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(54) Title: HCV INHIBITORS AND METHODS OF USING THEM

(57) Abstract: The present invention comprises tetrazoloquinoline-compounds that are inhibitors of HCV. Compositions comprising the compounds in combination with a pharmaceutically acceptable carrier are also disclosed, as are methods of using the compounds and compositions to inhibit HCV infection of a cell, particular in the form of treating HCV infection in a mammal.

HCV INHIBITORS AND METHODS OF USING THEM

This application claims priority from U.S. Provisional Patent Application No. 60/506,556, filed on September 26, 2003 and from U.S. Provisional Patent Application No. 60/576,536, filed on June 3, 2004.

BACKGROUND OF THE INVENTION**Field of the Invention**

[0001] The present invention is in the field of small molecule inhibitors of HCV and methods of using them to inhibit HCV.

Summary of the Related Art

[0002] The hepatitis C virus (HCV) is one of the most important causes of chronic liver disease in the United States. It accounts for about 15 percent of acute viral hepatitis, 60 to 70 percent of chronic hepatitis, and up to 50 percent of cirrhosis, end-stage liver disease, and liver cancer. Almost 4 million Americans, or 1.8 percent of the U.S. population, have antibody to HCV (anti-HCV), indicating ongoing or previous infection with the virus. Hepatitis C causes an estimated 8,000 to 10,000 deaths annually in the United States.

[0003] A distinct and major characteristic of hepatitis C is its tendency to cause chronic liver disease. At least 75 percent of patients with acute hepatitis C ultimately develop chronic infection, and most of these patients have accompanying chronic liver disease.

[0004] Chronic hepatitis C varies greatly in its course and outcome. At one end of the spectrum are patients who have no signs or symptoms of liver disease and completely normal levels of serum liver enzymes. Liver biopsy usually shows some degree of chronic hepatitis, but the degree of injury is usually mild, and the overall prognosis may be good. At the other end of the spectrum are patients with severe hepatitis C who have symptoms, HCV RNA in serum, and elevated serum liver enzymes, and who ultimately develop cirrhosis and end-stage liver disease. In the middle of the spectrum are many patients who have few or no symptoms, mild to moderate elevations in liver enzymes, and an uncertain prognosis. Researchers estimate that at least 20 percent of patients with chronic hepatitis C develop cirrhosis, a process that takes 10 to 20 years. After 20 to 40 years, a smaller percentage of patients with chronic disease develop liver cancer. The therapy of chronic hepatitis C has evolved steadily since alpha interferon was first approved for use in this disease more than ten years ago. At the present time, the optimal regimen appears to be a 24- or 48-week course of the combination of pegylated alpha interferon and ribavirin.

[0005] Two forms of peginterferon have been developed and studied in large clinical trials: peginterferon alfa-2a (Pegasys®: Hoffman La Roche: Nutley, NJ) and peginterferon alfa-2b (Pegintron®: Schering-Plough Corporation, Kenilworth, NJ). These two products are roughly

equivalent in efficacy and safety, but have different dosing regimens. Peginterferon alfa-2a is given subcutaneously in a dose of 180 mcg per week. Peginterferon alfa-2b is given subcutaneously weekly in doses of 1.5 mcg per kilogram per week (thus in the range of 75 to 150 mcg per week).

[0006] Ribavirin is an oral antiviral agent that has activity against a broad range of viruses. By itself, ribavirin has little effect on HCV, but adding it to interferon increases the sustained response rate by two- to three-fold. For these reasons, combination therapy is now recommended for hepatitis C and interferon monotherapy is applied only when there are specific reasons not to use ribavirin.

[0007] Ribavirin is an oral medication, given twice a day in 200-mg capsules for a total daily dose of 800 to 1,200 mg based upon body weight and the form of peginterferon. When combined with peginterferon alfa-2b, the recommended dose of ribavirin is 800 mg per day. When combined with peginterferon alfa-2a, the dose of ribavirin is 1,000 mg for patients who weigh less than 75 kilograms (165 pounds) and 1,200 mg for those who weight more than 75 kilograms. In all situations, ribavirin is given in two divided doses daily.

[0008] At the present, peginterferon alfa-2a has not been approved for use in chronic hepatitis C in the United States and is available only in clinical trials. Thus, only peginterferon alfa-2b is available for general use.

[0009] Combination therapy leads to rapid improvements in serum ALT levels and disappearance of detectable HCV RNA in up to 70 percent of patients. However, long-term improvement in hepatitis C occurs only if HCV RNA disappears during therapy and stays undetectable once therapy is stopped. Among patients who become HCV RNA negative during treatment, a proportion relapse when therapy is stopped. The relapse rate is lower in patients treated with combination therapy compared with monotherapy. Thus, a 48-week course of combination therapy using peginterferon and ribavirin yields a sustained response rate of approximately 55 percent. A similar course of peginterferon monotherapy yields a sustained response rate of only 35 percent. A response is considered "sustained" if HCV RNA remains undetectable for six months or more after stopping therapy.

[0010] The optimal duration of treatment varies depending on whether interferon monotherapy or combination therapy is used, as well as by HCV genotype. For patients treated with peginterferon monotherapy, a 48-week course is recommended, regardless of genotype. For patients treated with combination therapy, the optimal duration of treatment depends on viral genotype. Patients with genotypes 2 and 3 have a high rate of response to combination treatment (70 to 80 percent), and a 24-week course of combination therapy yields results equivalent to those of a 48-week course. In contrast, patients with genotype 1 have a lower rate of response to combination therapy (40 to 45 percent), and a 48-week course yields a significantly better sustained response rate. Again, because of the variable responses to treatment, testing for HCV genotype is clinically useful when using combination therapy.

[0011] In view of the foregoing, there is a desire for alternative, more effective agents for treating HCV infection.

SUMMARY OF THE INVENTION

[0012] The invention provides compounds and methods for treating HCV infection. The invention provides new inhibitors of HCV.

[0013] In a first aspect, the invention provides compounds that are useful as inhibitors of HCV.

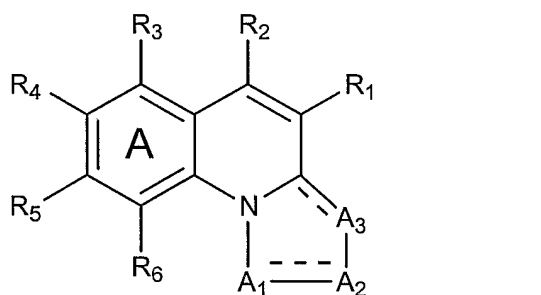
[0014] In a second aspect, the invention provides a composition comprising an inhibitor of HCV according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent.

[0015] In a third aspect, the invention provides a method of inhibiting HCV in a cell, comprising contacting a cell in which inhibition of HCV is desired with an inhibitor of HCV of the invention.

[0016] The foregoing merely summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

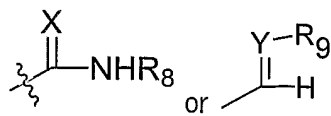
[0017] The first aspect of the invention provides for compounds represented by formula I



or a pharmaceutically acceptable salt thereof wherein

R_1 and R_2 are independently hydrogen, C_1 - C_6 -alkyl, heterocyclic, C_1 - C_6 -alkyl-OH, aryl, heteroaryl, halogen, cyano, -CO-H, -CO-OH, -CO-OR₇, -CO-NH₂, -CO-NHR₇, -CO-NR₇R₇, -CO-NH-OH, -CO-NH-OR₇, -CO-N(R₇)-OR₇, -CO-R₇, -SO₂NH₂, -SO₂NHR₇, -SO₂NR₇R₇, -SO₂-heteroaryl, -SO₂-aryl, -NHR₇, C_1 - C_6 -alkyl-NH(R₇)-aryl, -NH(R₇)-aryl, -CO-heteroaryl, -NH-CO-O-R₇-aryl, -NH-CO-NH-SO₂-aryl, -NH-CO-OR₇, -NH-CO-NH(C_1 - C_6 -alkyl) or -NH-CO-(C_1 - C_6 -alkyl), wherein each of the heteroaryl and aryl groups are optionally substituted with C_1 - C_6 -alkyl, nitro, hydroxy, C_1 - C_6 -alkoxy, -CO-O-(C_1 - C_6 -alkyl), cyano, -O-halo(C_1 - C_6 -alkyl), halo(C_1 - C_6 -alkyl) or halogen; or

R_1 or R_2 is a group selected from



wherein R_8 is hydrogen or hydroxy; X is =NH or =S, Y is =N-, and R_9 is hydroxy, C_1-C_6 -alkoxy or aryl optionally substituted with hydroxy or C_1-C_6 -alkyl; or

R_1 and R_2 together with the carbon atoms to which they are attached form a mono or bicyclic aryl or heteroaryl;

R_3 , R_4 , R_5 and R_6 are independently hydrogen, nitro, C_1-C_6 -alkyl, aryl, -O-halo(C_1-C_6 -alkyl), halo(C_1-C_6 -alkyl), -O-(C_3-C_6 -cycloalkyl), -S-(C_1-C_6 -alkyl), heterocyclyl, C_1-C_6 -alkoxy, -(C_1-C_6 -alkoxy)-aryl, azido, halogen, -OCF₃, -CF₃, -CO-H, -CO-OH, -CO-OR₇, -CO-NH₂, -CO-NHR₇, -CO-NR₇R₇, -CO-N(R₇)OR₇, -CO-R₇, -SO₂-(C_1-C_6 -alkyl), -SO₂NH₂, -SO₂NHR₇, -SO₂NR₇R₇, -CO-heteroaryl, -NH₂, -NHR₇, -NR₇R₇, -OH, -N(R₇)-CO-R₇, -NHSO₂R₇, -N(R₇)-CO-OR₇ or -N(R₇)-CO-NR₇R₇;

R_4 and R_5 together with the carbon atoms to which they are attached form a heteroaryl;

R_7 is a cation, C_0-C_6 -alkyl, -(C_1-C_6 -alkyl)-OH, -(C_1-C_6 -alkyl)-O-(C_1-C_6 -alkyl), -(C_1-C_6 -alkyl)-CN, C_2-C_6 -alkene, heterocyclyl, aryl, heteroaryl or -(C_1-C_6 -alkyl)-aryl, wherein each of the aryl, heterocyclyl and heteroaryl groups are optionally substituted with C_1-C_6 -alkyl, nitro, hydroxy, C_1-C_6 -alkoxy, -CO-O-(C_1-C_6 -alkyl), cyano, -O-halo(C_1-C_6 -alkyl), halo(C_1-C_6 -alkyl) or halogen;

A_1 , A_2 and A_3 are independently carbon, oxygen, or nitrogen, wherein the carbon or nitrogen is optionally substituted with halo or C_1-C_6 -alkyl; and

ring A optionally contains from 1 to 2 nitrogen atoms;

provided that when A_1 , A_2 , and A_3 are N:

R_1 to R_6 are not all hydrogen;

when R_2 to R_6 are hydrogen, R_1 is not -CH₃, -CO-phenyl, -CO-H or chloro;

when R_1 and R_3 to R_6 are hydrogen, R_2 is not bromo, -CH₂-OH, cyano, iodo, -CO-OH, -CH₃, -CH₂OCH₃, morpholino, -CH₂NH-CH₂CH₃, vinyl, -CH₂CH₃, chloro, -CH₂NH₂ or azido;

when R_1 to R_3 and R_5 to R_6 are hydrogen, R_4 is not chloro, ethynyl or -CH₃;

when R_1 to R_4 and R_6 are hydrogen, R_5 is not -CH₃ or -CH₂NH-isopropyl;

when R_1 to R_5 are hydrogen, R_6 is not -CH₂Br, chloro, -CH₃, -CH₂-OH, -CO-H, -NO₂, -NH₂, acetamido, -CH₂OCH₃, -CH₂-CN, propyl, iodo or -CH₂OCH₂CH₃; and

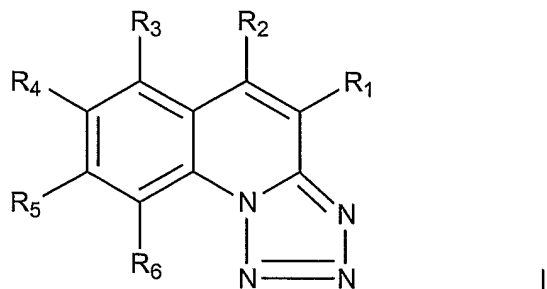
the compounds of formula I are not one of the following combinations

A_1	A_2	A_3	R_1	R_2	R_3	R_4	R_5	R_6
N	N	N	-CO-H	-H	-H	-H	-CH ₃	-H
N	N	N	-CO-OH	-H	-H	-N ₃	-N ₃	-H
N	N	N	-CO-OH	-H	-H	-OCH ₃	-OCH ₃	-H
N	N	N	-CO-H	-H	-H	-H	-CH ₃	-H
N	N	N	-H	-CH ₃	-H	-H	-OCH ₃	-H
N	N	N	-CN	piperidyl	-H	-H	-H	-H
N	N	N	-H	-Cl	-H	-H	-H	-CH ₃

A ₁	A ₂	A ₃	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
N	N	N	-CN	-Cl	-H	-H	-H	-H
N	N	N	-H	-CH ₃	-H	-CH ₂ CH ₃	-H	-H
C	N	N	-H	-CH ₃	-H	-H	-H	-H
C	N	N	-H	-H	-H	-H	-H	-H
N	N	N	-H	-CH ₃	-H	-H	-H	-F
N	N	N	-H	-CH ₃	-H	-H	-H	-Br
N	N	N	-CH ₃	-Cl	-H	-H	-H	-H
N	N	N	-CH ₂ CH ₃	-Cl	-H	-H	-H	-H
N	N	N	-H	-Cl	-H	-H	-H	-CH ₂ NHCH ₃
N	N	N	-H	-Cl	-H	-CH ₃	-H	-H
N	N	N	-H	-Cl	-H	-H	-H	-CH ₃
N	N	N	-H	-Cl	-H	-H	-H	-Cl
N	N	N	-H	-N ₃	-H	-CH ₃	-H	-H
N	N	N	-H	-N ₃	-H	-H	-H	-Cl
N	N	N	-H	-N ₃	-H	-CH ₃	-H	-H
N	N	N	-CH ₃	-Cl	-H	-H	-H	-CH ₃
N	N	N	-H	-CH ₂ Cl	-H	-H	-H	-CH ₂ Cl
N	N	N	-CH ₃	-Cl	-H	-H	-H	-Cl
N	N	N	-H	-CH ₃	-H	-H	-H	-CH ₃
N	N	N	-H	-CH ₃	-H	-CH ₃	-H	-H
N	N	N	-CH ₃	-Cl	-H	-H	-H	-F
N	N	N	-H	-Cl	-H	-H	-H	-F
N	N	N	-H	-Cl	-Cl	-H	-H	-Cl
N	N	N	-H	-Cl	-H	-H	-H	-CH ₃
N	N	N	-H	-CH ₃	-H	-H	-H	-CH ₂ CH ₃
N	N	N	-H	-CH ₃	-H	-CH ₂ CH ₃	-H	-H
N	N	N	-H	morpholino	-H	-Cl	-H	-Cl
N	N	N	-H	-CH ₃	-H	-Cl	-H	-H
N	N	N	-Cl	-CH ₃	-H	-H	-H	-H
N	N	N	-H	-CH ₃	-H	-H	-H	-Cl

[0018] In one embodiment of the invention, the compounds of formula I are compounds wherein A₁, A₂ and A₃ are independently carbon or nitrogen each optionally substituted with halo or C₁-C₆-alkyl. In a preferred embodiment one of A₁, A₂ and A₃ is carbon optionally substituted with halo or C₁-C₆-alkyl. Preferably, halo is chloro, fluoro or bromo and C₁-C₆-alkyl is methyl, ethyl, or propyl. More preferably, halo is chloro and C₁-C₆-alkyl is methyl.

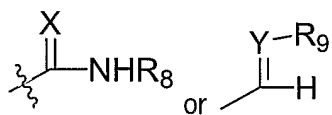
[0019] The invention also provides for compounds represented by formula II



or a pharmaceutically acceptable salt thereof wherein

R_1 and R_2 are independently hydrogen, C_1 - C_6 -alkyl, heterocyclic, C_1 - C_6 -alkyl-OH, aryl, heteroaryl, halogen, cyano, -CO-H, -CO-OH, -CO-OR₇, -CO-NH₂, -CO-NHR₇, -CO-NR₇R₇, -CO-NH-OH, -CO-NH-OR₇, -CO-N(R₇)-OR₇, -CO-R₇, -SO₂NH₂, -SO₂NHR₇, -SO₂NR₇R₇, -SO₂-heteroaryl, -SO₂-aryl, -NHR₇, C_1 - C_6 -alkyl-NH(R₇)-aryl, -NH(R₇)-aryl, -CO-heteroaryl, -NH-CO-O-R₇-aryl, -NH-CO-NH-SO₂-aryl, -NH-CO-OR₇, -NH-CO-NH-(C_1 - C_6 -alkyl) or -NH-CO-(C_1 - C_6 -alkyl), wherein each of the heteroaryl and aryl groups are optionally substituted with C_1 - C_6 -alkyl, nitro, hydroxy, C_1 - C_6 -alkoxy, -CO-O-(C_1 - C_6 -alkyl), cyano, -O-halo(C_1 - C_6 -alkyl), halo(C_1 - C_6 -alkyl) or halogen; or

R_1 or R_2 is a group selected from



wherein R_8 is hydrogen or hydroxy; X is =NH or =S; Y is =N-, and R_9 is hydroxy, C_1 - C_6 -alkoxy or aryl optionally substituted with hydroxy or C_1 - C_6 -alkyl; or

R_1 and R_2 together with the carbon atoms to which they are attached form a mono or bicyclic aryl or heteroaryl;

R_3 , R_4 , R_5 and R_6 are independently hydrogen, nitro, C_1 - C_6 -alkyl, aryl, -O-halo(C_1 - C_6 -alkyl), halo(C_1 - C_6 -alkyl), -O-(C_3 - C_6 -cycloalkyl), -S-(C_1 - C_6 -alkyl), heterocyclyl, C_1 - C_6 -alkoxy, -(C_1 - C_6 -alkoxy)-aryl, azido, halogen, -OCF₃, -CF₃, -CO-H, -CO-OH, -CO-OR₇, -CO-NH₂, -CO-NHR₇, -CO-NR₇R₇, -CO-N(R₇)-OR₇, -CO-R₇, -SO₂-(C_1 - C_6 -alkyl), -SO₂NH₂, -SO₂NHR₇, -SO₂NR₇R₇, -CO-heteroaryl, -NH₂, -NHR₇, -NR₇R₇, -OH, -N(R₇)-CO-R₇, -NHSO₂R₇, -N(R₇)-CO-OR₇ or -N(R₇)-CO-NR₇R₇;

R_4 and R_5 together with the carbon atoms to which they are attached form a heteroaryl;

R_7 is a cation, C_0 - C_6 -alkyl, -(C_1 - C_6 -alkyl)-OH, -(C_1 - C_6 -alkyl)-O-(C_1 - C_6 -alkyl), -(C_1 - C_6 -alkyl)-CN, C_2 - C_6 -alkene, heterocyclyl, aryl, heteroaryl or -(C_1 - C_6 -alkyl)-aryl, wherein each of the aryl, heterocyclyl and heteroaryl groups are optionally substituted with C_1 - C_6 -alkyl, nitro, hydroxy, C_1 - C_6 -alkoxy, -CO-O-(C_1 - C_6 -alkyl), cyano, -O-halo(C_1 - C_6 -alkyl), halo(C_1 - C_6 -alkyl) or halogen; and

provided that:

R_1 to R_6 are not all hydrogen;

when R₂ to R₆ are hydrogen, R₁ is not -CO-phenyl, -CO-H or chloro;

when R₁ and R₃ to R₆ are hydrogen, R₂ is not bromo, -CH₂-OH, cyano, iodo, -CO-OH, -CH₃, -CH₂OCH₃, morpholino, -CH₂NH-CH₂CH₃, vinyl, -CH₂CH₃, chloro, -CH₂NH₂ or azido;

when R₁ to R₃ and R₅ to R₆ are hydrogen, R₄ is not chloro, ethynyl or -CH₃;

when R₁ to R₄ and R₆ are hydrogen, R₅ is not -CH₃ or -CH₂NH-isopropyl;

when R₁ to R₅ are hydrogen, R₆ is not -CH₂Br, chloro, -CH₃, -CH₂-OH, -CO-H, -NO₂, -NH₂, acetamido, -CH₂OCH₃, -CH₂-CN, propyl, iodo or -CH₂OCH₂CH₃; and

the compounds of formula II are not one of the following combinations

R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
-CO-H	-H	-H	-H	-CH ₃	-H
-CO-OH	-H	-H	-N ₃	-N ₃	-H
-CO-OH	-H	-H	-OCH ₃	-OCH ₃	-H
-CO-H	-H	-H	-H	-CH ₃	-H
-H	-CH ₃	-H	-H	-OCH ₃	-H
-CN	piperidyl	-H	-H	-H	-H
-H	-Cl	-H	-H	-H	-CH ₃
-CN	-Cl	-H	-H	-H	-H
-H	-CH ₃	-H	-CH ₂ CH ₃	-H	-H
-H	-CH ₃	-H	-H	-H	-F
-H	-CH ₃	-H	-H	-H	-Br
-CH ₃	-Cl	-H	-H	-H	-H
-CH ₂ CH ₃	-Cl	-H	-H	-H	-H
-H	-Cl	-H	-H	-H	-CH ₂ NHCH ₃
-H	-Cl	-H	-CH ₃	-H	-H
-H	-Cl	-H	-H	-H	-CH ₃
-H	-Cl	-H	-H	-H	-Cl
-H	-N ₃	-H	-CH ₃	-H	-H
-H	-N ₃	-H	-H	-H	-Cl
-H	-N ₃	-H	-CH ₃	-H	-H
-CH ₃	-Cl	-H	-H	-H	-CH ₃
-H	-CH ₂ Cl	-H	-H	-H	-CH ₂ Cl
-CH ₃	-Cl	-H	-H	-H	-Cl
-H	-CH ₃	-H	-H	-H	-CH ₃
-H	-CH ₃	-H	-CH ₃	-H	-H
-CH ₃	-Cl	-H	-H	-H	-F
-H	-Cl	-H	-H	-H	-F

R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
-H	-Cl	-Cl	-H	-H	-Cl
-H	-Cl	-H	-H	-H	-CH ₃
-H	-CH ₃	-H	-H	-H	-CH ₂ CH ₃
-H	-CH ₃	-H	-CH ₂ CH ₃	-H	-H
-H	morpholino	-H	-Cl	-H	-Cl
-H	-CH ₃	-H	-Cl	-H	-H
-Cl	-CH ₃	-H	-H	-H	-H
-H	-CH ₃	-H	-H	-H	-Cl

[0020] In one embodiment of the invention, the compounds of formula II are compounds wherein R₁ is -CO-NH-OR₇, R₅ is halogen, R₂ to R₄ and R₆ are hydrogen. More preferably, R₇ is hydrogen and R₅ is chloro.

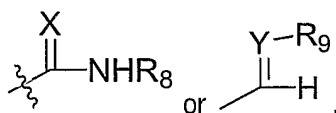
[0021] In another embodiment, the compounds of formula II are compounds wherein R₁ is aryl optionally substituted with one or more halo(C₁-C₆-alkyl), cyano, -O-halo(C₁-C₆-alkyl), or halogen, R₅ is halogen, R₂ to R₄ and R₆ are hydrogen. More preferably, the compounds are compounds wherein R₁ is phenyl optionally substituted with one or more -CF₃ or F and R₅ is chloro.

[0022] In yet another embodiment, the compounds of formula II are compounds wherein R₁ is -CO-NH-OR₇, R₆ is halogen and R₂ to R₅ are hydrogen. Preferred compounds of this embodiment are compound wherein R₇ is isobutyl, propyl, isopropyl or ethyl and R₆ is chloro.

[0023] In one other embodiment, the compounds of formula II are compounds wherein R₁ is -NH-CO-OR₇, R₅ is halogen, R₂ to R₄ and R₆ are hydrogen, preferably R₇ is tertbutyl and R₅ is chloro.

[0024] In another embodiment according to formula II, the compounds are compounds wherein R₁ is -CO-OR₇, R₆ is halo(C₁-C₆-alkyl) and R₂ to R₅ are hydrogen, preferably the compound are compounds wherein R₇ is hydrogen and R₆ is -CF₃.

[0025] In still another embodiment, the compounds according to formula II are compounds wherein R₁ is -NH-CO-NH-SO₂-aryl, -NH-CO-NH-(C₁-C₆-alkyl), C₁-C₆-alkyl-OH, -CO-H, -CO-NH₂, -CO-NH-R₇, -CO-NH-OR₇, -SO₂-aryl, -SO₂-heteroaryl, heteroaryl, -CO-OR₇ or a group represented by



wherein R₈ is hydrogen or hydroxy, X is =N or =S, Y is =N-, and R₉ is hydroxy or C₁-C₆-alkoxy; R₄ and R₅ are independently selected from hydrogen, -S-(C₁-C₆-alkyl), C₁-C₆-alkyl, -O-(C₃-C₆-cycloalkyl), C₁-C₆-alkoxy, halogen, -SO₂-(C₁-C₆-alkyl), heterocyclyl, -O-halo(C₁-C₆-alkyl), halo(C₁-C₆-alkyl), -NH₂ or together with the carbon atom to which they are attached form a heteroaryl group; R₂, R₃ and R₆ are hydrogen; and wherein the each of the aryl, heteroaryl and heterocyclyl groups are optionally

substituted with -CO-O-(C₁-C₆-alkyl), C₁-C₆-alkyl, nitro, hydroxy, C₁-C₆-alkoxy, cyano, -O-halo(C₁-C₆-alkyl), halo(C₁-C₆-alkyl) or halogen.

[0026] In another embodiment, the compounds according to formula II are compounds wherein R₁ and R₂ are independently -NH(R₇)-aryl, -CO-OH, -CO-OR₇, C₁-C₆-alkyl, aryl or together with the carbon atoms to which they are attached form a bicyclic heteroaryl; R₃ to R₆ are hydrogen; and wherein each of the aryl and heteroaryl groups are optionally substituted with -CO-O-(C₁-C₆-alkyl), C₁-C₆-alkyl, nitro, hydroxy, C₁-C₆-alkoxy, cyano, -O-halo(C₁-C₆-alkyl), halo(C₁-C₆-alkyl) or halogen.

[0027] In another embodiment, the compounds of formula II are compounds wherein R₁ is -CO-OH, -CO-OR₇, or -CO-NH-OR₇; R₆ is C₁-C₆-alkyl, halogen, or -O-(C₁-C₆-alkyl); and R₂ to R₅ are hydrogen.

[0028] In still another embodiment, the compounds according to formula II are compounds wherein R₁ is -CO-OR₇; R₃ is azido or C₁-C₆-alkyl; and R₂, R₄ to R₆ are hydrogen.

[0029] In a second aspect, the invention comprises a composition comprising a compound of any one of paragraphs [0017]-[0028] and a pharmaceutically acceptable carrier, excipient, or diluent.

[0030] In a third aspect, the invention provides a method of inhibiting HCV in a cell, comprising contacting a cell in which inhibition of HCV is desired with an inhibitor of HCV according to any one of paragraphs [0017]-[0028] or a composition according to paragraph [0029]. Because compounds of the invention inhibit HCV, they are also useful research tools for *in vitro* study HCV infections in cells and cellular systems.

[0031] In a preferred embodiment of the third aspect, the invention comprises a method of treating an HCV infection in a mammal, preferably a human, comprising administering to the mammal a therapeutically effective amount of a composition according to paragraph [0029].

Definitions

[0032] Unless expressly stated to the contrary, the following definitions apply uniformly throughout. For simplicity, the substituents have been defined primarily as univalent chemical moieties (e.g., alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances. All atoms are understood to have their normal number of valences for bond formation (i.e., 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). Also, where a chemical structure exists in multiple tautomeric forms, all are envisioned as part of the invention.

[0033] The term hydrocarbyl refers to a saturated, mono- or poly-unsaturated straight, branched or cyclic hydrocarbon and specifically includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, 3-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, acetylenyl, propynyl, cyclopropyl, and -C≡C-CH₂(alkyl) (including -C≡C-CH₂(CH₃)). A hydrocarbyl moiety may be defined to include a "C₀-C_n-hydrocarbyl," "C₀-C_n-alkyl," or the

like, in which n is an integer, as in "aryl-C₀-C₃-alkyl." In these instances a "C₀" moiety represents a direct bond. So, for example, "aryl-C₀-C₃-alkyl" encompasses both aryl-C₁-C₆-alkyl moieties as well as aryl moieties (C₀-alkyl).

[0034] An "aryl" group is a C₆-C₁₄ aromatic moiety comprising one to three aromatic rings, which is optionally substituted. Preferably, the aryl group is a C₆-C₁₀ aryl group. Preferred aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is (C₆-C₁₀)aryl-(C₁-C₆)alkyl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0035] The term heteroatom means O, S, or N.

[0036] A "heterocyclyl" group is a mono-, bi-, or tri-cyclic structure having from 3 to 14 atoms, wherein one or more annular atoms are selected from the group consisting of N, O, and S. The heterocyclic group is optionally substituted on carbon at one or more positions. The heterocyclic group is also independently optionally substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, aralkoxycarbonyl, or on sulfur with oxo or lower alkyl. Preferred heterocyclic groups include, without limitation, epoxy, aziridinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, oxazolidinonyl, and morpholino. In certain preferred embodiments, the heterocyclic group is fused to an aryl, heteroaryl, or cycloalkyl group. Examples of such fused heterocycles include, without limitation, tetrahydroquinoline and dihydrobenzofuran. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0037] In certain preferred embodiments, the heterocyclic group is a heteroaryl group. As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from zero to three heteroatoms per ring selected from the group consisting of N, O, and S, provided there is at least one heteroatom. A "heteroaralkyl" or "heteroarylalkyl" group comprises a heteroaryl group covalently linked to an alkyl group, either of which is independently optionally substituted or unsubstituted. Preferred heteroaralkyl groups comprise a C₁-C₆ alkyl group and a heteroaryl group having 5, 6, 9, or 10 ring atoms. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0038] For simplicity, reference to a "C_n-C_m" heterocyclyl or "C_n-C_m" heteroaryl means a heterocyclyl or heteroaryl having from "n" to "m" annular atoms, where "n" and "m" are integers. Thus, for example, a C₅-C₆-heterocyclyl is a 5- or 6- membered ring having at least one heteroatom, and includes pyrrolidinyl (C₅) and piperidinyl (C₆); C₆-heteroaryl includes, for example, pyridyl and pyrimidyl.

[0039] Preferred heterocyclyls and heteroaryls include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothienyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1H-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinoliny, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny, oxazolyl, oxazolidiny, pyrimidinyl, phenanthridiny, phenanthroliny, phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny, phthalaziny, piperaziny, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, puriny, pyranyl, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridooxazole, pyridoimidazole, pyridothiazole, pyridiny, pyridyl, pyrimidinyl, pyrrolidinyl, pyrroliny, 2H-pyrrolyl, pyrrolyl, quinazoliny, quinoliny, 4H-quinoliziny, quinoxaliny, quinuclidiny, tetrahydrofuranyl, tetrahydroisoquinoliny, tetrahydroquinoliny, tetrazolyl, 6H-1,2,5-thiadiaziny, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thienyl, triaziny, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0040] Open valences on the radical moieties described herein can occur on any one (or more for divalent radicals) of the atoms within the moiety. For example, the C₃ alkyl moiety includes both propyl and isopropyl. As another example, a divalent C₄ alkylene moiety includes both tetramethylene (-CH₂(CH₂)₂CH₂-) and ethylethylene (-CH(CH₂CH₃)CH₂-).

[0041] A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluor-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4 dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl. As another example, an oxo-substituted moiety is one in which both hydrogens of a methylene (-CH₂-) are replaced with an oxygen to form a carbonyl (-CO-).

[0042] Substituents can be protected or unprotected as necessary, as known to those skilled in the art or as taught, for example, in Greene, *et al.*, "Protective Groups in Organic Synthesis," John Wiley and Sons, Third Edition, 1999.

[0043] As used herein, the term pharmaceutically acceptable salt(s) refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric

"acid," succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid. In another preferred embodiment, the invention comprises the compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR^+ Z^-$, wherein R is hydrogen, alkyl, or benzyl, and Z is a counter-ion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamate, mandelate, benzoate, and diphenylacetate). For the purposes of the specification and claims, the term salt is intended to encompass complexes as well.

[0044] As employed herein, when a moiety (e.g., cycloalkyl, hydrocarbyl, aryl, heteroaryl, heterocyclic, urea, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (e.g., an annular -CH- substituted with oxo is -C(O)-) nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, , alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

- (a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino,
- (b) C₁-C₅ alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ alkoxy, C₁-C₈ alkoxy carbonyl, aryloxy carbonyl, C₂-C₈ acyl, C₂-C₈ acylamino, C₁-C₈ alkylthio, arylalkylthio, arylthio, C₁-C₈ alkylsulfinyl, arylalkylsulfinyl, arylsulfinyl, C₁-C₈ alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C₀-C₆ N-alkyl carbamoyl, C₂-C₁₅ N,N-dialkylcarbamoyl, C₃-C₇ cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C₃-C₇ heterocycle, C₅-C₁₅ heteroaryl, or any of these rings fused or spiro-fused to a cycloalkyl, heterocycle, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; and
- (c) $-(CH_2)_s-NR^{30}R^{31}$, wherein s is from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6, and R³⁰ and R³¹ are each independently hydrogen, cyano, oxo, carboxamido, amidino, C₁-C₈ hydroxyalkyl, C₁-C₃ alkylaryl, aryl-C₁-C₃ alkyl, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ alkoxy, C₁-C₈ alkoxy carbonyl, aryloxy carbonyl, aryl-C₁-C₃ alkoxy carbonyl, C₂-C₈ acyl, C₁-C₈ alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, aroyl,

aryl, cycloalkyl, heterocyclyl, or heteroaryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; or

R³⁰ and R³¹ taken together with the N to which they are attached form a heterocyclyl or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents from (a), above.

[0045] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine. As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent. The term "acylamino" refers to an amide group attached at the nitrogen atom (*i.e.*, R-CO-NH-). The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom (*i.e.*, NH₂-CO-). The nitrogen atom of an acylamino or carbamoyl substituent is additionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom. The term "amino" is meant to include NH₂, alkylamino, arylamino, and cyclic amino groups. The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

[0046] The term "radical" as used herein means a chemical moiety comprising one or more unpaired electrons.

[0047] A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluoro-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4 dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl. Included within this definition are methylenes (-CH₂-) substituted with oxygen to form carbonyl (-CO-).

[0048] An "unsubstituted" moiety as defined above (*e.g.*, unsubstituted cycloalkyl, unsubstituted heteroaryl, etc.) means that moiety as defined above that does not have any of the optional substituents for which the definition of the moiety (above) otherwise provides. Thus, for example, while an "aryl" includes phenyl and phenyl substituted with a halo, "unsubstituted aryl" does not include phenyl substituted with a halo.

[0049] Preferred embodiments of a particular genus of compounds of the invention include combinations of preferred embodiments.

[0050] As used herein, the term pharmaceutically acceptable salt(s) refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid, and polygalacturonic acid.

The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR + Z^-$, wherein R is hydrogen, alkyl, or benzyl, and Z is a counter-ion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamate, mandelate, benzyloate, and diphenylacetate).

[0051] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. The term "therapeutically effective amount" is meant to denote a dosage sufficient to inhibit proliferation of the virus in the patient. A preferred dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01–3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

[0052] The compound is conveniently administered in any suitable unit dosage form, including but not limited to one containing 1 to 3000 mg, preferably 5 to 500 mg of active ingredient per unit dosage form. An oral dosage of 1–500, preferably 10–250, more preferably 25–250 mg is usually suitable.

[0053] The active ingredient should be administered to achieve peak plasma concentrations of the active compound of about 0.001–30 μM , preferably about 0.01–10 μM . This may be achieved, for example, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient.

[0054] The concentration of active compound in the drug composition will depend on absorption, distribution, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

[0055] Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

[0056] The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a dispersing agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterores; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials that modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or enteric agents. See generally "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA.

[0057] The active compound or pharmaceutically acceptable salt thereof can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. Syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[0058] The active compound or pharmaceutically acceptable salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, other anti-inflammatories, or antiviral compounds.

[0059] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerin, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

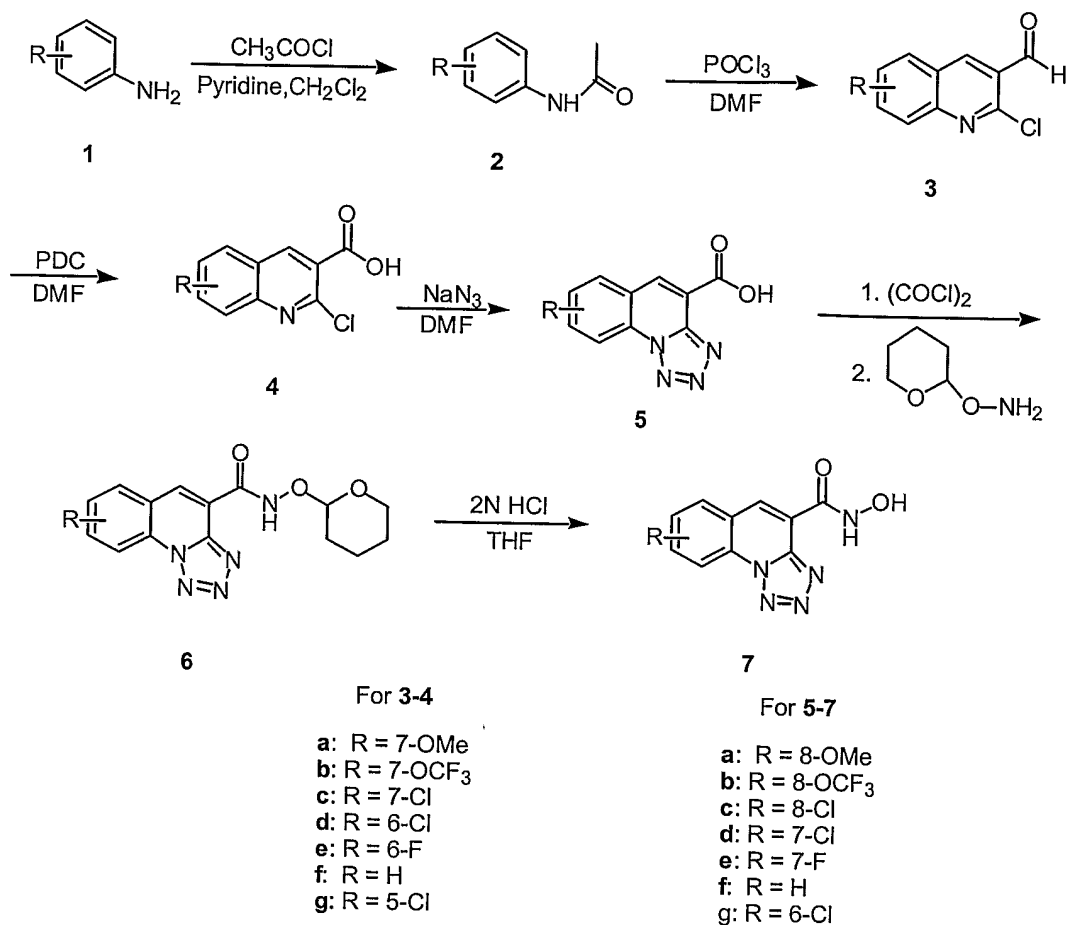
[0060] If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

[0061] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be

used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polyacetic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation (CA) and Gilford Pharmaceuticals (Baltimore, Md.). Liposomal suspensions may also be pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearyl phosphatidyl ethanolamine, stearyl phosphatidylcholine, arachadoyl phosphatidylcholine, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. Aqueous solutions of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives are then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

Synthesis

[0062] The compounds of the invention can be synthesized according to the schemes presented below using methods well known to those skilled in the art. For example, methods that can be used to make the compounds of the invention are described in Shehata *et al.*, Monatshefte fur Chemie 121: pp 1017-1021 and Meth-Cohn *et al.*, J.C.S. Perkin I: pp 2509-2517, both of which are incorporated by reference in their entirety. One skilled in the art will recognize that the substituents of the starting compound **1** can be varied using well known synthetic procedures. For example, various types of substitution reactions can take place on the phenyl group of compound **1** to give the alkoxy, alkyl, haloalkyl, or sulfonylalkyl product. Similarly, various types of substitution reactions or condensation reactions on any of the species in Scheme 1 will result in the various compounds described in this invention. For example, compound **5** can be reacted with any suitable amine instead of H₂N-OTHP.



[0063] Representative procedure for the preparation of 2,7-dichloroquinoline-3-carboxaldehyde (3c): To a dry reaction flask equipped with a reflux condenser, a magnetic stirring bar and a rubber septum with a N₂ inlet was placed 3-chloroacetanilide (**2**, 8.45 g, 50 mmol) and POCl₃ (34 mL, 365 mmol). The reaction mixture was cooled to 0 °C and to it was added DMF (10.5 mL, 135 mmol) over a period of 20 minutes. It was stirred at that temperature for 1 h and then at 65-75 °C for 24 h. The resulting slurry was cooled to room temperature, poured over a crushed-ice (1 Kg), digested for 1 h, the resulting solid was filtered, washed well with water and dried to give 5.26g (47%) of the desired 2,7-dichloroquinoline-3-carboxaldehyde (**3c**). ¹H NMR (CDCl₃, 300 MHz): δ 10.54 (s, 1H), 8.74 (s, 1H), 8.07 (d, 1H, J = 2.1 Hz), 7.93 (d, 1H, J = 9.0 Hz), 7.61 (dd, 1H, J = 2.4 and 8.7 Hz); LCMS (m/z): 226 (M⁺).

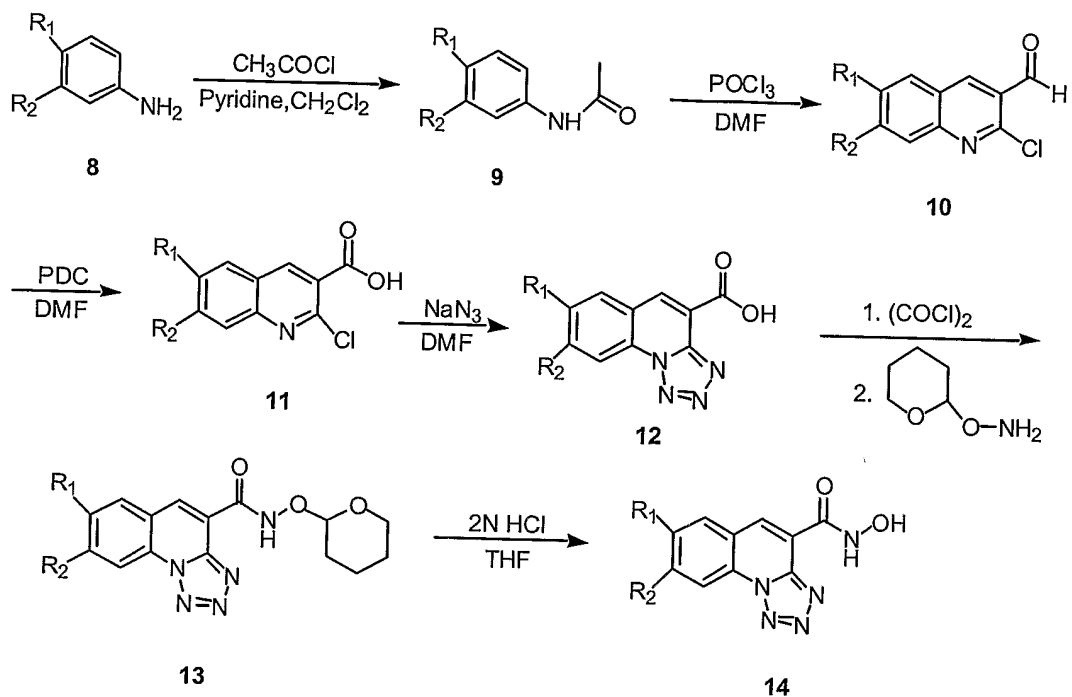
[0064] Representative procedure for the preparation of 2,7-dichloroquinoline-3-carboxylic acid (4c): A dry reaction flask equipped with a magnetic stirring bar and a rubber septum was charged with 2,7-dichloroquinoline-3-carboxaldehyde (**3c**, 1.1 g, 5 mmol), PDC (3.76 g, 10 mmol) and dry DMF (5 mL) and stirred at room temperature for 24 h. The reaction mixture was diluted with water (500 mL), filtered, the filtrate was saturated with NaCl and the resulting aqueous

the solution was extracted with EtOAc (3 x 200 mL). The EtOAc extract was dried over anhydrous Na₂SO₄ and solvent was removed to give 1.02 g (85%) of the desired 2,7-dichloroquinoline-3-carboxylic acid (**4c**). TLC Rf: 0.12 (20% MeOH/EtOAc); ¹H NMR (acetone d₆, 300 MHz): 8.96 (s, 1H); 8.22 (d, 1H, J = 9.0 Hz), 8.04 (d, 1H, J = 1.8 Hz), 7.97 (bs, 1H), 7.74 (dd, 1H, J = 1.8 and 8.7 Hz); LCMS (m/z): 241 (MH⁺).

[0065] Representative procedure for the preparation of 8-chlorotetrazolo[1,5-a]quinoline-4-carboxylic acid (5c): To a dry reaction vial with a screw cap was placed 2,7-dichloroquinoline-3-carboxylic acid (0.241 g, 1 mmol), sodium azide (0.078 g, 1.2 mmol) and dry DMF (3 mL) and shaken at 65-75 °C for a period of 24 h. The reaction mixture was diluted with water (100 mL), saturated with NaCl, the resulting solid was filtered and dried to give 0.100 g (41%) of the carboxytetrazole **5c**. TLC Rf: 0.06 (20% MeOH/EtOAc); ¹H NMR (DMSO d₆ + CDCl₃, 300 MHz): δ 8.71 (bs, 1H), 8.60 (s, 1H), 8.30 (d, 1H, J = 7.8 Hz), 7.79 (d, 1H, J = 7.5 Hz); LCMS (m/z): 249 (MH⁺).

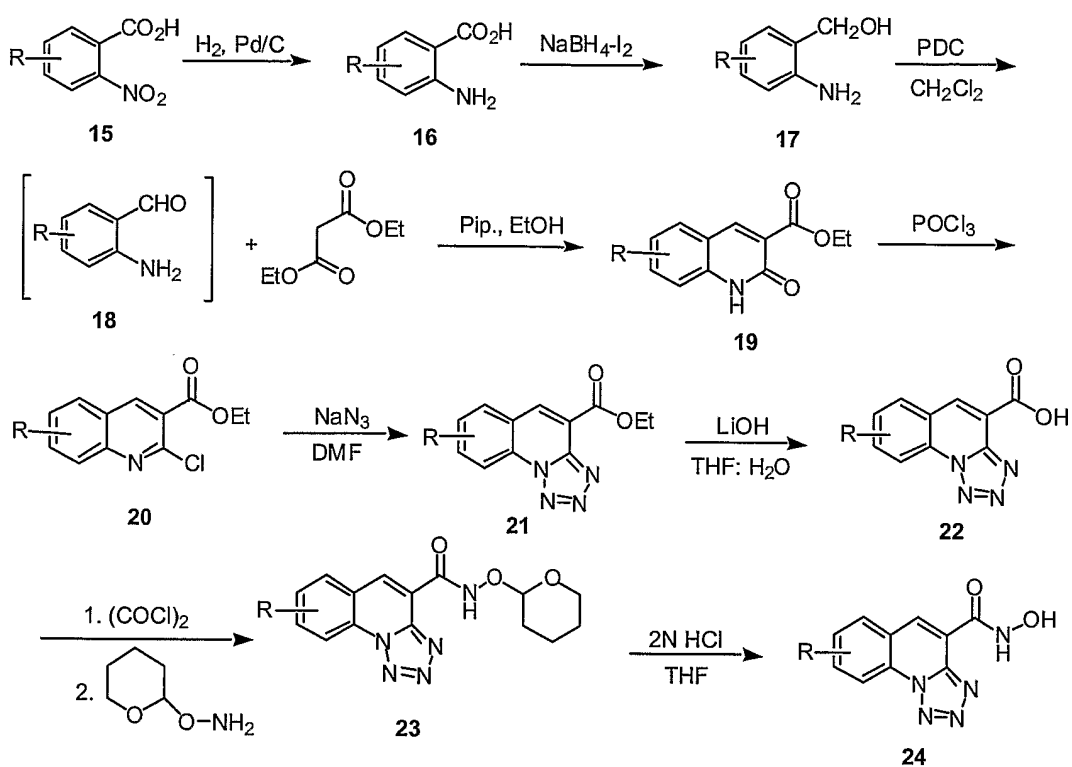
[0066] Representative procedure for the preparation of 8-chloro-N-(tetrahydro-2H-pyran-2-yloxy)tetrazolo[1,5-a]quinoline-4-carboxamide (6c): To a suspension of carboxytetrazole (**5c**, 0.05 g, 0.2 mmol) in CH₂Cl₂ (5 mL) at 0 °C under N₂ was added DMF (4-drops) followed by (COCl)₂ (1M CH₂Cl₂, 0.15 mL, 0.3 mmol) and the reaction was stirred for 1h. The reaction solvent was removed and the resulting residue of acid chloride was dried under high vacuum. The acid chloride was then suspended in CH₂Cl₂ (5 mL), cooled to 0 °C, to it was added pyridine (0.033 mL, 0.4 mmol) followed by H₂N-OTHP (0.035 g, 0.3 mmol) and stirred at room temperature for 24 h. The CH₂Cl₂ solution was washed with water, dried and solvent was evaporated. The resulting residue was filtered through a pad of silica gel to obtain the requisite oxamic acid ester **6c**. ¹H NMR (CDCl₃, 300 MHz): δ 11.58 (s, 1H), 8.92 (s, 1H), 8.74 (d, 1H, J = 1.8 Hz), 8.10 (d, 1H, J = 8.1 Hz), 7.77 (dd, 1H, J = 1.8 Hz and 8.7 Hz), 5.26 (m, 1H), 4.15 (m, 1H), 3.76 (m, 1H), 2.10-1.50 (m, 6H); LCMS (m/z): 347 (MH⁺).

[0067] Representative procedure for the preparation of 8-chloro-N-hydroxytetrazolo[1,5-a]quinoline-4-carboxamide (7c): To a solution of THP oxamate **6c** (0.035 g, 0.1 mmol) in THF (1 mL) was added 2N HCl (1 mL) and stirred at room temperature for 6 h. The reaction solvent was removed under a reduced pressure and the resulting aqueous solution was diluted with water. The precipitated solid was filtered, washed with water and dried to give the desired oxamic acid **7c**. ¹H NMR (CDCl₃, 300 MHz): δ 8.80 (s, 1H), 8.64 (bd, 1H), 8.06 (d, 1H, J = 8.1 Hz), 7.70 (dd, 1H, J = 2.4 and 8.7 Hz), LCMS (m/z): 264 (MH⁺).



For **8-14** **a:** $\text{R}_1 = \text{R}_2 = -\text{OCH}_2\text{CH}_2\text{O}-$
 b: $\text{R}_1 = \text{R}_2 = \text{OMe}$
 c: $\text{R}_1 = \text{OMe}, \text{R}_2 = \text{Cl}$

[0068] By using above representative procedures the compounds **10-14** were prepared.



[0069] Representative procedure for the preparation of 2-amino-4-

(trifluoromethyl)benzylalcohol (17a): To a suspension of anthranilic acid **16a** (2.04 g, 10 mmol), NaBH₄ (0.912 g, 24 mmol) in THF (10 mL) under N₂ at 0 °C was added I₂ (2.54 g, 10 mmol) solution in THF (10 mL) over a period of 10-15 minutes. The resulting reaction mixture was stirred at room temperature for 30 minutes and then at reflux for 24 h. The reaction mixture was cooled to room temperature and MeOH was added very slowly to the mixture till the clear solution was formed. The solvent was removed and the residue was stirred with 20% KOH (20 mL) at room temperature for 4 h, extracted with CH₂Cl₂ (3 x 100 mL), dried (Na₂SO₄) and solvent was removed to obtain 1.91 g (100%) of the requisite alcohol **17a**. ¹H NMR (CDCl₃, 300 MHz): δ 7.15 (d, 1H, J = 7.5 Hz), 6.94 (d, 1H, J = 7.5 Hz), 6.91 (s, 1H), 4.71 (s, 2H).

[0070] Representative procedure for the preparation of 2-amino-4-

(trifluoromethyl)benzaldehyde (18a): A dry reaction flask equipped with a stirring bar and a rubber septum was charged with 2-amino-4-(trifluoromethyl)benzylalcohol (**17a**, 1.91 g, 10 mmol), PDC (4.51 g, 12 mmol) and CH₂Cl₂ (20 mL). The resulting mixture was stirred at room temperature

for 4 h, diluted with CH_2Cl_2 (100 mL), filtered through a small pad of celite. The combined filtrate was concentrated and dried to provide 1.54 g (81%) of the desired amino aldehyde **18a**. ^1H NMR (CDCl_3 , 300 MHz): δ 9.94 (s, 1H), 7.61 (d, 1H, $J = 7.5$ Hz), 6.95 (d, 1H, $J = 8.4$ Hz), 6.91 (s, 1H).

[0071] Representative procedure for the preparation of ethyl 7-(trifluoromethyl)-2-quinolone-3-carboxylate (19a): A dry reaction flask was charged with aldehyde **18a** (1.54 g, 8.14 mmol), diethyl malonate (12.73 mL, 81.4 mmol), piperidine (3.22 mL, 32.59 mmol) and EtOH (25 mL). The resulting mixture was refluxed for 24 h, concentrated, diluted with n-hexanes (100 mL) and the product was allowed to precipitate. The desired product was filtered, washed with additional amount of n-hexanes and dried to give 0.738 g (32%) of the 2-quinolone **19a**. ^1H NMR (CDCl_3 , 300 MHz): δ 8.58 (s, 1H), 7.81 (d, 1H, $J = 8.7$ Hz), 7.67 (s, 1H), 7.49 (d, 1H, $J = 8.1$ Hz), 4.47 (q, 2H, $J = 7.2$ Hz), 1.47 (t, 3H, $J = 7.5$ Hz).

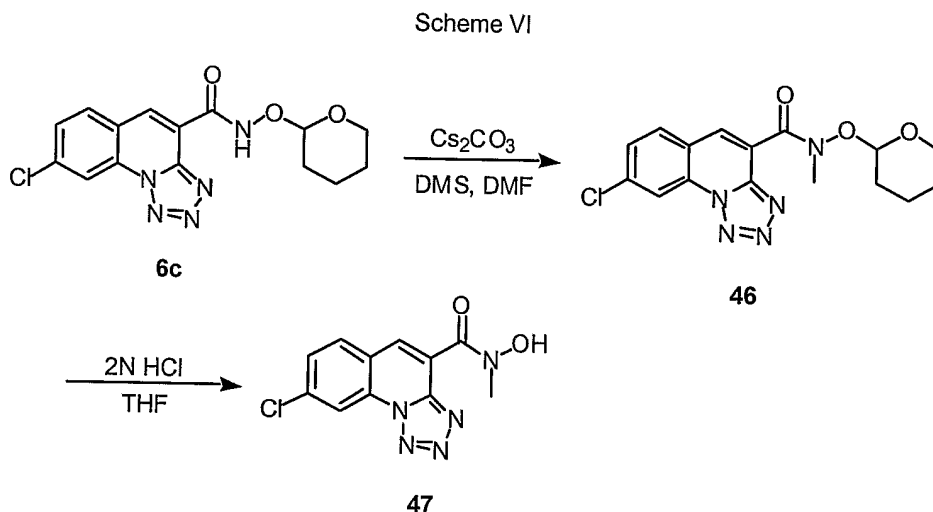
[0072] Representative procedure for the preparation of ethyl 2-chloro-7-(trifluoromethyl)quinoline-3-carboxylate (20a): To a dry reaction flask was placed quinolone **19a** (1 g, 3.5 mmol), POCl_3 (7 mL) and heated at 80-90 °C for 24 h. The reaction mixture upon cooling to room temperature was poured over crushed ice, digested for 1 h, saturated with NaCl and 0.948 g (89%) of the desired product was isolated by filtration and flash chromatography (silica gel, 10% EtOAc/Hex). ^1H NMR (CDCl_3 , 300 MHz): δ 8.70 (s, 1H), 8.37 (s, 1H), 8.04 (d, 1H, $J = 8.7$ Hz), 7.80 (dd, 1H, $J = 1.5$ and 8.7 Hz), 4.50 (q, 2H, $J = 7.2$ Hz), 1.47 (t, 3H, $J = 6.9$ Hz); LCMS (m/z): 304 (MH^+).

[0073] Representative procedure for the preparation of ethyl 8-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylate (21a): A dry reaction flask was charged with ethyl 2-chloro-7-(trifluoromethyl)quinoline-3-carboxylate (**20a**, 0.065 g, 0.21 mmol), NaN_3 (0.017 g, 0.26 mmol) and DMF (1.5 mL), and heated at 65-75 °C for 8 h. The resulting mixture was poured over water (100 mL), saturated with NaCl, the solid obtained was filtered, washed with water and dried to give 0.038 g (58%) the desired compound (**21a**). ^1H NMR (CDCl_3 , 300 MHz): δ 9.04 (s, 1H), 8.79 (s, 1H), 8.27 (d, 1H, $J = 8.1$ Hz), 8.02 (bd, 1H, $J = 8.4$ Hz), 4.63 (q, 2H, $J = 7.2$ Hz), 1.54 (t, 3H, $J = 7.2$ Hz); LCMS (m/z): 311 (MH^+).

[0074] Representative procedure for the preparation of 8-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylic acid (22a): A suspension of **21a** (0.03 g, 0.1 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.021 g, 0.5 mmol) in THF: H_2O (1:1, 2 mL) was stirred at room temperature for 3h, concentrated, diluted with water and filtered. The filtrate upon acidification (cold 2N HCl) gave the solid, which was filtered and dried to afford 0.02 g (71%) of the desired product **22a**. ^1H NMR ($\text{CD}_3\text{OD} + \text{CDCl}_3$, 300 MHz): δ 8.99 (s, 1H), 8.81 (s, 1H), 8.25 (d, 1H, $J = 9.0$ Hz), 7.98 (bd, 1H, $J = 6.9$ Hz); LCMS (m/z): 282 (MH^+).

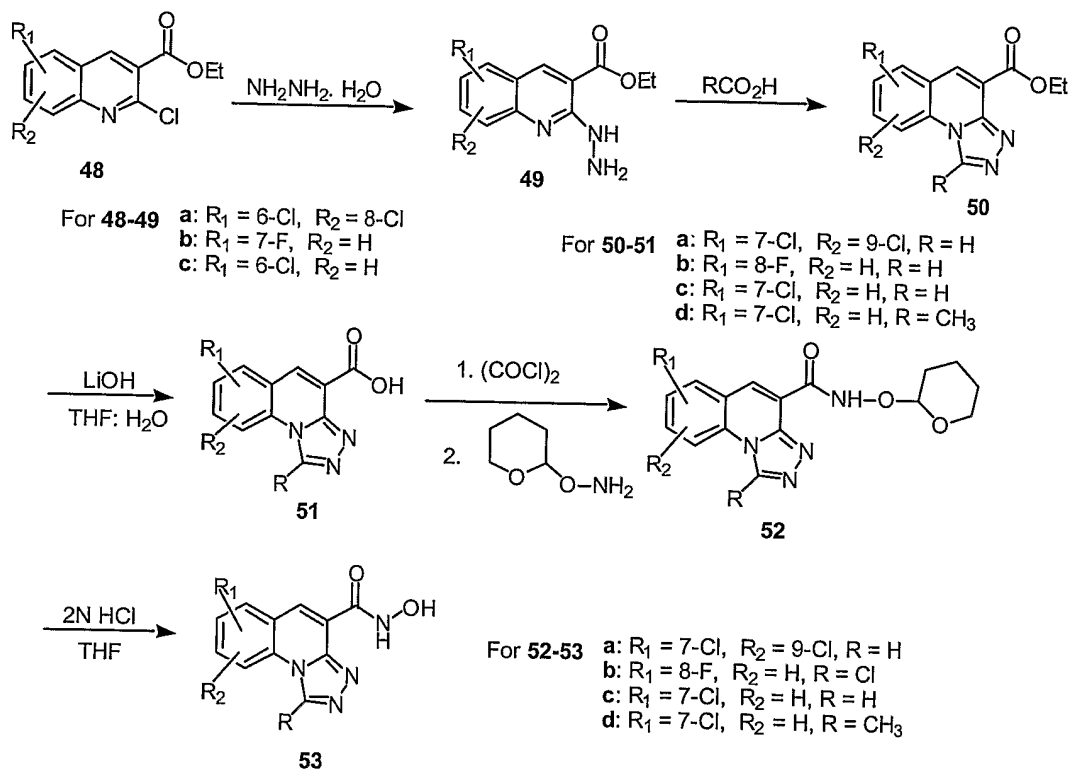
Preparation of 8-chloroquinoline-4-carboxylic acid (35): 2-Hydroxyquinoline-4-carboxylic acid (**34**, 2.57 g, 13.6 mmol) and POCl₃ (25 mL) were refluxed for 24 h. The reaction mixture was poured onto crushed-ice (300 g). The solid that separated was filtered, washed with water, and dried well under high vacuum afforded 2.47 g (87%) white flasks of desired product. ¹H NMR (CDCl₃, 300 MHz): δ 8.67 (d, 1H, J = 8.4 Hz), 7.91 (d, 1H, J = 8.1 Hz), 7.83 (s, 1H), 7.67 (t, 1H, J = 7.2 Hz), 7.54 (t, 1H, J = 7.2 Hz); LCMS (m/z): 208 (MH⁺).

[0078] Compounds **36-38** were prepared by using above representative procedures of compounds **5-7**.



[0079] Preparation of 8-chloro-N-methyl-N-(tetrahydro-2H-pyran-2-yloxy)tetrazolo[1,5-a]quinoline-4-carboxamide (46): Compound **6c** (65 mg, 0.19 mmol) was dissolved in dry DMF (1.0 mL), Cs₂CO₃ (121 mg, 0.37 mmol) was added, stirred at room temperature for 15 minutes and then dimethylsulfate (21 μl) was added. The reaction mixture was stirred at room temperature for 24 h, poured into water, left aside for 1 h, the solid that separated was filtered, dried to provide 32 mg (47%) of desired product as colorless liquid. ¹H NMR (CDCl₃, 300 MHz): δ 8.66 (s, 1H), 8.25 (s, 1H), 7.93 (d, 1H, J = 8.4 Hz), 7.67 (dd, 1H, J = 2.1 and 8.5 Hz), 5.36 (t, 1H, J = 3.6 Hz), 4.26 (s, 3H), 3.97 (m, 1H), 3.70 (m, 1H), 1.90 (m, 3H), 1.66 (m, 3H); LCMS (m/z): 278 (M-84).

[0080] Compound **47** was prepared by using above representative procedure of compound **7**.



[0081] Representative procedure for the preparation of ethyl 6,8-dichloro-2-

hydrazinoquinoline-4-carboxylate (49a): To a warm (40 °C) solution of compound **48a** (0.6848 g, 2.26 mmol) in ethanol (100 mL) was added hydrazine hydrate (0.11 mL, 2.26 mmol) and heated at 40 °C for over-night. Again hydrazine hydrate (0.11 mL, 2.26 mmol) was added and stirred at that temperature for 24 h. The reaction mixture was concentrated, absorbed on a minimum amount of silica gel and chromatographed (silical gel, flash, n-hexanes 10% to 20% to 50% EtOAc) to afford 0.5765 g (85%) of desired product as colorless solid. ¹H NMR (CDCl₃, 300 MHz): δ 8.89 (s, 1H), 8.51 (s, 1H), 7.70 (s, 1H), 7.55 (s, 1H), 4.40 (q, 2H, J = 7.2 Hz), 4.35 (br s, 2H), 1.43 (t, 3H, J = 7.2 Hz); LCMS (m/z): 300 (MH⁺).

[0082] Representative procedure for the preparation of ethyl 7,9-dichloro-s-

triazolo[4,3-a]quinoline-4-carboxylate (50a): Compound **49a** (0.288 g, 0.96 mmol) and formic acid (5 mL) were refluxed for 24 h. The reaction mixture was diluted with water (50 mL), neutralized with solid sodium bicarbonate. The solid was filtered, washed with water and dried well to afford 0.2783 g (93%) of desired product as colorless solid. ¹H NMR (CDCl₃, 300 MHz): δ 10.29 (s, 1H), 8.22 (s, 1H), 7.85 (m, 2H), 4.57 (q, 2H, J = 6.9 Hz), 1.50 (t, 3H, J = 7.2 Hz); LCMS (m/z): 309 (MH⁺).

[0083] Compounds **51-53** were prepared by using above representative procedures of compounds **22a** and 6-7.

[0084] Abbreviations and acronyms used in the examples include: POCl₃, phosphorus oxychloride; PDC, pyridium dichromate; CH₂Cl₂, dichloromethane; DMF, N,N-dimethylformamide; I₂, iodine; EtOAc, ethyl acetate; EtOH, ethyl alcohol; h, hour; LiOH.H₂O, lithium hydroxide monohydrate; HPLC, high performance liquid chromatography; LCMS, liquid chromatography mass spectrum (using HPLC); ether, diethyl ether; MeOH, methanol; Na₂SO₄, sodium sulfate; Cs₂CO₃, cesium carbonate; NaN₃, sodium azide; KOH, potassium hydroxide; NaOH, sodium hydroxide; NaBH₄, sodium borohydride; NMR, nuclear magnetic resonance spectroscopy; (COCl)₂, oxalyl chloride; hex, hexanes; NaCl, sodium chloride; THF, tetrahydrofuran; TLC, thin layer chromatography

Biological Assay

[0085] The following assay examples illustrate the HCV inhibitory properties of the compounds of the invention.

Assay Example 1

HCV Replicon Assay

[0086] Actively dividing 5-2Luc replicon cells were seeded at the density of 5000-7500 cells/well in the volume of 90 µl/well into 96 well plate(s). The cells were then incubated at 37°C and 5% CO₂ for 24 hours. The 5-2 cells are replicon cells licensed from Ralf Bartenschlager (Germany) and have a self-replicating RNA molecule in the Huh7 cell; the RNA contains HCV non-structural proteins that make the self-replication possible.

[0087] Various concentrations of compounds (in the volume of 10 µl) were added into each well 24 hours after seeding the cells. The cells were incubated for another 24 hours before luciferase assay.

[0088] After incubating the 5-2Luc replicon cells with the compounds for 24 hours, media were aspirated from each well and Bright-Glo (Pharmacia) luciferase assay reagents were added to each well according to the manufacturer's manual. Briefly, the Bright-Glo reagent was diluted with equal volume of PBS and an aliquote (100 µl) was added to each well. After incubating the plate at room temperature for 5 minutes, luciferase counts were taken using a luminometer.

Assay Example 2

Luciferase Counter Assay

[0089] Actively dividing CMV-Luc cells (Luc cells in which DNA construct (CMV promoter followed by Luciferase gene) is permanently integrated into the chromosome of Huh7 cells) were seeded at the density of 5000-7500 cells/well in the volume of 90 µl/well into 96 well plate(s). The cells were then incubated at 37°C and 5% CO₂ for 24 hours.

[0090] Various concentrations of compounds (in the volume of 10 μ l) were added into each well 24 hours after seeding the cells. The cells were incubated with the compounds for another 24 hours before luciferase assay.

[0091] After incubating the CMV-Luc cells with the compounds for 24 hours, media were aspirated from each well and Bright-Glo (Pharmacia) luciferase assay reagents were added to each well according to the manufacturer's manual. Luciferase counts were taken using a luminometer.

[0092] The activity of a number of compounds according to the invention measured by the luciferase assay is displayed in Table 1.

Assay Example 3

Immunoblotting Assay

[0093] Actively dividing 9-13 replicon cells (Huh7 cells comprising an HCV replicon) were seeded at the density of 1×10^5 cells/well in the volume of 2 ml/well into 6 well plate(s). The cells were then incubated at 37°C and 5% CO₂ for 24 hours.

[0094] Various concentrations of compounds (in the volume of 10 μ l) were added into each well 24 hours after seeding the cells. The cells were incubated with the compounds for another 48 hours.

[0095] Protein samples were prepared from the cultured cells and resolved on a SDS-PAGE gel.

[0096] After electrophoresis, the protein samples on the SDS-PAGE gel were transferred to a nitrocellulose membrane.

[0097] The membrane was blocked with 5% non-fat milk in PBS for 1 hr at room temperature.

[0098] Primary antibody incubation was performed for 1 hour at room temperature before the membrane was washed for 3 times with PBST (PBS plus 0.1% Tween 20), 15 minutes each.

[0099] Horse Radish Peroxidase conjugated secondary antibody incubation was performed for 1 hour at room temperature before the membrane was washed for 3 times with PBST (PBS plus 0.1% Tween 20), 15 minutes each.

[0100] The membrane was then soaked in substrate solution (Pierce) and exposed to a film.

Assay Example 4

TaqMan RT-PCR Assay

[0101] Actively dividing 9-13 replicon cells were seeded at the density of 3×10^4 cells/well in the volume of 1 ml/well into 24 well plate(s). The cells were then incubated at 37°C and 5% CO₂ for 24 hours.

[0102] Various concentrations of compounds (in the volume of 10 μ l) were added into each well 24 hours after seeding the cells. The cells were incubated with the compounds for another 24 hours.

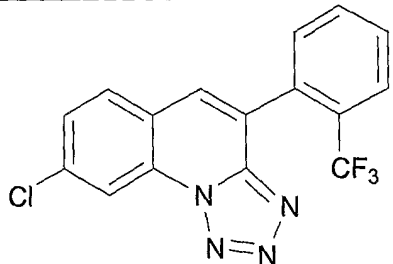
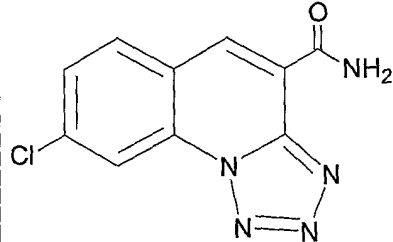
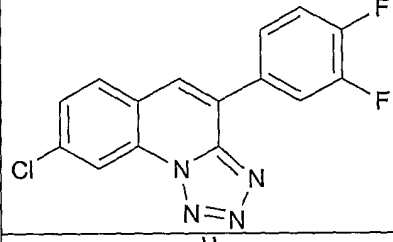
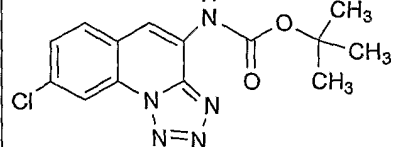
[0103] After incubating the 9-13 replicon cells with the compounds for 24 hours, media were aspirated off and RNA samples were prepared from each well.

[0104] TaqMan® (Roche Molecular Systems) one step RT-PCR was performed using the RNA samples according to the manufacturer's manual. Briefly, properly diluted RNA sample, upstream primer, downstream primer, FAM-labeled probe oligo were mixed and water was added to make up the volume to 25 µl. Equal volume of 2X TaqMan Master Mix were added and the reaction was performed in an ABI Prism 7700 Sequence Detector (Applied Biosystems).

[0105] The compounds in Table 1 to 3 immediately below were prepared essentially using the methods described herein and illustrated in the schemes. All of the compounds in this application were named using Chemdraw Ultra version 6.0.2, which is available through Cambridgesoft.co, 100 Cambridge Park Drive, Cambridge, MA 02140, Namepro version 5.09, which is available from ACD labs, 90 Adelaide Street West, Toronto, Ontario, M5H, 3V9, Canada, or were derived therefrom.

[0106] The compounds of Table 1 below exhibited greater than 20% inhibitory activity.

Table 1

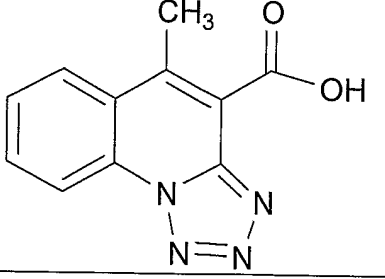
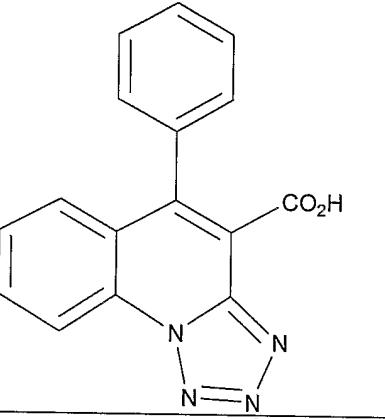
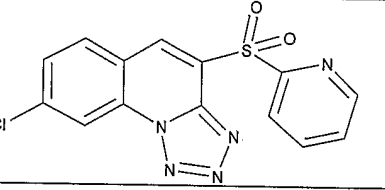
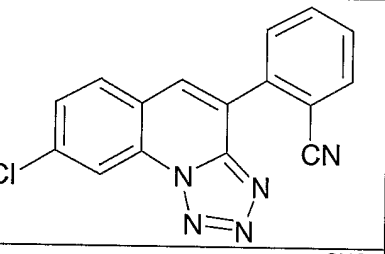
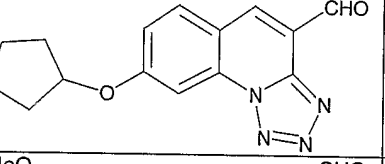
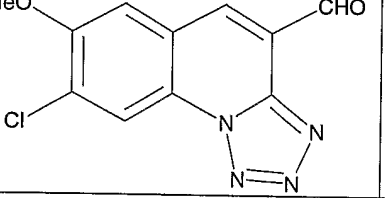
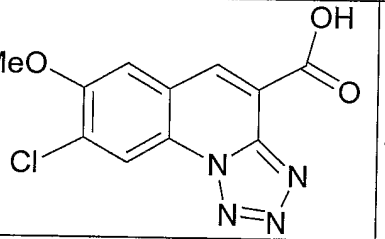
Structure	Name
	8-chloro-4-[2-(trifluoromethyl)phenyl]tetrazolo[1,5-a]quinoline
	8-chlorotetrazolo[1,5-a]quinoline-4-carboxamide
	8-chloro-4-(3,4-difluorophenyl)tetrazolo[1,5-a]quinoline
	tert-butyl (8-chlorotetrazolo[1,5-a]quinolin-4-yl)carbamate

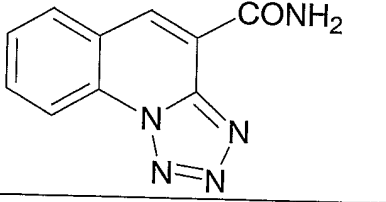
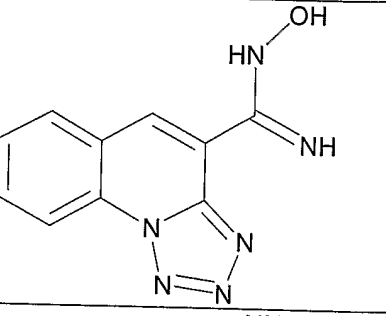
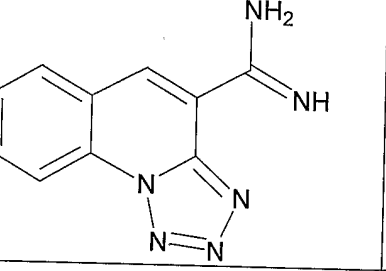
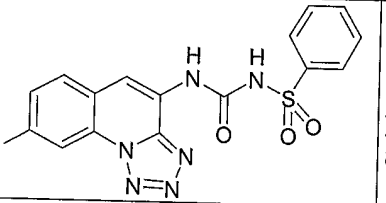
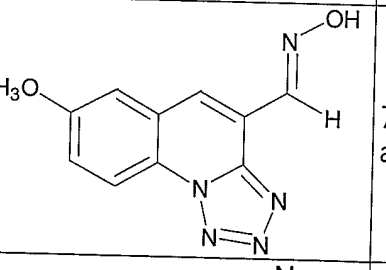
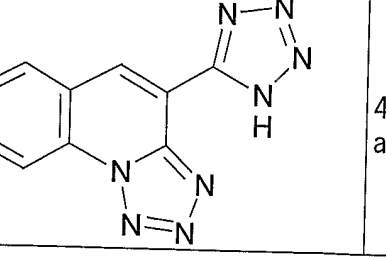
Structure	Name
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	9-chloro-N-isobutoxytetrazolo[1,5-a]quinoline-4-carboxamide
	9-chloro-N-propoxytetrazolo[1,5-a]quinoline-4-carboxamide
	9-chloro-N-isopropoxytetrazolo[1,5-a]quinoline-4-carboxamide
	9-chloro-N-ethoxytetrazolo[1,5-a]quinoline-4-carboxamide
	8-chloro-N-hydroxytetrazolo[1,5-a]quinoline-4-carboxamide

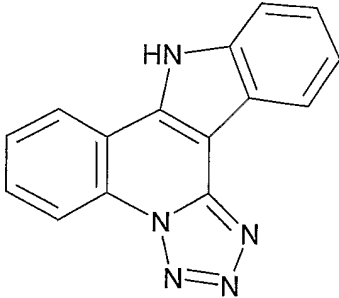
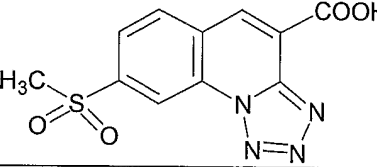
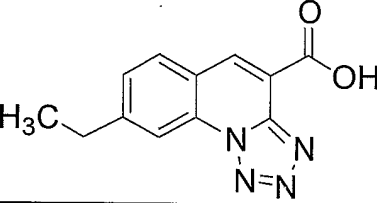
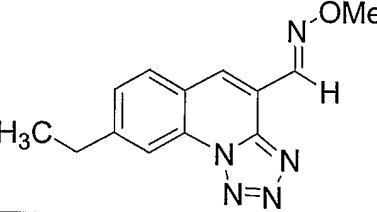
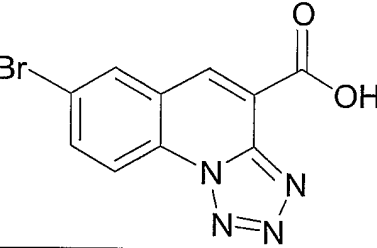
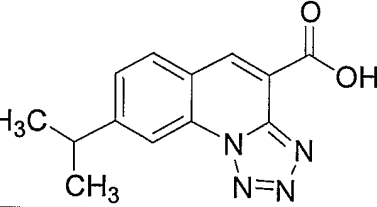
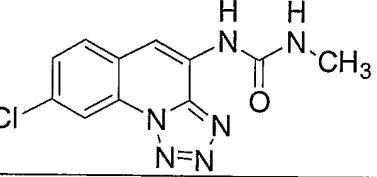
[0107] The compounds of Table 2 exhibited 5% to 20% inhibitory activity.

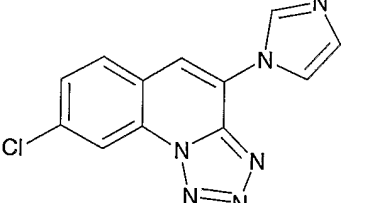
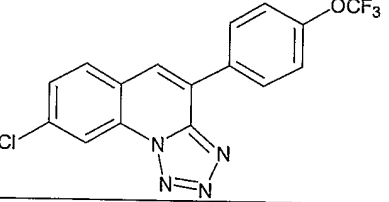
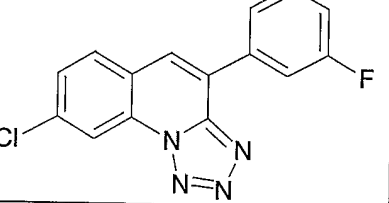
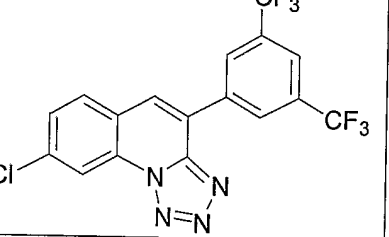
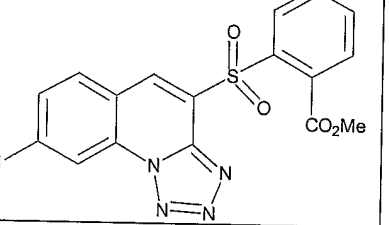
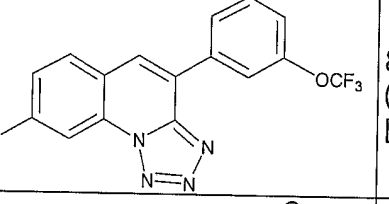
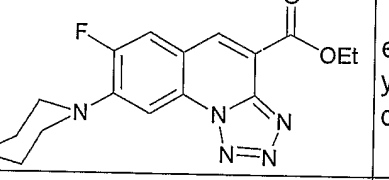
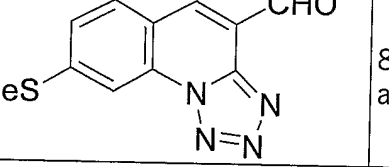
Table 2

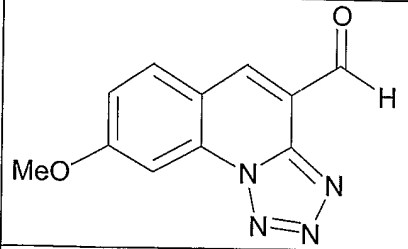
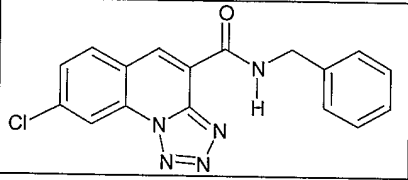
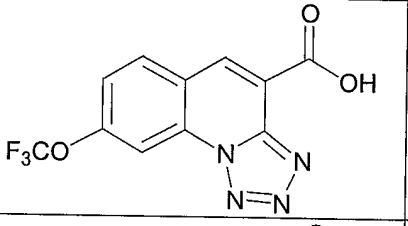
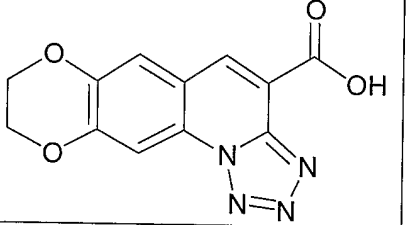
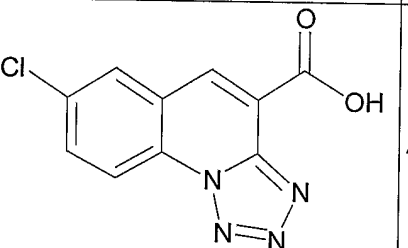
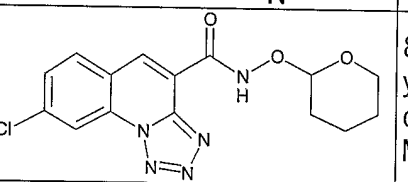
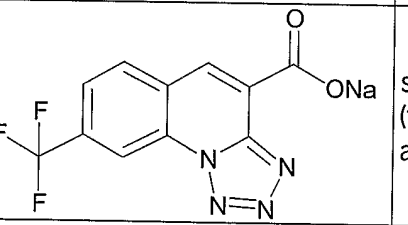
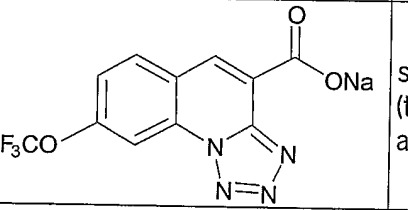
Structure	Name
	N-benzyltetrazolo[1,5-a]quinolin-5-amine

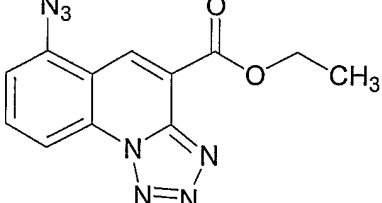
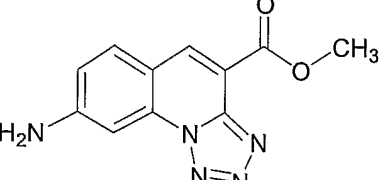
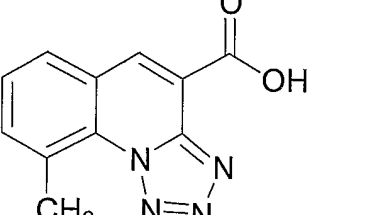
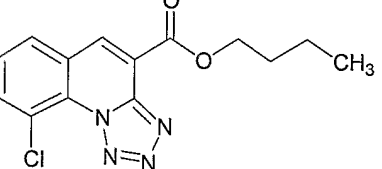
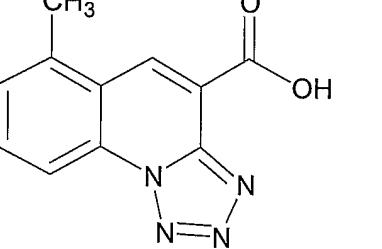
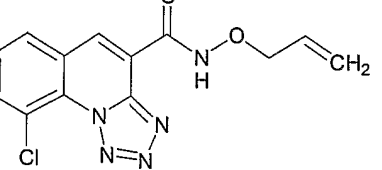
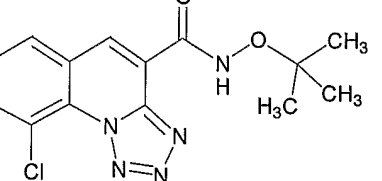
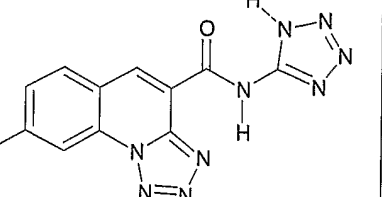
Structure	Name
	5-methyltetrazolo[1,5-a]quinoline-4-carboxylic acid
	5-phenyltetrazolo[1,5-a]quinoline-4-carboxylic acid
	8-chloro-4-(pyridin-2-ylsulfonyl)tetrazolo[1,5-a]quinoline
	2-(8-chlorotetrazolo[1,5-a]quinolin-4-yl)benzotrile
	8-(cyclopentyloxy)tetrazolo[1,5-a]quinoline-4-carbaldehyde
	8-chloro-7-methoxytetrazolo[1,5-a]quinoline-4-carbaldehyde
	8-chloro-7-methoxytetrazolo[1,5-a]quinoline-4-carboxylic acid

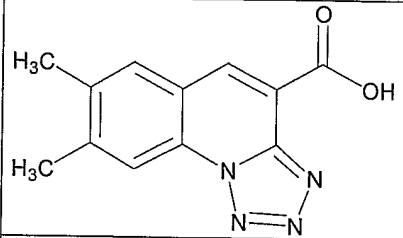
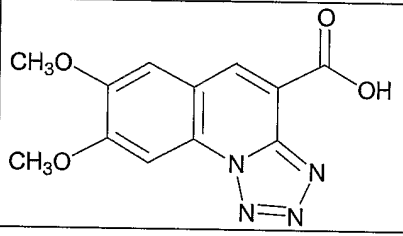
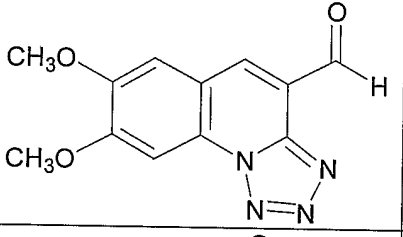
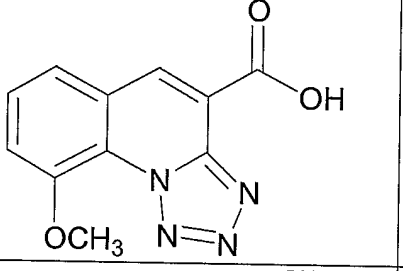
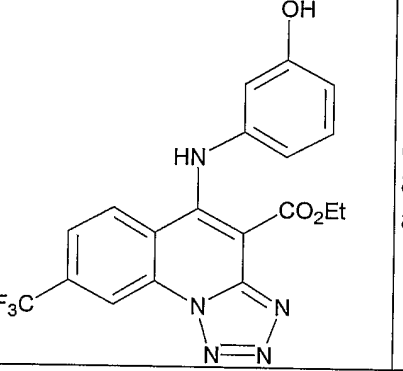
Structure	Name
 <p>Chemical structure of tetrazolo[1,5-a]quinoline-4-carboxamide, showing a benzene ring fused to a quinoline ring, which is further fused to a tetrazole ring. A carboxamide group (-CONH₂) is attached to the 4-position of the quinoline ring.</p>	<p>tetrazolo[1,5-a]quinoline-4-carboxamide</p>
 <p>Chemical structure of N-hydroxytetrazolo[1,5-a]quinoline-4-carboximidamide, showing a benzene ring fused to a quinoline ring, which is further fused to a tetrazole ring. A carboximidamide group (-C(=NH)NHOH) is attached to the 4-position of the quinoline ring.</p>	<p>N-hydroxytetrazolo[1,5-a]quinoline-4-carboximidamide</p>
 <p>Chemical structure of tetrazolo[1,5-a]quinoline-4-carboximidamide, showing a benzene ring fused to a quinoline ring, which is further fused to a tetrazole ring. A carboximidamide group (-C(=NH)NH₂) is attached to the 4-position of the quinoline ring.</p>	<p>tetrazolo[1,5-a]quinoline-4-carboximidamide</p>
 <p>Chemical structure of N-(((8-chlorotetrazolo[1,5-a]quinolin-4-yl)amino)carbonyl)benzenesulfonamide, showing a benzene ring fused to a quinoline ring, which is further fused to a tetrazole ring. A chlorine atom is attached to the 8-position of the quinoline ring. An amino group (-NH-) is attached to the 4-position of the quinoline ring, which is further attached to a carbonyl group (-C(=O)-), which is further attached to a benzenesulfonamide group (-NH-SO₂-C₆H₅).</p>	<p>N-(((8-chlorotetrazolo[1,5-a]quinolin-4-yl)amino)carbonyl)benzenesulfonamide</p>
 <p>Chemical structure of 7-methoxytetrazolo[1,5-a]quinoline-4-carbaldehyde oxime, showing a benzene ring fused to a quinoline ring, which is further fused to a tetrazole ring. A methoxy group (-OCH₃) is attached to the 7-position of the quinoline ring. An aldehyde group (-CHO) is attached to the 4-position of the quinoline ring, which is further attached to an oxime group (-NHOH).</p>	<p>7-methoxytetrazolo[1,5-a]quinoline-4-carbaldehyde oxime</p>
 <p>Chemical structure of 4-(1H-tetrazol-5-yl)tetrazolo[1,5-a]quinoline, showing a benzene ring fused to a quinoline ring, which is further fused to a tetrazole ring. A 1H-tetrazol-5-yl group is attached to the 4-position of the quinoline ring.</p>	<p>4-(1H-tetrazol-5-yl)tetrazolo[1,5-a]quinoline</p>

Structure	Name
	9H-indolo[3,2-c]tetrazolo[1,5-a]quinoline
	8-(methylsulfonyl)tetrazolo[1,5-a]quinoline-4-carboxylic acid
	8-ethyltetrazolo[1,5-a]quinoline-4-carboxylic acid
	8-ethyltetrazolo[1,5-a]quinoline-4-carbaldehyde O-methyloxime
	7-bromotetrazolo[1,5-a]quinoline-4-carboxylic acid
	8-isopropyltetrazolo[1,5-a]quinoline-4-carboxylic acid
	N-(8-chlorotetrazolo[1,5-a]quinolin-4-yl)-N'-methylurea

Structure	Name
	8-chloro-4-(1H-imidazol-1-yl)tetrazolo[1,5-a]quinoline
	8-chloro-4-[4-(trifluoromethoxy)phenyl]tetrazolo[1,5-a]quinoline
	8-chloro-4-(3-fluorophenyl)tetrazolo[1,5-a]quinoline
	4-[3,5-bis(trifluoromethyl)phenyl]-8-chlorotetrazolo[1,5-a]quinoline
	methyl 2-[(8-chlorotetrazolo[1,5-a]quinolin-4-yl)sulfonyl]benzoate
	8-chloro-4-[3-(trifluoromethoxy)phenyl]tetrazolo[1,5-a]quinoline
	ethyl 7-fluoro-8-piperidin-1-yltetrazolo[1,5-a]quinoline-4-carboxylate
	8-(methylthio)tetrazolo[1,5-a]quinoline-4-carbaldehyde

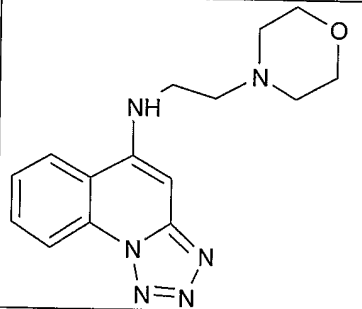
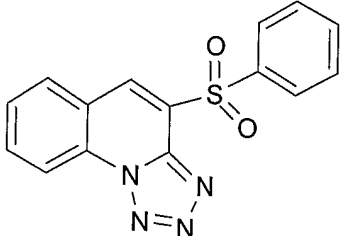
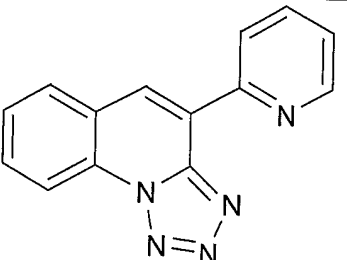
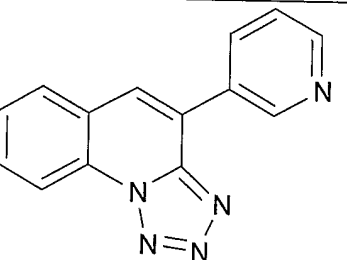
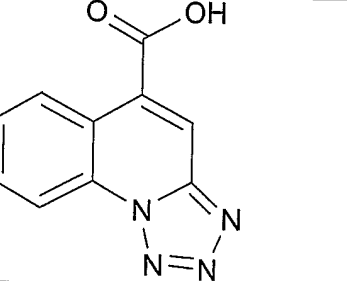
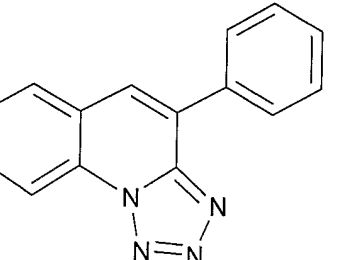
Structure	Name
	8-methoxytetrazolo[1,5-a]quinoline-4-carbaldehyde
	N-benzyl-8-chlorotetrazolo[1,5-a]quinoline-4-carboxamide
	8-(trifluoromethoxy)tetrazolo[1,5-a]quinoline-4-carboxylic acid
	8,9-dihydro[1,4]dioxino[2,3-g]tetrazolo[1,5-a]quinoline-4-carboxylic acid
	7-chlorotetrazolo[1,5-a]quinoline-4-carboxylic acid
	8-chloro-N-(tetrahydro-2H-pyran-2-yloxy)tetrazolo[1,5-a]quinoline-4-carboxamide M-H ⁺ = 346
	sodium 8-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylate
	sodium 8-(trifluoromethoxy)tetrazolo[1,5-a]quinoline-4-carboxylate

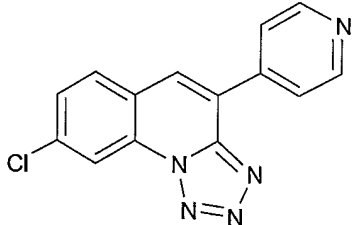
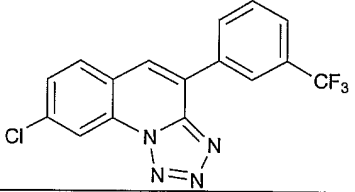
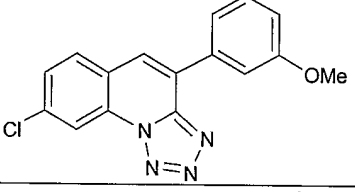
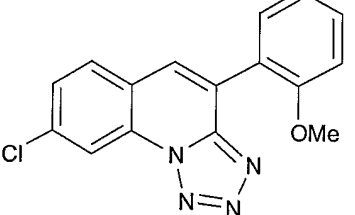
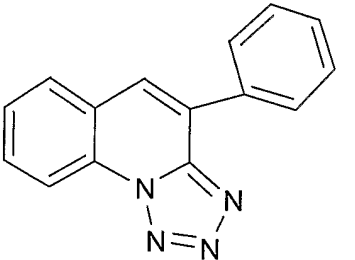
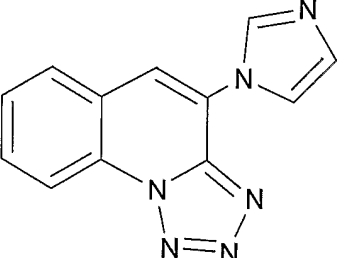
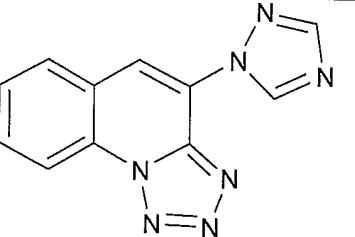
Structure	Name
	ethyl 6-azidotetrazolo[1,5-a]quinoline-4-carboxylate
	methyl 8-aminotetrazolo[1,5-a]quinoline-4-carboxylate
	9-methyltetrazolo[1,5-a]quinoline-4-carboxylic acid
	butyl 9-chlorotetrazolo[1,5-a]quinoline-4-carboxylate
	6-methyltetrazolo[1,5-a]quinoline-4-carboxylic acid
	N-(allyloxy)-9-chlorotetrazolo[1,5-a]quinoline-4-carboxamide
	N-(tert-butoxy)-9-chlorotetrazolo[1,5-a]quinoline-4-carboxamide
	8-fluoro-N-1H-tetrazol-5-yltetrazolo[1,5-a]quinoline-4-carboxamide

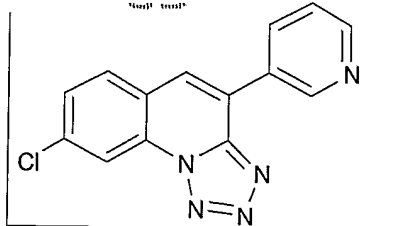
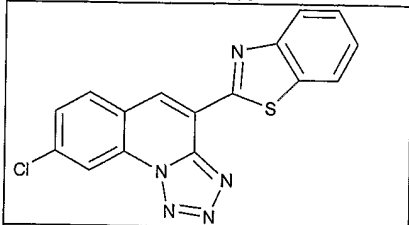
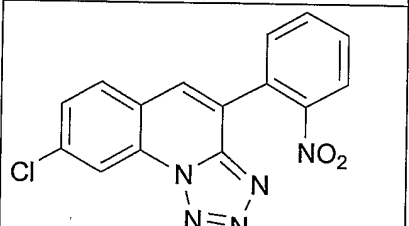
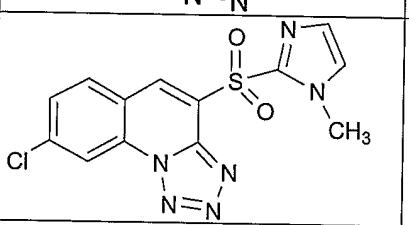
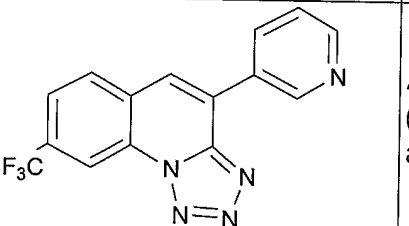
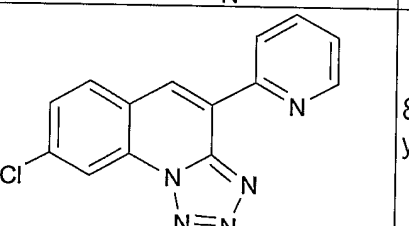
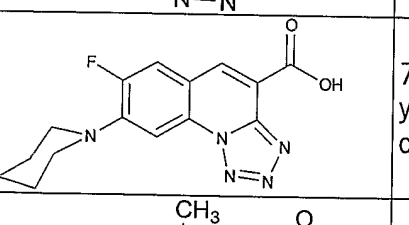
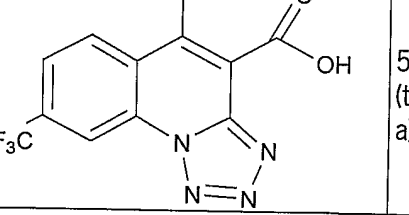
Structure	Name
	7,8-dimethyltetrazolo[1,5-a]quinoline-4-carboxylic acid
	7,8-dimethoxytetrazolo[1,5-a]quinoline-4-carboxylic acid
	7,8-dimethoxytetrazolo[1,5-a]quinoline-4-carbaldehyde
	9-methoxytetrazolo[1,5-a]quinoline-4-carboxylic acid
	ethyl 5-[(3-hydroxyphenyl)amino]-8-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylate

[0108] Compounds exhibiting less than 5% inhibitory activity are listed in Table 3 below.

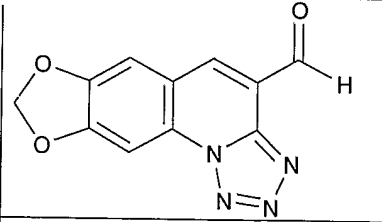
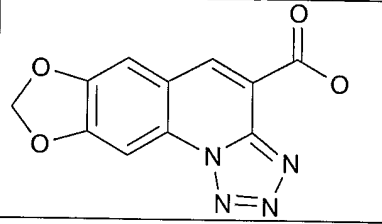
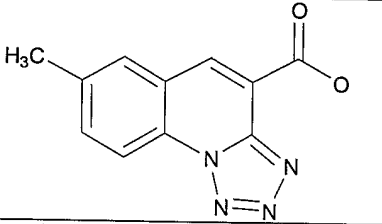
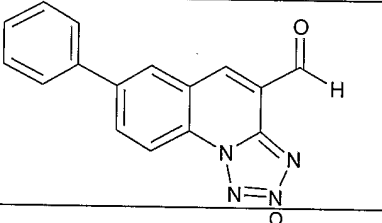
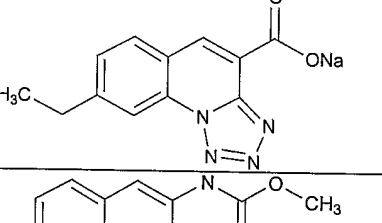
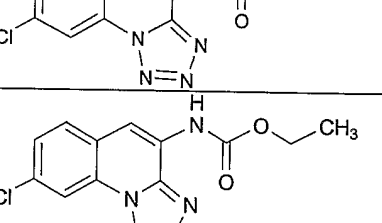
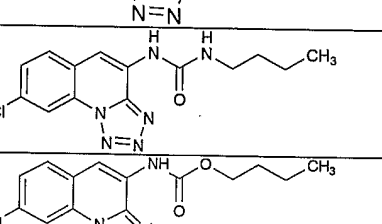


Table 3

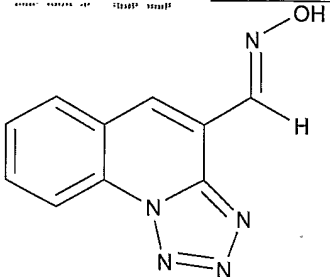
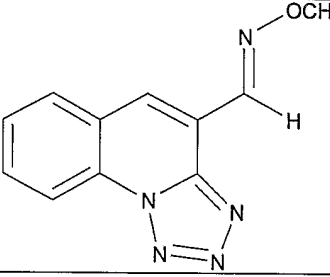
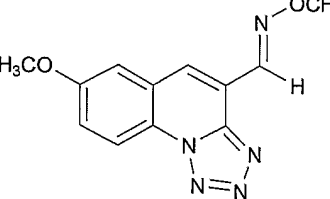
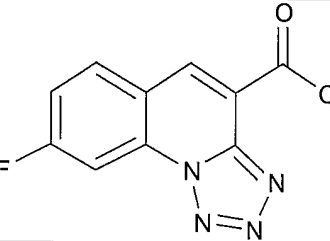
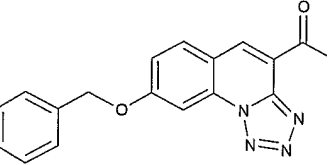
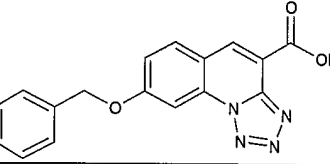
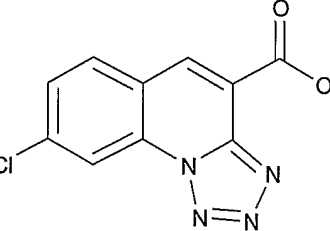
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	4-(phenylsulfonyl)tetrazolo[1,5-a]quinoline
	4-pyridin-2-yltetrazolo[1,5-a]quinoline
	4-pyridin-3-yltetrazolo[1,5-a]quinoline
	tetrazolo[1,5-a]quinoline-5-carboxylic acid
	4-phenyltetrazolo[1,5-a]quinoline

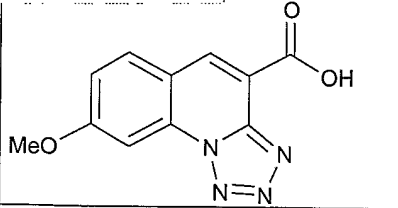
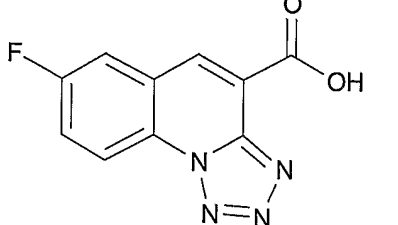
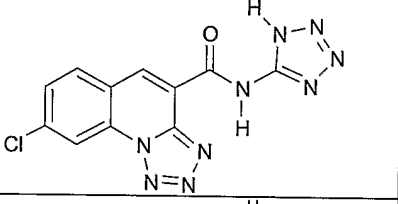
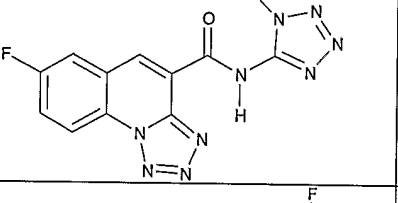
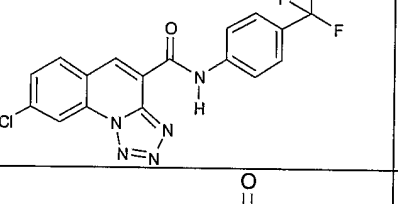
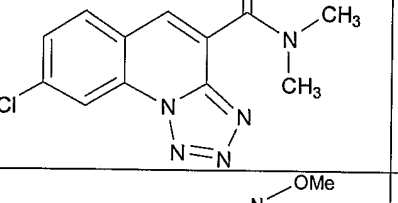
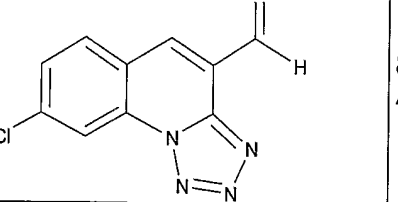
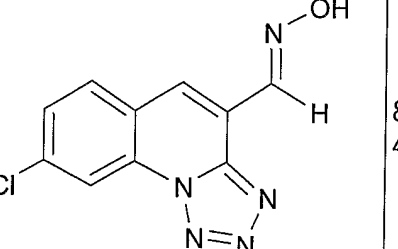
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	8-chloro-4-[3-(trifluoromethyl)phenyl]tetrazolo[1,5-a]quinoline
	8-chloro-4-(3-methoxyphenyl)tetrazolo[1,5-a]quinoline
	8-chloro-4-(2-methoxyphenyl)tetrazolo[1,5-a]quinoline
	4-phenyltetrazolo[1,5-a]quinoline
	4-(1H-imidazol-1-yl)tetrazolo[1,5-a]quinoline
	4-(1H-1,2,4-triazol-1-yl)tetrazolo[1,5-a]quinoline

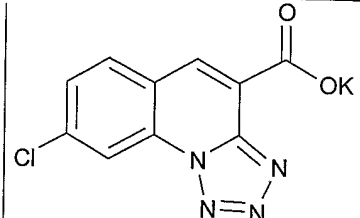
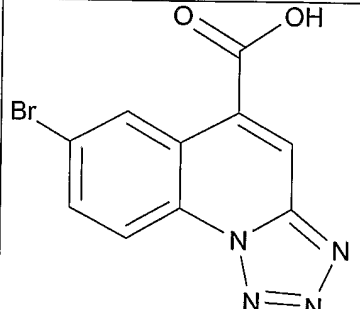
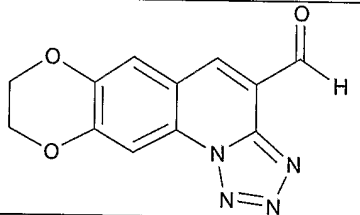
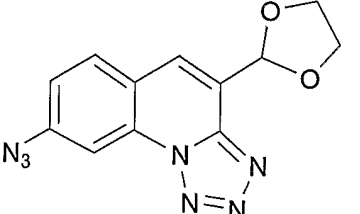
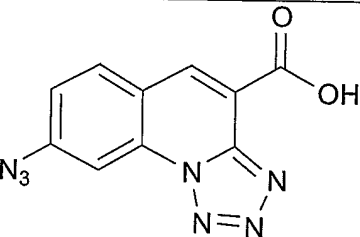
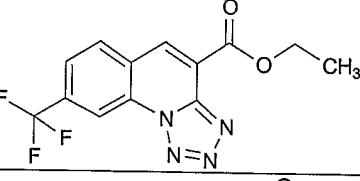
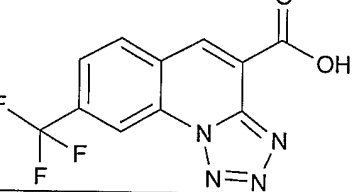
	<p>8-chloro-4-pyridin-3-yltetrazolo[1,5-a]quinoline</p>
	<p>4-(1,3-benzothiazol-2-yl)-8-chlorotetrazolo[1,5-a]quinoline</p>
	<p>8-chloro-4-(2-nitrophenyl)tetrazolo[1,5-a]quinoline</p>
	<p>8-chloro-4-[(1-methyl-1H-imidazol-2-yl)sulfonyl]tetrazolo[1,5-a]quinoline</p>
	<p>4-pyridin-3-yl-8-(trifluoromethyl)tetrazolo[1,5-a]quinoline</p>
	<p>8-chloro-4-pyridin-2-yltetrazolo[1,5-a]quinoline</p>
	<p>7-fluoro-8-piperidin-1-yltetrazolo[1,5-a]quinoline-4-carboxylic acid</p>
	<p>5-methyl-8-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylic acid</p>

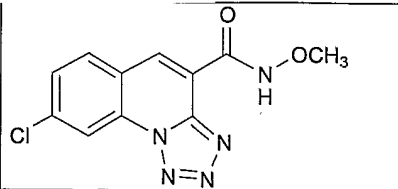
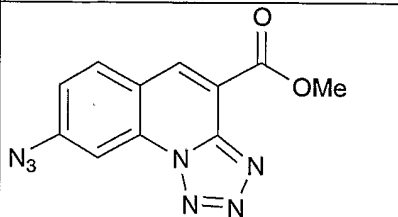
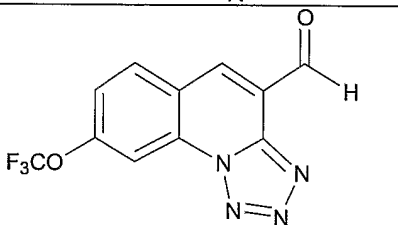
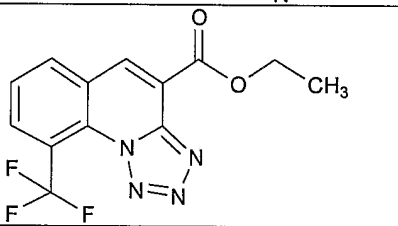
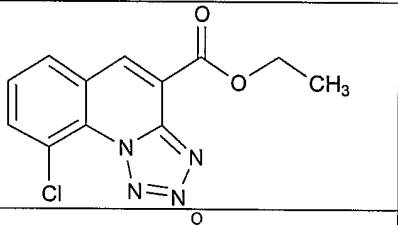
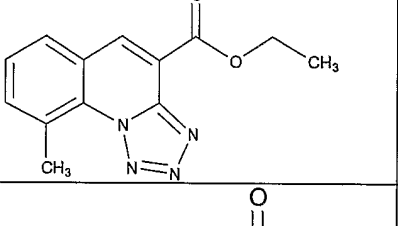
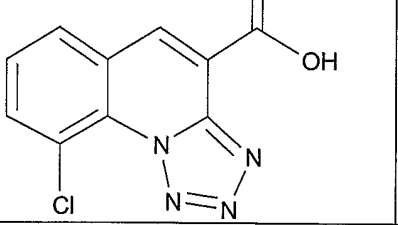
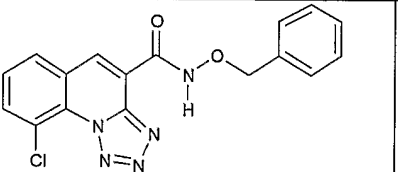
	<p>8-chloro-5-methyltetrazolo[1,5-a]quinoline-4-carboxylic acid</p>
	<p>N-methyltetrazolo[1,5-a]quinolin-5-amine</p>
	<p>tetrazolo[1,5-a]quinoline-4-carbothioamide</p>
	<p>8-methyltetrazolo[1,5-a]quinoline-4-carboxylic acid</p>
	<p>8-isopropoxytetrazolo[1,5-a]quinoline-4-carboxylic acid</p>
	<p>8-methoxy-6-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylic acid</p>
	<p>6-methoxy-8-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylic acid</p>
	<p>benzyl (8-chlorotetrazolo[1,5-a]quinolin-4-yl)carbamate</p>

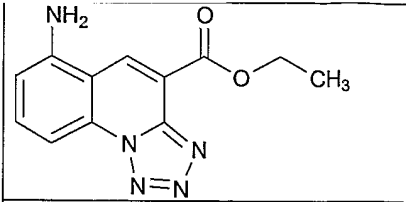
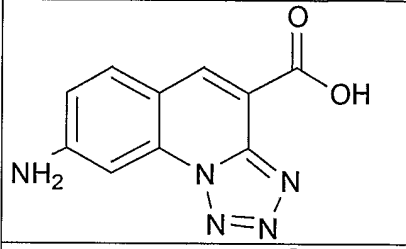
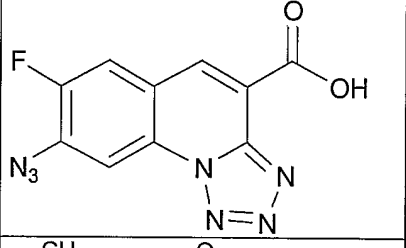
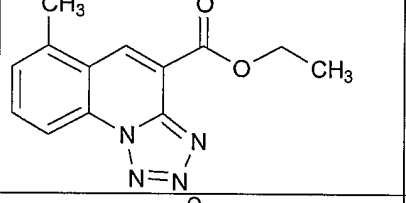
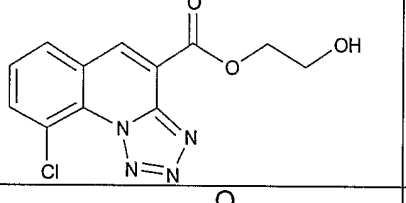
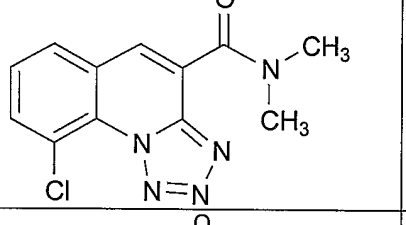
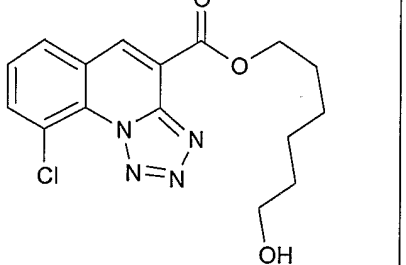
	<p>[1,3]dioxolo[4,5-g]tetrazolo[1,5-a]quinoline-4-carbaldehyde</p>
	<p>[1,3]dioxolo[4,5-g]tetrazolo[1,5-a]quinoline-4-carboxylic acid</p>
	<p>7-methyltetrazolo[1,5-a]quinoline-4-carboxylic acid</p>
	<p>7-phenyltetrazolo[1,5-a]quinoline-4-carbaldehyde</p>
	<p>sodium 8-ethyltetrazolo[1,5-a]quinoline-4-carboxylate</p>
	<p>methyl (8-chlorotetrazolo[1,5-a]quinolin-4-yl)carbamate</p>
	<p>ethyl (8-chlorotetrazolo[1,5-a]quinolin-4-yl)carbamate</p>
	<p>N-butyl-N'-(8-chlorotetrazolo[1,5-a]quinolin-4-yl)urea</p>
	<p>butyl (8-chlorotetrazolo[1,5-a]quinolin-4-yl)carbamate</p>

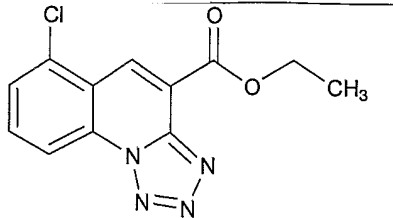
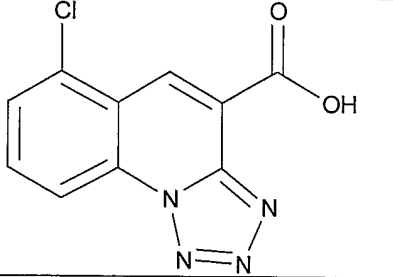
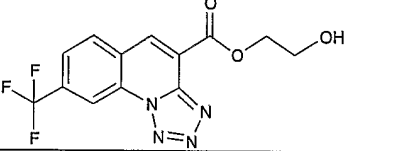
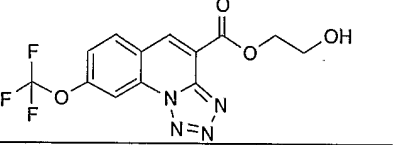
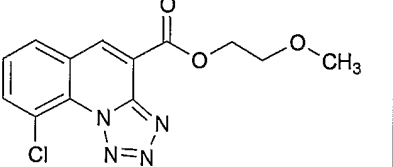
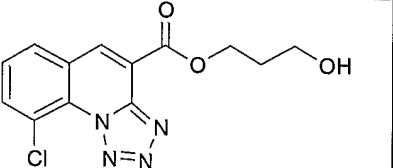
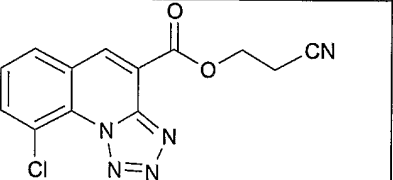
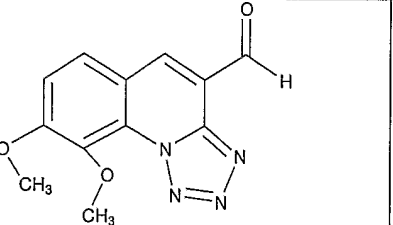
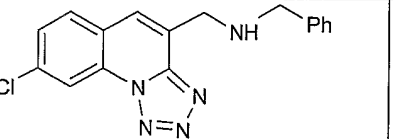
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	tetrazolo[1,5-a]quinoline-4-carbaldehyde O-methyloxime
	7-methoxytetrazolo[1,5-a]quinoline-4-carbaldehyde O-methyloxime
	8-fluorotetrazolo[1,5-a]quinoline-4-carboxylic acid
	8-(benzyloxy)tetrazolo[1,5-a]quinoline-4-carbaldehyde
	8-(benzyloxy)tetrazolo[1,5-a]quinoline-4-carboxylic acid
	8-chlorotetrazolo[1,5-a]quinoline-4-carboxylic acid

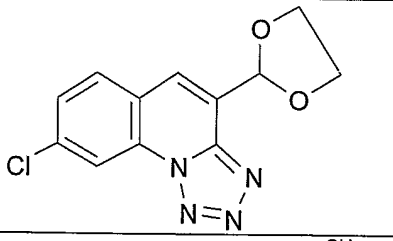
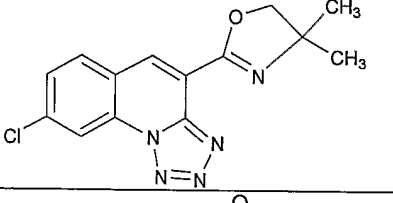
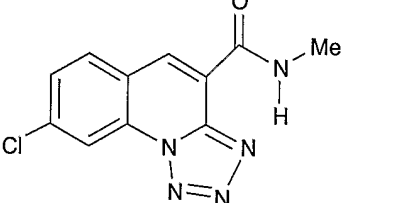
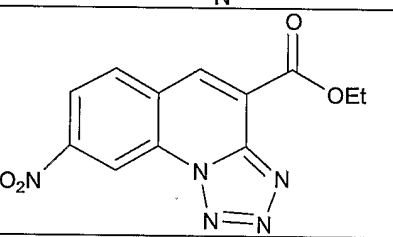
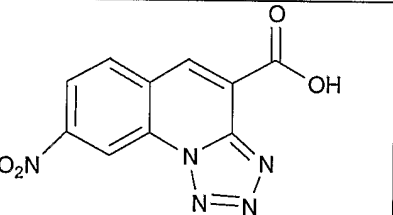
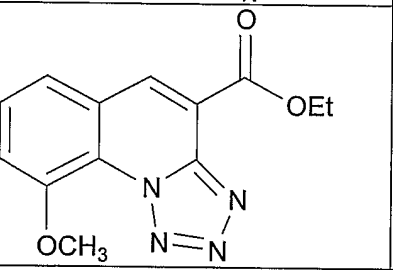
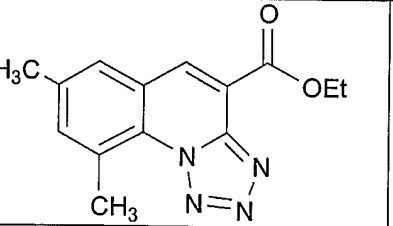
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	7-fluorotetrazolo[1,5-a]quinoline-4-carboxylic acid
	8-chloro-N-1H-tetrazol-5-yltetrazolo[1,5-a]quinoline-4-carboxamide
	7-fluoro-N-1H-tetrazol-5-yltetrazolo[1,5-a]quinoline-4-carboxamide
	8-chloro-N-[4-(trifluoromethyl)phenyl]tetrazolo[1,5-a]quinoline-4-carboxamide
	8-chloro-N,N-dimethyltetrazolo[1,5-a]quinoline-4-carboxamide
	8-chlorotetrazolo[1,5-a]quinoline-4-carbaldehyde O-methyloxime
	8-chlorotetrazolo[1,5-a]quinoline-4-carbaldehyde oxime

	potassium 8-chlorotetrazolo[1,5-a]quinoline-4-carboxylate
	7-bromotetrazolo[1,5-a]quinoline-5-carboxylic acid
	8,9-dihydro[1,4]dioxino[2,3-g]tetrazolo[1,5-a]quinoline-4-carbaldehyde
	8-azido-4-(1,3-dioxolan-2-yl)tetrazolo[1,5-a]quinoline
	8-azidotetrazolo[1,5-a]quinoline-4-carboxylic acid
	ethyl 8-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylate
	8-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylic acid

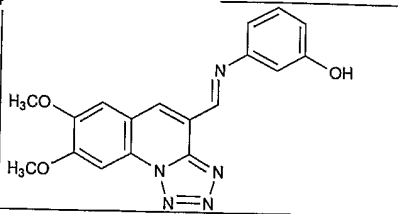
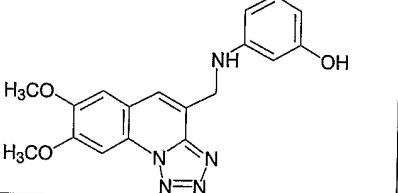
	8-chloro-N-methoxytetrazolo[1,5-a]quinoline-4-carboxamide
	methyl 8-azidotetrazolo[1,5-a]quinoline-4-carboxylate
	8-(trifluoromethoxy)tetrazolo[1,5-a]quinoline-4-carbaldehyde
	ethyl 9-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylate
	ethyl 9-chlorotetrazolo[1,5-a]quinoline-4-carboxylate
	ethyl 9-methyltetrazolo[1,5-a]quinoline-4-carboxylate
	9-chlorotetrazolo[1,5-a]quinoline-4-carboxylic acid
	N-(benzyloxy)-9-chlorotetrazolo[1,5-a]quinoline-4-carboxamide

	ethyl 6-aminotetrazolo[1,5-a]quinoline-4-carboxylate
	8-aminotetrazolo[1,5-a]quinoline-4-carboxylic acid
	8-azido-7-fluorotetrazolo[1,5-a]quinoline-4-carboxylic acid
	ethyl 6-methyltetrazolo[1,5-a]quinoline-4-carboxylate
	2-hydroxyethyl 9-chlorotetrazolo[1,5-a]quinoline-4-carboxylate
	9-chloro-N,N-dimethyltetrazolo[1,5-a]quinoline-4-carboxamide
	6-hydroxyhexyl 9-chlorotetrazolo[1,5-a]quinoline-4-carboxylate

	ethyl 6-chlorotetrazolo[1,5-a]quinoline-4-carboxylate
	6-chlorotetrazolo[1,5-a]quinoline-4-carboxylic acid
	2-hydroxyethyl 8-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylate
	2-hydroxyethyl 8-(trifluoromethoxy)tetrazolo[1,5-a]quinoline-4-carboxylate
	2-methoxyethyl 9-chlorotetrazolo[1,5-a]quinoline-4-carboxylate
	3-hydroxypropyl 9-chlorotetrazolo[1,5-a]quinoline-4-carboxylate
	2-cyanoethyl 9-chlorotetrazolo[1,5-a]quinoline-4-carboxylate
	8,9-dimethoxytetrazolo[1,5-a]quinoline-4-carbaldehyde
	N-benzyl-1-(8-chlorotetrazolo[1,5-a]quinolin-4-yl)methanamine

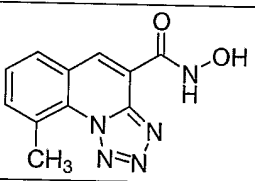
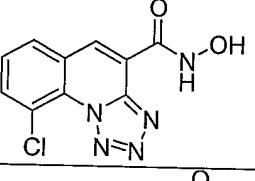
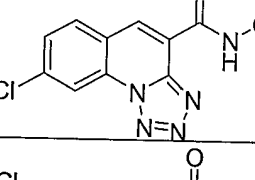
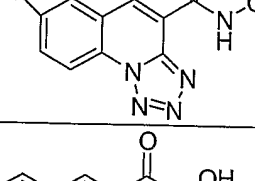
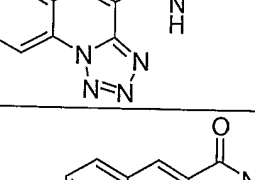
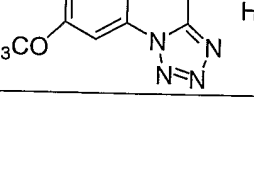
	8-chloro-4-(1,3-dioxolan-2-yl)tetrazolo[1,5-a]quinoline
	8-chloro-4-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)tetrazolo[1,5-a]quinoline
	8-chloro-N-methyltetrazolo[1,5-a]quinoline-4-carboxamide
	ethyl 8-nitrotetrazolo[1,5-a]quinoline-4-carboxylate
	8-nitrotetrazolo[1,5-a]quinoline-4-carboxylic acid
	ethyl 9-methoxytetrazolo[1,5-a]quinoline-4-carboxylate
	ethyl 7,9-dimethyltetrazolo[1,5-a]quinoline-4-carboxylate

	<p>7,9-dimethyltetrazolo[1,5-a]quinoline-4-carboxylic acid</p>
	<p>isobutyl 8-azido-7-fluorotetrazolo[1,5-a]quinoline-4-carboxylate</p>
	<p>ethyl 7,9-dichlorotetrazolo[1,5-a]quinoline-4-carboxylate</p>
	<p>7,9-dichlorotetrazolo[1,5-a]quinoline-4-carboxylic acid</p>
	<p>8-tert-butyltetrazolo[1,5-a]quinoline-4-carboxylic acid</p>
	<p>isobutyl 8-amino-7-fluorotetrazolo[1,5-a]quinoline-4-carboxylate</p>
	<p>ethyl 8-aminotetrazolo[1,5-a]quinoline-4-carboxylate</p>
	<p>2-hydroxyethyl 8-chlorotetrazolo[1,5-a]quinoline-4-carboxylate</p>
	<p>4-[(hydroxyamino)methyl]-7,8-dimethoxytetrazolo[1,5-a]quinoline</p>

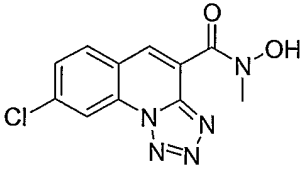
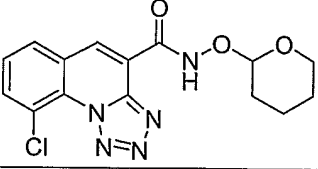
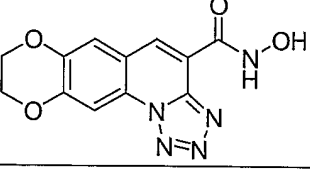
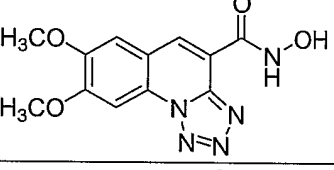
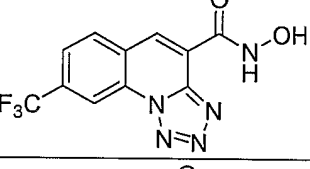
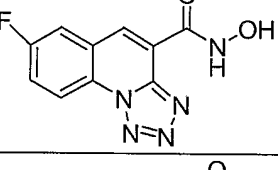
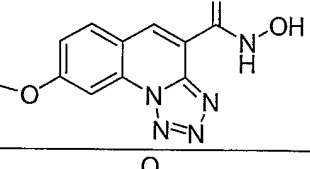
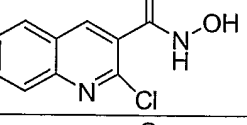
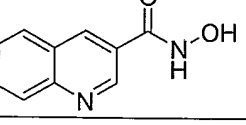
	3-(((1E)-(7,8-dimethoxytetrazolo[1,5-a]quinolin-4-yl)methylene)amino)phenol
	3-(((7,8-dimethoxytetrazolo[1,5-a]quinolin-4-yl)methyl)amino)phenol

[0109] Compounds listed in Table 4 below also exhibit inhibitory activity.

Table 4

Structure	Name	Activity (IC50)	M-H ⁺
	<i>N</i> -hydroxy-9-methyltetrazolo[1,5-a]quinoline-4-carboxamide	+++	244
	9-chloro- <i>N</i> -hydroxytetrazolo[1,5-a]quinoline-4-carboxamide	+++	264
	8-chloro- <i>N</i> -hydroxytetrazolo[1,5-a]quinoline-4-carboxamide	+++	264
	7-chloro- <i>N</i> -hydroxytetrazolo[1,5-a]quinoline-4-carboxamide	+++	264
	<i>N</i> -hydroxytetrazolo[1,5-a]quinoline-4-carboxamide	+++	230
	<i>N</i> -hydroxy-8-(trifluoromethoxy)tetrazolo[1,5-a]quinoline-4-carboxamide	+++	312

Structure	Name	Activity (IC50)	M-H ⁺
	8-chloro- <i>N</i> -hydroxy-7-methoxytetrazolo[1,5-a]quinoline-4-carboxamide	+++	292
	8-chloro-7-methoxy- <i>N</i> -(tetrahydro-2 <i>H</i> -pyran-2-yloxy)tetrazolo[1,5-a]quinoline-4-carboxamide	+	294
	8-methoxy- <i>N</i> -(tetrahydro-2 <i>H</i> -pyran-2-yloxy)tetrazolo[1,5-a]quinoline-4-carboxamide	+	342
	7-chloro- <i>N</i> -(tetrahydro-2 <i>H</i> -pyran-2-yloxy)tetrazolo[1,5-a]quinoline-4-carboxamide	+	346
	7,8-dimethoxy- <i>N</i> -(tetrahydro-2 <i>H</i> -pyran-2-yloxy)tetrazolo[1,5-a]quinoline-4-carboxamide	+++	372
	9-methyl- <i>N</i> -(tetrahydro-2 <i>H</i> -pyran-2-yloxy)tetrazolo[1,5-a]quinoline-4-carboxamide	+	326
	methyl tetrazolo[1,5-a]quinoline-5-carboxylate	+	229
	<i>N</i> -(tetrahydro-2 <i>H</i> -pyran-2-yloxy)tetrazolo[1,5-a]quinoline-4-carboxamide	+	313
	<i>N</i> -(tetrahydro-2 <i>H</i> -pyran-2-yloxy)-8-(trifluoromethoxy)tetrazolo[1,5-a]quinoline-4-carboxamide	+	396

Structure	Name	Activity (IC50)	M-H ⁺
	8-chloro- <i>N</i> -hydroxy- <i>N</i> -methyltetrazolo[1,5- <i>a</i>]quinoline-4-carboxamide	+	278
	9-chloro- <i>N</i> -(tetrahydro-2 <i>H</i> -pyran-2-yloxy)tetrazolo[1,5- <i>a</i>]quinoline-4-carboxamide	+	346
	<i>N</i> -hydroxy-8,9-dihydro[1,4]dioxino[2,3- <i>g</i>]tetrazolo[1,5- <i>a</i>]quinoline-4-carboxamide	+++	286
	<i>N</i> -hydroxy-7,8-dimethoxytetrazolo[1,5- <i>a</i>]quinoline-4-carboxamide	+++	288
	<i>N</i> -hydroxy-8-(trifluoromethyl)tetrazolo[1,5- <i>a</i>]quinoline-4-carboxamide	+++	298
	7-fluoro- <i>N</i> -hydroxytetrazolo[1,5- <i>a</i>]quinoline-4-carboxamide	+++	246
	<i>N</i> -hydroxy-8-methoxytetrazolo[1,5- <i>a</i>]quinoline-4-carboxamide	+	260
	2-chloro- <i>N</i> -hydroxyquinoline-3-carboxamide	+	
	<i>N</i> -hydroxyquinoline-3-carboxamide	+	

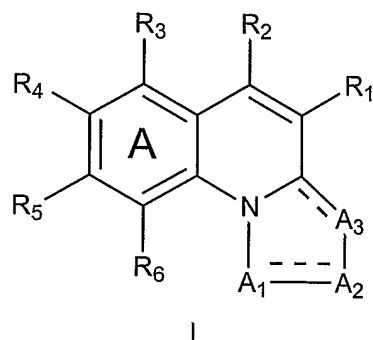
Structure	Name	Activity (IC50)	M-H ⁺
	<i>N</i> -(tetrahydro-2 <i>H</i> -pyran-2-yloxy)tetrazolo[1,5- <i>a</i>]quinoline-5-carboxamide	+	314
	<i>N</i> -hydroxytetrazolo[1,5- <i>a</i>]quinoline-5-carboxamide	+	230
	7,9-dimethyl- <i>N</i> -(tetrahydro-2 <i>H</i> -pyran-2-yloxy)tetrazolo[1,5- <i>a</i>]quinoline-4-carboxamide	+	340
	<i>N</i> -hydroxy-7,9-dimethyltetrazolo[1,5- <i>a</i>]quinoline-4-carboxamide	+++	258
	7,9-dichloro- <i>N</i> -hydroxytetrazolo[1,5- <i>a</i>]quinoline-4-carboxamide	+++	298
	7,9-dichloro- <i>N</i> -(tetrahydro-2 <i>H</i> -pyran-2-yloxy)tetrazolo[1,5- <i>a</i>]quinoline-4-carboxamide	+	380
	methyl 8-fluoro-[1,2,4]triazolo[4,3- <i>a</i>]quinoline-4-carboxylate	+	246
	8-fluoro-[1,2,4]triazolo[4,3- <i>a</i>]quinoline-4-carboxylic acid	+	232
	ethyl 7-chloro-1-methyl-[1,2,4]triazolo[4,3- <i>a</i>]quinoline-4-carboxylate	+	290

Structure	Name	Activity (IC50)	M-H ⁺
	ethyl 7,9-dichloro-[1,2,4]triazolo[4,3-a]quinoline-4-carboxylate	+	310
	7,9-dichloro-[1,2,4]triazolo[4,3-a]quinoline-4-carboxylic acid	+	282
	ethyl 7-chloro-[1,2,4]triazolo[4,3-a]quinoline-4-carboxylate	+	276
	7,9-dichloro-N-(tetrahydro-2H-pyran-2-yloxy)-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide	+	379
	5-(5-(dichloromethyl)-1,3,4-oxadiazol-2-yl)tetrazolo[1,5-a]quinoline	+	321
	1-chloro-8-fluoro-N-(tetrahydro-2H-pyran-2-yloxy)-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide	+	365
	7-chloro-N-(tetrahydro-2H-pyran-2-yloxy)-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide	+	345
	6-chloro-N-(tetrahydro-2H-pyran-2-yloxy)tetrazolo[1,5-a]quinoline-4-carboxamide	+	348

Structure	Name	Activity (IC50)	M-H ⁺
	7-chloro-N-hydroxy-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide	+++	263
	6-chloro-N-hydroxytetrazolo[1,5-a]quinoline-4-carboxamide	+++	264
	7,9-dichloro-N-hydroxy-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide	+++	297
	7-chloro-N-hydroxy-1-methyl-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide	+++	277
	1-chloro-8-fluoro-N-hydroxy-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide	+++	281

+++ means less than 10 μ M+ means greater than 10 μ M

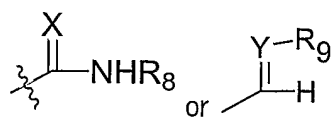
1. A compound of the formula



or a pharmaceutically acceptable salt thereof wherein

R₁ and R₂ are independently hydrogen, C₁-C₆-alkyl, heterocyclic, C₁-C₆-alkyl-OH, aryl, heteroaryl, halogen, cyano, -CO-H, -CO-OH, -CO-OR₇, -CO-NH₂, -CO-NHR₇, -CO-NR₇R₇, -CO-NH-OH, -CO-NH-OR₇, -CO-N(R₇)-OR₇, -CO-R₇, -SO₂NH₂, -SO₂NHR₇, -SO₂NR₇R₇, -SO₂-heteroaryl, -SO₂-aryl, -NHR₇, C₁-C₆-alkyl-NH(R₇)-aryl, -NH(R₇)-aryl, -CO-heteroaryl, -NH-CO-O-R₇-aryl, -NH-CO-NH-SO₂-aryl, -NH-CO-OR₇, -NH-CO-NH-(C₁-C₆-alkyl) or -NH-CO-(C₁-C₆-alkyl), wherein each of the heteroaryl and aryl groups are optionally substituted with C₁-C₆-alkyl, nitro, hydroxy, C₁-C₆-alkoxy, -CO-O-(C₁-C₆-alkyl), cyano, -O-halo(C₁-C₆-alkyl), halo(C₁-C₆-alkyl) or halogen; or

R₁ or R₂ is a group selected from



wherein R₈ is hydrogen or hydroxy; X is =NH or =S, Y is =N-, and R₉ is hydroxy, C₁-C₆-alkoxy or aryl optionally substituted with hydroxy or C₁-C₆-alkyl; or

R₁ and R₂ together with the carbon atoms to which they are attached form a mono or bicyclic aryl or heteroaryl;

R₃, R₄, R₅ and R₆ are independently hydrogen, nitro, C₁-C₆-alkyl, aryl, -O-halo(C₁-C₆-alkyl), halo(C₁-C₆-alkyl), -O-(C₃-C₆-cycloalkyl), -S-(C₁-C₆-alkyl), heterocyclyl, C₁-C₆-alkoxy, -(C₁-C₆-alkoxy)-aryl, azido, halogen, -OCF₃, -CF₃, -CO-H, -CO-OH, -CO-OR₇, -CO-NH₂, -CO-NHR₇, -CO-NR₇R₇, -CO-N(R₇)OR₇, -CO-R₇, -SO₂-(C₁-C₆-alkyl), -SO₂NH₂, -SO₂NHR₇, -SO₂NR₇R₇, -CO-heteroaryl, -NH₂, -NHR₇, -NR₇R₇, -OH, -N(R₇)-CO-R₇, -NHSO₂R₇, -N(R₇)-CO-OR₇ or -N(R₇)-CO-NR₇R₇;

R₄ and R₅ together with the carbon atoms to which they are attached form a heteroaryl;

R₇ is a cation, C₀-C₆-alkyl, -(C₁-C₆-alkyl)-OH, -(C₁-C₆-alkyl)-O-(C₁-C₆-alkyl), -(C₁-C₆-alkyl)-CN, C₂-C₆-alkene, heterocyclyl, aryl, heteroaryl or -(C₁-C₆-alkyl)-aryl, wherein each of the aryl, heterocyclyl and

heteroaryl groups are optionally substituted with C₁-C₆-alkyl, nitro, hydroxy, C₁-C₆-alkoxy, -CO-O-(C₁-C₆-alkyl), cyano, -O-halo(C₁-C₆-alkyl), halo(C₁-C₆-alkyl) or halogen;

A₁, A₂ and A₃ are independently carbon, oxygen, or nitrogen, wherein the carbon or nitrogen is optionally substituted with halo or C₁-C₆-alkyl; and

ring A optionally contains from 1 to 2 nitrogen atoms;

provided that when A₁, A₂, and A₃ are N:

R₁ to R₆ are not all hydrogen;

when R₂ to R₆ are hydrogen, R₁ is not -CH₃, -CO-phenyl, -CO-H or chloro;

when R₁ and R₃ to R₆ are hydrogen, R₂ is not bromo, -CH₂-OH, cyano, iodo, -CO-OH, -CH₃, -CH₂OCH₃, morpholino, -CH₂NH-CH₂CH₃, vinyl, -CH₂CH₃, chloro, -CH₂NH₂ or azido;

when R₁ to R₃ and R₅ to R₆ are hydrogen, R₄ is not chloro, ethynyl or -CH₃;

when R₁ to R₄ and R₆ are hydrogen, R₅ is not -CH₃ or -CH₂NH-isopropyl;

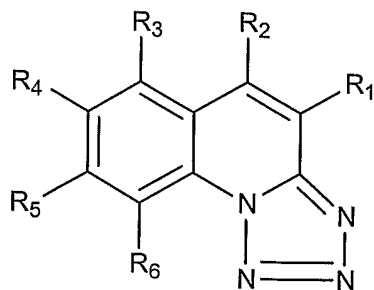
when R₁ to R₅ are hydrogen, R₆ is not -CH₂Br, chloro, -CH₃, -CH₂-OH, -CO-H, -NO₂, -NH₂, acetamido, -CH₂OCH₃, -CH₂CN, propyl, iodo or -CH₂OCH₂CH₃; and

the compounds of formula I are not one of the following combinations

A ₁	A ₂	A ₃	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
N	N	N	-CO-H	-H	-H	-H	-CH ₃	-H
N	N	N	-CO-OH	-H	-H	-N ₃	-N ₃	-H
N	N	N	-CO-OH	-H	-H	-OCH ₃	-OCH ₃	-H
N	N	N	-CO-H	-H	-H	-H	-CH ₃	-H
N	N	N	-H	-CH ₃	-H	-H	-OCH ₃	-H
N	N	N	-CN	piperidyl	-H	-H	-H	-H
N	N	N	-H	-Cl	-H	-H	-H	-CH ₃
N	N	N	-CN	-Cl	-H	-H	-H	-H
N	N	N	-H	-CH ₃	-H	-CH ₂ CH ₃	-H	-H
C	N	N	-H	-CH ₃	-H	-H	-H	-H
C	N	N	-H	-H	-H	-H	-H	-H
N	N	N	-H	-CH ₃	-H	-H	-H	-F
N	N	N	-H	-CH ₃	-H	-H	-H	-Br
N	N	N	-CH ₃	-Cl	-H	-H	-H	-H
N	N	N	-CH ₂ CH ₃	-Cl	-H	-H	-H	-H
N	N	N	-H	-Cl	-H	-H	-H	-CH ₂ NHCH ₃

A ₁	A ₂	A ₃	R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
N	N	N	-H	-Cl	-H	-CH ₃	-H	-H
N	N	N	-H	-Cl	-H	-H	-H	-CH ₃
N	N	N	-H	-Cl	-H	-H	-H	-Cl
N	N	N	-H	-N ₃	-H	-CH ₃	-H	-H
N	N	N	-H	-N ₃	-H	-H	-H	-Cl
N	N	N	-H	-N ₃	-H	-CH ₃	-H	-H
N	N	N	-CH ₃	-Cl	-H	-H	-H	-CH ₃
N	N	N	-H	-CH ₂ Cl	-H	-H	-H	-CH ₂ Cl
N	N	N	-CH ₃	-Cl	-H	-H	-H	-Cl
N	N	N	-H	-CH ₃	-H	-H	-H	-CH ₃
N	N	N	-H	-CH ₃	-H	-CH ₃	-H	-H
N	N	N	-CH ₃	-Cl	-H	-H	-H	-F
N	N	N	-H	-Cl	-H	-H	-H	-F
N	N	N	-H	-Cl	-Cl	-H	-H	-Cl
N	N	N	-H	-Cl	-H	-H	-H	-CH ₃
N	N	N	-H	-CH ₃	-H	-H	-H	-CH ₂ CH ₃
N	N	N	-H	-CH ₃	-H	-CH ₂ CH ₃	-H	-H
N	N	N	-H	morpholino	-H	-Cl	-H	-Cl
N	N	N	-H	-CH ₃	-H	-Cl	-H	-H
N	N	N	-Cl	-CH ₃	-H	-H	-H	-H
N	N	N	-H	-CH ₃	-H	-H	-H	-Cl

2. The compound according to claim 1 of the formula

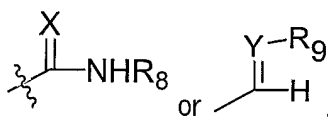


II

or a pharmaceutically acceptable salt thereof wherein

R_1 and R_2 are independently hydrogen, C₁-C₆-alkyl, heterocyclic, C₁-C₆-alkyl-OH, aryl, heteroaryl, halogen, cyano, -CO-H, -CO-OH, -CO-OR₇, -CO-NH₂, -CO-NHR₇, -CO-NR₇R₇, -CO-NH-OH, -CO-NH-OR₇, -CO-N(R₇)-OR₇, -CO-R₇, -SO₂NH₂, -SO₂NHR₇, -SO₂NR₇R₇, -SO₂-heteroaryl, -SO₂-aryl, -NHR₇, C₁-C₆-alkyl-NH(R₇)-aryl, -NH(R₇)-aryl, -CO-heteroaryl, -NH-CO-O-R₇-aryl, -NH-CO-NH-SO₂-aryl, -NH-CO-OR₇, -NH-CO-NH-(C₁-C₆-alkyl) or -NH-CO-(C₁-C₆-alkyl), wherein each of the heteroaryl and aryl groups are optionally substituted with C₁-C₆-alkyl, nitro, hydroxy, C₁-C₆-alkoxy, -CO-O-(C₁-C₆-alkyl), cyano, -O-halo(C₁-C₆-alkyl), halo(C₁-C₆-alkyl) or halogen; or

R_1 or R_2 is a group selected from



wherein R_8 is hydrogen or hydroxy; X is =NH or =S; Y is =N-, and R_9 is hydroxy, C₁-C₆-alkoxy or aryl optionally substituted with hydroxy or C₁-C₆-alkyl; or

R_1 and R_2 together with the carbon atoms to which they are attached form a mono or bicyclic aryl or heteroaryl;

R_3 , R_4 , R_5 and R_6 are independently hydrogen, nitro, C₁-C₆-alkyl, aryl, -O-halo(C₁-C₆-alkyl), halo(C₁-C₆-alkyl), -O-(C₃-C₆-cycloalkyl), -S-(C₁-C₆-alkyl), heterocyclyl, C₁-C₆-alkoxy, -(C₁-C₆-alkoxy)-aryl, azido, halogen, -OCF₃, -CF₃, -CO-H, -CO-OH, -CO-OR₇, -CO-NH₂, -CO-NHR₇, -CO-NR₇R₇, -CO-N(R₇)-OR₇, -CO-R₇, -SO₂-(C₁-C₆-alkyl), -SO₂NH₂, -SO₂NHR₇, -SO₂NR₇R₇, -CO-heteroaryl, -NH₂, -NHR₇, -NR₇R₇, -OH, -N(R₇)-CO-R₇, -NHSO₂R₇, -N(R₇)-CO-OR₇ or -N(R₇)-CO-NR₇R₇;

R_4 and R_5 together with the carbon atoms to which they are attached form a heteroaryl;

R_7 is a cation, C₀-C₆-alkyl, -(C₁-C₆-alkyl)-OH, -(C₁-C₆-alkyl)-O-(C₁-C₆-alkyl), -(C₁-C₆-alkyl)-CN, C₂-C₆-alkene, heterocyclyl, aryl, heteroaryl or -(C₁-C₆-alkyl)-aryl, wherein each of the aryl, heterocyclyl and heteroaryl groups are optionally substituted with C₁-C₆-alkyl, nitro, hydroxy, C₁-C₆-alkoxy, -CO-O-(C₁-C₆-alkyl), cyano, -O-halo(C₁-C₆-alkyl), halo(C₁-C₆-alkyl) or halogen; and

provided that:

R_1 to R_6 are not all hydrogen;

when R_2 to R_6 are hydrogen, R_1 is not -CO-phenyl, -CO-H or chloro;

when R_1 and R_3 to R_6 are hydrogen, R_2 is not bromo, -CH₂-OH, cyano, iodo, -CO-OH, -CH₃, -CH₂OCH₃, morpholino, -CH₂NH-CH₂CH₃, vinyl, -CH₂CH₃, chloro, -CH₂NH₂ or azido;

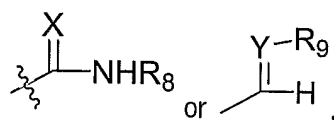
when R_1 to R_3 and R_5 to R_6 are hydrogen, R_4 is not chloro, ethynyl or -CH₃;

when R_1 to R_4 and R_6 are hydrogen, R_5 is not -CH₃ or -CH₂NH-isopropyl;

when R_1 to R_5 are hydrogen, R_6 is not -CH₂Br, chloro, -CH₃, -CH₂-OH, -CO-H, -NO₂, -NH₂, acetamido, -CH₂OCH₃, -CH₂-CN, propyl, iodo or -CH₂OCH₂CH₃; and

R ₁	R ₂	R ₃	R ₄	R ₅	R ₆
-CO-H	-H	-H	-H	-CH ₃	-H
-CO-OH	-H	-H	-N ₃	-N ₃	-H
-CO-OH	-H	-H	-OCH ₃	-OCH ₃	-H
-CO-H	-H	-H	-H	-CH ₃	-H
-H	-CH ₃	-H	-H	-OCH ₃	-H
-CN	piperidyl	-H	-H	-H	-H
-H	-Cl	-H	-H	-H	-CH ₃
-CN	-Cl	-H	-H	-H	-H
-H	-CH ₃	-H	-CH ₂ CH ₃	-H	-H
-H	-CH ₃	-H	-H	-H	-F
-H	-CH ₃	-H	-H	-H	-Br
-CH ₃	-Cl	-H	-H	-H	-H
-CH ₂ CH ₃	-Cl	-H	-H	-H	-H
-H	-Cl	-H	-H	-H	-CH ₂ NHCH ₃
-H	-Cl	-H	-CH ₃	-H	-H
-H	-Cl	-H	-H	-H	-CH ₃
-H	-Cl	-H	-H	-H	-Cl
-H	-N ₃	-H	-CH ₃	-H	-H
-H	-N ₃	-H	-H	-H	-Cl
-H	-N ₃	-H	-CH ₃	-H	-H
-CH ₃	-Cl	-H	-H	-H	-CH ₃
-H	-CH ₂ Cl	-H	-H	-H	-CH ₂ Cl
-CH ₃	-Cl	-H	-H	-H	-Cl
-H	-CH ₃	-H	-H	-H	-CH ₃
-H	-CH ₃	-H	-CH ₃	-H	-H
-CH ₃	-Cl	-H	-H	-H	-F
-H	-Cl	-H	-H	-H	-F
-H	-Cl	-Cl	-H	-H	-Cl
-H	-Cl	-H	-H	-H	-CH ₃
-H	-CH ₃	-H	-H	-H	-CH ₂ CH ₃
-H	-CH ₃	-H	-CH ₂ CH ₃	-H	-H
-H	morpholino	-H	-Cl	-H	-Cl
-H	-CH ₃	-H	-Cl	-H	-H
-Cl	-CH ₃	-H	-H	-H	-H
-H	-CH ₃	-H	-H	-H	-Cl

- The compound according to claim 2 wherein R₁ is -CO-NH-OR₇, R₅ is halogen, and R₂ to R₄ and R₆ are hydrogen.
4. The compound according to claim 3 wherein R₇ is hydrogen and R₅ is chloro.
 5. The compound according to claim 2 wherein R₁ is aryl optionally substituted with one or more halo(C₁-C₆-alkyl), cyano, -O-halo(C₁-C₆-alkyl), or halogen, R₅ is halogen, R₂ to R₄ and R₆ are hydrogen.
 6. The compound according to claim 5 wherein R₁ is phenyl optionally substituted with one or more -CF₃ or F and R₅ is chloro.
 7. The compound according to claim 2 wherein R₁ is -CO-NH-OR₇, R₆ is halogen and R₂ to R₅ are hydrogen.
 8. The compound according to claim 7 wherein R₇ is isobutyl, propyl, isopropyl or ethyl and R₆ is chloro.
 9. The compound according to claim 2 wherein R₁ is -NH-CO-OR₇, R₅ is halogen, R₂ to R₄ and R₆ are hydrogen.
 10. The compound according to claim 9 wherein R₇ is tert-butyl and R₅ is chloro.
 11. The compound according to claim 2 wherein R₁ is -CO-OR₇, R₆ is halo(C₁-C₆-alkyl) and R₂ to R₅ are hydrogen.
 12. The compound according to claim 11 wherein R₇ is hydrogen and R₆ is -CF₃.
 13. The compound according to claim 2 wherein R₁ is -NH-CO-NH-SO₂-aryl, -NH-CO-NH-(C₁-C₆-alkyl), C₁-C₆-alkyl-OH, -CO-H, -CO-NH₂, -CO-NH-R₇, -CO-NH-OR₇, -SO₂-aryl, -SO₂-heteroaryl, heteroaryl, -CO-OR₇ or a group represented by



wherein R₈ is hydrogen or hydroxy, X is =N or =S, Y is -N-, R₉ is hydroxy or C₁-C₆-alkoxy; R₄ and R₅ are independently selected from hydrogen, -S-(C₁-C₆-alkyl), C₁-C₆-alkyl, -O-(C₃-C₆-cycloalkyl), C₁-C₆-alkoxy, halogen, -SO₂-(C₁-C₆-alkyl), heterocyclyl, -O-halo(C₁-C₆-alkyl), halo(C₁-C₆-alkyl), -NH₂ or together with the carbon atom to which they are attached form a heteroaryl group; R₂, R₃ and R₆ are hydrogen; and wherein the each of the aryl, heteroaryl and

- heterocycliyl groups are optionally substituted with -CO-O-(C₁-C₆-alkyl), C₁-C₆-alkyl, nitro, hydroxy, C₁-C₆-alkoxy, cyano, -O-halo(C₁-C₆-alkyl), halo(C₁-C₆-alkyl) or halogen.
14. The compound according to claim 2 wherein R₁ and R₂ are independently selected from is -NH(R₇)-aryl, -CO-OH, -CO-OR₇, C₁-C₆-alkyl, aryl or together with the carbon atoms to which they are attached form a bicyclic heteroaryl; R₃ to R₆ are hydrogen; and wherein each of the aryl and heteroaryl groups are optionally substituted with -CO-O-(C₁-C₆-alkyl), C₁-C₆-alkyl, nitro, hydroxy, C₁-C₆-alkoxy, cyano, -O-halo(C₁-C₆-alkyl), halo(C₁-C₆-alkyl) or halogen.
 15. The compound according to claim 2 wherein R₁ is -CO-OH, -CO-OR₇, or -CO-NH-OR₇; R₆ is C₁-C₆-alkyl, halogen, or -O-(C₁-C₆-alkyl); and R₂ to R₅ are hydrogen.
 16. The compound according to claim 2 wherein R₁ is -CO-OR₇; R₃ is azido or C₁-C₆-alkyl; and R₂, R₄ to R₆ are hydrogen.
 17. The compound according to claim 1 wherein A₁, A₂ and A₃ are independently carbon or nitrogen each optionally substituted with halo or C₁-C₆-alkyl.
 18. The compound according to claim 17 wherein any one of A₁, A₂ and A₃ is carbon optionally substituted with halo or C₁-C₆-alkyl.
 19. The compound according to claim 18 wherein any one of A₁, A₂ and A₃ is substituted with halo.
 20. The compound according to claim 19 wherein halo is chloro.
 21. The compound according to claim 18 wherein any one of A₁, A₂ and A₃ is substituted with C₁-C₆-alkyl.
 22. The compound according to claim 21 wherein C₁-C₆-alkyl is methyl.
 23. A compound according to claim 1 which is
8-chloro-4-[2-(trifluoromethyl)phenyl]tetrazolo[1,5-a]quinoline
8-chlorotetrazolo[1,5-a]quinoline-4-carboxamide
8-chloro-4-(3,4-difluorophenyl)tetrazolo[1,5-a]quinoline
tert-butyl (8-chlorotetrazolo[1,5-a]quinolin-4-yl)carbamate
9-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylic acid
9-chloro-N-isobutoxytetrazolo[1,5-a]quinoline-4-carboxamide
9-chloro-N-propoxytetrazolo[1,5-a]quinoline-4-carboxamide

- 9-chloro-N-isopropoxytetrazolo[1,5-a]quinoline-4-carboxamide
9-chloro-N-ethoxytetrazolo[1,5-a]quinoline-4-carboxamide,
8-chloro-N-hydroxytetrazolo[1,5-a]quinoline-4-carboxamide, or
a pharmaceutically acceptable salt thereof.
24. A compound according to claim 1 which is
8-chloro-4-[2-(trifluoromethyl)phenyl]tetrazolo[1,5-a]quinoline;
8-chlorotetrazolo[1,5-a]quinoline-4-carboxamide;
8-chloro-4-(3,4-difluorophenyl)tetrazolo[1,5-a]quinoline;
tert-butyl (8-chlorotetrazolo[1,5-a]quinolin-4-yl)carbamate;
9-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylic acid;
9-chloro-N-isobutoxytetrazolo[1,5-a]quinoline-4-carboxamide;
9-chloro-N-propoxytetrazolo[1,5-a]quinoline-4-carboxamide;
9-chloro-N-isopropoxytetrazolo[1,5-a]quinoline-4-carboxamide;
9-chloro-N-ethoxytetrazolo[1,5-a]quinoline-4-carboxamide;
8-chloro-N-hydroxytetrazolo[1,5-a]quinoline-4-carboxamide;
N-benzyltetrazolo[1,5-a]quinolin-5-amine;
5-methyltetrazolo[1,5-a]quinoline-4-carboxylic acid;
5-phenyltetrazolo[1,5-a]quinoline-4-carboxylic acid;
8-chloro-4-(pyridin-2-ylsulfonyl)tetrazolo[1,5-a]quinoline;
2-(8-chlorotetrazolo[1,5-a]quinolin-4-yl)benzotrile;
8-(cyclopentyloxy)tetrazolo[1,5-a]quinoline-4-carbaldehyde;
8-chloro-7-methoxytetrazolo[1,5-a]quinoline-4-carbaldehyde;
8-chloro-7-methoxytetrazolo[1,5-a]quinoline-4-carboxylic acid;
tetrazolo[1,5-a]quinoline-4-carboxamide;
N-hydroxytetrazolo[1,5-a]quinoline-4-carboximidamide;
tetrazolo[1,5-a]quinoline-4-carboximidamide;
N-[(8-chlorotetrazolo[1,5-a]quinolin-4-yl)amino]carbonyl)benzenesulfonamide;
7-methoxytetrazolo[1,5-a]quinoline-4-carbaldehyde oxime;
4-(1H-tetrazol-5-yl)tetrazolo[1,5-a]quinoline;
9H-indolo[3,2-c]tetrazolo[1,5-a]quinoline;
8-(methylsulfonyl)tetrazolo[1,5-a]quinoline-4-carboxylic acid;
8-ethyltetrazolo[1,5-a]quinoline-4-carboxylic acid;
8-ethyltetrazolo[1,5-a]quinoline-4-carbaldehyde O-methylxime;
7-bromotetrazolo[1,5-a]quinoline-4-carboxylic acid;

8-isopropyltetrazolo[1,5-a]quinoline-4-carboxylic acid;
N-(8-chlorotetrazolo[1,5-a]quinolin-4-yl)-N'-methylurea;
8-chloro-4-(1H-imidazol-1-yl)tetrazolo[1,5-a]quinoline;
8-chloro-4-[4-(trifluoromethoxy)phenyl]tetrazolo[1,5-a]quinoline;
8-chloro-4-(3-fluorophenyl)tetrazolo[1,5-a]quinoline;
4-[3,5-bis(trifluoromethyl)phenyl]-8-chlorotetrazolo[1,5-a]quinoline;
methyl 2-[(8-chlorotetrazolo[1,5-a]quinolin-4-yl)sulfonyl]benzoate;
8-chloro-4-[3-(trifluoromethoxy)phenyl]tetrazolo[1,5-a]quinoline;
ethyl 7-fluoro-8-piperidin-1-yltetrazolo[1,5-a]quinoline-4-carboxylate;
8-(methylthio)tetrazolo[1,5-a]quinoline-4-carbaldehyde;
8-methoxytetrazolo[1,5-a]quinoline-4-carbaldehyde;
N-benzyl-8-chlorotetrazolo[1,5-a]quinoline-4-carboxamide;
8-(trifluoromethoxy)tetrazolo[1,5-a]quinoline-4-carboxylic acid;
8,9-dihydro[1,4]dioxino[2,3-g]tetrazolo[1,5-a]quinoline-4-carboxylic acid;
7-chlorotetrazolo[1,5-a]quinoline-4-carboxylic acid;
8-chloro-N-(tetrahydro-2H-pyran-2-yloxy)tetrazolo[1,5-a]quinoline-4-carboxamide;
sodium 8-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylate;
sodium 8-(trifluoromethoxy)tetrazolo[1,5-a]quinoline-4-carboxylate;
ethyl 6-azidotetrazolo[1,5-a]quinoline-4-carboxylate;
methyl 8-aminotetrazolo[1,5-a]quinoline-4-carboxylate;
9-methyltetrazolo[1,5-a]quinoline-4-carboxylic acid;
butyl 9-chlorotetrazolo[1,5-a]quinoline-4-carboxylate;
6-methyltetrazolo[1,5-a]quinoline-4-carboxylic acid;
N-(allyloxy)-9-chlorotetrazolo[1,5-a]quinoline-4-carboxamide;
N-(tert-butoxy)-9-chlorotetrazolo[1,5-a]quinoline-4-carboxamide;
8-fluoro-N-1H-tetrazol-5-yltetrazolo[1,5-a]quinoline-4-carboxamide;
7,8-dimethyltetrazolo[1,5-a]quinoline-4-carboxylic acid;
7,8-dimethoxytetrazolo[1,5-a]quinoline-4-carboxylic acid;
7,8-dimethoxytetrazolo[1,5-a]quinoline-4-carbaldehyde;
9-methoxytetrazolo[1,5-a]quinoline-4-carboxylic acid;
ethyl 5-[(3-hydroxyphenyl)amino]-8-(trifluoromethyl)tetrazolo[1,5-a]quinoline-4-carboxylate;
N-hydroxy-9-methyltetrazolo[1,5-a]quinoline-4-carboxamide;
9-chloro-N-hydroxytetrazolo[1,5-a]quinoline-4-carboxamide;
8-chloro-N-hydroxytetrazolo[1,5-a]quinoline-4-carboxamide;
7-chloro-N-hydroxytetrazolo[1,5-a]quinoline-4-carboxamide;

N-hydroxytetrazolo[1,5-*a*]quinoline-4-carboxamide;
N-hydroxy-8-(trifluoromethoxy)tetrazolo[1,5-*a*]quinoline-4-carboxamide;
8-chloro-*N*-hydroxy-7-methoxytetrazolo[1,5-*a*]quinoline-4-carboxamide;
8-chloro-7-methoxy-*N*-(tetrahydro-2*H*-pyran-2-yloxy)tetrazolo[1,5-*a*]quinoline-4-carboxamide;
8-methoxy-*N*-(tetrahydro-2*H*-pyran-2-yloxy)tetrazolo[1,5-*a*]quinoline-4-carboxamide;
7-chloro-*N*-(tetrahydro-2*H*-pyran-2-yloxy)tetrazolo[1,5-*a*]quinoline-4-carboxamide;
7,8-dimethoxy-*N*-(tetrahydro-2*H*-pyran-2-yloxy)tetrazolo[1,5-*a*]quinoline-4-carboxamide;
9-methyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)tetrazolo[1,5-*a*]quinoline-4-carboxamide;
methyl tetrazolo[1,5-*a*]quinoline-5-carboxylate;
N-(tetrahydro-2*H*-pyran-2-yloxy)tetrazolo[1,5-*a*]quinoline-4-carboxamide;
N-(tetrahydro-2*H*-pyran-2-yloxy)-8-(trifluoromethoxy)tetrazolo[1,5-*a*]quinoline-4-carboxamide;
8-chloro-*N*-hydroxy-*N*-methyltetrazolo[1,5-*a*]quinoline-4-carboxamide;
9-chloro-*N*-(tetrahydro-2*H*-pyran-2-yloxy)tetrazolo[1,5-*a*]quinoline-4-carboxamide;
N-hydroxy-8,9-dihydro[1,4]dioxino[2,3-*g*]tetrazolo[1,5-*a*]quinoline-4-carboxamide;
N-hydroxy-7,8-dimethoxytetrazolo[1,5-*a*]quinoline-4-carboxamide;
N-hydroxy-8-(trifluoromethyl)tetrazolo[1,5-*a*]quinoline-4-carboxamide;
7-fluoro-*N*-hydroxytetrazolo[1,5-*a*]quinoline-4-carboxamide;
N-hydroxy-8-methoxytetrazolo[1,5-*a*]quinoline-4-carboxamide;
N-(tetrahydro-2*H*-pyran-2-yloxy)tetrazolo[1,5-*a*]quinoline-5-carboxamide;
N-hydroxytetrazolo[1,5-*a*]quinoline-5-carboxamide;
tetrazolo[1,5-*a*]thieno[2,3-*e*]pyridine-4-carboxylic acid;
N-(tetrahydro-2*H*-pyran-2-yloxy)tetrazolo[1,5-*a*]thieno[2,3-*e*]pyridine-4-carboxamide;
N-hydroxytetrazolo[1,5-*a*]thieno[2,3-*e*]pyridine-4-carboxamide;
7,9-dimethyl-*N*-(tetrahydro-2*H*-pyran-2-yloxy)tetrazolo[1,5-*a*]quinoline-4-carboxamide;
N-hydroxy-7,9-dimethyltetrazolo[1,5-*a*]quinoline-4-carboxamide;
7,9-dichloro-*N*-hydroxytetrazolo[1,5-*a*]quinoline-4-carboxamide;
7,9-dichloro-*N*-(tetrahydro-2*H*-pyran-2-yloxy)tetrazolo[1,5-*a*]quinoline-4-carboxamide;
methyl 8-fluoro-[1,2,4]triazolo[4,3-*a*]quinoline-4-carboxylate;
8-fluoro-[1,2,4]triazolo[4,3-*a*]quinoline-4-carboxylic acid;
ethyl 7-chloro-1-methyl-[1,2,4]triazolo[4,3-*a*]quinoline-4-carboxylate;
ethyl 7,9-dichloro-[1,2,4]triazolo[4,3-*a*]quinoline-4-carboxylate;
7,9-dichloro-[1,2,4]triazolo[4,3-*a*]quinoline-4-carboxylic acid;
ethyl 7-chloro-[1,2,4]triazolo[4,3-*a*]quinoline-4-carboxylate;
7,9-dichloro-*N*-(tetrahydro-2*H*-pyran-2-yloxy)-[1,2,4]triazolo[4,3-*a*]quinoline-4-carboxamide;
5-(5-(dichloromethyl)-1,3,4-oxadiazol-2-yl)tetrazolo[1,5-*a*]quinoline;

1-chloro-8-fluoro-N-(tetrahydro-2H-pyran-2-yloxy)-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide;
7-chloro-N-(tetrahydro-2H-pyran-2-yloxy)-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide;
6-chloro-N-(tetrahydro-2H-pyran-2-yloxy)tetrazolo[1,5-a]quinoline-4-carboxamide;
7-chloro-N-hydroxy-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide;
6-chloro-N-hydroxytetrazolo[1,5-a]quinoline-4-carboxamide;
7,9-dichloro-N-hydroxy-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide;
7-chloro-N-hydroxy-1-methyl-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide;
1-chloro-8-fluoro-N-hydroxy-[1,2,4]triazolo[4,3-a]quinoline-4-carboxamide;
or a pharmaceutically acceptable salt thereof.

25. A composition comprising a compound of any one of claims 1 to 24 and a pharmaceutically acceptable carrier.
26. A method of inhibiting HCV proliferation comprising contacting an HCV infected cell with a compound according to any one of claims 1 to 25.
27. A method of treating a mammal infected with an HCV infection, the method comprising administering to the mammal a therapeutically effective amount of a composition according to claim 25.
28. The method according to claim 27 wherein the mammal is a human.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/031705

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 C07D471/14 C07D491/14 C07D215/54 A61K31/4709
A61K31/4745 A61P31/12

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

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)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 149 467 A1 (ELI LILLY AND CO.) 30 March 1973 (1973-03-30) examples 1-3,9-11,16-46 -----	1,17,18
X	WO 95/26348 A1 (MERRELL DOW PHARMACEUTICALS INC., USA) 5 October 1995 (1995-10-05) claims 2,5,6 -----	1,2,13, 17,25
X	WO 97/48704 A1 (MINNESOTA MINING AND MANUFACTURING CO., USA) 24 December 1997 (1997-12-24) examples 5,6,8,9,11,12,17,20,21 -----	1,2,14, 17,25
X	WO 02/28837 A1 (JANSSEN PHARMACEUTICA N.V., BELG.) 11 April 2002 (2002-04-11) page 82; table 5; compounds 411,413 ----- -/--	1,2,14, 17,25

 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

24 January 2005

Date of mailing of the international search report

07/02/2005

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/031705

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 120 484 A (MERRELL DOW PHARMACEUTICALS, INC., USA) 3 October 1984 (1984-10-03) examples 12,13	1,2,13, 17,25
X	US 4 000 151 A (HESTER, JACKSON B., JR.) 28 December 1976 (1976-12-28) examples 2,12,18,21,24,27,30,33,36	1,17,18, 25
X	DATABASE BEILSTEIN XP002313584 Database accession no. BEILSTEIN REGSISTRY NUMBER : 13090-43-2 s-triazolo'1,5-a!quinoline & HETEROCYCLES, vol. 31, no. 2, 1990, pages 289-304,	1,17,18
X	TETRAHEDRON, vol. 54, 1998, pages 3913-3918, XP002313579 compound 15	1,17,18
X	JOURNAL OF ORGANIC CHEMISTRY, vol. 44, no. 2, 1979, pages 285-287, XP002313578 page 286; compound 7	1,17,18
X	TETRAHEDRON LETTERS, vol. 21, 1980, pages 3723-3726, XP002313580 page 3724; compound 12	1,17,18
X	JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 27, no. 263, 1990, pages 263-268, XP002313581 scheme 4, compound 10a, p264	1,17,18
X	JOURNAL OF ORGANIC CHEMISTRY, vol. 20, 1955, pages 1443-1447, XP002313582 compound IV	1,17,18
X	DE 22 06 012 A (ASPRO-NICHOLAS LTD, SLOUGH, GB) 24 August 1972 (1972-08-24) claim 2; examples 1,20	1,17,18
A	JOURNAL OF VIRAL HEPATITIS, 2003, pages 405-412, XP002313583 page 409; figure 4	1-28
A	WO 03/064456 A (GORYS VIDA J ; LLINAS-BRUNET MONTSE (CA); BOEHRINGER INGELHEIM INT (DE) 7 August 2003 (2003-08-07) claim 1	1-28

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/031705

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 162 196 A (JAPAN TOBACCO INC) 12 December 2001 (2001-12-12) claim 1 -----	1-28
A	WO 03/007945 A (BEAULIEU PIERRE LOUIS ; BOEHRINGER INGELHEIM CA LTD (CA); GOULET SYLVI) 30 January 2003 (2003-01-30) claims 1,47,48 -----	1-28
A	WO 03/040112 A (RIGEL PHARMACEUTICALS INC ; GOFF DANE (US); LU HENRY (US); SINGH RAJIN) 15 May 2003 (2003-05-15) claims 1,22 -----	1-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/031705

Box II Observations where certain claims were found unsearchable (Continuation of item 2 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:

Although claims 26-28 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 III Observations where unity of invention is lacking (Continuation of item 3 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/US2004/031705

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2149467	A1	30-03-1973	AR 195289 A1 28-09-1973
			AR 215825 A1 15-11-1979
			AT 326651 B 29-12-1975
			AT 445174 A 15-03-1975
			AT 324767 B 25-09-1975
			AU 461057 B2 15-05-1975
			AU 4539772 A 14-02-1974
			BE 787536 A1 14-02-1973
			BG 19623 A1 10-10-1975
			BG 20354 A3 05-11-1975
			BG 24409 A3 10-02-1978
			CA 997766 A1 28-09-1976
			CA 1016068 A2 23-08-1977
			CH 564016 A5 15-07-1975
			CH 552942 A 30-08-1974
			CS 190371 B2 31-05-1979
			DD 104176 A5 05-03-1974
			DD 107462 A5 05-08-1974
			DE 2239892 A1 01-03-1973
			DK 139832 B 30-04-1979
			EG 10668 A 31-03-1976
			ES 405899 A1 01-08-1975
			GB 1374369 A 20-11-1974
			HU 167272 B 27-09-1975
			IE 36916 B1 30-03-1977
			IL 40060 A 31-08-1976
			IT 962096 B 20-12-1973
			JP 48028642 A 16-04-1973
			JP 57060321 B 18-12-1982
			KR 7900421 A 14-05-1979
			MY 20078 A 31-12-1978
			NL 7210957 A ,B, 20-02-1973
			PH 10204 A 27-09-1976
			PL 94442 B1 31-08-1977
			RO 63409 A1 15-09-1978
			RO 79165 A1 25-06-1982
			SE 405313 B 04-12-1978
			SE 422059 B 15-02-1982
			SE 7507384 A 27-06-1975
			SU 554815 A3 15-04-1977
US 3839569 A 01-10-1974			
YU 204372 A1 18-06-1982			
ZA 7205365 A 27-03-1974			
WO 9526348	A1	05-10-1995	AT 167863 T 15-07-1998
			AU 686761 B2 12-02-1998
			AU 1845495 A 17-10-1995
			CA 2184694 A1 05-10-1995
			CN 1144527 A ,B 05-03-1997
			DE 69503229 D1 06-08-1998
			DE 69503229 T2 24-12-1998
			DK 751945 T3 12-04-1999
			EP 0751945 A1 08-01-1997
			ES 2120185 T3 16-10-1998
			FI 963808 A 24-09-1996
			GR 3027563 T3 30-11-1998
			HU 9602614 A 28-11-1996
			JP 9510968 T 04-11-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/031705

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9526348	A1	NO 964009 A	22-11-1996
		NZ 281496 A	26-02-1998
		ZA 9502287 A	09-01-1996
WO 9748704	A1	24-12-1997	
		US 5741908 A	21-04-1998
		AT 264326 T	15-04-2004
		AU 721036 B2	22-06-2000
		AU 3956597 A	07-01-1998
		CA 2257846 A1	24-12-1997
		DE 69632207 D1	19-05-2004
		DK 912565 T3	09-08-2004
		EP 0912565 A1	06-05-1999
		ES 2215203 T3	01-10-2004
		JP 2000512995 T	03-10-2000
		KR 2000016783 A	25-03-2000
		NO 986002 A	18-12-1998
		NO 20032132 A	18-12-1998
		NO 20032133 A	18-12-1998
		NO 20032134 A	18-12-1998
		NZ 333169 A	25-08-2000
		PT 912565 T	31-08-2004
		US 5998619 A	07-12-1999
		US 2002188127 A1	12-12-2002
US 2003130516 A1	10-07-2003		
US 2003153762 A1	14-08-2003		
US 6150523 A	21-11-2000		
US 2004019213 A1	29-01-2004		
US 6437131 B1	20-08-2002		
WO 0228837	A1	11-04-2002	
		AU 9384701 A	15-04-2002
		BG 107672 A	30-01-2004
		BR 0114253 A	01-07-2003
		CA 2421782 A1	11-04-2002
		CZ 20031145 A3	17-12-2003
		EP 1332133 A1	06-08-2003
		HR 20030229 A1	30-06-2003
		HU 0302167 A2	28-10-2003
		JP 2004510764 T	08-04-2004
		MX PA03002907 A	24-06-2003
		NO 20031474 A	05-05-2003
		PL 360677 A1	20-09-2004
		SK 5212003 A3	02-03-2004
US 2004082592 A1	29-04-2004		
EP 0120484	A	03-10-1984	
		US 4496569 A	29-01-1985
		AT 26717 T	15-05-1987
		AU 558762 B2	05-02-1987
		AU 2595384 A	27-09-1984
		CA 1252100 A1	04-04-1989
		DE 3463271 D1	27-05-1987
		DK 165584 A ,B,	26-09-1984
		EP 0120484 A1	03-10-1984
		ES 8601970 A1	01-03-1986
		GR 81463 A1	11-12-1984
		IE 57072 B1	22-04-1992
		IL 71318 A	30-11-1986
JP 1735334 C	17-02-1993		
JP 4015791 B	19-03-1992		

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/031705

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
EP 0120484	A	JP 59176287	A 05-10-1984	
		KR 9003649	B1 28-05-1990	
		MX 9203341	A1 01-08-1992	
		NO 841156	A ,B, 26-09-1984	
		NZ 207582	A 08-10-1986	
		PH 20353	A 04-12-1986	
		PT 78288	A ,B 01-04-1984	
		ZA 8402067	A 31-10-1984	
		<hr/>		
US 4000151	A	28-12-1976	NONE	
<hr/>				
DE 2206012	A	24-08-1972	AU 7420774	A 15-04-1976
			BE 779128	A1 30-05-1972
			CH 539643	A 31-07-1973
			CH 539644	A 14-09-1973
			DE 2206012	A1 24-08-1972
			FR 2125378	A5 29-09-1972
			GB 1347493	A 27-02-1974
			IE 36079	B1 18-08-1976
			PH 9467	A 16-12-1975
			SE 7413349	A 23-10-1974
			US 3887566	A 03-06-1975
			<hr/>	
WO 03064456	A	07-08-2003	CA 2370396	A1 01-08-2003
			BR 0307408	A 28-12-2004
			WO 03064456	A1 07-08-2003
			CA 2474156	A1 07-08-2003
			EP 1474441	A1 10-11-2004
			US 2003187018	A1 02-10-2003
<hr/>				
EP 1162196	A	12-12-2001	AU 763356	B2 17-07-2003
			AU 2401701	A 09-07-2001
			BR 0008525	A 02-01-2002
			CA 2363274	A1 05-07-2001
			EP 1162196	A1 12-12-2001
			HU 0202263	A2 28-12-2002
			NO 20014134	A 22-10-2001
			NZ 514403	A 25-10-2002
			SK 13752001	A3 02-07-2002
			US 2004097438	A1 20-05-2004
			US 2003050320	A1 13-03-2003
			CN 1342145	T 27-03-2002
			CZ 20013424	A3 13-02-2002
			ID 30204	A 15-11-2001
			WO 0147883	A1 05-07-2001
			JP 2001247550	A 11-09-2001
			RU 2223761	C2 20-02-2004
TR 200103147	T1 21-06-2002			
ZA 200107870	A 25-09-2002			
<hr/>				
WO 03007945	A	30-01-2003	WO 03007945	A1 30-01-2003
			CA 2448737	A1 30-01-2003
			EP 1411928	A1 28-04-2004
			US 2003236251	A1 25-12-2003
<hr/>				
WO 03040112	A	15-05-2003	BR 0206266	A 30-12-2003
			CA 2465189	A1 15-05-2003
			EP 1451162	A1 01-09-2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/031705

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03040112	A	WO 03040112 A1	15-05-2003
		US 2003165561 A1	04-09-2003
		US 2004236112 A1	25-11-2004
