (1.12 g, 2.34 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one to give two compounds after chromatographic purification. The fraction with higher Rf value afforded the title compound of example 31as a white solid (422 mg, 36.7 % yield).

C.I. m/z 492.1 [M+1].

EXAMPLE 32

6-[(5-Chloro-thiophen-2-yl)-methoxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-methoxy-phenyl)-1-methyl-1H-quinolin-2-one

From the reaction of example 31C, the fraction with lower Rf value afforded the title compound of example 32 as a white solid (50 mg, 4.2 % yield).

C.I. m/z 506.2 [M+1].

EXAMPLE 33

6-[Amino-(5-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-methoxy-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 3, except that 6-[(5-chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3methoxy-phenyl)-1-methyl-1H-quinolin-2-one (43 mg, 0.087 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one, to give the title compound as a white solid (18 mg, 42 % yield).

C.I. m/z 493.1 [M+1].

EXAMPLE 34

6-[(6-Chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-isopropoxy-phenyl)-1H-quinolin-2-one

34A. 3-(6-Bromo-2-methoxy-quinolin-4-yl)-phenol

To a solution of 6-bromo-4-(3-methoxy-phenyl)-2-methoxy-quinoline (1.31 g, 3.81 mmol) in dichloromethane (CH_2Cl_2. 30 ml) was added a solution of BBr3 in CH_2Cl_2 (1M, 11.4 ml, 1 1.4 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. It was poured into water. The organic layer was washed with brine, dried over MgSO4 and concentratred to give the tiltle compound of example **34A** (640 mg, 41% yield).

34B. 6-Bromo-4-(3-isopropoxy-phenyl)-2-methoxy-quinoline

To a solution of the title compound of example **34A** (460 mg, 1.39 mmol) in DMF (10 ml) were added cesium carbonate (Cs_2CO_3, 906 mg, 2.78 mmol) and isopropylbromide (0.458 ml, 4.88 mmol). The reaction mixture was stirred at ambient temperature for 15 hours. Additional 0.041 ml) of (bromomethyl)cyclopropane and 100 mg of Cs2CO3 were added. The reaction mixture was heated at 60 °C for 1 hour after which time it was partitioned between ethyl ether and water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude title compound of example **34B** (458 mg, 89 % yield).

CI-MS: m/z 372.1, 374.1 [M+1].

34C. 6-[(6-Chloro-pyridin-3-yl)-[4-(3-isopropoxy-phenyl)-2-methoxy-quinolin-6-yl]-(3-methyl-3H-imidazol-4-yl)-methanol

Following the same procedure as that described in example 1E, 6-bromo-4-(3-isopropoxy-phenyl)-2-methoxy-quinoline (238.4 mg, 0.640 mmol) and (6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanone (156 mg, 0.705 mmol) generated the title compound of 34C (80 mg, 24% yield).

34D. 6-[(6-Chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-isopropoxy-phenyl)-1H-quinolin-2-one

Following the same procedure as described in example 1F, 6-[(6-chloro-pyridin-3-yl)-[4-(3-isopropoxy-phenyl)-2-methoxy-quinolin-6-yl]-(3-methyl-3H-imidazol-4-yl)-methanol (75 mg, 0.14 mmol) was treated with HCl in aqueous THF to yield the title compound (20 mg, 27 % yield).

C.I. m/z 581.0 [M+1].

EXAMPLE 35

6-[(5-Chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-hydroxy-phenyl)-1-methyl-1H-quinolin-2-one

Following the same procedure as that described in Example **34A**, the title compound of example **31** (100 mg, 0.203 mmol0 was treated with BBr3 in CH_2Cl_2 (1M, 1.02 ml, 1.02 mmol) to give the title compound (64 mg, 67% yield).

C.I. m/z 478.1 [M+1].

EXAMPLE 36

4-(3-Chloro-phenyl)-6-(hydroxy-di-pyridin-3-yl-methyl)-1-methyl-1H-quinolin-2-one

36A [4-(3-Chloro-phenyl)-2-methoxy-quinolin-6-yl]-di-pyridin-3-yl-methanol

Following the same procedure as that described in example 1E, 6-bromo-4-(3-methoxy-phenyl)-2-methoxy-quinoline (400 mg, 1.15 mmol) and di-pyridin-3-yl-methanone (232 mg, 1.26 mmol) generated the title compound of **36A** (303 mg, 58 % yield).

C.I. m/z 454.0, 456.0 [M+1].

36B. 4-(3-Chloro-phenyl)-6-(hydroxy-di-pyridin-3-yl-methyl)-1H-quinolin-2-one

Following the same procedure as described in example 1F, [4-(3-chloro-phenyl)-2-methoxy-quinolin-6-yl]-di-pyridin-3-yl-methanol (300 mg, 0.66 mmol) was treated with HCl in aqueous THF to yield the title compound (290 mg, 100 % yield).

C.I. m/z 581.0 [M+1].

36C. 4-(3-Chloro-phenyl)-6-(hydroxy-di-pyridin-3-yl-methyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 2, except that 4-(3-chloro-phenyl)-6-(hydroxy-di-pyridin-3-yl-methyl)-1H-quinolin-2-one (78 mg, 0.178 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one to give the title compound of example **36C** as a white solid (23 mg, 29 % yield).

C.I. m/z 454.2 [M+1].

EXAMPLE 37

4-(3-Ethoxy-phenyl)-6-(hydroxy-di-pyridin-3-yl-methyl)-1-methyl-1H-quinolin-2-one

37A. [4-(3-Ethoxy-phenyl)-2-methoxy-quinolin-6-yl]-di-pyridin-3-yl-methanol

Following the same procedure as that described in example 1E, 6-bromo-4-(3-ethoxy-phenyl)-2-methoxy-quinoline (400 mg, 1.11 mmol) and di-pyridin-3-yl-methanone (225 mg, 1.22 mmol) generated the title compound of **37A** (212 mg, 41.2 % yield).

C.I. m/z 464.1 [M+1].

37B. 4-(3-Ethoxy-phenyl)-6-(hydroxy-di-pyridin-3-yl-methyl)-1H-quinolin-2-one

Following the same procedure as described in example 1F, [4-(3-ethoxy-phenyl)-2-methoxy-quinolin-6-yl]-di-pyridin-3-yl-methanol (212 mg, 0.457 mmol) was treated with HCl in aqueous THF to yield the title compound (91 mg, 44.3 % yield).

C.I. m/z 450.1 [M+1].

37C. 4-(3-Ethoxy-phenyl)-6-(hydroxy-di-pyridin-3-yl-methyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 2, except that 4-(3-ethoxy-phenyl)-6-(hydroxy-di-pyridin-3-yl-methyl)-1H-quinolin-2-one (91 mg, 0.202 mmol) was used in the place 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one to give the title compound of example **37C** as a white solid (12 mg, 13 % yield).

C.I. m/z 464.1 [M+1].

EXAMPLE 38

4-(3-Chloro-phenyl)-6-[hydroxy-(3-methyl-3H-imidazol-4-yl)-quinolin-3-yl-methyl]-1-methyl-1H-quinolin-2-one

38A [4-(3-Chloro-phenyl)-2-methoxy-quinolin-6-yl]-(3-methyl-3H-imidazol-4-yl)-quinolin-3-yl-methanol

Following the same procedure as that described in Example 1E, 6-bromo-4-(3-methoxy-phenyl)-2-methoxy-quinoline (233 mg, 0.668 mmol) and (quinolin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanone (232 mg, 1.26 mmol) generated the title compound of **38A** (81 mg, 24 % yield).

C.I. m/z 507.1 [M+1].

38B. 4-(3-Chloro-phenyl)-6-[hydroxy-(3-methyl-3H-imidazol-4-yl)-quinolin-3-yl-methyl]-1H-quinolin-2-one

Following the same procedure as described in Example 1F, the title compound of 38A (81 mg, 0.16 mmol) was treated with HCl in aqueous THF to yield the title compound of example **38B** (56.4 mg, 71 % yield).

C.I. m/z 493.0, 495.0 [M+1].

38C. 4-(3-Chloro-phenyl)-6-[hydroxy-(3-methyl-3H-imidazol-4-yl)-quinolin-3-yl-methyl]-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 2, except that 4-(3-chloro-phenyl)-6-[hydroxy-(3-methyl-3H-imidazol-4-yl)-quinolin-3-yl-methyl]-1H-quinolin-2-one (56.4 mg, 0.115 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one to give the title compound of example **38C** as a white solid (31 mg, 53 % yield).

C.I. m/z 507.2 [M+1].

EXAMPLE 39

6-[Amino-(3-methyl-3H-imidazol-4-yl)-quinolin-3-yl-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 3, except that 4-(3-chloro-phenyl)-6-[hydroxy-(3-methyl-3H-imidazol-4-yl)-quinolin-3-yl-methyl]-1-methyl-1H-quinolin-2-one (26 mg, 0.0514 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one, to give the title compound as a white solid (8.3 mg, 32 % yield).

C.I. m/z 506.2 [M+1].

EXAMPLE 40

4-(3-Chloro-phenyl)-6-[(5-chloro-thiophen-2-yl)-imidazol-1-yl-methyl]-1-methyl-1H-quinolin-2-one

40A [4-(3-Chloro-phenyl)-2-methoxy-quinolin-6-yl]-(5-chloro-thiophen-2-yl)-methanone

To a solution of 6-bromo-4-(3-chloro-phenyl)-2-methoxy-quinoline (500 mg, 1.43 mmol) in THF (2 ml) was added n-buthyl lithium (2.5 M in hexane, 0.63 ml, 1.58 mmol) dropwise at -78°C under an atmosphere of dry N_2 . After stirring at -78°C for 30 minutes, a solution of 5-chloro-thiophene-2-carboxylic acid methoxy-methyl-amide (440 mg, 2.15 mmol) in THF (1ml) was added. The reaction mixture was allowed to warm to ambient temperature and stirred for 15 hours. To the mixture was added a saturated aqueous solution of ammonium chloride at 0°C. THF was removed from the resulting heterogeneous solution. The aqueous mixture was extracted with chloroform ($CHCl_3$). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to yield the crude product. It was chromatographed on silica gel with MeOH-$CHCl_3$-NH_4OH (2 : 98 : 0.2 to 5 : 95 : 0.5) as eluents to afford the title compound of example **40A** (273.5 mg, 46 % yield).

CI-MS: m/z 414.0 [M + 1].

40B 4-(3-Chloro-phenyl)-6-(5-chloro-thiophene-2-carbonyl)-1-1H-quinolin-2-one

Following the same procedure as that in example 1F, [4-(3-chloro-phenyl)-2-methoxy-quinolin-6-yl]-(5-chloro-thiophen-2-yl)-methanone (273 mg, 0.66 mmol) was treated with HCl in aqueous THF to give the title compound of example **40B** as a white solid (145 mg, 53 % yield).

C.I. m/z 413.0, 415.0 [M+1].

40C. 4-(3-Chloro-phenyl)-6-(5-chloro-thiophene-2-carbonyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 2, except that 4-(3-chloro-phenyl)-6-(5-chloro-thiophene-2-carbonyl)-1-1H-quinolin-2-one (56 mg, 0.14 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one to give the title compound of example **40C** as a white solid (58 mg, 100 % yield).

C.I. m/z 413.9 [M+1].

40D. 4-(3-Chloro-phenyl)-6-[(5-chloro-thiophen-2-yl)-hydroxy-methyl]-1-methyl-1H-quinolin-2-one

To a suspension of 4-(3-chloro-phenyl)-6-(5-chloro-thiophene-2-carbonyl)-1-methyl-1H-quinolin-2-one (58 mg, 0.154 mmol) in MeOH (1 ml) was added sodium borohydride as solid ($NaBH_4$, 7 mg, 0.185 mmol) at 0°C. The reaction mixture was stirred at 0°C for one hour after which time it was partitioned between chloroform and water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give an off-white solid (49 mg , 78.5% yield).

40E 6-[Chloro-(5-chloro-thiophen-2-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one

To a solution of 4-(3-chloro-phenyl)-6-[(5-chloro-thiophen-2-yl)-hydroxy-methyl]-1-methyl-1H-quinolin-2-one 49 mg, 0.12 mmol) in CH_2Cl_2 (0.5 ml) was added thionyl chloride dropwise. The reaction mixture was stirred at room temperature for four hours. Thionyl chloride was removed under reduced pressure. The crude chloride was taken up in toluene and concentrated under vacuum to give a yellow solid which was used without further purification.

40F 4-(3-Chloro-phenyl)-6-[(5-chloro-thiophen-2-yl)-imidazol-1-yl-methyl]-1-methyl-1H-quinolin-2-one

The crude product from example 40E was dissolved in acetonitrile (CH_3CN, 1 ml0. To this solution were added imidazole (29 mg, 0.42 mmol) and K_2CO_3 (58 mg, 0.42 mmol). The mixture was refluxed for 15 hours after which time it was partitioned between chloroform and water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel with MeOH-$CHCl_3$-NH_4OH (2 : 98 : 0.2) as eluents to afford the title compound (17 mg, 30 % yield for two steps).

CI-MS: m/z 398.0, 400.0 [M - $C_3H_3N_2$ (imidazole)].

EXAMPLE 41

6-[Benzo[b]thiophen-2-yl-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one

41A. Benzo[b]thiophen-2-yl-[4-(3-chloro-phenyl)-2-methoxy-quinolin-6-yl]-(3-methyl-3H-imidazol-4-yl)-methanol

Following the same procedure as described in example 1E, 6-bromo-4-(3-chloro-phenyl)-2-methoxy-quinoline (273 mg, 0.784 mmol) and benzo[b]thiophen-2-yl-(3-methyl-3H-imidazol-4-yl)-methanone (247 mg, 1.01 mmol) generated the title compound of **41A** (248 mg, 62 % yield).

C.I. m/z 507.1 [M+1].

41B. 6-[Benzo[b]thiophen-2-yl-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1H-quinolin-2-one

Following the same procedure as described in example 1F, benzo[b]thiophen-2-yl-[4-(3-chloro-phenyl)-2-methoxy-quinolin-6-yl]-(3-methyl-3H-imidazol-4-yl)-methanol (147.2 mg, 0.287 mmol) was treated with HCl in aqueous THF to yield the title compound of **41B** as a yellow solid (40 mg, 28 % yield).

41C. 6-[Benzo[b]thiophen-2-yl-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one

The same procedure was used as that in example 2, except that 6-[benzo[b]thiophen-2-yl-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1H-quinolin-2-one (40 mg, 0.08 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one to give the title compound as a white solid (5.3 mg, 13 % yield)

C.I. m/z 512.1 [M+1].

EXAMPLE 42

6-[Amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1H-quinolin-2-one

To 6-Bromo-4-(3-chloro-phenyl)-2-methoxy-quinoline (20.95 g, 42.76 mmol) in toluene (150 ml) under an atmosphere of dry N_2 was added thionyl chloride (31.19 ml, 427 mmol) dropwise. The reaction mixture was heated at 85°C for 15 hours. Solvent and the excess thionyl chloride were removed under reduced pressure. The crude chloride was taken up in toluene and concentrated under vacuum. The resulting solid was dissolved in THF (10 ml) and to this solution at –78°C was bubbled ammonia gas (NH_3) for 10 minutes. The reaction mixture was stirred at ambient temperature under an atmosphere of N_2 for additional 1.5 hours. After removal of THF, the product mixture was partitioned between $CHCl_3$ and water. The organic layer was washed, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel with $CHCl_3$ then MeOH-$CHCl_3$-NH_4OH (2 : 98 : 0.1 to 7 : 93 : 0.1) as eluents to afford the titled compound (17.89 g, 88 % yield).

C.I. m/z 473.8 [M+1].

EXAMPLE 43

4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-[(4-methoxy-benzylidene)-amino]-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

43A. 4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-[(4-methoxy-benzylidene)-amino]-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one

To a solution of the title compound of example 42 (11.89 g, 25.03 mmol) in acetic acid (75 ml) was added *p*-anisaldehyde (6.09 ml, 50.06 mmol) dropwise. The reaction mixture was stirred at ambient temperature for 4 hours after which time it was cooled to 0°C. 10 ml of ammonia hydroxide was added followed by addition of ethyl acetate. After separation, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to yield the crude product. It was chromatographed on silica gel with MeOH-$CHCl_3$-NH_4OH (1 : 99 : 0.1 to 5 : 95 : 0.1) as eluents to afford the title compound of Example 43A as a white solid (11.58 g, 78 % yield).

CI-MS: m/z 594.1, 596.1 [M + 1].

43B. 4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-[(4-methoxy-benzylidene)-amino]-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

To a solution of the title compound of example 43A (10.78 g, 18.14 mmol) in THF (2.5 ml) was added (bromomethyl)cyclopropane (2.42 ml, 24.96 mmol), benzyltriethylammonium chloride (2.59 g, 11.34 mmol), sodium iodide (0.85 g, 5.67 mmol) and a solution of 40 % aqueous NaOH (30 ml). The reaction mixture was heated at 65°C for 4 hours after which time THF was removed. The crude product mixture was partitioned between $CHCl_3$ and water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel MeOH-$CHCl_3$-NH_4OH (1.5 : 98.5 : 0.1 to) as the eluents to afford the title compound as a white solid (8.49 g, 13.10 mmol, 72 % yield).

CI-MS: m/z 648.1 [M+1].

EXAMPLE 44 and EXAMPLE 45

(+) and (-) Enantiomers of 4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-[(4-methoxy-benzylidene)-amino]-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

The title compound of Example 43 (1.322 g) was separated into its enantiomers and purified by high-performance liquid chromatography over CHIRALCEL™ OD (manufactured by Daicel Chemical Industries, LTD, Osaka, Japan) (2.2 cm x 25 cm, 10 μm; eluent: Hexane/ethanol/methanol/diethylamine 80/10/10/0.1; 25°C). Under these conditions, 0.595 g of the faster eluting enantiomer A (Example 44): (+)-4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-[(4-methoxy-benzylidene)-amino]-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one, and 0.511 g of the slower moving enantiomer B (Example 45): (-)-4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-[(4-methoxy-benzylidene)-amino]-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one were obtained. Both enantiomers were >99% optical pure.

EXAMPLE 46

4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-(4-methoxy-benzylamino)-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

46A. 4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-(4-methoxy-benzylamino)-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one

To 6-Bromo-4-(3-chloro-phenyl)-2-methoxy-quinoline (1.08 g, 2.21 mmol) in toluene (8.5 ml) under an atmosphere of dry N_2 was added thionyl chloride (1.61 ml, 22.06 mmol) dropwise. The reaction mixture was heated at 85°C for 15 hours. Solvent and the excess thionyl chloride were removed under reduced pressure. The crude chloride was taken up in toluene and concentrated under vacuum. The resulting solid was dissolved in THF (10 ml) and to this solution at –78°C was added p-methoxybenzylamine (1.44 ml, 11.03 mmol) in THF (2 ml). The reaction mixture was stirred at –78°C for 3 hours under an atmosphere of N_2 for 3 hours. After removal of THF, the product mixture was partitioned between $CHCl_3$ and water. The organic layer was washed, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel with MeOH-$CHCl_3$-NH_4OH (2 : 98 : 0.1) as eluents to afford the titled compound of Example 46A (0.482 g, 52 % yield).

C.I. m/z 596.1 [M+1].

46B. 4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-(4-methoxy-benzylamino)-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

The same procedure was used as that described in example 43B, except that 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-(4-methoxy-benzylamino)-(3-methyl-3H-imidazol-4-

yl)-methyl]-1H-quinolin-2-one (0.682 g, 1.14 mmol) was used in the place of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-[(4-methoxy-benzylidene)-amino]-(3-methyl-3H-imidazol-4-yl)-methyl]-1H-quinolin-2-one to give the title compound (0.315 g, 0.485 mmol, 43 % yield).

C.I. m/z 650.1 [M+1].

EXAMPLE 47 and EXAMPLE 48

(+) and (-) Enantiomers of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-(4-methoxy-benzylamino)-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

The title compound of Example 46, 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-(4-methoxy-benzylamino)-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (3.05 g) was separated into its enantiomers and purified by high-performance liquid chromatography over CHIRALPAK™ AD (manufactured by Daicel Chemical Industries, LTD, Osaka, Japan) (2.2 cm x 25 cm, 10 μm; eluent: Hexane/ethanol/methanol/ diethylamine 80/10/10/0.1; 25°C). Under these conditions, 1.56 g of the faster eluting enantiomer A (Example 47): (+)-4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-(4-methoxy-benzylamino)-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one, and 1.07 g of the slower moving enantiomer B (Example 48): (-)-4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-(4-methoxy-benzylamino)-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one were obtained. Both enantiomers were >99% optical pure.

EXAMPLE 49

(+)-6-[Amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one

Procedure 1, Conversion of Example 45

To a solution of the title compound of Example 45, the slower moving enantiomer of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-[(4-methoxy-benzylidene)-amino]-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (1.41 g, 1.74 mmol) in THF (200 ml) was added 2N hydrochloric acid (20 ml) slowly. The reaction mixture was stirred at ambient temperature for 1.5 hour after which time it was cooled to 0°C. An aqueous solution of potassium carbonate was added followed by addition of ethyl acetate. After separation, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel with $MeOH-CHCl_3-NH_4OH$ (1: 99 : 0.1 to 2 : 98 : 0.1) as the eluents to afford the title compound as a white solid (0.844 g, 1.59 mmol, 90 % yield). It is the faster eluting enantiomer of 6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one with >99 % optical purity.

C.I. m/z: 530.1, 532.1 [M+1].

Procedure 2, Conversion of Example 48

To a solution of the title compound of Example 48 (the slower moving enantiomer), (-)4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-(4-methoxy-benzyl-amino)-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (1.07 g, 1.64 mmol) in dichloromethane (6.5 ml) was added trifluoroacetic acid (TFA, 6.5 ml) slowly at 0°C. The reaction mixture was stirred at ambient temperature for 80 minutes after which time it was diluted with DCM (10 ml) and was poured into a chilled aqueous solution of potassium carbonate. After separation, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel with $MeOH-CHCl_3-NH_4OH$ (1.5: 98.5 : 0.15) as the eluents to afford the title compound as a white solid (0.588 g, 1.11 mmol, 68 % yield). It is the faster eluting enantiomer of 6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one with >99 % optical purity.

C.I. m/z: 530.1, 532.1 [M+1].

EXAMPLE 50

(-)-6-[Amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one

Procedure 1, Conversion of Example 44

Following the same procedure as that described in Example 49 for the conversion of Example 45, the title compound of Example 44, the faster eluting enantiomer of 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-[(4-methoxy-benzylidene)-amino]-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (1.98 g, 3.05 mmol) afforded the title compound as a white solid (1.51 g, 2.85 mmol, 93 % yield). It is the slower moving enantiomer of 6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one with >99 % optical purity.

C.I. m/z: 530.1, 532.1 [M+1].

Procedure 2, Conversion of Example 47

Following the same procedure as that described in Example 49 for the conversion of Example 48, the title compound of Example 47 (the faster eluting enantiomer, (+)-4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-(4-methoxy-benzylamino)-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (0.249 g, 0.384 mmol) afforded the title compound as a white solid (0.137 g, 0.252 mmol, 66 % yield). It is the slower moving enantiomer of 6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one with >98 % optical purity.

C.I. m/z: 530.1, 532.1 [M+1].

EXAMPLE 51

6-[Amino-(6-methyl-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one

51A. [4-(3-chloro-phenyl)-2-methoxy-quinolin-6-yl]-(6-methyl-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanol.

Following the same procedure as that described in Example 1E, 6-bromo-4-(3-chloro-phenyl)-2-methoxy-quinoline (0.200 g, 0.574 mmol) and (6-methyl-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanone (0.105 g, 0.522 mmol) generated 0.118 g (48% yield) of [4-(3-chloro-phenyl)-2-methoxy-quinolin-6-yl]-(6-methyl-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methanol.

C.I. m/z: 470.9[M+1].

51B. 6-[Amino-(6-methyl-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1H-quinolin-2-one

To the title compound of Example 51A (0.118 g, 0.251 mmol) in toluene (5 ml) under an atmosphere of dry N_2 was added thionyl chloride (0.18 ml, 2.51 mmol) dropwise. The reaction mixture was heated at 85°C for 15 hours. Solvent and the excess thionyl chloride were removed under reduced pressure. The crude chloride was taken up in toluene and concentrated under vacuum. The resulting solid was dissolved in THF (10 mL) and to this solution at –78°C was bubbled ammonia gas (NH_3) for 10 minutes. The reaction mixture was stirred at ambient temperature under an atmosphere of N_2 for additional 1.5 hours. After removal of THF, the product mixture was partitioned between $CHCl_3$ and water. The organic layer was washed, dried over $MgSO_4$ and concentrated under vacuum to give a brown solid. This was chromatographed on silica gel with $CHCl_3$ then MeOH-$CHCl_3$-NH_4OH (5 : 95 : 0.1 to 10 : 89 : 1) as eluents to afford the title compound of Example 51B as a white solid (53 mg, 0.116 mmol, 46.4 % yield).

C.I. m/z 456.3 [M+1].

51C. 6-[Amino-(6-methyl-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one

To a solution of the title compound of Example 51B (26 mg, 0.057 mmol) in THF (2.5 ml) was added a solution of 40 % aqueous NaOH (0.1 ml), benzyltriethylammonium chloride (6.5 mg. 0.074 mmol) and methyl iodide (0.0046 ml, 0.0743 mmol). The reaction mixture was stirred at ambient temperature for 3 hours after which time THF was removed. The crude product mixture was partitioned between $CHCl_3$ and water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was purified by thin layer chromatography with MeOH-$CHCl_3$-NH_4OH (5 : 95 : 0.1) as the mobile phase to afford the title compound as a white solid (14.4 mg, 0.031 mmol, 54 % yield).

CI-MS: m/z 470.0 [M+1].

EXAMPLE 52

6-[Amino-(6-methyl-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one

To a solution of the title compound of Example 51B (26 mg, 0.057 mmol) in THF (2.5 ml) was added (bromomethyl)cyclopropane (0.0075 ml, 0.080 mmol), benzyltriethylammonium chloride (6.5 mg, 0.0286 mmol), sodium iodide (2.57 mg, 0.0171 mmol) and a solution of 40% aqueous NaOH (0.57 ml). The reaction mixture was heated at 65°C for 3 hours after which time THF was removed. The crude product mixture was partitioned between $CHCl_3$ and water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel with MeOH-$CHCl_3$-NH_4OH (2 : 98 : 0.1 to 5 : 95 : 0.1) as the eluents to afford the title compound as a white solid (11 mg, 0.022 mmol, 38 % yield).

CI-MS: m/z 510.3 [M+1].

EXAMPLE 53

6-[Amino-(pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one

To a solution of the title compound of Example 7, 6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one (0.408 g, 0.77 mmol) in pyridine (0.77 ml) was added trichloroethyl chloroformate (0.159 ml, 1.15 mmol) at 0°C. The reaction mixture was gradually warmed to room temperature and stirred overnight. After removal of pyridine, the product mixture was taken into dichloromethane and water. After separation, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel with MeOH-$CHCl_3$-NH_4OH (1 : 99 : 0.1) as the eluents to afford the trichloroethyl carbamate as a white solid (0.451 g, 0.64 mmol, 83 % yield).

CI-MS: m/z 705.8, 708.0 [M+1].

To a solution of the trichloroethyl carbamate (34 mg, 0.048 mmol) in formic acid (0.96 ml) was added zinc powder (87 mg). The reaction mixture was stirred at ambient temperature for 15 minutes. After addition of methanol, the mixture was filtered through the celite, followed by a saturated solution of potassium carbonate. The filtrated was evaporated and was extracted with chloroform. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel with MeOH-$CHCl_3$-NH_4OH (2: 98: 0.) as the eluents to afford the title compound as a white solid (25 mg, 100 % yield).

CI-MS: m/z 496.1 [M+1].

EXAMPLE 54 and EXAMPLE 55

(+) and (-) Enantiomers of 4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one

To a solution of the title compound of Example 43 (4.31 g, 6.64 mmol) in THF (30 ml) was added 38 ml of 1N sulfuric acid. After the mixture was cooled to 0°C, a solution of sodium nitrite ($NaNO_2$, 1.45 g, 20.99 mmol) in water (10 ml) was added dropwise. The reaction mixture was stirred at ambient temperature for 7 hours after which time ethyl acetate was added. The organic layer was washed with saturated potassium carbonate, brine, dried over $MgSO_4$ and concentrated under vacuum to give the crude product. It was chromatographed on silica gel with MeOH-$CHCl_3$-NH_4OH (2: 98: 0.1) as the eluents to afford the title compound of Example 6, 4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one as a white solid (3.32 g, 94 % yield).

CI-MS: m/z 530.9 [M+1].

(+/-)-4-(3-Chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (3.002 g) was separated into its enantiomers and purified by high-performance liquid chromatography over CHIRALCEL™ OD (manufactured by Daicel Chemical Industries, LTD, Osaka, Japan) (2.2 cm x 25 cm, 10 μm; eluent: Hexane/ethanol/methanol 85/7.5/7.5; 25°C). Under these conditions, 1.14 g of the faster eluting enantiomer A, (Example 54): (-)-4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one and 0.7 g of the slower moving enantiomer B (Example 55): (+)-4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one were obtained.

Both enantiomers were >98 % optically pure.

EXAMPLE 56

(+)-6-[Amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one, dihydrochloride salt

To a solution of (+)-4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (0.844 g, 1.59 mmol) in DCM (10 ml) was added a solution of HCl in ethyl ether (1M, 4,77 ml, 4.77 mmol). The slurry solution was stirred for 2 hours. After filtration, the title compound of example 56 was obtained as a white solid (0.78 g, 1.29 mmol, 81.4 % yield).

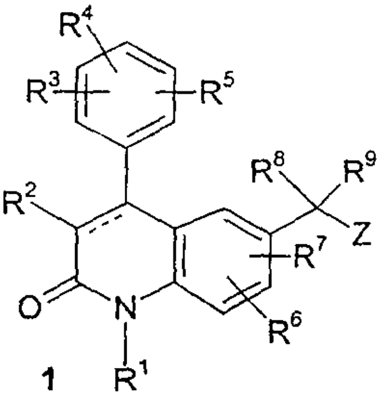
EXAMPLE 57

(-)-6-[Amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one, dihydrochloride salt

Following the same procedure as that described in example 56, (-)-4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one (0.252 g, 0.474 mmol) generated the dihydrochloride salt as a white solid (0.167 g, 0.28 mmol, 58 % yield).

What is claimed is:

1. A compound of the formula:



1

or a pharmaceutically acceptable salt or solvate thereof wherein:

the dashed line indicates an optional second bond connecting C-3 and C-4 of the quinolin-2-one ring;

R^1 is selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_qC(O)R^{12}$, $-(CR^{13}R^{14})_qC(O)OR^{15}$, $-(CR^{13}R^{14})_qOR^{12}$, $-(CR^{13}R^{14})_qCSO_2R^{15}$, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said cycloalkyl, aryl and heterocyclic R^1 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^1 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 4 R^6 groups;

R^2 is halo, cyano, $-C(O)OR^{15}$, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH=NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

R^8 is H, $-OR^{12}$, $-OC(O)R^{12}$, $-NR^{12}R^{13}$, $-N=CR^{12}R^{13}$, $-NR^{12}C(O)R^{13}$, cyano, $-C(O)OR^{13}$, $-SR^{12}$, or $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said heterocyclic R^8 groups are substituted by 1 to 4 R^6 groups;

R^9 is $-(CR^{13}R^{14})_t$(imidazolyl) or $-(CR^{13}R^{14})_t$(pyridinyl) wherein said imidazolyl or pyridinyl moiety is substituted by 1 or 2 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5 and each q is independently an integer from 1 to 5;

each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_q$ or $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of q or t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H.

2. The compound of claim 1 wherein R^1 is H, C_1-C_6 alkyl, or cyclopropylmethyl. The compound of claim 1 wherein R^8 is $-NR^{12}R^{13}$, $-OR^{12}$, or $-(CR^{13}R^{14})t$ (4-10 membered heterocyclic) substituted with from 1 to 4 R^6 groups, wherein said 4-10 membered heterocyclic is selected from triazolyl, imidazolyl, pyrazolyl, and piperidinyl.

3. The compound of claim 1 wherein R^8 is H, $-OR^{12}$, $-OC(O)R^{12}$, $-NR^{12}R^{13}$, $-NR^{12}C(O)R^{13}$, cyano, $-C(O)OR^{13}$, $-SR^{12}$, or $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said heterocyclic R^8 groups are substituted by 1 to 4 R^6 groups;

4. The compound of claim 2 wherein R^8 is hydroxy, amino, or triazolyl.

5. The compound of claim 1 wherein R^3, R^4, R^5 and R^6 are independently selected from H, halo, and C_1-C_6 alkoxy.

6. A compound according to claim 1 selected from the group consisting of:

6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one (enantiomer A);

6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one (enantiomer B);

4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one;

6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one;

4-(3-chloro-phenyl)-6-[(5-chloro-pyridin-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-methyl-1H-quinolin-2-one;

6-[amino-(5-chloro-pyridin-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one;

6-[amino-(5-chloro-pyridin-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one;

6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3,5-dichloro-phenyl)-1-methyl-1H-quinolin-2-one;

6-[amino-(5-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one;

6-[(5-Chloro-thiophen-2-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one;

amino-(5-chloro-thiophen-2-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one;

6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one;

6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethoxy-phenyl)-1-methyl-1H-quinolin-2-one;

6-[benzo[b]thiophen-2-yl-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one;

6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1H-quinolin-2-one;

(-)-6-[amino-(6-chloro-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one;

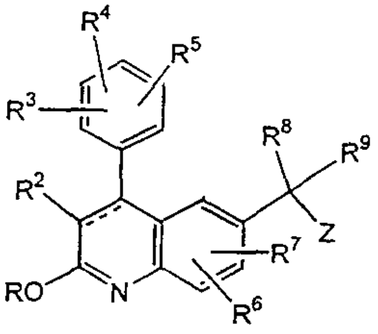
6-[amino-(6-methyl-pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one;

6-[amino-(pyridin-3-yl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-cyclopropylmethyl-1H-quinolin-2-one;

(+)-4-(3-chloro-phenyl)-6-[(6-chloro-pyridin-3-yl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-1-cyclopropylmethyl-1H-quinolin-2-one; and

pharmaceutically acceptable salts and solvates of any of said compounds.

7. A compound of the formula



2

wherein:

the dashed line indicates an optional second bond connecting C-3 and C-4 of the quinoline ring;

R is C_1-C_6 alkyl;

R^2 is halo, cyano, -C(O)OR^{15}, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -OR^{12}, -C(O)R^{12}, -C(O)OR^{12}, -NR^{13}C(O)OR^{15}, -OC(O)R^{12}, -NR^{13}SO$_2$R^{15}, -SO$_2$NR^{12}R^{13}, -NR^{13}C(O)R^{12}, -C(O)NR^{12}R^{13}, -NR^{12}R^{13}, -CH=NOR^{12}, -S(O)$_j$R^{12} wherein j is an integer from 0 to 2, -(CR^{13}R^{14})$_t$(C$_6$-C$_{10}$ aryl), -(CR^{13}R^{14})$_t$(4-10 membered heterocyclic), -(CR^{13}R^{14})$_t$(C$_3$-C$_{10}$ cycloalkyl), and -(CR^{13}R^{14})$_t$C≡CR^{16}; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -NR^{13}SO$_2$R^{15}, -SO$_2$NR^{12}R^{13}, -C(O)R^{12}, -C(O)OR^{12}, -OC(O)R^{12}, -NR^{13}C(O)OR^{15}, -NR^{13}C(O)R^{12}, -C(O)NR^{12}R^{13}, -NR^{12}R^{13}, -OR^{12}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -(CR^{13}R^{14})$_t$(C$_6$-C$_{10}$ aryl), and -(CR^{13}R^{14})$_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

R^8 is H, $-OR^{12}$, $-OC(O)R^{12}$, $-NR^{12}R^{13}$, $-NR^{12}C(O)R^{13}$, cyano, $-C(O)OR^{13}$, $-SR^{12}$, or $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said heterocyclic R^8 groups are substituted by 1 to 4 R^6 groups;

R^9 is $-(CR^{13}R^{14})_t$(imidazolyl) or $-(CR^{13}R^{14})_t$(pyridinyl) wherein said imidazolyl or pyridinyl moiety is substituted by 1 or 2 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

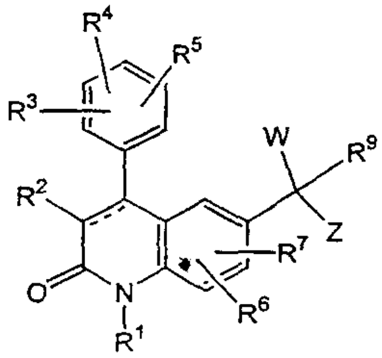
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H.

8. A compound of the formula



13

wherein:

the dashed line indicates an optional second bond connecting C-3 and C-4 of the quinolin-2-one ring;

W is selected from fluoro, chloro, bromo, and iodo;

R^1 is selected from H, C_1-C_{10} alkyl, -$(CR^{13}R^{14})_qC(O)R^{12}$, -$(CR^{13}R^{14})_qC(O)OR^{15}$, -$(CR^{13}R^{14})_qOR^{12}$, -$(CR^{13}R^{14})_qCSO_2R^{15}$, -$(CR^{13}R^{14})_t(C_3$-$C_{10}$ cycloalkyl), -$(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said cycloalkyl, aryl and heterocyclic R^1 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^1 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 4 R^6 groups;

R^2 is halo, cyano, -$C(O)OR^{15}$, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -OR^{12}, -$C(O)R^{12}$, -$C(O)OR^{12}$, -$NR^{13}C(O)OR^{15}$, -$OC(O)R^{12}$, -$NR^{13}SO_2R^{15}$, -$SO_2NR^{12}R^{13}$, -$NR^{13}C(O)R^{12}$, -$C(O)NR^{12}R^{13}$, -$NR^{12}R^{13}$, -$CH{=}NOR^{12}$, -$S(O)_jR^{12}$ wherein j is an integer from 0 to 2, -$(CR^{13}R^{14})_t(C_6$-C_{10} aryl), -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic), -$(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and -$(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$NR^{13}SO_2R^{15}$, -$SO_2NR^{12}R^{13}$, -$C(O)R^{12}$, -$C(O)OR^{12}$, -$OC(O)R^{12}$, -$NR^{13}C(O)OR^{15}$, -$NR^{13}C(O)R^{12}$, -$C(O)NR^{12}R^{13}$, -$NR^{12}R^{13}$, -OR^{12}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -$(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

R^9 is -$(CR^{13}R^{14})_t$(imidazolyl) or -$(CR^{13}R^{14})_t$(pyridinyl) wherein said imidazolyl or pyridinyl moiety is substituted by 1 or 2 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, -$(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), -$(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$NR^{13}C(O)R^{14}$, -$C(O)NR^{13}R^{14}$, -$NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5 and each q is independently an integer from 1 to 5;

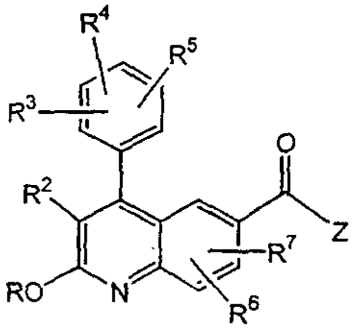
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_q$ or $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of q or t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H.

9. A compound of the formula



29

wherein:

R is C_1-C_6 alkyl;

R^2 is halo, cyano, $-C(O)OR^{15}$, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH=NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, -$(CR^{13}R^{14})_t$(C_3-C_{10} cycloalkyl), -$(CR^{13}R^{14})_t$(C_6-C_{10} aryl), and -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -C(O)R^{13}, -C(O)OR^{13}, -OC(O)R^{13}, -NR^{13}C(O)R^{14}, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

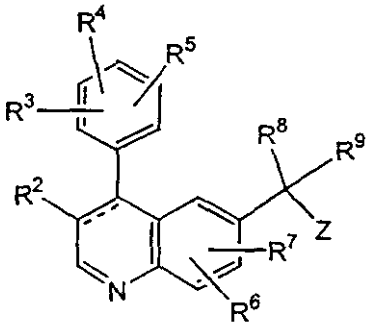
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as -$(CR^{13}R^{14})_t$ each is independently defined for each iteration t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and -Si$R^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H.

10. A compound of the formula



12

or a pharmaceutically acceptable salt or solvate thereof wherein:

the dashed line indicates an optional second bond connecting C-3 and C-4 of the quinoline ring;

R^2 is halo, cyano, -C(O)OR^{15}, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -OR^{12},

$-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH=NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6-C_{10}$ aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3-C_{10}$ cycloalkyl), and $-(CR^{13}R^{14})_tC\equiv CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6-C_{10}$ aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

R^8 is H, $-OR^{12}$, $-OC(O)R^{12}$, $-NR^{12}R^{13}$, $-NR^{12}C(O)R^{13}$, cyano, $-C(O)OR^{13}$, $-SR^{12}$, or $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said heterocyclic R^8 groups are substituted by 1 to 4 R^6 groups;

R^9 is $-(CR^{13}R^{14})_t$(imidazolyl) or $-(CR^{13}R^{14})_t$(pyridinyl) wherein said imidazolyl or pyridinyl moiety is substituted by 1 or 2 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3-C_{10}$ cycloalkyl), $-(CR^{13}R^{14})_t(C_6-C_{10}$ aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

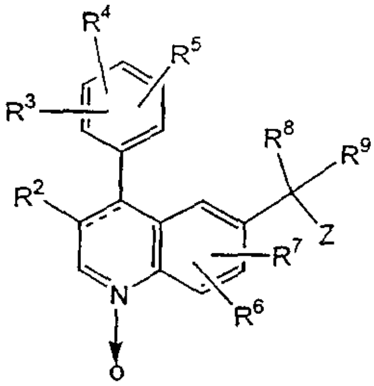
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H.

11. A compound of the formula



6

or a pharmaceutically acceptable salt or solvate thereof wherein:

the dashed line indicates an optional second bond connecting C-3 and C-4 of the quinoline ring;

R^2 is halo, cyano, $-C(O)OR^{15}$, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH{=}NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

R^8 is H, $-OR^{12}$, $-OC(O)R^{12}$, $-NR^{12}R^{13}$, $-NR^{12}C(O)R^{13}$, cyano, $-C(O)OR^{13}$, $-SR^{12}$, or $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said heterocyclic R^8 groups are substituted by 1 to 4 R^6 groups;

R^9 is $-(CR^{13}R^{14})_t$(imidazolyl) or $-(CR^{13}R^{14})_t$(pyridinyl) wherein said imidazolyl or pyridinyl moiety is substituted by 1 or 2 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

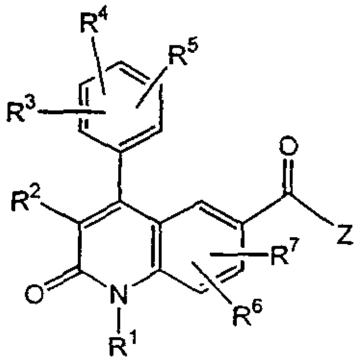
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H.

12. A compound of the formula



30

wherein:

R^1 is selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_qC(O)R^{12}$, $-(CR^{13}R^{14})_qC(O)OR^{15}$, $-(CR^{13}R^{14})_qOR^{12}$, $-(CR^{13}R^{14})_qCSO_2R^{15}$, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said cycloalkyl, aryl and heterocyclic R^1 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^1 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 4 R^6 groups;

R^2 is halo, cyano, $-C(O)OR^{15}$, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$,

-C(O)NR^{12}R^{13}, -NR^{12}R^{13}, -CH=NOR^{12}, -S(O)$_j$R^{12} wherein j is an integer from 0 to 2, -(CR^{13}R^{14})$_t$(C$_6$-C$_{10}$ aryl), -(CR^{13}R^{14})$_t$(4-10 membered heterocyclic), -(CR^{13}R^{14})$_t$(C$_3$-C$_{10}$ cycloalkyl), and -(CR^{13}R^{14})$_t$C≡CR^{16}; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C$_6$-C$_{10}$ aryl group, a C$_5$-C$_8$ saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -NR^{13}SO$_2$R^{15}, -SO$_2$NR^{12}R^{13}, -C(O)R^{12}, -C(O)OR^{12}, -OC(O)R^{12}, -NR^{13}C(O)OR^{15}, -NR^{13}C(O)R^{12}, -C(O)NR^{12}R^{13}, -NR^{12}R^{13}, -OR^{12}, C$_1$-C$_{10}$ alkyl, C$_2$-C$_{10}$ alkenyl, C$_2$-C$_{10}$ alkynyl, -(CR^{13}R^{14})$_t$(C$_6$-C$_{10}$ aryl), and -(CR^{13}R^{14})$_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

each R^{12} is independently selected from H, C$_1$-C$_{10}$ alkyl, -(CR^{13}R^{14})$_t$(C$_3$-C$_{10}$ cycloalkyl), -(CR^{13}R^{14})$_t$(C$_6$-C$_{10}$ aryl), and -(CR^{13}R^{14})$_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C$_6$-C$_{10}$ aryl group, a C$_5$-C$_8$ saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -C(O)R^{13}, -C(O)OR^{13}, -OC(O)R^{13}, -NR^{13}C(O)R^{14}, -C(O)NR^{13}R^{14}, -NR^{13}R^{14}, hydroxy, C$_1$-C$_6$ alkyl, and C$_1$-C$_6$ alkoxy;

each t is independently an integer from 0 to 5 and each q is independently an integer from 1 to 5;

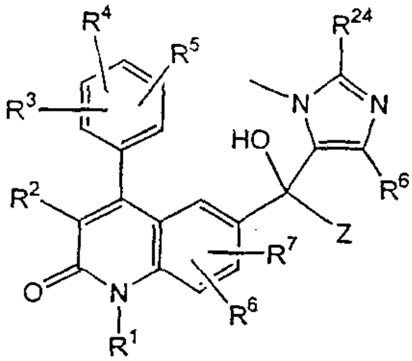
each R^{13} and R^{14} is independently H or C$_1$-C$_6$ alkyl, and where R^{13} and R^{14} are as -(CR^{13}R^{14})$_q$ or -(CR^{13}R^{14})$_t$ each is independently defined for each iteration of q or t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and -SiR^{17}R^{18}R^{19}; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H.

13. A compound of the formula



26

wherein:

R^{24} is selected from $-SR^{20}$ and $-SiR^{21}R^{22}R^{23}$, wherein R^{20} is selected from H and phenyl, and R^{21}, R^{22}, and R^{23} are independently selected from C_1-C_6 alkyl and phenyl;

R^1 is selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_qC(O)R^{12}$, $-(CR^{13}R^{14})_qC(O)OR^{15}$, $-(CR^{13}R^{14})_qOR^{12}$, $-(CR^{13}R^{14})_qCSO_2R^{15}$, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), wherein said cycloalkyl, aryl and heterocyclic R^1 groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^1 groups, except H but including any optional fused rings referred to above, are optionally substituted by 1 to 4 R^6 groups;

R^2 is halo, cyano, $-C(O)OR^{15}$, or a group selected from the substituents provided in the definition of R^{12};

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH=NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, -$(CR^{13}R^{14})_t$(C_3-C_{10} cycloalkyl), -$(CR^{13}R^{14})_t$(C_6-C_{10} aryl), and -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -C(O)R^{13}, -C(O)OR^{13}, -OC(O)R^{13}, -NR^{13}C(O)R^{14}, -C(O)N$R^{13}R^{14}$, -N$R^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5 and each q is independently an integer from 1 to 5;

each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as -$(CR^{13}R^{14})_q$ or -$(CR^{13}R^{14})_t$ each is independently defined for each iteration of q or t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and -Si$R^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H.

14. A method of inhibiting abnormal cell growth in a mammal comprising administering to said mammal an amount of a compound of claim 1, claim 7, claim 10, or claim 11, or a pharmaceutically acceptable salt or solvate thereof, that is effective in inhibiting farnesyl protein transferase.

15. A method of inhibiting abnormal cell growth in a mammal comprising administering to said mammal an amount of a compound of claim 1, claim 7, claim 10, or claim 11, or a pharmaceutically acceptable salt or solvate thereof, that is effective in inhibiting abnormal cell growth.

16. A method of inhibiting abnormal cell growth in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of claim 1, claim 7, claim 10, or claim 11, or a pharmaceutically acceptable salt or solvate thereof, in combination with a chemotherapeutic.

17. A pharmaceutical composition for inhibiting abnormal cell growth in a mammal comprising an amount of a compound of claim 1, claim 7, claim 10, or claim 11, or a pharmaceutically acceptable salt or solvate thereof, that is effective in inhibiting farnesyl protein transferase, and a pharmaceutically acceptable carrier.

18. A pharmaceutical composition for inhibiting abnormal cell growth in a mammal comprising an amount of a compound of claim 1, claim 7, claim 10, or claim 11, or a pharmaceutically acceptable salt or solvate thereof, that is effective in inhibiting abnormal cell growth, and a pharmaceutically acceptable carrier.

19. A pharmaceutical composition for inhibiting abnormal cell growth in a mammal which comprises a therapeutically effective amount of a compound of claim 1, claim 7, claim 10, or claim 11, or a pharmaceutically acceptable salt or solvate thereof, in combination with a chemotherapeutic.

20. A method of treating a disease or condition selected from lung cancer, NSCLC (non small cell lung cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), pediatric malignancy, neoplasms of the central nervous system, (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas), Barrett's esophagus (pre-malignant syndrome), neoplastic cutaneous disease, psoriasis, mycoses fungoides, benign prostatic hypertrophy, human papilloma virus (HPV), and restinosis in a mammal comprising administering to said mammal an amount of a compound of claim 1, claim 7, claim 10, or claim 11, that is effective in inhibiting farnesyl protein transferase.

21. A method of treating a disease or condition selected from lung cancer, NSCLC (non small cell lung cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), pediatric

malignancy, neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas), Barrett's esophagus (pre-malignant syndrome), neoplastic cutaneous disease, psoriasis, mycoses fungoides, benign prostatic hypertrophy, human papilloma virus (HPV), and restinosis in a mammal comprising administering to said mammal an amount of a compound of claim 1, claim 7, claim 10, or claim 11, that is effective in treating said disease.

22. A pharmaceutical composition for treating a disease or condition selected from lung cancer, NSCLC (non small cell lung cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), pediatric malignancy, neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas), Barrett's esophagus (pre-malignant syndrome), neoplastic cutaneous disease, psoriasis, mycoses fungoides, benign prostatic hypertrophy, human papilloma virus (HPV), and restinosis in a mammal comprising an amount of a compound of claim 1, claim 7, claim 10, or claim 11, that is effective in inhibiting farnesyl protein transferase, and a pharmaceutically acceptable carrier.

23. A pharmaceutical composition for treating a disease or condition selected from lung cancer, NSCLC (non small cell lung cancer), bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), pediatric malignancy, neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas), Barrett's esophagus (pre-

malignant syndrome), neoplastic cutaneous disease, psoriasis, mycoses fungoides, benign prostatic hypertrophy, human papilloma virus (HPV), and restinosis in a mammal comprising an amount of a compound of claim 1, claim 7, claim 10, or claim 11, that is effective in treating said disease, and a pharmaceutically acceptable carrier.

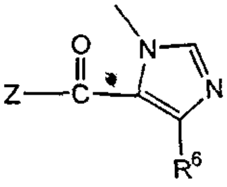
24. A method of treating abnormal cell growth in a mammal, which method comprises administering to the mammal an amount of a compound of claim 1, claim 7, claim 10, or claim 11, and an amount of one or more substances selected from MMP-2 inhibitors, MMP-9 inhibitors, signal transduction inhibitors, antiproliferative agents, and agents capable of blocking CTLA4, wherein the amounts of the compound and the substance or substances are together effective in treating abnormal cells growth.

25. A pharmaceutical composition for treating abnormal cell growth in a mammal, which composition comprises an amount of a compound of claim 1, claim 7, claim 10, or claim 11, and an amount of one or more substances selected from MMP-2 inhibitors, MMP-9 inhibitors, signal transduction inhibitors, antiproliferative agents, and agents capable of blocking CTLA4, and a pharmaceutically acceptable carrier, wherein the amounts of the compound and the substance or substances are together effective in treating abnormal cells growth.

26. A method for inhibiting abnormal cell growth in a mammal which method comprises administering to the mammal an amount of claim 1, claim 7, claim 10, or claim 11, in combination with radiation therapy, wherein the amount of the compound is in combination with the radiation therapy effective in inhibiting abnormal cell growth in the mammal.

27. A method for sensitizing abnormal cells in a mammal to treatment with radiation therapy, which method comprises administering to the mammal an amount of a compound of claim 1, claim 6, claim 10, or claim 11, which amount is effective in sensitizing abnormal cells to treatment with radiation.

28. A method of synthesizing a compound of the formula



11a

wherein

R^6 is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH=NOR^{12}$,

$-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6-C_{10}$ aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3-C_{10}$ cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6-C_{10}$ aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3-C_{10}$ cycloalkyl), $-(CR^{13}R^{14})_t(C_6-C_{10}$ aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

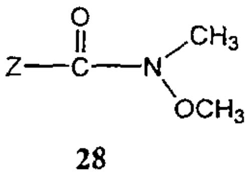
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H;

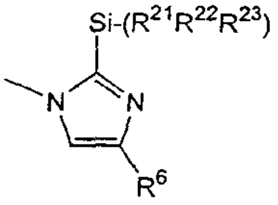
which method comprises reacting in an appropriate solvent in the presence of a suitable base a compound of the formula



28

wherein Z is as defined above;

with a compound of the formula

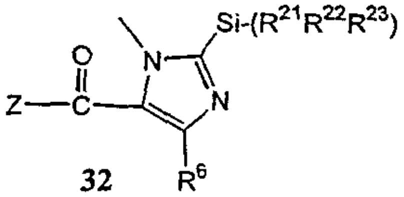


33

wherein R^6 is as defined above, and

R^{21}, R^{22}, and R^{23} are each independently selected from C_1-C_6 alkyl and phenyl;

thereby obtaining a compound of the formula

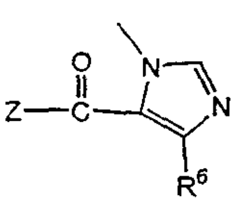


32

;

and reacting the compound of formula 32 so obtained in an appropriate solvent with acetic acid or with a fluoride reagent.

29. A method of synthesizing a compound of the formula



11a

wherein

R^6 is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH{=}NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-NR^{13}C(O)OR^{15}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-OR^{12}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

Z is an aromatic 4-10 membered heterocyclic group, substituted by 1 to 4 R^6 substituents;

each R^{12} is independently selected from H, C_1-C_{10} alkyl, $-(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-C(O)NR^{13}R^{14}$, $-NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

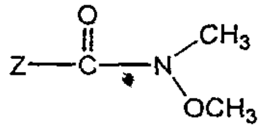
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as $-(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and $-SiR^{17}R^{18}R^{19}$; and,

R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H;

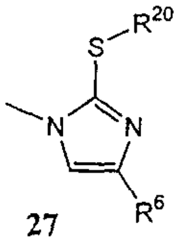
which method comprises reacting in an appropriate solvent in the presence of a suitable base a compound of the formula



28

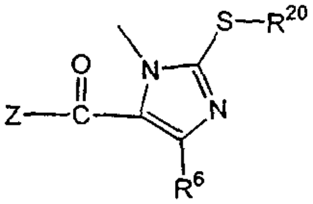
wherein Z is as defined above;

with a compound of the formula



27

wherein R^6 is as defined above and R^{20} is selected from H and phenyl; thereby obtaining a compound of the formula



31

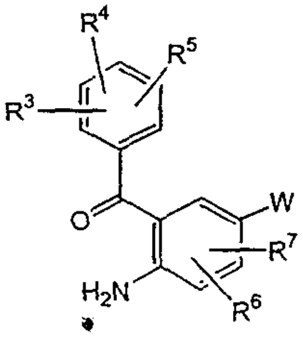
;

and removing from the compound of formula 31 so obtained the $-SR^{20}$ group, either:

a) reductively, with a nickel catalyst; or

b) oxidatively, with nitric acid or with aqueous hydrogen peroxide in acetic acid.

30. A method of synthesizing a compound of the formula



23

wherein

each R^3, R^4, R^5, R^6, and R^7 is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, $-OR^{12}$, $-C(O)R^{12}$, $-C(O)OR^{12}$, $-NR^{13}C(O)OR^{15}$, $-OC(O)R^{12}$, $-NR^{13}SO_2R^{15}$, $-SO_2NR^{12}R^{13}$, $-NR^{13}C(O)R^{12}$, $-C(O)NR^{12}R^{13}$, $-NR^{12}R^{13}$, $-CH{=}NOR^{12}$, $-S(O)_jR^{12}$ wherein j is an integer from 0 to 2, $-(CR^{13}R^{14})_t(C_6$-C_{10} aryl), $-(CR^{13}R^{14})_t$(4-10 membered heterocyclic), $-(CR^{13}R^{14})_t(C_3$-C_{10}

cycloalkyl), and -$(CR^{13}R^{14})_tC{\equiv}CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$NR^{13}SO_2R^{15}$, -$SO_2NR^{12}R^{13}$, -$C(O)R^{12}$, -$C(O)OR^{12}$, -$OC(O)R^{12}$, -$NR^{13}C(O)OR^{15}$, -$NR^{13}C(O)R^{12}$, -$C(O)NR^{12}R^{13}$, -$NR^{12}R^{13}$, -OR^{12}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -$(CR^{13}R^{14})_t$(C_6-C_{10} aryl), and -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

each R^{12} is independently selected from H, C_1-C_{10} alkyl, -$(CR^{13}R^{14})_t$(C_3-C_{10} cycloalkyl), -$(CR^{13}R^{14})_t$(C_6-C_{10} aryl), and -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic); said cycloalkyl, aryl and heterocyclic R^{12} groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and the foregoing R^{12} substituents, except H but including any optional fused rings, are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$C(O)R^{13}$, -$C(O)OR^{13}$, -$OC(O)R^{13}$, -$NR^{13}C(O)R^{14}$, -$C(O)NR^{13}R^{14}$, -$NR^{13}R^{14}$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each t is independently an integer from 0 to 5;

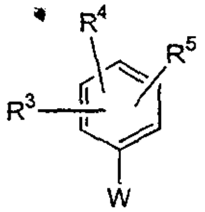
each R^{13} and R^{14} is independently H or C_1-C_6 alkyl, and where R^{13} and R^{14} are as -$(CR^{13}R^{14})_t$ each is independently defined for each iteration of t in excess of 1;

R^{15} is selected from the substituents provided in the definition of R^{12} except R^{15} is not H;

R^{16} is selected from the list of substituents provided in the definition of R^{12} and -$SiR^{17}R^{18}R^{19}$; and,

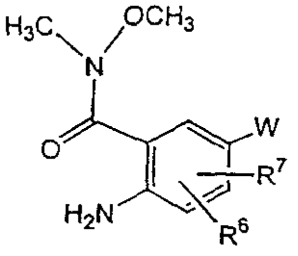
R^{17}, R^{18} and R^{19} are each independently selected from the substituents provided in the definition of R^{12} except at least one of R^{17}, R^{18} and R^{19} is not H;

which method comprises reacting, at a temperature of from about -78° C to about 0° C, in the presence of a suitable base and in an appopriate solvent a compound of formula



34

wherein W is an appropriate leaving group, and R^3, R^4 and R^5 are as defined above, with a compound of the formula

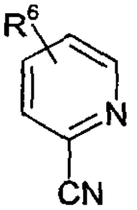


35

wherein R^6 and R^7 are as defined above.

31. A method according to claim 30, wherein the appropriate solvent is ethyl ether.

32. A method of synthesizing a compound of the formula

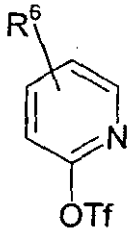


37

wherein R^6 is selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10}alkynyl, halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -OR^{12}, -$C(O)R^{12}$, -$C(O)OR^{12}$, -$NR^{13}C(O)OR^{15}$, -$OC(O)R^{12}$, -$NR^{13}SO_2R^{15}$, -$SO_2NR^{12}R^{13}$, -$NR^{13}C(O)R^{12}$, -$C(O)NR^{12}R^{13}$, -$NR^{12}R^{13}$, -$CH=NOR^{12}$, -$S(O)_jR^{12}$ wherein j is an integer from 0 to 2, -$(CR^{13}R^{14})_t(C_6$-C_{10} aryl), -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic), -$(CR^{13}R^{14})_t(C_3$-C_{10} cycloalkyl), and -$(CR^{13}R^{14})_tC\equiv CR^{16}$; and wherein the cycloalkyl, aryl and heterocyclic moieties of the foregoing groups are optionally fused to a C_6-C_{10} aryl group, a C_5-C_8 saturated cyclic group, or a 4-10 membered heterocyclic group; and said alkyl, alkenyl, cycloalkyl, aryl and heterocyclic groups are optionally substituted by 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -$NR^{13}SO_2R^{15}$, -$SO_2NR^{12}R^{13}$, -$C(O)R^{12}$, -$C(O)OR^{12}$, -$OC(O)R^{12}$, -$NR^{13}C(O)OR^{15}$, -$NR^{13}C(O)R^{12}$, -$C(O)NR^{12}R^{13}$, -$NR^{12}R^{13}$, -OR^{12}, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, -$(CR^{13}R^{14})_t(C_6$-C_{10} aryl), and -$(CR^{13}R^{14})_t$(4-10 membered heterocyclic);

which method comprises

a) reacting with a metal cyanide, in the presence of a palladium catalyst and in an appropriate solvent, at a temperature of about 25° C to about 100° C, a compound of the formula



36

wherein Tf is $-SO_2-CF_3$ and R^6 is as defined above;
thereby obtaining a compound of the formula **37**.

INTERNATIONAL SEARCH REPORT

Inte ,onal Application No
PCT/IB 00/00121

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 A61K31/47 C07D409/14 C07D401/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 21701 A (JANSSEN PHARMACEUTICA N.V.) 19 June 1997 (1997-06-19) cited in the application claims	1,8,12, 13,17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search 9 May 2000	Date of mailing of the international search report 18/05/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Van Bijlen, H

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 00/00121

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 14-16, 20,21,24,26 and 27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 00/00121

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9721701 A	19-06-1997	AU 711142 B	07-10-1999
		AU 7294896 A	03-07-1997
		BG 102458 A	30-06-1999
		BR 9610745 A	13-07-1999
		CN 1203598 A	30-12-1998
		CZ 9801573 A	14-10-1998
		EP 0865440 A	23-09-1998
		HR 960576 A	28-02-1998
		HU 9900185 A	28-04-1999
		JP 10511405 T	04-11-1998
		NO 980927 A	08-06-1998
		NZ 320244 A	29-06-1999
		PL 325962 A	17-08-1998
		SK 70498 A	07-10-1998
		US 6037350 A	14-03-2000

[19]中华人民共和国国家知识产权局

[51]Int. Cl⁷

C07D401/14

A61K 31/47　C07D409/14

C07D401/06

H 01103

[12]发明专利申请公开说明书

[21]申请号　00803668.3

[43]公开日　2002年3月13日

[11]公开号　CN 1340051A

[22]申请日　2000.2.4　**[21]申请号**　00803668.3

[30]优先权

[32]1999.2.11　[33]US [31]60/119,702

[86]国际申请　PCT/IB00/00121　2000.2.4

[87]国际公布　WO00/47574　英　2000.8.17

[85]进入国家阶段日期　2001.8.10

[71]申请人　辉瑞产品公司

地址　美国康涅狄格

[72]发明人　杨秉薇

[74]专利代理机构　中国国际贸易促进委员会专利商标事务所)

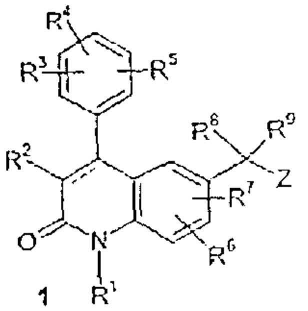
代理人　李华英

权利要求书24页　说明书79页　附图页数0页

[54]发明名称　可用作抗癌剂的杂芳基取代的喹啉－2－酮衍生物

[57]摘要

本发明涉及式(1)化合物及其药学上可接受的盐和溶剂化物，其中 R^1、R^2、R^3、R^4、R^5、R^6、R^7、R^8、R^9和Z是如本文所定义的。本发明还涉及包含式(1)化合物的药物组合物，和通过将式(1)化合物对哺乳动物给药而抑制哺乳动物异常细胞生长、包括癌症的方法。本发明还涉及可用于合成式(1)化合物的中间体和方法。



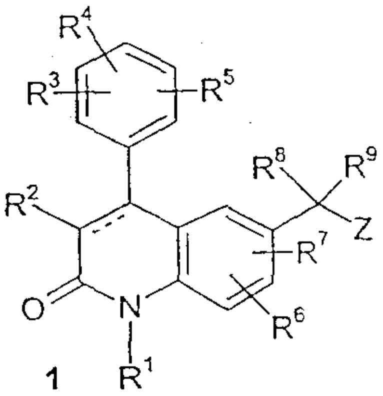
1

(1)

ISSN1008-4274

知识产权出版社出版

1、式 1 化合物



1

或其药学上可接受的盐或溶剂化物，其中：

虚线表示可选的连接喹啉-2-酮环 C-3 与 C-4 的第二条键；

R^1 选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_qC(O)R^{12}$、$-(CR^{13}R^{14})_qC(O)OR^{15}$、$-(CR^{13}R^{14})_qOR^{12}$、$-(CR^{13}R^{14})_qCSO_2R^{15}$、$-(CR^{13}R^{14})_t(C_3$-$C_{10}$ 环烷基)、$-(CR^{13}R^{14})_t(C_6$-C_{10} 芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环)，其中所述环烷基、芳基和杂环 R^1 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^1 基团除 H 以外、但包括上述任意可选的稠合环，都可选地被 1 至 4 个 R^6 基团取代；

R^2 是卤、氰基、$-C(O)OR^{15}$ 或选自由 R^{12} 定义所提供的取代基的基团；

每个 R^3、R^4、R^5、R^6 和 R^7 独立地选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH{=}NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6$-C_{10} 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t(C_3$-C_{10} 环烷基)和 $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、

$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、$-(CR^{13}R^{14})_t$(C_6-C_{10}芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环)；

Z是芳族4-10元杂环基，被1-4个R^6取代基取代；

R^8是H、$-OR^{12}$、$-OC(O)R^{12}$、$-NR^{12}R^{13}$、$-N=CR^{12}R^{13}$、$-NR^{12}C(O)R^{13}$、氰基、$-C(O)OR^{13}$、$-SR^{12}$或$-(CR^{13}R^{14})_t$(4-10元杂环)，其中所述杂环R^8基团被1至4个R^6基团取代；

R^9是$-(CR^{13}R^{14})_t$(咪唑基)或$-(CR^{13}R^{14})_t$(吡啶基)，其中所述咪唑基或吡啶基部分被1或2个R^6取代基取代；

每个R^{12}独立地选自H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_t$(C_3-C_{10}环烷基)、$-(CR^{13}R^{14})_t$(C_6-C_{10}芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环)；所述环烷基、芳基和杂环R^{12}基团可选地与C_6-C_{10}芳基、C_5-C_8饱和环基或4-10元杂环基稠合；上述R^{12}取代基除H以外但包括任意可选的稠合环，都可选地被1至3个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6烷基和C_1-C_6烷氧基；

每个t独立地是0至5的整数，每个q独立地是1至5的整数；

每个R^{13}和R^{14}独立地是H或C_1-C_6烷基，其中若q或t超过1，则$-(CR^{13}R^{14})_q$或$-(CR^{13}R^{14})_t$中每次重复定义的R^{13}和R^{14}是各自独立的；

R^{15}选自由R^{12}定义所提供的取代基，但是R^{15}不是H；

R^{16}选自由R^{12}定义所提供的取代基列表和$-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18}和R^{19}各自独立地选自由R^{12}定义所提供的取代基，但是至少R^{17}、R^{18}和R^{19}之一不是H。

2、权利要求1的化合物，其中R^1是H、C_1-C_6烷基或环丙基甲基。权利要求1的化合物，其中R^8是$-NR^{12}R^{13}$、$-OR^{12}$或被1至4个R^6基团取代的$-(CR^{13}R^{14})_t$(4-10元杂环)，其中所述4-10元杂环选自三唑基、咪唑基、吡唑基和哌啶基。

3、权利要求1的化合物，其中R^8是H、$-OR^{12}$、$-OC(O)R^{12}$、$-NR^{12}R^{13}$、$-NR^{12}C(O)R^{13}$、氰基、$-C(O)OR^{13}$、$-SR^{12}$或$-(CR^{13}R^{14})_t$(4-10元杂环)，其中所述杂环R^8基团被1至4个R^6基团取代。

4、权利要求 2 的化合物，其中 R^8 是羟基、氨基或三唑基。

5、权利要求 1 的化合物，其中 R^3、R^4、R^5 和 R^6 独立地选自 H、卤和 C_1-C_6 烷氧基。

6、根据权利要求 1 的化合物，选自下组：

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-甲基-1H-喹啉-2-酮（对映异构体 A）；

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-甲基-1H-喹啉-2-酮（对映异构体 B）；

4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)甲基]-1-环丙基甲基-1H-喹啉-2-酮；

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-环丙基甲基-1H-喹啉-2-酮；

4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-羟基-(3-甲基-3H-咪唑-4-基)甲基]-1-甲基-1H-喹啉-2-酮；

6-[氨基-(5-氯-吡啶-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-甲基-1H-喹啉-2-酮；

6-[氨基-(5-氯-吡啶-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-环丙基甲基-1H-喹啉-2-酮；

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3,5-二氯苯基)-1-甲基-1H-喹啉-2-酮；

6-[氨基-(5-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮；

6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1-甲基-1H-喹啉-2-酮；

氨基-(5-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基苯基)-1-甲基-1H-喹啉-2-酮；

6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基苯基)-1-甲基-1H-喹啉-2-酮；

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲

基]-4-(3-乙氧基苯基)-1-甲基-1H-喹啉-2-酮;

6-[苯并[b]噻吩-2-基-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮;

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1H-喹啉-2-酮;

(-)-6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-环丙基甲基-1H-喹啉-2-酮;

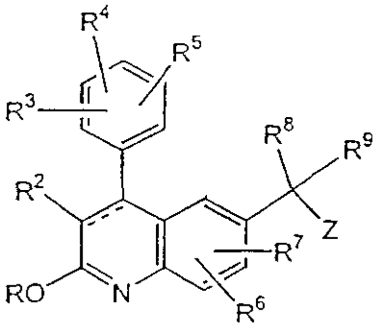
6-[氨基-(6-甲基-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-甲基-1H-喹啉-2-酮;

6-[氨基-(吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮;

(+)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)甲基]-1-环丙基甲基-1H-喹啉-2-酮; 和

任意上述化合物的药学上可接受的盐和溶剂化物。

7、下式化合物



2

其中:

虚线表示可选的连接喹啉环C-3与C-4的第二条键;

R是C_1-C_6烷基;

R^2是卤、氰基、-C(O)OR^{15}或选自由R^{12}定义所提供的取代基的基团;

每个R^3、R^4、R^5、R^6和R^7独立地选自H、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、-OR^{12}、-C(O)R^{12}、-C(O)OR^{12}、-NR^{13}C(O)OR^{15}、-OC(O)R^{12}、-N$R^{13}$$SO_2$$R^{15}$、-$SO_2NR^{12}$$R^{13}$、-N$R^{13}$C(O)$R^{12}$、-C(O)N$R^{12}$$R^{13}$、-N$R^{12}$$R^{13}$、-CH=NO$R^{12}$、

$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t(C_3-C_{10}$ 环烷基)和$-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个 R^6 取代基取代；

R^8 是 H、$-OR^{12}$、$-OC(O)R^{12}$、$-NR^{12}R^{13}$、$-NR^{12}C(O)R^{13}$、氰基、$-C(O)OR^{13}$、$-SR^{12}$ 或$-(CR^{13}R^{14})_t$(4-10 元杂环)，其中所述杂环 R^8 基团被 1 至 4 个 R^6 基团取代；

R^9 是$-(CR^{13}R^{14})_t$(咪唑基)或$-(CR^{13}R^{14})_t$(吡啶基)，其中所述咪唑基或吡啶基部分被 1 或 2 个 R^6 取代基取代；

每个 R^{12} 独立地选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_t(C_3-C_{10}$ 环烷基)、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12} 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6 烷基和 C_1-C_6 烷氧基；

每个 t 独立地是 0 至 5 的整数；

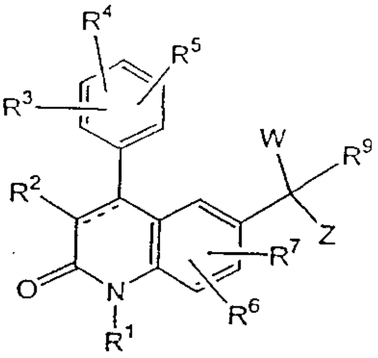
每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6 烷基，其中若 t 超过 1，则$-(CR^{13}R^{14})_t$ 中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和$-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H。

8、下式化合物



13

其中：

虚线表示可选的连接喹啉-2-酮环 C-3 与 C-4 的第二条键；

W 选自氟、氯、溴和碘；

R^1 选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_qC(O)R^{12}$、$-(CR^{13}R^{14})_qC(O)OR^{15}$、$-(CR^{13}R^{14})_qOR^{12}$、$-(CR^{13}R^{14})_qCSO_2R^{15}$、$-(CR^{13}R^{14})_t$($C_3$-$C_{10}$ 环烷基)、$-(CR^{13}R^{14})_t$(C_6-C_{10} 芳基)和 $-(CR^{13}R^{14})_t$(4-10 元杂环)，其中所述环烷基、芳基和杂环 R^1 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^1 基团除 H 以外、但包括上述任意可选的稠合环，都可选地被 1 至 4 个 R^6 基团取代；

R^2 是卤、氰基、$-C(O)OR^{15}$ 或选自由 R^{12} 定义所提供的取代基的基团；

每个 R^3、R^4、R^5、R^6 和 R^7 独立地选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH{=}NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t$(C_6-C_{10} 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t$(C_3-C_{10} 环烷基)和 $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、

C_2-C_{10} 炔基、-$(CR^{13}R^{14})_t$(C_6-C_{10} 芳基)和-$(CR^{13}R^{14})_t$(4-10 元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个 R^6 取代基取代；

R^9 是-$(CR^{13}R^{14})_t$(咪唑基)或-$(CR^{13}R^{14})_t$(吡啶基)，其中所述咪唑基或吡啶基部分被 1 或 2 个 R^6 取代基取代；

每个 R^{12} 独立地选自 H、C_1-C_{10} 烷基、-$(CR^{13}R^{14})_t$(C_3-C_{10} 环烷基)、-$(CR^{13}R^{14})_t$(C_6-C_{10} 芳基)和-$(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12} 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6 烷基和 C_1-C_6 烷氧基；

每个 t 独立地是 0 至 5 的整数，每个 q 独立地是 1 至 5 的整数；

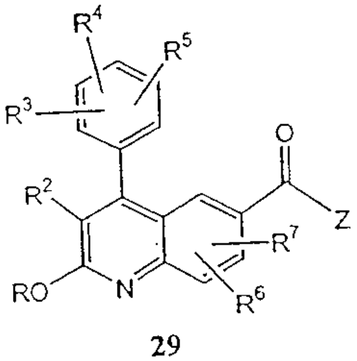
每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6 烷基，其中若 q 或 t 超过 1，则-$(CR^{13}R^{14})_q$ 或-$(CR^{13}R^{14})_t$ 中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和 $-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H。

9、下式化合物



29

其中：

R 是 C_1-C_6 烷基；

R^2 是卤、氰基、$-C(O)OR^{15}$ 或选自由 R^{12} 定义所提供的取代基的基团；

每个 R^3、R^4、R^5、R^6 和 R^7 独立地选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、

C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、-OR^{12}、-$C(O)R^{12}$、-$C(O)OR^{12}$、-$NR^{13}C(O)OR^{15}$、-$OC(O)R^{12}$、-$NR^{13}SO_2R^{15}$、-$SO_2NR^{12}R^{13}$、-$NR^{13}C(O)R^{12}$、-$C(O)NR^{12}R^{13}$、-$NR^{12}R^{13}$、-$CH=NOR^{12}$、-$S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、-$(CR^{13}R^{14})_t$(C_6-C_{10}芳基)、-$(CR^{13}R^{14})_t$(4-10 元杂环)、-$(CR^{13}R^{14})_t$(C_3-C_{10}环烷基)和-$(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与$C_6$-$C_{10}$芳基、$C_5$-$C_8$饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、-$NR^{13}SO_2R^{15}$、-$SO_2NR^{12}R^{13}$、-$C(O)R^{12}$、-$C(O)OR^{12}$、-$OC(O)R^{12}$、-$NR^{13}C(O)OR^{15}$、-$NR^{13}C(O)R^{12}$、-$C(O)NR^{12}R^{13}$、-$NR^{12}R^{13}$、-OR^{12}、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、-$(CR^{13}R^{14})_t$(C_6-C_{10}芳基)和-$(CR^{13}R^{14})_t$(4-10 元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个R^6取代基取代；

每个R^{12}独立地选自 H、C_1-C_{10}烷基、-$(CR^{13}R^{14})_t$(C_3-C_{10}环烷基)、-$(CR^{13}R^{14})_t$(C_6-C_{10}芳基)和-$(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环R^{12}基团可选地与C_6-C_{10}芳基、C_5-C_8饱和环基或 4-10 元杂环基稠合；上述R^{12}取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、-$C(O)R^{13}$、-$C(O)OR^{13}$、-$OC(O)R^{13}$、-$NR^{13}C(O)R^{14}$、-$C(O)NR^{13}R^{14}$、-$NR^{13}R^{14}$、羟基、C_1-C_6烷基和C_1-C_6烷氧基；

每个 t 独立地是 0 至 5 的整数；

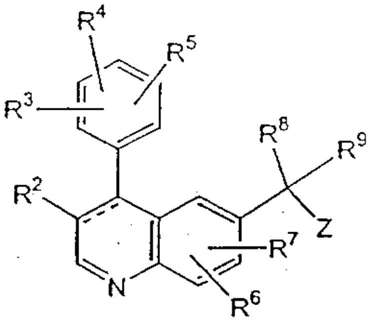
每个R^{13}和R^{14}独立地是 H 或C_1-C_6烷基，其中若 t 超过 1，则-$(CR^{13}R^{14})_t$中每次重复定义的R^{13}和R^{14}是各自独立的；

R^{15}选自由R^{12}定义所提供的取代基，但是R^{15}不是 H；

R^{16}选自由R^{12}定义所提供的取代基列表和-$SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18}和R^{19}各自独立地选自由R^{12}定义所提供的取代基，但是至少R^{17}、R^{18}和R^{19}之一不是 H。

10、下式化合物



12

或其药学上可接受的盐或溶剂化物，其中：

虚线表示可选的连接喹啉环 C-3 与 C-4 的第二条键；

R^2 是卤、氰基、$-C(O)OR^{15}$ 或选自由 R^{12} 定义所提供的取代基的基团；

每个 R^3、R^4、R^5、R^6 和 R^7 独立地选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t(C_3-C_{10}$ 环烷基) 和 $-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基) 和 $-(CR^{13}R^{14})_t$(4-10 元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个 R^6 取代基取代；

R^8 是 H、$-OR^{12}$、$-OC(O)R^{12}$、$-NR^{12}R^{13}$、$-NR^{12}C(O)R^{13}$、氰基、$-C(O)OR^{13}$、$-SR^{12}$ 或 $-(CR^{13}R^{14})_t$(4-10 元杂环)，其中所述杂环 R^8 基团被 1 至 4 个 R^6 基团取代；

R^9 是 $-(CR^{13}R^{14})_t$(咪唑基) 或 $-(CR^{13}R^{14})_t$(吡啶基)，其中所述咪唑基或吡啶基部分被 1 或 2 个 R^6 取代基取代；

每个 R^{12} 独立地选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_t(C_3-C_{10}$ 环烷基)、

$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环)；所述环烷基、芳基和杂环$R^{12}$基团可选地与$C_6-C_{10}$芳基、$C_5-C_8$饱和环基或4-10元杂环基稠合；上述$R^{12}$取代基除H以外但包括任意可选的稠合环，都可选地被1至3个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6烷基和C_1-C_6烷氧基；

每个t独立地是0至5的整数；

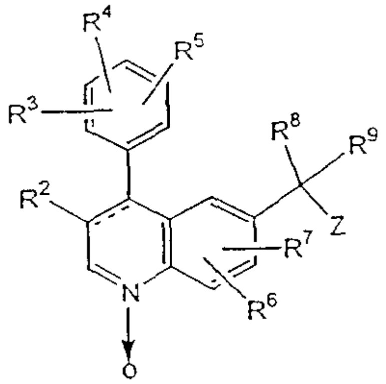
每个R^{13}和R^{14}独立地是H或C_1-C_6烷基，其中若t超过1，则$-(CR^{13}R^{14})_t$中每次重复定义的R^{13}和R^{14}是各自独立的；

R^{15}选自由R^{12}定义所提供的取代基，但是R^{15}不是H；

R^{16}选自由R^{12}定义所提供的取代基列表和$-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18}和R^{19}各自独立地选自由R^{12}定义所提供的取代基，但是至少R^{17}、R^{18}和R^{19}之一不是H。

11、下式化合物



6

或其药学上可接受的盐或溶剂化物，其中：

虚线表示可选的连接喹啉环C-3与C-4的第二条键；

R^2是卤、氰基、$-C(O)OR^{15}$或选自由R^{12}定义所提供的取代基的基团；

每个R^3、R^4、R^5、R^6和R^7独立地选自H、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中j是0至2的整数、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)、$-(CR^{13}R^{14})_t$(4-10元杂环)、$-(CR^{13}R^{14})_t(C_3-C_{10}$环烷基)和

$-(CR^{13}R^{14})_tC \equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、$-(CR^{13}R^{14})_t$(C_6-C_{10} 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个 R^6 取代基取代；

R^8 是 H、$-OR^{12}$、$-OC(O)R^{12}$、$-NR^{12}R^{13}$、$-NR^{12}C(O)R^{13}$、氰基、$-C(O)OR^{13}$、$-SR^{12}$ 或$-(CR^{13}R^{14})_t$(4-10 元杂环)，其中所述杂环 R^8 基团被 1 至 4 个 R^6 基团取代；

R^9 是$-(CR^{13}R^{14})_t$(咪唑基)或$-(CR^{13}R^{14})_t$(吡啶基)，其中所述咪唑基或吡啶基部分被 1 或 2 个 R^6 取代基取代；

每个 R^{12} 独立地选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_t$(C_3-C_{10} 环烷基)、$-(CR^{13}R^{14})_t$(C_6-C_{10} 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12} 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6 烷基和 C_1-C_6 烷氧基；

每个 t 独立地是 0 至 5 的整数；

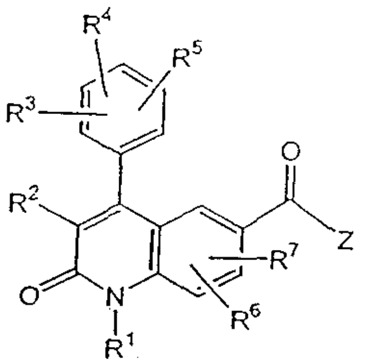
每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6 烷基，其中若 t 超过 1，则$-(CR^{13}R^{14})_t$ 中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和$-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H。

12、下式化合物



30

其中:

R^1选自H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_qC(O)R^{12}$、$-(CR^{13}R^{14})_qC(O)OR^{15}$、$-(CR^{13}R^{14})_qOR^{12}$、$-(CR^{13}R^{14})_qCSO_2R^{15}$、$-(CR^{13}R^{14})_t(C_3-C_{10}$环烷基)、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环),其中所述环烷基、芳基和杂环$R^1$基团可选地与$C_6$-$C_{10}$芳基、$C_5$-$C_8$饱和环基或4-10元杂环基稠合;上述$R^1$基团除H以外、但包括上述任意可选的稠合环,都可选地被1至4个R^6基团取代;

R^2是卤、氰基、$-C(O)OR^{15}$或选自由R^{12}定义所提供的取代基的基团;

每个R^3、R^4、R^5、R^6和R^7独立地选自H、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中j是0至2的整数、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)、$-(CR^{13}R^{14})_t$(4-10元杂环)、$-(CR^{13}R^{14})_t(C_3-C_{10}$环烷基)和$-(CR^{13}R^{14})_tC{\equiv}CR^{16}$;其中上述基团的环烷基、芳基和杂环部分可选地与$C_6$-$C_{10}$芳基、$C_5$-$C_8$饱和环基或4-10元杂环基稠合;所述烷基、烯基、环烷基、芳基和杂环基可选地被1至3个取代基取代,取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环);

Z是芳族4-10元杂环基,被1-4个R^6取代基取代;

每个R^{12}独立地选自H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_t(C_3-C_{10}$环烷基)、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环);所述环烷基、芳

基和杂环 R^{12} 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6 烷基和 C_1-C_6 烷氧基；

每个 t 独立地是 0 至 5 的整数，每个 q 独立地是 1 至 5 的整数；

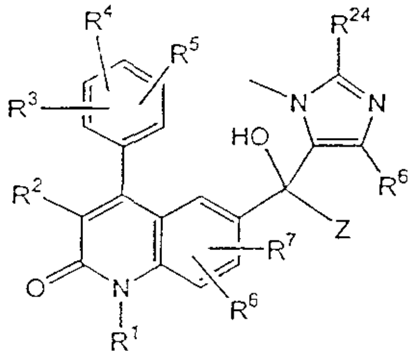
每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6 烷基，其中若 q 或 t 超过 1，则 $-(CR^{13}R^{14})_q$ 或 $-(CR^{13}R^{14})_t$ 中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和 $-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H。

13、下式化合物



26

其中：

R^{24} 选自 $-SR^{20}$ 和 $-SiR^{21}R^{22}R^{23}$，其中 R^{20} 选自 H 和苯基，R^{21}、R^{22} 和 R^{23} 独立地选自 C_1-C_6 烷基和苯基；

R^1 选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_qC(O)R^{12}$、$-(CR^{13}R^{14})_qC(O)OR^{15}$、$-(CR^{13}R^{14})_qOR^{12}$、$-(CR^{13}R^{14})_qCSO_2R^{15}$、$-(CR^{13}R^{14})_t(C_3$-$C_{10}$ 环烷基)、$-(CR^{13}R^{14})_t(C_6$-C_{10} 芳基) 和 $-(CR^{13}R^{14})_t$(4-10 元杂环)，其中所述环烷基、芳基和杂环 R^1 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^1 基团除 H 以外、但包括上述任意可选的稠合环，都可选地被 1 至 4 个 R^6 基团取代；

R^2 是卤、氰基、$-C(O)OR^{15}$ 或选自由 R^{12} 定义所提供的取代基的基团；

每个 R^3、R^4、R^5、R^6 和 R^7 独立地选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6$-C_{10} 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t(C_3$-C_{10} 环烷基)和 $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、$-(CR^{13}R^{14})_t(C_6$-C_{10} 芳基)和 $-(CR^{13}R^{14})_t$(4-10 元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个 R^6 取代基取代；

每个 R^{12} 独立地选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_t(C_3$-C_{10} 环烷基)、$-(CR^{13}R^{14})_t(C_6$-C_{10} 芳基)和 $-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12} 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6 烷基和 C_1-C_6 烷氧基；

每个 t 独立地是 0 至 5 的整数，每个 q 独立地是 1 至 5 的整数；

每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6 烷基，其中若 q 或 t 超过 1，则 $-(CR^{13}R^{14})_q$ 或 $-(CR^{13}R^{14})_t$ 中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和 $-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H。

14、抑制哺乳动物异常细胞生长的方法，该方法包括将抑制法呢基

蛋白转移酶有效量的权利要求 1、权利要求 7、权利要求 10 或权利要求 11 的化合物或其药学上可接受的盐或溶剂化物对所述哺乳动物给药。

15、抑制哺乳动物异常细胞生长的方法，该方法包括将抑制异常细胞生长有效量的权利要求 1、权利要求 7、权利要求 10 或权利要求 11 的化合物或其药学上可接受的盐或溶剂化物对所述哺乳动物给药。

16、抑制哺乳动物异常细胞生长的方法，该方法包括将治疗学上有效量的权利要求 1、权利要求 7、权利要求 10 或权利要求 11 的化合物或其药学上可接受的盐或溶剂化物与化学治疗剂结合对所述哺乳动物给药。

17、抑制哺乳动物异常细胞生长的药物组合物，该组合物包含抑制法呢基蛋白转移酶有效量的权利要求 1、权利要求 7、权利要求 10 或权利要求 11 的化合物或其药学上可接受的盐或溶剂化物和药学上可接受的载体。

18、抑制哺乳动物异常细胞生长的药物组合物，该组合物包含抑制异常细胞生长有效量的权利要求 1、权利要求 7、权利要求 10 或权利要求 11 的化合物或其药学上可接受的盐或溶剂化物和药学上可接受的载体。

19、抑制哺乳动物异常细胞生长的药物组合物，该组合物包含治疗学上有效量的权利要求 1、权利要求 7、权利要求 10 或权利要求 11 的化合物或其药学上可接受的盐或溶剂化物和药学上可接受的载体。

20、治疗哺乳动物疾病或状态的方法，该疾病或状态选自肺癌、NSCLC（非小细胞肺癌）、骨癌、胰腺癌、皮肤癌、头部与颈部癌症、皮肤或眼内黑素瘤、子宫癌、卵巢癌、直肠癌、肛门区癌症、胃癌、结肠癌、乳腺癌、妇科肿瘤（例如子宫肉瘤、输卵管癌、子宫内膜癌、宫颈癌、阴道癌或外阴癌）、何杰金氏病、食道癌、小肠癌、内分泌系统癌症（例如甲状腺癌、甲状旁腺癌或肾上腺癌）、软组织肉瘤、尿道癌、阴茎癌、前列腺癌、慢性或急性白血病、儿童期实体瘤、淋巴细胞淋巴瘤、膀胱癌、肾或输尿管癌症（例如肾细胞癌、肾盂癌）、儿科恶性肿

瘤、中枢神经系统肿瘤（例如原发性CNS淋巴瘤、脊椎轴肿瘤、脑干神经胶质瘤或垂体腺瘤）、巴雷特食道（恶化前综合征）、肿瘤形成性皮肤疾病、牛皮癣、蕈样真菌病、良性前列腺肥大、人乳头状瘤病毒(HPV)和再狭窄，该方法包括将抑制法呢基蛋白转移酶有效量的权利要求1、权利要求7、权利要求10或权利要求11的化合物对所述哺乳动物给药。

21、治疗哺乳动物疾病或状态的方法，该疾病或状态选自肺癌、NSCLC（非小细胞肺癌）、骨癌、胰腺癌、皮肤癌、头部与颈部癌症、皮肤或眼内黑素瘤、子宫癌、卵巢癌、直肠癌、肛门区癌症、胃癌、结肠癌、乳腺癌、妇科肿瘤（例如子宫肉瘤、输卵管癌、子宫内膜癌、宫颈癌、阴道癌或外阴癌）、何杰金氏病、食道癌、小肠癌、内分泌系统癌症（例如甲状腺癌、甲状旁腺癌或肾上腺癌）、软组织肉瘤、尿道癌、阴茎癌、前列腺癌、慢性或急性白血病、儿童期实体瘤、淋巴细胞淋巴瘤、膀胱癌、肾或输尿管癌症（例如肾细胞癌、肾盂癌）、儿科恶性肿瘤、中枢神经系统肿瘤（例如原发性CNS淋巴瘤、脊椎轴肿瘤、脑干神经胶质瘤或垂体腺瘤）、巴雷特食道（恶化前综合征）、肿瘤形成性皮肤疾病、牛皮癣、蕈样真菌病、良性前列腺肥大、人乳头状瘤病毒(HPV)和再狭窄，该方法包括将治疗所述疾病有效量的权利要求1、权利要求7、权利要求10或权利要求11的化合物对所述哺乳动物给药。

22、治疗哺乳动物疾病或状态的药物组合物，该疾病或状态选自肺癌、NSCLC（非小细胞肺癌）、骨癌、胰腺癌、皮肤癌、头部与颈部癌症、皮肤或眼内黑素瘤、子宫癌、卵巢癌、直肠癌、肛门区癌症、胃癌、结肠癌、乳腺癌、妇科肿瘤（例如子宫肉瘤、输卵管癌、子宫内膜癌、宫颈癌、阴道癌或外阴癌）、何杰金氏病、食道癌、小肠癌、内分泌系统癌症（例如甲状腺癌、甲状旁腺癌或肾上腺癌）、软组织肉瘤、尿道癌、阴茎癌、前列腺癌、慢性或急性白血病、儿童期实体瘤、淋巴细胞淋巴瘤、膀胱癌、肾或输尿管癌症（例如肾细胞癌、肾盂癌）、儿科恶性肿瘤、中枢神经系统肿瘤（例如原发性CNS淋巴瘤、脊椎轴肿瘤、脑干神经胶质瘤或垂体腺瘤）、巴雷特食道（恶化前综合征）、肿瘤形成性皮肤疾病、牛皮癣、蕈样真菌病、良性前列腺肥大、人乳头状瘤病毒

(HPV)和再狭窄，该组合物包含抑制法呢基蛋白转移酶有效量的权利要求1、权利要求7、权利要求10或权利要求11的化合物和药学上可接受的载体。

23、治疗哺乳动物疾病或状态的药物组合物，该疾病或状态选自肺癌、NSCLC（非小细胞肺癌）、骨癌、胰腺癌、皮肤癌、头部与颈部癌症、皮肤或眼内黑素瘤、子宫癌、卵巢癌、直肠癌、肛门区癌症、胃癌、结肠癌、乳腺癌、妇科肿瘤（例如子宫肉瘤、输卵管癌、子宫内膜癌、宫颈癌、阴道癌或外阴癌）、何杰金氏病、食道癌、小肠癌、内分泌系统癌症（例如甲状腺癌、甲状旁腺癌或肾上腺癌）、软组织肉瘤、尿道癌、阴茎癌、前列腺癌、慢性或急性白血病、儿童期实体瘤、淋巴细胞淋巴瘤、膀胱癌、肾或输尿管癌症（例如肾细胞癌、肾盂癌）、儿科恶性肿瘤、中枢神经系统肿瘤（例如原发性CNS淋巴瘤、脊椎轴肿瘤、脑干神经胶质瘤或垂体腺瘤）、巴雷特食道（恶化前综合征）、肿瘤形成性皮肤疾病、牛皮癣、蕈样真菌病、良性前列腺肥大、人乳头状瘤病毒(HPV)和再狭窄，该组合物包含治疗所述疾病有效量的权利要求1、权利要求7、权利要求10或权利要求11的化合物和药学上可接受的载体。

24、治疗哺乳动物异常细胞生长的方法，该方法包括将一定量的权利要求1、权利要求7、权利要求10或权利要求11的化合物和一定量的一种或多种选自MMP-2抑制剂、MMP-9抑制剂、信号转导抑制剂、抗增殖剂和能够阻滞CTLA4的药物的物质对哺乳动物给药，其中化合物与一种或多种所述物质的量的总和可有效治疗异常细胞生长。

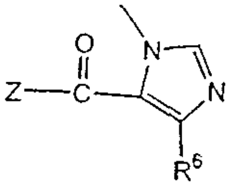
25、治疗哺乳动物异常细胞生长的药物组合物，该组合物包含一定量的权利要求1、权利要求7、权利要求10或权利要求11的化合物和一定量的一种或多种选自MMP-2抑制剂、MMP-9抑制剂、信号转导抑制剂、抗增殖剂和能够阻滞CTLA4的药物的物质，和药学上可接受的载体，其中化合物与一种或多种所述物质的量的总和可有效治疗异常细胞生长。

26、抑制哺乳动物异常细胞生长的方法，该方法包括将一定量的权利要求1、权利要求7、权利要求10或权利要求11的化合物与放射疗

法结合施用于哺乳动物，其中所述化合物的量与放射疗法结合能够有效抑制哺乳动物异常细胞生长。

27、致使哺乳动物异常细胞对放射疗法敏感的方法，该方法包括将致使异常细胞对放射治疗敏感有效量的权利要求 1、权利要求 6、权利要求 10 或权利要求 11 的化合物对哺乳动物给药。

28、合成下式化合物的方法，



11a

其中

R^6 选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t$(C_6-C_{10} 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t$(C_3-C_{10} 环烷基)和$-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、$-(CR^{13}R^{14})_t$(C_6-C_{10} 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个 R^6 取代基取代；

每个 R^{12} 独立地选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_t$(C_3-C_{10} 环烷基)、$-(CR^{13}R^{14})_t$(C_6-C_{10} 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12} 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、

三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6烷基和C_1-C_6烷氧基；

每个t独立地是0至5的整数；

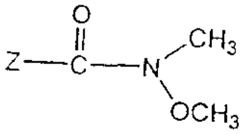
每个R^{13}和R^{14}独立地是H或C_1-C_6烷基，其中若t超过1，则$-(CR^{13}R^{14})_t$中每次重复定义的R^{13}和R^{14}是各自独立的；

R^{15}选自由R^{12}定义所提供的取代基，但是R^{15}不是H；

R^{16}选自由R^{12}定义所提供的取代基列表和$-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18}和R^{19}各自独立地选自由R^{12}定义所提供的取代基，但是至少R^{17}、R^{18}和R^{19}之一不是H；

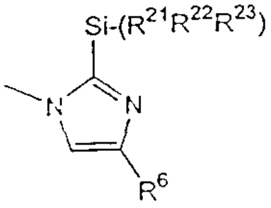
该方法包括在适当的溶剂中，在适合的碱的存在下，使下式化合物



28

其中Z是如上所定义的；

与下式化合物反应，

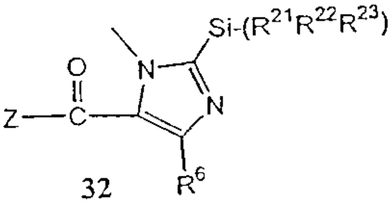


33

其中R^6是如上所定义的，

R^{21}、R^{22}和R^{23}各自独立地选自C_1-C_6烷基和苯基；

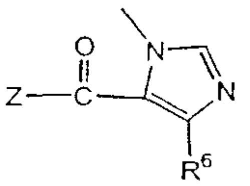
从而得到下式化合物



32

再在适当的溶剂中，使所得式32化合物与乙酸或氟化物试剂反应。

29、合成下式化合物的方法，



11a

其中

R^6选自H、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中j是0至2的整数、$-(CR^{13}R^{14})_t(C_6$-C_{10}芳基)、$-(CR^{13}R^{14})_t$(4-10元杂环)、$-(CR^{13}R^{14})_t(C_3$-C_{10}环烷基)和$-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与$C_6$-$C_{10}$芳基、$C_5$-$C_8$饱和环基或4-10元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被1至3个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、$-(CR^{13}R^{14})_t(C_6$-C_{10}芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环)；

Z是芳族4-10元杂环基，被1-4个R^6取代基取代；

每个R^{12}独立地选自H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_t(C_3$-C_{10}环烷基)、$-(CR^{13}R^{14})_t(C_6$-C_{10}芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环)；所述环烷基、芳基和杂环R^{12}基团可选地与C_6-C_{10}芳基、C_5-C_8饱和环基或4-10元杂环基稠合；上述R^{12}取代基除H以外但包括任意可选的稠合环，都可选地被1至3个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6烷基和C_1-C_6烷氧基；

每个t独立地是0至5的整数；

每个R^{13}和R^{14}独立地是H或C_1-C_6烷基，其中若t超过1，则$-(CR^{13}R^{14})_t$中每次重复定义的R^{13}和R^{14}是各自独立的；

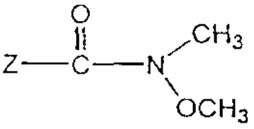
R^{15}选自由R^{12}定义所提供的取代基，但是R^{15}不是H；

R^{16}选自由R^{12}定义所提供的取代基列表和$-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18}和R^{19}各自独立地选自由R^{12}定义所提供的取代基，但是至

少 R^{17}、R^{18} 和 R^{19} 之一不是 H;

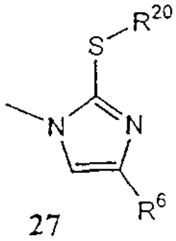
该方法包括在适当的溶剂中，在适合的碱的存在下，使下式化合物



28

其中 Z 是如上所定义的;

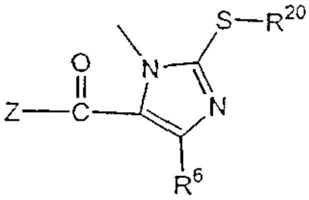
与下式化合物反应，



27

其中 R^6 是如上所定义的，R^{20} 选自 H 和苯基;

从而得到下式化合物



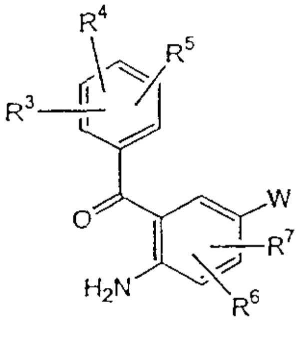
31

再从所得式 31 化合物中除去 $-SR^{20}$ 基团，方法是:

a) 用镍催化剂还原; 或者

b) 在乙酸中用硝酸或含水过氧化氢氧化。

30、合成下式化合物的方法，



23

其中

每个 R^3、R^4、R^5、R^6 和 R^7 独立地选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t(C_3-C_{10}$ 环烷基) 和 $-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基) 和 $-(CR^{13}R^{14})_t$(4-10 元杂环)；

每个 R^{12} 独立地选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_t(C_3-C_{10}$ 环烷基)、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基) 和 $-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12} 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6 烷基和 C_1-C_6 烷氧基；

每个 t 独立地是 0 至 5 的整数；

每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6 烷基，其中若 t 超过 1，则 $-(CR^{13}R^{14})_t$ 中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

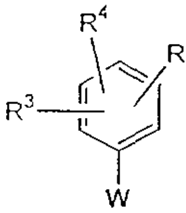
R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和 $-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H；

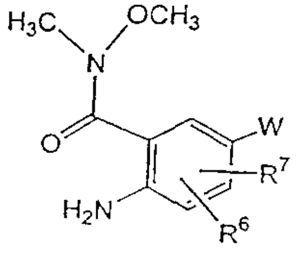
该方法包括在约-78℃至约 0℃的温度下，在适合的碱的存在下，

在适当的溶剂中，使下式化合物



34

其中 W 是适当的离去基团，R^3、R^4 和 R^5 是如上所定义的，
与下式化合物反应，

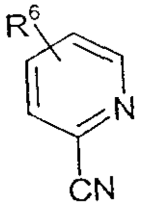


35

其中 R^6 和 R^7 是如上所定义的。

31、根据权利要求 30 的方法，其中该适当的溶剂是乙醚。

32、合成下式化合物的方法，



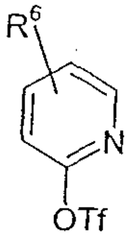
37

其中 R^6 选自 H、C_1–C_{10} 烷基、C_2–C_{10} 烯基、C_2–C_{10} 炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6$–C_{10} 芳基)、$-(CR^{13}R^{14})_t$(4–10 元杂环)、$-(CR^{13}R^{14})_t(C_3$–C_{10} 环烷基) 和 $-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6–C_{10} 芳基、C_5–C_8 饱和环基或 4–10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲

氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；

该方法包括

a)在钯催化剂的存在下，在适当的溶剂中，在约 25℃至约 100℃的温度下，使金属氰化物与下式化合物反应，



36

其中 Tf 是$-SO_2-CF_3$，R^6是如上所定义的；

从而得到式 37 化合物。

说　明　书

可用作抗癌剂的杂芳基取代的喹啉-2-酮衍生物

发明背景

本发明涉及一系列杂芳基取代的喹啉-2-酮衍生物，它们可用于哺乳动物过度增殖性疾病的治疗，例如癌症。

本发明还涉及在哺乳动物、尤其是人过度增殖性疾病的治疗中使用该化合物的方法和含有该化合物的药物组合物。

致癌基因经常编码刺激细胞生长和致有丝分裂的信号转导途径的蛋白质组分。致癌基因在培养细胞内的表达引起细胞转化，以细胞在软琼脂中生长的能力和形成致密转化灶的细胞生长为特征，该转化灶缺乏由非转化细胞所表现的接触抑制。某些致癌基因的突变和/或过度表达经常与人的癌症有关。

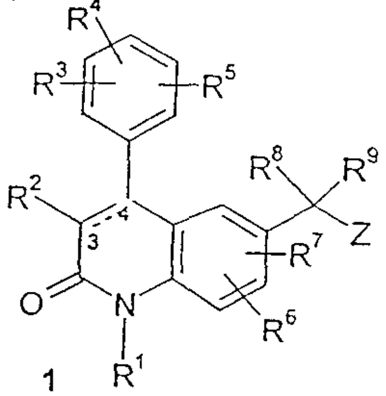
为了获得转化的可能性，Ras 致癌基因蛋白的前体必须经历位于羧基末端四肽中的半胱氨酸残基的法呢基化作用。因此已经提出催化这种修饰作用的酶、即法呢基蛋白转移酶的抑制剂作为对抗其中 Ras 有助于转化的肿瘤的药物。突变后的 Ras 致癌形式常见于多种人的癌症，最显著地见于 50%以上结肠和胰腺癌 (Kohl 等《科学》(Science), Vol. 260, 1834-1837, 1993)。本发明化合物表现作为法呢基蛋白转移酶抑制剂的活性，因此据信可用作抗癌与抗肿瘤剂。进一步地，本发明化合物可能对任何依靠法呢基蛋白转移酶增殖的肿瘤都有活性。

其他据称具有抑制法呢基蛋白转移酶活性的化合物参见国际申请公报 WO 97/21701，发明名称为“法呢基蛋白转移酶抑制性(咪唑-5-基)甲基-2-喹啉酮衍生物”，国际公开日为 1997 年 6 月 19 日；国际申请公报 WO 97/16443，发明名称为“法呢基转移酶抑制性 2-喹啉酮衍生物”，国际公开日为 1997 年 5 月 9 日；PCT/IB99/01393，于 1999 年 8 月 5 日提交，发明名称为“可用作抗癌剂的 2-喹啉酮衍生物”；和 PCT/IB99/01398，于 1999 年 8 月 6 日提交，发明名称为“可用作抗癌剂的炔基取代的喹啉-2-酮衍生物”；所有这些均全文结合在此作为参考。

前述 Kohl 等文献以及本申请下文所讨论的参考文献也全文结合在此作为参考。

发明概述

本发明涉及式 1 化合物



1

或其药学上可接受的盐或溶剂化物，其中：

虚线表示可选的连接喹啉-2-酮环 C-3 与 C-4 的第二条键；

R^1 选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_qC(O)R^{12}$、$-(CR^{13}R^{14})_qC(O)OR^{15}$、$-(CR^{13}R^{14})_qOR^{12}$、$-(CR^{13}R^{14})_qCSO_2R^{15}$、$-(CR^{13}R^{14})_t(C_3$-$C_{10}$ 环烷基）、$-(CR^{13}R^{14})_t(C_6$-C_{10} 芳基）和 $-(CR^{13}R^{14})_t$(4-10 元杂环)，其中所述环烷基、芳基和杂环 R^1 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^1 基团除 H 以外、但包括上述任意可选的稠合环，都可选地被 1 至 4 个 R^6 基团取代；

R^2 是卤、氰基、$-C(O)OR^{15}$ 或选自由 R^{12} 定义所提供的取代基的基团；

每个 R^3、R^4、R^5、R^6 和 R^7 独立地选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6$-C_{10} 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环）、$-(CR^{13}R^{14})_t(C_3$-C_{10} 环烷基）和 $-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选

自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个 R^6 取代基取代；

R^8 是 H、$-OR^{12}$、$-OC(O)R^{12}$、$-NR^{12}R^{13}$、$-N=CR^{12}R^{13}$、$-NR^{12}C(O)R^{13}$、氰基、$-C(O)OR^{13}$、$-SR^{12}$ 或$-(CR^{13}R^{14})_t$(4-10 元杂环)，其中所述杂环 R^8 基团被 1 至 4 个 R^6 基团取代；

R^9 是$-(CR^{13}R^{14})_t$(咪唑基)或$-(CR^{13}R^{14})_t$(吡啶基)，其中所述咪唑基或吡啶基部分被 1 或 2 个 R^6 取代基取代；

每个 R^{12} 独立地选自 H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_t(C_3-C_{10}$环烷基)、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12} 基团可选地与 C_6-C_{10}芳基、C_5-C_8饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6烷基和 C_1-C_6烷氧基；

每个 t 独立地是 0 至 5 的整数，每个 q 独立地是 1 至 5 的整数；

每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6烷基，其中若 q 或 t 超过 1，则$-(CR^{13}R^{14})_q$或$-(CR^{13}R^{14})_t$中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和$-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H。

优选的式 1 化合物是其中 Z 是被 1 至 4 个 R^6 取代基取代的 5 或 6 元芳族杂环基的那些。更优选的式 1 化合物是其中 Z 是被 1 至 4 个 R^6 取代基取代的吡啶或噻吩基的那些。其他优选的式 1 化合物是其中 Z 是被 1 至 4 个 R^6 取代基取代的与苯基稠合的 5 或 6 元芳族杂环基的那些。优选地，Z 包含 1 至 3 个选自 O、S 和 N 的杂原子。

其他优选的式 1 化合物是其中 R^1 是 H、C_1-C_6 烷基或环丙基甲基的那些。

其他优选的式 1 化合物是其中 R^8 是被 1 至 4 个 R^6 基团取代的 $-NR^{12}R^{13}$、$-OR^{12}$ 或 $-(CR^{13}R^{14})_t$(4-10 元杂环)的那些，其中所述 4-10 元杂环选自三唑基、咪唑基、吡唑基和哌啶基。更优选地，所述杂环被一个 R^6 基团取代。优选地，R^8 是羟基、氨基或三唑基。

其他优选的式 1 化合物是其中 R^8 是 H、$-OR^{12}$、$-OC(O)R^{12}$、$-NR^{12}R^{13}$、$-NR^{12}C(O)R^{13}$、氰基、$-C(O)OR^{13}$、$-SR^{12}$ 或 $-(CR^{13}R^{14})_t$(4-10 元杂环)的那些，其中所述杂环 R^8 基团被 1 至 4 个 R^6 基团取代。

其他优选的式 1 化合物是其中 R^3、R^4、R^5 和 R^6 独立地选自 H、卤和 C_1-C_6 烷氧基的那些。

优选的本发明化合物包括:

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-甲基-1H-喹啉-2-酮(对映异构体 A);

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-甲基-1H-喹啉-2-酮(对映异构体 B);

4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)甲基]-1-环丙基甲基-1H-喹啉-2-酮;

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-环丙基甲基-1H-喹啉-2-酮;

4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-羟基-(3-甲基-3H-咪唑-4-基)甲基]-1-甲基-1H-喹啉-2-酮;

6-[氨基-(5-氯-吡啶-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-甲基-1H-喹啉-2-酮;

6-[氨基-(5-氯-吡啶-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-环丙基甲基-1H-喹啉-2-酮;

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3,5-二氯苯基)-1-甲基-1H-喹啉-2-酮;

6-[氨基-(5-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲

基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮;

6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1-甲基-1H-喹啉-2-酮;

氨基-(5-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基苯基)-1-甲基-1H-喹啉-2-酮;

6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基苯基)-1-甲基-1H-喹啉-2-酮;

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基苯基)-1-甲基-1H-喹啉-2-酮;

6-[苯并[b]噻吩-2-基-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮;

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1H-喹啉-2-酮;

(-)-6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-环丙基甲基-1H-喹啉-2-酮;

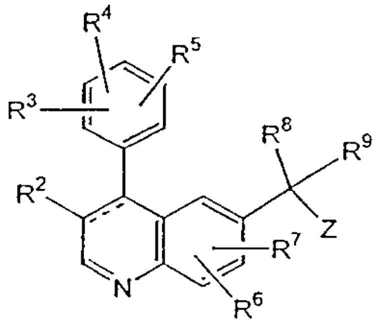
6-[氨基-(6-甲基-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯苯基)-1-甲基-1H-喹啉-2-酮;

6-[氨基-(吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮;

(+)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)甲基]-1-环丙基甲基-1H-喹啉-2-酮; 和

上述化合物的药学上可接受的盐和溶剂化物。

本发明还涉及式 12 化合物



12

其中：

虚线表示可选的连接喹啉环 C-3 与 C-4 的第二条键；

R^2是卤、氰基、$-C(O)OR^{15}$或选自由R^{12}定义所提供的取代基的基团；

每个R^3、R^4、R^5、R^6和R^7独立地选自 H、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t(C_3-C_{10}$环烷基)和$-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与$C_6-C_{10}$芳基、$C_5-C_8$饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个R^6取代基取代；

R^8是 H、$-OR^{12}$、$-OC(O)R^{12}$、$-NR^{12}R^{13}$、$-NR^{12}C(O)R^{13}$、氰基、$-C(O)OR^{13}$、$-SR^{12}$或$-(CR^{13}R^{14})_t$(4-10 元杂环)，其中所述杂环R^8基团被 1 至 4 个R^6基团取代；

R^9是$-(CR^{13}R^{14})_t$(咪唑基)或$-(CR^{13}R^{14})_t$(吡啶基)，其中所述咪唑基或吡啶基部分被 1 或 2 个R^6取代基取代；

每个R^{12}独立地选自 H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_t(C_3-C_{10}$环烷基)、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环$R^{12}$基团可选地与$C_6-C_{10}$芳基、$C_5-C_8$饱和环基或 4-10 元杂环基稠合；上述$R^{12}$取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6烷基和C_1-C_6烷氧基；

每个 t 独立地是 0 至 5 的整数；

每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6 烷基，其中若 t 超过 1，则 $-(CR^{13}R^{14})_t$ 中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

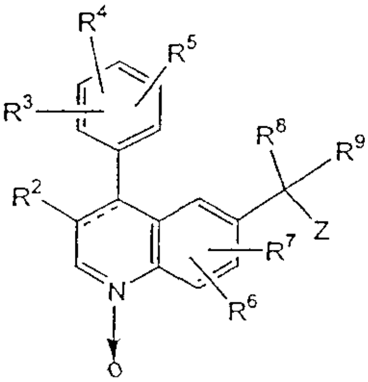
R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和 $-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H。

式 12 化合物是可用于制备式 1 化合物的中间体。式 12 化合物也是式 1 化合物的药物前体，本发明还包括式 12 化合物的药学上可接受的盐和溶剂化物。

本发明还涉及式 6 化合物



6

其中：

虚线表示可选的连接喹啉环 C-3 与 C-4 的第二条键；

R^2 是卤、氰基、$-C(O)OR^{15}$ 或选自由 R^{12} 定义所提供的取代基的基团；

每个 R^3、R^4、R^5、R^6 和 R^7 独立地选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6$-C_{10} 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t(C_3$-C_{10} 环烷基) 和 $-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选

自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个 R^6 取代基取代；

R^8 是 H、$-OR^{12}$、$-OC(O)R^{12}$、$-NR^{12}R^{13}$、$-NR^{12}C(O)R^{13}$、氰基、$-C(O)OR^{13}$、$-SR^{12}$ 或$-(CR^{13}R^{14})_t$(4-10 元杂环)，其中所述杂环 R^8 基团被 1 至 4 个 R^6 基团取代；

R^9 是$-(CR^{13}R^{14})_t$(咪唑基)或$-(CR^{13}R^{14})_t$(吡啶基)，其中所述咪唑基或吡啶基部分被 1 或 2 个 R^6 取代基取代；

每个 R^{12} 独立地选自 H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_t(C_3-C_{10}$环烷基)、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12} 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6烷基和 C_1-C_6烷氧基；

每个 t 独立地是 0 至 5 的整数；

每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6烷基，其中若 t 超过 1，则$-(CR^{13}R^{14})_t$中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

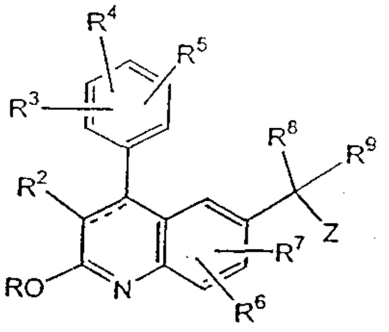
R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和$-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H。

式 6 化合物是可用于制备式 1 化合物的中间体。式 6 化合物也是式 1 化合物的药物前体，本发明还包括式 6 化合物的药学上可接受的盐和溶剂化物。

本发明还涉及式 2 化合物



2

其中:

虚线表示可选的连接喹啉环 C-3 与 C-4 的第二条键;

R 是 C_1-C_6烷基;

R^2是卤、氰基、$-C(O)OR^{15}$或选自由 R^{12}定义所提供的取代基的基团;

每个 R^3、R^4、R^5、R^6和 R^7独立地选自 H、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t(C_3-C_{10}$环烷基)和$-(CR^{13}R^{14})_tC\equiv CR^{16}$;其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10}芳基、C_5-C_8饱和环基或 4-10 元杂环基稠合;所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代,取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、$-(CR^{13}R^{14})_t(C_6-C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环);

Z 是芳族 4-10 元杂环基,被 1-4 个 R^6取代基取代;

R^8是 H、$-OR^{12}$、$-OC(O)R^{12}$、$-NR^{12}R^{13}$、$-NR^{12}C(O)R^{13}$、氰基、$-C(O)OR^{13}$、$-SR^{12}$或$-(CR^{13}R^{14})_t$(4-10 元杂环),其中所述杂环 R^8基团被 1 至 4 个 R^6基团取代;

R^9是$-(CR^{13}R^{14})_t$(咪唑基)或$-(CR^{13}R^{14})_t$(吡啶基),其中所述咪唑基或吡啶基部分被 1 或 2 个 R^6取代基取代;

每个 R^{12} 独立地选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_t(C_3-C_{10}$ 环烷基)、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)和 $-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12} 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6 烷基和 C_1-C_6 烷氧基；

每个 t 独立地是 0 至 5 的整数；

每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6 烷基，其中若 t 超过 1，则 $-(CR^{13}R^{14})_t$ 中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和 $-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H。

式 2 化合物是可用于制备式 1 化合物的中间体。式 2 化合物也是式 1 化合物的药物前体，本发明还包括式 2 化合物的药学上可接受的盐和溶剂化物。

本发明还涉及抑制包括人在内的哺乳动物异常细胞生长的方法，该方法包括将抑制法呢基蛋白转移酶有效量的如上所定义的式 1、2、12 或 6 化合物或其药学上可接受的盐或溶剂化物对所述哺乳动物给药。

本发明还涉及抑制包括人在内的哺乳动物异常细胞生长的方法，该方法包括将抑制异常细胞生长有效量的如上所定义的式 1、2、12 或 6 化合物或其药学上可接受的盐或溶剂化物对所述哺乳动物给药。

本发明还涉及哺乳动物异常细胞生长的抑制方法，该方法包括将治疗学上有效量的式 1、2、12 或 6 化合物或其药学上可接受的盐或溶剂化物与化学治疗剂结合对所述哺乳动物给药。在一种实施方式中，该化学治疗剂选自由有丝分裂抑制剂、烷基化剂、抗代谢剂、嵌入抗生素、生长因子抑制剂、细胞周期抑制剂、酶、拓扑异构酶抑制剂、生物反应调节剂、抗激素和抗雄激素组成的组。

本发明进一步涉及抑制哺乳动物异常细胞生长的方法，该方法包括将一定量式 1、2、12 或 6 化合物或其药学上可接受的盐或溶剂化物与放射疗法结合施用于哺乳动物，其中的式 1、2、12 或 6 化合物、盐或溶剂化物的量与放射疗法结合在抑制哺乳动物异常细胞生长中是有效的。施用放射疗法的工艺是本领域已知的，这些工艺可以用在本文所述的联合疗法中。在这种联合疗法中，本发明化合物的给药可以根据本文所述加以决定。

据信式 1、2、12 或 6 化合物能够使异常细胞对放射治疗更敏感，放射治疗的目的是杀死和/或抑制这类细胞的生长。因此，本发明进一步涉及致使哺乳动物异常细胞对放射治疗敏感的方法，该方法包括将一定量式 1、2、12 或 6 化合物或其药学上可接受的盐或溶剂化物对哺乳动物给药，该量在致使异常细胞对放射治疗敏感中是有效的。该方法中化合物、盐或溶剂化物的量可以根据本文所述确定该化合物有效量的手段加以决定。

本发明还涉及用于抑制包括人在内的哺乳动物异常细胞生长的药物组合物，其中包含抑制法呢基蛋白转移酶有效量的如上所定义的式 1、2、12 或 6 化合物或其盐或溶剂化物，和药学上可接受的载体。

本发明还涉及用于抑制包括人在内的哺乳动物异常细胞生长的药物组合物，其中包含抑制细胞生长有效量的如上所定义的式 1、2、12 或 6 化合物或其盐或溶剂化物，和药学上可接受的载体。

本发明还涉及用于抑制包括人在内的哺乳动物异常细胞生长的药物组合物，其中包含治疗学上有效量的式 1、2、12 或 6 化合物或其药学上可接受的盐或溶剂化物与化学治疗剂的组合，和药学上可接受的载体。在一种实施方式中，该化学治疗剂选自由有丝分裂抑制剂、烷基化剂、抗代谢剂、嵌入抗生素、生长因子抑制剂、细胞周期抑制剂、酶、拓扑异构酶抑制剂、生物反应调节剂、抗激素和抗雄激素组成的组。

本发明还涉及用于治疗哺乳动物疾病或状态的方法和药物组合物，该疾病或状态选自肺癌、NSCLC（非小细胞肺癌）、骨癌、胰腺癌、皮肤癌、头部与颈部癌症、皮肤或眼内黑素瘤、子宫癌、卵巢癌、直肠癌、

肛门区癌症、胃癌、结肠癌、乳腺癌、妇科肿瘤（例如子宫肉瘤、输卵管癌、子宫内膜癌、宫颈癌、阴道癌或外阴癌）、何杰金氏病、食道癌、小肠癌、内分泌系统癌症（例如甲状腺癌、甲状旁腺癌或肾上腺癌）、软组织肉瘤、尿道癌、阴茎癌、前列腺癌、慢性或急性白血病、儿童期实体瘤、淋巴细胞淋巴瘤、膀胱癌、肾或输尿管癌症（例如肾细胞癌、肾盂癌）、儿科恶性肿瘤、中枢神经系统肿瘤（例如原发性CNS淋巴瘤、脊椎轴肿瘤、脑干神经胶质瘤或垂体腺瘤）、巴雷特食道（恶化前综合征）、肿瘤形成性皮肤疾病、牛皮癣、蕈样真菌病、良性前列腺肥大、人乳头状瘤病毒(HPV)和再狭窄，该组合物包含抑制法呢基蛋白转移酶有效量的式1、2、12或6化合物或该化合物的药学上可接受的盐或溶剂化物。

本发明还涉及用于治疗哺乳动物疾病或状态的方法和药物组合物，该疾病或状态选自肺癌、NSCLC（非小细胞肺癌）、骨癌、胰腺癌、皮肤癌、头部与颈部癌症、皮肤或眼内黑素瘤、子宫癌、卵巢癌、直肠癌、肛门区癌症、胃癌、结肠癌、乳腺癌、妇科肿瘤（例如子宫肉瘤、输卵管癌、子宫内膜癌、宫颈癌、阴道癌或外阴癌）、何杰金氏病、食道癌、小肠癌、内分泌系统癌症（例如甲状腺癌、甲状旁腺癌或肾上腺癌）、软组织肉瘤、尿道癌、阴茎癌、前列腺癌、慢性或急性白血病、儿童期实体瘤、淋巴细胞淋巴瘤、膀胱癌、肾或输尿管癌症（例如肾细胞癌、肾盂癌）、儿科恶性肿瘤、中枢神经系统肿瘤（例如原发性CNS淋巴瘤、脊椎轴肿瘤、脑干神经胶质瘤或垂体腺瘤）、巴雷特食道（恶化前综合征）、肿瘤形成性皮肤疾病、牛皮癣、蕈样真菌病、良性前列腺肥大、人乳头状瘤病毒(HPV)和再狭窄，该组合物包含治疗所述疾病有效量的式1、2、12或6化合物或该化合物的药学上可接受的盐或溶剂化物。

本发明还涉及用于抑制哺乳动物异常细胞生长的方法和药物组合物，该组合物包含一定量的式1、2、12或6化合物或其药学上可接受的盐或溶剂化物和一定量的一种或多种选自抗血管生成剂、信号转导抑制剂和抗增殖剂的物质，所述量的总和能够有效抑制异常细胞生长。

抗血管生成剂可以与式1、2、12或6化合物结合用在本文所述的

方法和药物组合物中，例如MMP-2(基质-金属蛋白酶2)抑制剂、MMP-9(基质-金属蛋白酶9)抑制剂和COX-II(环加氧酶II)抑制剂。有用的COX-II抑制剂的实例包括CELEBREX™(alecoxib)、valdecoxib和rofecoxib。有用的基质-金属蛋白酶抑制剂描述在WO 96/33172(1996年10月24日公开)、WO 96/27583(1996年3月7日公开)、欧洲专利申请No. 97304971.1(1997年7月8日提交)、欧洲专利申请No. 99308617.2(1999年10月29日提交)、WO 98/07697(1998年2月26日公开)、WO 98/03516(1998年1月29日公开)、WO 98/34918(1998年8月13日公开)、WO 98/34915(1998年8月13日公开)、WO 98/33768(1998年8月6日公开)、WO 98/30566(1998年7月16日公开)、欧洲专利申请606,046(1994年7月13日公开)、欧洲专利申请931,788(1999年7月28日公开)、WO 90/05719(1990年5月31日公开)、WO 99/52910(1999年10月21日公开)、WO 99/52889(1999年10月21日公开)、WO 99/29667(1999年6月17日公开)、PCT国际申请No. PCT/IB98/01113(1998年7月21日提交)、欧洲专利申请No. 99302232.1(1999年3月25日提交)、英国专利申请9912961.1(1999年6月3日提交)、美国临时申请No. 60/148,464(1999年8月12日提交)、美国专利5,863,949(1999年1月26日颁布)、美国专利5,861,510(1999年1月19日颁布)和欧洲专利申请780,386(1997年6月25日公开)，所有这些均全文结合在此作为参考。优选的MMP-2和MMP-9抑制剂是几乎没有或没有抑制MMP-1活性的那些。更优选地，是相对于其他基质-金属蛋白酶(即MMP-1、MMP-3、MMP-4、MMP-5、MMP-6、MMP-7、MMP-8、MMP-10、MMP-11、MMP-12和MMP-13)而言选择性地抑制MMP-2和/或MMP-9的那些。

可用于本发明的MMP抑制剂的一些具体实例是AG-3340、RO 32-3555、RS 13-0830和下列化合物:

3-[[4-(4-氟-苯氧基)-苯磺酰]-(1-羟基氨基甲酰基-环戊基)氨基]-丙酸;

3-外-3-[4-(4-氟-苯氧基)-苯磺酰氨基]-8-氧杂-二环并[3.2.1]辛烷-3-羧酸羟基酰胺;

(2R,3R)1-[4-(2-氯-4-氟-苄氧基)-苯磺酰]-3-羟基-3-甲基-哌啶-2-羧酸羟基酰胺;

4-[4-(4-氟-苯氧基)-苯磺酰氨基]-四氢-吡喃-4-羧酸羟基酰胺;

3-[[4-(4-氟-苯氧基)-苯磺酰]-(1-羟基氨基甲酰基-环丁基)-氨基]-丙酸;

4-[4-(4-氯-苯氧基)-苯磺酰氨基]-四氢-吡喃-4-羧酸羟基酰胺;

(R)3-[4-(4-氯-苯氧基)-苯磺酰氨基]-四氢-吡喃-3-羧酸羟基酰胺;

(2R,3R)1-[4-(4-氟-2-甲基-苄氧基)-苯磺酰]-3-羟基-3-甲基-哌啶-2-羧酸羟基酰胺;

3-[[4-(4-氟-苯氧基)-苯磺酰]-(1-羟基氨基甲酰基-1-甲基-乙基)氨基]-丙酸;

3-[[4-(4-氟-苯氧基)-苯磺酰]-(4-羟基氨基甲酰基-四氢-吡喃-4-基)-氨基]-丙酸;

3-外-3-[4-(4-氯-苯氧基)-苯磺酰氨基]-8-氧杂-二环并[3.2.1]辛烷-3-羧酸羟基酰胺;

3-内-3-[4-(4-氟-苯氧基)-苯磺酰氨基]-8-氧杂-二环并[3.2.1]辛烷-3-羧酸羟基酰胺; 和

(R)3-[4-(4-氟-苯氧基)-苯磺酰氨基]-四氢-呋喃-3-羧酸羟基酰胺;

和所述化合物的药学上可接受的盐和溶剂化物。

其他抗血管生成剂、包括其他COX-II抑制剂和其他MMP抑制剂,也可以用在本发明中。

式1、2、12或6化合物也可以与下列药物合用:信号转导抑制剂,例如能够抑制EGFR(表皮生长因子受体)反应的药物,例如EGFR抗体、EGF抗体和EGFR抑制剂;VEGF(血管内皮生长因子)抑制剂;和erbB2受体抑制剂,例如与erbB2受体结合的有机分子或抗体,例如

HERCEPTIN™ (Genentech, Inc. of South San Francisco, California, USA)。

EGFR抑制剂例如描述在WO 95/19970（1995年7月27日公开）、WO 98/14451（1998年4月9日公开）、WO 98/02434（1998年1月22日公开）和美国专利5,747,498（1998年5月5日颁布），这些物质可以用在本文所述的本发明中。EGFR-抑制剂包括但不限于单克隆抗体C225和抗-EGFR 22Mab (ImClone Systems Incorporated of New York, New York, USA)、化合物ZD-1839 (AstraZeneca)、BIBX-1382 (Boehringer Ingelheim)、MDX-447 (Medarex Inc. of Annandale, New Jersey, USA)、OLX-103 (Merck & Co. of Whitehouse Station, New Jersey, USA)、VRCTC-310 (Ventech Research)和EGF融合毒素(Seragen Inc. of Hopkinton, Massachusettes)。这些和其他EGFR-抑制剂可以用在本发明中。

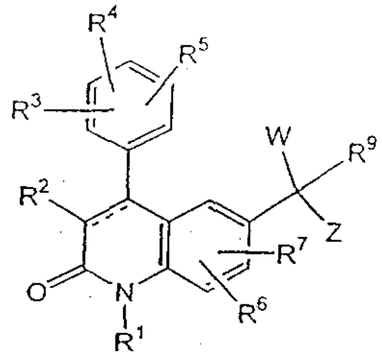
VEGF抑制剂、例如SU-5416和SU-6668 (Sugen Inc. of South San Francisco, California, USA)，也可以与式1、2、12或6化合物结合。VEGF抑制剂例如描述在WO 99/24440（1999年5月20日公开）、PCT国际申请PCT/IB99/00797（1999年5月3日提交）、WO 95/21613（1995年8月17日公开）、WO 99/61422（1999年12月2日公开）、美国专利5,834,504（1998年11月10日颁布）、WO 98/50356（1998年11月12日公开）、美国专利5,883,113（1999年3月16日颁布）、美国专利5,886,020（1999年3月23日颁布）、美国专利5,792,783（1998年8月11日颁布）、WO 99/10349（1999年3月4日公开）、WO 97/32856（1997年9月12日公开）、WO 97/22596（1997年6月26日公开）、WO 98/54093（1998年12月3日公开）、WO 98/02438（1998年1月22日公开）、WO 99/16755（1999年4月8日公开）和WO 98/02437（1998年1月22日公开），所有这些均全文结合在此作为参考。其他一些可用于本发明的具体VEGF抑制剂实例是IM862 (Cytran Inc. of Kirkland, Washington, USA); Genentech, Inc. of South San Francisco的抗VEGF单克隆抗体;

和血管酶，即来自 Ribozyme (Boulder, Colorado)和 Chiron (Emeryville, California)的合成核酶。这些和其他 VEGF 抑制剂可以用在本文所述的本发明中。

此外，erbB2 受体抑制剂、例如 GW-282974 (Glaxo Wellcome plc) 和单克隆抗体 AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Texas, USA)与 2B-1 (Chiron)，也可以与式 1、2、12 或 6 化合物结合，例如描述在 WO 98/02434（1998 年 1 月 22 日公开）、WO 99/35146（1999 年 7 月 15 日公开）、WO 99/35132（1999 年 7 月 15 日公开）、WO 98/02437（1998 年 1 月 22 日公开）、WO 97/13760（1997 年 4 月 17 日公开）、WO 95/19970（1995 年 7 月 27 日公开）、美国专利 5,587,458（1996 年 12 月 24 日颁布）和美国专利 5,877,305（1999 年 3 月 2 日颁布），所有这些均全文结合在此作为参考。可用于本发明的 erbB2 受体抑制剂还描述在 1999 年 1 月 27 日提交的美国临时申请 No. 60/117,341 和 1999 年 1 月 27 日提交的美国临时申请 No. 60/117,346，二者全文结合在此作为参考。按照本发明，描述在上述 PCT 申请、美国专利和美国临时申请中的 erbB2 受体抑制剂化合物与物质以及其他抑制 erbB2 受体的化合物与物质都可以与式 1、2、12 或 6 化合物合用。

式 1、2、12 或 6 化合物还可以与其他治疗异常细胞生长或癌症的药物合用，后者包括但不限于能够增强抗肿瘤免疫应答的药物，例如 CTLA4（细胞毒性淋巴细胞抗原 4）抗体，和其他能够阻滞 CTLA4 的药物；和抗增殖剂，例如其他法呢基蛋白转移酶抑制剂，例如描述在上文“背景”部分所引用的参考文献中的法呢基蛋白转移酶抑制剂。可以用在本发明中的具体 CTLA4 抗体包括描述在美国临时申请 60/113,647（1998 年 12 月 23 日提交）中的那些，其全文引用在此作为参考，不过其他 CTLA4 抗体也可以用在本发明中。

本发明还涉及式 13 化合物



13

其中:

虚线表示可选的连接喹啉-2-酮环 C-3 与 C-4 的第二条键;

W 选自氟、氯、溴和碘;

R^1 选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_qC(O)R^{12}$、$-(CR^{13}R^{14})_qC(O)OR^{15}$、$-(CR^{13}R^{14})_qOR^{12}$、$-(CR^{13}R^{14})_qCSO_2R^{15}$、$-(CR^{13}R^{14})_t$($C_3$-$C_{10}$ 环烷基)、$-(CR^{13}R^{14})_t$(C_6-C_{10} 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环),其中所述环烷基、芳基和杂环 R^1 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合;上述 R^1 基团除 H 以外、但包括上述任意可选的稠合环,都可选地被 1 至 4 个 R^6 基团取代;

R^2 是卤、氰基、$-C(O)OR^{15}$ 或选自由 R^{12} 定义所提供的取代基的基团;

每个 R^3、R^4、R^5、R^6 和 R^7 独立地选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t$(C_6-C_{10} 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t$(C_3-C_{10} 环烷基)和 $-(CR^{13}R^{14})_tC{\equiv}CR^{16}$;其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合;所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代,取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、$-(CR^{13}R^{14})_t$(C_6-C_{10} 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环);

Z 是芳族 4-10 元杂环基，被 1-4 个 R^6 取代基取代；

R^9 是 $-(CR^{13}R^{14})_t$（咪唑基）或 $-(CR^{13}R^{14})_t$（吡啶基），其中所述咪唑基或吡啶基部分被 1 或 2 个 R^6 取代基取代；

每个 R^{12} 独立地选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_t(C_3-C_{10}$ 环烷基)、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)和 $-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12} 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6 烷基和 C_1-C_6 烷氧基；

每个 t 独立地是 0 至 5 的整数，每个 q 独立地是 1 至 5 的整数；

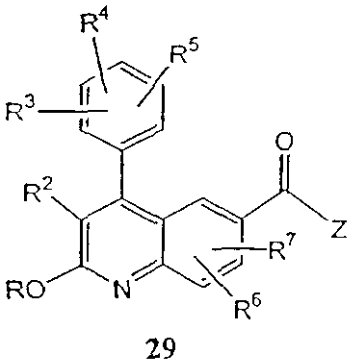
每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6 烷基，其中若 q 或 t 超过 1，则 $-(CR^{13}R^{14})_q$ 或 $-(CR^{13}R^{14})_t$ 中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和 $-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H。式 13 化合物是可用于制备式 1 化合物的中间体。

本发明还涉及式 29 化合物



29

其中：

R 是 C_1-C_6 烷基；

R^2 是卤、氰基、$-C(O)OR^{15}$ 或选自由 R^{12} 定义所提供的取代基的基团；

每个 R^3、R^4、R^5、R^6 和 R^7 独立地选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、

C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、-OR^{12}、-C(O)R^{12}、-C(O)OR^{12}、-NR^{13}C(O)OR^{15}、-OC(O)R^{12}、-NR^{13}SO$_2$R^{15}、-SO$_2$NR^{12}R^{13}、-NR^{13}C(O)R^{12}、-C(O)NR^{12}R^{13}、-NR^{12}R^{13}、-CH=NOR^{12}、-S(O)$_j$R^{12}——其中 j 是 0 至 2 的整数、-(CR^{13}R^{14})$_t$(C_6-C_{10}芳基)、-(CR^{13}R^{14})$_t$(4-10 元杂环)、-(CR^{13}R^{14})$_t$(C_3-C_{10}环烷基)和-(CR^{13}R^{14})$_t$C≡CR^{16}；其中上述基团的环烷基、芳基和杂环部分可选地与C_6-C_{10}芳基、C_5-C_8饱和环基或4-10元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被1至3个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、-NR^{13}SO$_2$R^{15}、-SO$_2$NR^{12}R^{13}、-C(O)R^{12}、-C(O)OR^{12}、-OC(O)R^{12}、-NR^{13}C(O)OR^{15}、-NR^{13}C(O)R^{12}、-C(O)NR^{12}R^{13}、-NR^{12}R^{13}、-OR^{12}、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、-(CR^{13}R^{14})$_t$(C_6-C_{10}芳基)和-(CR^{13}R^{14})$_t$(4-10元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个 R^{6}取代基取代；

每个 R^{12}独立地选自 H、C_1-C_{10}烷基、-(CR^{13}R^{14})$_t$(C_3-C_{10}环烷基)、-(CR^{13}R^{14})$_t$(C_6-C_{10}芳基)和-(CR^{13}R^{14})$_t$(4-10元杂环)；所述环烷基、芳基和杂环 R^{12}基团可选地与C_6-C_{10}芳基、C_5-C_8饱和环基或 4-10 元杂环基稠合；上述 R^{12}取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、-C(O)R^{13}、-C(O)OR^{13}、-OC(O)R^{13}、-NR^{13}C(O)R^{14}、-C(O)NR^{13}R^{14}、-NR^{13}R^{14}、羟基、C_1-C_6烷基和C_1-C_6烷氧基；

每个 t 独立地是 0 至 5 的整数；

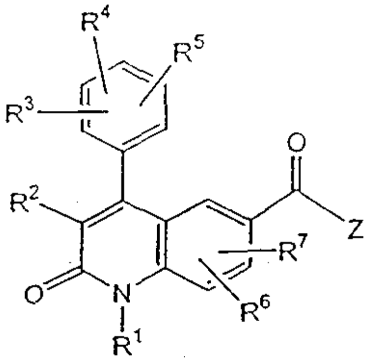
每个 R^{13}和 R^{14}独立地是 H 或 C_1-C_6烷基，其中若 t 超过 1，则-(CR^{13}R^{14})$_t$中每次重复定义的 R^{13}和 R^{14}是各自独立的；

R^{15}选自由 R^{12}定义所提供的取代基，但是 R^{15}不是 H；

R^{16}选自由 R^{12}定义所提供的取代基列表和-SiR^{17}R^{18}R^{19}；

R^{17}、R^{18}和 R^{19}各自独立地选自由 R^{12}定义所提供的取代基，但是至少 R^{17}、R^{18}和 R^{19}之一不是 H。式 29 化合物是可用于制备式 1 化合物的中间体。

本发明还涉及式 30 化合物



30

其中:

R^1选自H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_qC(O)R^{12}$、$-(CR^{13}R^{14})_qC(O)OR^{15}$、$-(CR^{13}R^{14})_qOR^{12}$、$-(CR^{13}R^{14})_qCSO_2R^{15}$、$-(CR^{13}R^{14})_t$($C_3$-$C_{10}$环烷基)、$-(CR^{13}R^{14})_t$($C_6$-$C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环),其中所述环烷基、芳基和杂环$R^1$基团可选地与$C_6$-$C_{10}$芳基、$C_5$-$C_8$饱和环基或4-10元杂环基稠合;上述$R^1$基团除H以外、但包括上述任意可选的稠合环,都可选地被1至4个R^6基团取代;

R^2是卤、氰基、$-C(O)OR^{15}$或选自由R^{12}定义所提供的取代基的基团;

每个R^3、R^4、R^5、R^6和R^7独立地选自H、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH{=}NOR^{12}$、$-S(O)_jR^{12}$——其中j是0至2的整数、$-(CR^{13}R^{14})_t$(C_6-C_{10}芳基)、$-(CR^{13}R^{14})_t$(4-10元杂环)、$-(CR^{13}R^{14})_t$(C_3-C_{10}环烷基)和$-(CR^{13}R^{14})_tC\equiv CR^{16}$;其中上述基团的环烷基、芳基和杂环部分可选地与$C_6$-$C_{10}$芳基、$C_5$-$C_8$饱和环基或4-10元杂环基稠合;所述烷基、烯基、环烷基、芳基和杂环基可选地被1至3个取代基取代,取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、$-(CR^{13}R^{14})_t$(C_6-C_{10}芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环);

Z是芳族4-10元杂环基,被1-4个R^6取代基取代;

每个R^{12}独立地选自H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_t$(C_3-C_{10}环烷基)、

$-(CR^{13}R^{14})_t$(C_6-C_{10}芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环)；所述环烷基、芳基和杂环R^{12}基团可选地与C_6-C_{10}芳基、C_5-C_8饱和环基或4-10元杂环基稠合；上述R^{12}取代基除H以外但包括任意可选的稠合环，都可选地被1至3个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6烷基和C_1-C_6烷氧基；

每个t独立地是0至5的整数，每个q独立地是1至5的整数；

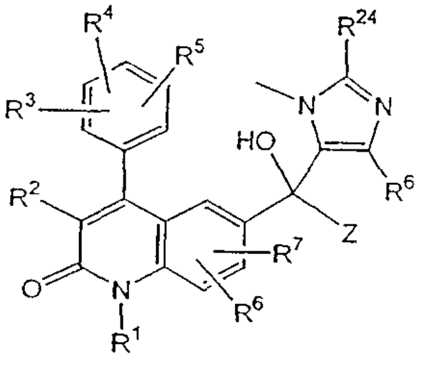
每个R^{13}和R^{14}独立地是H或C_1-C_6烷基，其中若q或t超过1，则$-(CR^{13}R^{14})_q$或$-(CR^{13}R^{14})_t$中每次重复定义的R^{13}和R^{14}是各自独立的；

R^{15}选自由R^{12}定义所提供的取代基，但是R^{15}不是H；

R^{16}选自由R^{12}定义所提供的取代基列表和$-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18}和R^{19}各自独立地选自由R^{12}定义所提供的取代基，但是至少R^{17}、R^{18}和R^{19}之一不是H。式30化合物是可用于制备式1化合物的中间体。

本发明还涉及式26化合物



26

其中：

R^{24}选自$-SR^{20}$和$-SiR^{21}R^{22}R^{23}$，其中R^{20}选自H和苯基，R^{21}、R^{22}和R^{23}独立地选自C_1-C_6烷基和苯基；

R^1选自H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_qC(O)R^{12}$、$-(CR^{13}R^{14})_qC(O)OR^{15}$、$-(CR^{13}R^{14})_qOR^{12}$、$-(CR^{13}R^{14})_qCSO_2R^{15}$、$-(CR^{13}R^{14})_t$($C_3$-$C_{10}$环烷基)、$-(CR^{13}R^{14})_t$($C_6$-$C_{10}$芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环)，其中所述环烷基、芳基和杂环$R^1$基团可选地与$C_6$-$C_{10}$芳基、$C_5$-$C_8$饱和环基或4-10元杂环基稠合；上述$R^1$基团除H以外、但包括上述任意可选的稠合环，都

可选地被 1 至 4 个 R^6 基团取代；

R^2 是卤、氰基、$-C(O)OR^{15}$ 或选自由 R^{12} 定义所提供的取代基的基团；

每个 R^3、R^4、R^5、R^6 和 R^7 独立地选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t(C_3-C_{10}$ 环烷基) 和 $-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基) 和 $-(CR^{13}R^{14})_t$(4-10 元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个 R^6 取代基取代；

每个 R^{12} 独立地选自 H、C_1-C_{10} 烷基、$-(CR^{13}R^{14})_t(C_3-C_{10}$ 环烷基)、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基) 和 $-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12} 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6 烷基和 C_1-C_6 烷氧基；

每个 t 独立地是 0 至 5 的整数，每个 q 独立地是 1 至 5 的整数；

每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6 烷基，其中若 q 或 t 超过 1，则 $-(CR^{13}R^{14})_q$ 或 $-(CR^{13}R^{14})_t$ 中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

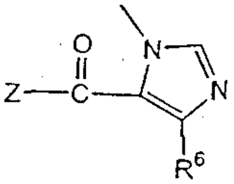
R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和 $-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至

少 R^{17}、R^{18}和 R^{19}之一不是 H。式 26 化合物是可用于制备式 1 化合物的中间体。

本发明还涉及合成下式化合物的方法，



11a

其中

R^6选自 H、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6$-C_{10} 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t(C_3$-C_{10} 环烷基)和$-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10}芳基、C_5-C_8饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、$-(CR^{13}R^{14})_t(C_6$-C_{10} 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；

Z 是芳族 4-10 元杂环基，被 1-4 个 R^6取代基取代；

每个 R^{12}独立地选自 H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_t(C_3$-C_{10}环烷基)、$-(CR^{13}R^{14})_t(C_6$-C_{10}芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12}基团可选地与 C_6-C_{10}芳基、C_5-C_8饱和环基或 4-10 元杂环基稠合；上述 R^{12}取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6烷基和 C_1-C_6烷氧基；

每个 t 独立地是 0 至 5 的整数；

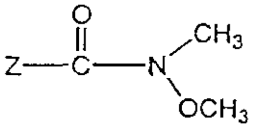
每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6 烷基，其中若 t 超过 1，则 $-(CR^{13}R^{14})_t$ 中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和 $-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H；

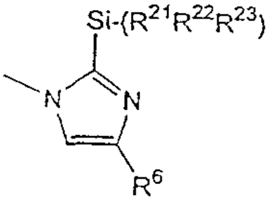
该方法包括在适当的溶剂中，在适合的碱的存在下，使下式化合物



28

其中 Z 是如上所定义的；

与下式化合物反应，

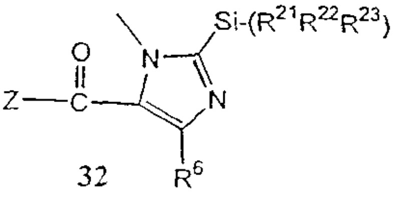


33

其中 R^6 是如上所定义的，

R^{21}、R^{22} 和 R^{23} 各自独立地选自 C_1-C_6 烷基和苯基；

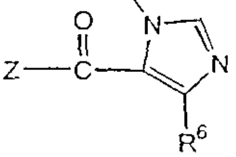
从而得到下式化合物



32

再在适当的溶剂中，使所得式 32 化合物与乙酸或氟化物试剂反应。所述方法可以用于制备式 1 化合物。

本发明还涉及合成下式化合物的方法，



11a

其中

R^6选自H、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中j是0至2的整数、$-(CR^{13}R^{14})_t$(C_6-C_{10}芳基)、$-(CR^{13}R^{14})_t$(4-10元杂环)、$-(CR^{13}R^{14})_t$(C_3-C_{10}环烷基)和$-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与$C_6$-$C_{10}$芳基、$C_5$-$C_8$饱和环基或4-10元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被1至3个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、$-(CR^{13}R^{14})_t$(C_6-C_{10}芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环)；

Z是芳族4-10元杂环基，被1-4个R^6取代基取代；

每个R^{12}独立地选自H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_t$(C_3-C_{10}环烷基)、$-(CR^{13}R^{14})_t$(C_6-C_{10}芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环)；所述环烷基、芳基和杂环R^{12}基团可选地与C_6-C_{10}芳基、C_5-C_8饱和环基或4-10元杂环基稠合；上述R^{12}取代基除H以外但包括任意可选的稠合环，都可选地被1至3个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6烷基和C_1-C_6烷氧基；

每个t独立地是0至5的整数；

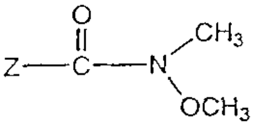
每个R^{13}和R^{14}独立地是H或C_1-C_6烷基，其中若t超过1，则$-(CR^{13}R^{14})_t$中每次重复定义的R^{13}和R^{14}是各自独立的；

R^{15}选自由R^{12}定义所提供的取代基，但是R^{15}不是H；

R^{16}选自由R^{12}定义所提供的取代基列表和$-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18}和R^{19}各自独立地选自由R^{12}定义所提供的取代基，但是至少R^{17}、R^{18}和R^{19}之一不是H；

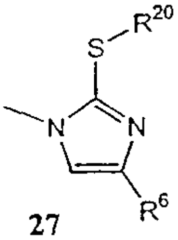
该方法包括在适当的溶剂中，在适合的碱的存在下，使下式化合物



28

其中 Z 是如上所定义的；

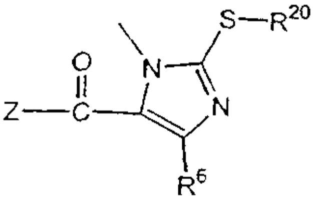
与下式化合物反应，



27

其中 R^6 是如上所定义的，R^{20} 选自 H 和苯基；

从而得到下式化合物



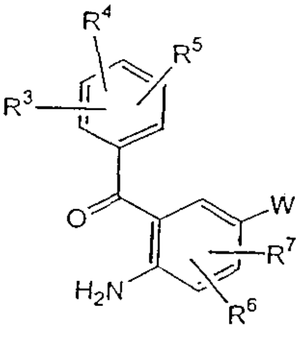
31

再从所得式 31 化合物中除去$-SR^{20}$基团，方法是：

a) 用镍催化剂还原；或者

b) 在乙酸中用硝酸或含水过氧化氢氧化。所述方法可以用于制备式 1 化合物。

本发明还涉及合成下式化合物的方法，



23

其中：

每个R^3、R^4、R^5、R^6和R^7独立地选自H、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中j是0至2的整数、$-(CR^{13}R^{14})_t(C_6$-C_{10}芳基)、$-(CR^{13}R^{14})_t$(4-10元杂环)、$-(CR^{13}R^{14})_t(C_3$-C_{10}环烷基)和$-(CR^{13}R^{14})_tC{\equiv}CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与$C_6$-$C_{10}$芳基、$C_5$-$C_8$饱和环基或4-10元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被1至3个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、$-(CR^{13}R^{14})_t(C_6$-C_{10}芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环)；

每个R^{12}独立地选自H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_t(C_3$-C_{10}环烷基)、$-(CR^{13}R^{14})_t(C_6$-C_{10}芳基)和$-(CR^{13}R^{14})_t$(4-10元杂环)；所述环烷基、芳基和杂环R^{12}基团可选地与C_6-C_{10}芳基、C_5-C_8饱和环基或4-10元杂环基稠合；上述R^{12}取代基除H以外但包括任意可选的稠合环，都可选地被1至3个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6烷基和C_1-C_6烷氧基；

每个t独立地是0至5的整数；

每个R^{13}和R^{14}独立地是H或C_1-C_6烷基，其中若t超过1，则$-(CR^{13}R^{14})_t$中每次重复定义的R^{13}和R^{14}是各自独立的；

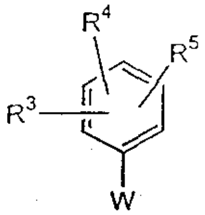
R^{15}选自由R^{12}定义所提供的取代基，但是R^{15}不是H；

R^{16}选自由R^{12}定义所提供的取代基列表和$-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18}和R^{19}各自独立地选自由R^{12}定义所提供的取代基，但是至少R^{17}、R^{18}和R^{19}之一不是H；

该方法包括在约-78℃至约0℃的温度下，在适合的碱的存在下，

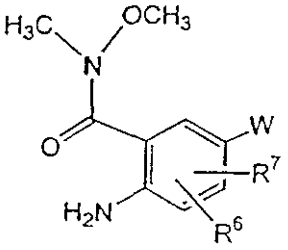
在适当的溶剂中，使下式化合物



34

其中 W 是适当的离去基团，R^3、R^4 和 R^5 是如上所定义的，

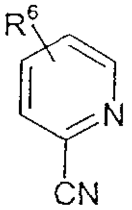
与下式化合物反应，



35

其中 R^6 和 R^7 是如上所定义的。所述方法可以用于制备式 1 化合物。在上述用于合成式 23 化合物的方法的优选实施方式中，式 34 化合物与式 35 化合物反应的溶剂是乙醚。

本发明还涉及合成下式化合物的方法，



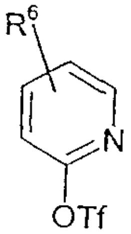
37

其中 R^6 选自 H、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6$-C_{10} 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t(C_3$-C_{10} 环烷基) 和 $-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3

个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；

该方法包括

a)在钯催化剂的存在下，在适当的溶剂中，在约 25℃至约 100℃的温度下，使金属氰化物与下式化合物反应，

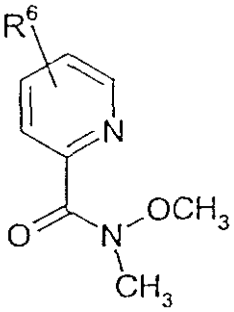


36

其中 Tf 是$-SO_2-CF_3$而 R^6 如上所述；

从而得到式 37 化合物。该方法可用于式 1 化合物的制备。

在前段所述方法的一种实施方式中，进一步合成了下式化合物，



28a

其中

R^6 选自 H、C_1-C_{10}烷基、C_2-C_{10}烯基、C_2-C_{10}炔基、卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-OR^{12}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-NR^{13}C(O)OR^{15}$、$-OC(O)R^{12}$、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-CH=NOR^{12}$、$-S(O)_jR^{12}$——其中 j 是 0 至 2 的整数、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)、$-(CR^{13}R^{14})_t$(4-10 元杂环)、$-(CR^{13}R^{14})_t(C_3-C_{10}$ 环烷基)和$-(CR^{13}R^{14})_tC\equiv CR^{16}$；其中上述基团的环烷基、芳基和杂环部分可选地与 C_6-C_{10}芳基、C_5-C_8饱和环基或 4-10 元杂

环基稠合；所述烷基、烯基、环烷基、芳基和杂环基可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-NR^{13}SO_2R^{15}$、$-SO_2NR^{12}R^{13}$、$-C(O)R^{12}$、$-C(O)OR^{12}$、$-OC(O)R^{12}$、$-NR^{13}C(O)OR^{15}$、$-NR^{13}C(O)R^{12}$、$-C(O)NR^{12}R^{13}$、$-NR^{12}R^{13}$、$-OR^{12}$、C_1-C_{10} 烷基、C_2-C_{10} 烯基、C_2-C_{10} 炔基、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；

每个 R^{12} 独立地选自 H、C_1-C_{10}烷基、$-(CR^{13}R^{14})_t(C_3-C_{10}$ 环烷基)、$-(CR^{13}R^{14})_t(C_6-C_{10}$ 芳基)和$-(CR^{13}R^{14})_t$(4-10 元杂环)；所述环烷基、芳基和杂环 R^{12} 基团可选地与 C_6-C_{10} 芳基、C_5-C_8 饱和环基或 4-10 元杂环基稠合；上述 R^{12} 取代基除 H 以外但包括任意可选的稠合环，都可选地被 1 至 3 个取代基取代，取代基独立地选自卤、氰基、硝基、三氟甲基、三氟甲氧基、叠氮基、$-C(O)R^{13}$、$-C(O)OR^{13}$、$-OC(O)R^{13}$、$-NR^{13}C(O)R^{14}$、$-C(O)NR^{13}R^{14}$、$-NR^{13}R^{14}$、羟基、C_1-C_6烷基和 C_1-C_6烷氧基；

每个 t 独立地是 0 至 5 的整数；

每个 R^{13} 和 R^{14} 独立地是 H 或 C_1-C_6 烷基，其中若 t 超过 1，则$-(CR^{13}R^{14})_t$中每次重复定义的 R^{13} 和 R^{14} 是各自独立的；

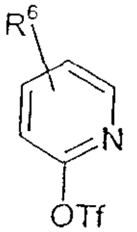
R^{15} 选自由 R^{12} 定义所提供的取代基，但是 R^{15} 不是 H；

R^{16} 选自由 R^{12} 定义所提供的取代基列表和$-SiR^{17}R^{18}R^{19}$；

R^{17}、R^{18} 和 R^{19} 各自独立地选自由 R^{12} 定义所提供的取代基，但是至少 R^{17}、R^{18} 和 R^{19} 之一不是 H；

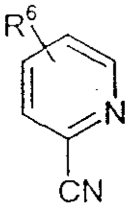
该实施方式包括

a)在钯催化剂的存在下，在适当的溶剂中，在约 25℃至约 100℃的温度下，使金属氰化物与下式化合物反应，



其中 Tf 是$-SO_2-CF_3$，R^1是如上所定义的；

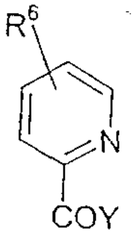
从而得到下式化合物，



37

b)将所得式 37 化合物用适合的碱或适合的酸在水解条件下处理；

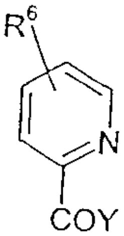
从而得到下式化合物，



38

其中 Y 是 OH；

c)将所得式 38 化合物转化为下式化合物，



38

其中 Y 是 Cl 或 N1-咪唑；

d)在适合的碱的存在下，在适当的溶剂中，在约 0℃至约 40℃的温度下，将(c)中所得式 38 化合物用 N,O-二甲基羟胺处理。所述实施方式也可以用于制备式 1 化合物。

本文所用的“异常细胞生长”是指不受正常规则机理支配的细胞生长（例如缺乏接触抑制作用）。这包括但不限于下列异常生长：(1)表达活化的Ras致癌基因的肿瘤细胞（肿瘤），既有良性的也有恶性的；(2)其中Ras蛋白作为另一种基因中的致癌突变结果而被活化的肿瘤细胞，既有良性的也有恶性的；(3)其他发生异常Ras活化的增殖性疾病的良性与恶性细胞。这类良性增殖性疾病的实例是牛皮癣、良性前列腺肥大、人乳头状瘤病毒(HPV)和再狭窄。“异常细胞生长”也指和包括由法呢基蛋白转移酶活性导致的异常细胞生长，既有良性的也有恶性的。

本文所用的动词“治疗”除非另有指示，表示逆转、减轻、抑制该术语适用的病症或疾病的进展，或者预防该病症或疾病，或该病症或疾病的一种或多种症状。本文所用的名词“治疗”指如刚才所定义的动词“治疗”的动作。

本文所用的术语“卤”除非另有指示，表示氟、氯、溴或碘。优选的卤代基团是氟、氯和溴。

本文所用的术语“烷基”除非另有指示，包括具有直链或支链部分的饱和一价烃原子团。烷基的实例包括但不限于甲基、乙基、丙基、异丙基和叔丁基。

本文所用的术语“环烷基”除非另有指示，包括环状烷基部分，其中的烷基是如上所定义的。该定义包括多环基团，例如二环的和三环的。

本文所用的术语“烯基”除非另有指示，包括具有至少一条碳-碳双键的烷基部分，其中的烷基是如上所定义的。

本文所用的术语“炔基”除非另有指示，包括具有至少一条碳-碳叁键的烷基部分，其中的烷基是如上所定义的。炔基的实例包括但不限于乙炔基和2-丙炔基。

本文所用的术语“烷氧基”除非另有指示，包括O-烷基，其中的烷基是如上所定义的。

本文所用的术语“芳基”除非另有指示，包括通过除去一个氢而从芳族烃衍生的有机原子团，例如苯基或萘基。

本文所用的术语“杂环”除非另有指示，表示含有一个或多个各自选自 O、S 和 N 的杂原子的芳族和非芳族杂环基团（包括饱和的杂环基团），其中杂环基团的每个环具有 4 至 10 个原子。非芳族杂环基团可以包括仅具有 4 个原子的环，但是芳族杂环必须具有至少 5 个原子。本发明的杂环基团除非另有指示，可以含有一个环或一个以上的环，也就是它们可以是单环的或多环的，例如二环的（可以包含非芳族和/或芳族环）。优选地，本发明的二环杂环基团在它们的环系中含有 6-9 个原子。本发明的单环杂环基团优选地含有 5 或 6 个原子。芳族多环杂环基团包括苯并稠合的环系。本发明的杂环基团还可以包括被一个或多个氧代部分取代的环系。4 元杂环基团的实例是氮杂环丁烷基（从氮杂环丁烷衍生）。5 元杂环基团的实例是噻唑基，10 元杂环基团的实例是喹啉基。非芳族杂环基团的实例是吡咯烷基、四氢呋喃基、四氢噻吩基、四氢吡喃基、四氢噻喃基、哌啶子基、吗啉代、硫吗啉代、噻噁烷基、哌嗪基、氮杂环丁烷基、哌啶基、1,2,3,6-四氢吡啶基、吡咯啉基、二氢吲哚基、2H-吡喃基、4H-吡喃基、二噁烷基、1,3-二氧杂环戊基、吡唑啉基、二氢吡喃基、二氢噻吩基、二氢呋喃基、吡唑烷基、咪唑啉基、咪唑烷基、3-氮杂二环并[3.1.0]己烷基、3-氮杂二环并[4.1.0]庚烷基、3H-吲哚基和喹嗪基。芳族杂环基团的实例是吡啶基、咪唑基、嘧啶基、吡唑基、三唑基、吡嗪基、四唑基、呋喃基、噻吩基、异噁唑基、噻唑基、噁唑基、异噻唑基、吡咯基、喹啉基、异喹啉基、吲哚基、苯并咪唑基、苯并呋喃基、噌啉基、吲唑基、吲嗪基、酞嗪基、哒嗪基、三嗪基、异吲哚基、蝶呤基、噁二唑基、噻二唑基、呋咱基、苯并呋咱基、苯并噻吩基、苯并噻唑基、苯并噁唑基、喹唑啉基、喹喔啉基、萘啶基和呋吡啶基。可能的话，从上列化合物衍生的上述基团可以是 C-连接或 N-连接的。例如，从吡咯衍生的基团可以是吡咯-1-基（N-连接）或吡咯-3-基（C-连接）。

若 q 或 t 超过 1，则-$(CR^{13}R^{14})_q$或-$(CR^{13}R^{14})_t$中每次重复定义的 R^{13} 和 R^{14} 是各自独立的。这意味着，例如，若 q 或 t 是 2，则包括-$CH_2CH(CH_3)$-类型的亚烷基部分和其他不对称的支链基团。

本文所用的术语“药学上可接受的盐”除非另有指示，包括可能存在于式 1 化合物中的酸性或碱性基团的盐。例如，药学上可接受的盐包括羧酸基团的钠、钙和钾盐，和氨基的盐酸盐。氨基的其他药学上可接受的盐是氢溴酸盐、硫酸盐、硫酸氢盐、磷酸盐、磷酸氢盐、磷酸二氢盐、乙酸盐、琥珀酸盐、柠檬酸盐、酒石酸盐、乳酸盐、扁桃酸盐、甲磺酸盐和对甲苯磺酸盐。这些盐的制备描述如下。

某些式 1 化合物可能具有不对称中心，因此存在不同的对映异构形式。式 1 化合物的所有旋光异构体和立体异构体及其混合物视为在本发明的范围内。关于式 1 化合物，本发明包括外消旋物、一种或多种对映异构形式、一种或多种非对映异构形式或其混合物的使用。式 1 化合物还可以存在互变异构体。本发明涉及所有这些互变异构体及其混合物的使用。

本发明还包括式 1 化合物的药物前体，该药物前体是包含游离氨基的式 1 化合物的衍生物，所述衍生物包含所述氨基的酰胺、脲或肽衍生物。这些药物前体可以包含氨基酸残基，或两个或多个、例如至多四个氨基酸残基的多肽链，它们通过肽键共价结合。可用于制备本发明药物前体的氨基酸残基包括用三个字母表示的 20 种天然来源的氨基酸、4-羟基脯氨酸、羟基赖氨酸、demosine、isodemosine、3-甲基组氨酸、正缬氨酸、β-丙氨酸、γ-氨基丁酸、瓜氨酸、高半胱氨酸、高丝氨酸、鸟氨酸和甲硫氨酸砜。优选的氨基酸残基是具有非极性基团的那些，例如 Ala、Val、Nval、Leu、Met、Gly、Pro、Phe，或具有碱性极性基团的那些，例如 Lys。

本发明还包括式 1 化合物的药物前体，该药物前体是本文所述的式 2 化合物、式 12 化合物和式 6 化合物。

本发明还包括同位素标记的化合物，它们等同于式 1 所述化合物，但是事实上一个或多个原子被原子质量或质量数不同于自然界常见的原子质量或质量数的原子所代替。可以结合在本发明化合物种的同位素实例包括氢、碳、氮、氧、磷、氟和氯的同位素，分别例如 ^{2}H、^{3}H、^{13}C、^{14}C、^{15}N、^{18}O、^{17}O、^{31}P、^{32}P、^{35}S、^{18}F 和 ^{36}Cl。含有上述同位素和/或其

他原子的其他同位素的本发明化合物、其药物前体、所述化合物或所述药物前体的药学上可接受的盐都在本发明的范围内。某些同位素标记的本发明化合物例如结合了放射性同位素，例如 ^{3}H 和 ^{14}C，可用于药物和/或底物的组织分布测定。氚(^{3}H)和碳-14 (^{14}C)同位素是特别优选的，因为它们易于制备和检测。进一步地，用更重的同位素取代，例如氘(^{2}H)，因代谢稳定性更高可以提供某些治疗上的优点，例如延长体内半衰期或减少剂量需求，因此在有些情况下可能是优选的。同位素标记的本发明式 1 化合物及其药物前体一般可以这样制备，进行下列流程和/或实施例中所公开的操作，并用易于获得的同位素标记试剂代替非同位素标记试剂。

按照本发明的方法，可以用式 1、2、6 或 12 化合物或其药学上可接受的盐或溶剂化物治疗的患者例如包括已被诊断患有下列疾病的患者：肺癌、NSCLC（非小细胞肺癌）、骨癌、胰腺癌、皮肤癌、头部与颈部癌症、皮肤或眼内黑素瘤、子宫癌、卵巢癌、直肠癌、肛门区癌症、胃癌、结肠癌、乳腺癌、妇科肿瘤（例如子宫肉瘤、输卵管癌、子宫内膜癌、宫颈癌、阴道癌或外阴癌）、何杰金氏病、食道癌、小肠癌、内分泌系统癌症（例如甲状腺癌、甲状旁腺癌或肾上腺癌）、软组织肉瘤、尿道癌、阴茎癌、前列腺癌、慢性或急性白血病、儿童期实体瘤、淋巴细胞淋巴瘤、膀胱癌、肾或输尿管癌症（例如肾细胞癌、肾盂癌）、儿科恶性肿瘤、中枢神经系统肿瘤（例如原发性 CNS 淋巴瘤、脊椎轴肿瘤、脑干神经胶质瘤或垂体腺瘤）、肿瘤形成性皮肤疾病（例如牛皮癣、蕈样真菌病）或巴雷特食道（恶化前综合征）。

式 1、2、12 和 6 化合物及其药学上可接受的盐和溶剂化物各自还可以独立地进一步在新辅助/辅助疗法中用于减轻伴有前段所述疾病的症状以及伴有异常细胞生长的症状。这样的疗法可以是单一疗法，或者可以与化学疗法和/或免疫疗法结合。

按照本发明方法可以治疗的患者还包括患有如上所定义的异常细胞生长的患者。

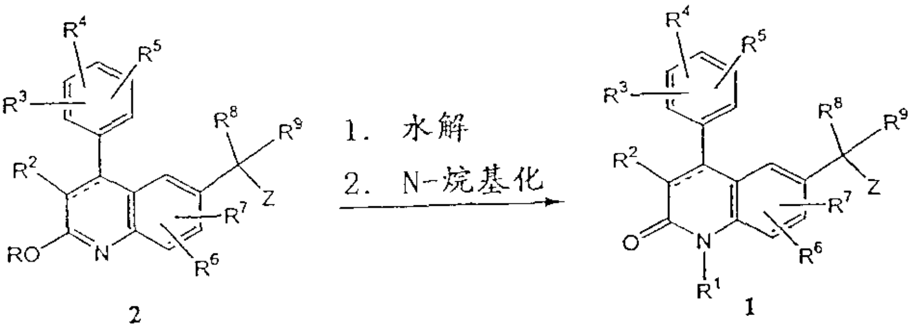
发明的详细说明

下列流程和实施例中，"Et"代表乙基部分，"Me"代表甲基部分。因此，例如"OEt"表示乙醇。另外，"THF"表示四氢呋喃，"DMF"表示二甲基甲酰胺。

式 1 化合物可以如下所述加以制备。

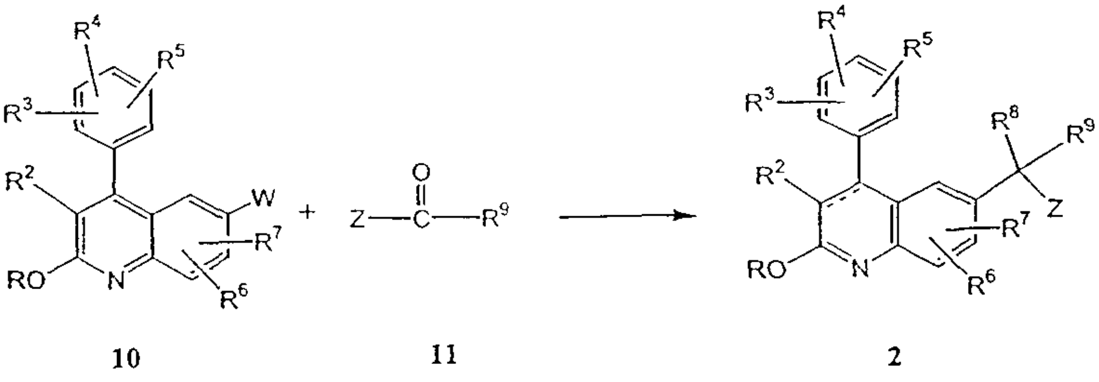
根据下列流程 1，式 1 化合物可以这样制备：水解式 2 的中间体醚，其中 R 是 C_1-C_6烷基，水解采用本领域技术人员所熟悉的方法，例如在含水酸溶液中搅拌式 2 的中间体醚。适当的酸例如盐酸。按照本领域技术人员所熟悉的 N-烷基化方法，所得其中 R^1是氢的式 1 喹啉酮可以转化为其中 R^1具有除氢以外的如上所定义含义的喹啉酮。

流程 1



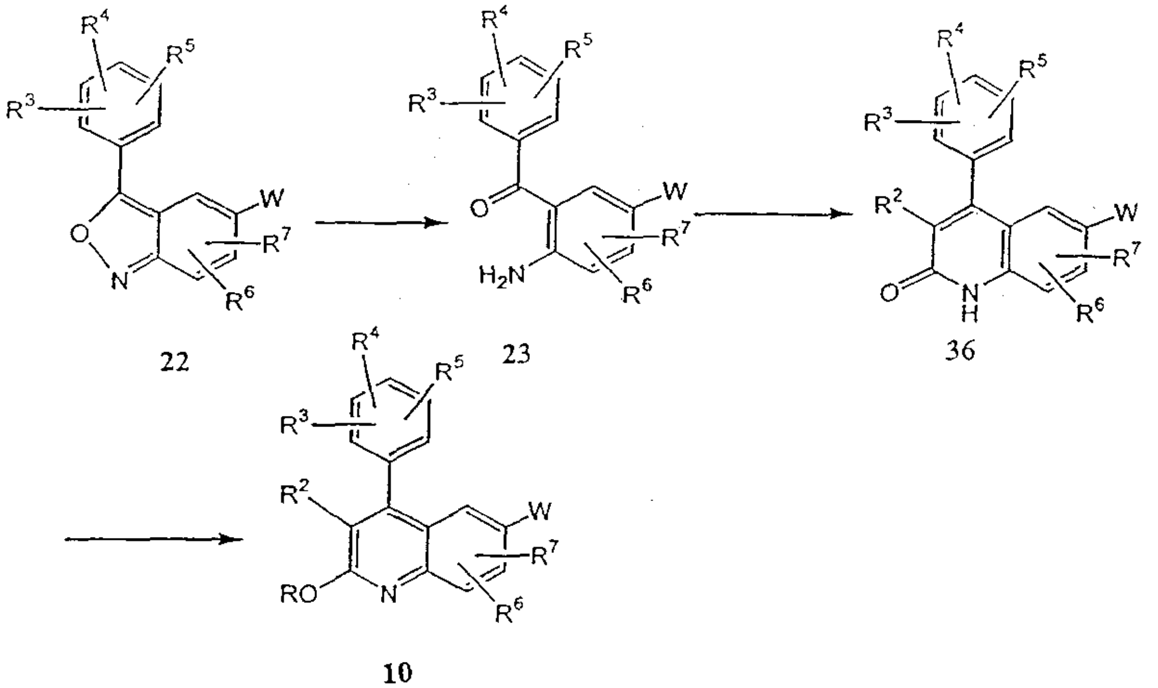
根据下列流程 2，上述式 2 中间体可以这样制备：将其中 W 是适当的离去基团、例如卤的式 10 中间体与式 11 的中间体酮反应。通过式 10 中间体转化为有机金属化合物进行该反应：将其用强碱搅拌，例如丁基锂，随后加入式 11 的中间体酮。尽管该反应首先生成羟基衍生物（R^8是羟基），不过通过进行本领域技术人员所熟悉的官能团变换，所述羟基衍生物可以转化为其中 R^8具有另一种定义的其他中间体。

流程 2



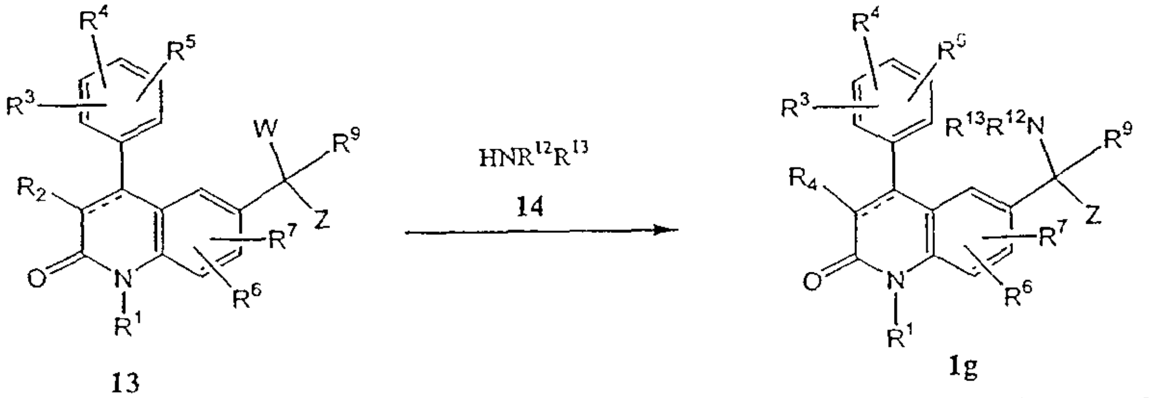
根据下列流程 3，式 36 化合物、即其中虚线是一条键且 R^1 是氢的式 1 化合物,可以经由式 22 中间体的异噁唑部分的开环作用加以制备:在水的存在下将其用酸搅拌，例如 $TiCl_3$。所得式 23 中间体随后用适合的试剂处理，例如 R^2CH_2COCl 或 $R^2CH_2COOC_2H_5$，其中 R 是如上所定义的，直接得到式 36 化合物，或者得到中间体，用碱处理可以转化为式 36 化合物，碱例如叔丁醇钾。式 36 中间体可以转化为式 10 中间体:将其用 o-烷基化试剂搅拌一段时间，例如三甲基氧鎓四氟硼酸酯（BF_4OMe_3），通常为 4 至 15 小时，随后加入强碱，例如含水氢氧化钠。

流程 3



根据下列流程 4，其中 R^8 是式$-NR^{12}R^{13}$原子团、其中 R^{12} 和 R^{13} 如上所述的式 1 化合物（所述化合物由下列式 1(g) 所代表）可以这样制备：将其中 W 是适当离去基团、例如卤的式 13 中间体与式 14 试剂反应。所述反应可以这样进行：在适当的溶剂中，例如 THF，搅拌各试剂。

流程 4

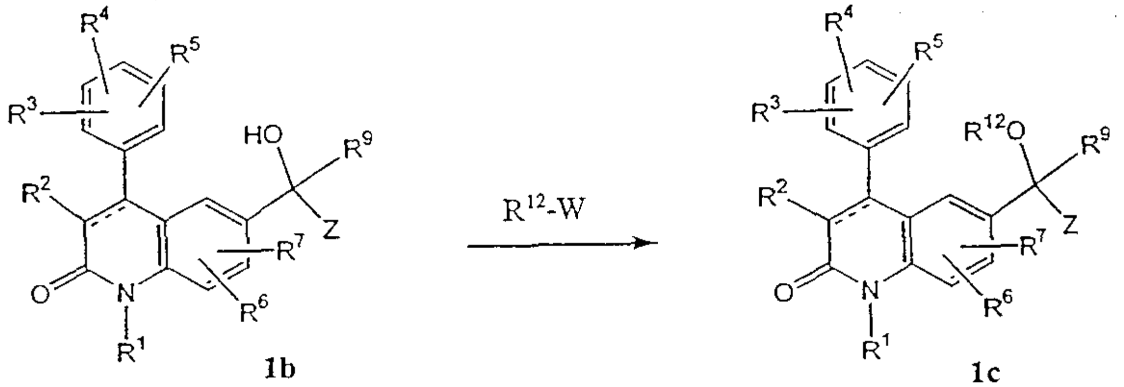


按照本领域技术人员所熟悉的氢化方法，其中虚线代表一条键的式 (1g) 化合物或式 1 的其他实施方式可以转化为其中虚线不代表一条键的化合物。按照本领域技术人员所熟悉的氧化方法，其中虚线不代表一条键的化合物可以转化为其中虚线代表一条键的化合物。

关于下列流程 5，其中 R^8 是羟基的式 1 化合物（所述化合物由式

1(b)所代表)可以转化为其中R^{12}具有除氢以外上述含义的式1(c)化合物：采用本领域技术人员已知的方法，包括O-烷基化或O-酰基化反应；例如在适当的条件下，例如在偶极非质子溶剂中，例如DMF，在碱的存在下，例如氢化钠，将式1(b)化合物与烷基化试剂反应，例如R^{12}-W，其中R^{12}如上所述。W是适合的离去基团，例如卤代基团或磺酰基。

流程5

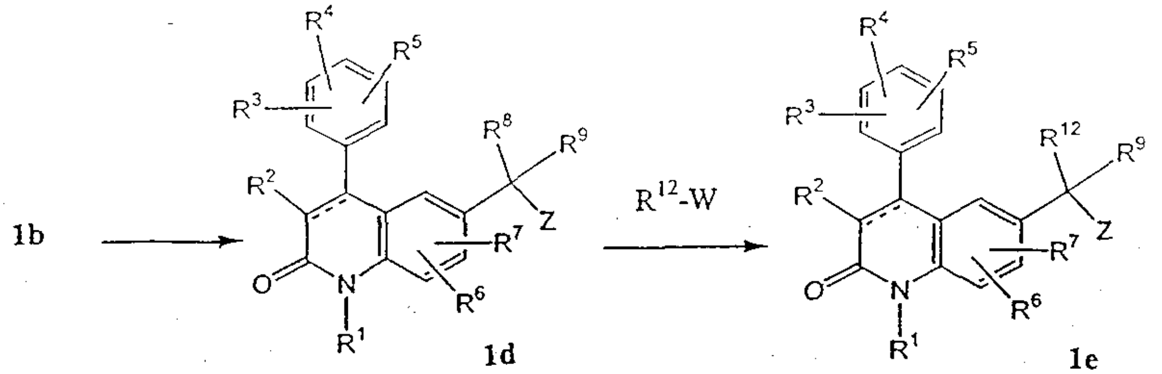


作为上述反应操作的替代选择，式1(c)化合物也可以这样制备：在酸性介质中，将式1(b)化合物与式R^{12}-OH试剂反应，其中R^{12}如上所述。

式1(b)化合物还可以转化为其中R^{12}是氢且R^{13}被C_1-C_6烷基羰基取代的式1(g)化合物：在酸性介质中，例如硫酸，将式1(b)化合物与C_1-C_6烷基-CN进行里特反应。进一步地，式1(b)化合物还可以转化为其中R^{12}和R^{13}是氢的式1(g)化合物：将式1(b)化合物与乙酸铵反应，随后用NH_3(aq.)处理。

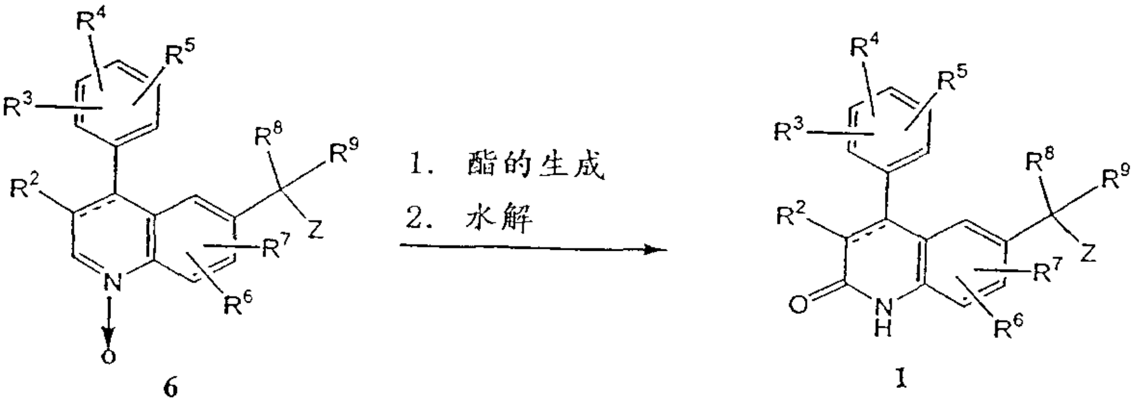
根据下列流程6，上述式1(b)化合物还可以转化为其中R^8是氢的式1(d)化合物：使式1(b)化合物受到适当的还原条件处理，例如在适当还原剂的存在下，例如硼氢化钠，在三氟乙酸中搅拌，或者在甲酰胺的存在下，在乙酸中搅拌式1(b)化合物。进一步地，其中R^8是氢的式1(d)化合物可以转化为其中R^{12}是C_1-C_{10}烷基的式1(e)化合物：在适当的溶剂中，例如二甘醇二甲醚，在碱的存在下，例如叔丁醇钾，将式1(d)化合物与其中W是适当离去基团的式5试剂反应。

流程6



根据下列流程 7，式 1 化合物可以这样制备：将式 6 硝酮与羧酸酐反应，例如乙酸酐，由此在喹啉部分的 2-位生成对应的酯。利用碱，例如碳酸钾，所述喹啉酯可以就地水解为对应的喹啉酮。

流程 7



或者，式 1 化合物可以这样制备：在碱的存在下，例如含水碳酸钾，将式 6 硝酮与含有亲电试剂的磺酰基反应，例如对甲苯磺酰氯。该反应最初涉及 2-羟基喹啉衍生物的生成，随后互变异构化为所需的喹啉酮衍生物。本领域技术人员所熟悉的相转移催化条件的应用可以提高反应速率。

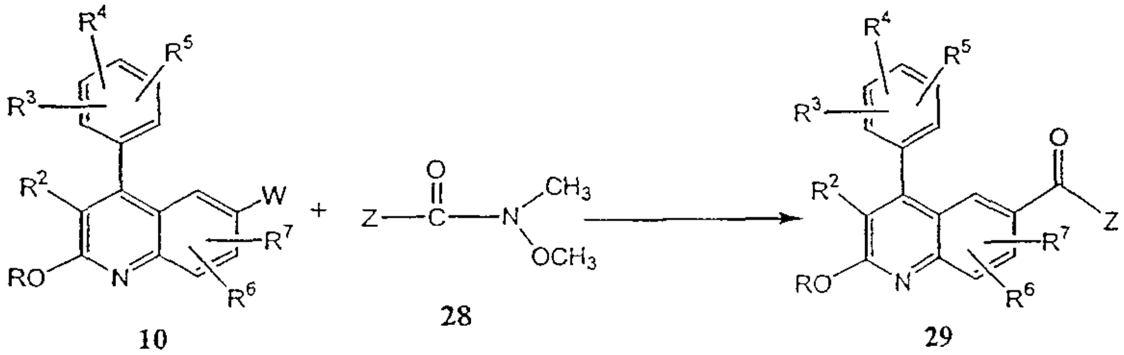
式 1 化合物还可以通过上述式 6 化合物的分子内光化学重排加以制备。所述重排可以这样进行：将各试剂溶于反应惰性溶剂，在 366nm 波长下照射。为了最小化不良副反应或者减少量子产率，使用脱气的溶液并且在惰性气氛下进行反应是有利的，例如不含氧的氩或氮气。

式 1 化合物的取代基可以经由本领域技术人员所熟悉的反应或官能团变换转化为式 1 范围内的其他取代基。上文已经描述了大量这样的变换。其他实例是羧酸酯水解为对应的羧酸或醇；酰胺水解为对应的羧酸或胺；腈水解为对应的酰胺；通过本领域技术人员所熟悉的重氮化反应，随

后重氮基被氢取代，咪唑或苯基部分上的氨基可以被氢取代；醇可以转化为酯和醚；伯胺可以转化为仲胺或叔胺；双键可以氢化为对应的单键。

根据下列流程8，其中R是如上所定义的C_1-C_6烷基的式29中间体可以这样制备：在适当的条件下，将式10中间体与式28中间体或其官能衍生物反应。通过式10中间体转化为有机金属化合物进行该反应：将其与强碱搅拌，例如丁基锂，随后加入式28的中间体酰胺。

流程8

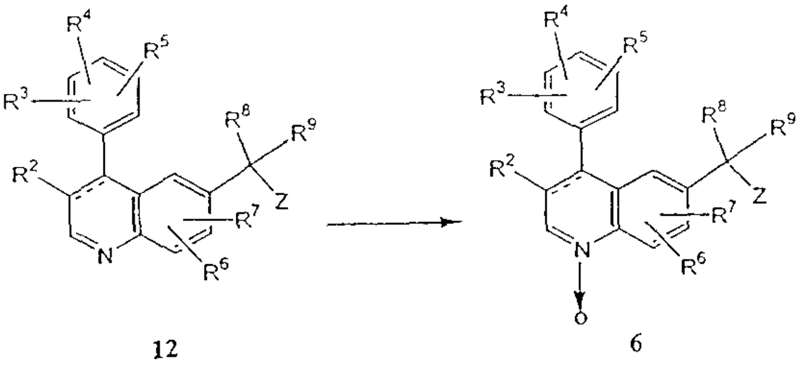


根据下列流程9，式6的中间体硝酮可以这样制备：在适当的溶剂中，例如二氯甲烷，将式12喹啉衍生物用适当的氧化剂进行N-氧化，例如间氯过苯甲酸或H_2O_2。

所述N-氧化作用也可以针对式12喹啉的前体进行。

式12中间体可以经由式6化合物体内代谢为式1化合物。因此，式12和6中间体可以充当式1化合物的药物前体。另外，式2中间体可以体内代谢为式1化合物。因此，式2化合物也被本发明视为“药物前体”。这些药物前体在本发明的范围内。

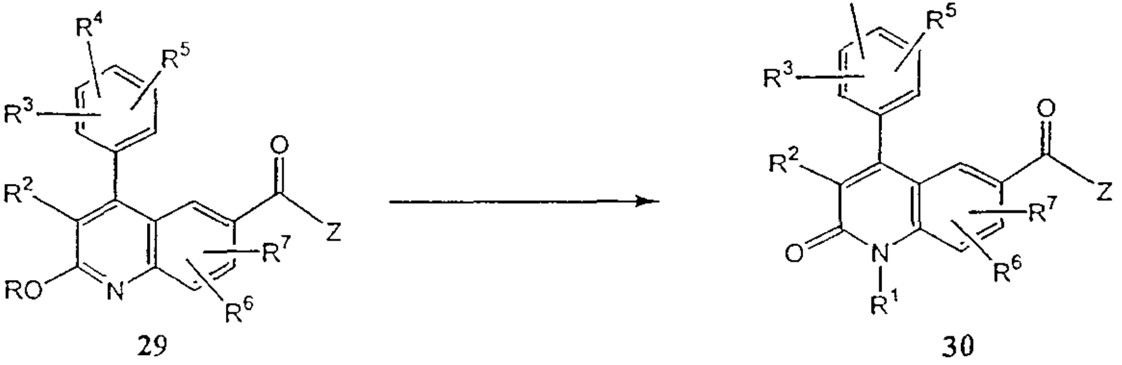
流程9



根据下列流程10，式30化合物可以这样制备：水解其中R是C_1-C_6烷基的式29中间体，水解按照本领域技术人员所熟悉的方法，例如在

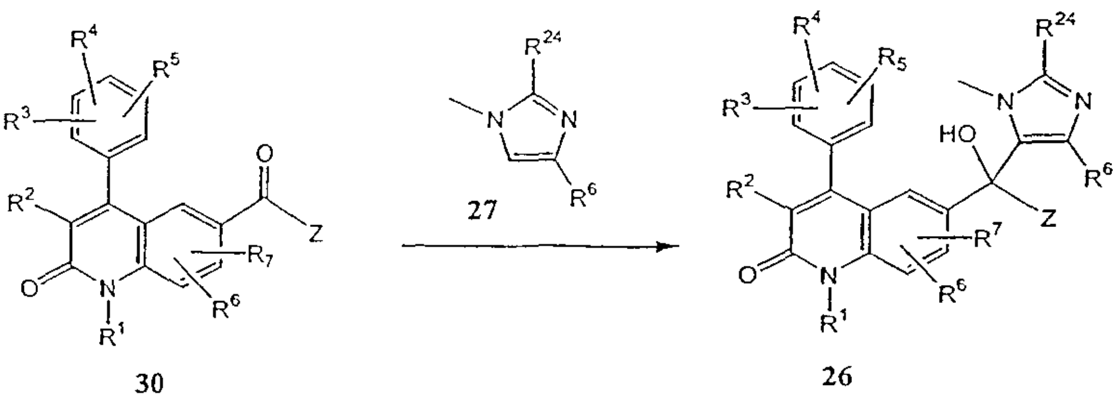
路易斯酸的存在下，在含水酸溶液或有机溶剂中搅拌式 29 中间体。适当的酸例如盐酸。适当的路易斯酸和溶剂例如碘代三甲基硅烷和二氯甲烷。通过本领域技术人员所熟悉的 N-烷基化方法，所得其中 R^1 是氢的式 30 喹啉酮可以转化为其中 R^1 具有除氢以外如上所定义含义的喹啉酮。

流程 10



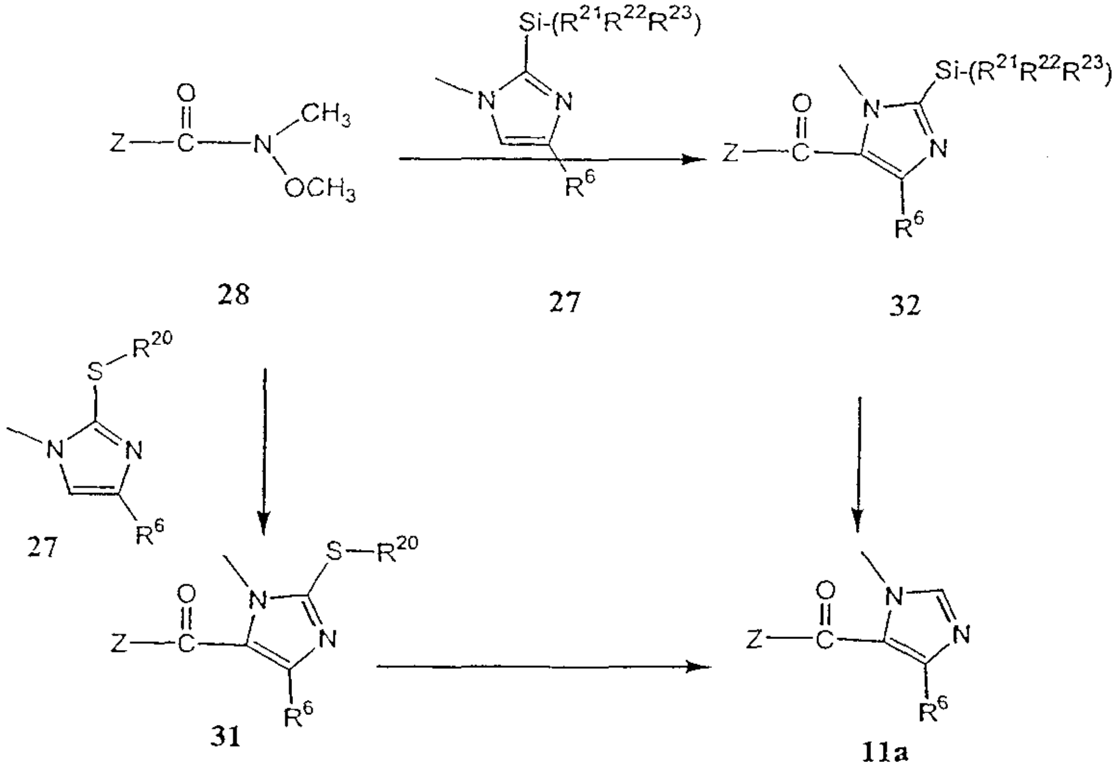
根据下列流程 11，式 26 化合物可以这样制备：将式 30 化合物与式 27 中间体反应，其中 R^{24} 是 SR^{20} 或 $SiR^{21}R^{22}R^{23}$，R^{20} 是 H 或苯基，R^{21}、R^{22} 和 R^{23} 独立地选自 C_1-C_6 烷基和苯基。该反应需要适合的碱的存在，例如叔丁基锂（当 R^{24} 是 SR^{20} 且 R^{20} = H 时）或 2,2,6,6-四甲基哌啶锂（当 R^{24} 是 SR^{20} 且 R^{20} = 苯基时）或正丁基锂（当 R^{24} 是 $SiR^{21}R^{22}R^{23}$ 时），并且在适当的溶剂中，例如 THF。$-SR^{20}$ 基团可以这样从式 26 化合物中除去：用镍催化剂还原，例如阮内镍，或者在乙酸中用硝酸或含水过氧化氢氧化。若 R^{24} 是 $SiR^{21}R^{22}R^{23}$，则 R^{24} 可以这样从式 26 化合物中除去：在溶剂中，例如四氢呋喃，与乙酸或氟化物试剂反应，例如四丁基氟化铵(TBAF)。由此可以合成式 1 化合物。

流程 11



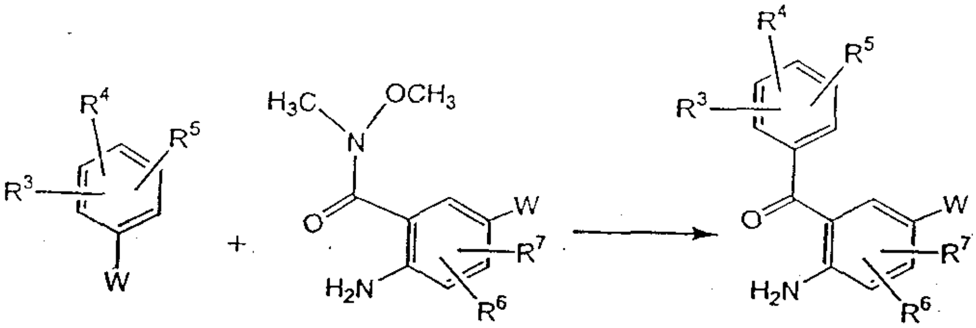
对于流程 12，式 11a 中间体是其中 R^9 是被 R^6 取代的咪唑的式 11 化合物，其中 R^6 是如上所定义的，该中间体可以这样制备：将式 28 中间体与其中 R^{21}、R^{22}、R^{23} 是 C_1-C_6 烷基或苯基的式 27 中间体反应，生成式 32 中间体。该反应需要适合的碱的存在，例如正丁基锂，并且在适当的溶剂中，例如 THF。在溶剂中，例如四氢呋喃，式 32 中间体与乙酸或氟化物试剂反应，例如 TBAF，得到式 11a 化合物。或者，式 11a 化合物可以这样制备：将式 28 化合物与其中 R^{20} 是 H 或苯基的式 27 中间体反应。该反应需要适合的碱的存在，例如叔丁基锂（当 R^{20} = H 时）或 2,2,6,6-四甲基哌啶锂（当 R^{20} = 苯基时），并且在适当的溶剂中，例如 THF。$-SR^{20}$ 基团可以这样从式 31 化合物中除去：用镍催化剂还原，例如阮内镍，或者在乙酸中用硝酸或含水过氧化氢氧化。

流程 12



根据流程 13，式 23 中间体也可以这样合成：将其中 W 是适当的离去基团、例如卤的式 34 中间体与式 35 的中间体酰胺反应。该反应需要适合的碱的存在，例如正丁基锂，并且在适当的溶剂中，例如二乙醚，在约-78 至约 0℃ 的温度下。

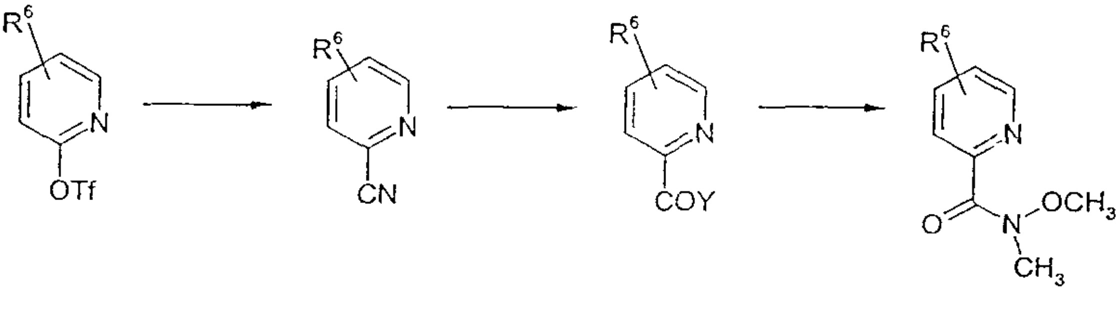
流程 13



34　35　23

根据流程 14，式 28a 中间体是其中 Z 是被 R^6 取代的吡啶的式 28 化合物，该中间体可以这样制备：在钯催化剂的存在下，例如四(三苯膦)钯，在适当的溶剂中，例如 THF 或 DMF，在约 25 至约 100℃的温度下，将式 36 中间体与金属氰化物反应，例如 $Zn(CN)_2$ 或 NaCN。随后在本领域技术人员所熟悉的水解条件下，将所得式 37 中间体用碱或酸处理，得到式 38a 化合物，它是其中 Y 是-OH 的式 38 化合物。利用本领域技术人员所熟悉的方法，式 38 中间体可以转化为它的活化形式，即中间体 38b，它是其中 Y 是-Cl 或 N1-咪唑的式 38 化合物。随后用 N,O-二甲基羟胺转化为 28a：在碱的存在下，例如三乙胺、吡啶或 4-二甲氨基吡啶，在适当的溶剂中，例如二氯甲烷，在约 0 至约 40℃的温度下。流程 14 中，"Tf"代表三氟甲磺酰，即 $-SO_2-CF_3$。

流程 14



36　37　38　28a

式 1 化合物和上述一些中间体可以在它们的结构中具有一个或多个立体形成中心。这样的立体形成中心可以存在 R 或 S 构型。肟部分可以存在 E 或 Z 构型，例如 R^3、R^4、R^5、R^6 或 R^7 是 $-CH=NOR^{12}$。

如上述方法制备的式 1 化合物一般是对映异构体的外消旋混合物，它们可以按照本领域技术人员所熟悉的拆分操作加以彼此分离。式 1

的外消旋化合物通过与适合的手性酸的反应可以转化为对应的非对映异构盐形式。所述非对映异构盐形式随后例如通过选择结晶或分步结晶加以分离，用碱使对映异构体从中释放出来。分离式 1 化合物的对映异构形式的替代方式涉及液相色谱法，并采用手性固定相。所述纯的立体化学异构形式还可以从相应适当原料的纯的立体化学异构形式衍生，只要立体定向地发生反应即可。优选地，如果需要特殊的立体异构体，所述化合物将通过立体定向的制备方法加以合成。这些方法将有利地采用对映异构纯的原料。

碱性式 1 化合物能够与各种无机和有机酸形成多种不同的盐。尽管这样的盐在药学上必须是对动物给药可接受的，不过在实践中通常需要最初从反应混合物中分离到式 1 化合物的药学上不可接受的盐，然后通过碱性试剂的处理，将后者转化为游离碱化合物，随后将游离碱转化为药学上可接受的酸加成盐。本发明碱化合物的酸加成盐是易于制备的：在含水溶剂介质或适合的有机溶剂中，例如甲醇或乙醇，将碱化合物用基本上当量的选定无机或有机酸处理。一旦蒸发溶剂，易于得到所需的固体盐。向游离碱在有机溶剂中的溶液中加入适当的无机或有机酸，所需的酸加成盐也可以从中沉淀出来。式 1 化合物的阳离子盐按类似方法制备，不过要进行羧基与适当的阳离子盐试剂的反应，例如钠、钾、钙、镁、铵、N,N’-二苄基乙二胺、N-甲基葡糖胺（葡甲胺）、乙醇胺、氨基三丁醇或二乙醇胺。

式 1、12 和 6 化合物及其药学上可接受的盐和溶剂化物（以下统称为“治疗化合物”）可以通过口服、透皮（例如借助贴剂的使用）、肠胃外或局部方式给药。口服给药是优选的。一般，式 1、12 和 6 化合物及其药学上可接受的盐和溶剂化物最可取的给药剂量范围从约 1.0mg 至约 500mg 每天，优选地从约 1 至约 100mg 每天，单次或分次（即多次）给药。治疗化合物的每日给药剂量范围通常将从约 0.01 至约 10mg 每 kg 体重每天，单次或分次给药。剂量可因所治疗人员的体重与条件和所选择的特定给药途径而异。在有些情况下，低于上述范围下限的剂量水平可能更为适合，而在其他情况下，即使采用更大的剂量，

也不会导致任何有害的副作用，只要先将这种更大的剂量分成若干小剂量，在一整天内给药即可。

治疗化合物可以单独给药，或者结合药学上可接受的载体或稀释剂，通过前述两种途径之一给药，并且给药可以分单次或多次进行。更确切地，本发明的新治疗化合物可以以多种不同的剂型给药，也就是它们可以与各种药学上可接受的惰性载体结合成为片剂、胶囊剂、锭剂、糖锭剂、硬糖剂、粉剂、喷雾剂、霜剂、油膏剂、栓剂、胶冻剂、凝胶剂、糊剂、洗剂、软膏剂、酏剂、糖浆剂等。这样的载体包括固体稀释剂或填充剂、无菌的含水介质和各种无毒的有机溶剂等。而且，口服药物组合物可以适当地加入甜味剂和/或矫味剂。

关于口服给药，可以采用片剂，其中含有各种赋形剂，例如微晶纤维素、柠檬酸钠、碳酸钙、磷酸二钙和甘氨酸，以及各种崩解剂，例如淀粉（优选为玉米、马铃薯或木薯淀粉）、藻酸和某些复合硅酸盐，以及造粒粘合剂，如聚乙烯吡咯烷酮、蔗糖、明胶和阿拉伯胶。另外，润滑剂对压片来说常常也是非常有用的，例如硬脂酸镁、月桂基硫酸钠和滑石。还可以采用相似类型的固体组合物作为胶囊中的填充剂；在这方面优选的材料还包括乳糖或奶糖，以及大分子聚乙二醇。当口服给药需要含水的悬液和/或酏剂时，可以将活性成分与各种甜味或矫味剂、着色剂或染剂混合，如果需要的话，还可以混合乳化和/或悬浮剂以及稀释剂，例如水、乙醇、丙二醇、甘油及其各种组合。

关于肠胃外给药，可以采用治疗化合物在芝麻或花生油或含水丙二醇中的溶液。如果必要的话，水溶液应当被适当缓冲，首先赋予液体稀释剂以等渗性。这些水溶液适合于静脉内注射的目的。油溶液适合于动脉内、肌内和皮下注射的目的。按照本领域技术人员熟知的标准药学工艺，易于实现所有这些溶液在无菌条件下的制备。

另外，将治疗化合物通过局部方式给药也是可能的，按照标准药学实践，这可以优选地借助霜剂、胶冻剂、凝胶剂、糊剂、软膏剂等进行。

治疗化合物还可以对人以外的哺乳动物给药。对哺乳动物给药的剂量将取决于动物种类和所治疗的疾病或病症。治疗化合物对动物给药的

剂型可以是胶囊剂、大丸剂、片剂或液体顿服剂。治疗化合物还可以通过注射或者作为植入物对动物给药。按照标准兽医实践，这些制剂按常规方式制备。作为替代选择，治疗化合物可以与动物饲料一起给药，为此可以制备浓缩饲料添加剂或预混合物，用于与正常的动物饲料混合。

关于本文所述的联合疗法和药物组合物，本领域的普通技术人员在本文所述化合物的有效量和化疗剂或其他药物的已知或所述有效量的基础上，可以确定本发明化合物和化疗剂或其他可用于抑制异常细胞生长的药物（例如其他抗增殖剂、抗血管生成剂、信号转导抑制剂或免疫系统增强剂）的有效量。有关这些疗法和组合物的制剂和给药途径基于本文关于包含本发明化合物作为唯一活性剂的组合物和疗法所述的信息，和关于联合应用的化疗剂或其他药物所提供的信息。

式 1 化合物表现出作为 Ras 法呢基化作用抑制剂的活性，可用于包括人在内的哺乳动物癌症的治疗和异常细胞生长的抑制。式 1 化合物作为 Ras 法呢基化作用抑制剂的活性可以通过它们相对于对照而言的体外抑制 Ras 法呢基转移酶的能力加以测定。下面描述一种这类操作的实例。

按 96-孔测定格式，利用包含匀化脑组织的胞溶部分的人法呢基转移酶(FTase)粗制剂筛选化合物。胞溶部分是这样制备的：在 100ml 蔗糖/$MgCl_2$/EDTA 缓冲液中匀化大约 40 克新鲜组织（利用 Dounce 匀化器，10-15 冲程），在 4℃下，将匀化产物在 1000g 下离心 10 分钟，在 4℃下，将上清液在 17000g 下再次离心 15 分钟，然后收集所得上清液。稀释该上清液，使其含有最终浓度为 50mM 的 Tris HCl (pH 7.5)、5mM DTT、0.2M KCl、20μM $ZnCl_2$、1mM PMSF，在 4℃下，在 178000g 下再次离心 90 分钟。上清液称为“粗 FTase”，测定蛋白质浓度，等分，贮藏在-70℃下。

用于测量人 FTase 体外抑制作用的测定法是 Amersham LifeScience 所述方法的变体，使用它们的法呢基转移酶(3H)闪烁接近测定(SPA)试剂盒(TRKQ 7010)。在 100μl 体积中测定 FTase 的酶活性，其中含有 50mM N-(2-羟乙基)哌嗪-N-(2-乙磺酸) (HEPES) pH

7.5、30mMmgCl$_2$、20mM KCl、25mM Na$_2$HPO$_4$、5mM 二硫苏糖醇(DTT)、0.01% Triton X-100、5%二甲基亚砜(DMSO)、20mg 粗 FTase、0.12mM [3H]-法呢基焦磷酸酯([3H]-FPP; 36000 dpm/pmol, Amersham LifeScience)和 0.2μM 生物素基化 Ras 肽 KTKCVIS (Bt-KTKCVIS)，后者肽在其α氨基上被 N-末端生物素基化，通过室内 HPLC 合成和纯化。加入酶引发反应，加入 EDTA 终止反应（TRKQ 7010 试剂盒中的终止试剂），然后在 37℃下培养 45 分钟。每孔加入 150μl 涂有抗生蛋白链菌素的 SPA 珠粒(TRKQ 7010)并将反应混合物在室温下培养 30 分钟，捕获异戊烯基化和未异戊烯基化的 Bt-KTKCVIS。利用 MicroBeta 1450 平板计数器测定与 SPA 珠粒结合的放射剂量。在这些测定条件下，酶的活性与异戊烯基受体、Bt-KTKCVIS 和粗 FTase 的浓度呈线性关系，可以检测对 Bt-KTKCVIS 与 FTase 相互作用的抑制作用。酶的活性关于异戊烯基供体 FPP 是饱和的。测定反应时间也在线性范围内。

通常将供试化合物溶于 100% DMSO。计算在供试化合物的存在下，含氚法呢基相对于对照孔（没有抑制剂）的结合百分率，测定法呢基转移酶活性的抑制作用。从所得剂量-反应测定 IC$_{50}$ 值，它是产生 Bt-KTKCVIS 的半数最大法呢基化作用所需的浓度。

利用上述测定法，测定了下列实施例中的所有式 1 标题化合物体外抑制人法呢基转移酶活性的能力，发现抑制生物素基化 KTKCVIS-肽的法呢基化作用的 IC$_{50}$ 值大约小于或等于 500nM。

提供下列实施例，以阐述本发明的各个方面。它们无意、也不应被解释为将发明限制在这里所完整描述的范围内，发明范围见权利要求书。

实施例 1

4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮

1A. 5-溴-3-(3-氯-苯基)-苯并[c]异噁唑

在 0℃、干燥 N$_2$ 气氛下，向氢氧化钠(19.8g, 495mmol)的甲醇(36ml)溶液中加入 3-氯乙腈(17.5ml, 149mmol)。混合物在 0℃下搅

拌 30 分钟；在相同温度下加入 1-溴-4-硝基苯(20g，99mmol)固体。溶液在室温下搅拌 3 小时，然后加热回流一小时。反应混合物冷却至环境温度，在真空下除去 MeOH。使所得红色的油在乙酸乙酯(EtOAc)与水之间分配。有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到黄褐色固体。将该固体悬浮在 MeOH 中，沉淀出 1A 标题化合物，为黄色固体(17.3g，55.9mmol，56.7%收率)，使用时无需进一步纯化。

1B. (2-氨基-5-溴-苯基)-(3-氯-苯基)-甲酮

向实施例 1A 标题化合物(22.14g，78.1mmol)的 THF (300ml)溶液中加入 276ml 氯化钛(II)(在 20-30wt.%盐酸(HCl)中的 10wt.%溶液)。反应混合物搅拌 1.5 小时。然后将反应混合物倒入冰水中。从所得不均匀溶液中除去 THF。含水混合物用二氯甲烷(DCM)萃取。DCM 层连续用含水饱和 $NaHCO_3$ 和盐水洗涤。DCM 层经 $MgSO_4$ 干燥，过滤，在真空下浓缩，得到 1B 标题化合物，为浅黄色固体(21.86g，70.4mmol，98%收率)。该固体在使用时无需进一步纯化。

1C. 6-溴-4-(3-氯-苯基)-1H-喹啉-2-酮

在干燥 N_2 气氛下，将实施例 1B 标题化合物(21.86g，70.4mmol)悬浮在无水甲苯(140ml)中。向该溶液中按顺序加入 26.7ml (282mmol)乙酸酐(Ac_2O)、80ml (56.3mmol)三乙胺(NEt_3)和 8.60g (70.4mmol) 4-二甲氨基吡啶(DMAP)。然后加热反应混合物至回流，在该温度下搅拌 20 小时。反应混合物冷却至环境温度，经吸滤法收集沉淀。固体用乙醚(Et_2O)洗涤，在真空下干燥，得到实施例 1C 标题化合物(21.57g)。蒸发滤液，将残余物悬浮在冷的 EtOAc 中，生成沉淀，得到另外 4.64g 标题化合物。得到共计 20.21g (60.4mmol，85.8%收率)的实施例 1C 标题化合物，使用时无需进一步纯化。

1D. 6-溴-4-(3-氯-苯基)-2-甲氧基-喹啉

在干燥 N_2 气氛下，将实施例 1C 标题化合物(6.45g，19.4mmol)悬浮在 DCM (30ml)中。向该悬液中加入三甲基氧鎓四氟硼酸酯(BF_4OMe_3，2.99g，20.2mmol)。反应混合物在环境温度下搅拌 15 小时。然后在 0℃下冷却，加入 10%含水 NaOH 溶液(40ml)。使反应混合

物温热至室温，搅拌六小时，然后使其在DCM与水之间分配。DCM层用盐水洗涤，经$MgSO_4$干燥，在真空下浓缩，得到6.11g粗产物。经色谱法纯化，用DCM作为洗脱剂，得到实施例1D标题化合物，为黄色固体，5.23g（15mmol，78%收率）。

Cl-MS：m/z 348/350.

1E. [4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲醇

在-78℃、干燥N_2气氛下，向实施例1D标题化合物(1.47g，348.6mmol)的THF（10ml)溶液中滴加正丁基锂(2.5M己烷溶液，1.58ml)。在-78℃下搅拌30分钟后，加入(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲酮(582.7mg，2.64mmol)的THF（10ml)溶液。使反应混合物温热至环境温度，搅拌15小时。在0℃下，向混合物中加入氯化铵的饱和水溶液。从所得不均匀溶液中除去THF。含水混合物用氯仿($CHCl_3$)萃取。有机层用盐水洗涤，经$MgSO_4$干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用$MeOH-CHCl_3-NH_4OH$(2:98:0.2至5:95:0.5)作为洗脱剂，得到实施例1E标题化合物，为黄色固体(943mg，1.92mmol，73%收率)。

Cl-MS：m/z 491.1，493.1 [M + 1].

1F. 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮

向实施例1E标题化合物(4.67g，9.53mmol)的THF（340ml)溶液中滴加浓氯化氢(HCl，14ml)。混合物在60℃下加热5小时。冷却至室温后，除去THF。水溶液用40%含水NaOH调至pH = ~9，用$CHCl_3$萃取若干次。合并后的有机层用盐水洗涤，经$MgSO_4$干燥，在真空下浓缩，得到实施例1标题化合物，为不完全白色固体(2.46g，5.17mmol，54%收率)。

Cl-MS：m/z 476.8.

实施例2

4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑

-4-基)-甲基]-1-甲基-1H-喹啉-2-酮

向 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮(351mg, 0.737mmol)的 THF (15ml)溶液中加入 40%含水 NaOH (2ml)、苄基三乙基氯化铵(84mg, 0.369mmol)和甲基碘(0.078ml, 1.25mmol)的 THF (4ml)溶液。反应混合物在环境温度下搅拌 4 小时，然后使其在 $CHCl_3$ 与水之间分配。有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用 MeOH-$CHCl_3$-NH_4OH (2:98:0.2 至 5:95:0.5)作为洗脱剂，得到标题化合物，为白色固体(200.3mg, 0.408mmol, 55%收率)。

Cl-MS: m/z 491.1.

实施例 3

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮

将 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮(2g, 4.08mmol)溶于 25ml 亚硫酰氯($SOCl_2$)，在室温、干燥 N_2 气氛下搅拌 2 小时。在减压下除去亚硫酰氯。将粗的氯化物溶于甲苯，在真空下浓缩。将所得固体溶于 THF (20ml)，向该溶液中通入氨气(NH_3)达 30 分钟。反应混合物在环境温度、NH_3 气氛下搅拌 15 小时。除去 THF 后，使产物混合物在 $CHCl_3$ 与水之间分配。有机层洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到棕色固体。经过硅胶色谱法纯化，用 $CHCl_3$、然后用 MeOH-$CHCl_3$-NH_4OH (1:99:0.1)作为洗脱剂，得到标题化合物，为白色固体(1.065 g, 2.02mmol, 50%收率)。

C. 1. m/z 490.2, 492.2 [M+1].

实施例 4 和实施例 5

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮对映异构体的分离

将实施例 3 标题化合物 6-[氨基-(4-氯-苯基)-(3-甲基-3H-咪唑

-4-基)-甲基]-4-(3-乙炔基-苯基)-1-甲基-1H-喹啉-2-酮(159mg)分离为它的对映异构体，在 CHIRALCEL™ OD (Daicel Chemical Industries, LTD, Osaka, Japan 制造) (2.2cm x 25cm, 10μm；洗脱剂：己烷/乙醇/甲醇/二乙胺 80/10/10/0.02；25℃)上经过高效液相色谱法纯化。在这些条件下，得到 28mg 快速洗脱的对映异构体 A (实施例 4)和 3mg 的慢速移动的对映异构体 B (实施例 5)。两种对映异构体的光学纯度都>97%。

实施例 6

4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮

向实施例 1 标题化合物 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮 (100mg, 0.210mmol)的 DMF (2ml)溶液中加入 NaCl (8mg)、碳酸铯(Cs_2CO_3, 103mg, 0.315mmol)和(溴甲基)环丙烷(0.041ml, 0.420mmol)。反应混合物在环境温度下搅拌 15 小时。另外加入 0.041ml (溴甲基)环丙烷和 100mg Cs_2CO_3。反应混合物在 60℃下加热 1 小时，然后使其在 $CHCl_3$ 与水之间分配。有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用 MeOH-$CHCl_3$-NH_4OH (3:97:0)作为洗脱剂，得到标题化合物，为白色固体(25mg, 22%收率)。

Cl-MS: m/z 531.1,533.1 [M+1].

实施例 7

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮

采用与实施例 3 相同的操作，但是用 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮(400mg, 0.75mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮，得到标题化合物，为白色固体，137mg (0.26mmol, 34%收率)。

C. I. m/z 530.1,532.1 [M+1].

实施例 8

4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-异丁基-1H-喹啉-2-酮

按照与实施例 6 所述相同的操作，用 1-溴-2-甲基丙烷(0.041ml, 0.42mmol)代替(溴甲基)环丙烷。4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮(99.8mg, 0.21mmol)的烷基化作用得到标题化合物，为白色固体，20mg (0.038mmol, 18%收率)。

C. I. m/z 533.1,535.1 [M+1].

实施例 9

4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3-氯-苯基)-2-甲氧基-喹啉(2.89g, 8.31mmol)和(5-氯-吡啶-2-基)-(3-甲基-3H-咪唑-4-基)-甲酮(1.47g, 6.65mmol)生成 4.05g 粗的[4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲醇。

按照与实施例 1F 所述相同的操作，将所得[4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲醇在含水 THF 中用 HCl 处理，得到标题化合物，1.02g (2.14mmol, 26%收率)。

C. I. m/z 477.1,479.1 [M+1].

实施例 10

4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮

采用与实施例 2 所述相同的操作，但是用 4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮(230mg, 0.485mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到标题化合

物，为白色固体，195mg（0.40mmol，81%收率）。

实施例 11

6-[氨基-(5-氯-吡啶-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例 3 所述相同的操作，用 4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮(170mg，0.35mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮，得到标题化合物，为白色固体，69mg（0.14mmol，40%收率）。

C. I. m/z 490.0 [M+1].

实施例 12

4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮

采用与实施例 6 所述相同的操作，但是用 4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮(550mg，1.16mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到标题化合物，57mg（0.11mmol，9%收率）。

C. I. m/z 531.1 [M+1].

实施例 13

6-[氨基-(5-氯-吡啶-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮

采用与实施例 3 所述相同的操作，但是用 4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮(258mg，0.486mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮，得到标题化合物，为白色固体，112mg（0.21mmol，43%收率）。

C. I. m/z 530.0 [M+1].

实施例 14

4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-环丙基氨基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮

关于对应氯化物的生成，采用与实施例2相同的操作，但是用4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮(55mg, 0.112mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮。将所得氯化物溶于 DMF (8ml)。向该溶液中加入碳酸钾(K_2CO_3)和环丙胺(0.049ml, 0.786mmol)。反应混合物在环境温度下搅拌 15 小时，然后使其在 $CHCl_3$ 与水之间分配。有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用 $MeOH-CHCl_3-NH_4OH$ (2:98:0.2 至 5:95:0.5)作为洗脱剂，得到标题化合物，为白色固体(19mg, 0.036mmol, 32%收率)。

C. I. m/z 529.9 [M+1].

实施例 15

4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-环丙基氨基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮

采用与实施例 14 相同的操作，但是用 4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮(52mg, 0.098mmol)代替 4-(3-氯-苯基)-6-[(5-氯-吡啶-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮，得到标题化合物，为白色固体(24mg, 0.042mmol, 43%收率)。

C. I. m/z 569.9 [M+1].

实施例 16

6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3,5-二氯-苯基)-1-甲基-1H-喹啉-2-酮

16A. 6-溴-4-(3,5-二氯-苯基)-1H-喹啉-2-酮

采用与实施例 1C 相同的操作，但是用(2-氨基-5-溴苯基)-(3,5-二氯-苯基)-甲酮(1.50g, 4.35mmol)代替(2-氨基-5-溴-苯基)-(3-

氯-苯基)-甲酮，得到 16A 标题化合物，为白色固体，1.61g (100%收率)。

16B. 6-溴-4-(3,5-二氯-苯基)-2-甲氧基-喹啉

采用与实施例 1D 相同的操作，但是用 6-溴-4-(3,5-二氯-苯基)-1H-喹啉-2-酮(6.42g，17.4mmol)代替 6-溴-4-(3-氯-苯基)-1H-喹啉-2-酮，得到 16B 标题化合物，为白色固体，3.47g (52%收率)。

16C. [4-(3,5-二氯-苯基)-2-甲氧基-喹啉-6-基]-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲醇

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3,5-二氯-苯基)-2-甲氧基-喹啉(1.88g，4.91mmol)和(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲酮(0.94g，4.27mmol)生成 16C 标题化合物，为黄色固体(0.885g，39.5%收率)。

16D. 4-(3,5-二氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮

按照与实施例 1F 所述相同的操作，将[4-(3,5-二氯-苯基)-2-甲氧基-喹啉-6-基]-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲醇(886mg，1.68mmol)在 THF 中用 HCl 处理，得到 16D 标题化合物。它直接用于下面的反应，无需进一步纯化。

16E. 6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3,5-二氯-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例 2 相同的操作，但是用 4-(3,5-二氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮(~1.68mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到 16E 标题化合物，为白色固体，388.6mg (44%收率，16D 和 16E)。

C. I. m/z 525.0,527.0 [M+1].

实施例 17

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲

基]-4-(3,5-二氯-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例 3 相同的操作，但是用 6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3,5-二氯-苯基)-1-甲基-1H-喹啉-2-酮(298.6mg，0.567mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮，得到标题化合物，为白色固体，40mg (0.076mmol，13%收率)。

C. I. m/z 523.9，526.0[M+1].

实施例 18

4-(3-氯-苯基)-6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮

18A. [4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(5-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲醇

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3-氯-苯基)-2-甲氧基-喹啉(1.0g，1.87mmol)和(5-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲酮(170mg，3.44mmol)生成 18A 标题化合物，为黄色固体(919mg，65%收率)。

C. I. m/z 507.1 [M+1].

18B. 4-(3-氯-苯基)-6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮

按照与实施例 1F 所述相同的操作，将[4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(5-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲醇(740mg，1.49mmol)在含水 THF 中用 HCl 处理，得到 18B 标题化合物，为黄色固体，469.2mg (0.97mmol，65%收率)。

C. I. m/z 483.9 [M+1].

18C. 4-(3-氯-苯基)-6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮

采用与实施例 2 相同的操作，但是用 4-(3-氯-苯基)-6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮(76mg，0.157mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟

基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到标题化合物，为白色固体，49mg（0.10mmol，63%收率）

C. I. m/z 497.9 [M+1].

实施例 19

6-[氨基-(5-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例 3 相同的操作，但是用 4-(3-氯-苯基)-6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮(69mg，0.139mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶- 3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮，得到标题化合物，为白色固体，14mg（0.028mmol，20%收率）。

C. I. m/z 523.9, 526.0 [M+1].

实施例 20

4-(3-氯-苯基)-6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮

采用与实施例 6 相同的操作，但是用 4-(3-氯-苯基)-6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮(75mg，0.155mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶- 3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到标题化合物(15mg，20%收率)。

C. I. m/z 536.2, 538.2 [M+1].

实施例 21

4-(3-氯-苯基)-6-[(3-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮

21A. [4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(3-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲醇

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3-氯-苯基)-2-甲氧基-喹啉(300mg，0.859mmol)和(3-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲酮(230mg，1.032mmol)生成 21A 标题化合物，为黄色

固体(218.5mg，51%收率)。

21B. 4-(3-氯-苯基)-6-[(3-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮

按照与实施例1F所述相同的操作，将[4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(3-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲醇(208mg，0.42mmol)在含水THF中用HCl处理，得到21B标题化合物，为黄色固体(164.7mg，81%收率)。

21C. 4-(3-氯-苯基)-6-[(3-氯-噻吩-2-基)-羟基-(3-甲基-3H咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮

采用与实施例2相同的操作，但是用4-(3-氯-苯基)-6-[(3-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮(164.7mg，0.342mmol)代替4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到标题化合物，为白色固体(70mg，41%收率)。

C. I. m/z [M+1].

实施例22

6-[氨基-(3-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例3相同的操作，但是用4-(3-氯-苯基)-6-[(3-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮(65mg，0.13mmol)代替4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮，得到标题化合物，为白色固体(4.7mg，7%收率)。

C. I. m/z 459.0 [M+1].

实施例23

6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1H-喹啉-2-酮

23A. 6-溴-4-(3-乙氧基-苯基)-2-甲氧基-喹啉

向6-溴-4-(3-乙氧基-苯基)-1H-喹啉-2-酮(7.4g，21.5mmol)

的 60ml 二氯乙烷悬液中加入三甲基氧鎓四氟硼酸酯(BF_4OMe_3, 3.66g, 24.7mmol)。所得混合物在环境温度下搅拌过夜。冷却至 0℃后，滴加 60ml 10%含水 NaOH。反应混合物在环境温度下搅拌六小时。然后使其在二氯甲烷与水之间分配。有机层用盐水洗涤，经 $MgSO_4$ 干燥，过滤，在真空下浓缩，得到不完全白色固体。该固体经过快速硅胶色谱法纯化，用二氯甲烷洗脱，得到 23A 标题化合物，为白色固体(4.48g, 58%收率)。

23B. (5-氯-噻吩-2-基)-[4-(3-乙氧基-苯基)-2-甲氧基-喹啉-6-基]-(3-甲基-3H-咪唑-4-基)-甲醇

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3-乙氧基-苯基)-2-甲氧基-喹啉(800mg, 2.23mmol)和(5-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲酮(610mg, 2.68mmol)生成 23B 标题化合物(810mg, 72%收率)。

23C. 6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1H-喹啉-2-酮

按照与实施例 1F 所述相同的操作，将(5-氯-噻吩-2-基)-[4-(3-乙氧基-苯基)-2-甲氧基-喹啉-6-基]-(3-甲基-3H-咪唑-4-基)-甲醇(810mg, 1.60mmol)在含水 THF 中用 HCl 处理，得到标题化合物(578mg, 74%收率)。

C.I. m/z 492.1 [M+1]

实施例 24

6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基-甲基]-4-(3-乙氧基-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例 2 相同的操作，但是用 6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1H-喹啉-2-酮(578.4mg, 1.18mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到标题化合物，为白色固体(241mg, 40.4%收率)。

C. I. m/z 506.2 [M+1].

实施例 25

氨基-(5-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例 3 相同的操作，但是用 6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1-甲基-1H-喹啉-2-酮(240mg, 0.47mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮，得到标题化合物，为白色固体(196mg, 82%收率)。

C. I. m/z 505.1,507.2 [M+1].

实施例 26

6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1H-喹啉-2-酮

26A. (6-氯-吡啶-3-基)-[4-(3-乙氧基-苯基)-2-甲氧基-喹啉-6-基]-(3-甲基-3H-咪唑-4-基)-甲醇

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3-乙氧基-苯基)-2-甲氧基-喹啉(2g, 5.59mmol)和(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲酮(1.48g, 6.70mmol)生成 26A 标题化合物(1.458g, 52%收率)。

26B. 6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1H-喹啉-2-酮

按照与实施例 1F 所述相同的操作，将(6-氯-吡啶-3-基)-[4-(3-乙氧基-苯基)-2-甲氧基-喹啉-6-基]-(3-甲基-3H-咪唑-4-基)-甲醇(1.458g, 2.92mmol)在含水 THF 中用 HCl 处理，得到标题化合物(1.21g, 85%收率)。

C. I. m/z 487.2 [M+1].

实施例 27

6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例 2 相同的操作，但是用 6-[(6-氯-吡啶-3-基)-羟基

-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1H-喹啉-2-酮(80.6mg, 0.166mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到标题化合物，为白色固体(43mg, 52%收率)。

C. I. m/z 501.2 [M+1].

实施例 28

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例 3 相同的操作，但是用 6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1-甲基-1H-喹啉-2-酮(20mg, 0.04mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮，得到标题化合物，为白色固体(4.5mg, 22.5%收率)。

C. I. m/z 501.2 [M+1].

实施例 29

6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1-异丁基-1H-喹啉-2-酮

采用与实施例 8 相同的操作，由 6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1H-喹啉-2-酮(50mg, 0.103mmol)和 1-溴-2-甲基丙烷(0.022ml, 0.206mmol)生成标题化合物，为白色固体(24mg, 40%收率)。

C. I. m/z 543.3 [M+1].

实施例 30

6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-4-(3-乙氧基-苯基)-1H-喹啉-2-酮

采用与实施例 8 相同的操作，由 6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-乙氧基-苯基)-1H-喹啉-2-酮(50mg, 0.103mmol)和(溴甲基)环丙烷(0.020ml, 0.206mmol)生成标题化合物，为白色固体(4mg, 7%收率)。

C. I.. m/z 541.3 [M+1].

实施例 31

6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-甲氧基-苯基)-1-甲基-1H-喹啉-2-酮

31A. (5-氯-噻吩-2-基)-[2-甲氧基-4-(3-甲氧基-苯基)-喹啉-6-基]-(3-甲基-3H-咪唑-4-基)-甲醇

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3-甲氧基-苯基)-2-甲氧基-喹啉(1g, 2.91mmol)和(5-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲酮(0.78g, 3.49mmol)生成 31A 标题化合物(1.147g, 80.2%收率)。

C. I. m/z 492.1 [M+1].

31B. 6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-甲氧基-苯基)-1H-喹啉-2-酮

按照与实施例 1F 所述相同的操作，将(5-氯-噻吩-2-基)-[4-(3-甲氧基-苯基)-2-甲氧基-喹啉-6-基]-(3-甲基-3H-咪唑-4-基)-甲醇(1.14g, 2.34mmol)在含水 THF 中用 HCl 处理，得到 31B 标题化合物(1.12g, 100%收率)。

C. I. m/z 478.1 [M+1].

31C. 6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-甲氧基-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例 2 相同的操作，但是用 6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-甲氧基-苯基)-1H-喹啉-2-酮(1.12g, 2.34mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，色谱纯化后得到两种化合物。由具有较高 R_f 值的部分得到实施例 31 标题化合物，为白色固体(422mg, 36.7%收率)。

C. I. m/z 492.1 [M+1].

实施例 32

6-[(5-氯-噻吩-2-基)-甲氧基-(3-甲基-3H-咪唑-4-基)-甲

基]-4-(3-甲氧基-苯基)-1-甲基-1H-喹啉-2-酮

同实施例31C的反应，由具有较低R_f值的部分得到实施例32标题化合物，为白色固体(50mg，4.2%收率)。

C. I. m/z 506.2 [M+1].

实施例33

6-[氨基-(5-氯-噻吩-2-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-甲氧基-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例3相同的操作，但是用6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-甲氧基-苯基)-1-甲基-1H-喹啉-2-酮(43mg，0.087mmol)代替4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮，得到标题化合物，为白色固体(18mg，42%收率)。

C. I. m/z 493.1 [M+1].

实施例34

6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-异丙氧基-苯基)-1H-喹啉-2-酮

34A. 3-(6-溴-2-甲氧基-喹啉-4-基)-苯酚

在0℃下，向6-溴-4-(3-甲氧基-苯基)-2-甲氧基-喹啉(1.31g，3.81mmol)的二氯甲烷(CH_2Cl_2，30ml)溶液中加入BBr_3的CH_2Cl_2溶液(1M，11.4ml，11.4mmol)。使反应混合物温热至室温，搅拌4小时。将其倒入水中。有机层用盐水洗涤，经$MgSO_4$干燥，浓缩，得到实施例34A标题化合物(640mg，41%收率)。

34B. 6-溴-4-(3-异丙氧基-苯基)-2-甲氧基-喹啉

向实施例34A标题化合物(460mg，1.39mmol)的DMF (10ml)溶液中加入碳酸铯(Cs_2CO_3，906mg，2.78mmol)和异丙基溴(0.458ml，4.88mmol)。反应混合物在环境温度下搅拌15小时。另外加入0.041ml(溴甲基)环丙烷和100mg Cs_2CO_3。反应混合物在60℃下加热1小时，然后使其在乙醚与水之间分配。有机层用盐水洗涤，经$MgSO_4$干燥，在真空下浓缩，得到粗的实施例34B标题化合物(458mg，89%收率)。

Cl-MS: m/z 372.1, 374.1 [M+1].

34C. 6-[(6-氯-吡啶-3-基)-[4-(3-异丙氧基-苯基)-2-甲氧基-喹啉-6- 基]-(3-甲基-3H-咪唑-4-基)-甲醇

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3-异丙氧基-苯基)-2-甲氧基-喹啉(238.4mg，0.640mmol)和(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲酮(156mg，0.705mmol)生成 34C 标题化合物(80mg，24%收率)。

34D. 6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-异丙氧基-苯基)-1H-喹啉-2-酮

按照与实施例 1F 所述相同的操作，将 6-[(6-氯-吡啶-3-基)-[4-(3-异丙氧基-苯基)-2-甲氧基-喹啉-6-基]-(3-甲基-3H-咪唑-4-基)-甲醇(75mg，0.14mmol)在含水 THF 中用 HCl 处理，得到标题化合物(20mg，27%收率)。

C. I. m/z 581.0 [M+1].

实施例 35

6-[(5-氯-噻吩-2-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-羟基-苯基)-1-甲基-1H-喹啉-2-酮

按照与实施例 34A 所述相同的操作，将实施例 31 标题化合物(100mg，0.203mmol)用 BBr_3 的 CH_2Cl_2 溶液(1M，1.02ml，1.02mmol)处理，得到标题化合物(64mg，67%收率)。

C. I. m/z 478.1 [M+1].

实施例 36

4-(3-氯-苯基)-6-(羟基-二-吡啶-3-基-甲基)-1-甲基-1H-喹啉-2-酮

36A. [4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-二-吡啶-3-基-甲醇

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3-甲氧基-苯基)-2-甲氧基-喹啉(400mg，1.15mmol)和二-吡啶-3-基-甲酮(232mg，1.26mmol)生成 36A 标题化合物(303mg，58%收率)。

C. I. m/z 454.0,456.0 [M+1].

36B. 4-(3-氯-苯基)-6-(羟基-二-吡啶-3-基-甲基)-1H-喹啉-2-酮

按照与实施例 1F 所述相同的操作，将[4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-二-吡啶-3-基-甲醇(300mg, 0.66mmol)在含水 THF 中用 HCl 处理，得到标题化合物(290mg, 100%收率)。

C. I. m/z 581.0 [M+1].

36C. 4-(3-氯-苯基)-6-(羟基-二-吡啶-3-基-甲基)-1-甲基-1H-喹啉-2-酮

采用与实施例 2 相同的操作，但是用 4-(3-氯-苯基)-6-(羟基-二-吡啶-3-基-甲基)-1H-喹啉-2-酮(78mg, 0.178mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到实施例 36C 标题化合物，为白色固体(23mg, 29%收率)。

C. I. m/z 454.2 [M+1].

实施例 37

4-(3-乙氧基-苯基)-6-(羟基-二-吡啶-3-基-甲基)-1-甲基-1H-喹啉-2-酮

37A. [4-(3-乙氧基-苯基)-2-甲氧基-喹啉-6-基]-二-吡啶-3-基-甲醇

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3-乙氧基-苯基)-2-甲氧基-喹啉(400mg, 1.11mmol)和二-吡啶-3-基-甲酮(225mg, 1.22mmol)生成 37A 标题化合物(212mg, 41.2%收率)。

C. I. m/z 464.1 [M+1].

37B. 4-(3-乙氧基-苯基)-6-(羟基-二-吡啶-3-基-甲基)-1H-喹啉-2-酮

按照与实施例 1F 所述相同的操作，将[4-(3-乙氧基-苯基)-2-甲氧基-喹啉-6-基]-二-吡啶-3-基-甲醇(212mg, 0.457mmol)在含水 THF 中用 HCl 处理，得到标题化合物(91mg, 44.3%收率)。

C. I. m/z 450.1 [M+1].

37C. 4-(3-乙氧基-苯基)-6-(羟基-二-吡啶-3-基-甲基)-1-甲基-1H-喹啉-2-酮

采用与实施例 2 相同的操作，但是用 4-(3-乙氧基-苯基)-6-(羟基-二-吡啶-3-基-甲基)-1H-喹啉-2-酮(91mg，0.202mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到实施例 37C 标题化合物，为白色固体(12mg，13%收率)。

C. I. m/z 464.1 [M+1].

实施例 38

4-(3-氯-苯基)-6-[羟基-(3-甲基-3H-咪唑-4-基)-喹啉-3-基甲基]-1-甲基-1H-喹啉-2-酮

38A. [4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(3-甲基-3H-咪唑-4-基)-喹啉-3-基-甲醇

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3-甲氧基-苯基)-2-甲氧基-喹啉(233mg，0.668mmol)和(喹啉-3-基)-(3-甲基-3H-咪唑-4-基)-甲酮(232mg，1.26mmol)生成 38A 标题化合物(81mg，24%收率)。

C. I. m/z 507.1 [M+1].

38B. 4-(3-氯-苯基)-6-[羟基-(3-甲基-3H-咪唑-4-基)-喹啉-3-基甲基]-1H-喹啉-2-酮

按照与实施例 1F 所述相同的操作，将 38A 标题化合物(81mg，0.16mmol)在含水 THF 中用 HCl 处理，得到实施例 38B 标题化合物(56.4mg，71%收率)。

C. I. m/z 493.0,495.0 [M+1].

38C. 4-(3-氯-苯基)-6-[羟基-(3-甲基-3H-咪唑-4-基)-喹啉-3-基甲基]-1-甲基-1H-喹啉-2-酮

采用与实施例 2 相同的操作，但是用 4-(3-氯-苯基)-6-[羟基-(3-甲基-3H-咪唑-基)-喹啉-3-基-甲基]-1H-喹啉-2-酮(56.4mg， 0.115mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到实施例 38C 标题化合物，为白色固体(31mg，53%收率)。

C. I. m/z 507.2 [M+1].

实施例 39

6-[氨基-(3-甲基-3H-咪唑-4-基)-喹啉-3-基-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例 3 相同的操作，但是用 4-(3-氯-苯基)-6-[羟基-(3-甲基-3H-咪唑-4-基)-喹啉-3-基-甲基]-1-甲基-1H-喹啉-2-酮(26mg，0.0514mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-甲基-1H-喹啉-2-酮，得到标题化合物，为白色固体(8.3mg，32%收率)。

C. I. m/z 506.2 [M+1].

实施例 40

4-(3-氯-苯基)-6-[(5-氯-噻吩-2-基)-咪唑-1-基甲基]-1-甲基-1H-喹啉-2-酮

40A. [4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(5-氯-噻吩-2-基)-甲酮

在-78℃、干燥 N_2 气氛下，向 6-溴-4-(3-氯-苯基)-2-甲氧基-喹啉(500mg，1.43mmol)的 THF (2ml)溶液中滴加正丁基锂(2.5M 己烷溶液，0.63ml，1.58mmol)。在-78℃下搅拌 30 分钟后，加入 5-氯-噻吩-2-羧酸甲氧基-甲基-酰胺(440mg，2.15mmol)的 THF (1ml)溶液。使反应混合物温热至环境温度，搅拌 15 小时。在 0℃下，向混合物中加入氯化铵的饱和水溶液。从所得不均匀溶液中除去 THF。含水混合物用氯仿($CHCl_3$)萃取。有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用 $MeOH-CHCl_3-NH_4OH$ (2:98:0.2 至 5:95:0.5)作为洗脱剂，得到实施例 40A 标题化合物(273.5mg，46%收率)。

Cl-MS: m/z 414.0 [M + 1].

40B. 4-(3-氯-苯基)-6-(5-氯-噻吩-2-羰基)-1-1H-喹啉-2-酮

按照与实施例 1F 相同的操作，将[4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(5-氯-噻吩-2-基)-甲酮(273mg，0.66mmol)在含水 THF 中用 HCl 处理，得到实施例 40B 标题化合物，为白色固体(145mg，53%收率)。

C. I. m/z 413.0，415.0 [M+1].

40C. 4-(3-氯-苯基)-6-(5-氯-噻吩-2-羰基)-1-甲基-1H-喹啉-2-酮

采用与实施例 2 相同的操作，但是用 4-(3-氯-苯基)-6-(5-氯-噻吩-2-羰基)-1-1H-喹啉-2-酮(56mg，0.14mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到实施例 40C 标题化合物，为白色固体(58mg，100%收率)。

C. I. m/z 413.9 [M+1].

40D. 4-(3-氯-苯基)-6-[(5-氯-噻吩-2-基)-羟基-甲基]-1-甲基-1H-喹啉-2-酮

在 0℃下，向 4-(3-氯-苯基)-6-(5-氯-噻吩-2-羰基)-1-甲基-1H-喹啉-2-酮 (58mg，0.154mmol)的 MeOH (1ml)溶液中加入硼氢化钠固体($NaBH_4$，7mg，0.185mmol)。反应混合物在 0℃下搅拌一小时，然后使其在氯仿与水之间分配。有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到不完全白色固体(49mg，78.5%收率)。

40E. 6-[氯-(5-氯-噻吩-2-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮

向 4-(3-氯-苯基)-6-[(5-氯-噻吩-2-基)-羟基-甲基]-1-甲基-1H-喹啉-2-酮(49mg，0.12mmol)的 CH_2Cl_2 (0.5ml)溶液中滴加亚硫酰氯。反应混合物在室温下搅拌四小时。在减压下除去亚硫酰氯。将粗的氯化物溶于甲苯，在真空下浓缩，得到黄色固体，使用时无需进一步纯化。

40F. 4-(3-氯-苯基)-6-[(5-氯-噻吩-2-基)-咪唑-1-基-甲基]-1-甲基-1H-喹啉-2-酮

将实施例 40E 粗产物溶于乙腈(CH_3CN, 1ml)。向该溶液中加入咪唑(29mg, 0.42mmol)和 K_2CO_3 (58mg, 0.42mmol)。混合物回流 15 小时，然后使其在氯仿与水之间分配。有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用 MeOH-$CHCl_3$-NH_4OH (2:98:0.2)作为洗脱剂，得到标题化合物(17mg, 30%收率，两步)。

Cl-MS: m/z 398.0,400.0 [M-C3H3N2 (imidazole)].

实施例 41

6-[苯并[b]噻吩-2-基-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮

41A. 苯并[b]噻吩-2-基-[4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(3-甲基-3H-咪唑-4-基)-甲醇

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3-氯-苯基)-2-甲氧基-喹啉(273mg, 0.784mmol)和苯并[b]噻吩-2-基-(3-甲基-3H-咪唑-4-基)-甲酮(247mg, 1.01mmol)生成 41A 标题化合物(248mg, 62%收率)。

C. I. m/z 507.1 [M+1].

41B. 6-[苯并[b]噻吩-2-基-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1H-喹啉-2-酮

按照与实施例 1F 所述相同的操作，将苯并[b]噻吩-2-基-[4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(3-甲基-3H-咪唑-4-基)-甲醇(147.2mg, 0.287mmol)在含水 THF 中用 HCl 处理，得到 41B 标题化合物，为黄色固体(40mg, 28%收率)。

41C. 6-[苯并[b]噻吩-2-基-羟基- (3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮

采用与实施例 2 相同的操作，但是用 6-[苯并[b]噻吩 2-基-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1H-喹啉-2-酮(40mg, 0.08mmol)代替 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到标题化合物，

为白色固体(5.3mg，13%收率)。

C. I. m/z 512.1 [M+1].

实施例 42

6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1H-喹啉-2-酮

在干燥 N_2 气氛下，向 6-溴-4-(3-氯-苯基)-2-甲氧基-喹啉(20.95g，42.76mmol)的甲苯(150ml)溶液中滴加亚硫酰氯(31.19ml，427mmol)。反应混合物在 85℃下加热 15 小时。在减压下除去溶剂和过量亚硫酰氯。将粗的氯化物溶于甲苯，在真空下浓缩。将所得固体溶于 THF (10ml)，在-78℃下向该溶液中通入氨气(NH_3)达 10 分钟。反应混合物在环境温度、N_2 气氛下再搅拌 1.5 小时。除去 THF 后，使产物混合物在 $CHCl_3$ 与水之间分配。有机层洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用 $CHCl_3$、然后用 $MeOH-CHCl_3-NH_4OH$ (2:98:0.1 至 7:93:0.1)作为洗脱剂，得到标题化合物(17.89 g，88%收率)。

C. 1. m/z 473.8 [M+1].

实施例 43

4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-[(4-甲氧基-亚苄基)-氨基]-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮

43A. 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-[(4-甲氧基-亚苄基)-氨基]-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮

向实施例 42 标题化合物(11.89g，25.03mmol)的乙酸(75ml)溶液中滴加对茴香醛(6.09ml，50.06mmol)。反应混合物在环境温度下搅拌 4 小时，然后冷却至 0℃。加入 10ml 氢氧化铵，再加入乙酸乙酯。分离后，有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用 $MeOH-CHCl_3-NH_4OH$ (1:99:0.1 至 5:95:0.1)作为洗脱剂，得到实施例 43A 标题化合物，为白色固体(11.58g，78%收率)。

Cl-MS：m/z 594.1,596.1 [M + 1].

43B. 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-[(4-甲氧基-亚苄基)-氨基]-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮

向实施例43A标题化合物(10.78g, 18.14mmol)的THF (2.5ml)溶液中加入(溴甲基)环丙烷(2.42ml, 24.96mmol)、苄基三乙基氯化铵(2.59g, 11.34mmol)、碘化钠(0.85g, 5.67mmol)和40%含水NaOH溶液(30ml)。反应混合物在65℃下加热4小时，然后除去THF。使粗产物混合物在$CHCl_3$与水之间分配。有机层用盐水洗涤，经硫酸镁干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用$MeOH-CHCl_3-NH_4OH$ (1.5:98.5:0.1)作为洗脱剂，得到标题化合物，为白色固体(8.49g, 13.10mmol, 72%收率)。

Cl-MS: m/z 648.1 [M+1].

实施例44和实施例45

4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-[(4-甲氧基-亚苄基)-氨基]-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮的(+)与(-)对映异构体

将实施例43标题化合物(1.322g)分离为它的对映异构体，在CHIRALCEL™ OD (Daicel Chemical Industries, LTD, Osaka, Japan制造) (2.2cm x 25cm, 10μm; 洗脱剂：乙烷/乙醇/甲醇/二乙胺80/10/10/0.1; 25℃)上经过高效液相色谱法纯化。在这些条件下，得到0.595g快速洗脱的对映异构体A (实施例44): (+)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-[(4-甲氧基-亚苄基)-氨基]-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮和0.511g慢速移动的对映异构体B (实施例45): (-)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-[(4-甲氧基-亚苄基)-氨基]-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮。两种对映异构体的光学纯度都>99%。

实施例46

4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-(4-甲氧基-苄氨

基)-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮

46A. 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-(4-甲氧基-苄氨基)-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮

在干燥N_2气氛下，向6-溴-4-(3-氯-苯基)-2-甲氧基-喹啉(1.08g, 2.21mmol)的甲苯(8.5ml)溶液中滴加亚硫酰氯(1.61ml, 22.06mmol)。反应混合物在85℃下加热15小时。在减压下除去溶剂和过量亚硫酰氯。将粗产物溶于甲苯，在真空下浓缩。将所得固体溶于THF (10ml)，在-78℃下向该溶液中加入对甲氧基苄胺(1.44ml, 11.03mmol)的THF (2ml)溶液。反应混合物在-78℃、N_2气氛下搅拌3小时。除去THF后，使产物混合物在$CHCl_3$与水之间分配。有机层洗涤，经$MgSO_4$干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用$MeOH-CHCl_3-NH_4OH$ (2:98:0.1)作为洗脱剂，得到实施例46A标题化合物(0.482g, 52%收率)。

C. I. m/z 596.1 [M+1].

46B. 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-(4-甲氧基-苄氨基)-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮

采用与实施例43B所述相同的操作，但是用4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-(4-甲氧基-苄氨基)-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮(0.682g, 1.14mmol)代替4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-[(4-甲氧基-亚苄基)-氨基]-(3-甲基-3H-咪唑-4-基)-甲基]-1H-喹啉-2-酮，得到标题化合物(0.315g, 0.485mmol, 43%收率)。

C. I. m/z 650.1 [M+1].

实施例47和实施例48

4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-(4-甲氧基-苄氨基)-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮的(+)与(-)对映异构体

将实施例46标题化合物4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-(4-甲氧基-苄氨基)-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基

甲基-1H-喹啉-2-酮(3.05g)分离为它的对映异构体，在 CHIRALCEL™ OD (Daicel Chemical Industries, LTD, Osaka, Japan 制造)(2.2cm x 25cm, 10μm; 洗脱剂：己烷/乙醇/甲醇/二乙胺 80/10/10/0.1; 25℃)上经过高效液相色谱法纯化。在这些条件下，得到 1.56 g 快速洗脱的对映异构体 A (实施例 47)：(+)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-(4-甲氧基-苄氨基)-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮和 1.07g 慢速移动的对映异构体 B (实施例 48)：(-)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-(4-甲氧基-苄氨基)-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮。两种对映异构体的光学纯度都> 99%。

实施例 49

(+)-6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮

操作 1，实施例 45 的转化

向实施例 45 标题化合物、即 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-[(4-甲氧基-亚苄基)-氨基]-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮的慢速移动的对映异构体(1.41g, 1.74mmol)的 THF (200ml)溶液中缓慢加入 2N 盐酸(20ml)。反应混合物在环境温度下搅拌 1.5 小时，然后冷却至 0℃。加入碳酸钾的水溶液，再加入乙酸乙酯。分离后，有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用 MeOH-$CHCl_3$-NH_4OH (1:99:0.1 至 2:98:0.1)作为洗脱剂，得到标题化合物，为白色固体(0.844g, 1.59mmol, 90%收率)。它是 6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮的快速洗脱的对映异构体，光学纯度> 99 %。

C. I. m/z: 530.1, 532.1 [M+1].

操作 2，实施例 48 的转化

在 0℃下，向实施例 48 标题化合物(慢速移动的对映异构体)(-)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-(4-甲氧基-苄氨

基)-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮(1.07g, 1.64mmol)的二氯甲烷(6.5ml)溶液中缓慢加入三氟乙酸(TFA, 6.5ml)。反应混合物在环境温度下搅拌 80 分钟，然后用 DCM (10ml)稀释，倒入冷却的碳酸钾水溶液。分离后，有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用 $MeOH-CHCl_3-NH_4OH$ (1.5:98.5:0.15)作为洗脱剂，得到标题化合物，为白色固体(0.588g, 1.11mmol, 68%收率)。它是 6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮的快速洗脱的对映异构体，光学纯度> 99 %。

C. I. m/z: 530.1, 532.1 [M+1].

实施例 50

(-)-6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮

操作 1，实施例 44 的转化

按照与实施例 49 关于实施例 45 的转化所述相同的操作，从实施例 44 标题化合物、即 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-[(4-甲氧基-亚苄基)-氨基]-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮的快速洗脱的对映异构体(1.98g, 3.05mmol)得到标题化合物，为白色固体(1.51g, 2.85mmol, 93%收率)。它是 6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮的慢速移动的对映异构体，光学纯度> 99 %。

C. I. m/z: 530.1, 532.1 [M+1].

操作 2，实施例 47 的转化

按照与实施例 49 关于实施例 48 的转化所述相同的操作，从实施例 47 标题化合物(快速洗脱的对映异构体)(+)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-(4-甲氧基-苄氨基)-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮(0.249g, 0.384mmol)得到标题化合物，为白色固体(0.137g, 0.252mmol, 66%收率)。它是 6-[氨基-(6-

氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮的慢速移动的对映异构体，光学纯度>98%。

C. I. m/z: 530.1,532.1 [M+1].

实施例 51

6-[氨基-(6-甲基-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮

51A. [4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(6-甲基-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲醇

按照与实施例 1E 所述相同的操作，由 6-溴-4-(3-氯-苯基)-2-甲氧基-喹啉(0.200g, 0.574mmol)和(6-甲基-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲酮(0.105g, 0.522mmol)生成 0.118g (48%收率)[4-(3-氯-苯基)-2-甲氧基-喹啉-6-基]-(6-甲基-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲醇。

C. I. m/z: 470.9 [M+1].

51B. 6-[氨基-(6-甲基-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1H-喹啉-2-酮

在干燥 N_2 气氛下，向实施例 51A 标题化合物(0.118g, 0.251mmol)的甲苯(5ml)溶液中滴加亚硫酰氯(0.18ml, 2.51mmol)。反应混合物在 85℃下加热 15 小时。在减压下除去溶剂和过量亚硫酰氯。将粗的氯化物溶于甲苯，在真空下浓缩。将所得固体溶于 THF (10ml)，在-78℃下向该溶液中通入氨气(NH_3)达 10 分钟。反应混合物在环境温度、N_2 气氛下另外搅拌 1.5 小时。除去 THF 后，使产物混合物在 $CHCl_3$ 与水之间分配。有机层洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到棕色固体。经过硅胶色谱法纯化，用 $CHCl_3$、再用 MeOH-$CHCl_3$-NH_4OH (5:95:0.1 至 10:89:1)作为洗脱剂，得到实施例 51B 标题化合物，为白色固体(53mg, 0.116mmol, 46.4%收率)。

C. I. m/z 456.3 [M+1].

51C. 6-[氨基-(6-甲基-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-甲基-1H-喹啉-2-酮

向实施例 51B 标题化合物(26mg，0.057mmol)的 THF (2.5ml)溶液中加入 40%含水 NaOH (0.1ml)、苄基三乙基氯化铵(6.5mg，0.074mmol)和甲基碘(0.0046ml，0.0743mmol)。反应混合物在环境温度下搅拌 3 小时，然后除去 THF。使粗产物混合物在 $CHCl_3$ 与水之间分配。有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过薄层色谱法纯化，用 MeOH-$CHCl_3$-NH_4OH (5:95:0.1)作为移动相，得到标题化合物，为白色固体(14.4mg，0.031mmol，54%收率)。

Cl-MS：m/z 470.0 [M+1].

实施例 52

6-[氨基-(6-甲基-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮

向实施例 51B 标题化合物(26mg，0.057mmol)的 THF (2.5ml)溶液中加入(溴甲基)环丙烷(0.0075ml，0.080mmol)、苄基三乙基氯化铵(6.5mg. 0.0286mmol)、碘化钠(2.57mg，0.0171mmol)和 40%含水 NaOH 溶液(0.57ml)。反应混合物在 65℃下加热 3 小时，然后除去 THF。使粗产物混合物在 $CHCl_3$ 与水之间分配。有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用 MeOH-$CHCl_3$-NH_4OH (2:98:0.1 至 5:95:0.1)作为洗脱剂，得到标题化合物，为白色固体(11mg，0.022mmol，38%收率)。

Cl-MS：m/z 510.3 [M+1].

实施例 53

6-[氨基-(吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮

在 0℃下，向实施例 7 标题化合物 6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮(0.408g，0.77mmol)的吡啶(0.77ml)溶液中加入三氯乙基氯甲酸酯(0.159ml，1.15mmol)。使反应混合物逐渐温热至室温，搅拌过夜。除去吡啶后，将产物混合物溶于二氯甲烷和水。分离后，有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过

硅胶色谱法纯化，用 MeOH-$CHCl_3$-NH_4OH (1:99:0.1)作为洗脱剂，得到三氯乙基氨基甲酸酯，为白色固体(0.451g，0.64mmol，83%收率)。

Cl-MS：m/z 705.8,708.0 [M+1].

向三氯乙基氨基甲酸酯(34mg，0.048mmol)的甲酸(0.96ml)溶液中加入锌粉(87mg)。反应混合物在环境温度下搅拌 15 分钟。加入甲醇后，混合物通过硅藻土过滤，再加入碳酸钾的饱和溶液。滤液蒸发，用氯仿萃取。有机层用盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用 MeOH-$CHCl_3$-NH_4OH (2:98:0.)作为洗脱剂，得到标题化合物，为白色固体(25mg，100%收率)。

Cl-MS：m/z 496.1 [M+1].

实施例 54 和实施例 55

4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮的(+)与(-)对映异构体

向实施例 43 标题化合物(4.31g，6.64mmol)的 THF (30ml)溶液中加入 38ml 1N 硫酸。混合物冷却至 0℃后，滴加亚硝酸钠($NaNO_2$，1.45g，20.99mmol)的水(10ml)溶液。反应混合物在环境温度下搅拌 7 小时，然后加入乙酸乙酯。有机层用饱和碳酸钾、盐水洗涤，经 $MgSO_4$ 干燥，在真空下浓缩，得到粗产物。经过硅胶色谱法纯化，用 MeOH-$CHCl_3$-NH_4OH (2:98:0.1)作为洗脱剂，得到实施例 6 标题化合物 4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮，为白色固体(3.32g，94%收率)。

Cl-MS：m/z 530.9 [M+1].

将(+/-)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮(3.002g)分离为它的对映异构体，在 CHIRALCEL™ OD (Daicel Chemical Industries, LTD, Osaka, Japan 制造) (2.2cm x 25cm，10μm；洗脱剂：己烷/乙醇/甲醇 85/7.5/7.5；25℃)上经过高效液相色谱法纯化。在这些条件下，得到 1.14g 快速洗脱的对映异构体 A (实施例 54)：

(-)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮和 0.7g 慢速移动的对映异构体 B (实施例 55)：(+)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮。两种对映异构体的光学纯度都> 98 %。

实施例 56

(+)-6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮二盐酸盐

向(+)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮(0.844g, 1.59mmol)的 DCM (10ml)溶液中加入 HCl 的乙醚溶液(1M, 4.77ml, 4.77mmol)。浆状溶液搅拌 2 小时。过滤后，得到实施例 56 标题化合物，为白色固体(0.78 g, 1.29mmol, 81.4%收率)。

实施例 57

(-)-6-[氨基-(6-氯-吡啶-3-基)-(3-甲基-3H-咪唑-4-基)-甲基]-4-(3-氯-苯基)-1-环丙基甲基-1H-喹啉-2-酮二盐酸盐

按照与实施例 56 所述相同的操作，由(-)-4-(3-氯-苯基)-6-[(6-氯-吡啶-3-基)-羟基-(3-甲基-3H-咪唑-4-基)-甲基]-1-环丙基甲基-1H-喹啉-2-酮(0.252g, 0.474mmol)生成二盐酸盐，为白色固体(0.167g, 0.28mmol, 58%收率)。