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(54) Title: HETEROCYCLIC ANTI-VIRAL COMPOUNDS COMPRISING METABOLIZABLE MOIETIES AND THEIR USES

(57) Abstract: The present invention relates to substituted prodrug and compositions thereof useful for treating or preventing Hepatitis C virus (HCV) infections. In particular, the present invention relates to prodrugs of substituted diphenyl-, diheteroaryl- and mixed phenyl heteroaryl substituted five-membered heterocycle compounds, compositions comprising the compounds and the use of such compounds and compositions to inhibit HCV replication and/or proliferation as a therapeutic approach towards the treatment and/or prevention of HCV infections in humans and animals.

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HETEROCYCLIC ANTI-VIRAL COMPOUNDS COMPRISING METABOLIZABLE MOIETIES AND THEIR USES

[0001] This application claims priority to U.S. Provisional application 60/556,625 filed March 26, 2004 and to U.S. Provisional application 60/582,903 filed June 24, 2004.

FIELD OF INVENTION

[0002] The present invention relates to substituted prodrug and compositions thereof useful for treating or preventing Hepatitis C virus (HCV) infections. In particular, the present invention relates to prodrugs of substituted diphenyl-, diheteroaryl- and mixed phenyl heteroaryl substituted five-membered heterocycle compounds, compositions comprising the compounds and the use of such compounds and compositions to inhibit HCV replication and/or proliferation as a therapeutic approach towards the treatment and/or prevention of HCV infections in humans and animals.

BACKGROUND OF THE INVENTION

[0003] Hepatitis C virus (HCV) infection is a global human health problem with approximately 150,000 new reported cases each year in the United States alone. HCV is a single stranded RNA virus, which is the etiological agent identified in most cases of non-A, non-B post-transfusion and post-transplant hepatitis and is a common cause of acute sporadic hepatitis (Choo *et al.*, *Science* 244:359, 1989; Kuo *et al.*, *Science* 244:362, 1989; and Alter *et al.*, in *Current Perspective in Hepatology*, p. 83, 1989).

[0004] It is estimated that more than 50% of patients infected with HCV become chronically infected and 20% of those develop cirrhosis of the liver within 20 years (Davis *et al.*, *New Engl. J. Med.* 321:1501, 1989; Alter *et al.*, in *Current Perspective in Hepatology*, p. 83, 1989; Alter *et al.*, *New Engl. J. Med.* 327:1899, 1992; and Dienstag *Gastroenterology* 85:430, 1983). Moreover, the only therapy available for treatment of HCV infection is interferon-α (INTRON® A, PEG-INTRON®A, Schering-Plough; ROFERON-A®, PEGASys®, Roche). Most patients are unresponsive, however, and among the responders, there is a high recurrence rate within 6-12 months after cessation of treatment (Liang *et al.*, *J. Med. Virol.* 40:69, 1993). Ribavirin, a guanosine analog with broad spectrum activity against many RNA and DNA viruses, has been shown in clinical trials to be effective against chronic HCV infection when used in combination with interferon- (*see, e.g.*, Poynard *et al.*, *Lancet* 352:1426-1432, 1998; Reichard *et al.*, *Lancet* 351:83-87, 1998), and this combination therapy has been recently approved (REBETRON, Schering-Plough; see also Fried *et al.*, 2002, N. Engl. J. Med. 347:975-982). However, the

response rate is still at or below 50%. Therefore, additional compounds for treatment and prevention of HCV infection are needed.

SUMMARY OF THE INVENTION

[0005] The invention provides compounds, compositions and methods comprising substituted heterocyclic prodrugs that are potent inhibitors of Hepatitis C virus ("HCV") replication and/or proliferation.

[0006] In a second aspect, the invention provides methods of making the prodrugs of formula (I). Specific embodiments of the methods are illustrated in FIGS. 1-10. In one embodiment, the method for synthesizing compounds according to structural formula (I) comprises acetylating a compound according to structural formula (III) with a dihaloacetyl halide.

[0007] In a third aspect, the invention provides prodrug compositions. The compositions generally comprise prodrugs of the invention, or salts, hydrates, solvates, or N-oxides thereof and a suitable excipient, carrier or diluent. The composition may be formulated for veterinary uses or for use in humans.

[0008] The prodrugs of the invention, the resultant active drug transformed from the prodrug, or the active compound produced after metabolism are potent inhibitors of HCV replication and/or proliferation. Accordingly, in still a fourth aspect, the invention provides methods of inhibiting HCV replication and/or proliferation, comprising contacting a Hepatitis C virion with an amount of a prodrug or composition of the invention effective to inhibit its replication or proliferation. The methods may be practiced either *in vitro* or *in vivo*, and may be used as a therapeutic approach towards the treatment and/or prevention of HCV infections.

[0009] In a fifth aspect, the invention provides methods of treating, preventing, and/or inhibiting HCV infections. The methods generally involve administering to a subject that has an HCV infection or that is at risk of developing an HCV infection with an amount of a prodrug or composition of the invention effective to treat or prevent the HCV infection. The method may be practiced in animals in veterinary contexts or in humans.

BRIEF DESCRIPTION OF THE FIGURES

[0010] Fig. 1 shows a general synthetic scheme for phosphonate containing compounds of the invention.

[0011] Fig. 2 shows an alternative general synthetic scheme for phosphonate containing compounds compounds of the invention.

[0012] Fig. 3 shows synthetic schemes for two phosphonate containing compounds of the invention.

[0013] Fig. 4 shows a general synthetic scheme for ester containing compounds of the invention.

[0014] Fig. 5 shows an alternative general synthetic scheme for ester containing compounds of the invention.

[0015] Fig. 6 shows a synthetic scheme for an ester containing compound of the invention.

[0016] Fig. 7 shows a synthetic scheme for an ester containing compound of the invention.

[0017] Figs. 8a and 8b show a synthetic scheme for a dioxolenone containing compound of the invention.

[0018] Figs. 9a and 9b show a synthetic scheme for a dioxolenone containing compound of the invention.

[0019] Fig. 10 shows a synthetic scheme for a dioxolenone containing compound of the invention.

[0020] Fig. 11 shows a synthetic scheme for preparing compound **311a**, an alkyl acetamide.

[0021] Fig. 12 shows a general synthetic scheme for preparing alkyl acetamide containing prodrugs.

[0022] Fig. 13 shows a synthetic scheme for preparing compound **409a**, an alkyl acetamide.

[0023] Fig. 14 shows an general synthetic scheme for preparing alkylacetamide containing prodrugs.

[0024] Fig. 15 shows a synthetic scheme for preparing compound **605a**, an alkyl acetamide.

[0025] Fig. 16 shows a general synthetic scheme for preparing alkyl acetamide containing prodrugs.

[0026] Figs. 17A and 17B show the metabolism of the active parent compound in human microsomes.

[0027] Figs. 18A and 18B show the hydrolysis of the active parent compound in rat.

[0028] Fig. 19 shows the hydrolysis of the active parent compound in cynomolgus monkey.

[0029] Figs. 20A and 20B show excretion of the active parent compound in rat.

[0030] Figs. 21A, 21b and 21C show the absorption of the active parent compound in cynomolgus monkey.

[0031] Fig. 22 shows the excretion of the active parent compound in rat.

[0032] Fig. 23 shows a synthetic scheme for preparing compound 1045.

[0033] Fig. 24 shows a synthetic scheme for preparing compound 1046.

[0034] Fig. 25 shows a synthetic scheme for preparing compound 1047.

[0035] Fig. 26 shows a synthetic scheme for preparing compound 1048.

[0036] Fig. 27 shows a synthetic scheme for preparing compound 1028.

[0037] Fig. 28 shows a synthetic scheme for preparing compound 1027.

[0038] Fig. 29 shows a synthetic scheme for preparing compound 1010.

[0039] Fig. 30 shows a synthetic scheme for preparing compound 1014.

[0040] Fig. 31 shows a synthetic scheme for preparing compound 1024.

[0041] Fig. 32 shows a synthetic scheme for preparing compound 1034.

[0042] Fig. 33 shows a synthetic scheme for preparing compound 1037.

[0043] Fig. 34 shows a synthetic scheme for preparing compound 1042.

[0044] Fig. 35 shows a synthetic scheme for preparing compound 1044.

DETAILED DESCRIPTION OF THE INVENTION

[0045] The invention provides compounds, compositions and methods comprising substituted heterocyclic prodrugs that are potent inhibitors of Hepatitis C virus ("HCV") replication and/or proliferation.

[0046] In the first aspect, the invention provides a compound of the formula

$$A\text{-}B\text{-}C\text{-}(C(O))_s\text{-}N(R^{11})\text{-}C(O)\text{-}CX_2\text{-}R^{12} \qquad (I)$$

or a pharmaceutically acceptable salt, hydrate, solvate or N-oxide thereof, wherein

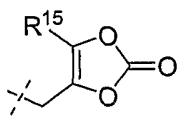
A is a phenyl or six-membered heteroaryl ring having from one to five of the same or different R^{20} substituents, provided that at least one of the substituents is positioned at the *ortho* position;

B is a saturated, unsaturated, or aromatic heteroatomic ring having from one to three annular heteroatoms selected from N, O, and S, where the A and C moieties are attached to non-adjacent ring atoms of B, provided that when the B includes more than one annular oxygen atom, the oxygen atoms are not adjacent;

C is a phenyl or a heteroaryl ring; in certain embodiments, wherein when C is phenyl, it is substituted relative to the B moiety at the *meta* position with the $-(C(O))_r\text{-}N(R^{11})\text{-}C(O)\text{-}CX_2\text{-}R^{12}$, or when C is a heteroaryl group, the B moiety and the $-(C(O))_r\text{-}N(R^{11})\text{-}C(O)\text{-}CX_2\text{-}R^{12}$ moiety are positioned on C with only one ring atom of C between them;

s is 0 or 1;

R^{11} is selected from the group consisting of hydrogen, lower alkyl, $-(CHR^{10})_n\text{-}J\text{-}G$, or a group of the formula



;

each X is independently H or halo, provided both X are not H;

R^{12} is selected from the group consisting of hydrogen, -O-C(O)-alkyl, $-C(O)OR^{16}$, $-C(O)R^{17}$ and $-P(O)(OR^{18})OR^{19}$;

R^{15} is lower alkyl, arylalkyl, aryl, substituted cycloheteroalkyl, cycloheteroalkyl, substituted cycloalkyl, cycloalkyl, $-C(O)OR^{18}$ or $-CH_2-OR^{30}$;

R^{30} is hydrogen, lower alkyl or a sugar moiety;

R^{16} is selected from the group consisting of aryl-C_1-C_6 alkyl, aryl, substituted cycloheteroalkyl, cycloheteroalkyl, substituted cycloalkyl, cycloalkyl, $-C(O)OR^{16}$ or $-CH_2-OR^{30}$, (C_{1-15}) alkyl and (C_{7-15}) arylalkyl;

R^{17} is selected from the group consisting of lower alkyl, $-N(R^c)_2$, N-morpholino, N-piperazino and N-pyrrolidino;

each R^c is independently R^b or alternatively, the both R^c taken together with the nitrogen atom to which they are bonded form a 5-, 6- or 7-membered cycloheteroalkyl which optionally includes from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S;

each R^b is independently hydrogen or R^a;

R^a is selected from the group consisting of alkyl, hydroxyalkyl, cycloalkyl, heteroalkyl, C_0-C_6 alkyl-cycloheteroalkyl, substituted C_0-C_6 alkyl-cycloheteroalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

R^{18} is H, lower alkyl, aryl or arylalkyl;

R^{19} is H, lower alkyl, aryl or arylalkyl;

n is 0, 1, 2, 3 or 4;

each R^{10} is independently hydrogen or lower alkyl;

J is selected from the group consisting of $-(CH_2)_{1-3}-$, -O-, $-O-(CH_2)_{1-3}-$, -CH(OH)-, -C(=O)-, $-S(O)_m-$, $-C(=NR^{23})-$, $-C(=NOR^{29})-$, $-C(N-N-(R^{25})_2)-$, $-C(N-NR^{27}C(=O)N-(R^{27})_2)-$ and $-C(Z-R^{28})_2-$;

m is 0, 1, or 2;

R^{23} is selected from the group consisting of hydrogen, lower alkyl, aryl, substituted aryl, arylalkyl and substituted arylalkyl;

R^{29} is selected from the group consisting of hydrogen, lower alkyl, aryl, substituted aryl, arylalkyl and substituted arylalkyl;

each R^{25} is independently selected from the group consisting of hydrogen, lower alkyl, aryl, substituted aryl, arylalkyl and substituted arylalkyl;

each R^{27} is independently selected from the group consisting of hydrogen, lower alkyl, aryl, substituted aryl, arylalkyl and substituted arylalkyl;

each Z is independently -O- or -S-;

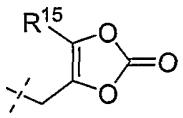
each R^{28} is independently selected from the group consisting of lower alkyl, aryl, substituted aryl, arylalkyl and substituted arylalkyl or alternatively, the two R^{18}'s taken together with the heteroatoms to which they are bonded form a 5, 6 or 7 membered cycloheteroalkyl;

G is selected from the group consisting of aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, cycloheteroalkyl and substituted cycloheteroalkyl; and

each R^{20} is, independently of the other, selected from the group consisting of -OH, -SH, -CN, -C(O)H, -NO_2, halo, fluoro, chloro, bromo, iodo, lower alkyl, substituted lower alkyl, lower heteroalkyl, substituted lower heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower alkylthio, substituted lower alkylthio, lower alkoxy, substituted lower alkoxy, methoxy, substituted methoxy, lower heteroalkoxy, substituted lower heteroalkoxy, cycloalkoxy, substituted cycloalkoxy, cycloheteroalkoxy, substituted cycloheteroalkoxy, lower haloalkoxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, amino, lower di- or monoalkylamino, substituted lower di- or monoalkylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, phenoxy, substituted phenoxy, arylalkyl, substituted arylalkyl, arylalkyloxy, substituted arylalkyloxy, benzyl, benzyloxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkyloxy, substituted heteroarylalkyloxy, carboxyl, lower alkoxycarbonyl, substituted lower alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, arylalkyloxycarbonyl, substituted arylalkyloxycarbonyl, carbamate, substituted carbamate, carbamoyl, substituted carbamoyl, thiocarbamoyl, substituted thiocarbamoyl, ureas, substituted ureas, thioureas, substituted thioureas, sulfamoyl, substituted sulfamoyl and a group of the formula -L-R^{14}, where "L" is a linker and R^{14} is cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl;

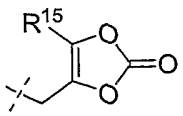
provided that when R^{11} is hydrogen or lower alkyl, then R^{12} is not hydrogen.

[0047] In Embodiment A1 according to formula (I), s is 1, R^{12} is -H, and R^{11} is a group of the formula



wherein R^{15} is -CH_2-OR^{30}. In some embodiments, R^{30} is a sugar moiety.

[0048] In Embodiment A according to formula (I), s is 0, R^{12} is -H, and R^{11} is a group of the formula



wherein R^{15} is lower alkyl, arylalkyl, aryl, cycloheteroalkyl, cycloalkyl, or -CH_2-OR^{30}. In some embodiments, R^{15} is piperidyl, pyrrolidinyl, t-butyl, benzyl, cyclobutyl or propyl. In some embodiments R^{15} is -CH_2-OR^{30}. In some embodiments, R^{30} is a sugar moiety.

[0049] In Embodiment B according to formula (I), s is 0, R^{11} is selected from the group consisting of hydrogen or -$(CHR^{10})_n$-J-G, wherein n is 0,1 or 2, J is -$(CH_2)_{1-3}$-, -C(O)-, -O- or-O-$(CH_2)_{1-3}$-,and G is substituted aryl, cycloheteroalkyl, substituted cycloheteroalkyl or heteroaryl. In some embodiments, R^{11} is hydrogen. In some embodiments G is pyrrolidinyl, morpholinyl or imidazolyl. In some embodiments G is phenyl substituted with methoxy, -chloro, fluoro, CH_2-P(O)(OR^b)(OR^b), -O-P(O)(OR^b)(OR^b), methyl, -O-C(O)-NH-R^b, -NR^bC(O)OR^b, ethyl-piperazinyl, piperazinyl, t-butyl-O-C-(O)-piperazinyl, -O-$(CH_2)_{0-4}$-R^b,or -C(O)OR^b, wherein R^b is -H, propyl, t-butyl, ethyl, or morpholinyl.

[0050] In Embodiment C according to formula (I), s is 0, each X is chloro, and R^{12} is selected from the group consisting of hydrogen, -C(O)OR^{15}, -C(O)R^{17} and -P(O)(OR^{18})OR^{19}; R^{15} is lower alkyl, arylalkyl, substituted cycloalkyl, or cycloalkyl; R^{17} is selected from the group consisting of lower alkyl, -N(R^c)$_2$, or N-morpholino; each R^c is independently hydrogen, alkyl, hydroxyalkyl, C_0-C_6 alkyl-cycloheteroalkyl, or heteroarylalkyl; and R^{18} and R^{19} are independently H or lower alkyl. In some embodiments, R^{12} is -P(O)(OR^{18})OR^{19} wherein R^{18} and R^{19} are both -H, ethyl or propyl. In some embodiments R^{12} is -C(O)OR^{15}. In some embodiments, R^{15} is adamantane methyl, propyl, -CH_2-phenyl, t-butyl, cyclohexyl, or cyclohexyl substituted with methyl, propyl, or pentyl. In some embodiments R^{12} is -C(O)R^{17}. In some embodiments, R^{17} is methyl, N-morpholino, or -N(R^c)$_2$. In some embodiments, each R^c is independently hydrogen, -$(CH_2)_3$-morpholinyl, -CH_2-pyridinyl or -$(CH_2)_2$-OH.

[0051] In Embodiment D according to formula (I), s is 0 and A is phenyl substituted with at least two R^{20} groups selected from the group consisting of halo, lower alkoxy, carboxyl, lower haloalkyl, cycloalkyl, lower alkoxycarbonyl and -L-R^{14}, wherein "L" is a -O- and R^{14} is cycloheteroalkyl or substituted cycloheteroalkyl. In some embodiments, A represents a phenyl ring substituted at the 2- and 6-positions with the same or different R^{20} substituent. In some embodiments one R^{20} is halo and the other R^{20} is lower alkoxy, lower haloalkyl or cycloalkyl. In some embodiments, one R^{20} is chloro and the other R^{20} is methoxy, -CF_3, or cyclopropyl. In some embodiments one R^{20} is halo and the other R^{20} is carboxyl or lower alkoxycarbonyl. In

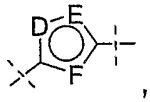
some embodiments, one R^{20} is chloro and the other R^{20} is methoxycarbonyl. In some embodiments one R^{20} is halo and the other R^{20} is -O-R^{14}, wherein R^{14} is morpholinyl or morpholinyl substituted with -C(O)-O-t-butyl or -C(O)-CH_3.

[0052] In Embodiment E according to formula (I), s is 0 and A represents a pyrid-2-yl ring substituted at the 3-position with an R^{20} substituent, a pyrid-3-yl ring substituted at the 2- and 4-positions with the same or different R^{20} substituents or a pyrid-4-yl ring substituted at the 3- and 5-positions with the same or different R^{20} substituents. In some embodiments, each R^{20} is independently selected from the group consisting of halo, lower dialkylamino and -L-R^{14}, wherein "L" is a -O- and R^{14} is cycloheteroalkyl. In some embodiments each R^{20} is independently selected from the group consisting of chloro, -$N(CH_3)_2$, and -O-R^{14}, wherein R^{14} is morpholinyl.

[0053] In Embodiment F according to formula (I), s is 0 and C represents a phenyl ring, a pyrid-2-yl ring or a pyrid-3-yl ring.

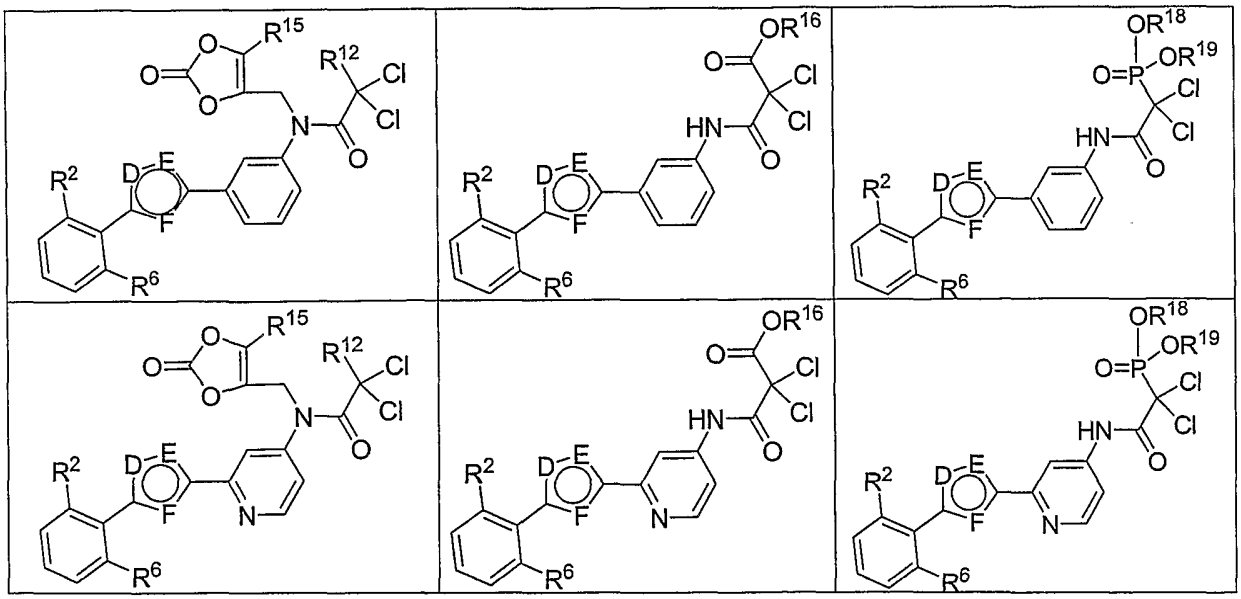
[0054] In Embodiment G according to formula (I), s is 0 and B represents a isoxazolyl, pyrazolyl, oxadiazolyl or triazolyl ring.

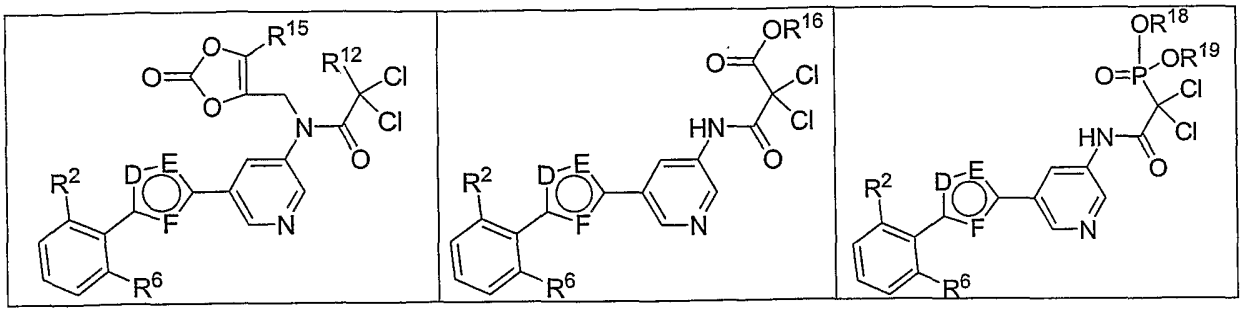
[0055] In Embodiment H according to formula (I), s is 0 and B is



wherein D, E and F are each, independently of one another, selected from N, O and CH, provided that at least two of D, E and F are other than CH and D and E are not both simultaneously O.

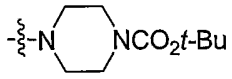
[0056] In Embodiment I according to formula (I), s is 0 and each X is -Cl. In many examples of Embodiment I, A is phenyl and C is phenyl or pyridyl. More particularly, in some examples, the compound is according to one of the following nine formula:



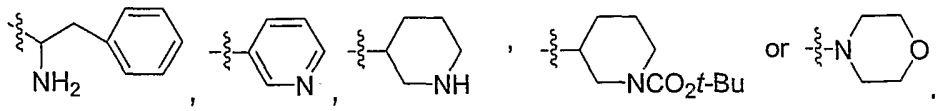


wherein R^2 and R^6 are R^{20} and each, independently of one another, is selected from the group consisting of -OH, -NO_2, halo, fluoro, chloro, bromo, iodo, lower alkyl, methyl, lower heteroalkyl, (C_3-C_6) cycloalkyl, 5- or 6-membered cycloheteroalkyl, N-morpholinyl, N-methyl-N-piperazinyl, N-piperadinyl, substituted N-piperadinyl, 4-(N-piperadinyl)-N-piperadinyl, 4-amino-N-piperadinyl, lower alkoxy, methoxy, ethoxy, lower alkylthio, methylthio, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower haloalkyloxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, aryl, phenyl, arylalkyl, benzyl, aryloxy, phenoxy, arylalkyloxy, benzyloxy, 5- or 6-membered heteroaryl, lower alkyloxycarbonyl, sulfamoyl and -L-R^{14}, where L is -$(CH_2)_{1-3}$- or -O-$(CH_2)_{1-3}$- and R^{14} is a 5- or 6-membered cycloheteroalkyl or N-morpholinyl. In some embodiments, R^2 and R^6 are each, independently of one another, selected from the group consisting of chloro, bromo, iodo and fluoro. In some embodiments, D is O, E is N and F is CH, or D is N, E is O and F is CH. In some embodiments, R^{12} is -H and R^{15} is lower alkyl, arylalkyl, aryl, cycloheteroalkyl, cycloalkyl, or a sugar moiety. In some embodiments, R^{15} is piperidyl, pyrrolidinyl, t-butyl, benzyl, cyclobutyl or propyl. In some embodiments, R^{16} is lower alkyl or cycloalkyl. Preferably, R^{16} is t-butyl or adamantane. In some embodiments, R^{18} is -H or lower alkyl and R^{19} is H or lower alkyl. In some embodiments, R^{18} and R^{19} are both -H, ethyl or propyl.

[0057] In Embodiment J according to formula (I), s is 0 and G is aryl or substituted aryl. In some embodiments, G is phenyl substituted with one or more groups selected from hydrogen, -F, -Cl, –OMe, -CO_2H, -CO_2*t*-Bu, -CH_2CO_2Et, methyl -OC(O)CH_3, -OC(O)$CH_2N(CH_3)_2$, -OC(O)$CH_2N(CH_3)$Boc, –OC(O)$CH_2NH(CH_3)$, or



[0058] In Embodiment K according to formula (I), s is 0 and G is substituted arylalkyl, heteroaryl, cycloheteroalkyl or substituted cycloheteroalkyl. In some examples, G is

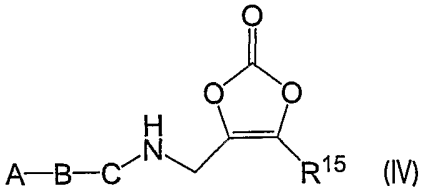


[0059] In Embodiment L according to formula (I) are compounds that, when administered to a cell comprising a hepatitis C virion, inhibits HCV replication and/or proliferation, and have an IC_{50} of 10 μM or less, as measured in an *in vitro* assay.

[0060] In the third aspect, the invention provides a composition comprising a pharmaceutically acceptable vehicle and a compound according to the first aspect and Embodiments A1-L.

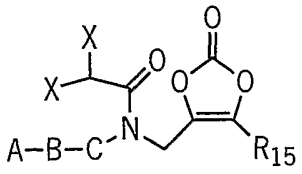
[0061] In the fourth aspect, the invention provides a method of inhibiting replication and/or proliferation of a hepatitis C ("HC") virion, comprising the step of contacting an HC virion with an amount of a compound according to according to the first aspect and Embodiments A-L effective to inhibit replication and/or proliferation of the HC virion. In some embodiments, the method is practiced *in vitro* or *in vivo*. In some embodiments, the method of treating or preventing an HCV infection, comprising the step of administering to a subject an amount of a compound according to according to the first aspect and Embodiments A-L effective to treat or prevent an HCV infection. In some embodiments, the subject is a human. In some embodiments, the compound is administered in an amount of about 0.1 mg/kg/day to 200 mg/kg/day. In some embodiments, the compound is administered in an amount of about 10 mg/kg/day to 100 mg/kg/day. In some embodiments compound is administered orally, intravenously or subcutaneously. In some embodiments, the method is practiced therapeutically in a subject having an HCV infection, or practiced prophylactically in a subject at risk of developing an HCV infection.

[0062] In one embodiment according to the second aspect, the invention provides an intermediate compound useful for synthesizing substituted heterocycle compounds, said intermediate compound having the formula (IV):



(IV)

wherein A, B, C and R^{15} are as defined in the first aspect and Embodiments A-L. Like the compounds of structural formulae (I) and (III), the double bonding pattern of the "**B**" ring will depend upon the identities of the heteroatoms therein. The invention also comprises a method of synthesizing a heterocycle compound of formula (XI):



(XI)

wherein A, B, C, X and R^{15} are as defined in the first aspect and Embodiments A-L, comprising dihaloacetylating a compound of the formula (IV), thereby yielding a compound according to formula (XI).

[0063] In Embodiment M according to the second aspect, the invention provides starting and intermediate compounds useful for synthesizing the compounds of the invention. Representative starting and intermediate compounds useful for synthesizing prodrugs of the invention include compounds **201, 203, 205, 207, 209, 301, 401, 403, 405, 501, 503, 603, 605, 801, 803, 805, 807, 903, 905, 1003,** and **1005** as depicted in Figs. 1-10.

[0064] Prodrugs having the structural formulae (I) and (II) can be prepared from heterocyclic compounds described in US Serial Nos. 10/ 286,017, filed November 1, 2002, 60/467,650, filed May 2, 2003, 60/467,811, filed May 2, 2003, 10/440,349, filed May 15, 2003, 10/646,348, filed August 22, 2003, the contents of which are incorporated herein in their entirety.

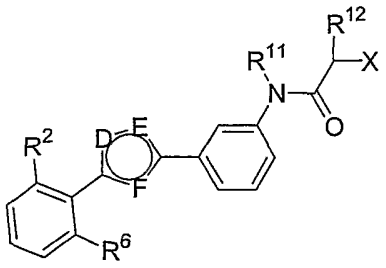
[0065] In Embodiment N according to the third aspect, some starting materials used for making compounds of the invention are according to structural formula (III)

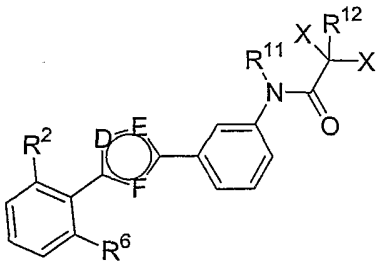
$$A\text{-}B\text{-}C\text{-}NH_2 \qquad (III)$$

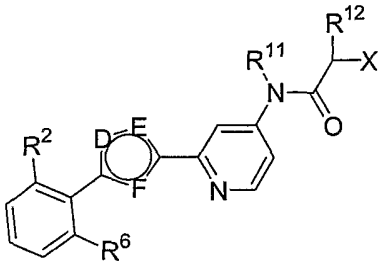
wherein A, B and C are as previously defined. Compounds having structural formula (III) are treated with, for example, either a 2, 2-dihalo-2-(dialkoxyphosphonyl)acetyl halide or a 2-(alkyloxycarbonyl)-2,2-dichloroacetyl chloride to form the corresponding acetamides. Alternatively, compounds having structural formula (III) are treated with 4-bromomethyl-5-alkyl-1,3-dioxol-2-one to provide corresponding N-[(5-alkyl-1,3-dioxolene-2-one-4-yl)methylene]anilines. Optionally, the acetamide or aniline can be further treated with a dihaloacetyl halide to form prodrugs to structural formulae (I).

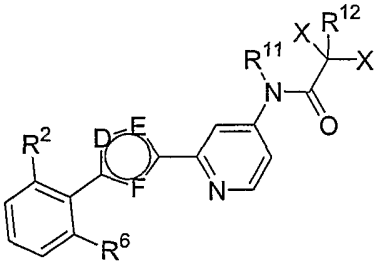
[0066] In Embodiment N1, according to the third aspect, prodrug moieties of the invention may be pre-incorporated into, for example, an acetamide intermediate containing ring C. In one example, such intermediates contain an alkynyl group that is used in conjunction with another intermediate containing ring A. When combined, for example in a [3+2] cycloaddition reaction to form ring B, prodrug compounds of the invention are formed.

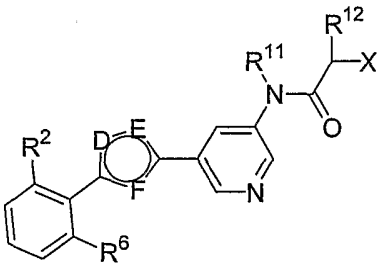
[0067] In Embodiment O according to the first aspect, prodrugs having formulae (V) through (X) are useful to treat HCV infection. These include

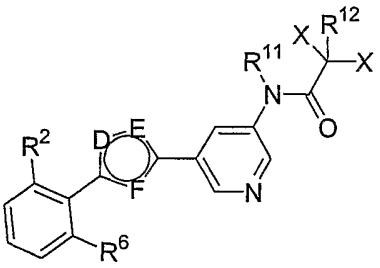

(V)


(VI)


(VII)


(VIII)


(IX)


(X)

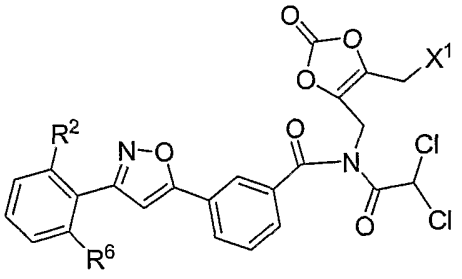
or their pharmaceutically acceptable salts, hydrates, solvates and N-oxides thereof, wherein:

D, E and F are each, independently of one another, selected from N, O and CH, provided that at least two of D, E and F are other than CH and D and E are not both simultaneously O;

R^2 and R^6 are R^{20} and each, independently of one another, is selected from the group consisting of -OH, $-NO_2$, halo, fluoro, chloro, bromo, iodo, lower alkyl, methyl, lower heteroalkyl, (C_3-C_6) cycloalkyl, 5- or 6-membered cycloheteroalkyl, N-morpholinyl, N-methyl-N-piperazinyl, N-piperadinyl, substituted N-piperadinyl, 4-(N-piperadinyl)-N-piperadinyl, 4-amino-N-piperadinyl, lower alkoxy, methoxy, ethoxy, lower alkylthio, methylthio, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower haloalkyloxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, aryl, phenyl, arylalkyl, benzyl, aryloxy, phenoxy, arylalkyloxy, benzyloxy, 5- or 6-membered heteroaryl, lower alkyloxycarbonyl, sulfamoyl and $-L-R^{14}$, where L is $-(CH_2)_{1-3}-$ or $-O-(CH_2)_{1-3}-$ and R^{14} is a 5- or 6-membered cycloheteroalkyl or N-morpholinyl; and

each individual X, R^{11} and R^{12} are as previously defined. In some embodiments, D is O, E is N and F is CH, or D is N, E is O and F is CH.

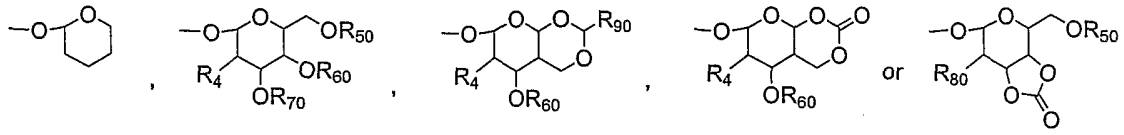
[0068] In Embodiment P, the invention provides compounds of the formula (XII)



(XII)

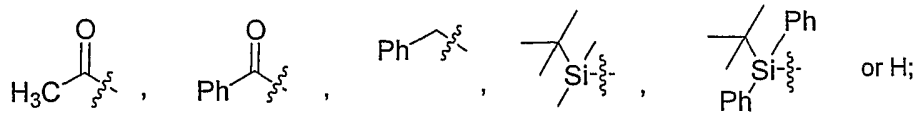
wherein R^2 and R^6 are R^{20} and each, independently of one another, is selected from the group consisting of -OH, -NO_2, halo, fluoro, chloro, bromo, iodo, lower alkyl, methyl, lower heteroalkyl, (C_3-C_6) cycloalkyl, 5- or 6-membered cycloheteroalkyl, N-morpholinyl, N-methyl-N-piperazinyl, N-piperadinyl, substituted N-piperadinyl, 4-(N-piperadinyl)-N-piperadinyl, 4-amino-N-piperadinyl, lower alkoxy, methoxy, ethoxy, lower alkylthio, methylthio, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower haloalkyloxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, aryl, phenyl, arylalkyl, benzyl, aryloxy, phenoxy, arylalkyloxy, benzyloxy, 5- or 6-membered heteroaryl, lower alkyloxycarbonyl, sulfamoyl and -L-R^{14}, where L is -$(CH_2)_{1-3}$- or -O-$(CH_2)_{1-3}$- and R^{14} is a 5- or 6-membered cycloheteroalkyl or N-morpholinyl;

X^1 is hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 alkoxy-C_1-C_6 alkoxy, poly-C_1-C_6 alkoxy or a sugar moiety, or X^1 is any substituted or unsubstituted tetrahydropyran or 6-(hydroxymethyl)-tetrahydro-2H-pyran-2,4,5-triol, hexahydropyrano[2,3-d][1,3]dioxine-5,7-diol or 5,7-dihydroxy-hexahydropyrano[2,3-d][1,3]dioxin-2-one, or 6-hydroxy-4-(hydroxymethyl)-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-2-one. In some embodiments, X^1 is one of the following substructures:



wherein R_{50}, R_{60} and R_{70} are independently C_1-C_6 alkyl, C_0-C_6 alkylaryl, acyl, C_0-C_6 alkyl-C(=O)-aryl, C_0-C_6 alkyl-C(=O)-C_1-C_6 alkyl, acetyl, benzoyl, benzyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, hydrogen, or -$Si(R_{100})_3$, wherein each R_{100} is the same or different and is C_1-C_6 alkyl or C_0-C_6 alkylaryl; R_{80} is C_1-C_6 alkyl, methyl or hydrogen; and R_{90} is -H, or any alkyl chain or aryl group or substituted aryl group. For example,

R_{50}, R_{60} and R_{70} are independently

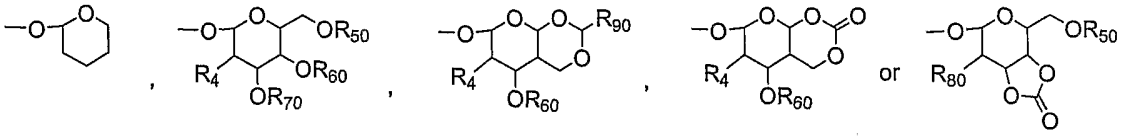


R_{80} is -H or -CH_3; and

R_{90} is C_1-C_6 alkyl, aryl or substituted aryl. For example, X^1 may be hydroxyethoxy, methoxymethoxy or polyethylene glycol. In some embodiments R^2 and R^6 are each, independently of one another, selected from the group consisting of chloro, bromo, iodo and fluoro.

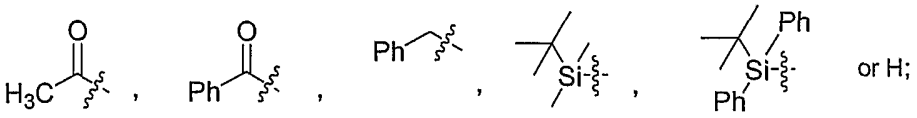
Definitions

[0069] As used herein, the following terms are intended to have the following meanings: A "sugar moiety" is any substituted or unsubstituted saccharide having the general composition $(CH_2O)_n$ and simple derivatives thereof. For examples, a sugar moiety is any naturally occurring monosaccharide including, but not limited to, $(CH_2O)_6$ or $C_6H_{12}O_6$ molecules such as aldoses, for example, D-glucose and ketoses, for example, D-fructose. A sugar moiety also includes naturally occurring disaccharides that are formed chemically or enzymatically from two monosaccharides $2((CH_2O)_6)$ minus an H_2O molecule to give $C_{12}H_{22}O_{11}$. For example, a sugar moiety includes molecules like lactose (milk sugar), maltose (malt sugar) and sucrose (cane sugar). A sugar moiety also comprises sugars in cyclic form, for example, glucose, α-D-glucose and/or its anomeric form β-D-glucose, fructose, the five-membered ring furanose form of fructose and the six-membered ring pyranose form of fructose. Additionally, a sugar moiety includes a tetrahydropyranyloxy group substituted with at least one hydroxyl or alkoxyl. For example, a sugar moiety any substituted or unsubstituted tetrahydropyran or 6-(hydroxymethyl)-tetrahydro-2H-pyran-2,4,5-triol, hexahydropyrano[2,3-d][1,3]dioxine-5,7-diol or 5,7-dihydroxy-hexahydropyrano[2,3-d][1,3]dioxin-2-one, 6-hydroxy-4-(hydroxymethyl)-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-2-one, or any of the following structures:



wherein R_{50}, R_{60} and R_{70} are independently C_1-C_6 alkyl, C_0-C_6 alkylaryl, acyl, C_0-C_6 alkyl-C(=O)aryl, C_0-C_6 alkyl-C(=O)-C_1-C_6 alkyl, acetyl, benzoyl, benzyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, hydrogen, or -$Si(R_{100})_3$, wherein each R_{100} is the same or different and is C_1-C_6 alkyl or C_0-C_6 alkylaryl; R_{80} is C_1-C_6 alkyl, methyl or hydrogen, and R_{90} is -H, or any alkyl chain or aryl group or substituted aryl group. For example,

R_{50}, R_{60} and R_{70} are independently



R_{80} is -H or -CH_3; and

R_{90} is C_1-C_6 alkyl, aryl or substituted aryl.

[0070] "Alkyl," by itself or as part of another substituent, refers to a saturated or unsaturated, branched, straight-chain or cyclic monovalent hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene or alkyne. Typical alkyl groups include, but are not limited to, methyl; ethyls such as ethanyl, ethenyl, ethynyl; propyls such as t-butyl, isopropyl, propan-1-yl, propan-2-yl, cyclopropan-1-yl, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), cycloprop-1-en-1-yl; cycloprop-2-en-1-yl, prop-1-yn-1-yl , prop-2-yn-1-yl, *etc.*; butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl , but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like.

[0071] The term "alkyl" is specifically intended to include groups having any degree or level of saturation, *i.e.*, groups having exclusively single carbon-carbon bonds, groups having one or more double carbon-carbon bonds, groups having one or more triple carbon-carbon bonds and groups having mixtures of single, double and triple carbon-carbon bonds. Where a specific level of saturation is intended, the expressions "alkanyl," "alkenyl," and "alkynyl" are used. Preferably, an alkyl group comprises from 1 to 15 carbon atoms (C_1-C_{15} alkyl), more preferably from 1 to10 carbon atoms (C_1-C_{10} alkyl) and even more preferably from 1 to 6 carbon atoms (C_1-C_6 alkyl or lower alkyl).

[0072] "Alkanyl," by itself or as part of another substituent, refers to a saturated branched, straight-chain or cyclic alkyl radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkanyl groups include, but are not limited to, methanyl; ethanyl; propanyls such as propan-1-yl, propan-2-yl (isopropyl), cyclopropan-1-yl, etc.; butanyls such as butan-1-yl, butan-2-yl (*sec*-butyl), 2-methyl-propan-1-yl (isobutyl), 2-methyl-propan-2-yl (t-butyl), cyclobutan-1-yl, *etc.*; and the like.

[0073] "Alkenyl," by itself or as part of another substituent, refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The group may be in either the *cis* or *trans* conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl , prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl ; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl , but-2-en-1-yl, but-2-en-2-yl, buta-1,3-

dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, *etc.*; and the like.

[0074] "Alkynyl," by itself or as part of another substituent refers to an unsaturated branched, straight-chain or cyclic alkyl radical having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl, etc.; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, *etc.*; and the like.

[0075] "Alkyldiyl" by itself or as part of another substituent refers to a saturated or unsaturated, branched, straight-chain or cyclic divalent hydrocarbon group derived by the removal of one hydrogen atom from each of two different carbon atoms of a parent alkane, alkene or alkyne, or by the removal of two hydrogen atoms from a single carbon atom of a parent alkane, alkene or alkyne. The two monovalent radical centers or each valency of the divalent radical center can form bonds with the same or different atoms. Typical alkyldiyl groups include, but are not limited to, methandiyl; ethyldiyls such as ethan-1,1-diyl, ethan-1,2-diyl, ethen-1,1-diyl, ethen-1,2-diyl; propyldiyls such as propan-1,1-diyl, propan-1,2-diyl, propan-2,2-diyl, propan-1,3-diyl, cyclopropan-1,1-diyl, cyclopropan-1,2-diyl, prop-1-en-1,1-diyl, prop-1-en-1,2-diyl, prop-2-en-1,2-diyl, prop-1-en-1,3-diyl, cycloprop-1-en-1,2-diyl, cycloprop-2-en-1,2-diyl, cycloprop-2-en-1,1-diyl, prop-1-yn-1,3-diyl, etc.; butyldiyls such as, butan-1,1-diyl, butan-1,2-diyl, butan-1,3-diyl, butan-1,4-diyl, butan-2,2-diyl, 2-methyl-propan-1,1-diyl, 2-methyl-propan-1,2-diyl, cyclobutan-1,1-diyl; cyclobutan-1,2-diyl, cyclobutan-1,3-diyl, but-1-en-1,1-diyl, but-1-en-1,2-diyl, but-1-en-1,3-diyl, but-1-en-1,4-diyl, 2-methyl-prop-1-en-1,1-diyl, 2-methanylidene-propan-1,1-diyl, buta-1,3-dien-1,1-diyl, buta-1,3-dien-1,2-diyl, buta-1,3-dien-1,3-diyl, buta-1,3-dien-1,4-diyl, cyclobut-1-en-1,2-diyl, cyclobut-1-en-1,3-diyl, cyclobut-2-en-1,2-diyl, cyclobuta-1,3-dien-1,2-diyl, cyclobuta-1,3-dien-1,3-diyl, but-1-yn-1,3-diyl, but-1-yn-1,4-diyl, buta-1,3-diyn-1,4-diyl, etc.; and the like. Where specific levels of saturation are intended, the nomenclature alkanyldiyl, alkenyldiyl and/or alkynyldiyl is used. Where it is specifically intended that the two valencies are on the same carbon atom, the nomenclature "alkylidene" is used. In preferred embodiments, the alkyldiyl group comprises from 1 to 6 carbon atoms (C1-C6 alkyldiyl). Also preferred are saturated acyclic alkanyldiyl groups in which the radical centers are at the terminal carbons, *e.g.*, methandiyl (methano); ethan-1,2-diyl (ethano); propan-1,3-diyl (propano); butan-1,4-diyl (butano); and the like (also referred to as alkylenos, defined *infra*).

[0076] "Alkyleno," by itself or as part of another substituent, refers to a straight-chain saturated or unsaturated alkyldiyl group having two terminal monovalent radical centers derived

by the removal of one hydrogen atom from each of the two terminal carbon atoms of straight-chain parent alkane, alkene or alkyne. The locant of a double bond or triple bond, if present, in a particular alkyleno is indicated in square brackets. Typical alkyleno groups include, but are not limited to, methano; ethylenos such as ethano, etheno, ethyno; propylenos such as propano, prop[1]eno, propa[1,2]dieno, prop[1]yno, etc.; butylenos such as butano, but[1]eno, but[2]eno, buta[1,3]dieno, but[1]yno, but[2]yno, buta[1,3]diyno, etc.; and the like. Where specific levels of saturation are intended, the nomenclature alkano, alkeno and/or alkyno is used. In preferred embodiments, the alkyleno group is (C_1-C_6) or (C_1-C_3) alkyleno. Also preferred are straight-chain saturated alkano groups, e.g., methano, ethano, propano, butano, and the like.

[0077] "Alkoxy," by itself or as part of another substituent, refers to a radical of the formula -OR, where R is an alkyl or cycloalkyl group as defined herein. Representative examples alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, cyclopropyloxy, cyclopentyloxy, cyclohexyloxy and the like.

[0078] "Alkoxycarbonyl," by itself or as part of another substituent, refers to a radical of the formula -C(O)-alkoxy, where alkoxy is as defined herein.

[0079] "Alkylthio," by itself or as part of another substituent, refers to a radical of the formula -SR, where R is an alkyl or cycloalkyl group as defined herein. Representative examples of Alkylthio groups include, but are not limited to, methylthio, ethylthio, propylthio, isopropylthio, butylthio tert-butylthio, cyclopropylthio, cyclopentylthio, cyclohexylthio, and the like.

[0080] "Aryl," by itself or as part of another substituent, refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system, as defined herein. Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like. Preferably, an aryl group comprises from 6 to 20 carbon atoms (C_6-C_{20} aryl), more preferably from 6 to 15 carbon atoms (C_6-C_{15} aryl) and even more preferably from 6 to 10 carbon atoms (C_6-C_{10} aryl).

[0081] "Arylalkyl," by itself or as part of another substituent, refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl group as, as defined herein. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-

1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. Where specific alkyl moieties are intended, the nomenclature arylalkanyl, arylalkenyl and/or arylalkynyl is used. Preferably, an arylalkyl group is (C_6-C_{30}) arylalkyl, e.g., the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_1-C_{10}) alkyl and the aryl moiety is (C_6-C_{20}) aryl, more preferably, an arylalkyl group is (C_6-C_{20}) arylalkyl, e.g., the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_1-C_8) alkyl and the aryl moiety is (C_6-C_{12}) aryl, and even more preferably, an arylalkyl group is (C_6-C_{15}) arylalkyl, e.g., the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_1-C_5) alkyl and the aryl moiety is (C_6-C_{10}) aryl.

[0082] "Aryloxy," by itself or as part of another substituent, refers to a radical of the formula -O-aryl, where aryl is as defined herein.

[0083] "Arylalkyloxy, by itself or as part of another substituent, refers to a radical of the formula -O-arylalkyl, where arylalkyl is as defined herein.

[0084] "Aryloxycarbonyl," by itself or as part of another substituent, refers to a radical of the formula -C(O)-O-aryl, where aryl is as defined herein.

[0085] "Carbamoyl," by itself or as part of another substituent, refers to a radical of the formula -C(O)NR'R", where R' and R" are each, independently of one another, selected from the group consisting of hydrogen, alkyl and cycloalkyl as defined herein, or alternatively, R' and R", taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered cycloheteroalkyl ring as defined herein, which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, S and N.

[0086] "Cycloalkyl," by itself or as part of another substituent, refers to a saturated or unsaturated cyclic alkyl radical, as defined herein. Where a specific level of saturation is intended, the nomenclature "cycloalkanyl" or "cycloalkenyl" is used. Typical cycloalkyl groups include, but are not limited to, groups derived from cyclopropane, cyclobutane, cyclopentane, cyclohexane, and the like. Preferably, the cycloalkyl group comprises from 3 to 10 ring atoms (C_3-C_{10} cycloalkyl) and more preferably from 3 to 7 ring atoms (C_3-C_7 cycloalkyl). The cycloalkyl group also includes polycyclic groups such as, but not limited to, adamantane, and the like.

[0087] "Cycloheteroalkyl," by itself or as part of another substituent, refers to a saturated or unsaturated cyclic alkyl radical in which one or more carbon atoms (and optionally any associated hydrogen atoms) are independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atom(s) include, but are not limited to, N, P, O, S, Si, *etc.* Where a specific level of saturation is intended, the nomenclature "cycloheteroalkanyl" or "cycloheteroalkenyl" is used. Typical cycloheteroalkyl groups include, but are not limited to,

groups derived from epoxides, azirines, thiiranes, imidazolidine, morpholine, piperazine, piperidine, pyrazolidine, pyrrolidone, quinuclidine, and the like. Preferably, the cycloheteroalkyl group comprises from 3 to 10 ring atoms (3-10 membered cycloheteroalkyl) and more preferably from 5 to 7 ring atoms (5-7 membered cycloheteroalkyl).

[0088] A cycloheteroalkyl group may be substituted at a heteroatom, for example, a nitrogen atom, with a lower alkyl group. As specific examples, N-methyl-imidazolidinyl, N-methyl-morpholinyl, N-methyl-piperazinyl, N-methyl-piperidinyl, N-methyl-pyrazolidinyl and N-methyl-pyrrolidinyl are included within the definition of "cycloheteroalkyl." A cycloheteralkyl group may be attached to the remainder of the molecule *via* a ring carbon atom or a ring heteroatom.

[0089] The term "heterocycle" as used herein mean a cycloheteroalkyl, heteroaryl or parent heteroaromatic ring system. Heterocycle includes groups that are, for example, saturated, unsaturated, or aromatic heteroatomic ring systems.

[0090] "Dialkylamino" or "Monoalkylamino," by themselves or as part of other substituents, refer to radicals of the formula –NRR and -NHR, respectively, where each R is independently selected from the group consisting of alkyl and cycloalkyl, as defined herein. Representative examples of dialkylamino groups include, but are not limited to, dimethylamino, methylethylamino, di-(1-methylethyl)amino, (cyclohexyl)(methyl)amino, (cyclohexyl)(ethyl)amino, (cyclohexyl)(propyl)amino and the like. Representative examples of monalkylamino groups include, but are not limited to, methylamino, ethylamino, propylamino, isopropylamino, cyclohexylamino, and the like.

[0091] "Halogen" or "Halo," by themselves or as part of another substituent, refer to a fluoro, chloro, bromo and/or iodo radical.

[0092] "Haloalkyl," by itself or as part of another substituent, refers to an alkyl group as defined herein in which one or more of the hydrogen atoms is replaced with a halo group. The term "haloalkyl" is specifically meant to include monohaloalkyls, dihaloalkyls, trihaloalkyls, *etc.* up to perhaloalkyls. The halo groups substituting a haloalkyl can be the same, or they can be different. For example, the expression "(C_1-C_2) haloalkyl" includes 1-fluoromethyl, 1-fluoro-2-chloroethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1,1-difluoroethyl, 1,2-difluoroethyl, 1,1,1-trifluoroethyl, perfluoroethyl, *etc.*

[0093] "Haloalkyloxy," by itself or as part of another substituent, refers to a group of the formula -O-haloalkyl, where haloalkyl is as defined herein.

[0094] "Heteroalkyl," "Heteroalkanyl," "Heteroalkenyl," "Heteroalkynyl," "Heteroalkyldiyl" and "Heteroalkyleno," by themselves or as part of other substituents, refer to alkyl, alkanyl, alkenyl,

alkynyl, alkyldiyl and alkyleno groups, respectively, in which one or more of the carbon atoms (and optionally any associated hydrogen atoms), are each, independently of one another, replaced with the same or different heteroatoms or heteroatomic groups. Typical heteroatoms or heteroatomic groups which can replace the carbon atoms include, but are not limited to, O, S, N, Si, -NH-, -S(O)-, -$S(O)_2$-, -S(O)NH-, -$S(O)_2$NH- and the like and combinations thereof. The heteroatoms or heteroatomic groups may be placed at any interior position of the alkyl, alkenyl or alkynyl groups. Examples of such heteroalkyl, heteroalkanyl, heteroalkenyl and/or heteroalkynyl groups include –CH_2-CH_2-O-CH_3, -CH_2-CH_2-NH-CH_3, -CH_2-CH_2-N(CH_3)-CH_3, -CH_2-S-CH_2,-CH_3, -CH_2-CH_2-S(O)-CH_3, -CH_2-CH_2-$S(O)_2$-CH_3, -CH=CH-O-CH_3, -CH_2-CH=N-O-CH_3, and –CH_2-CH_2-O-C=CH. For heteroalkyldiyl and heteroalkyleno groups, the heteratom or heteratomic group can also occupy either or both chain termini. For such groups, no orientation of the group is implied.

[0095] "Heteroaryl," by itself or as part of another substituent, refers to a monovalent heteroaromatic radical derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring systems, as defined herein. Typical heteroaryl groups include, but are not limited to, groups derived from acridine, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like. Preferably, the heteroaryl group comprises from 5 to 20 ring atoms (5-20 membered heteroaryl), more preferably from 5 to 10 ring atoms (5-10 membered heteroaryl). Preferred heteroaryl groups are those derived from furan, thiophene, pyrrole, benzothiophene, benzofuran, benzimidazole, indole, pyridine, pyrazole, quinoline, imidazole, oxazole, isoxazole and pyrazine.

[0096] "Heteroarylalkyl" by itself or as part of another substituent refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heteroaryl group. Where specific alkyl moieties are intended, the nomenclature heteroarylalkanyl, heteroarylakenyl and/or heteroarylalkynyl is used. In preferred embodiments, the heteroarylalkyl group is a 6-21 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the heteroarylalkyl is (C1-C6) alkyl and the heteroaryl moiety is a 5-15-membered heteroaryl. In particularly preferred embodiments, the heteroarylalkyl is a 6-13 membered heteroarylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety is (C1-C3) alkyl and the heteroaryl moiety is a 5-10 membered heteroaryl.

[0097] "Parent Aromatic Ring System" refers to an unsaturated cyclic or polycyclic ring system having a conjugated π electron system. Specifically included within the definition of "parent aromatic ring system" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, fluorene, indane, indene, phenalene, *etc.* Typical parent aromatic ring systems include, but are not limited to, aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene and the like.

[0098] "Parent Heteroaromatic Ring System" refers to a parent aromatic ring system in which one or more carbon atoms (and optionally any associated hydrogen atoms) are each independently replaced with the same or different heteroatom. Typical heteroatoms to replace the carbon atoms include, but are not limited to, N, P, O, S, Si, *etc.* Specifically included within the definition of "parent heteroaromatic ring system" are fused ring systems in which one or more of the rings are aromatic and one or more of the rings are saturated or unsaturated, such as, for example, benzodioxan, benzofuran, chromane, chromene, indole, indoline, xanthene, *etc.* Typical parent heteroaromatic ring systems include, but are not limited to, arsindole, carbazole, β-carboline, chromane, chromene, cinnoline, furan, imidazole, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene and the like.

[0100] "Pharmaceutically acceptable salt" refers to a salt of a compound of the invention which is made with counterions understood in the art to be generally acceptable for pharmaceutical uses and which possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid,

1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like; or (2) salts formed when an acidic proton present in the parent compound is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, morpholine, piperidine, dimethylamine, diethylamine and the like. Also included are salts of amino acids such as arginates and the like, and salts of organic acids like glucurmic or galactunoric acids and the like (*see, e.g.*, Berge *et al.*, 1977, *J. Pharm. Sci.* 66:1-19).

[0101] "Pharmaceutically acceptable vehicle" refers to a diluent, adjuvant, excipient or carrier that is acceptable for human use.

[0102] "Protecting group" refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry*, 3rd Ed., 1999, John Wiley & Sons, NY and Harrison *et al.*, *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative amino protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl ("CBZ"), *tert*-butoxycarbonyl ("Boc"), trimethylsilyl ("TMS"), 2-trimethylsilyl-ethanesulfonyl ("SES"), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl ("FMOC"), nitro-veratryloxycarbonyl ("NVOC") and the like. Representative hydroxyl protecting groups include, but are not limited to, those where the hydroxyl group is either acylated (e.g., methyl and ethyl esters, acetate or propionate groups or glycol esters) or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPPS groups) and allyl ethers.

[0103] "Progroup" refers to a type of protecting group that, when used to mask a functional group within an active drug to form a promoiety, converts the drug into a prodrug. Progroups are typically attached to the functional group of the drug *via* bonds that are cleavable under specified conditions of use. Thus, a progroup is that portion of a promoiety that cleaves to release the functional group under the specified conditions of use. As a specific example, an

amide promoiety of the formula -NH-C(O)CH_3 comprises the progroup -C(O)CH_3. Various phosphonate, ester and dioxolenone progroups and their uses are described herein.

[0104] "Substituted," when used to modify a specified group or radical, means that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent(s). Substituent groups useful for substituting saturated carbon atoms in the specified group or radical include, but are not limited to -R^a, halo, -O^-, =O, -OR^b, -SR^b, -S^-, =S, -NR^cR^c, =NR^b, =N-OR^b, trihalomethyl, -CF_3, -CN, -OCN, -SCN, -NO, -NO_2, =N_2, -N_3, -$S(O)_2R^b$, -$S(O)_2NR^b$, -$S(O)_2O^-$, -$S(O)_2OR^b$, -$OS(O)_2R^b$, -$OS(O)_2O^-$, -$OS(O)_2OR^b$, -$P(O)(O^-)_2$, -$P(O)(OR^b)(O^-)$, -CH_2-$P(O)(OR^b)(OR^b)$, -O-$P(O)(OR^b)(OR^b)$, -$P(O)(OR^b)(OR^b)$, -$C(O)R^b$, -$C(S)R^b$, -$C(NR^b)R^b$, -$C(O)O^-$, -$C(O)OR^b$, -$C(S)OR^b$, -$C(O)NR^cR^c$, -$C(NR^b)NR^cR^c$, -$OC(O)R^b$, -$OC(S)R^b$, -$OC(O)O^-$, -$OC(O)OR^b$, -$OC(S)OR^b$, -$NR^bC(O)R^b$, -$NR^bC(S)R^b$, -$NR^bC(O)O^-$, -$NR^bC(O)OR^b$, -$NR^bC(S)OR^b$, -$NR^bC(O)NR^cR^c$, -$NR^bC(NR^b)R^b$ and –$NR^bC(NR^b)NR^cR^c$, where R^a is selected from the group consisting of alkyl, cycloalkyl, heteroalkyl, cycloheteroalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl; each R^b is independently hydrogen or R^a; and each R^c is independently R^b or alternatively, the two R^cs are taken together with the nitrogen atom to which they are bonded form a 5-, 6- or 7-membered cycloheteroalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S. As specific examples, -NR^cR^c is meant to include –NH_2, -NH-alkyl, N-pyrrolidinyl and N-morpholinyl.

[0105] Similarly, substituent groups useful for substituting unsaturated carbon atoms in the specified group or radical include, but are not limited to, -R^a optionally substituted with C_1-C_4-alkyl or C(O)OR^b, halo, -O^-, -O-$(CH_2)_{0-4}$-R^b, -SR^b, -S^-, -NR^cR^c, trihalomethyl, -CF_3, -CN, -OCN, -SCN, -NO, -NO_2, -N_3, -$S(O)_2R^b$, -$S(O)_2O^-$, -$S(O)_2OR^b$, -$OS(O)_2R^b$, -$OS(O)_2O^-$, -$OS(O)_2OR^b$, -$P(O)(O^-)_2$, -$P(O)(OR^b)(O^-)$, -$P(O)(OR^b)(OR^b)$, -$C(O)R^b$, -$C(S)R^b$, -$C(NR^b)R^b$, -$C(O)O^-$, -$C(O)OR^b$, -$C(S)OR^b$, -$C(O)NR^cR^c$, -$C(NR^b)NR^cR^c$, -$OC(O)R^b$, -$OC(S)R^b$, -$OC(O)O^-$, -$OC(O)OR^b$, -O-C(O)-NH-R^b, -$OC(S)OR^b$, -$NR^bC(O)R^b$, -$NR^bC(S)R^b$, -$NR^bC(O)O^-$, -$NR^bC(O)OR^b$, -$NR^bC(S)OR^b$, -$NR^bC(O)NR^cR^c$, -$NR^bC(NR^b)R^b$ and –$NR^bC(NR^b)NR^cR^c$, where R^a, R^b and R^c are as previously defined. Additional substituent groups for substituting unsaturated carbon atoms are C_1-C_4-alkyl moieties substituted with one of the foregoing moieties.

[0106] Substituent groups useful for substituting nitrogen atoms in heteroalkyl and cycloheteroalkyl groups include, but are not limited to, -R^a, -O^-, -OR^b, -SR^b, -S^-, -NR^cR^c, trihalomethyl, -CF_3, -CN, -NO, -NO_2, -$S(O)_2R^b$, -$S(O)_2O^-$, -$S(O)_2OR^b$, -$OS(O)_2R^b$, -$OS(O)_2O^-$, -$OS(O)_2OR^b$, -$P(O)(O^-)_2$, -$P(O)(OR^b)(O^-)$, -$P(O)(OR^b)(OR^b)$, -$C(O)R^b$, -$C(S)R^b$, -$C(NR^b)R^b$, -$C(O)OR^b$, -$C(S)OR^b$, -$C(O)NR^cR^c$, -$C(NR^b)NR^cR^c$, -$OC(O)R^b$, -$OC(S)R^b$, -$OC(O)OR^b$, -$OC(S)OR^b$, -$NR^bC(O)R^b$, -$NR^bC(S)R^b$, -$NR^bC(O)OR^b$,

$-NR^bC(S)OR^b$, $-NR^bC(O)NR^cR^c$, $-NR^bC(NR^b)R^b$ and $-NR^bC(NR^b)NR^cR^c$, where R^a, R^b and R^c are as previously defined.

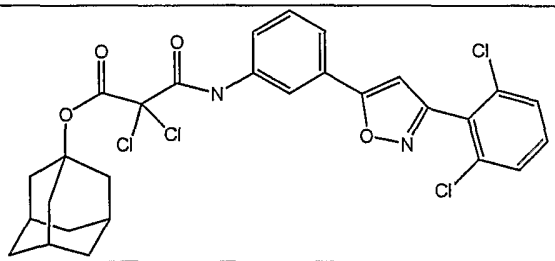
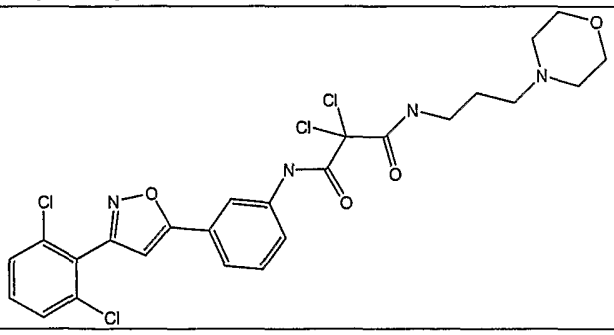
[0107] Substituent groups from the above lists useful for substituting other specified groups or atoms will be apparent to those of skill in the art.

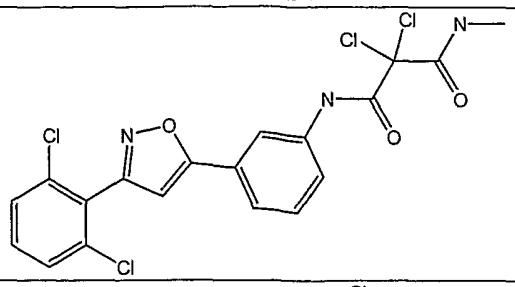
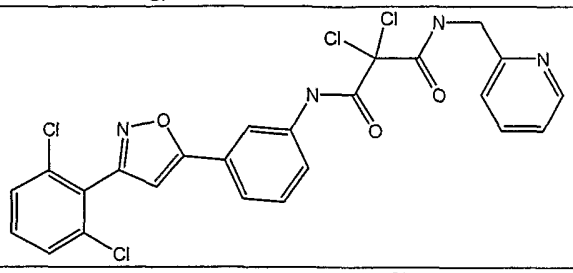
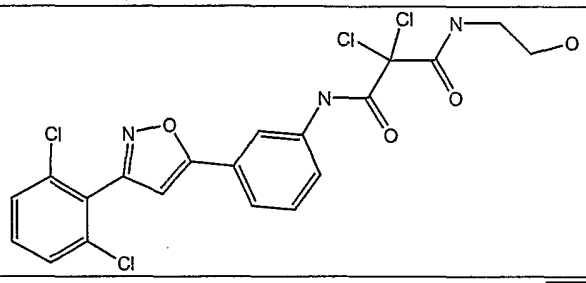
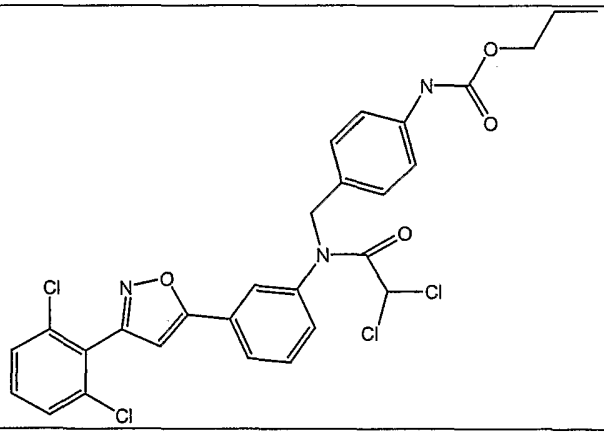
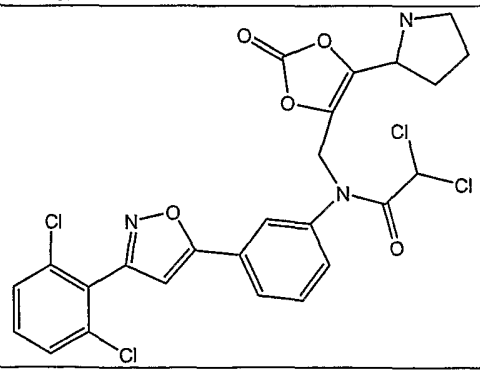
[0108] The substituents used to substitute a specified group can be further substituted, typically with one or more of the same or different groups selected from the various groups specified above.

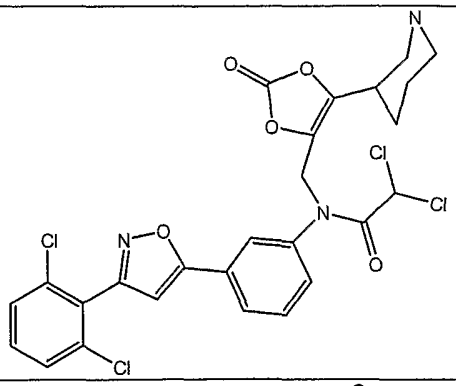
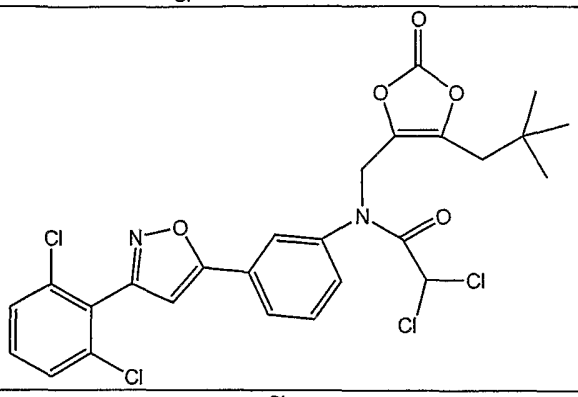
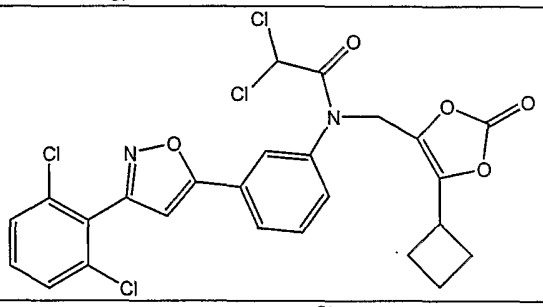
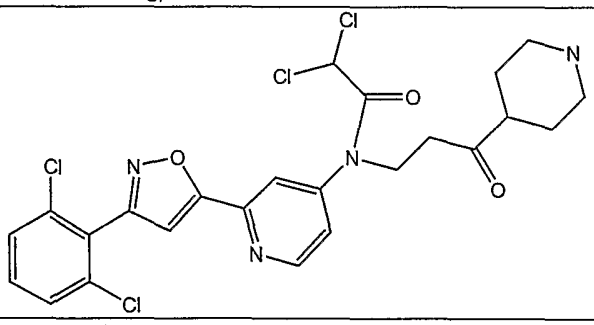
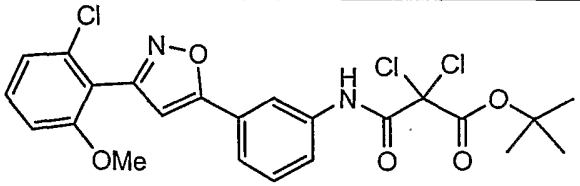
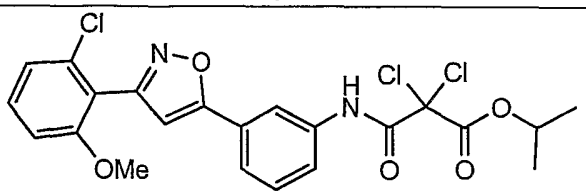
[0109] "Sulfamoyl," by itself or as part of another substituent, refers to a radical of the formula $-S(O)_2NR'R''$, where R' and R" are each, independently of one another, selected from the group consisting of hydrogen, alkyl and cycloalkyl as defined herein, or alternatively, R' and R", taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered cycloheteroalkyl ring as defined herein, which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, S and N.

[0110] Some examples of prodrugs of the invention are provided in TABLES 1 through 13. These examples merely serve to illustrate some embodiments of the invention and in no way limit the scope of the invention. Also included in the invention are the various regioisomers and hydro isomers of the prodrugs described herein, including the various regioisomers and hydro isomers of the prodrugs of structural formulae (I) through (XI) and TABLES 1 through 13.

TABLE 1

Cpd No.	Structure
1008	
1009	

Cpd No.	Structure
1010	
1011	
1012	
1013	
1014	

Cpd No.	Structure
1015	
1016	
1017	
1018	
1019	
1020	

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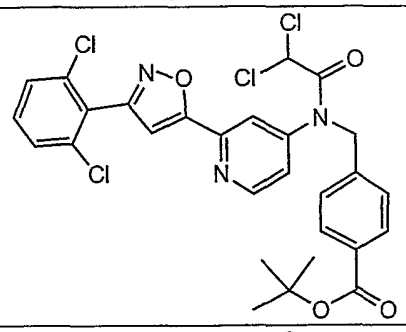
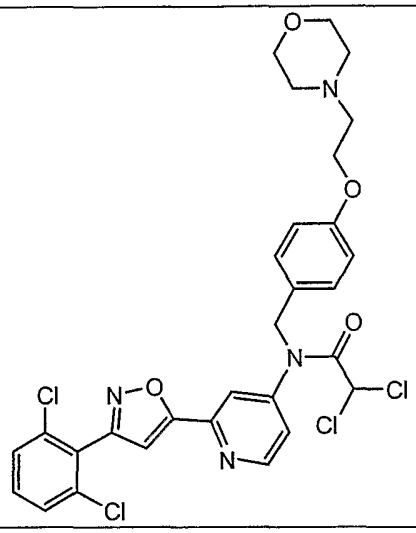
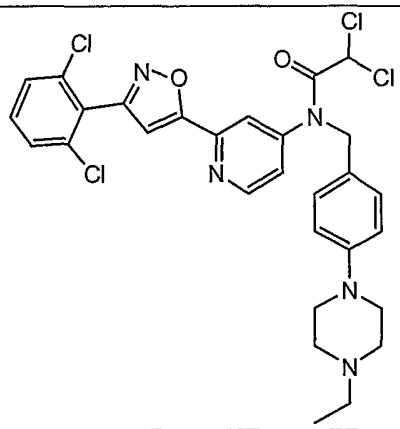
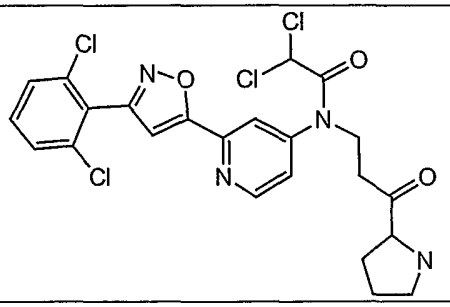
1021	
1022	
1023	
1024	

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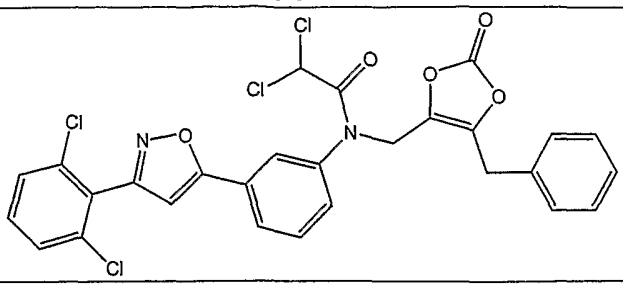
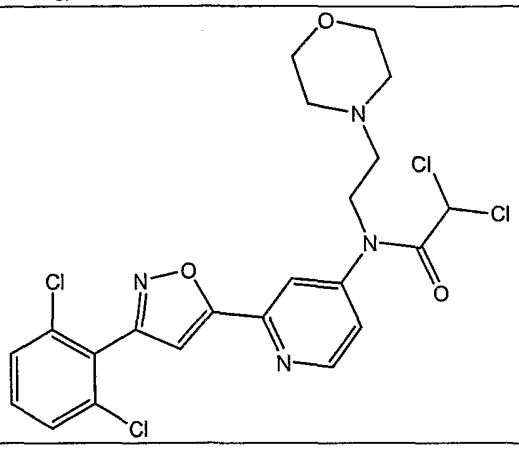
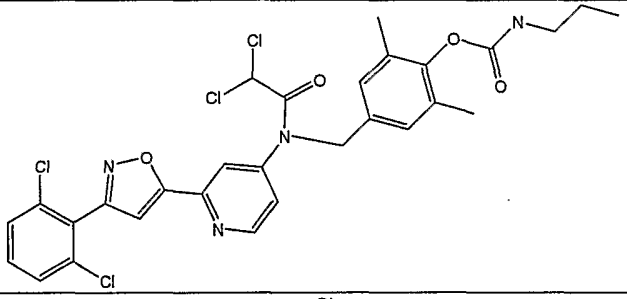
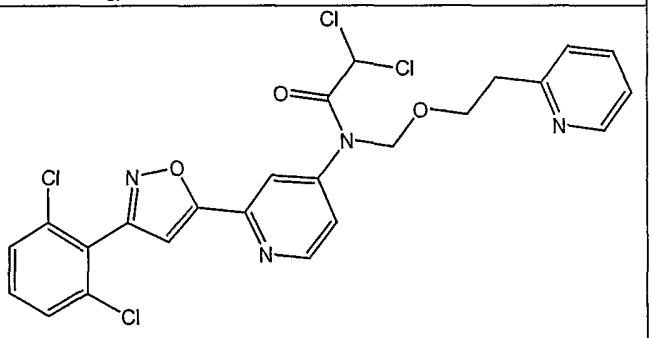
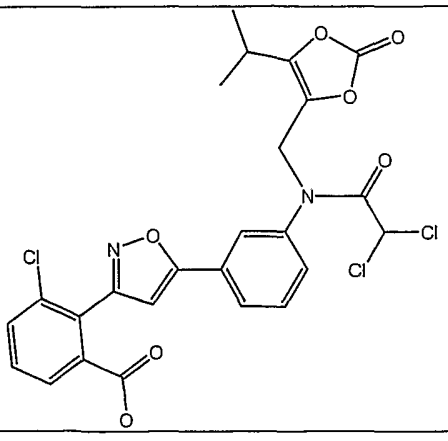
1025	
1026	
1027	
1028	
1029	

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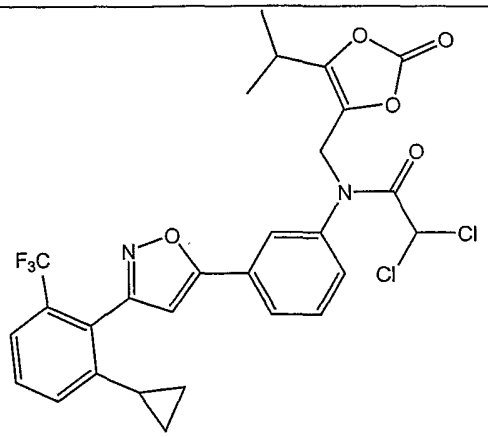
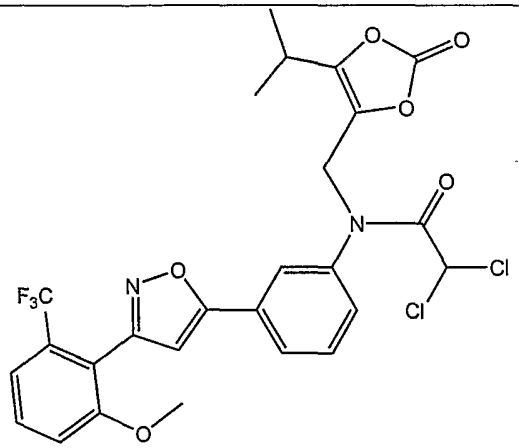
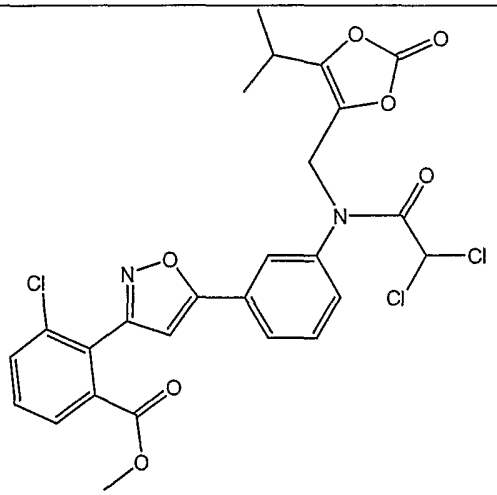
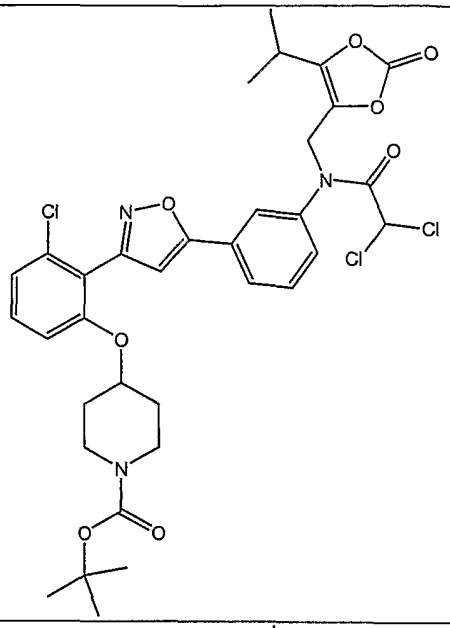
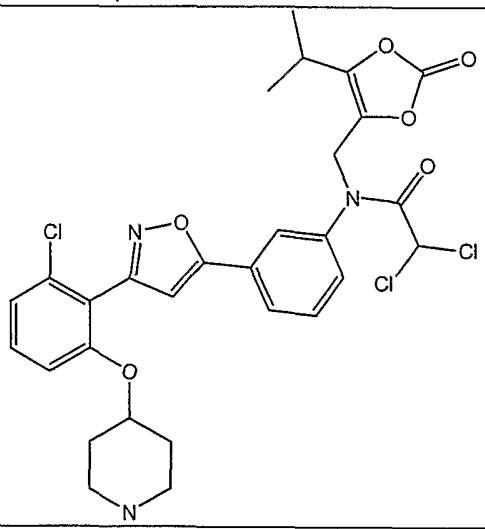
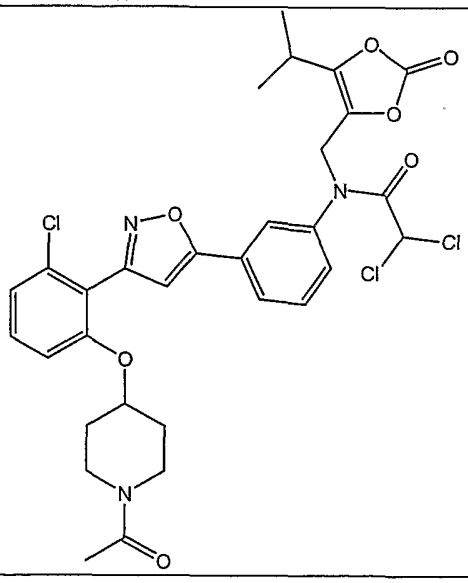
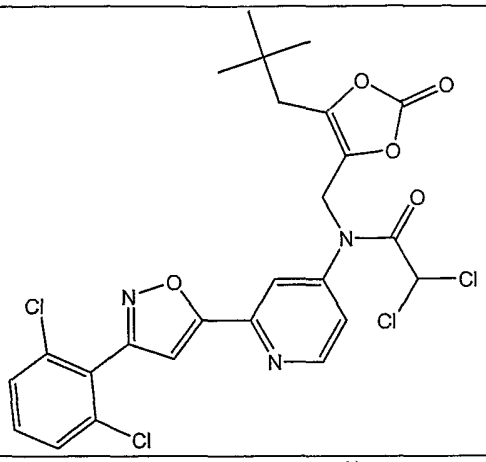
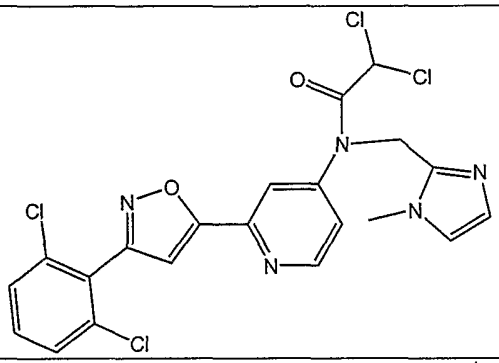
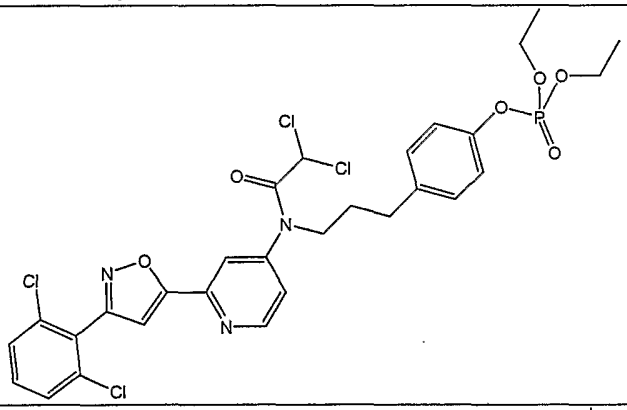
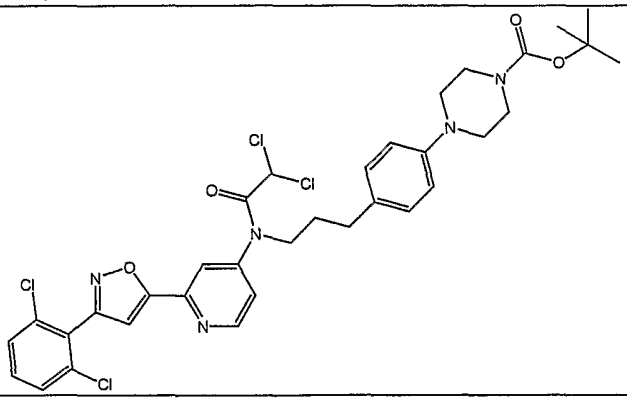
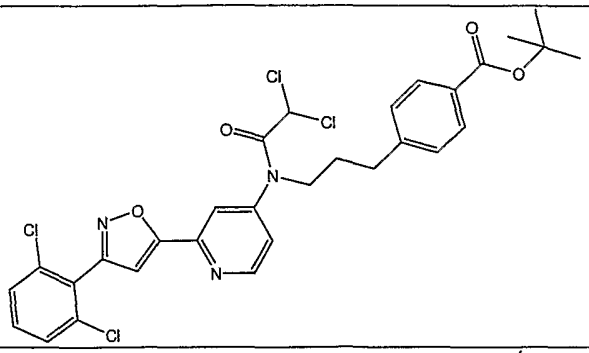
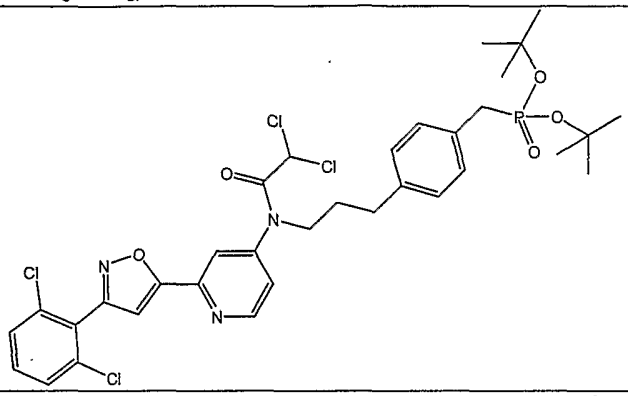
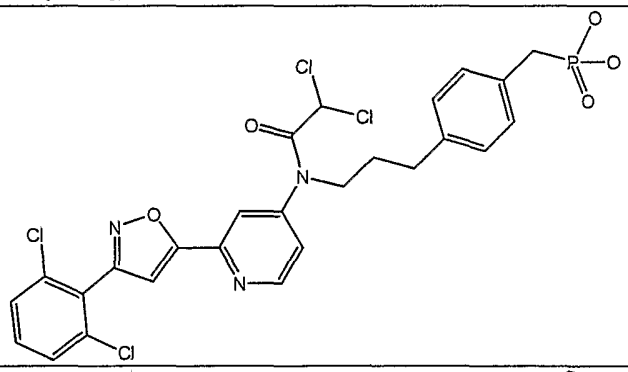
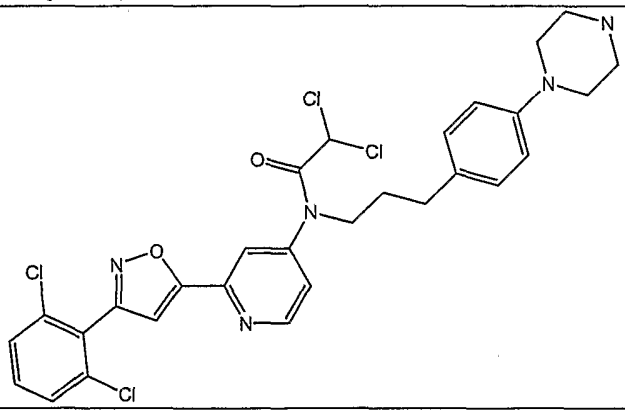
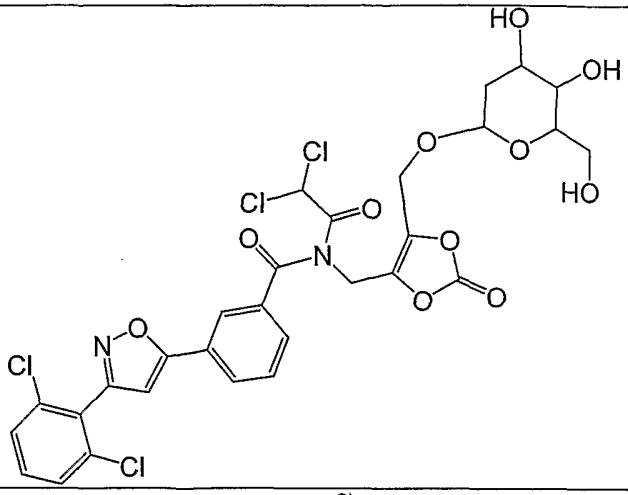
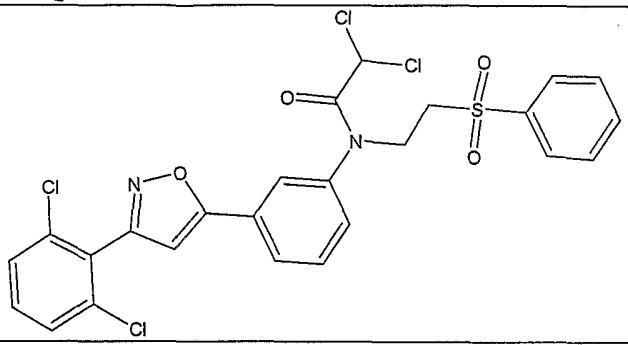
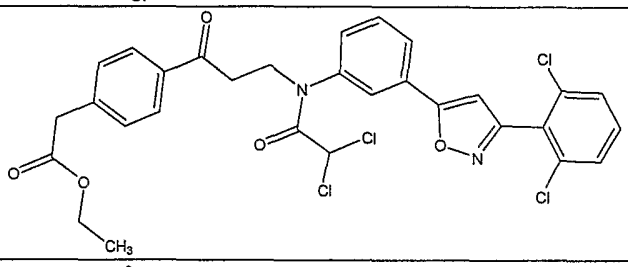
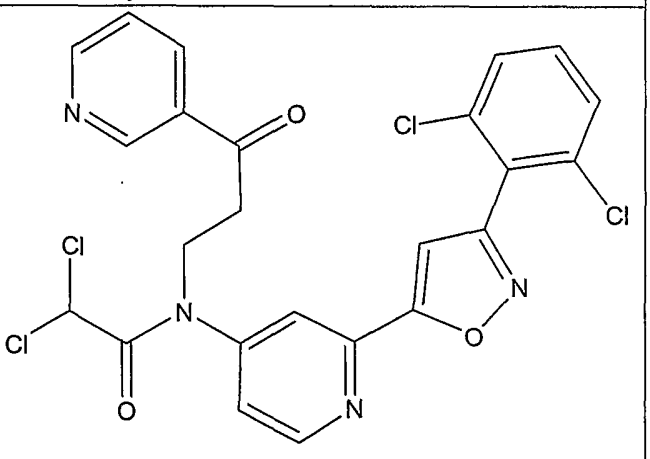
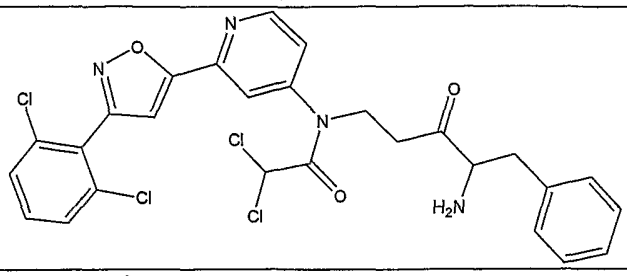
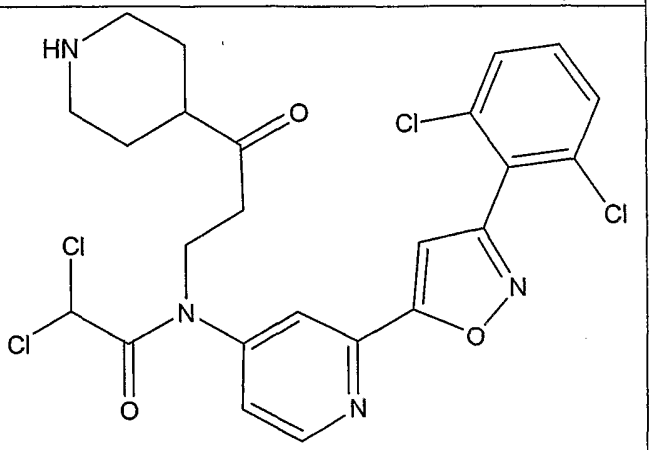
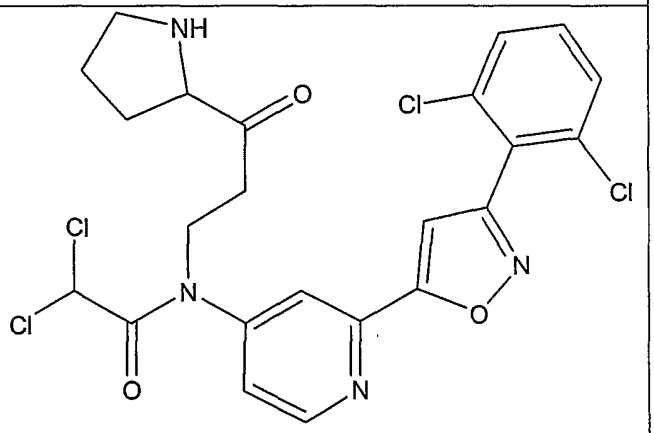
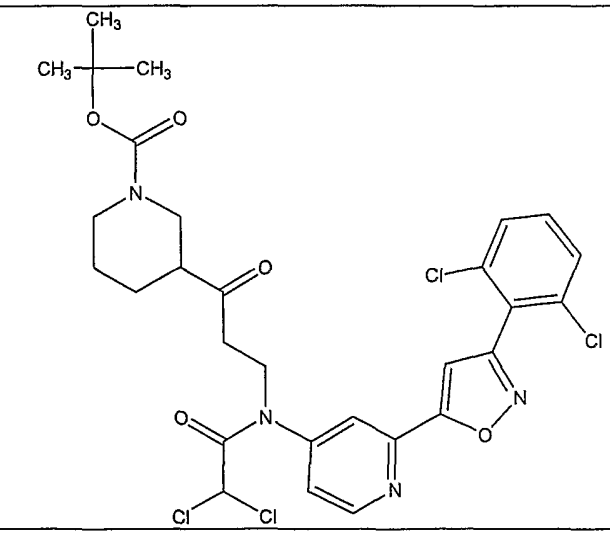
1030	
1031	
1032	

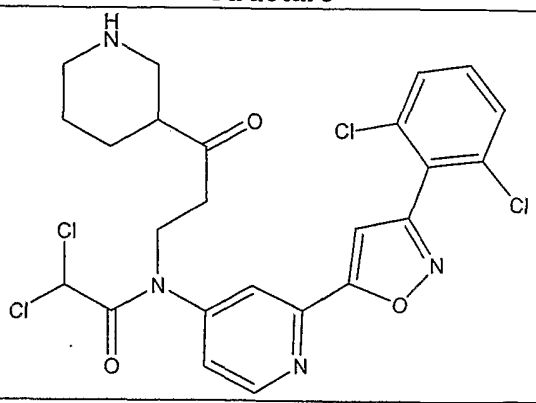
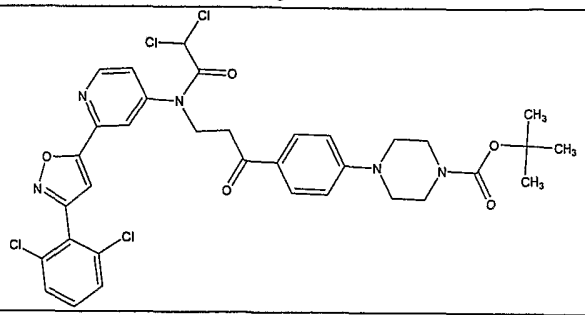
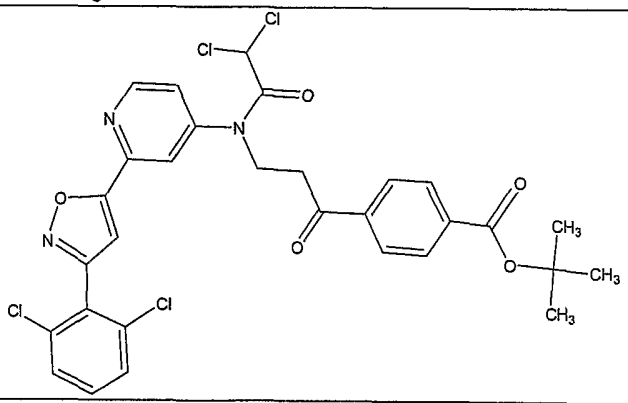
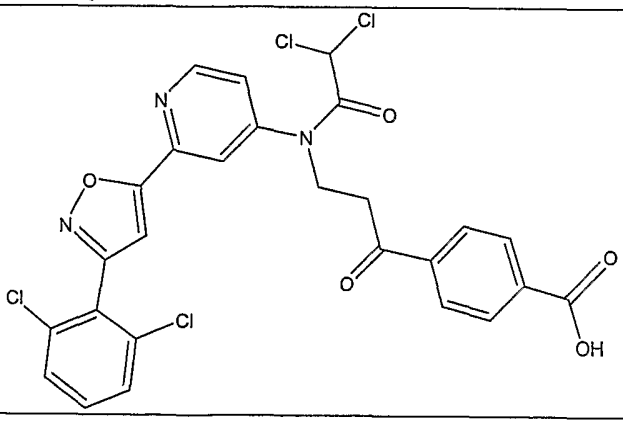
Cpd No.	Structure
1033	
1034	
1035	

Cpd No.	Structure
1036	
1037	
1038	
1039	

Cpd No.	Structure
1040	
1041	
1042	
1043	

Cpd No.	Structure
1044	
1045	
1049	
1046	

Cpd No.	Structure
1050	
1051	
1052	
1053	

Cpd No.	Structure
1054	
1055	
1056	
1047	

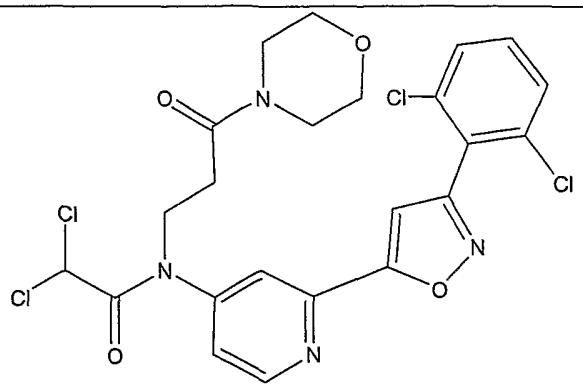
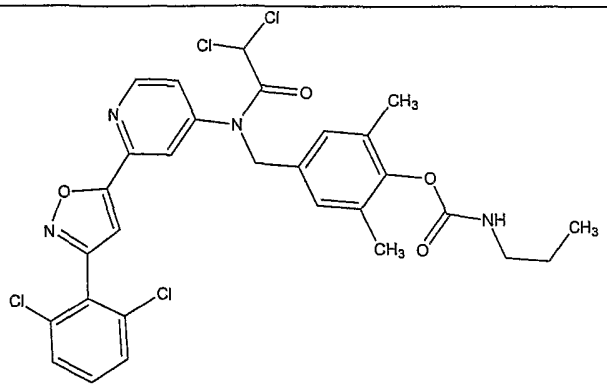
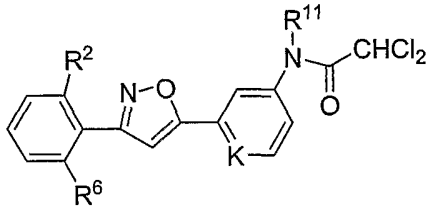
Cpd No.	Structure
1048	
1057	

TABLE 2



R^{11} = -(CHR^{10})$_n$-J-G

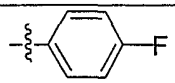
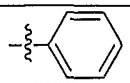
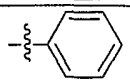
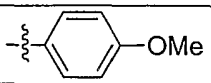
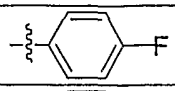
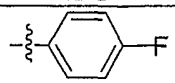
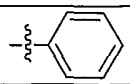
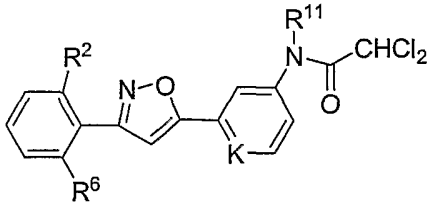
#	R^2	R^6	K	R^{10}	n	J	G
311a	Cl	Cl	-CH-	H	2	-C(O)-	
101a	Cl	Cl	-CH-	H	2	-SO_2-	
102a	Cl	Cl	-CH-	H	2	-C(O)-	
103a	Cl	Cl	-CH-	H	2	-C(O)-	
104a	Cl	Cl	-CH-	H	2	-C(O)-	
105a	Cl	Cl	-CH-	H	1	-C(O)-	
106a	Cl	Cl	-CH-	H	2	-CH_2-	
407a	Cl	Cl	-CH-	CH_3, H *	2	-C(O)-	

TABLE 2



$R^{11} = -(CHR^{10})_n\text{-}J\text{-}G$

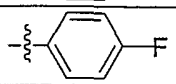
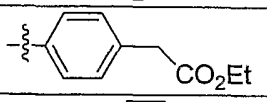
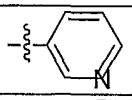
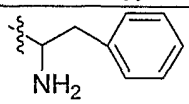
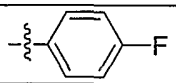
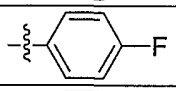
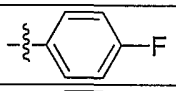
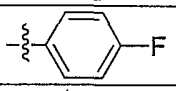
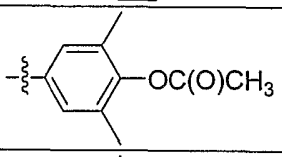
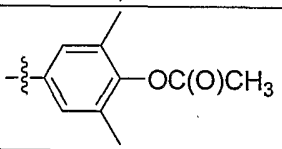
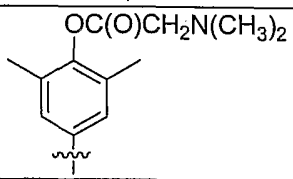
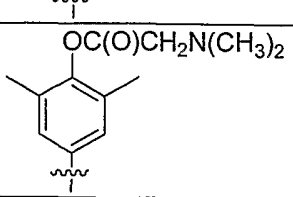
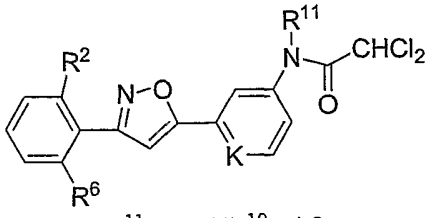
#	R^2	R^6	K	R^{10}	n	J	G
108a	Cl	Cl	-CH-	H	2	$-C(NOCH_3)-$	
109a	Cl	Cl	-CH-	H	2	-CH(OH)-	
110a	Cl	Cl	-CH-	H	2	-C(O)-	
111a	Cl	Cl	-CH-	H	2	-C(O)-	
112a	Cl	Cl	-N-	H	2	-C(O)-	
113a	OMe	Cl	-CH-	H	2	-C(O)-	
114a	CF_3		-CH-	H	2	-C(O)-	
115a	Cl	Cl	-N-		0	$-CH_2-$	
116a	Cl	Cl	-N-	H	1	$-CH_2-$	
117a	Cl	Cl	-CH-		0	$-CH_2-$	
118a	Cl	Cl	-N-		0	$-CH_2-$	
119a	Cl	Cl	-CH-		0	$-CH_2-$	
120a	Cl	Cl	-N-		0	$-CH_2-$	

TABLE 2



$R^{11} = -(CHR^{10})_n$-J-G

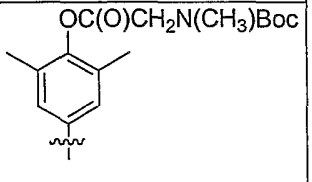
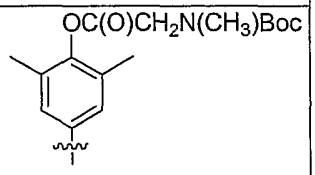
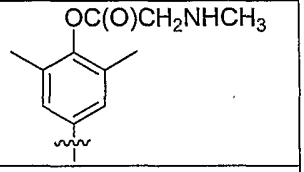
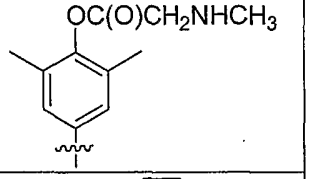
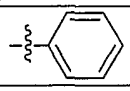
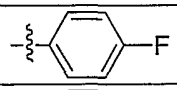
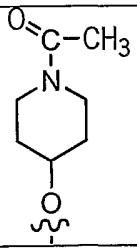
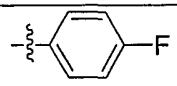
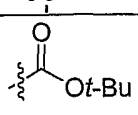
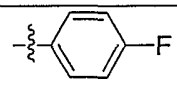
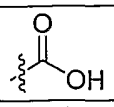
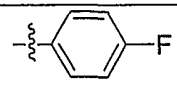
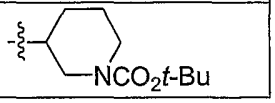
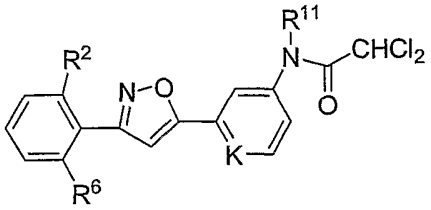
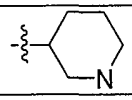
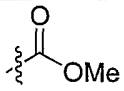
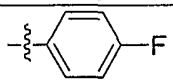
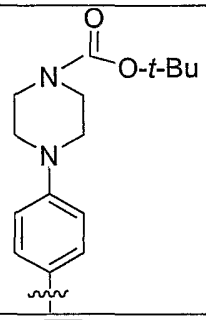
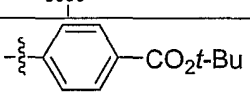
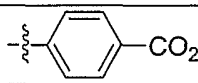
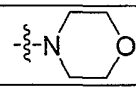
#	R^2	R^6	K	R^{10}	n	J	G
121a	Cl	Cl	-CH-		0	$-CH_2-$	
122a	Cl	Cl	-N-		0	$-CH_2-$	
123a	Cl	Cl	-CH-		0	$-CH_2-$	
124a	Cl	Cl	-N-		0	$-CH_2-$	
125a	Cl	Cl	-CH-		0	$-CH_2-$	
605a	Cl	Cl	-N-	H	2	-C(O)-	
127a	Cl		-CH-	H	2	-C(O)-	
128a	Cl		-CH-	H	2	-C(O)-	
129a	Cl		-CH-	H	2	-C(O)-	
130a	Cl	Cl	-CH-	H	2	-C(O)-	

TABLE 2

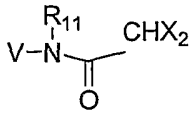


R^{11} = -(CHR^{10})$_n$-J-G

#	R^2	R^6	K	R^{10}	n	J	G
131a	Cl	Cl	-CH-	H	2	-C(O)-	
132a	Cl	Cl	-N-	H	2	-CH_2-	
133a	Cl		-CH-	H	2	-C(O)-	
134a	Cl	Cl	-N-	H	2	-C(O)-	
135a	Cl	Cl	-N-	H	2	-C(O)-	
136a	Cl	Cl	-N-	H	2	-C(O)-	
137a	Cl	Cl	-N-	H	2	-C(O)-	

The * indicates that R^{10} is methyl when attached to the carbon atom adjacent to the nitrogen atom and is hydrogen otherwise.

[0111] The skilled artisan will further appreciate that the progroups described herein (*i.e.*, -R^{11} and -C(O)CHX_2) may be combined with any therapeutic agent which has a primary amine or primary sulfonamide to provide prodrugs of the therapeutic agent. Accordingly, compounds according to structural Formula (IV) are also provided herein:



(IV)

wherein R^{11} and X are as defined, *supra*, and V-N is a primary amine containing therapeutic agent or a primary sulfonamide containing therapeutic agent where one of the hydrogen atoms of the amine has been replaced with -R^{11} and the other hydrogen atom has been replaced by -C(O)CHX_2. Many such therapeutic agents (*i.e.*, V-NH_2, V-SO_2NH_2) are known in the art and include, but are not

limited to, abacavir, acadesine, acediasulfone, amiloride, aminorex, cisapride, metoclopramide, mexiletine, pamidronate, pramipexole, prazosin, procainamide, dimethoxyphenethylamine, aletamine, amphetamine, aspartame, chlortermine, dopamine, L-Dopa, etryptamine, methyldopamine, norepinephrine, norepinephrine, enviroxime, triamterene, pipedemic acid, tyleno, epirvir, lamuvidine, zidovudone, cipro, ciprofluxavir, gantavol, gantrisin, salmeterol, and similar compounds. Other therapeutic agents (*i.e.*, V-NH_2, V-SO_2NH_2) which may be used in the current invention will be obvious to the skilled artisan.

Uses and Administration

[0112] Owing to their ability to inhibit HCV replication, the metabolically active agents of the prodrugs of the invention and/or compositions thereof can be used in a variety of contexts. For example, the prodrugs of the invention can be used as controls in *in vitro* assays to identify additional more or less potent anti HCV prodrugs. As another example, the prodrugs of the invention and/or compositions thereof can be used as preservatives or disinfectants in clinical settings to prevent medical instruments and supplies from becoming infected with HCV virus. When used in this context, the prodrugs of the invention and/or composition thereof may be applied to the instrument to be disinfected at a concentration that is a multiple, for example 1X, 2X, 3X, 4X, 5X or even higher, of the measured IC_{50} for the metabolically active agent of the prodrug.

[0113] In a specific embodiment, the prodrugs and/or compositions can be used to "disinfect" organs for transplantation. For example, a liver or portion thereof being prepared for transplantation can be perfused with a solution comprising an inhibitory prodrug of the invention prior to implanting the organ into the recipient. This method has proven successful with lamuvidine (3TC, Epivir®, Epivir-HB®) for reducing the incidence of hepatitis B virus (HBV) infection following liver transplant surgery/therapy. Quite interestingly, it has been found that such perfusion therapy not only protects a liver recipient free of HBV infection (HBV-) from contracting HBV from a liver received from an HBV+ donor, but it also protects a liver from an HBV- donor transplanted into an HBV+ recipient from attack by HBV. The prodrugs of the invention may be used in a similar manner prior to organ or liver transplantation.

[0114] The prodrugs of the invention and/or compositions thereof find particular use in the treatment and/or prevention of HCV infections in animals and humans. When used in this context, the prodrugs may be administered *per se*, but are typically formulated and administered in the form of a pharmaceutical composition. The exact composition will depend upon, among other things, the method of administration and will apparent to those of skill in the art. A wide variety of

suitable pharmaceutical compositions are described, for example, in *Remington's Pharmaceutical Sciences*, 20th ed., 2001).

[0115] Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the prodrugs suspended in diluents, such as water, saline or PEG 400; (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as liquids, solids, granules or gelatin; (c) suspensions in an appropriate liquid; and (d) suitable emulsions. Tablet forms can include one or more of lactose, sucrose, mannitol, sorbitol, calcium phosphates, corn starch, potato starch, microcrystalline cellulose, gelatin, colloidal silicon dioxide, talc, magnesium stearate, stearic acid, and other excipients, colorants, fillers, binders, diluents, buffering agents, moistening agents, preservatives, flavoring agents, dyes, disintegrating agents, and pharmaceutically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, e.g., sucrose, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin or sucrose and acacia emulsions, gels, and the like containing, in addition to the active ingredient, carriers known in the art.

[0116] The prodrug of choice, alone or in combination with other suitable components, can be made into aerosol formulations (*i.e.*, they can be "nebulized") to be administered via inhalation. Aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like.

[0117] Suitable formulations for rectal administration include, for example, suppositories, which consist of the packaged nucleic acid with a suppository base. Suitable suppository bases include natural or synthetic triglycerides or paraffin hydrocarbons. In addition, it is also possible to use gelatin rectal capsules which consist of a combination of the prodrug of choice with a base, including, for example, liquid triglycerides, polyethylene glycols, and paraffin hydrocarbons.

[0118] Formulations suitable for parenteral administration, such as, for example, by intraarticular (in the joints), intravenous, intramuscular, intradermal, intraperitoneal, and subcutaneous routes, include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. In the practice of this invention, compositions can be administered, for example, by intravenous infusion, orally, topically, intraperitoneally, intravesically or intrathecally. Parenteral administration, oral administration, subcutaneous administration and intravenous administration are the preferred methods of administration. A specific example of a suitable solution formulation

may comprise from about 0.5-100 mg/ml prodrug and about 1000 mg/ml propylene glycol in water. Another specific example of a suitable solution formulation may comprise from about 0.5-100 mg/ml prodrug and from about 800-1000 mg/ml polyethylene glycol 400 (PEG 400) in water.

[0119] A specific example of a suitable suspension formulation may include from about 0.5-30 mg/ml prodrug and one or more excipients selected from the group consisting of: about 200 mg/ml ethanol, about 1000 mg/ml vegetable oil (e.g., corn oil), about 600-1000 mg/ml fruit juice (e.g., grape juice), about 400-800 mg/ml milk, about 0.1 mg/ml carboxymethylcellulose (or microcrystalline cellulose), about 0.5 mg/ml benzyl alcohol (or a combination of benzyl alcohol and benzalkonium chloride) and about 40-50 mM buffer, pH 7 (e.g., phosphate buffer, acetate buffer or citrate buffer or, alternatively 5% dextrose may be used in place of the buffer) in water.

[0120] A specific example of a suitable liposome suspension formulation may comprise from about 0.5-30 mg/ml prodrug, about 100-200 mg/ml lecithin (or other phospholipid or mixture of phospholipids) and optionally about 5 mg/ml cholesterol in water. For subcutaneous administration of a prodrug, a liposome suspension formulation including 5 mg/ml prodrug in water with 100 mg/ml lecithin and 5 mg/ml prodrug in water with 100 mg/ml lecithin and 5 mg/ml cholesterol provides good results. This formulation may be used for other prodrugs of the invention.

[0121] The formulations of prodrugs can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials. Injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

[0122] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the prodrug. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. The composition can, if desired, also contain other compatible therapeutic agents, discussed in more detail, below.

[0123] In therapeutic use for the treatment of HCV infection, the prodrugs utilized in the pharmaceutical method of the invention are administered to patients diagnosed with HCV infection at dosage levels suitable to achieve therapeutic benefit. By therapeutic benefit is meant that the administration of prodrug leads to a beneficial effect in the patient over time. For example, therapeutic benefit is achieved when the HCV titer or load in the patient is either reduced or stops

increasing. Therapeutic benefit is also achieved if the administration of prodrug slows or halts altogether the onset of the organ damage that or other adverse symptoms typically accompany HCV infections, regardless of the HCV titer or load in the patient.

[0124] The prodrugs of the invention and/or compositions thereof may also be administered prophylactically in patients who are at risk of developing HCV infection, or who have been exposed to HCV, to prevent the development of HCV infection. For example, the prodrugs of the invention and/or compositions thereof may be administered to hospital workers accidentally stuck with needles while working with HCV patients to lower the risk of, or avoid altogether, developing an HCV infection.

[0125] Initial dosages suitable for administration to humans may be determined from *in vitro* assays or animal models. For example, an initial dosage may be formulated to achieve a serum concentration that includes the IC_{50} of the particular metabolically active agent of the prodrug being administered, as measured in an *in vitro* assay. Alternatively, an initial dosage for humans may be based upon dosages found to be effective in animal models of HCV infection. Suitable model systems are described, for example, in Muchmore, 2001, Immunol. Rev. 183:86-93 and Lanford & Bigger, 2002, Virology, 293:1-9, and the referenced cited therein. As one example, the initial dosage may be in the range of about 0.01 mg/kg/day to about 200 mg/kg/day, or about 0.1 mg/kg/day to about 100 mg/kg/day, or about 1 mg/kg/day to about 50 mg/kg/day, or about 10 mg/kg/day to about 50 mg/kg/day, can also be used. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the prodrug being employed. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular prodrug in a particular patient. Determination of the proper dosage for a particular situation is within the skill of the practitioner. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the prodrug. Thereafter, the dosage is increased by small increments until the optimum effect under circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

Combination Therapy

[0126] In certain embodiments of the present invention, the prodrugs of the invention and/or compositions thereof can be used in combination therapy with at least one other therapeutic agent. A prodrug of the invention and/or composition thereof and the therapeutic agent can act additively or, more preferably, synergistically. The prodrug of the invention and/or a composition

thereof may be administered concurrently with the administration of the other therapeutic agent(s), or it may be administered prior to or subsequent to administration of the other therapeutic agent(s).

[0127] In one embodiment, the prodrugs of the invention and/or compositions thereof are used in combination therapy with other antiviral agents or other therapies known to be effective in the treatment or prevention of HCV. As a specific example, the prodrugs of the invention and/or compositions thereof may be used in combination with known antivirals, such as ribavirin (see, e.g., US Patent No. 4,530,901). As another specific example, the prodrugs of the invention and/or compositions thereof may also be administered in combination with one or more of the compounds described in any of the following: U.S. Patent No. 6,143,715; U.S. Patent No. 6,323,180; U.S. Patent No. 6,329,379; U.S. Patent No. 6,329,417; U.S. Patent No. 6,410,531; U.S. Patent No. 6,420,380; and U.S. Patent No. 6,448,281.

[0128] Yet another specific example, the prodrugs of the invention and/or compositions thereof may be used in combination with interferons such as α–interferon, β–interferon and/or γ-interferon. The interferons may be unmodified, or may be modified with moieties such as polyethylene glycol (pegylated interferons). Many suitable unpegylated and pegylated interferons are available commercially, and include, by way of example and not limitation, recombinant interferon alpha-2b such as Intron-A interferon available from Schering Corporation, Kenilworth, N.J., recombinant interferon alpha-2a such as Roferon interferon available from Hoffmann-La Roche, Nutley, N.J., recombinant interferon alpha-2C such as Berofor alpha 2 interferon available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, Conn., interferon alpha-n1, a purified blend of natural alpha interferons such as Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from the Glaxo-Wellcome Ltd., London, Great Britain, or a consensus alpha interferon such as those described in U.S. Pat. Nos. 4,897,471 and 4,695,623 (especially Examples 7, 8 or 9 thereof) and the specific product available from Amgen, Inc., Newbury Park, Calif., or interferon alpha-n3 a mixture of natural alpha interferons made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, Conn., under the Alferon Tradename, pegylated interferon-2b available from Schering Corporation, Kenilworth, N.J. under the tradename PEG-Intron A and pegylated interferon-2a available from Hoffmann-LaRoche, Nutley, N.J. under the tradename Pegasys.

[0129] As yet another specific example, the prodrugs of the invention and/or compositions thereof may be administered in combination with both ribovirin and an interferon.

Methods of Synthesis

[0130] The prodrugs of the invention may be obtained *via* synthetic methods illustrated in FIGS. 1-36. It should be understood that in FIGS. 1-36, R^2, R^6, R^{16}, R^{18} and R^{19} are as previously defined for structural formulae herein.

[0131] Starting materials useful for preparing prodrugs of the invention and intermediates thereof are commercially available or can be prepared by well-known synthetic methods (*see, e.g.*, Harrison *et al.*, "Compendium of Synthetic Organic Methods", Vols. 1-8 (John Wiley and Sons, 1971-1996); "Beilstein Handbook of Organic Chemistry," Beilstein Institute of Organic Chemistry, Frankfurt, Germany; Feiser *et al.*, "Reagents for Organic Synthesis," Volumes 1-21, Wiley Interscience; Trost *et al.*, "Comprehensive Organic Synthesis," Pergamon Press, 1991; "Theilheimer's Synthetic Methods of Organic Chemistry," Volumes 1-45, Karger, 1991; March, "Advanced Organic Chemistry," Wiley Interscience, 1991; Larock "Comprehensive Organic Transformations," VCH Publishers, 1989; Paquette, "Encyclopedia of Reagents for Organic Synthesis," 3d Edition, John Wiley & Sons, 1995). Other methods for synthesis of the compounds described herein and/or starting materials are either described in the art or will be readily apparent to the skilled artisan. Accordingly, the synthetic methods and strategy presented herein are illustrative rather than comprehensive.

[0132] It should be understood that the following general methods are meant to be illustrative. For example, the synthetic routes described focus on isoxazole "B" rings. However, heterocyclic rings in place of an isoxazole "B" ring as described throughout the specification can be employed by the skilled artisan. Additionally, substituents utilized in the Figures correspond to those described throughout the specification. Manipulation and choice of substituents are within the knowledge of a skilled artisan.

[0133] One method for synthesizing substituted diphenyl isoxazoles according to structural formula (VI) or phenyl-pyridyl isoxazoles according to structural formula (VIII) (in either case, when D is N, E is O and F is -CH-) is provided in FIG. 1. Referring to FIG. 1, condensation of ethynyl(hetero)aromatics **201** with 2, 2-dihalo-2-(disubstitutedoxyphosphonyl)acetyl chloride **203** under basic conditions, provides N-substituted-ethynyl(hetero)aromatics **205**. Treatment of **205** with 2,6-disubstituted-N-hydroxybenzenecarboximidoyl chloride **207** under basic conditions provides phosphonate ester containing 3,5-disubstituted isoxazoles **209**, which may be optionally de-esterified with trimethylsilyl bromide to yield the phosphonic acid containing 3,5-disubstituted isoxazoles **211**.

[0134] A different method for synthesizing substituted diphenyl isoxazoles according to structural formula (VI) or phenyl-pyridyl isoxazoles according to structural formula (VIII) (in either case, when D is N, E is O and F is -CH-) is provided in FIG. 2. Referring to FIG. 2, condensation of 3,5-disubstituted isoxazoles **301** with 2, 2-dihalo-2-(disubstitutedoxyphosphonyl)acetyl chloride **203** under basic conditions, provides phosphonate ester containing 3,5-disubstituted isoxazoles **209**. Optional treatment of **209** with trimethylsilyl bromide provides the phosphonic acid containing 3,5-disubstituted isoxazoles **211**. Preparation of **301** and similar compounds is known in the art can be prepared by the methods disclosed in US Serial No. 10/646,348, filed August 22, 2003, US Serial Nos. 10/286,017, filed November 1, 2002 and 10/440,349, filed May 15, 2003, WO 04/018463 and WO 03/040112, the contents of which are incorporated herein in their entirety.

[0135] A specific example of the synthetic method of FIG. 2 is illustrated in FIG. 3 for the preparation of diphenyl isoxazoles **405** and **407**. Preparation of **401** and similar compounds is known in the art and can be prepared by the methods disclosed in US Serial Nos. 10/286,017, filed November 1, 2002 and 10/440,349, filed May 15, 2003, and WO 03/040112, the contents of which are incorporated herein in their entirety.

[0136] A method for synthesizing substituted diphenyl isoxazoles according to structural formula (VI) or phenyl-pyridyl isoxazoles according to structural formula (VIII) (in either case, when D is N, E is O and F is -CH-) is provided in FIG. 4. Referring to FIG. 4, condensation of ethynyl(hetero)aromatics **201** with 2-(alkyloxycarbonyl)-2,2-dichloroacetyl chloride **603** under basic conditions, provides N-substituted-ethynyl(hetero)aromatics **605**. Treatment of **605** with 2,6-disubstituted-N-hydroxybenzenecarboximidoyl chloride **207** under basic conditions provides carboxylate ester containing 3,5-disubstituted isoxazoles **609**.

[0137] Another method for synthesizing substituted diphenyl isoxazoles according to structural formula (VI) or phenyl-pyridyl isoxazoles according to structural formula (VIII) (in either case, when D is N, E is O and F is -CH-) is provided in FIG. 5. Referring to FIG. 5, condensation of diphenyl/pyridyl isoxazole **301** with 2-(alkyloxycarbonyl)-2,2-dichloroacetyl chloride **603** under basic conditions, provides carboxylate ester containing 3,5-disubstituted isoxazoles **705**.

[0138] A specific example of the synthetic method of FIG. 4 is illustrated in FIG. 6 for the preparation of diphenyl isoxazole **809**.

[0139] A specific example of the synthetic method of FIG. 5 is illustrated in FIG. 7 for the preparation of phenyl-pyridyl isoxazole **505**. Referring to FIG. 7, condensation of pyridyl

isoxazole **501** with 2-(t-butyloxycarbonyl)-2,2-dichloroacetyl chloride **503** under basic conditions, provides carboxylate ester containing 3,5-disubstituted isoxazoles **505**.

[0140] Still another method for synthesizing substituted diphenyl isoxazole according to structural formula (VI) (when D is N, E is O and F is -CH-) is provided in FIG. 8B. Referring to FIG. 8B, condensation of 3,5-disubstituted isoxazole **401** with 4-bromomethyl-5-methyl-1,3-dioxolene-2-one **903 (see FIG. 8A)** under basic conditions, provides N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]]-N-[(5-methyl-1,3-dioxolene-2-one-4-yl)methylene]aniline **905**. Treatment of **905** with dichloroacetyl chloride under basic conditions provided 2,2-dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]phenyl]-N-[(5-methyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide **907**.

[0141] FIG. 9A depicts a method to prepare 4-bromomethyl-5-*t*-butyl-1,3-dioxolene-2-one **1003**, useful in the synthesis of 2,2-dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]phenyl]-N-[(5-*t*-butyl-1,3-dioxolene-2-one-4-yl)methylene]acetamide **1007.** Referring to FIG. 9B, condensation of 3-(2,6-dichlorophenyl)-5-(3-aminophenyl)isoxazole **401** with 4-bromomethyl-5-*t*-butyl-1,3-dioxolene-2-one **1003** under basic conditions, provides N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-N-[5-t-butyl-1,3-dioxolene-2-one-4-yl)methylene]aniline **1005**. Treatment of **1005** with dichloroacetyl chloride under basic conditions provided 2,2-dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]phenyl]-N-[(5-*t*-butyl-1,3-dioxolene-2-one-4-yl)methylene]acetamide **1007**.

[0142] A method for synthesizing substituted phenyl-pyridyl isoxazole according to structural formula (VIII) (when D is N, E is O and F is -CH-) is provided in FIG. 10. Referring to FIG. 10, condensation of pyridyl isoxazole **501** with 4-bromomethyl-5-*t*-butyl-1,3-dioxolene-2-one **1003** under basic conditions, provides N-[2'-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]4-pyridyl]-N-[5-t-butyl-1,3-dioxolene-2-one-4-yl)methylene]amine **1105.** Treatment of **1105** with dichloroacetyl chloride under basic conditions provided 2,2-dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]-2-pyridyl]-N-[(5-*t*-butyl-1,3-dioxolene-2-one-4-yl)methylene]acetamide **1107**.

[0143] The methods described in FIGS. 1, 4 and 6 above may be readily adapted for the synthesis of pyrazoles by substituting hydrazine for hydroxylamine in the reaction sequence. Further, those of skill in the art will appreciate that isoxazole regioisomers of those depicted in the above FIGS. 1-10 may be synthesized by merely interchanging the reactive functionalities of the two different aromatic rings.

[0144] In FIGS. 1-10, substituents R^2 and R^6 (R^{20}'s) may include reactive functional groups that require protection during synthesis. Selection of suitable protecting groups will depend on the identity of the functional group and the synthesis method employed, and will be apparent to

those of skill in the art. Guidance for selecting suitable protecting groups can be found in Greene & Wuts, *supra*, and the various other references cited therein.

[0145] Further guidance for carrying out 1,3-dipolar cycloaddition reactions, also named 1,3-dipolar additions, [3+2] cyclizations or [3+2] cycloadditions, can be found in "Cycloaddition Reactions in Organic Synthesis", (Kobayashi, S. and Jorgensen, K. A., Editors), 2002, Wiley-VCH Publishers, pp. 1 - 332 pages (specifically, Chapters 6 and 7 on [3+2] cycloadditions and 1,3-dipolar additions, pp. 211 - 248 and 249 - 300); "1,3-Dipolar Cycloaddition", *Chemistry of Heterocyclic Compounds*, Vol. 59, (Padwa, A. and Pearson, W., Editors), 2002, John Wiley, New York, pp. 1-940; "Nitrile Oxides, Nitrones, Nitronates in Organic Synthesis: Novel Strategies in Synthesis", Torssel, K. B. G., 1988, VCH Publishers, New York, pp. 1-332; Barnes & Spriggs, 1945, *J. Am. Chem Soc.* 67:134; and Anjaneyulu *et al.*, 1995, *Indian J. Chem.*, Sect. 5 34(11):933-938).

[0146] Further guidance for synthesizing isoxazoles may be found in M. Sutharchanadevi, R. Murugan in *Comprehensive Heterocyclic Chemistry II*, A.R. Katritzky, C.W. Rees, E.F.V. Scriven, Eds.; Pergamon Press, Oxford, Vol. 3, p. 221; R. Grünager, P, Vita-Finzi in *Heterocyclic Compounds, Vol. 49, Isoxazoles, Part one*, John Wiley and Sons, New York, 1991; K. B. G. Torssell, *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*, VCH Publishers, New York, 1988; Y-Y. Ku, T. Grieme, P. Sharma,, Y.-M. Pu, P. Raje, H. Morton, S. King *Organic Letters*, 2001, 3, 4185; V. G. Desai, S. G. Tilve *Synth. Comm.*, 1999, 29, 3017; X. Wei, J. Fang, Y. Hu, H. Hu *Synthesis*, 1992, 1205; C. Kashima, N. Yoshihara, S. Shirai *Heterocycles*, 1981, 16, 145; A.S.R. Anjaneyulu, G.S. Rani, K.G. Annapurna, U. V. Mallavadhani, Y.L.N. Murthy *Indian J. Chem. Sect B*, 1995, 34, 933; R.P. Barnes, A.S. Spriggs, *J. Am. Chem. Soc.*, 1945, 67, 134; A. Alberola, L. Calvo, A.G. Ortega, M.L. Sábada, M.C. Sañudo, S.G. Granda, E.G. Rodriguez *Heterocycles*, 1999, 51, 2675; X. Wang, J. Tan, K. Grozinger *Tetrahedron Lett.* 2000, 41, 4713; A. R. Katritzky, M. Wang, S. Zhang, M.V. Voronkov *J. Org. Chem.*, 2001, 66, 6787; and J. Bohrisch, M. Pätzel, C. Mügge, J. Liebscher *Synthesis*, 1991, 1153.. Further guidance for synthesizing pyrazoles may be found in J. Elguero in *Comprehensive Heterocyclic Chemistry II*, A.R. Katritzky, C.W. Reees, E.F.V. Scriven., Eds.; Pergamon Press, Oxford, 1996; Vol. 3, p.1.

EXAMPLES

[0147] The following examples are provided by way of illustration only and not by way of limitation. Those of skill in the art will readily recognize a variety of noncritical parameters that could be changed or modified to yield essentially similar results.

[0148] The prodrugs of TABLES 1-13 were synthesized according to the methods described below or illustrated in FIGS. 1-16. Melting points were obtained using an Electrothermal IA9100 series digital melting point apparatus. All Melting points are uncorrected. Elemental analysis was performed by Desert Analytics, Tuscon, AZ. NMR spectra were obtained on a 300 MHz Varian Mercury system. Microwave reactions were carried out in the Personal Chemistry, SmithCreator microwave. LC-MS was performed on a Waters Micromass ZQ instrument with electrospray ionization. The HPLC component was a Waters Model 2690 Separation module coupled to a Waters Model 996 photodiode array detector at 254 nm wavelength. The specific LC-MS method used to analyze particular prodrugs, indicated for each prodrug in parentheses, are provided below:

Method W

[0149] This method utilized a 2.1x250 mm 5 μM C-18 Altima reversed phase column (Alltech) with a flow rate of 0.25 mL/min and a gradient of 5-85% acetonitrile with water containing 0.1% trifluoroacetic acid over 36 min. The gradient then ramps to 100% acetonitrile over 0.5 min and continues at 100% acetonitrile for 3.5 min.

Method X

[0150] This method utilized a 2.1x250 mm 5 μM C-18 Altima reversed phase column (Alltech) with a flow rate of 0.25 mL/min and a gradient of 5-85% acetonitrile with water containing 0.1% trifluoroacetic acid over 15 min. The gradient then ramps to 100% acetonitrile over 0.5 min and continues at 100% acetonitrile for 2.5 min.

Method Y

[0151] This method utilized a 2.1x150 mm Agilent Zorbax 5 μM C-18 reversed phase column with a flow rate of 0.3 mL/min and a gradient of 10-100% acetonitrile with water containing 0.1% trifluoroacetic acid over 16 min, then continuing for 2 min with 100% acetonitrile.

Method Y1

[0152] This method utilized a 2.1x150 mm Agilent Zorbax 5 μM C-18 reversed phase column with a flow rate of 0.3 mL/min and a gradient of 5-100% acetonitrile with water containing 0.05% formic acid over 15 min, then continuing for 5 min with 100% acetonitrile.

Method Z

[0153] This method utilized a 2.1x5 mm Agilent Zorbax 5 μM C-18 reversed phase column with a flow rate of 0.5 mL/min and a gradient of 5-100% acetonitrile with water containing 0.1% trifluoroacetic acid over 8 min, then continuing for 2 min with 100% acetonitrile.

Method A

[0154] LC-MS was performed on a Waters Micromass ZMD instrument with electrospray ionization. This method utilized a 2.1x5 mm Agilent Zorbax 5 μM C-18 reversed phase column with a flow rate of 0.3 mL/min and a gradient of 10-100% acetonitrile with water containing 0.05% formic acid over 10 min, then continuing for 8 min with 100% acetonitrile.

Method B

[0155] This method utilized a 2.1x5 mm Agilent Zorbax 5 μM C-18 reversed phase column with a flow rate of 0.8 mL/min and a gradient of 5-95% acetonitrile with water containing 0.05% formic acid over 5 min, then continuing for 2 min with 95% acetonitrile.

Phosphonate Containing Prodrugs

[0156] Phosphonate containing compounds of the invention, which may be used as prodrugs, can be synthesized using the general synthetic schemes described in Figs. 1 and 2. Syntheses of phosphonate containing prodrugs are provided below.

Synthesis of 2,2-dichloro-2-(diethoxyphosphonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide

[0157] Reference may be made to Figure 1 for illustration of the following synthesis descriptions. Fig. 3 shows an alternative synthetic scheme to prepare the final products. Diethylphosphonoacetic acid (5.6 g, 28.6 mmol) in methylene chloride (CH_2Cl_2, 50 mL) was treated with oxalyl chloride (3.7 mL, 42.9 mmol) followed by several drops of N,N-dimethylformamide (DMF). The reaction stirred at room temperature for 2 h and then the solvent was removed under vacuum to yield diethylphosphonoacetyl. Sulfuryl chloride (9.6 mL) was carefully added to the acid chloride, resulting in immediate evolution of gas. Then a catalytic amount of aluminum chloride was added. The mixture was heated at 80 °C for 3.5 h. The mixture was cooled and then distilled at approximately 1.3 mm Hg to give 2,2-dichloro-2-(diethoxyphosphonyl)acetyl chloride chloride (**203**, wherein X=Cl, R^{18}=R^{19}=Et) as a viscous colorless liquid (3.95 g, b.p. 95-110 °C).

[0158] 3-Ethynylaniline (**201**, wherein W=CH; 1.64 g, 14 mmol) was dissolved in methylene chloride (10 mL) with triethylamine (Et_3N, 2.56 mL, 18.2 mmol). The solution was cooled to 4 °C under nitrogen and then a solution of 2,2-dichloro-2-(diethoxyphosphonyl)acetyl chloride (**203**, wherein X=Cl, R^{18}=R^{19}=Et; 3.95 g, 14 mmol) in methylene chloride (10 mL) was added dropwise. The reaction was allowed to warm to room temperature overnight with stirring. The reaction mixture was washed with 10% aqueous hydrochloric acid, water and saturated aqueous sodium

bicarbonate. The organic phase was then dried over anhydrous sodium sulfate, filtered, and the filtrate concentrated under vacuum to afford the crude product, 1-[2',2'-dichloro-2'-(diethoxyphosphonyl) acetylamino]-3-ethynyl benzene (**205**, wherein W=CH, X=Cl, R^{18}=R^{19}=Et), as a beige solid (4.11 g) which was used in the next step without further purification; MW=364 confirmed by LC-MS, t_r= 14.31 min (**Method Y**) MH^+=362-366.

[0159] 1-[2',2'-Dichloro-2'-(diethoxyphosphonyl)acetylamino]-3-ethynyl benzene (**205**, wherein W=CH, X=Cl, R^{18}=R^{19}=Et; 0.36 g, 1 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) and then treated with 2,6-dichloro-N-hydroxybenzenecarboximidoyl chloride (**207**, where inR^2=R^6=Cl; 0.23 g, 1 mmol) and triethylamine (0.26 mL, 1.3 mmol). After stirring at room temperature for 15 min, the reaction was heated at reflux for 4 h. The mixture was then cooled to room temperature and diluted with ethyl acetate. The organic solution was washed with brine and then dried over anhydrous sodium sulfate, filtered, and the filtrate concentrated under vacuum. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 25% ethyl acetate in hexanes to give 2,2-dichloro-2-(diethoxyphosphonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide (**209**, wherein W=CH, X=Cl, R^{18}=R^{19}=Et, R^2=R^6=Cl) as a white solid (103 mg); MW=552 confirmed by LC-MS, t_r= 17.25 min (**Method Y**) MH^+=550-554.

Synthesis of 2,2-dichloro-2-(dihydroxyphosphonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide

[0160] 2,2-Dichloro-2-(diethoxyphosphonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide (**209**, wherein W=CH, X=Cl, R^{18}=R^{19}=Et, R^2=R^6=Cl; 254 mg) was dissolved in anhydrous methylene chloride (1 mL). Then, trimethylsilyl bromide (1.0 mL, 7.6 mmol, Aldrich) was added. The reaction stirred for 27 h at room temperature. The volatiles were removed under vacuum to give a pale yellow foam which was dissolved in methanol:water (1:1) and shaken for 30 min. The mixture was filtered through Celite and the filter cake was washed with ethyl acetate. The filtrate was washed with brine, dried over anhydrous sodium sulfate, filtered and the filtrate concentrated under vacuum to give the 2,2-dichloro-2-(dihydroxyphosphonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide (**211**, wherein W=CH, X=Cl, R^2=R^6=Cl) as a pale yellow solid (59 mg); MW=496 confirmed by LC-MS, t_r= 10.15 min (**Method Y**) MH^+=494-500

[0161] The following prodrugs were made by similar methods as those described above and/or in Figures 1-3.

[0162] **Cpd. 1:** 2'-chloro-2'-(diethoxyphosphonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=516 confirmed by LC-MS, t_r= 14.47 min (**Method Y**) MH^+=514-518

[0163] **Cpd. 2:** 2'-chloro-2'-(diethoxyphosphonyl)-2-fluoro-N-[3-[3-(2,6-dichlorophenyl)- 5-isoxazoyl]phenyl] acetamide; MW=534 confirmed by LC-MS, t_r= 15.52 min (**Method Y**) MH^+=534-537

[0164] **Cpd. 3:** 2'-(diethoxyphosphonyl)- 2',2'-difluoro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=519 confirmed by LC-MS, t_r= 15.27 min (**Method Y**) MH^+=517-521

[0165] **Cpd. 4:** 2',2'-dichloro-2'-(diisopropoxyphosphonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=580 confirmed by LC-MS, t_r= 17.22 min (**Method Y**) MH^+=578-582

[0166] **Cpd. 5:** 2',2'-dichloro-2'-(diethoxyphosphonyl)-N-[3-[3-(2-trifluoromethylphenyl)-5-isoxazoyl]phenyl] acetamide; MW=551 confirmed by LC-MS, t_r= 15.67 min (**Method Y**)

[0167] **Cpd. 6:** 2',2'-dichloro-2'-(diethoxyphosphonyl)-N-[3-[3-(2-fluoro-6-trifluoromethylphenyl)-5-isoxazoyl]phenyl] acetamide; MW=569 confirmed by LC-MS, t_r= 15.64 min (**Method Y**) MH^+=567-571

Ester Containing Prodrugs

[0168] Ester containing compounds of the invention, which may be used as prodrugs, can be synthesized using the general synthetic schemes described in Figs. 5 and 6. Syntheses of phosphonate containing prodrugs are provided below.

Synthesis of 2',2'-dichloro-2'-(t-butoxycarbonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl]acetamide

[0169] Reference may be made to Figure 4 for illustration of the following synthesis description. Mono-t-butyl malonate (Aldrich, 10 g, 62.5 mmol) was dissolved in methylene chloride (40 mL) and treated with oxalyl chloride (8.8 mL, 84 mmol) followed by several drops of N,N-dimethylformamide. After 80 min the reaction was concentrated under vacuum to yield the malonyl acid chloride t-butyl ester. The acid chloride was treated with sulfuryl chloride (23 mL) and a catalytic amount of aluminum chloride. The mixture was heated for 3.5 h at 80 °C, whereupon NMR analysis showed complete consumption of starting material. The reaction was distilled at 1.3 mm Hg to give 5.73 g of 2-(t-butoxycarbonyl)-2,2-dichloroacetyl chloride (**603**, wherein R^{16}=*t*-butyl; b.p. 52-70 °C).

[0170] 3-Ethynylaniline (**601**, wherein W=CH; 2.72 g, 23.3 mmol) was dissolved in methylene chloride (10 mL) with triethylamine (4.25 mL, 30.3 mmol). The solution was cooled to 4 °C under nitrogen and then a solution of 2-(t-butoxycarbonyl)-2,2-dichloroacetyl chloride (**603**, wherein R^{16}=*t*-butyl; 5.73 g, 23.3 mmol) in methylene chloride (20 mL) was added dropwise. The reaction was allowed to warm to room temperature overnight. The reaction mixture was washed with saturated aqueous sodium bicarbonate and brine. The reaction was then dried over anhydrous sodium sulfate, filtered, and the filtrate concentrated under vacuum. The crude product was purified by flash column chromatography, on silica gel, eluting with 20% ethyl acetate in hexanes to afford the product, 1-[2'-(t-butoxycarbonyl)-2',2'-dichloroacetylamino]-3-ethynylbenzene (**605**, wherein W=CH, X=Cl, R^{16}=*t*-butyl), as an amber oil. Crystallization from hexanes and ethyl acetate gave brown crystals (3.07 g).

[0171] 1-[2'-(t-Butoxycarbonyl)-2',2'-dichloroacetylamino]-3-ethynylbenzene (**605**, wherein W=CH, X=Cl, R^{16}=*t*-butyl; 0.70 g, 2.13 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) and then treated with 2,6-dichloro-N-hydroxybenzenecarboximidoyl chloride (**607**, wherein R^2=R^6=Cl; 0.48 g, 2.13 mmol) and triethylamine (0.40 mL, 2.8 mmol) to generate the corresponding nitrile oxide *in situ*. After stirring at room temperature for 15 min, the reaction was heated at reflux for 5.5 h, during which time a [3+2] cycloaddition reaction occurred. The mixture was then cooled to room temperature and diluted with ethyl acetate. The organic solution was washed with brine and then dried over anhydrous sodium sulfate, filtered, and the filtrate concentrated under vacuum. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 20% ethyl acetate in hexanes to give 2',2'-dichloro-2'-(t-butoxycarbonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl]acetamide (**609**, wherein W=CH, X=Cl, R^2=R^6=Cl, R^{16}=*t*-butyl) as a white solid (426 mg); MW=516 confirmed by LC-MS, t_r= 15.40 min (**Method A**) MH^+=514-518.

Synthesis of 2',2'-dichloro-2'-(isopropoxycarbonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide

[0172] Reference may be made to Figure 6 for illustration of the following synthesis description. Meldrum's acid (8.0 g, 55.6 mmol) and isopropanol (3.34 g, 55.6 mmol) were heated at reflux in acetonitrile (CH_3N, ACN, 30 mL) for 24 h. The reaction was concentrated under vacuum to yield mono-isopropyl malonate, which was used directly for the next step.

[0173] The mono-isopropyl malonate, prepared above (55.6 mmol) was dissolved in methylene chloride (40 mL) and then treated with oxalyl chloride (7.77 mL, 89 mmol) and several drops of N,N-dimethylformamide. After 1.5 h the reaction was concentrated under vacuum and

then treated with sulfuryl chloride (20 mL) followed by a catalytic amount of aluminum chloride. The reaction was heated at 80 °C for 4 h, where upon NMR revealed the starting material was completely consumed. The mixture was cooled and then distilled at approximately 1.3 mm Hg to give 2-(isopropoxycarbonyl)-2,2-dichloroacetyl chloride **803** as a clear liquid (5.67 g. b.p. 55 °C).

[0174] 3-Ethynylaniline **801** (2.86 g, 24.4 mmol) was dissolved in methylene chloride (40 mL) with triethylamine (4.46 mL, 31.7 mmol). The solution was cooled to 4 °C under nitrogen and then a solution of 2-(isopropoxycarbonyl)-2,2-dichloroacetyl chloride **803** (5.67 g, 24.4 mmol) in methylene chloride (20 mL) was added dropwise. The reaction was allowed to warm to room temperature overnight. The reaction mixture was washed with 10% aqueous hydrochloric acid, water and saturated aqueous sodium bicarbonate. The reaction was then dried over anhydrous sodium sulfate, filtered, and the filtrate concentrated under vacuum. The crude product was purified by flash column chromatography, on silica gel, eluting with 20% ethyl acetate in hexanes to afford the product, 1-[2'-(isopropoxycarbonyl)-2',2'-dichloroacetylamino]-3-ethynylbenzene **805**, as an oil which solidified upon standing; MW=314 confirmed by LC-MS, t_r= 16.27 min (**Method A**) MH^+=312-316.

[0175] 1-[2'-(Isopropoxycarbonyl)-2',2'-dichloroacetylamino]-3-ethynylbenzene **805** (0.27 g, 0.86 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) and treated with 2,6-dichloro-N-hydroxybenzenecarboximidoyl chloride **807** (0.19 g, 0.86 mmol) and triethylamine (0.15 mL) to generate the corresponding nitrile oxide *in situ*. The mixture was stirred at room temperature for 30 min, then heated to reflux for 5 h during which time a [3+2] cycloaddition reaction occurred. The reaction was cooled, diluted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered and the filtrate concentrated under vacuum. The crude product was purified by flash column chromatography, on silica gel, eluting with 20% ethyl acetate in hexanes to give 2',2'-dichloro-2'-(isopropoxycarbonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide **809** as a white solid; MW=502 confirmed by LC-MS, t_r= 18.82 min (**Method Y**) MH^+=500-504.

[0176] The following prodrugs were made by similar methods as those described above and/or in Figures 4-7. FIGS. 4 and 5 show alternative synthetic approaches to prepare prodrugs of the invention. Additionaly, the teachings of Page, P.C.B.; Moore, J.P.G.; Mansfield, I.; McKenzie, M.J.; Bowler, W.B.; Gallagher, J.A. Tetrahedron. 57, 1837 (2001) provide various methods to prepare starting materials for the prodrugs.

[0177] **Cpd. 8:** 2',2'-dichloro-2'-(1S-ethoxycarbonyl-1-methylmethyleneoxycarbonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=560 confirmed by LC-MS, t_r= 16.92 min (**Method Y**) MH^+=558-56

[0178] **Cpd. 9:** 2',2'-dichloro-2'-[(1S)-endo-borneyloxycarbonyl]-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=593 confirmed by LC-MS, t_r= 14.62 min (**Method Y**) MH^+=591-595

[0179] **Cpd. 1008:** 2',2'-dichloro-2'-(1-adamantyloxycarbonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=594 confirmed by LC-MS, t_r= 14.77 min (**Method A**) MH^+=592-596

[0180] **Cpd. 11:** 2',2'-dichloro-2'-[(1R, 2S, 5R)-menthyloxycarbonyl]-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=598 confirmed by LC-MS, t_r= 15.12 min (**Method A**) MH^+=596-600

[0181] **Cpd. 12:** 2',2'-dichloro-2'-(sec-butoxycarbonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=516 confirmed by LC-MS, t_r= 15.78 min (**Method Y**) MH^+=514-518

[0182] **Cpd. 13:** 2',2'-dichloro-2'-(cyclohexyloxycarbonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=542 confirmed by LC-MS, t_r= 16.20 min (**Method A**) MH^+=540-544

[0183] **Cpd. 14:** (2',2'-dichloro-2'-(neopentyloxycarbonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=530 confirmed by LC-MS, t_r= 15.78 min (**Method A**) MH^+=528-532

[0184] **Cpd. 15:** (2',2'-dichloro-2'-(t-butoxycarbonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=516 confirmed by LC-MS, t_r= 15.40 min (**Method A**) MH^+=514-518

[0185] **Cpd. 16:** 2',2'-dichloro-2'-(isopropoxycarbonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=502 confirmed by LC-MS, t_r= 19.11 min (**Method Y**) MH^+=500-504

[0186] **Cpd. 17:** 2',2'-dichloro-2'-(benzyloxycarbonyl)-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=550 confirmed by LC-MS, t_r= 19.23 min (**Method Y**) MH^+=548-552

[0187] **Cpd. 18:** 2',2'-dichloro-2'-(methoxycarbonyl)-N-[2-[3-(2,6-dichlorophenyl)-5-isoxazoyl]phenyl] acetamide; MW=474 confirmed by LC-MS, t_r= 17.00 min (**Method Y**) MH^+=472-476

[0188] **Cpd. 505:** 2',2'-dichloro-2'-(t-butoxycarbonyl)-N-[2-[3-(2,6-dichlorophenyl)-5-isoxazoyl]-(4-pyridyl)] acetamide; MW=518 confirmed by LC-MS, t_r= 17.04 min (**Method Y**) MH^+=516-520

[0189] **Cpd. 25:** 2',2'-dichloro-2'-(t-butoxycarbonyl)-N-[3-[3-(2-chloro-6-methoxyphenyl)-5-isoxazoyl]phenyl] acetamide; MW=511 confirmed by LC-MS, t_r= 17.02 min (**Method Y**) MH^+=509-513

[0190] **Cpd. 26:** 2',2'-dichloro-2'-(methoxycarbonyl)-N-[3-[3-(2-cyclopropyl-6-trifluoromethylphenyl)-5-isoxazoyl]phenyl] acetamide; MW=513 confirmed by LC-MS, t_r= 18.06 min (**Method Y**) MH^+=511-515

[0191] **Cpd. 27:** 2',2'-dichloro-2'-(methoxycarbonyl)-N-[3-[3-(2-chloro-6-methoxyphenyl)-5-isoxazoyl]phenyl] acetamide; MW=526 confirmed by LC-MS, t_r= 16.70 min (**Method Y**) MH^+=524-528

[0192] **Cpd. 28:** 2',2'-dichloro-2'-(methoxycarbonyl)-N-[3-[3-(6-chloro-2-dimethylamino-3-pyridine-1-yl)-5-isoxazoyl]phenyl] acetamide; MW=483 confirmed by LC-MS, t_r= 14.49 min (**Method Y**) MH^+=481-485

[0193] **Cpd. 29:** 2',2'-dichloro-2'-(methoxycarbonyl)-N-[3-[3-(2-trifluoromethylphenyl)-5-isoxazoyl]phenyl] acetamide; MW=473 confirmed by LC-MS, t_r= 15.88 min (**Method Y**) MH^+=471-475

[0194] **Cpd. 30:** 2',2'-dichloro-2'-(methoxycarbonyl)-N-[3-[3-(2-fluoro-6-trifluoromethylphenyl)-5-isoxazoyl]phenyl] acetamide; MW=491 confirmed by LC-MS, t_r= 17.21 min (**Method Y**) MH^+=489-493

Dioxolenone Containing Prodrugs

[0195] Dioxolenone containing compounds of the invention, which may be used as prodrugs, can be synthesized using general procedures similar to the specific examples provided below.

Synthesis of 2,2-Dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]]-N-[(5-methyl-1,3-dioxolene-2-one-4-yl)methylene] Acetamide

[0196] To a solution of 4,5-dimethyl-1,3-dioxolene-2-one (TCI, 10 g, 88 mmol) and N-bromosuccinimide (Fluka, 15.69 g, 88 mmol) in carbon tetrachloride (250 mL) was added benzoyl peroxide (Acros, 500 mg, 2.1 mmol). The reaction mixture was then refluxed for 2.5 h after which time the volatiles were evaporated under vacuum. The resulting residue was triturated with some carbon tetrachloride, filtered and the solid cake was washed with carbon tetrachloride. The filtrate volatiles were removed under vacuum and the yellow oily residue was

distilled under vacuum (2-5 torr) to give 4-bromomethyl-5-methyl-1,3-dioxolene-2-one **903** (8.35 g, b.p. 94-98 °C, 49%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 4.21 (s, 2H), 2.17 (s, 3H).

[0197] A mixture of 3-(2,6-dichlorophenyl)-5-(3-aminophenyl)isoxazole **401** (117 mg, 0.4 mmol), 4-bromomethyl-5-methyl-1,3-dioxol-2-one **903** (Sakamoto, F. et al. *Chem. Pharm. Bull.* **1984**, *32*, 2241) (85 mg, 0.44 mmol), sodium bicarbonate (40 mg, 0.5 mmol) in acetonitrile (5 mL) was allowed to reflux for 3 h. The reaction mixture was then concentrated under vacuum, and the resulting residue was partitioned between ethyl acetate (30 mL) and brine (30 mL). The separated organic layer was washed with brine (2x20 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated under vacuum. Column chromatography (neat methylene chloride) provided N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]]-N-[(5-methyl-1,3-dioxolene-2-one-4-yl)methylene]aniline **905** (65 mg, 41%). ^{1}H NMR ($CDCl_3$) δ 7.47 (d, *J=1.7 Hz*, 1H), 7.45 (d, *J=0.6 Hz*, 1H), 7.38 (d, *J=6.9 Hz*, 1H), 7.34 (t, *J=6.9 Hz*, 1H), 7.25 (dt, *J=7.7, 1.4 Hz*, 1H), 7.16 (t, *J=2.0 Hz*, 1H), 6.74 (dq, *J=8.0, 1.1 Hz*, 1H), 6.61 (s, 1H), 4.22 (d, *J=0.6 Hz*, 1H), 2.23 (s, 3H). MS (*m/z*): 417 (MH^+).

[0198] To an ice-cold solution of N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]]-N-[(5-methyl-1,3-dioxolene-2-one-4-yl)methylene]aniline **905** (65 mg, 0.2 mmol) in methylene chloride (2 mL) was added, dropwise, triethylamine (25 µl, 18 mg, 0.2 mmol), followed by dichloroacetyl chloride (17 µL, 26 mg, 0.2 mmol). The resulting reaction mixture was allowed to warm up to room temperature over 90 min. Methylene chloride (10 mL) and saturated ammonium chloride solution were then added to the reaction mixture. The layers were separated and the organic layer was washed with saturated ammonium chloride solution (1x20 mL) and dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated under vacuum. Column chromatography, on silica gel, eluting with neat methylene chloride, provided 2,2-dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]phenyl]-N-[(5-methyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide **907** (51 mg, 62%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.00 (dq, *J=8.0, 1.1 Hz*, 1H), 7.84 (t, *J=1.7 Hz*, 1H), 7.70 (t, *J=7.8 Hz*, 1H), 7.50-7.37 (m, 4H), 6.76 (s, 1H), 5.91 (s, 1H), 4.72 (br s, 2H), 2.25 (s, 3H). MS (*m/z*): 527 (MH^+).

Synthesis of 2,2-Dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-isoxazol-5'-yl]]phenyl]-N-[(5-t-butyl-1,3-dioxolene-2-one-4-yl)methylene] Acetamide

[0199] Reference may be made to Figure 9 for illustration of the following synthesis description. By the procedure of Mottet [Mottet, C. *et al. J. Org. Chem.* **1999**, *64*, 1380] A solution of ethyl 4,4-dimethyl-3-oxo-pentanoate (40 mL, 38.7 g, 225 mmol) and benzyl alcohol (28

mL, 29.3 g, 270 mmol) in toluene (1.5 L) was heated so the toluene refluxed halfway up the refluxing tube (oil bath temperature 120 °C) overnight. After being cooled down to room temperature, the volatiles were evaporated under vacuum and the resulting crude oil was purified by column chromatography, on silica gel, eluting with neat methylene chloride. The desired product, benzyl 4,4-dimethyl-3-oxo-pentanoate, was obtained as a colorless oil (39.5 g, 75%). ^{1}H NMR ($CDCl_3$) δ 7.39-7.37 (m, 5H), 5.20 (s, 2H), 3.64 (d, 2H), 1.20 (s, 9H).

[0200] A cold solution (ice bath) of benzyl 4,4-dimethyl-3-oxo-pentanoate (14.23 g, 61 mmol) in acetonitrile (500 mL) was added 4-acetamidobenzenesulfonyl azide (14.60 g, 61 mmol) and triethylamine (25.4 mL, 18.4 g, 182 mmol). The yellow reaction mixture was allowed to stir at 0 °C for 30 min, then at room temperature overnight. The reaction mixture was concentrated under vacuum and the resulting solid white residue was triturated with ethyl ether/hexanes (2:1, 3x200 mL) and filtered. The filtrate was concentrated under vacuum and purified by column chromatography, on silica gel, eluting with 15% ethyl acetate/hexanes, to provide benzyl 2-diazo-4,4-dimethyl-3-oxo-pentanoate (15.66 g, 99%). ^{1}H NMR ($CDCl_3$) δ 7.39-7.37 (m, 5H), 5.27 (s, 2H), 1.33 (s, 9H).

[0201] To a solution of benzyl 2-diazo-4,4-dimethyl-3-oxo-pentanoate (15.66 g, 60.2 mmol) in tetrahydrofuran/water (2:1, 375 mL) was added rhodium (II) acetate dimer ($Rh_2(OAc)_4$, Aldrich, 525 mg, 1.2 mmol) in three portions (3x175 mg every 2 hrs) and the resultant green solution was heated at reflux overnight. The reaction mixture was concentrated under vacuum and the residue extracted with ethyl acetate (2x300 mL). The combined extracts were washed with brine (2x125 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated under vacuum to give 14.87 g of the crude yellow oil. Column chromatography, on silica gel, eluting with 10% ethyl acetate/hexanes, provided benzyl 4,4-dimethyl-2-hydroxy-3-oxo-pentanoate (7.5 g, 50%). ^{1}H NMR ($CDCl_3$) δ 7.39-7.36 (m, 5H), 5.23 (d, *J=2.7 Hz*, 2H), 5.09 (d, *J=8.3 Hz*, 2H), 3.97 (d, *J=8.3 Hz*, 2H), 1.20 (s, 9H).

[0202] By the procedure of Sun [Sun, C.-Q. *et al. Tet. Lett.* **2002**, *43*, 1161], an ice-cold solution of benzyl 4,4-dimethyl-2-hydroxy-3-oxo-pentanoate (3.8 g, 15.2 mmol) in tetrahydrofuran (75 mL) was treated with carbonyldiimidazole (CDI, 4.93 g, 30.4 mmol) followed by diisopropylethylamine (DIEA, 110 µL, 81 mg, 0.6 mmol). The reaction mixture was allowed to stir overnight without removal of the cold bath. The resulting reaction mixture was concentrated under vacuum and the residue partitioned between ethyl acetate (100 mL) and 5% potassium hydrogen sulfate solution (100 mL). The separated organic layer was washed with 5% potassium hydrogen sulfate solution (1x100 mL), water (2x100 mL), brine (2x100 mL), dried over anhydrous

magnesium sulfate, filtered and the filtrate concentrated under vacuum to give an oily residue. Column chromatography on silica gel, eluting with 10% ethyl acetate/hexanes, provided benzyl 5-*t*-butyl-1,3-dioxolene-2-one-4-carboxylate (2.8 g, 68%). ^{1}H NMR ($CDCl_3$) δ 7.42-7.41 (m, 5H), 5.34 (s, 2H), 1.42 (s, 9H).

[0203] By the procedure of Sun [Sun, C.-Q. *et al. Tet. Lett.* **2002**, *43*, 1161], a mixture of benzyl 5-*t*-butyl-1,3-dioxolene-2-one-4-carboxylate (6.0 g, 21.7 mmol) and $Pd(OH)_2/C$ (270 mg) in absolute ethanol (150 mL) was allowed to mix under hydrogen atmosphere at 18 psi for 1 h. The resulting reaction mixture was filtered through a bed of Celite and the filtrate was concentrated under vacuum to give 5-*t*-butyl-1,3-dioxolene-2-one-4-carboxylic acid (3.8 g, 94%). ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H).

[0204] By the procedure of Sun [Sun, C.-Q. *et al. Tet. Lett.* **2002**, *43*, 1161], an ice-cold solution of 5-*t*-butyl-1,3-dioxolene-2-one-4-carboxylic acid (1.2 g, 6.4 mmol) and N,N-dimethylformamide (70 µL) in methylene chloride (30 mL) was stirred and oxalyl chloride (630 µL, 0.92 g, 7.2 mmol) was added dropwise. The reaction mixture was allowed to stir at 0 °C for 30 min and at room temperature for 45 min before being concentrated and dried under vacuum. The residue containing carbonyl chloride was dissolved in methylene chloride (30 mL), cooled to -78 °C and treated with a solution of tetra-n-butylammonium borohydride (1.83 g, 7.1 mmol) in methylene chloride (30 mL). The reaction mixture was allowed to stir at -78 °C for 1 h. and quenched with 0.1 N hydrochloric acid solution (20 mL). The reaction mixture was allowed to warm up to room temperature after which the volatiles were removed under vacuum. The residue was partitioned between ethyl acetate (60 mL) and water (30 mL). The separated aqueous layer was saturated with sodium chloride and extracted with ethyl acetate (2x50 mL). The combined organic extracts were washed with brine (1x100 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated under vacuum to give an oily residue. Column chromatography, on silica gel, eluting with 40% ethyl acetate/hexanes, provided 5-*t*-butyl-4-hydroxymethyl-1,3-dioxolene-2-one (0.77 g, 69%). ^{1}H NMR ($CDCl_3$) δ 4.53 (d, *J=4.1 Hz*, 2H), 1.34 (s, 9H).

[0205] By the procedure of Sun [Sun, C.-Q. *et al. Tet. Lett.* **2002**, *43*, 1161], an ice-cold solution of 5-*t*-butyl-4-hydroxymethyl-1,3-dioxolene-2-one (0.77 g, 4.5 mmol) and methylene chloride (25 mL) was stirred and carbon tetrabromide (1.78 g, 5.4 mmol) and triphenylphosphine (1.30 g, 5.0 mmol) were added slowly. The yellow reaction mixture was allowed to stir at 0 °C for 35 min before being concentrated under vacuum. The yellow oily residue was adsorbed onto Celite and purified on a silica gel column, eluting with 10% ethyl acetate/hexanes, to provide 4-

bromomethyl-5-*t*-butyl-1,3-dioxolene-2-one **1003** (0.83 g, 79%). ^{1}H NMR ($CDCl_3$) δ 4.32 (s, 2H), 1.34 (s, 9H).

[0206] A mixture of 3-(2,6-dichlorophenyl)-5-(3-aminophenyl)isoxazole **401** (102 mg, 0.3 mmol), 4-bromomethyl-5-*t*-butyl-1,3-dioxolene-2-one **1003** (Sakamoto, F. et al. *Chem. Pharm. Bull.* **1984**, *32*, 2241) (87 mg, 0.4 mmol) and sodium bicarbonate (31 mg, 0.4 mmol) in acetonitrile (5 mL) was allowed to reflux under nitrogen atmosphere for 3 h. The reaction mixture was then concentrated under vacuum, and the resulting off-white residue was chromatographed, on silica gel, eluting with neat methylene chloride, to provide N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-N-[5-t-butyl-1,3-dioxolene-2-one-4-yl)methylene]aniline **1005** (125 mg, 81%). ^{1}H NMR ($CDCl_3$) δ 7.47 (d, *J=1.7 Hz*, 1H), 7.45 (d, *J=0.6 Hz*, 1H), 7.39-7.32 (m, 2H), 7.25 (dt, *J=6.6, 1.1 Hz*, 1H), 7.19 (t, *J=1.8 Hz*, 1H), 6.79 (ddd, *J=8.0, 2.5, 1.1 Hz*, 1H), 6.61 (s, 1H), 4.31 (s, 2H), 1.38 (s, 9H). MS (*m/z*): 459 (MH^+) confirmed by LC-MS, t_r= 16.98 min (**Method Y**).

[0207] To an ice-cold solution of N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazolyl]phenyl]-N-[5-t-butyl-1,3-dioxolene-2-one-4-yl)methylene]aniline **1005** (120 mg, 0.3 mmol) in dichloromethane (3 mL) was added dropwise diisopropylethylamine (55 µl, 41 mg, 0.3 mmol) followed by dichloroacetyl chloride (28 µL, 43 mg, 0.3 mmol). The reaction mixture was allowed to warm up to room temperature under nitrogen atmosphere over 2.5 h. Since the starting aniline was still present, additional diisopropylethylamine (50 µL, 37 mg, 0.3 mmol) and dichloroacetyl chloride (15 µL, 23 mg, 0.16 mmol) were added and the reaction mixture was allowed to stir overnight. Methylene chloride (20 mL) and saturated ammonium chloride solution (20 mL) were then added to the reaction mixture. The layers were separated and the organic layer was washed with saturated ammonium chloride solution (1x20 mL), brine (1x20 mL), dried over anhydrous magnesium sulfate, filtered and the filtrate concentrated under vacuum. Column chromatography, on silica gel, eluting with neat methylene chloride provided 2,2-dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]phenyl]-N-[(5-*t*-butyl-1,3-dioxolene-2-one-4-yl)methylene]acetamide **1007** (108 mg, 73%). ^{1}H NMR ($CDCl_3$) δ 8.00 (dt, *J=8.0, 1.1 Hz*, 1H), 7.82 (t, *J=187 Hz*, 1H), 7.69 (t, *J=7.9 Hz*, 1H), 7.50-7.36 (m, 4H), 6.74 (s, 1H), 5.88 (s, 1H), 5.13-4.72 (br d, 2H), 1.26 (s, 9H). MS (*m/z*): 569 (MH^+) confirmed by LC-MS, t_r= 16.88 min (**Method Y**).

[0208] The following prodrugs were made by similar methods as those described above. FIG. 10 is an alternative synthesis to prepare prodrugs on the invention.

[0209] Cpd. 31. 2,2-dichloro-N-[3'-[3'-(2'-chloro-6'-methoxyphenyl)-5'-isoxazoyl]phenyl]-N-[(5-methyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide; MW=524 confirmed by LC-MS, t_r= 15.00 min (**Method Y**) MH^+=522-526

[0210] Cpd. 32. 2,2-dichloro-N-[3'-[3'-(2',6'-dichloro-3'-pyridine-1-yl)-5'-isoxazoyl]phenyl]-N-[(5-methyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide; MW=527 confirmed by LC-MS, t_r= 14.25 min (**Method Y**) MH^+=525-529

[0211] Cpd. 33. 2,2-dichloro-N-[3'-[3'-(6'-chloro-2'-dimethylamino-3'-pyridine-1-yl)-5'-isoxazoyl]phenyl]-N-[(5-methyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide; MW=537 confirmed by LC-MS, t_r= 13.00 min (**Method Y**) MH^+=535-539

[0212] Cpd. 34. 2,2-dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]phenyl]-N-[(5-isopropyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide; MW=556 confirmed by LC-MS, t_r= 16.49 min (**Method Y**) MH^+=554-558

[0213] Cpd. 35. 2,2-dichloro-N-[3'-[3'-(6'-chloro-2'-dimethylamino-3'-pyridine-1-yl)-5'-isoxazoyl]phenyl]-N-[(5-isopropyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide; MW=566 confirmed by LC-MS, t_r= 7.18 min (**Method Z**) MH^+=564-568

[0214] Cpd. 36. 2,2-dichloro-N-[3'-[3'-(2'-chloro-6'-t-butoxycarbonylphenyl)-5'-isoxazoyl]phenyl]-N-[(5-isopropyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide; MW=622 confirmed by LC-MS, t_r= 18.50 min (**Method Y**) MH^+=620-624

[0215] Cpd. 37. 2,2-dichloro-N-[3'-[3'-(2'-chloro-6'-methoxyphenyl)-5'-isoxazoyl]phenyl]-N-[(5-isopropyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide; MW=553 confirmed by LC-MS, t_r= 16.46 min (**Method Y**) MH^+=551-554

[0216] Cpd. 38. 2,2-dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]phenyl]-N-[(5-n-propyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide; MW=556 confirmed by LC-MS, t_r= 12.45 min (**Method X**) MH^+=554-558

[0217] Cpd. 39. 2,2-dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]phenyl]-N-[(5-cyclohexyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide; MW=595 confirmed by LC-MS, t_r= 13.28 min (**Method X**) MH^+=593-597

[0218] Cpd. 40. 2,2-dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]phenyl]-N-[(5-ethyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide; MW=542 confirmed by LC-MS, t_r= 12.18 min (**Method X**) MH^+=540-544

[0219] Cpd. 41. 2,2-dichloro-N-[2'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl](4-pyridyl)]-N-[(5-methyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide

[0220] Cpd. 42. 2,2-dichloro-N-[2'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl](4-pyridyl)]-N-[(5-*i*-propyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide

[0221] Cpd. 1107.2,2-dichloro-N-[2'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl](4-pyridyl)]-N-[(5-*t*-butyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide

[0222] Cpd. 43. 2,2-dichloro-N-[2'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl](4-pyridyl)]-N-[(5-*n*-pentyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide

[0223] Cpd. 44. 2,2-dichloro-N-[3'-[3'-(2',6'-dichlorophenyl)-5'-isoxazoyl]phenyl]-N-[(5-ethoxycarbonyl-1,3-dioxolene-2-one-4-yl)methylene] acetamide; MW=586 confirmed by LC-MS, t_r= 12.10 min (**Method Y**) MH^+=584-588

Synthesis of 2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-(2-(phenylsulfonyl)ethyl)acetamide (See Fig. 23) (Cpd. 1045)

Synthesis of 3-Ethynyl-N-(2-(phenylsulfonyl)ethyl)benzenamine

[0224] 3-Ethynyl aniline (2.53 g, 21.6 mmol) and phenyl vinyl sulfone (4.36 g, 26 mmol) were heated at reflux in ethanol (50 mL) for 136 h. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and brine. The organic layer was separated and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel, eluting with 15:85 ethyl acetate:hexanes to provide 3-ethynyl-N-(2-(phenylsulfonyl)ethyl)benzenamine (1.21 g) as a brown solid. ^1H NMR ($CDCl_3$) δ 7.91 (m, 2H), 7.90-7.54 (m, 3H), 7.10 (t, 1H), 6.87 (d, 1H), 6.61 (br s, 1H), 6.53 (m, 1H) , 3.59 (t, 2H), 3.37 (t, 2H), 3.02 ppm (s, 1H). MW=285 confirmed by LC-MS, t_r= 12.72 min (**Method Y**) MH^+=286.

Synthesis of 2,2-Dichloro-N-(3-ethynylphenyl)-N-(2-(phenylsulfonyl)ethyl)acetamide

[0225] 3-Ethynyl-N-(2-(phenylsulfonyl)ethyl)benzenamine (1.21 g, 4.2 mmol) was dissolved in anhydrous methylene chloride (25 mL) with triethylamine (0.78 mL, 5.5 mmol). The mixture was cooled in an ice-bath under nitrogen, then a solution of dichloroacetyl chloride (0.45 mL, 4.6 mmol) in anhydrous dichloromethane (5 mL) was added dropwise. After the addition was completed the ice-bath was removed and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with methylene chloride and then washed successively with water, 10% hydrochloric acid and saturated sodium bicarbonate solution. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel, eluting with 30:70 ethyl acetate:hexanes to give 2,2-dichloro-N-(3-ethynylphenyl)-N-(2-(phenylsulfonyl)ethyl)acetamide (120 mg) as a yellow oil. ^1H NMR ($CDCl_3$): 7.90 (m, 2H), 7.68 (m, 1H), 7.58 (m, 2H), 7.43 (t, 1H), 7.33 (br s, 1H), 7.26 (m, 1H), 5.74 (s, 1H), 4.04 (t, 2H), 3.42 (t, 2H), 3.22 ppm (s, 1H). MW=396 confirmed by LC-MS, t_r= 13.61 min (**Method Y**) MH^+=394-398.

Synthesis of 2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-(2-(phenylsulfonyl)ethyl)acetamide (Cpd. 1045)

[0226] 2,6-Dichloro-N-hydroxybenzimidoyl chloride (90 mg, 0.40 mmol) and 2,2-dichloro-N-(3-ethynylphenyl)-N-(2-(phenylsulfonyl)ethyl)acetamide (120 mg, 0.21 mmol) were dissolved in anhydrous tetrahydrofuran (20 mL) and triethylamine (0.75 mL, 0.40 mmol). The mixture was stirred at room temperature for 15 min, then heated at reflux for 4h. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed successively with water and brine. The ethyl acetate solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting solid was purified by flash column chromatography on silica gel, eluting with 30:70 ethyl acetate:hexanes to give 2,2-dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-(2-(phenylsulfonyl)ethyl)acetamide (**Cpd. 1045**) as a white solid. ^{1}H NMR ($CDCl_3$): 7.89 (m, 3H), 7.87 (br s, 1H), 7.53-7.40 (m, 4H), 7.44-7.33 (m, 4H), 6.71 (s, 1H), 5.82 (s, 1H), 4.11 (t, 2H), 3.47 ppm (t, 2H). MW=584 confirmed by LC-MS, t_r= 12.13 min (**Method A**) MH^+=582-586.

Synthesis of 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-oxo-3-(pyridin-3-yl)propyl)acetamide (See Fig. 24)(Cpd. 1046)

Synthesis of N-Methoxy-N-methylnicotinamide

[0227] Diisopropylethylamine (33 mL, 190 mmol) was added, dropwise, to a solution of nicotinoyl chloride (8.9 g, 49.9 mmol) and N,O-dimethylhydroxylamine hydrochloride (6.6 g, 67.4 mmol) in anhydrous methylene chloride (120 mL) at 0 °C under nitrogen. The resulting mixture slowly warmed to room temperature overnight. The reaction was then diluted with methylene chloride and washed successively with water and brine. The aqueous layer was diluted with aqueous sodium bicarbonate solution and then extracted with methylene chloride. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel, eluting with 1:99 methanol:methylene chloride to provide N-methoxy-N-methylnicotinamide (6.8 g) as a yellow oil. ^{1}H NMR ($CDCl_3$): 8.93 (br s, 1H), 8.66 (m, 1H), 8.00 (m, 1H), 7.35 (m, 1H), 3.54 (s, 3H), 3.38 ppm (s, 3H).

Synthesis of 1-(Pyridin-3-yl)prop-2-en-1-one

[0228] Vinylmagnesium bromide (1M soln in THF, 24 mL, 24 mmol) was added to a solution of N-methoxy-N-methylnicotinamide (3.3 g, 19.8 mmol) in anhydrous tetrahydrofuran (40 mL) under nitrogen at 0 °C, dropwise and then stirred for an hour at 0 °C. The reaction warmed to

room temperature and then stirred for 80 min. Methanol (10 mL) and acetic anhydride (10 mL) were added to the reaction mixture. The mixture was allowed to stir for 10 min, and then concentrated to a volume of 25 mL. The reaction mixture was washed with water and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed successively with aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure at less than 40 °C. The resulting residue was purified by flash column chromatography on silica gel, eluting with 98:2 methylene chloride:methanol to provide 1-(pyridin-3-yl)prop-2-en-1-one (1.1 g) as a yellow oil.

Synthesis of 3-(2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)-1-(pyridin-3-yl)propan-1-one

[0229] 3-(2,6-Dichlorophenyl)-5-(5-amino-2-pyridyl)isoxazole (503 mg, 1.47 mmol), 1-(pyridin-3-yl)prop-2-en-1-one (550 mg, 4.1 mmol) and triethylamine (0.62 mL, 4.4 mmol) were dissolved in anhydrous acetonitrile (20 mL). The mixture was heated at 70 °C for 27 h. By TLC the reaction was ~50% complete but had not progressed during the last 5 h. The reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in methylene chloride and washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by chromatotron, eluting with 4:96 methanol:methylene chloride twice, to provide 3-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)-1-(pyridin-3-yl)propan-1-one (270 mg) as a yellow oil. ^{1}H NMR ($CDCl_3$): 9.10 (m, 1H), 8.73 (m, 1H), 8.18 (m, 2H), 7.40-7.27 (m, 4H), 6.25 (s, 1H), 6.47 (m, 1H), 5.42 (m, 1H), 3.70 (m, 2H), 3.30 ppm (m, 2H). MW=439 confirmed by LC-MS, t_r= 9.05 min (**Method Y**) MH^+=437-441.

Synthesis of 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-oxo-3-(pyridin-3-yl)propyl)acetamide (Cpd. 1046)

[0230] 3-(2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)-1-(pyridin-3-yl)propan-1-one (600 mg, 1.37 mmol) was dissolved in methylene chloride (10 mL) with triethylamine (381 µL, 2.73 mmol). The solution was cooled on an ice-water bath and then a solution of dichloroacetyl chloride (265 µL, 2.73 mmol) in methylene chloride (1 mL) was added dropwise. The reaction mixture was allowed to stir overnight while warming to room temperature. The solution was washed successively with water and saturated sodium bicarbonate solution, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel, eluting with 2:98 methanol:methylene

chloride to provide 2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-oxo-3-(pyridin-3-yl)propyl)acetamide (**Cpd. 1046, lot 2**, 220 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 9.15 (s, 1H), 8.80 (m, 1H), 8.70 (s, 1H), 8.20 (m, 1H), 8.00 (m, 1H), 7.40-7.20 (m, 3H), 6.00 (s, 1H), 4.30 (m, 2H), 3.40 ppm (m, 2H). MW=550 confirmed by LC-MS, t_r= 12.73 min (**Method Y**) MH^+=548-552.

Synthesis of 4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propanoyl)benzoic Acid (See Fig. 25) (Cpd. 1047)

Synthesis of *tert*-Butyl 4-Formylbenzoate

[0231] 4-Carboxybenzaldehyde (2.0 g, 13.3 mmol), 4-dimethylaminopyridine (0.41 g, 3.33 mmol), di-t-butyl dicarbonate (3.5 g, 16.0 mmol) and t-butanol (15 mL) were combined in dimethylformamide (30 mL) and heated at 50 °C overnight. The mixture was cooled to room temperature, poured into water and extracted with ether. The combined organic layers were washed successively with aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 4:1 hexanes:ethyl acetate to provide *tert*-butyl 4-formylbenzoate (1.42 g) as a colorless oil. ^{1}H NMR ($CDCl_3$): 10.05 (s, 1H), 8.10 (d, 2H), 7.89 (d, 2H), 1.60 ppm (s, 9H).

Synthesis of *tert*-Butyl 4-(1-Hydroxyallyl)benzoate

[0232] Vinylmagnesium bromide (1M soln in THF, 58 mL, 58 mmol) was added to a solution of the above aldehyde (9.88 g, 48 mmol) in anhydrous tetrahydrofuran (80 mL) under nitrogen at -70 °C, dropwise and then stirred for 30 min at -70 °C. The reaction was quenched cold with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate and the combined organic layers were washed brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure at less than 40 °C. The resulting residue was purified by flash column chromatography on silica gel, eluting with 9:1 hexanes:ethyl acetate to provide *tert*-butyl 4-(1-hydroxyallyl)benzoate (7.03 g) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): 7.94 (d, 2H), 7.39 (d, 2H), 6.00 (m, 1H), 5.36 (m, 1H), 5.22-5.18 (m, 2H), 2.22 (br s, 1H), 1.59 ppm (s, 9H).

Synthesis of *tert*-Butyl 4-Acryloylbenzoate

[0233] *tert*-Butyl 4-(1-hydroxyallyl)benzoate (7.03 g, 30.0 mmol), molecular sieves (4Å, powdered, 5.6 g) and pyridinium dichromate (13.6 g, 36 mmol) were combined in methylene chloride (400 mL) and allowed to stir at room temperature for 4 h. The reaction mixture was

filtered through a pad of Celite and the filtrated concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 95:5 hexanes:ethyl acetate to provide *tert*-butyl 4-acryloylbenzoate (1.2 g) as a yellow oil. ^{1}H NMR ($CDCl_3$): 8.07 (d, 2H), 7.93 (d, 2H), 7.12 (m, 1H), 6.43 (m, 1H), 5.97 (m, 1H), 1.60 ppm (s, 9H).

Synthesis of *tert*-Butyl 4-(3-(2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)propanoyl)benzoate

[0234] 3-(2,6-Dichlorophenyl)-5-(5-amino-2-pyridyl)isoxazole (300 mg, 0.88 mmol), *tert*-butyl 4-acryloylbenzoate (225 mg, 0.97 mmol) and triethylamine (0.27 mL, 1.94 mmol) were dissolved in anhydrous acetonitrile (4 mL) in a sealed vial. The mixture was heated at 80 °C overnight. The reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in methylene chloride and washed with brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified first on a plug of silica gel, eluting with 1:9 methanol:methylene chloride and then purified by chromatotron, eluting with 1:1 hexanes:ethyl acetate, to provide *tert*-butyl 4-(3-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)propanoyl)benzoate (78 mg) as a white solid. MW=538 confirmed by LC-MS, t_r= 12.61 min (**Method Y**) MH^+=536-540.

Synthesis of *tert*-Butyl 4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propanoyl)benzoate

[0235] *tert*-Butyl 4-(3-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)propanoyl)benzoate (58 mg, 0.13 mmol) was dissolved in methylene chloride (5 mL) with diisopropylethylamine (23 µL, 0.16 mmol). The solution was cooled on an ice-water bath and then a solution of dichloroacetyl chloride (13 µL, 0.16 mmol) in methylene chloride (1 mL) was added dropwise. The reaction mixture was allowed to stir overnight while warming to room temperature. The solution was washed successively with water and saturated sodium bicarbonate solution, then dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel, eluting with 1:1 hexanes:ethyl acetate to provide *tert*-butyl 4-(3-(2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propanoyl)benzoate (40 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 8.80 (m, 1H), 8.10 (m, 4H), 7.40 (m, 3H), 7.10 (s, 1H), 6.00 (s, 1H), 4.20 (m, 2H), 3.50 (m, 2H), 1.60 ppm (s, 9H). MW=649 confirmed by LC-MS, t_r= 18.03 min (**Method Y**) MH^+=647-651.

Synthesis of 4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propanoyl)benzoic Acid (Cpd. 1047)

[0236] Trifluoroacetic acid (2 mL) was added to a solution of *tert*-butyl 4-(3-(2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propanoyl)benzoate (35 mg, 0.064 mmol) in methylene chloride (2 mL) at 0 °C. The resulting mixture was allowed to stir at 0 °C for 5 hours, then concentrated under reduced pressure. The residue was dissolved in methylene chloride (2 mL) and concentrated under reduced pressure, twice more. And then lyophilized to produce 4-(3-(2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propanoyl)benzoic acid (**Cpd. 1047**, 27 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 8.91 (m, 1H), 8.20 (m, 2H), 8.00 (m, 2H), 7.40 (m, 3H), 7.10 (s, 1H), 6.00 (s, 1H), 4.30 (m, 2H), 3.50 ppm (m, 2H). MW=593 confirmed by LC-MS, t_r= 14.56 min (**Method Y**) MH^+=591-595.

Synthesis of 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-morpholino-3-oxopropyl)acetamide(See Fig. 26) (Cpd. 1048)

Synthesis of 3-(2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)-1-morpholinopropan-1-one

[0237] A mixture of 2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-amine hydrochloride (50 mg, 0.15 mmol) and 4-acryloylmorpholine (22 µL, 0.18 mmol) was heated at 150 °C for 17 h whereupon the LC-MS confirmed the starting material was consumed. The resulting residue was purified by flash column chromatography on silica gel, eluting with 98:2 methylene chloride:methanol to give 3-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)-1-morpholinopropan-1-one (29 mg) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): 8.28 (d, 1H), 7.47 (d, 1H), 7.44 (d, 1H), 7.36 (dd, 1H), 7.20 (d, 1H), 7.04 (s, 1H), 6.52 (dd, 1H), 5.37 (m, 1H), 3.74-3.64 (m, 8H), 3.51-3.46 (m, 2H), 2.67 ppm (t, 1H). MW=447 confirmed by LC-MS, t_r= 8.89 min (**Method Y**) MH^+=445-449.

Synthesis of 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-morpholino-3-oxopropyl)acetamide (Cpd. 1048)

[0238] 3-(2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)-1-morpholinopropan-1-one (25 mg, 0.05 mmol) was dissolved in anhydrous tetrahydrofuran (1 mL) with triethylamine (20 µL, 0.14 mmol). The mixture was cooled in an ice-bath under nitrogen, then a solution of dichloroacetyl chloride (8.1 µL, 0.08 mmol) in anhydrous tetrahydrofuran (0.5 mL) was added dropwise. After the addition was completed the ice-bath was removed and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with methylene chloride

and then washed successively with water, 10% hydrochloric acid and saturated sodium bicarbonate solution. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel, eluting with 98:2 methylene chloride:methanol to give 2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-morpholino-3-oxopropyl)acetamide (**Cpd. 1048**, 17 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 8.85 (d, 1H), 7.94 (d, 1H), 7.50 (d, 1H), 7.47 (d, 1H), 7.41 (d, 1H), 7.39 (m, 1H), 7.14 (s, 1H), 6.02 (br s, 1H), 3.75-3.68 (m, 6H), 3.63-3.60 (m, 2H), 3.56-3.53 (m, 2H), 2.81 ppm (t, 2H). MW=558 confirmed by LC-MS, t_r= 13.41 min (**Method Y**) MH^+=556-560.

[0239] **Cpd. 1045:** 2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-(2-(phenylsulfonyl)ethyl)acetamide; MW= 584 confirmed by LC-MS, t_r= 12.13 min (**Method A**) MH^+=582-586.

[0240] **Cpd. 1049:** Ethyl 2-(4-(3-(2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)acetamido)propanoyl)phenyl)acetate; MW= 633 confirmed by LC-MS, t_r= 12.84 min (**Method A**) MH^+=631-635.

[0241] **Cpd. 1046:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-oxo-3-(pyridin-3-yl)propyl)acetamide; MW= 550 confirmed by LC-MS, t_r= 14.04 min (**Method Y**) MH^+=548-552.

[0242] **Cpd. 1050:** N-(4-Amino-3-oxo-5-phenylpentyl)-2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamide; MW= 592 confirmed by LC-MS, t_r= 11.41 min (**Method A**) MH^+=590-594.

[0243] **Cpd. 1051:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-oxo-3-(piperidin-4-yl)propyl)acetamide; MW= 556 confirmed by LC-MS, t_r= 9.99 min (**Method Y**) MH^+=554-558.

[0244] **Cpd. 1052:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-oxo-3-(pyrrolidin-2-yl)propyl)acetamide; MW= 542 confirmed by LC-MS, t_r= 10.47 min (**Method Y**) MH^+=540-544.

[0245] **Cpd. 1053:** *tert*-Butyl 3-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propanoyl)piperidine-1-carboxylate; MW= 655 confirmed by LC-MS, t_r= 17.05 min (**Method Y**) MH^+=653-657.

[0246] **Cpd. 1054:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-oxo-3-(piperidin-3-yl)propyl)acetamide; MW= 555 confirmed b y LC-MS, t_r= 10.74 min (**Method Y**) MH^+=553-557.

[0247] **Cpd. 1055:** *tert*-Butyl 4-(4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propanoyl)phenyl)piperazine-1-carboxylate; MW= 733 confirmed by LC-MS, t_r= 17.53 min (**Method Y**) MH^+=731-735.

[0248] **Cpd. 1056:** *tert*-Butyl 4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propanoyl)benzoate; MW= 649 confirmed by LC-MS, t_r= 18.03 min (**Method Y**) MH^+=647-651.

[0249] **Cpd. 1047:** 4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propanoyl)benzoic acid; MW= 593 confirmed by LC-MS, t_r= 14.56 min (**Method Y**) MH^+=591-595.

[0250] **Cpd. 1048:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-morpholino-3-oxopropyl)acetamide; MW= 558 confirmed by LC-MS, t_r= 13.41 min (**Method Y**) MH^+=556-560.

Synthesis of 4-((2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)methyl)-2,6-dimethylphenyl Propylcarbamate (Cpd. 1057)

Synthesis of 4-Formyl-2,6-dimethylphenyl Propylcarbamate

[0251] 1-Isocyanatopropane (0.727 ml, 7.66 mmol) was added dropwise to a suspension of 4-hydroxy-3,5-dimethylbenzaldehyde (1 g, 6.66 mmol) and potassium carbonate (1.66 g, 12 mmol) at 0 °C in tetrahydrofuran (6 mL). The suspension was stirred at 0 °C for 30 min and then allowed to warm to room temperature and stirred for an additional 30 min. The suspension was concentrated under reduced pressure and the resulting residue was dissolved in ethyl acetate. The solution was washed with water, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography, on silica gel, eluting with 8:2 hexanes:ethyl acetate to yield 4-formyl-2,6-dimethylphenyl propylcarbamate.

Synthesis of 4-((2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)methyl)-2,6-dimethylphenyl Propylcarbamate

[0252] 2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-amine hydrochloride (200 mg, 0.59 mmol) and 4-formyl-2,6-dimethylphenyl propylcarbamate (151 mg, 0.644 mmol) were combined in 1,2-dichloroethane (5 mL) and treated with sodium triacetoxyborohydride (248 mg, 1.17 mmol) and acetic acid (37 µL, 0.644 mmol). The mixture was stirred at room temperature overnight. The reaction was quenched by addition of saturated sodium bicarbonate solution. The crude product was extracted with ethyl acetate (2 x 50 mL). The organic extract was dried over

anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography, on silica gel, eluting with 99:1 dichloromethane:methanol to yield 4-((2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)methyl)-2,6-dimethylphenyl propylcarbamate. ^{1}H NMR ($CDCl_3$): 8.2 (d, 1H), 7.4 (d, 1H), 7.2-7.3 (m, 2H), 7.0 (d, 2H), 6.4 (d, 1H), 5.1-5.2 (m, 2H), 4.3 (d, 2H), 3.2 (m, 2H), 2.2 (s, 6H), 1.6 (m, 2H), 1.0 ppm (m, 3H). MW=525 confirmed by LC-MS t_r=11.71 (**Method Y1**) MH^+=523-527.

Synthesis of 4-((2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)methyl)-2,6-dimethylphenyl Propylcarbamate (Cpd. 1057)

[0253] 4-((2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)methyl)-2,6-dimethylphenyl propylcarbamate (60 mg, 0.11 mmol) was dissolved in anhydrous dichloromethane with triethylamine (0.1 mL). The mixture was cooled in an ice-bath under nitrogen, then a solution of dichloroacetyl chloride (0.046 mL, 0.13 mmol) was added dropwise. After the addition was completed the ice-bath was removed and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and then washed successively with water, 10% hydrochloric acid and saturated sodium bicarbonate solution. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 30:70 ethyl acetate:hexanes to give 4-((2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)methyl)-2,6-dimethylphenyl propylcarbamate **(Cpd. 1057)**. ^{1}H NMR ($CDCl_3$): 8.7 (d, 1H), 7.8 (s, 1H), 7.4 (m, 1H), 7.3 (m, 1H), 7.1 (m, 2H), 6.9 (s, 2H), 6.0 (s, 1H), 5.1 (m, 1H), 5.0 (s, 2H), 3.2 (m, 2H), 2.1 (s, 6H), 2.6 (m, 2H), 1.0 ppm (m, 3H). MW=636 confirmed by LC-MS, t_r= 16.41 min (**Method Y1**) MH^+=634-638.

Synthesis of 2,2-Dichloro-N^1-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N^3-methylmalonamide (Cpd. 1010)

Synthesis of Methyl 2,2,3-Trichloro-3-oxopropanoate

[0254] Methyl malonyl chloride (3.2 g, 23,5 mmol) was heated with thionyl chloride (8 mL) and aluminum chloride (50 mg) under reflux for 5 h. The crude product was then distilled at ~20 mmHg to give methyl 2,2,3-trichloro-3-oxopropanoate (3.9 g) as a colorless liquid. This follows the procedure given by G. Castelfranchi and T. Perrotti, Annali di Chimica, 47, 1201-1224 (1957, Chemical Abstracts CA 52:40383). ^{1}H NMR ($CDCl_3$): 4.00 ppm (s, 3H).

Synthesis of Methyl 2,2-Dichloro-3-(3-ethynylphenylamino)-3-oxopropanoate (FIG. 29)

[0255] 3-Ethynylaniline (1.64 g, 14 mmol) was dissolved in dichloromethane (50 mL) with triethylamine (2.6 mL, 42 mmol). The resulting mixture was cooled in an ice-bath under nitrogen and then methyl 2,2,3-trichloro-3-oxopropanoate (3.2 g, 15.6 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature while stirring overnight. The reaction mixture was washed successively with water, 10% hydrochloric acid and saturated sodium bicarbonate solution. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give methyl 2,2-dichloro-3-(3-ethynylphenylamino)-3-oxopropanoate (1.34 g) as an amber syrup. The product was carried forward without further purification. ^{1}H NMR ($CDCl_3$): 8.40 (br s, 1H), 7.69 (m, 1H), 7.58 (m, 1H), 7.34 (m, 2H), 3.96 (s, 3H), 3.10 ppm (s, 1H).

Synthesis of Methyl 2,2-Dichloro-3-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenylamino)-3-oxopropanoate

[0256] Methyl 2,2-dichloro-3-(3-ethynylphenylamino)-3-oxopropanoate (1.34 g, 4.68 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) and treated with triethylamine (0.86 mL, 6.1 mmol) and then 2,6-dichloro-N-hydroxybenzimidoyl chloride (1.05 g, 4.71 mmol). After stirring 15 min at room temperature the mixture was heated at reflux for 4 h. The mixture was diluted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 2:8 ethyl acetate:hexanes to give methyl 2,2-dichloro-3-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenylamino)-3-oxopropanoate (1.27 g) as a white solid. ^{1}H NMR ($CDCl_3$): 8.54 (br s, 1H), 8.09 (m, 1H), 7.72 (m, 1H), 7.66 (m, 1H), 7.52 (m, 1H), 7.44 (m, 2H), 7.35 (m, 1H), 6.67 (s, 1H), 3.98 ppm (s, 3H). MW=474 confirmed by LC-MS, t_r= 15.97 min (**Method Y1**) MH^+=472-476.

Synthesis of 2,2-Dichloro-N^1-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N^3-methylmalonamide (Cpd. 1010)

[0257] Methyl 2,2-dichloro-3-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenylamino)-3-oxopropanoate (112 mg, 0.24 mmol) was dissolved in anhydrous tetrahydrofuran (2 mL). The mixture was treated with powered molecular sieves (4 Å, 200 mg) and bubbled with argon. Then the N-heterocyclic carbene catalyst (S. Nolan, J. Org. Chem, 68, 2812, 2003), 1,3-bis(1-adamantyl)imidazol-2-ylidene (11 mg) was added, followed by a solution of methylamine (1 mL, 2 M soln in THF). The mixture was shaken for 3 h at room temperature, then diluted with ethyl

acetate, washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 1:1 ethyl acetate:hexanes to give 2,2-dichloro-N^1-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N^3-methylmalonamide (31 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 9.36 (br s, 1H), 8.10 (s, 1H), 7.69 (m, 1H), 7.63 (m, 1H), 7.49-7.41 (m, 3H), 7.32 (m, 1H), 6.60 (m, 1H), 2.99 ppm (m, 3H). MW=474 confirmed by LC-MS, t_r= 14.45 min (**Method Y1**) MH^+=472-476.

Synthesis of 2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-((2-oxo-5-(pyrrolidin-2-yl)-1,3-dioxol-4-yl)methyl)acetamide Trifluoroacetate Salt (See Figure 30) (Cpd. 1014)

Synthesis of *tert*-Butyl 2-(3-(Benzyloxy)-3-oxopropanoyl)pyrrolidine-1-carboxylate (FIG. 30)

[0258] L-Boc-proline (16.1 g, 75 mmol), Meldrum's acid (10.8 g, 75 mmol) and 4-dimethylaminopyridine (18.3 g, 150 mmol) were dissolved in dichloromethane (250 mL). Then dicyclohexylcarbodiimide (15.5 g, 75 mmol) was added in several portions. The mixture stirred at room temperature for 2.5 d, followed by filtration through a pad of Celite. The filtrate was washed successively with water, 10% hydrochloric acid and saturated sodium bicarbonate solution. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow foam. The crude product was dissolved in acetonitrile (100 mL) with benzyl alchohol (8.11 g, 75 mmol) and heated at reflux for 6 h. The reaction mixture was concentrated under reduced pressure to give *tert*-butyl 2-(3-(benzyloxy)-3-oxopropanoyl)pyrrolidine-1-carboxylate. The product was carried forward without further purification. ^{1}H NMR ($CDCl_3$): 7.32 (s, 5H), 5.16 (s, 2H), 4.30 (m, 1H), 3.62-3.30 (m, 4H), 2.20-1.78 (m, 4H), 1.38 ppm (s, 9H).

Synthesis of *tert*-Butyl 2-(3-(Benzyloxy)-2-diazo-3-oxopropanoyl)pyrrolidine-1-carboxylate

[0259] *tert*-Butyl 2-(3-(benzyloxy)-3-oxopropanoyl)pyrrolidine-1-carboxylate was dissolved in acetonitrile (500 mL) and treated with 4-acetamidobenzenesulfonyl azide (18 g, 75 mmol). The solution was cooled in an ice-bath and then triethylamine (32 mL, 225 mmol) was added dropwise. After 1 h, the ice-bath was removed and the reaction was allowed to slowly warm to room temperature for 4 h. The solvent was concentrated under reduced pressure and the crude product was triturated with ether:hexanes (2:1) and filtered. The filtrate was concentrated and

the resulting residue was purified by flash column chromatography, on silica gel, eluting with 4:6 ethyl acetate:hexanes to give *tert*-butyl 2-(3-(benzyloxy)-2-diazo-3-oxopropanoyl)pyrrolidine-1-carboxylate (22.7 g) as an oil. ^{1}H NMR ($CDCl_3$): 7.35 (m, 5H), 5.35-5.15 (m, 3H), 3.62-3.38 (m, 2H), 2.22 (m, 1H), 1.82 (m, 3H), 1.44 (s) and 1.38 ppm (s) (9H, NHBoc, 2 carbamate rotamers).

Synthesis of *tert*-Butyl 2-(3-(Benzyloxy)-2-hydroxy-3-oxopropanoyl)pyrrolidine-1-carboxylate

[0260] *tert*-Butyl 2-(3-(benzyloxy)-2-diazo-3-oxopropanoyl)pyrrolidine-1-carboxylate (22.7 g) was dissolved in a mixture of tetrahydrofuran (400 mL) and water (200 mL) and treated with rhodium (II) acetate dimer (0.69 g). The mixture was heated at 100 °C for 5 h. The tetrahydrofuran was removed by concentration under reduced pressure and the aqueous solution was extracted (3 x 200 mL) with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give *tert*-butyl 2-(3-(benzyloxy)-2-hydroxy-3-oxopropanoyl)pyrrolidine-1-carboxylate (17.43 g) as a brown oil. The product was carried forward without further purification.

Synthesis of *tert*-Butyl 2-(5-(Benzyloxycarbonyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate

[0261] *tert*-Butyl 2-(3-(benzyloxy)-2-hydroxy-3-oxopropanoyl)pyrrolidine-1-carboxylate (17.43 g, 48.0 mmol) was dissolved in anhydrous tetrahydrofuran (400 mL) and treated with 1,1-carbodiimidazole (15.57 g, 96.0 mmol) and diisopropylethylamine (2 mL). The mixture was stirred for 2.5 days at room temperature. The mixture was concentrated under reduced pressure and partitioned between ethyl acetate and 1M aqueous potassium bisulfate. The organic layer was washed with water and brine and then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, to give *tert*-butyl 2-(5-(benzyloxycarbonyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate (4.14 g). ^{1}H NMR ($CDCl_3$): 7.38 (s, 5H), 5.32 (s, 2H), 5.40-5.20 (m, 1H), 3.60-3.40 (m, 2H), 2.30 (m, 1H), 2.10-1.85 (m, 3H), 1.45 (s) and 1.30 ppm (s) (9H, NHBoc, 2 carbamate rotamers).

Synthesis of 5-(1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl)-2-oxo-1,3-dioxole-4-carboxylic Acid

[0262] *tert*-Butyl 2-(5-(benzyloxycarbonyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate (4.14 g) was dissolved in ethanol (100 mL) and treated with 20% palladium hydroxide on carbon (530 mg) followed by shaking under 16 psi hydrogen for 1 h. The mixture was filtered through a pad

of Celite and the filtrate was concentrated under reduced pressure to provide 5-(1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)-2-oxo-1,3-dioxole-4-carboxylic acid (2.76 g) as an off white solid. ^{1}H NMR ($CDCl_3$): 7.87 (br s, 1H), 5.30 (m, 1H), 3.60-3.30 (m, 2H), 2.40-1.80 (m, 4H), 1.40 ppm (br s, 9H).

Synthesis of *tert*-Butyl 2-(5-(Hydroxymethyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate

[0263] 5-(1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl)-2-oxo-1,3-dioxole-4-carboxylic acid (2.76 g, 9.68 mmol) was dissolved in dichloromethane (50 mL) and treated with oxalyl chloride (1.31 mL, 14.5 mmol) followed by several drops of dimethylformamide. After 1 h, the mixture was concentrated under reduced pressure. The residue was dissolved in anhydrous dichloromethane (40 mL) and cooled to –70 °C under argon. Then a solution of tetrabutylammonium borohydride (2.85 g, 11.0 mmol) in anhydrous dichloromethane (20 mL) was added dropwise. After an hour at –70 °C the reaction was quenched with 1M aqueous potassium bisulfate (15 mL), followed by warming to room temperature. The reaction was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography, on silica gel, eluting with 1:1 ethyl acetate:hexanes to give *tert*-butyl 2-(5-(hydroxymethyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate (900 mg) as an oil. ^{1}H NMR ($CDCl_3$): 4.83 (m, 1H), 4.53 (m, 1H), 4.29 (m, 1H), 3.39 (m, 3H), 2.12 (m, 2H), 1.93 (m, 1H), 1.42 ppm (s, 9H).

Synthesis of *tert*-Butyl 2-(5-(Bromomethyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate

[0264] *tert*-Butyl 2-(5-(hydroxymethyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate (900 mg, 3.3 mmol) was dissolved in anhydrous dichloromethane (20 mL) and treated with carbon tetrabromide (1.31 g, 3.96 mmol). After cooling in an ice-bath under nitrogen, triphenylphosphine (950 mg, 3.63 mmol) was added. After 30 min, the ice-bath was removed and the mixture was stirred for 90 min at room temperature. The mixture was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography, on silica gel, eluting with 2:8 ethyl acetate:hexanes to give *tert*-butyl 2-(5-(bromomethyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate (770 mg) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): 4.70 (m, 1H), 4.42 (m, 1H), 4.19 (m, 1H), 3.50 (m, 2H), 2.40-1.80 (m, 4H), 1.41 ppm (s, 9H).

Synthesis of *tert*-Butyl 2-(5-((3-Ethynylphenylamino)methyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate

[0265] *tert*-Butyl 2-(5-(bromomethyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate (770 mg, 2.21 mmol) was dissolved in acetonitrile (10 mL) and treated with 3-ethynyl aniline (260 mg, 2.21 mmol) and sodium bicarbonate (250 mg). The mixture was heated at 80 °C for 3 h. The mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give *tert*-butyl 2-(5-((3-ethynylphenylamino)methyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate, which was carried forward without further purification. ^{1}H NMR ($CDCl_3$): 7.07 (m, 1H), 6.86 (m, 1H), 6.75 (m, 1H), 6.62 (m, 1H), 4.75 (m, 1H), 4.37 (m, 2H), 4.12 (m, 1H), 3.41 (m, 2H), 3.00 (m, 1H), 2.20-1.80 (m, 4H), 1.46 ppm (s, 9H).

Synthesis of *tert*-Butyl 2-(5-((2,2-Dichloro-N-(3-ethynylphenyl)acetamido)methyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate

[0266] *tert*-Butyl 2-(5-((3-ethynylphenylamino)methyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate (85 mg, 2.2 mmol) was dissolved in anhydrous dichloromethane (40 mL) with triethylamine (0.41 mL, 4.0 mmol). The mixture was cooled in an ice-bath under nitrogen, then a solution of dichloroacetyl chloride (0.29 mL, 3.0 mmol) was added dropwise. After the addition was completed the ice-bath was removed and the mixture was stirred at room temperature overnight. The reaction mixture was washed successively with 0.5M aqueous potassium bisulfate, water and saturated sodium bicarbonate solution. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, to give *tert*-butyl 2-(5-((2,2-dichloro-N-(3-ethynylphenyl)acetamido)methyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate (282 mg) as a beige solid. ^{1}H NMR ($CDCl_3$): 7.55 (m, 1H), 7.48 (m, 2H), 7.33 (m, 1H), 5.79 (s, 1H), 4.93 (m, 1H), 4.75 (m, 1H), 4.55 (m, 1H), 3.38 (m, 2H), 3.18 (s, 1H), 2.20-1.80 (m, 4H), 1.41 ppm (s, 9H).

Synthesis of *tert*-Butyl 2-(5-((2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)acetamido)methyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate

[0267] *tert*-Butyl 2-(5-((2,2-dichloro-N-(3-ethynylphenyl)acetamido)methyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate (282 mg, 0.57 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL) and treated with triethylamine (0.15 mL, 0.74 mmol) and then 2,6-dichloro-N-hydroxybenzimidoyl chloride (140 mg, 0.63 mmol). After stirring 15 min at room temperature

the mixture was heated at reflux for 3 h. The mixture was diluted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was by flash column chromatography, on silica gel, eluting with 3:7 ethyl acetate:hexanes to give *tert*-butyl 2-(5-((2,2-dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)acetamido)methyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate (310 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 7.92 (m, 1H), 7.80 (m, 1H), 7.62 (m, 1H), 7.32 (m, 1H), 6.70 (s, 1H), 5.89 (s, 1H), 5.07 (m, 1H), 4.82 (m, 1H), 4.60 (m, 1H), 3.39 (m, 2H), 2.20-1.80 (m, 4H), 1.41 ppm (s, 9H). MW=705 confirmed by LC-MS, t_r= 17.44 min (**Method Y1**) MH^+Na=702-708.

Synthesis of 2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-((2-oxo-5-(pyrrolidin-2-yl)-1,3-dioxol-4-yl)methyl)acetamide Trifluoroacetate Salt (Cpd. 1014)

[0268] *tert*-Butyl 2-(5-((2,2-dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)acetamido)methyl)-2-oxo-1,3-dioxol-4-yl)pyrrolidine-1-carboxylate (93 mg) was dissolved in anhydrous dichloromethane (3 mL) and cooled in an ice-bath under nitrogen. Then trifluoroacetic acid (2 mL) was added. After 90 min at 4 °C the mixture was concentrated under reduced pressure. The residue was dissolved and concentrated under reduced pressure again to give 2,2-dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-((2-oxo-5-(pyrrolidin-2-yl)-1,3-dioxol-4-yl)methyl)acetamide trifluoroacetate salt **(Cpd. 1014)** as a solid. ^{1}H NMR ($CDCl_3$): 7.96 (m, 1H), 7.86 (m, 1H), 7.64 (m, 1H), 7.47 (m, 3H), 7.34 (m, 1H), 6.73 (s, 1H), 5.88 (s, 1H), 5.10 (m, 1H), 4.73 (m, 2H), 3.53 (m, 2H), 2.55-2.15 ppm (m, 4H). MW=584 confirmed by LC-MS, t_r= 11.24 min (**Method Y1**) MH^+=582-586.

Synthesis of 6,6-Dichloro-4-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-1-(pyrrolidin-2-yl)hexane-1,5-dione (Cpd. 1024)

Synthesis of *tert*-Butyl 2-Acryloylpyrrolidine-1-carboxylate

[0269] *tert*-Butyl 2-(methoxy(methyl)carbamoyl)pyrrolidine-1-carboxylate (6.0 g, 23.2 mmol) was dissolved in anhydrous tetrahydrofuran (100 mL) and cooled to –78 °C. Upon cooling vinylmagnesium bromide (58.1 mL, 1.0 M soln in THF, 58.1 mmol) was added dropwise. The reaction was then heated at reflux for 2 h. The reaction mixture was cooled to 0 °C, diluted with 1N hydrochloric acid (75 mL) and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 8:2 hexanes:ethyl acetate, to provide *tert*-butyl 2-acryloylpyrrolidine-1-carboxylate (2.3 g) as an amber

oil. ^{1}H NMR ($CDCl_3$): 6.01-5.89 (m, 2H), 5.50 (d, 2H), 5.22-5.17 (t, 2H), 3.94 (m, 1H), 3.59 (m, 1H), 3.17 (m, 1H), 1.80 (m, 1H), 1.44 ppm (s, 9H).

Synthesis of *tert*-Butyl 2-(3-(2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)propanoyl)pyrrolidine-1-carboxylate (FIG. 31)

[0270] 2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-amine hydrochloride (400 mg, 1.2 mmol), *tert*-butyl 2-acryloylpyrrolidine-1-carboxylate (270 mg, 1.2 mmol) and triethylamine (0.42 mL, 3.0 mmol) were combined in acetonitrile (5 mL). The resulting solution was stirred in a sealed vial at 80 °C overnight. A second portion of *tert*-butyl 2-acryloylpyrrolidine-1-carboxylate (270 mg, 1.2 mmol) was added and heating was continued until desired product and starting material had a 1:1 ratio by LC-MS. The reaction mixture was cooled to room temperature and diluted with dichloromethane (10 mL). The organic mixture was washed successively with water and saturated sodium bicarbonate solution. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel, eluting with 1:1 ethyl acetate:hexanes to give *tert*-butyl 2-(3-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)propanoyl)pyrrolidine-1-carboxylate (125 mg) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): 8.22 (m, 1H), 7.44 (d, 2H), 7.38 (m, 1H), 7.19 (s, 1H), 6.98 (m, 1H), 6.50 (m, 1H), 4.36 (m, 1H), 3.65-3.40 (m, 6H), 2.90-2.78 (m, 4H), 1.97-1.79 (m, 1H), 1.56 ppm (s, 9H). MW=531 confirmed by LC-MS, t_r= 11.24 min (**Method Y1**) MH^+=529-533.

Synthesis of *tert*-Butyl 2-(6,6-Dichloro-4-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-5-oxohexanoyl)pyrrolidine-1-carboxylate

[0271] *tert*-Butyl 2-(3-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)propanoyl)pyrrolidine-1-carboxylate (125 mg, 0.24 mmol) was dissolved in anhydrous dichloromethane (3 mL) with triethylamine (0.40 mL, 0.29 mmol). The mixture was cooled in an ice-bath under nitrogen, then a solution of dichloroacetyl chloride (0.28 mL, 0.29 mmol) in anhydrous dichloromethane (1 mL) was added dropwise. After the addition was completed the ice-bath was removed and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with dichloromethane and then washed successively with water, 10% hydrochloric acid and saturated sodium bicarbonate solution. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 30:70 ethyl acetate:hexanes to give *tert*-butyl 2-(6,6-dichloro-4-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-

yl)-5-oxohexanoyl)pyrrolidine-1-carboxylate (62 mg) as a yellow oil. ^{1}H NMR ($CDCl_3$): 8.80 (m, 1H), 7.83 (s, 1H), 7.48 (m, 2H), 7.37 (m, 1H), 5.98 (br s, 1H), 4.26 (m, 1H), 4.10 (m, 2H), 3.59-3.39 (m, 2H), 2.96 (m, 2H), 2.19 (m, 1H), 1.84 (m, 1H), 1.41 ppm (s, 9H). MW=642 confirmed by LC-MS, t_r= 14.49 min (**Method Y1**) MH^+=640-644.

Synthesis of 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-oxo-3-(pyrrolidin-2-yl)propyl)acetamide (Cpd. 1024)

[0272] Trifluoroacetic acid (0.5 mL) was added to a solution of *tert*-butyl 2-(3-(2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propanoyl)pyrrolidine-1-carboxylate (62 mg, 0.10 mmol) in dichloromethane (2 mL) at 0 °C. The resulting mixture was allowed to stir at 0 °C for 2 h, then concentrated under reduced pressure. The residue was dissolved in dichloromethane (2 mL) and concentrated under reduced pressure, twice more. Lyophilization produced 2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-oxo-3-(pyrrolidin-2-yl)propyl)acetamide (**Cpd. 1024**, 63 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 8.91 (d, 1H), 7.98 (s, 1H), 7.50-7.37 (m, 4H), 7.12 (s, 1H), 6.08 (br s, 1H), 5.91 (s, 1H), 4.76 (m, 1H), 4.24-4.02 (m, 2H), 3.49 (m, 2H), 3.09 (m, 2H), 2.56 (m, 1H), 2.06 ppm (m, 3H). MW=542 confirmed by LC-MS, t_r= 10.47 min (**Method Y1**) MH^+=540-544.

Synthesis of 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-((2-(pyridin-2-yl)ethoxy)methyl)acetamide (Cpd. 1028)

Synthesis of 2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)-N-((2-(pyridin-2-yl)ethoxy)methyl)pyridin-4-amine

[0273] Sodium hydride (120 mg, 2.9 mmol) was added slowly to a solution of 2-(2-hydroxyethyl)pyridine (0.33 mL, 0.58 mmol) in anhydrous tetrahydrofuran (20 mL) at 0 °C. Once the evolution of hydrogen ceased 2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-amine hydrochloride (200 mg, 0.58 mmol) and paraformaldehyde (147 mg, 1.64 mmol) added. The resulting mixture was stirred at room temperature for 5 h and hydrolyzed with ice-cooled water and extracted with ethyl acetate. The organic extracts were washed with water, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield 2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)-N-((2-(pyridin-2-yl)ethoxy)methyl)pyridin-4-amine. The product was carried forward without further purification.

Synthesis of 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-((2-(pyridin-2-yl)ethoxy)methyl)acetamide (Cpd. 1028) (FIG. 27)

[0274] 2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)-N-((2-(pyridin-2-yl)ethoxy)methyl)pyridin-4-amine (100 mg, 0.24 mmol) was dissolved in anhydrous dichloromethane with triethylamine (0.4 mL, 0.29 mmol). The mixture was cooled in an ice-bath under nitrogen, then a solution of dichloroacetyl chloride (0.3 mL, 0.29 mmol) was added dropwise. After the addition was completed the ice-bath was removed and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and then washed successively with water, 10% hydrochloric acid and saturated sodium bicarbonate solution. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 99:1 dichloromethane:methanol to yield 2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-((2-(pyridin-2-yl)ethoxy)methyl)acetamide **(Cpd. 1028)**. ^{1}H NMR ($CDCl_3$): 8.7 (d, 1H), 8.6 (d, 1H), 7.8 (s, 1H), 7.4 (m, 2H), 7.2-7.1 (m, 3H), 7.0 (s, 1H), 6.0 (s, 1H), 5.1 (m, 1H), 5.0 (s, 2H), 4.1 (m, 2H), 3.1 ppm (m, 2H). MW=636 confirmed by LC-MS, t_r= 16.41 min (**Method Y1**) MH^+=634-638.

Synthesis of 2,2-Dichloro-N-(3-(3-(2-chloro-6-(piperidin-4-yloxy)phenyl)isoxazol-5-yl)phenyl)-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamide (See Figure 6) (Cpd. 1034)

Synthesis of 4-((3-Ethynylphenylamino)methyl)-5-isopropyl-1,3-dioxol-2-one

[0275] 3-Ethynylaniline (904 µL, 8.7 mmol) and 4-(bromomethyl)-5-isopropyl-1,3-dioxol-2-one (2.0 g, 9.09 mmol) were dissolved in acetonitrile (20 mL). Sodium bicarbonate (873 mg, 10.4 mmol) was added and the reaction mixture was heated at reflux under a nitrogen atmosphere overnight. The mixture was then concentrated under reduced pressure, extracted with ethyl acetate and washed with water. The organic layer was then dried over anhydrous sodium sulfate and concentrated under reduced pressure. Purification by column chromatography, on silica gel, eluting with 1:9 ethyl acetate:hexanes yielded 4-((3-ethynylphenylamino)methyl)-5-isopropyl-1,3-dioxol-2-one (570 mg) as a pale yellow foam. ^{1}H NMR ($CDCl_3$): 7.15 (t, 1H), 6.95 (m, 1H), 6.75 (m, 1H), 6.60 (m, 1H), 4.10 (s, 2H), 3.05 (s, 1H), 2.90 (s, 1H), 1.25 ppm (s, 6H). MW=257 confirmed by LC-MS, t_r= 13.66 min (**Method Y1**) MH^+=258.

Synthesis of 2,2-Dichloro-N-(3-ethynylphenyl)-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamide (FIG. 32)

[0276] 4-((3-Ethynylphenylamino)methyl)-5-isopropyl-1,3-dioxol-2-one (540 mg, 2.1 mmol) was dissolved in anhydrous dichloromethane (20 mL) with diisopropylethylamine (0.47 mL, 2.5 mmol). The mixture was cooled in an ice-bath under nitrogen, then a solution of dichloroacetyl chloride (0.24 mL, 2.5 mmol) in anhydrous dichloromethane (5 mL) was added dropwise. After the addition was completed the ice-bath was removed and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and then washed successively with water and brine. The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography, on silica gel, eluting with 1:9 ethyl acetate:hexanes to give 2,2-dichloro-N-(3-ethynylphenyl)-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamide (508 mg) as a beige solid. MW=368 confirmed by LC-MS, t_r= 14.11 min (**Method Y1**) MH^+=366-370.

Synthesis of tert-Butyl 4-(Tosyloxy)piperidine-1-carboxylate

[0277] 1-*tert*-Butoxycarbonyl-4-hydroxypiperidine (2 g, 9.95 mmol), *p*-toluenesulfonyl chloride (2.08 g, 10.9 mmol), triethylamine (1.6 mL, 11.9 mmol) and 4-dimethylaminopyridine (61 mg, 0.5 mmol) were dissolved in dichloromethane (50 mL). The resulting mixture was allowed to stir at room temperature overnight. The reaction mixture was diluted with dichloromethane and then washed successively with water, saturated sodium bicarbonate solution, and brine. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography, on silica gel, eluting with 1:9 ethyl acetate:hexanes to give *tert*-butyl 4-(tosyloxy)piperidine-1-carboxylate (1.42 g) as white solid. ^{1}H NMR ($CDCl_3$): 7.80 (d, 2H), 7.35 (d, 2H), 4.65 (m, 1H), 3.60 (m, 2H), 3.25 (m, 2H), 2.45 (s, 3H), 1.75 (m, 4H), 1.45 ppm (s, 9H).

Synthesis of *tert*-Butyl 4-(3-Chloro-2-formylphenoxy)piperidine-1-carboxylate

[0278] *tert*-Butyl 4-(tosyloxy)piperidine-1-carboxylate (1.42 g, 4.0 mmol) and 2-chloro-6-hydroxybenzaldehyde (620 mg, 3.3 mmol) were dissolved in N,N-dimethylformamide (20 mL) and potassium carbonate (552 mg, 4.0 mmol) was added. The reaction mixture was allowed to stir at 60 °C overnight. Ice was added and the mixture was acidified with 6N hydrochloric acid. The mixture was extracted with ethyl acetate and the organic layer was washed with brine. The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography, on silica gel,

eluting with 2:8 ethyl acetate:hexanes to give *tert*-butyl 4-(3-chloro-2-formylphenoxy)piperidine-1-carboxylate (430 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 10.50 (s, 1H), 7.35 (t, 1H), 7.05 (d, 1H), 6.90 (d, 1H), 4.60 (m, 1H), 3.65 (m, 2H), 3.45 (m, 2H), 1.85 (m, 4H),1.40 ppm (s, 9H).

Synthesis of (E)-*tert*-Butyl 4-(3-Chloro-2-((hydroxyimino)methyl)phenoxy)piperidine-1-carboxylate

[0279] *tert*-Butyl 4-(3-chloro-2-formylphenoxy)piperidine-1-carboxylate (430 mg, 1.3 mmol) and hydroxylamine hydrochloride (97 mg, 1.4 mmol) were dissolved in pyridine (15 mL) and allowed to stir at room temperature overnight. The mixture was then concentrated under reduced pressure to yield (E)-*tert*-butyl 4-(3-chloro-2-((hydroxyimino)methyl)phenoxy)piperidine-1-carboxylate (450 mg) as a light yellow oil. MW=354 confirmed by LC-MS, t_r= 17.67 min (**Method Y1**) MH^+= 353-355

Synthesis of tert-Butyl 4-(3-Chloro-2-(5-(3-(2,2-dichloro-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamido)phenyl)isoxazol-3-yl)phenoxy)piperidine-1-carboxylate

[0280] (E)-*tert*-Butyl 4-(3-chloro-2-((hydroxyimino)methyl)phenoxy)piperidine-1-carboxylate (200 mg, 0.56 mmol), 2,2-dichloro-N-(3-ethynylphenyl)-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamide (180 mg, 0.49 mmol), chloramine-T (140 mg, 0.62 mmol), and ethanol (2 mL) were placed in a sealed microwave vial. The reaction mixture was heated at 100 °C for 900 seconds. Once the reaction was complete the reaction mixture was concentrated under reduced pressure, extracted with ethyl acetate, and washed with cold 1N sodium hydroxide, water and brine. The organic solution was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography, on silica gel, eluting with 2:8 ethyl acetate:hexanes to give tert-butyl 4-(3-chloro-2-(5-(3-(2,2-dichloro-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamido)phenyl)isoxazol-3-yl)phenoxy)piperidine-1-carboxylate (110 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 7.95 (m, 1H), 7.75 (m, 1H), 7.65 (t, 1H), 7.40 (m, 2H), 7.15 (d, 1H), 6.90 (d, 1H), 6.75 (s, 1H), 5.85 (s, 1H), 4.60 (br s, 2H), 3.40 (m, 4H), 1.80 (m, 4H), 1.55 (s, 9H), 1.25 ppm (m, 6H). MW=721 confirmed by LC-MS, t_r= 17.60 min (**Method Y1**) MH^+= 719-723

Synthesis of 2,2-Dichloro-N-(3-(3-(2-chloro-6-(piperidin-4-yloxy)phenyl)isoxazol-5-yl)phenyl)-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamide (See Figure 32) (Cpd. 1034)

[0281] *tert*-Butyl 4-(3-chloro-2-(5-(3-(2,2-dichloro-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamido)phenyl)isoxazol-3-yl)phenoxy)piperidine-1-carboxylate (100 mg, 0.14 mmol)

was dissolved in dichloromethane (500 μL). The solution was cooled in an ice-bath and then a cooled solution of trifluoroacetic acid (3 mL) in dichloromethane (3 mL) was added dropwise. The reaction mixture was allowed to stir at 0 °C for 3 h. The reaction mixture was diluted with dichloromethane, washed with water, and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to yield 2,2-dichloro-N-(3-(3-(2-chloro-6-(piperidin-4-yloxy)phenyl)isoxazol-5-yl)phenyl)-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamide (**Cpd. 1034**, 60 mg) as a pale yellow foam. ^{1}H NMR ($CDCl_3$): 7.95 (m, 1H), 7.85 (m, 1H), 7.70 (t, 1H), 7.45 (m, 2H), 7.15 (m, 1H), 6.95 (m, 1H), 5.85 (s, 1H), 4.80 (br s, 2H), 3.15 (m, 1H), 1.20 ppm (m, 6H). MW=621 confirmed by LC-MS, t_r= 11.60 min (**Method Y1**) MH^+=619-623.

Synthesis of 2,2-Dichloro-N-(2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-((1-methyl-1H-imidazol-2-yl)methyl)acetamide (Cpd. 1037)

Synthesis of 2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)-N-((1-methyl-1H-imidazol-2-yl)methyl)pyridin-4-amine (FIG. 33)

[0282] 2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-amine hydrochloride (300 mg, 0.88 mmol), 1-methyl-2-imidazolecarboxaldehyde (193 mg, 1.75 mmol), sodium triacetoxyborohydride (187 mg, 1.75 mmol), and acetic acid (53 mg, 0.88 mmol) were combined in dichloromethane (10 mL). The resulting mixture was stirred at room temperature overnight. The solution was then washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 98:2 dichloromethane:methanol to yield 2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)-N-((1-methyl-1H-imidazol-2-yl)methyl)pyridin-4-amine (50 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 8.3 (m, 1H), 7.4 (m, 3H), 7.0 (m, 2H), 6.9 (s, 1H), 6.7 (m,1H), 6.5 (br s, 1H), 4.5 (m, 2H), 3.7 ppm (s, 3H). MW= 400 confirmed by LC-MS, t_r= 2.17 min (**Method B**) MH^+=398-402.

Synthesis of 2,2-Dichloro-N-(2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-((1-methyl-1H-imidazol-2-yl)methyl)acetamide (Cpd. 1037)

[0283] 2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)-N-((1-methyl-1H-imidazol-2-yl)methyl)pyridin-4-amine (40 mg, 0.1mmol) was dissolved in anhydrous dichloromethane (10 mL) with diisopropylethylamine (21 μL, 0.12 mmol). The mixture was cooled in an ice-bath, then a solution of dichloroacetyl chloride (12 μL, 0.12 mmol) in anhydrous dichloromethane (0.5 mL) was added dropwise. After the addition was complete the ice-bath was removed and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and then was washed with water. The organic solution was dried over anhydrous sodium sulfate, filtered

and concentrated under reduced pressure. The resulting residue was purified by prep-scale reverse phase high performance liquid chromatography to provide 2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-((1-methyl-1H-imidazol-2-yl)methyl)acetamide (**Cpd. 1037**, 5 mg), as a white solid. ^{1}H NMR ($CDCl_3$): 8.8 (m, 1H), 8.0 (s, 1H), 7.8 (m, 1H), 7.4 (m, 3H), 7.1 (s, 1H), 7.0 (s, 1H), 6.0 (s, 1H), 5.4 (s, 2H), 4.0 ppm (s, 3H). MW=509 confirmed by LC-MS, t_r= 10.83 min (**Method Y1**) MH^+=507-511.

Synthesis of 4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propyl)benzylphosphonic Acid (Cpd. 1042)

Synthesis of Di-*tert*-butyl 4-Iodobenzylphosphonate (FIG. 34)

[0284] Di-*tert*-butyl phosphite (4.8 g, 24.7 mmol) was dissolved in anhydrous tetrahydrofuran (40 mL). The solution was cooled to –70 °C under argon and then n-butyllithium (17 mL, 1.6 M soln in hexanes, 27.2 mmol) was added dropwise. The mixture stirred for 20 min at –70 °C, then was placed in an ice-bath for 30 min. 4-Iodobenzyl bromide (7.15 g, 24.0 mmol) in anhydrous tetrahydrofuran (20 mL) was added. The reaction was allowed to warm to room temperature while stirring overnight. The reaction was quenched with saturated aqueous ammonium chloride solution, followed by extraction with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 3:7 ethyl acetate:hexanes to provide di-*tert*-butyl 4-iodobenzylphosphonate (6.71 g) as a pale yellow solid. ^{1}H NMR ($CDCl_3$): 7.58 (m, 2H), 7.01 (m, 2H), 2.96 (d, 2H), 1.42 ppm (s, 18H).

Synthesis of Di-*tert*-butyl 4-(3-Oxopropyl)benzylphosphonate

[0285] Di-*tert*-butyl 4-iodobenzylphosphonate (6.71 g, 16.4 mmol) was dissolved in anhydrous N,N-dimethylformamide (50 mL) and treated with palladium (II) acetate (250 mg), tetrabutylammonium bromide (5.4 g, 16.8 mmol), anhydrous molecular sieves (4 Å, 4 g), sodium bicarbonate (3.52 g, 42 mmol) and allyl alcohol (1.73 mL, 34.9 mmol). The reaction mixture was bubbled with argon and then stirred at room temperature for 90 h. The reaction mixture was filtered through a pad of Celite. The filtrate was diluted with water and ether. The layers were separated and the aqueous layer was further extracted with ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 1:9 ethyl acetate:hexanes to provide di-*tert*-butyl 4-(3-

oxopropyl)benzylphosphonate (1.44 g) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): 9.79 (s, 1H), 7.17 (m, 2H), 7.08 (m, 2H), 2.97 (m, 2H), 2.78 (m, 2H), 1.42 ppm (s, 18H).

Synthesis of Di-*tert*-butyl 4-(3-(2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)propyl)benzylphosphonate

[0286] 2-(3-(2,6-Dichlorophenyl)isoxazol-5-yl)pyridin-4-amine hydrochloride (200 mg, 0.59 mmol), di-*tert*-butyl 4-(3-oxopropyl)benzylphosphonate (267 mg, 0.79 mmol), sodium triacetoxyborohydride (278 mg, 1.3 mmol), and acetic acid (39 μL , 0.59 mmol) were combined in anhydrous 1,2-dichloroethane (2 mL), and sonicated at room temperature for 3 h. The solution was filtered through a pad of Celite. The Celite was washed with ethyl acetate. The combined filtrates were washed with water, then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 98:2 dichloromethane:methanol to yield di-*tert*-butyl 4-(3-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)propyl)benzylphosphonate (180 mg) as a white solid. MW= 630 confirmed by LC-MS, t_r= 4.80 min (**Method B**) MH^+=628-632.

Synthesis of Di-*tert*-butyl 4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propyl)benzylphosphonate

[0287] Di-*tert*-butyl 4-(3-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-ylamino)propyl)benzylphosphonate (180 mg, 0.29mmol) was dissolved in anhydrous dichloromethane (20 mL) with diisopropylethylamine (66 μL, 0.34 mmol). The mixture was cooled in an ice-bath, then a solution of dichloroacetyl chloride (37 μL, 0.34 mmol) in dichloromethane (0.5 mL) was added dropwise. After the addition was complete the ice-bath was removed and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and then washed with water. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 98:2 dichloromethane:methanol to provide di-*tert*-butyl 4-(3-(2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propyl)benzylphosphonate (54 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 8.8 (m, 1H), 8.0 (s, 1H), 7.9 (m, 1H), 7.4 (m, 3H), 7.2 (m, 2H), 7.1 (s, 1H), 7.0 (m, 2H), 5.9 (s, 1H), 3.9 (m, 2H), 3.0 (m, 2H), 2.6 (m, 2H), 1.9 (m, 2H), 1.4 ppm (s, 18H). MW=741 confirmed by LC-MS, t_r= 17.50 min (**Method Y1**) MH^+=739-743.

Synthesis of 4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propyl)benzylphosphonic Acid (Cpd. 1042)

[0288] Trifluoroacetic acid (2.5 mL) was added to a solution of di-*tert*-butyl 4-(3-(2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propyl)benzylphosphonate (54 mg, 0.07 mmol) in dichloromethane (2.5 mL) at 0 °C. The resulting mixture was allowed to stir at 0 °C for 3 hours, then concentrated under reduced pressure. The resulting residue was purified by prep-scale reverse phase high performance liquid chromatography to provide 4-(3-(2,2-dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propyl)benzylphosphonic acid (**Cpd. 1042**, 10 mg) as a white solid. ^{1}H NMR ($CDCl_3$): 8.7 (m, 1H), 7.8 (m, 1H), 7.4 (m, 3H), 7.1 (m, 3H), 6.9 (m, 2H), 5.9 (s, 1H), 3.8 (m, 2H), 3.0 (m, 2H), 2.5 (m, 2H), 1.8 ppm (m, 2H). MW=628 confirmed by LC-MS, t_r= 12.06 min (**Method Y1**) MH^+=626-630.

Synthesis of 2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-((5-((4,5-dihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-2-oxo-1,3-dioxol-4-yl)methyl)acetamide (Cpd. 1044)

Synthesis of 4,5-Bis(bromomethyl)-1,3-dioxol-2-one (FIG. 35)

[0289] Bromomethyl-1,3-dioxolene (5 g, 25.92 mmol) and N-bromosuccinimide (4.61g, 25.92 mmol) were dissolved in carbon tetrachloride (250 mL). Benzoylperoxide (250 mg) was added and the mixture was allowed to heat at reflux for 5 h. The reaction mixture was cooled to room temperature and the solids were removed by filtration. The filtrate was concentrated under reduced pressure to give 4,5-bis(bromomethyl)-1,3-dioxol-2-one (5.25 g) as a light yellow oil. ^{1}H NMR ($CDCl_3$): 4.21 ppm (s, 4H).

Synthesis of 4-(Bromomethyl)-5-(hydroxymethyl)-1,3-dioxol-2-one

[0290] 4,5-Bis(bromomethyl)-1,3-dioxol-2-one (4.6 g, 16.9 mmol) was dissolved in acetonitrile (50 mL). Potassium formate (1.42 g, 16.9 mmol) was added to the solution. The mixture was stirred at room temperature for 12 h. The reaction was concentrated under reduced pressure and the crude residue was dissolved in hydrochloric acid/methanol (25 mL) at 0 °C. The reaction was allowed to stir at 0 °C for 3 h and then concentrated under reduced pressure. The crude product was purified by column chromatography, on silica gel, eluting with 2:1 hexanes:ethyl acetate to provide 4-(bromomethyl)-5-(hydroxymethyl)-1,3-dioxol-2-one (900 mg). ^{1}H NMR ($CDCl_3$): 4.51 (s, 2H), 4.30 ppm (s, 2H).

Synthesis of 4-((4,5-Bis(*tert*-butyldimethylsilyloxy)-6-((*tert*-butyldimethylsilyloxy)methyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-5-(bromomethyl)-1,3-dioxol-2-one

[0291] 4-(Bromomethyl)-5-(hydroxymethyl)-1,3-dioxol-2-one (0.25 g, 1.2 mmol) and tri-O-(*tert*-butyldimethylsilyl)-D-glucal (1.13 g, 2.3 mmol) were dissolved in anhydrous dichloromethane (10 mL). Camphorsulfonic acid (0.54 g, 2.3 mmol) was added at 0 °C and the reaction mixture was allowed to stir at 0 °C for 3.5 h. The reaction was diluted with dichloromethane (25 mL), washed with water and brine (2 x 25 mL) and dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 1:15 ethyl acetate:hexanes to provide 4-((4,5-bis(*tert*-butyldimethylsilyloxy)-6-((*tert*-butyldimethylsilyloxy)methyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-5-(bromomethyl)-1,3-dioxol-2-one. ^{1}H NMR ($CDCl_3$): 4.95 (d, 1H), 4.36 (d, 2H), 4.28 (d, 2H), 4.15 (m, 2H), 3.77-3.56 (m, 3H), 2.08 (m, 2H), 0.98 (s, 27H), 0.18 ppm (d, 18H).

Synthesis of 4-((4,5-Bis(*tert*-butyldimethylsilyloxy)-6-((*tert*-butyldimethylsilyloxy)methyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-5-((3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenylamino)methyl)-1,3-dioxol-2-one

[0292] 4-((4,5-Bis(*tert*-butyldimethylsilyloxy)-6-((*tert*-butyldimethylsilyloxy)methyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-5-(bromomethyl)-1,3-dioxol-2-one (0.64 g, 0.92 mmol), 706 aniline (0.28g, 0.92 mmol) and sodium bicarbonate (90 mg, 1.11 mmol) were dissolved in anhydrous acetonitrile (25 mL). The above reaction mixture was heated at reflux under an argon atmosphere for 2 d. The reaction mixture was cooled to room temperature and concentrated reduced pressure. The crude product was purified by flash column chromatography, on silica gel, eluting with 1:5 ethyl acetate:hexanes to provide 4-((4,5-bis(*tert*-butyldimethylsilyloxy)-6-((*tert*-butyldimethylsilyloxy)methyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-5-((3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenylamino)methyl)-1,3-dioxol-2-one. ^{1}H NMR ($CDCl_3$): 7.90 (s, 1H), 7.75 (m, 1H), 7.66 (m, 1H), 7.45-7.30 (m, 4H), 6.77 (s, 1H), 4.92 (m, 1H), 4.33 (m, 2H), 4.18 (m, 2H), 4.05 (m, 2H), 3.80-3.61 (m, 4H), 2.15 (m, 2H), 0.95 (s, 27H), 0.14 ppm (d, 18H). MW=922 confirmed by LC-MS, t_r= 14.99 min (**Method Y1**) MH^+=920-924.

Synthesis of N-((5-((4,5-Bis(*tert*-butyldimethylsilyloxy)-6-((*tert*-butyldimethylsilyloxy)methyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-2-oxo-1,3-dioxol-4-yl)methyl)-2,2-dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)acetamide

[0293] 4-((4,5-Bis(*tert*-butyldimethylsilyloxy)-6-((*tert*-butyldimethylsilyloxy)methyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-5-((3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenylamino)methyl)-1,3-dioxol-2-one

(100 mg, 0.11 mmol), diisopropylethylamine (250 □L, 0.14 mmol) and dichloroacetyl chloride (120 □L, 0.12 mmol) were dissolved in anhydrous dichloromethane (10 mL) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 3 h under argon. The reaction mixture was diluted with dichloromethane (25 mL) and then washed with water (10 mL) and brine (2 x 10 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography, on silica gel, eluting with 1:7 ethyl acetate:hexanes to provide N-((5-((4,5-bis(*tert*-butyldimethylsilyloxy)-6-((*tert*-butyldimethylsilyloxy)methyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-2-oxo-1,3-dioxol-4-yl)methyl)-2,2-dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)acetamide. ^{1}H NMR ($CDCl_3$): 7.82 (s, 1H), 7.65 (m, 1H), 7.55 (m, 1H), 7.45-7.30 (m, 4H), 6.60 (s, 1H), 5.85 (s, 1H), 4.98 (m, 1H), 4.28 (m, 2H), 4.08 (m, 2H), 3.92 (m, 2H), 3.78-3.55 (m, 3H), 2.18 (m, 2H), 0.84 (s, 27H), 0.19 ppm (d, 18H). MW=1033 confirmed by LC-MS, t_r= 16.78 min (**Method Y1**) MH^+=1031-1035.

Synthesis of 2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-((5-((4,5-dihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-2-oxo-1,3-dioxol-4-yl)methyl)acetamide (Cpd. 1044)

[0294] N-((5-((4,5-Bis(*tert*-butyldimethylsilyloxy)-6-((*tert*-butyldimethylsilyloxy)methyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-2-oxo-1,3-dioxol-4-yl)methyl)-2,2-dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)acetamide (100 mg, 0.10 mmol) and 50% TFA (0.25 mL) were dissolved in anhydrous dichloromethane (5 mL) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 1 h. After the removal of the solvents the crude residue was purified by silica gel chromatography (CH_2Cl_2/MeOH = 9/1) to obtain 2,2-dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-((5-((4,5-dihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-2-oxo-1,3-dioxol-4-yl)methyl)acetamidein. ^{1}H NMR (CD_3OD): 7.81 (s, 1H), 7.60 (m, 1H), 7.58 (m, 1H), 7.48-7.34 (m, 4H), 6.55 (s, 1H), 5.89 (s, 1H), 4.95 (m, 1H), 4.55-4.23 (m, 2H), 3.92 (m, 2H), 3.76-3.46 (m, 5H), 2.28 ppm (m, 2H). MW=690 confirmed by LC-MS, t_r= 10.82 min (**Method Y1**) MH^+=688-692.

[0295] **Cpd. 1008:** 1-Adamantyl 2,2-Dichloro-3-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenylamino)-3-oxopropanoate; MW=594 confirmed by LC-MS, t_r= 14.77 min (**Method A**) MH^+=591-597.

[0296] **Cpd. 1009:** 2,2-Dichloro-N^1-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N^3-(3-morpholinopropyl)malonamide; MW=586 confirmed by LC-MS, t_r= 10.76 min (**Method Y1**) MH^+=584-590.

[0297] **Cpd. 1010:** 2,2-Dichloro-N^1-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N^3-methylmalonamide; MW=473 confirmed by LC-MS, t_r= 14.27 min (**Method Y1**) MH^+=471-476.

[0298] **Cpd. 1011:** 2,2-Dichloro-N^1-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N^3-(pyridin-2-ylmethyl)malonamide; MW=550 confirmed by LC-MS, t_r= 13.17 min (**Method Y1**) MH^+=547-553.

[0299] **Cpd. 1012:** 2,2-Dichloro-N^1-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N^3-(2-hydroxyethyl)malonamide; MW=502 confirmed by LC-MS, t_r= 13.17 min (**Method Y1**) MH^+=499-505.

[0300] **Cpd. 1013:** Propyl 4-((2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)acetamido)methyl)phenylcarbamate; MW=607 confirmed by LC-MS, t_r= 16.90 min (**Method Y1**) MH^+=604-610.

[0301] **Cpd. 1014:** 2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-((2-oxo-5-(pyrrolidin-2-yl)-1,3-dioxol-4-yl)methyl)acetamide; MW=583 confirmed by LC-MS, t_r= 11.24 min (**Method Y1**) MH^+=580-586.

[0302] **Cpd. 1015:** 2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-((2-oxo-5-(piperidin-3-yl)-1,3-dioxol-4-yl)methyl)acetamide; MW=597 confirmed by LC-MS, t_r= 10.60 min (**Method Y1**) MH^+=594-600.

[0303] **Cpd. 1016:** 2,2-Dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)-N-((5-neopentyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamide; MW=582 confirmed by LC-MS, t_r= 13.08 min (**Method A**) MH^+=579-585.

[0304] **Cpd. 1017:** 2,2-Dichloro-N-((5-cyclobutyl-2-oxo-1,3-dioxol-4-yl)methyl)-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)acetamide; MW=568 confirmed by LC-MS, t_r= 12.77 min (**Method A**) MH^+=565-571.

[0305] **Cpd. 1018:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-oxo-3-(piperidin-4-yl)propyl)acetamide; MW=556 confirmed by LC-MS, t_r= 9.99 min (**Method Y1**) MH^+=553-559.

[0306] **Cpd. 1019:** *tert*-Butyl 2,2-Dichloro-3-(3-(3-(2-chloro-6-methoxyphenyl)isoxazol-5-yl)phenylamino)-3-oxopropanoate; MW=512 confirmed by LC-MS, t_r= 17.02 min (**Method Y1**) MH^+=510-514.

[0307] **Cpd. 1020:** Isopropyl 2,2-Dichloro-3-(3-(3-(2-chloro-6-methoxyphenyl)isoxazol-5-yl)phenylamino)-3-oxopropanoate; MW=498 confirmed by LC-MS, t_r= 16.55 min (**Method Y1**) MH^+=496-500.

[0308] **Cpd. 1021:** *tert*-Butyl 4-((2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)methyl)benzoate.

[0309] **Cpd. 1022:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(4-(2-morpholinoethoxy)benzyl)acetamide; MW=636 confirmed by LC-MS, t_r= 11.79 min (**Method Y1**) MH^+=634-638.

[0310] **Cpd. 1023:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(4-(4-ethylpiperazin-1-yl)benzyl)acetamide; MW=619 confirmed by LC-MS, t_r= 11.75 min (**Method Y1**) MH^+=617-621.

[0311] **Cpd. 1024:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-oxo-3-(pyrrolidin-2-yl)propyl)acetamide; MW=542 confirmed by LC-MS, t_r= 10.47 min (**Method Y1**) MH^+=540-544.

[0312] **Cpd. 1025:** N-((5-Benzyl-2-oxo-1,3-dioxol-4-yl)methyl)-2,2-dichloro-N-(3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)phenyl)acetamide; MW=604 confirmed by LC-MS, t_r= 16.78 min (**Method Y1**) MH^+=602-606.

[0313] **Cpd. 1026:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(2-morpholinoethyl)acetamide; MW=530 confirmed by LC-MS, t_r= 11.16 min (**Method Y**) MH^+=528-532.

[0314] **Cpd. 1027:** 4-((2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)methyl)-2,6-dimethylphenyl Propylcarbamate (FIG. 28); MW=636 confirmed by LC-MS, t_r= 16.41 min (**Method Y1**) MH^+=634-638.

[0315] **Cpd. 1028:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-((2-(pyridin-2-yl)ethoxy)methyl)acetamide; MW=552 confirmed by LC-MS, t_r= 12.08 min (**Method Y1**) MH^+=550-554.

[0316] **Cpd. 1029:** 3-Chloro-2-(5-(3-(2,2-dichloro-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamido)phenyl)isoxazol-3-yl)benzoic Acid; MW=565 confirmed by LC-MS, t_r= 15.00 min (**Method Y1**) MH^+=563-567.

[0317] **Cpd. 1030:** 2,2-Dichloro-N-(3-(3-(2-cyclopropyl-6-(trifluoromethyl)phenyl)isoxazol-5-yl)phenyl)-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamide; MW=595 confirmed by LC-MS, t_r= 17.15 min (**Method Y1**) MH^+=593-597.

[0318] **Cpd. 1031:** 2,2-Dichloro-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)-N-(3-(3-(2-methoxy-6-(trifluoromethyl)phenyl)isoxazol-5-yl)phenyl)acetamide; MW=585 confirmed by LC-MS, t_r= 15.98 min (**Method Y1**) MH^+=583-587.

[0319] **Cpd. 1032:** Methyl 3-Chloro-2-(5-(3-(2,2-dichloro-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamido)phenyl)isoxazol-3-yl)benzoate; MW=579 confirmed by LC-MS, t_r= 15.95 min (**Method Y1**) MH^+=577-581.

[0320] **Cpd. 1033:** *tert*-Butyl 4-(3-Chloro-2-(5-(3-(2,2-dichloro-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamido)phenyl)isoxazol-3-yl)phenoxy)piperidine-1-carboxylate ; MW=721 confirmed by LC-MS, t_r= 17.60 min (**Method Y1**) MH^+=719-723.

[0321] **Cpd. 1034:** 2,2-Dichloro-N-(3-(3-(2-chloro-6-(piperidin-4-yloxy)phenyl)isoxazol-5-yl)phenyl)-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamide; MW=621 confirmed by LC-MS, t_r= 11.60 min (**Method Y1**) MH^+=619-623.

[0322] **Cpd. 1035:** N-(3-(3-(2-(1-Acetylpiperidin-4-yloxy)-6-chlorophenyl)isoxazol-5-yl)phenyl)-2,2-dichloro-N-((5-isopropyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamide; MW=663 confirmed by LC-MS, t_r= 14.72 min (**Method Y**) MH^+=661-665.

[0323] **Cpd. 1036:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-((5-neopentyl-2-oxo-1,3-dioxol-4-yl)methyl)acetamide; MW=583 confirmed by LC-MS, t_r= 17.00 min (**Method Y1**) MH^+=581-585.

[0324] **Cpd. 1037:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-((1-methyl-1H-imidazol-2-yl)methyl)acetamide; MW=511 confirmed by LC-MS, t_r= 3.69 min (**Method B**) MH^+=509-513.

[0325] **Cpd. 1038:** 4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propyl)phenyl Diethyl Phosphate; MW=687 confirmed by LC-MS, t_r= 16.15 min (**Method Y1**) MH^+=685-689.

[0326] **Cpd. 1039:** *tert*-Butyl 4-(4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propyl)phenyl)piperazine-1-carboxylate; MW=719 confirmed by LC-MS, t_r= 18.02 min (**Method Y1**) MH^+=717-721.

[0327] **Cpd. 1040:** *tert*-Butyl 4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propyl)benzoate; MW=635 confirmed by LC-MS, t_r= 18.38 min (**Method Y1**) MH^+=633-637.

[0328] **Cpd. 1041:** Di-*tert*-Butyl 4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propyl)benzylphosphonate; MW=741 confirmed by LC-MS, t_r= 17.50 min (**Method Y1**) MH^+=739-743.

[0329] **Cpd. 1042:** 4-(3-(2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)acetamido)propyl)benzylphosphonic Acid; MW=629 confirmed by LC-MS, t_r= 12.06 min (**Method Y1**) MH^+=627-631.

[0330] **Cpd. 1043:** 2,2-Dichloro-N-(2-(3-(2,6-dichlorophenyl)isoxazol-5-yl)pyridin-4-yl)-N-(3-(4-(piperazin-1-yl)phenyl)propyl)acetamide; MW=629 confirmed by LC-MS, t_r= 11.73 min (**Method Y1**) MH^+=627-631.

[0331] **Cpd. 1044:** N-(2,2-Dichloroacetyl)-3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)-N-((5-((4,5-dihydroxy-6-(hydroxymethyl)-tetrahydro-2H-pyran-2-yloxy)methyl)-2-oxo-1,3-dioxol-4-yl)methyl)benzamide; MW=690 confirmed by LC-MS, t_r= 10.82 min (**Method Y1**) MH^+=688-692.

Synthesis of Compound 311a (Fig. 11)

Synthesis of N-[2-(4-Fluorobenzoyl)ethyl]-3-ethynylaniline (Compound 305a)

[0332] 3-Ethynylaniline **301a** (2.68 g, 22.8 mmol) was heated with 3-chloro-4'-fluoropropiophenone **303a** (3.86 g, 20.7 mmol) and triethylamine (3.85 mL, 24.7 mmol) in tetrahydrofuran (40 mL) at 65 °C for 14h. The reaction mixture was concentrated to a small volume, diluted with ethyl acetate and then washed with saturated sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated to a small volume. Upon cooling white crystals formed. These were filtered off to give N-[2-(4-fluorobenzoyl)ethyl]-3-ethynylaniline **305a**, (1.98 g). ^{1}H NMR ($CDCl_3$) δ 7.94-7.99 (m, 2H), 7.08-7.15 (m, 3H), 6.83-6.87 (m, 1H), 6.76 (m,1H), 6.61-6.64 (m,1H), 3.61 (t, *J=6.0*, 2H) , 3.25 (t, *J=6.0*, 2H), 3.02 (s, 1H). MS (m/z): 268 (MH^+) confirmed by LC-MS, t_r= 14.36 min (**Method Y**).

Synthesis of 2',2'-Dichloro-N-(3'-ethynylphenyl)-N-[2-(4-fluorobenzoyl)ethyl] Acetamide (Compound 307a)

[0333] N-[2-(4-fluorobenzoyl)ethyl]-3-ethynylaniline **305a** (1.69 g, 6.25 mmol) was dissolved in dichloromethane (40 mL) with triethylamine (1.14 mL, 1.3 molar equivalents). The solution was cooled on an ice-water bath and then a solution of dichloroacetyl chloride (0.66 mL, 1.1 molar equivalent) in dichloromethane (5 mL) was added dropwise. The reaction mixture was allowed to stir overnight while warming to room temperature. The solution was washed successively with water and saturated sodium bicarbonate solution, then dried over anhydrous sodium sulfate and concentrated under vacuum. Flash column chromatography, on silica gel, eluting with a mixture of 20% ethyl acetate in hexanes gave 2',2'-dichloro-N-(3'-ethynylphenyl)-N-[2-(4-fluorobenzoyl)ethyl] acetamide **307a** as a solid, (400 mg). ^{1}H NMR ($CDCl_3$) δ 7.84-7.94 (m, 2H), 7.51 (m, 1H), 7.42(m, 1H), 7.37 (m, 1H), 7.24-7.27 (m, 1H), 7.04-710 (m, 2H), 5.79 (s, 1H), 4.08 (t, J=7.7, 2H), 3.30 (t, *J=7.7*, 2H), 3.19 (s, 1H). MS (m/z): 376-380 (MH^+) confirmed by LC-MS, t_r= 14.72 min (**Method Y**).

Synthesis of 2',2'Dichloro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazolyl]phenyl]-N-[2-(4-fluorobenzoyl)ethyl] Acetamide (Compound 311a)

[0334] 2',2'-Dichloro-N-(3'-ethynylphenyl)-N-[2-(4-fluorobenzoyl)ethyl] acetamide **307a** (0.40 g, 1.05 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) and treated with 2,6-dichloro-N-hydroxybenzenecarboximidoyl chloride **309a** (0.25 g, 1.12 mmol) and triethylamine (0.20 mL, 1.42 mmol). The solution was heated at reflux for 4.5h. The reaction was then cooled to room temperature, diluted with ethyl acetate and washed with saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography, on silica gel, eluting with 20% ethyl acetate in hexanes. 2',2'-Dichloro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazolyl]phenyl]-N-[2-(4-fluorobenzoyl)ethyl] acetamide **100a** was obtained as a white solid, (165 mg). ^{1}H NMR ($CDCl_3$) δ 7.88-7.98 (m, 3H), 7.78 (broad s, 1H), 7.61 (t, *J=7.8*, 1H), 7.31-7.44 (m, 4H), 7.07-7.13 (m, 2H), 6.69 (s, 1H), 5,88 (s, 1H), 4.18 (t, *J=7.3*, 2H), 3.38 (t, *J=7.3*, 2H). MS (m/z): 564-568 (MH^+) confirmed by LC-MS, t_r= 12.81 min (**Method A**).

[0335] Similarly, various acetamides equivalent to that shown in FIG. 11 can be prepared according to the general reaction sequence depicted in FIG. 12, where W can be CH or N and X is a substituent, including hydrogen, on the aryl group.

Synthesis of Compound 407a (Fig. 13)

Synthesis of N-[2-(3-Benzoyl)propyl]-3-ethynylaniline (Compound 405a)

[0336] 3-Ethynylaniline **301a** (2.03 g, 17.8 mmol) was heated with phenyl propenyl ketone **403a** (2.27 g, 15.6 mmol) and triethylamine (2.67 mL,19 mmol) in tetrahydrofuran (40 mL) at 65 °C for 42h. The reaction mixture was concentrated to a small volume, diluted with ethyl acetate and then washed with saturated sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography, on silica gel, eluting with 20% ethyl acetate in hexanes to give N-[2-(3-benzoyl)propyl]-3-ethynylaniline **405a** as a pale yellow oil, (450 mg). ^{1}H NMR ($CDCl_3$) δ 7.91-7.94 (m, 2H), 7.53-7.57 (m, 1H), 7.42-7.48 (m, 2H), 7.09 (t, *J=7.8*, 1H), 6.82-6.85 (m, 1H), 6.74 (m, 1H), 6.61 (dd, *J=8.0, 2.5*, 1H), 4.14 (m, 1H), 3.92 (broad s, 1H), 3.28 (dd, *J=16,4, 4.2*, 1H), 3.08 (dd, *J=16.5, 7.2*, 1H), 3.01 (s, 1H), 1.33 (d, *J=6.3*, 3H). MS (m/z): 264 (MH^+) confirmed by LC-MS, t_r= 14.71 min (**Method Y**).

Synthesis of N-[2-(3-Benzoyl)propyl]-3-[3-(2,6-dichlorophenyl)-5-isoxazolyl] Aniline (Compound 407a)

[0337] N-[2-(3-Benzoyl)propyl]-3-ethynylaniline **405a** (0.45 g, 1.7 mmol) was dissolved in anhydrous tetrahydrofuran (20 mL) and treated with 2,6-dichloro-N-hydroxybenzenecarboximidoyl chloride **309a** (0.40 g, 1.8 mmol) and triethylamine (0.31 mL, 2.28 mmol). The solution was heated at reflux for 6h. The reaction was then cooled to room temperature, diluted with ethyl acetate and washed with saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by flash column chromatography, on silica gel, eluting with 20% ethyl acetate in hexanes. N-[2-(3-Benzoyl)propyl]-3-[5-[3-(2,6-dichlorophenyl)]isoxazolyl] aniline **407a** was obtained as a white solid, (330 mg). ^{1}H NMR ($CDCl_3$) δ 7.91-7.94 (m, 2H), 7.54 (m, 1H), 7.39-7.46 (m, 4H), 7.24-7.31 (m, 1H), 7.23 (m, 1H). 7.11-7.16 (m, 2H), 6.71 (m, 1H), 6.55 (s, 1H), 4.21 (m, 1H), 3.32 (dd, *J=16.4, 4.4*, 1H), 3.12 (dd, *J=16.4, 6.9*, 1H), 1.35 (d, *J=7.3*, 3H). MS (m/z): 449-453 (MH^+) confirmed by LC-MS, t_r= 17.40 min (**Method Y**).

Synthesis of 2',2'-Dichloro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazolyl]phenyl]-N-[2-(3-benzoyl)propyl] Acetamide (Compound 407a)

[0338] N-[2-(3-Benzoyl)propyl]-3-[3-(2,6-dichlorophenyl)-5-isoxazolyl] aniline **407a** (0.33 g, 0.73 mmol) was dissolved in dichloromethane (10 mL) with triethylamine (0.15 mL). The solution was cooled on an ice-water bath and then a solution of dichloroacetyl chloride (85 μL, 1.2 molar equivalents) in dichloromethane (2 mL) was added dropwise. The reaction mixture was allowed to stir overnight while warming to room temperature. The solution was washed successively with 10% aqueous hydrochloric acid, water and saturated sodium bicarbonate solution, then dried over anhydrous sodium sulfate and concentrated under vacuum. Flash column chromatography, on silica gel, eluting with a mixture of 25% ethyl acetate in hexanes gave 2',2'-dichloro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazolyl]phenyl]-N-[2-(3-benzoyl)propyl] acetamide **107a** as a white solid, (113 mg). ^{1}H NMR ($CDCl_3$) δ 7.95-7.98 (m, 2H), 7.91 (m, 1H), 7.65(m, 1H), 7.61 (m, 1H), 7.50-7.55 (m, 1H), 7.40-7.47 (m, 4H), 7.36-7.40 (m, 1H), 6.64 (broad s, 1H), 5.72 (broad s, 1H), 4.99 (m, 1H), 3.69 (dd, *J=16.2, 7.2*, 1H), 3.13 (dd, *J=16.2, 6.9*, 1H), 1.42 (d, *J=6.9*, 3H). MS (m/z): 583-587 (MH^+ + Na) confirmed by LC-MS, t_r= 12.93 min (**Method A**).

[0339] Similarly, various acetamides equivalent to that shown in FIG. 13 can be prepared according to the general reaction sequence depicted in FIG. 14, where W can be CH or N and X is a substituent, including hydrogen, on the aryl group.

Synthesis of Compound 605a (Fig. 15)

Synthesis of 3-(2,6-Dichlorophenyl)-5-[5-[N-[2-(4-fluorobenzoyl)ethyl]amino-2-pyridyl]isoxazole (Compound 603a)

[0340] 3-Chloro-4'-fluoropropiophenone **303a** (220 mg, 1.2 mmol) was added to a mixture of 3-(2,6-dichlorophenyl)-5-(5-amino-2-pyridyl)isoxazole **601a** (400 mg, 1.2 mmol) and triethylamine (0.3 mL, 2.4 mmol) in acetonitrile (40 mL). The solution was heated at reflux. After two hours a second portion of 3-chloro-4'-fluoropropiophenone (220 mg, 1.2 mmol) was added, along with a second portion of triethylamine (0.3 mL, 2.4 mmol). After stirring at reflux overnight, the reaction mixture was cooled to room temperature and then washed successively with water, 10% hydrochloric acid and saturated sodium bicarbonate solution. The organic solution was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by prep-scale reverse phase high performance liquid chromatography to give **603a** as a white solid (60 mg, 11%). ^{1}H NMR (300 MHz, $CDCl_3$): 8.33 (m, 1H), 8.00 (m, 2H), 7.39 (m, 5H), 7.17 (m, 2H), 6.64 (m, 1H), 3.81 (m, 2H), 3.38 ppm (m, 2H).

Synthesis of 2',2'-Dichloro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazolyl]-(pyridyl)]-N-[2-(4-fluorobenzoyl)ethyl] Acetamide (Compound 605a)

[0341] 3-(2,6-Dichlorophenyl)-5-[5-[N-[2-(4-fluorobenzoyl)ethyl]amino-2-pyridyl]isoxazole **603a** (60 mg, 0.17 mmol) was dissolved in dichloromethane (5 mL) with triethylamine (28 85 μL). The solution was cooled on an ice-water bath and then a solution of dichloroacetyl chloride (20 μL, 1.2 molar equivalents) in dichloromethane (0.5 mL) was added dropwise. The reaction mixture was allowed to stir overnight while warming to room temperature. The solution was washed successively with 10% aqueous hydrochloric acid, water and saturated sodium bicarbonate solution, then dried over anhydrous sodium sulfate and concentrated under vacuum. Purification by flash column chromatography, on silica gel, eluting with a mixture of 25% ethyl acetate in hexanes gave 2',2'-dichloro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazolyl]-(pyridyl)]-N-[2-(4-fluorobenzoyl)ethyl] acetamide **605a** as a white solid, (12 mg, 13%). ^{1}H NMR (300 MHz, $CDCl_3$): 8.82 (m, 1H), 7.92 (m, 3H), 7.40 (m, 4H), 7.18 (m, 3H), 6.00 (broad s, 1H), 4.27 (m, 2H), 3.43 ppm (m, 2H).

[0342] Similarly, various acetamides equivalent to that shown in FIG. 5 can be prepared according to the general reaction sequence depicted in FIG. 6, where W can be CH or N and X is a substituent, including hydrogen, on the aryl group.

[0343] The following compounds were prepared by the methods described herein.

[0344] **Cpd. 311a**: 2',2'-Dichloro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazolyl]phenyl]-N-[2-(4-fluorobenzoyl)ethyl] Acetamide; MW=566 confirmed by LC-MS, t_r= 12.81 min (**Method A**) MH^+=564-568

[0345] **Cpd. 102a**: 2',2'-Dichloro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazolyl]phenyl]-N-[2-(benzoyl)ethyl] Acetamide; MW=548 confirmed by LC-MS, t_r= 16.82 min (**Method Y**) MH^+=546-550

[0346] **Cpd. 103a**: 2',2'-Dichloro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazolyl]phenyl]-N-[2-(4-methoxybenzoyl)ethyl] Acetamide; MW=578 confirmed by LC-MS, t_r= 16.69 min (**Method Y**) MH^+=576-580

[0347] **Cpd. 104a**: 2',2'-Dichloro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazolyl]phenyl]-N-[2-(4-chlorobenzoyl)ethyl] Acetamide; MW=583 confirmed by LC-MS, t_r= 13.22 min (**Method A**) MH^+=581-585

[0348] **Cpd. 407a**: 2',2'-Dichloro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazolyl]phenyl]-N-[2-[3-(benzoyl)propyl] Acetamide; MW=562 confirmed by LC-MS, t_r= 12.93 min (**Method A**) M^+Na=582-586

[0349] **Cpd. 605a**: 2',2'-Dichloro-N-[3-[3-(2,6-dichlorophenyl)-5-isoxazolyl]-(4-pyridyl)]-N-[2-(4-fluorobenzoyl)ethyl] Acetamide; MW=567 confirmed by LC-MS, t_r= 16.31 min (**Method Y**) MH^+= 565-569

[0350] **Cpd. 127a**: 2',2'-Dichloro-N-[3-[3-[2-chloro-6-(N'-acetyl-4-piperdinyloxy)phenyl]-5-isoxazolyl]phenyl]-N-[2-(4-fluorobenzoyl)ethyl] Acetamide; MW=671 confirmed by LC-MS, t_r= 15.26 min (**Method Y**) MH^+= 669-673

[0351] **Cpd. 114a**: 2',2'-Dichloro-N-[3-[3-(2-cyclopropyl-6-trifluoromethylphenyl)-5-isoxazolyl]phenyl]-N-[2-(4-fluorobenzoyl)ethyl] Acetamide; MW=605 confirmed by LC-MS, t_r= 17.26 min (**Method Y**) MH^+= 603-607

[0352] **Cpd. 113a**: 2',2'-Dichloro-N-[3-[3-(2-chloro-6-methoxyphenyl)-5-isoxazolyl]phenyl]-N-[2-(4-fluorobenzoyl)ethyl] Acetamide; MW=562 confirmed by LC-MS, t_r= 16.44 min (**Method Y**) MH^+= 560-564

[0353] **Cpd. 128a**: 2',2'-Dichloro-N-[3-[3-(2-chloro-6-t-butoxycarbonylphenyl)-5-isoxazolyl]phenyl]-N-[2-(4-fluorobenzoyl)ethyl] Acetamide; MW=632 confirmed by LC-MS, t_r= 17.65 min (**Method Y**) MH^+= 630-634

[0354] **Cpd. 129a**: 2',2'-Dichloro-N-[3-[3-(2-chloro-6-hydroxycarbonylphenyl)-5-isoxazolyl]phenyl]-N-[2-(4-fluorobenzoyl)ethyl] Acetamide; MW=576 confirmed by LC-MS, t_r= min (**Method**) MH^+=574-578

[0355] **Cpd. 133a:** 2',2'-Dichloro-N-[3-[3-(2-chloro-6-methoxycarbonylphenyl)-5-isoxazolyl]phenyl]-N-[2-(4-fluorobenzoyl)ethyl] Acetamide; MW=590 confirmed by LC-MS, t_r= min (**Method Y**) MH^+= 588-592

Assays For Modulation Of HCV

[0356] As stated previously, the prodrugs of the invention or the metabolically active agents of the prodrug, A-B-C-NHCOCHX_2, are potent inhibitors of HCV replication and/or proliferation. The activity of the prodrugs of the invention, or their metabolites, can be confirmed in *in vitro* assays suitable for measuring inhibition of viral or retroviral replication and/or proliferation. The assays may investigate any parameter that is directly or indirectly under the influence of HCV, including, but not limited to, protein-RNA binding, translation, transcription, genome replication, protein processing, viral particle formation, infectivity, viral transduction, etc. Such assays are well-known in the art. Regardless of the parameter being investigated, in one embodiment, to examine the extent of inhibition, samples, cells, tissues, etc. comprising an HCV replicon or HCV RNA are treated with a potential inhibitory prodrug (test compound) and the value for the parameter compared to control cells (untreated or treated with a vehicle or other placebo). Control samples are assigned a relative activity value of 100%. Inhibition is achieved when the activity value of the metabolically active agent of the prodrug relative to the control is about 90%, preferably 50%, and more preferably 25-0%.

[0357] Alternatively, the extent of inhibition may be determined based upon the IC_{50} of the metabolically active agent of the prodrug in the particular assay, as will be described in more detail, below.

[0358] In one embodiment, the inhibitory activity of the metabolically active agent of the prodrug can be confirmed in a replicon assay that assesses the ability of a test compound to block or inhibit HCV replication in replicon cells. One example of a suitable replicon assay is the liver cell-line Huh 7-based replicon assay described in Lohmann et al., 1999, Science 285:110-113. A specific example of this replicon assay which utilizes luciferase translation is provided in the Examples Section. In one embodiment of this assay, the amount of test prodrug that yields a 50% reduction in translation as compared to a control cell (IC_{50}) may be determined.

[0359] Alternatively, the inhibitory activity of the metabolically active agents of the prodrugs can be confirmed using a quantitative Western immunoblot assay utilizing antibodies specific for HCV non-structural proteins, such as NS3, NS4A NS5A and NS5B. In one embodiment of this assay, replicon cells are treated with varying concentrations of test prodrug to determine the concentration of the metabolically active agent of the test prodrug that yields a 50% reduction in

the amount of a non-structural protein produced as compared to a control sample (IC_{50}). A single non-structural protein may be quantified or multiple non-structural proteins may be quantified. Antibodies suitable for carrying out such immunoblot assays are available commercially (e.g., from BIODESIGN International, Saco, ME).

[0360] Alternatively, the inhibitory activity of the metabolically active agent of the prodrugs may be confirmed in an HCV infection assay, such as the HCV infection assay described in Fournier *et al.*, 1998, J. Gen. Virol. 79(10):2367:2374, the disclosure of which is incorporated herein by reference. In one embodiment of this assay, the amount of test prodrug that is metabolized into an active agent that yields a 50% reduction in HCV replication or proliferation as compared to a control cell (IC_{50}) may be determined. The extent of HCV replication may be determined by quantifying the amount of HCV RNA present in HCV infected cells. A specific method for carrying out such an assay is provided in the Examples section.

[0361] As yet another example, the inhibitory activity of the metabolically active agent of the prodrugs can be confirmed using an assay that quantifies the amount of HCV RNA transcribed in treated replicon cells using, for example, a Taqman assay (Roche Molecular, Alameda, CA). In one embodiment of this assay, the amount of test prodrug that is metabolized into an active agent that yields a 50% reduction in transcription of one or more HCV RNAs as compared to a control sample (IC_{50}) may be determined.

[0362] Regardless of the assay used, metabolically active agents of the prodrugs are generally those which exhibit IC_{50}s in the particular assay in the range of about 1 mM or less. Prodrugs that are metabolized into active agents which exhibit lower IC_{50}s, for example, in the range of about 100 μM, 10 μM, 1 μM, 100 nM, 10 nM, 1 nM, or even lower, are particularly useful for as therapeutics or prophylactics to treat or prevent HCV infections.

Prodrugs of the Invention Metabolize into Active Agents that Inhibit HCV Translation or Replication

Replicon Assay

[0363] The inhibitory activity of certain prodrugs of the invention, which may inhibit HCV translation or replication prior to metablism and/or are metabolized into active agents, was confirmed using an HCV replicon assay. The HCV replicon can include such features as the HCV 5' untranslated region including the HCV IRES, the HCV 3' untranslated region, selected HCV genes encoding HCV polypeptides, selectable markers, and a reporter gene such as luciferase, GFP, *etc.* In the assay, actively dividing 5-2 Luc replicon-comprising cells (obtained from Ralf Bartenschlager; see Lohmann *et al.*, 1999, Science 285:110-113) were seeded at a density of

between about 5,000 and 7,500 cells/well onto 96 well plates (about 90 µl of cells per well) and incubated at 37 °C and 5% CO_2 for 24 hours. Then, the test prodrug (in a volume of about 10 µl) was added to the wells at various concentrations and the cells were incubated for an additional 24-48 hours before luciferase assay. The media was aspirated from each well and Bright-Glo (Promega, Madison, WI) luciferase assay reagents were added to each well according to the manufacturer's instructions. Briefly, the Bright-Glo reagent was diluted 1:1 with PBS and 100 µl of diluted reagent was added to each well. After 5 min of incubation at room temperature, luciferin emission was quantified with a luminometer. In this assay, the amount of test prodrug that yielded a 50% reduction in luciferase emission (IC_{50}) was determined. This IC_{50} value may represent the antiviral activity of the prodrug itself, the activity of prodrug transformed into its active metabolized form, or a combination of the two.

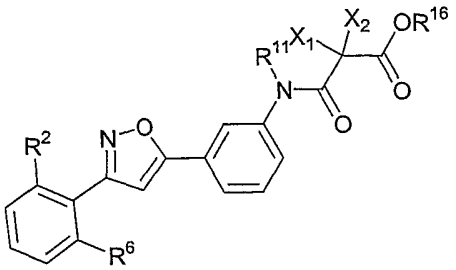
Western Blot Assay

[0364] Certain prodrugs of the invention, which may inhibit HCV translation or replication prior to metablism and/or are metabolized into active agents, were also tested for their ability to inhibit HCV replication using a quantitative Western blot analysis with antibodies specific for the HCV NS5A or other non-structural proteins. Actively dividing 9-13 replicon cells were seeded into 6-well plates at a density of $1X10^5$ cells/well in a volume of 2 ml/well and incubated at 37°C and 5% CO_2 for 24 hours. Various concentrations of test prodrugs (in a volume of 10 ul) were added to the wells and the cells incubated for another 48 hours. Protein samples were prepared from the cultured cells, resolved on a SDS-PAGE gel and transferred to a nitrocellulose membrane. The membrane was blocked with 5% non-fat milk in PBS for 1 hour at room temperature. Primary antibody (anti NS5A antibody; BIODESIGN International, Saco, ME) incubation was performed for 1 hour at room temperature, after which the membrane was washed 3 times (for 15 min per time) with PBST (PBS plus 0.1% Tween 20). Horseradish peroxidase conjugated secondary antibody incubation was performed for 1 hour at room temperature and the membrane was washed 3 times (for 15 min per time) with PBST. The membrane was then soaked in substrate solution (Pierce) and exposed to a film or quantified using an imager. In this assay, the amount of test prodrug that is believed to be transformed into an active agent under the given conditions that yielded a 50% reduction in the amount of NS5A protein translated as compared to a control sample (IC_{50}) was determined.

[0365] The results of the Replicon assays are provided in TABLES 3-12 and 14, below. In TABLES 3 through 12, a value of "+" indicates an IC_{50} of 10 µM or less in the specified assay; a value of "-" indicates an IC_{50} of greater than 10 µM in the specified assay. Many of the

metabolically active agents of the prodrugs exhibited IC_{50}s in the Replicon assay in the nanomolar range.

TABLE 3



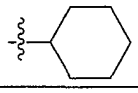
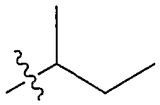
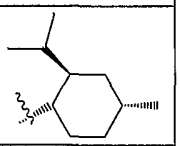
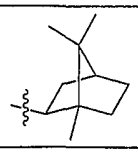
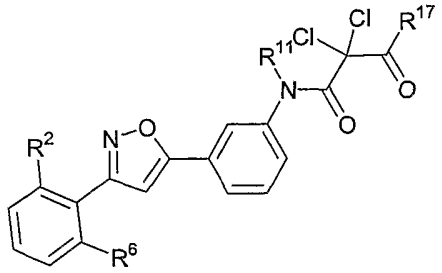
Cpd	Replicon	X_1	X_2	R^2	R^6	R^{11}	R^{16}
18	+	Cl	Cl	Cl	Cl	H	-Me
30	+	Cl	Cl	CF_3	F	H	-Me
29	+	Cl	Cl	CF_3	H	H	-Me
27	+	Cl	Cl	Cl	OMe	H	-Me
26	+	Cl	Cl	CF_3		H	-Me
16	+	Cl	Cl	Cl	Cl	H	$-CH(CH_3)_2$
17	+	Cl	Cl	Cl	Cl	H	$-CH_2$-phenyl
15	+	Cl	Cl	Cl	Cl	H	-*t*-butyl
13	+	Cl	Cl	Cl	Cl	H	
14	+	Cl	Cl	Cl	Cl	H	-neopentyl
809	+	Cl	Cl	Cl	Cl	H	-*i*-propyl
12	+	Cl	Cl	Cl	Cl	H	
11	+	Cl	Cl	Cl	Cl	H	
9	+	Cl	Cl	Cl	Cl	H	

TABLE 4



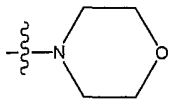
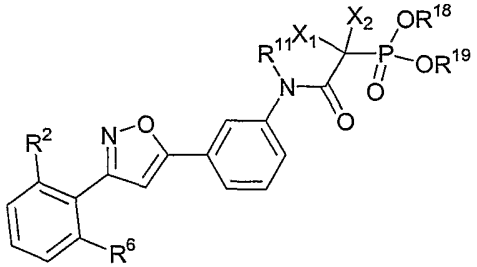
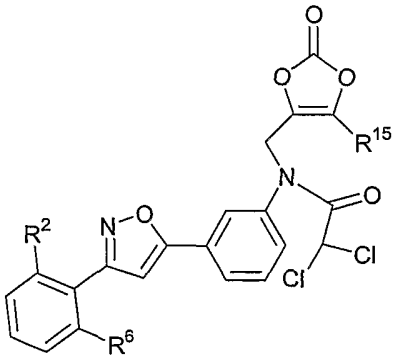
Cpd	Replicon	R^2	R^6	R^{11}	R^{17}
50	+	Cl	Cl	H	
10	-	Cl	Cl	H	-Me

TABLE 5



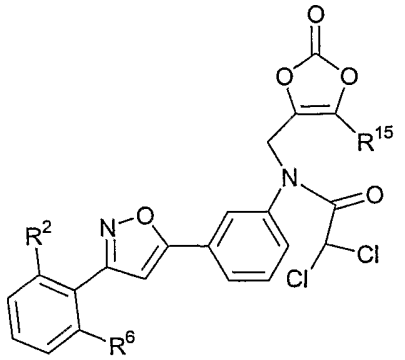
Cpd	Replicon	X1	X2	R^2	R^6	R^{11}	R^{18}/R^{19}
405	+	Cl	Cl	Cl	Cl	H	-Et/-Et
407	-	Cl	Cl	Cl	Cl	H	H/H
5	+	Cl	Cl	CF_3	H	H	-Et/-Et
6	+	Cl	Cl	CF_3	F	H	-Et/-Et
4	+	Cl	Cl	Cl	Cl	H	-*i*-propyl/-*i*-propyl
2	-	Cl	F	Cl	Cl	H	-Et/-Et
3	-	F	F	Cl	Cl	H	-Et/-Et

TABLE 6



Cpd	Replicon	R^2	R^6	R^{15}
907	+	Cl	Cl	-Me
31	+	Cl	OMe	-Me

TABLE 6



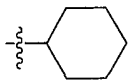
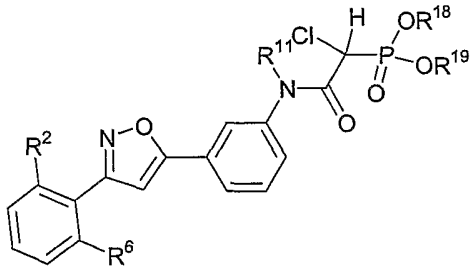
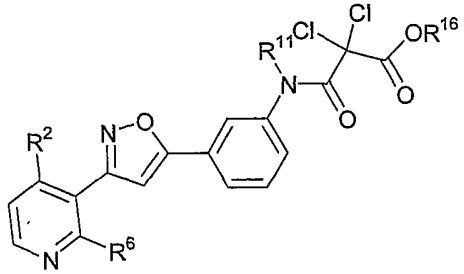
Cpd	Replicon	R^2	R^6	R^{15}
34	+	Cl	Cl	-*i*-propyl
40	+	Cl	Cl	-Et
39	+	Cl	Cl	
44	-	Cl	Cl	C(O)OEt
38	+	Cl	Cl	-n-propyl
36	+	Cl	-C(O)O-*t*-butyl	-*i*-propyl
37	+	Cl	-OMe	-*i*-propyl
1007	+	Cl	Cl	-*t*-butyl

TABLE 7



Cpd	Replicon	R^2	R^6	R^{11}	R^{18}/R^{19}
1	-	Cl	Cl	H	-Et/-Et

TABLE 8



Cpd	Replicon	R^2	R^6	R^{11}	R^{16}
28	+	Cl	$-N(CH_3)_2$	H	-Me

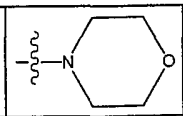
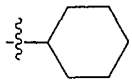
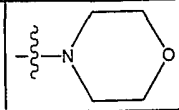
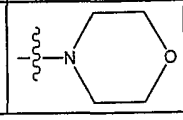
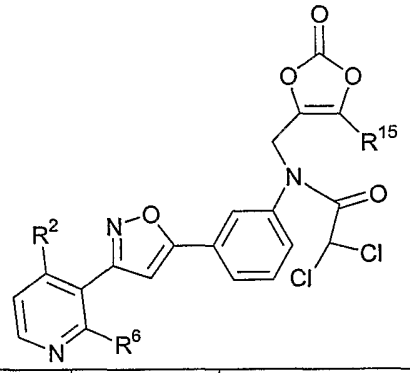
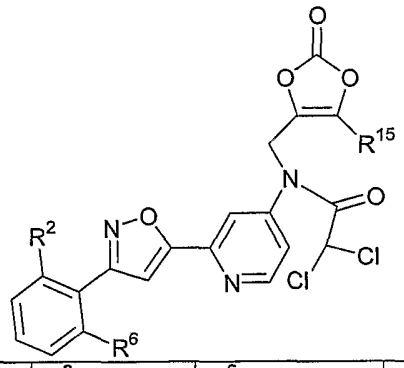
52	-		Cl	H	
54	-		Cl	H	-Et
56	-		Cl	H	-*t*-butyl

TABLE 9



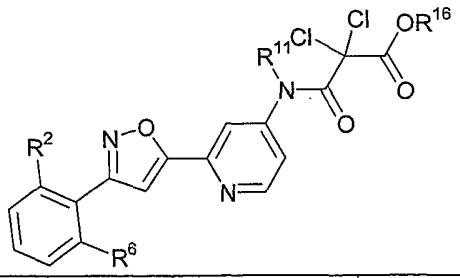
Cpd	Replicon	R^2	R^6	R^{15}
32	+	Cl	Cl	-Me
33	+	Cl	$-N(CH_3)_2$	-Me
35	+	Cl	$-N(CH_3)_2$	-*i*-propyl

TABLE 10



Cpd	Replicon	R^2	R^6	R^{15}
41	+	Cl	Cl	-Me
42	+	Cl	Cl	-*i*-propyl
1107	+	Cl	Cl	-*t*-butyl
43	+	Cl	Cl	-*n*-pentyl

TABLE 11



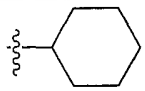
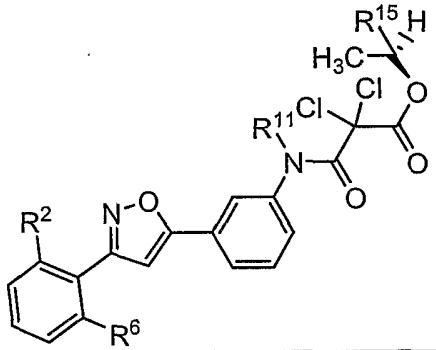
Cpd	Replicon	R^2	R^6	R^{11}	R^{16}
505	+	Cl	Cl	H	-t-butyl
23	+	Cl	Cl	H	

TABLE 12



Cpd	Replicon	R^2	R^6	R^{11}	R^{15}
8	+	Cl	Cl	H	C(O)OEt

Luciferase Counter Screen

[0366] A counter screen was used to identify non-specific inhibitors of the luciferase reporter gene. In the counter screen, a cell line carrying a construct such as a CMV-driven luciferase gene was used to identify metabolically active agents of the prodrugs that inhibit the reporter gene, and not HCV. In these CMV-Luc cells, the DNA construct, which comprises a luciferase gene downstream of a CMV promoter, is permanently integrated into the chromosome of Huh7 cells. For the counter screen, actively dividing CMV-Luc cells were seeded at a density of 5000-7500 cells/well in a volume of 90 ul/well into 96 well plate(s). The cells were then incubated at 37°C and 5% CO_2 for 24 hours. Various concentrations of test prodrugs (in a volume of 10 ul) were added to the wells and the cells were incubated for 24-48 hours. Media was aspirated from each well and Bright-Glo (Pharmacia) luciferase assay reagents were added to each well according to the manufacturer's manual. Luciferin counts were taken using a luminometer. IC_{50} values were greater than 10 μM in the counter screen luciferase inhibition assay for the metabolically active agents of the prodrugs of TABLES 1 through 12 that were tested.

PCR Assay

[0367] A TaqMan RT-PCR assay (Roche Molecular Systems, Pleasanton, CA) was used to analyze HCV RNA copy numbers, which confirmed that the viral genome of HCV is not being replicated. Actively dividing 9-13 replicon cells were seeded at a density of 3 x 10^4 cells/well in a volume of 1 ml/well into 24-well plates. The cells were then incubated at 37° C and 5% CO_2 for 24 hours. Various concentrations of test prodrugs (in a volume of 10 ul) were added to the wells and the cells were incubated for an additional 24-48 hours. Media was removed by aspiration and RNA samples prepared from each well. TaqMan one step RT-PCR (Roche Molecular Systems, Alameda, CA) was performed using the freshly prepared RNA samples according to the manufacturer's manual and analyzed on an ABI Prism 7700 Sequence Detector (Applied Biosystems). The ratio of HCV RNA to cellular GAPDH RNA was used as in indication of specificity of HCV inhibition to confirm that the viral genome was not replicated.

HCV Infection Assay

[0368] The activity of a prodrug that is metabolized into an active agent can also be confirmed in an HCV infection assay. The assay can be carried out essentially as described in Fournier et al., 1998, J. Gen. Virol. 79:2367-2374. Briefly, hepatocyte cells from a doner can be plated on Day 1. On Day 3, the cells would be inoculated with HCV virus and test prodrug added. On Day 5, the medium would be changed and test prodrug would be added. On Day 7, the medium would be changed and test prodrug would be added. On Day 8, the RNA would be isolated and the HCV RNA quantified using a Taqman assay. Prodrugs that are metabolized into an active agent that exhibit an IC_{50} of less than 10 μM in this assay can be identified.

Determination of Non-Toxicity of Prodrugs In Cell Culture

[0369] Prodrugs can be tested in a cytotoxicity assay with liver cells including an HCV replicon (5-2 Luc cells, 9-13 cells or Huh-7 cells). In the assay, cells can be seeded onto 96-well plates (approx. 7500 cells/well in a volume of 90 μl) and grown for 24 hr at 37°C. On day 2, various concentrations of test prodrug (in a volume of 10 μl) would be added to the wells and the cells would be grown for an additional 48 hr at 37°C. On day 3, an ATP-dependent R-Luciferase assay (Cell Titer Glo assay) would be performed to determine the number of viable cells. Prodrugs that are metabolized into an active agent exhibiting an CC_{50} of greater than 10 μM would be considered as non-toxic.

Animal Studies

[0370] The safety of prodrugs can be evaluated in rats by oral, subcutaneous and intravenous administration in several experiments. Doses as high as 30 mg/kg/day can be monitored. Experimental procedures are summarized below.

[0371] In a first study the toxicity of prodrugs can be evaluated either by the subcutaneous (SC) route or the intravenous (IV via jugular cannula) route of administration in Sprague Dawley rats. Two male rats would be used in each group. A dose escalation scheme would be employed where a prodrug would be delivered IV or SC for 3 consecutive days at a dose of 10 mg/kg (study Days 1-3) in a 80%:20% - PEG/water vehicle; delivered one day IV or SC dose of 30 mg/kg (study Day 4) in 100% PEG; and an IV dose of 60 mg/kg (study Day 5) in 100% PEG. Prodrugs could be identified as being well tolerated at doses up to and including 30 mg/kg by both routes of administration.

[0372] In a second study prodrugs can be was administered by the IV route at doses of 10 and 30 mg/kg in 100% PEG. The volume administered for the 10 mg/kg dose would be 0.67 ml/kg/day and volume given the 30 mg/kg group would be 2 ml/kg/day. In addition, there would be two control groups. One control would receive 100 % PEG alone at a volume of 2 ml/kg/day while the other would be an untreated sham control group. All groups (except for the untreated control with 3 male rats) would include 4 male rats each. Parameters of study would include: clinical observations, body weights, hematology, clinical chemistry, gross necropsy, organ weights, bone marrow assessment and histopathology of selected organs. Decreases in red blood cells, hemoglobin and hematocrit relative to the untreated control but not the vehicle control could be determined.

[0373] In a third study prodrugs can be compared with other compounds and administered at a dose of 10 and 30 mg/kg in 100 % PEG and delivered by IV at a concentration of 1 ml/kg/day first via a jugular cannula and when the cannula failed by the lateral tail vein. A vehicle control group would receive the 100% PEG alone at the same volume. Groups would comprise 3 males and 3 females each. Before reducing the dose to 10 and 30 mg/kg two rats would receive 100 mg/kg IV at a volume of 1 ml/kg. Parameters of study would include: clinical observations, body weights, hematology, clinical chemistry, gross necropsy, organ weights and histopathology of selected organs (including injection sites).

Sustained Plasma Levels

[0374] The pharmacokinetic properties of prodrugs can be calculated in rats, monkeys and chimpanzees using the intravenous and subcutaneous routes of administration with a variety of

different delivery vehicles. Sustained plasma levels can be determined with several different liposome suspension vehicles using subcutaneous administration: (i) 5 mg/ml prodrug in water with 100 mg/ml lecithin; (ii) 5 mg/ml prodrug in water with 200 mg/ml lecithin; and (iii) 5 mg/ml prodrug in water with 100 mg/ml lecithin and 5 mg/ml cholesterol. Based on these results, it is expected that other liposome formulations as are well-known in the art may be used to administer the prodrugs of the invention

[0375] The prodrugs of the invention are rapidly metabolized in microsomes from rat and human livers and, in part, converted to the active compound, A-B-C-NHCOCHX_2. Since the active compounds are degraded rapidly by non-NADPH dependent esterases, an esterase inhibitor, bis(p-nitrophenyl) phosphate (BNPP), was used in microsomal incubations to prevent degradation of the active compound. BNPP has been shown, with a number of prodrugs, to have no effect on the disappearance rate of the prodrugs in either rat or human microsomes. Metabolism of the prodrugs occurs by NADPH dependent enzyme(s), presumably P450. Although all of the prodrugs are rapidly metabolized in liver microsomes, the amount of active compound produced varies significantly among the compounds tested. Metabolic pathways have not been extensively explored but, for many of the compounds, the absence of the deacetylation product has been confirmed using LC/MS/MS. That is, the prodrug side-chain serves to prevent esterase attack leading to inactive, deacetylation products. Loss of the alkyl side-chain seems to be the preferred metabolic pathway. Additional studies have been conducted in microsomes isolated from human jejunum. The compounds, in general, are stable in these gut microsomes.

Methods:

[0376] Incubations were conducted using cryopreserved rat and human microsomes purchased from commercial sources. Incubations were conducted at a final protein concentration of 1mg/ml in phosphate buffer (100 mM, pH = 7.4) containing 1 mM NADPH. BNPP concentrations were 1 mM in the incubation mixture. Reaction was started by addition of the compounds (5 µl of 10µg/ml in water:DMSO; 9:1). Reactions were conducted at a volume of 100 uL in 96-well plates and reactions were quenched by addition of 50 µl of dimethyl sulfoxide containing 1% formic acid. Samples were prepared for analysis by addition of an internal standard (verapamil, 10 µl of 0.5 µM in water) and 100 µl of an organic solvent mixture (Acetonitrile:ethanol:DMSO; 2:1:1). Samples were centrifuged before analysis to remove precipitated proteins.

LC/MS/MS analysis:

[0377] A PE/Sciex 3000 instrument was used for all analyses. Samples were injected onto a Betasil C8 column (50 x 3mm; Thermo Electron Corp.) and eluted with an acetonitrile gradient. A heated nebulizer source was used as the interface between the HPLC column and the MS/MS. Quantitative analyses were conducted using the MRM mode of operation with specific parameters determined, in advance, for each compound. Standards were prepared in rat or human microsomes using the procedures outlined above and covered a range from 1 – 1000 ng/ml.

Pharmokinetic Studies:

[0378] Pharamcokinetic studies were conducted in rats containing surgically implanted cannula in the portal and jugular veins. Blood samples were taken simultaneously from both cannula at various times after oral administration of the compounds. In the portal vein, the prodrugs are detected and, in some cases, the active compound, A-B-C-NHCOCHX_2, has also been detected. The presence of active compound in the portal vein samples has been attributed to metabolism of the prodrug in transit through the gut wall. Surprisingly, the levels of inactive metabolite have been low. In the jugular samples, many, but not all, of the prodrugs have been detected in systemic circulation, depending on the hepatic extraction ratio of the prodrug. In contrast, oral administration of A-B-C-NHCOCHX_2 (where the "C" ring is a 2-pyridyl) results in high levels of inactive metabolite in the portal vein (attributed to esterase activity in the small intestine) and low levels of A-B-C-NHCOCHX_2.

[0379] Evidence for the conversion of prodrug 1107 to its active metabolite in rat liver was obtained by measuring prodrug and active compound concentrations in bile fluid. High levels of 1107 and resultant A-B-C-NHCOCHX_2 were detected in bile fluid for a period of four hours after oral administration. In contrast, no A-B-C-NHCOCHX_2 was detected in bile fluid after oral administration of equivalent A-B-C-NHCOCHX_2. The data suggests that prodrug 1107 accumulates in the liver and is slowly converted to the active dihaloacetamide. See Table 13.

Methods:

[0380] Compounds were dissolved in a mixture of TPGS:PEG:PG (35%:60%:5%) and diluted with saline for oral administration. Typically, 6.5mg of compound was dissolved in 1 ml of the organic mixture and added to 5.5 ml of saline. Animals were dosed with 5ml/kg of this mixture to give a typical dose of 5 mg/kg. All animal studies were conducted in male Spraque-Dawley rats and the animals were fasted overnight prior to dose administration. Surgeries (to implant blood sampling cannula) were conducted at least two days prior to the study. Blood samples (100 µl) were collected using sodium heparin as anticoagulant and added to 300µl of a mixture of

acetate buffer (100 mM, pH = 6.5):acetonitrile:ethanol:DMSO (2:1:1:2v/v). Samples were centrifuged and the supernatant was analyzed by LC/MS/MS using the procedures outlined above. Standards were prepared similarly using fresh rat blood from naive animals. See Table 13.

Table 13

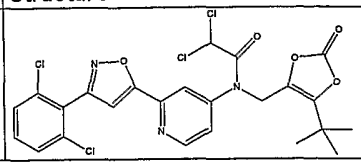
		Microsomal Stability				Rat PK		
		Half-life (min.)		% Conversion to active agent		Cmax, ng/ml		Hepatic extraction ratio of Prodrug
Cpd	Structure	Rat	Human	Rat	Human	Prodrug	Active Agent	
1107		-	-	-	~50	510	50	0.97

Table 14

Cpd. No.	Assay	Result Value (μM)
1018	HEPC_REPLICON-ICWESTERN	+++
1021	HEPC_REPLICON-ICWESTERN	++
1022	HEPC_REPLICON-ICWESTERN	+++
1023	HEPC_REPLICON-ICWESTERN	+++
1024	HEPC_REPLICON-ICWESTERN	+++
1026	HEPC_REPLICON-ICWESTERN	+
1027	HEPC_REPLICON-ICWESTERN	++
1028	HEPC_REPLICON-ICWESTERN	+
1037	HEPC_REPLICON-ICWESTERN	+
1038	HEPC_REPLICON-ICWESTERN	++
1039	HEPC_REPLICON-ICWESTERN	+
1040	HEPC_REPLICON-ICWESTERN	++
1041	HEPC_REPLICON-ICWESTERN	++
1041	HEPC_REPLICON-LUC	++
1042	HEPC_REPLICON-ICWESTERN	+
1043	HEPC_REPLICON-ICWESTERN	++
1043	HEPC_REPLICON-LUC	++
1044	HEPC_REPLICON-ICWESTERN	+++
1044	HEPC_REPLICON-LUC	+++

[0381] The results of the Replicon assays are provided in Tables 14 and 15. In Table 14, a value of "+++" means less than 1 μM; ++ means between 1 and 20 μM; + means greater than 20 μM. In TABLE 15, a value of "+" indicates an IC_{50} of 10 μM or less in the specified assay; a value of "-" indicates an IC_{50} of greater than 10 μM in the specified assay.

Table 15

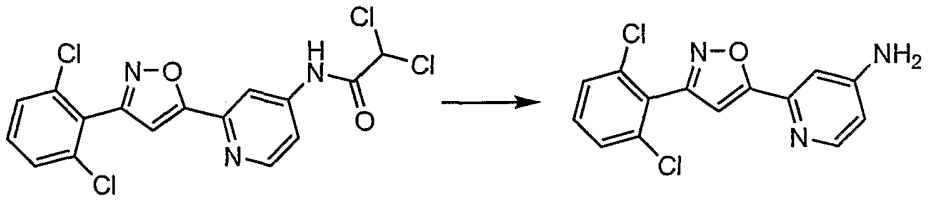
Cpd No.	Replicon
100a	+
102a	+
103a	+
104a	+
105a	+
106a	+
107a	+
108a	+
109a	+
110a	+
111a	+
112a	+
113a	+

Cpd No.	Replicon
114a	+
115a	+
116a	+
117a	+
118a	+
119a	+
120a	+
121a	-
122a	-
123a	+
124a	+
125a	-
126a	+

Cpd No.	Replicon
127a	+
128a	+
129a	+
130a	+
131a	+
132a	+
133a	+
134a	+
135a	+
136a	+
137a	+

Stabilization of the active parent compound by a prodrug approach.

[0382] The active parent compound is cleaved by esterase enzymes to an inactive metabolite in a reaction (for example, see scheme below) that does not require NADPH as a cofactor. Alkylation of the acetyl nitrogen stabilizes the active parent compound against direct attack by esterases and yet, if NADPH is added as a cofactor, conversion to the active parent compound occurs through CYP P450 enzyme activity. Because esterases are present in the gut, the active parent compound is extensively hydrolyzed during the absorption process. The prodrug approach prevents gut hydrolysis of the active parent compound and, because the liver contains high levels of P450 activity, the active parent compound is generated within the liver. Some results are shown in Figs. 17A and 17B.



Active Parent Ccompound
Cpd. 1059

Inactive Metabolite
Cpd. 1060

Oral Administration of the active parent compound – Hydrolysis in rats

[0383] Administered orally, the active parent compound is well absorbed but is extensively hydrolyzed to the inactive metabolite as demonstrated in this experiment in which plasma samples were taken from the portal vein of rats and analyzed for the active parent compound and the inactive metabolite. However, a portion of the active parent compound remains intact and the active parent compound concentrations increase in a linear fashion with dose. Because the

portal blood flows directly to the liver, this intact the active parent compound may exert an anti-viral effect in the liver. Some results are shown in Figs. 18A and 18B.

Dose (mg/kg)	Ratio Cpd. 1060/Cpd. 1059
2.5	29
5	88
30	24

Hydrolysis of the active parent compound in the cynomolgus monkey.

[0384] Consistent with results in rats, the active parent compound is extensively hydrolyzed in the gut of cynomolgus monkeys as shown by the high ratio of the inactive metabolite to the active parent compound in the portal vein of monkeys. A portion of the active parent compound present in the portal vein (and the inactive metabolite as well) is extracted by the liver resulting in lower concentrations reaching systemic circulation. The results are shown in Fig. 19.

Biliary excretion of the active parent compound and the inactive metabolite in rats following oral administration of the active parent compound.

[0385] The active parent compound that remains intact during absorption through the gut wall is primarily extracted in the liver and does not reach systemic circulation. Esterases are present in various tissues in the liver and may further degrade the active parent compound prior to reaching the HepC virus that is localized within hepatocyte cells. Experiments with radio-labeled the active parent compound indicate that the active parent compound is excreted from the body through bile (data not shown). In the experiment shown below, two doses of the active parent compound were administered orally to rats. Bile was collected in one-hour intervals for three hours. At the lower dose, 5 mg/kg, no intact the active parent compound was detected in the bile. At the higher dose, 30 mg/kg, the active parent compound was detected in bile - suggesting that the active parent compound escaped esterase activity. At both doses, however, the inactive metabolite concentrations in bile were substantially higher than the active parent compound concentrations. As discussed above, the inactive metabolite is generated, in part, in the gut. Additional inactive metabolite may be generated in the liver itself. The goal of the prodrug strategy has been to reduce or eliminate exogenous metabolism of the active parent compound and to generate the active parent compound in-situ (i.e. within hepatocytes) using enzymes which are endogenous to hepatocytes. The results are shown in Figs. 20A and 20B.

Absorption of the active parent compound and prodrugs in cynomolgus monkeys.

[0386] A number of prodrugs of the active parent compound, and the active parent compound itself, were administered orally to cynomolgus monkeys and portal vein samples were

analyzed. All of the prodrugs administered were detected in the portal vein and partial conversion of the prodrugs to the active parent compound was observed (thought to be the result of low levels of P450 activity present in the gut epithelium). The levels of the inactive metabolite were lower than those generated from direct administration of the active parent compound – the prodrug approach prevents gut metabolism to inactive inactive metabolite. The results are shown in Figs. 21A, 21B and 21C.

Biliary excretion of the active parent compound and the inactive metabolite following oral administration of prodrugs to rats.

[0387] Prodrugs were administered at a dose of 5mg/kg, the active parent compound was administered at a dose of 30mg/kg. Bile was collected for three hours in one-hour intervals and analyzed for the active parent compound. The data indicates that the prodrugs reached the liver, were converted into the active parent compound and that the the active parent compound was excreted unchanged. The concentrations of the active parent compound in the bile were substantially higher for a 5mg/kg dose of prodrug than for a 30mg/kg dose of the active parent compound. The results are shown in Fig 22.

[0388] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

[0389] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to one of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. A compound according to structural formula

$$A\text{-}B\text{-}C\text{-}(C(O))_s\text{-}N(R^{11})\text{-}C(O)\text{-}CX_2\text{-}R^{12}$$

or a pharmaceutically acceptable salt, hydrate, solvate or N-oxide thereof, wherein

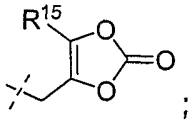
A is a phenyl or six-membered heteroaryl ring having from one to five of the same or different R^{20} substituents, provided that at least one of the substituents is positioned at the *ortho* position;

B is a saturated, unsaturated, or aromatic heteroatomic ring having from one to three annular heteroatoms selected from N, O, and S, where the A and C moieties are attached to non-adjacent ring atoms of B, provided that when the B includes more than one annular oxygen atom, the oxygen atoms are not adjacent;

C is a phenyl or a heteroaryl ring, wherein when C is phenyl, it is substituted relative to the B moiety at the *meta* position with the $-(C(O))_l-N(R^{11})-C(O)-CX_2-R^{12}$, or when C is a heteroaryl group, the B moiety and the $-(C(O))_l-N(R^{11})-C(O)-CX_2-R^{12}$ moiety are positioned on C with only one ring atom of C between them;

s is 0 or 1;

R^{11} is selected from the group consisting of hydrogen, lower alkyl, $-(CHR^{10})_n$-J-G, or a group of the formula



;

each X is independently H or halo, provided both X are not H;

R^{12} is selected from the group consisting of hydrogen, -O-C(O)-alkyl, $-C(O)OR^{16}$, $-C(O)R^{17}$ and $-P(O)(OR^{18})OR^{19}$;

R^{15} is lower alkyl, arylalkyl, aryl, substituted cycloheteroalkyl, cycloheteroalkyl, substituted cycloalkyl, cycloalkyl, $-C(O)OR^{18}$ or $-CH_2-OR^{30}$;

R^{30} is hydrogen, lower alkyl or a sugar moiety;

R^{16} is selected from the group consisting of aryl-C_1-C_6 alkyl, aryl, substituted cycloheteroalkyl, cycloheteroalkyl, substituted cycloalkyl, cycloalkyl, $-C(O)OR^{16}$ or $-CH_2-OR^{30}$, $(C_{1\text{-}15})$ alkyl and $(C_{7\text{-}15})$ arylalkyl;

R^{17} is selected from the group consisting of lower alkyl, $-N(R^c)_2$, N-morpholino, N-piperazino and N-pyrrolidino;

each R^c is independently R^b or alternatively, the both R^c taken together with the nitrogen atom to which they are bonded form a 5-, 6- or 7-membered cycloheteroalkyl which

optionally includes from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S;

each R^b is independently hydrogen or R^a;

R^a is selected from the group consisting of alkyl, hydroxyalkyl, cycloalkyl, heteroalkyl, C_0-C_6 alkyl-cycloheteroalkyl, substituted C_0-C_6 alkyl-cycloheteroalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

R^{18} is H, lower alkyl, aryl or arylalkyl;

R^{19} is H, lower alkyl, aryl or arylalkyl;

n is 0, 1, 2, 3 or 4;

each R^{10} is independently hydrogen or lower alkyl;

J is selected from the group consisting of $-(CH_2)_{1-3}-$, -O-, $-O-(CH_2)_{1-3}-$, -CH(OH)-, -C(=O)-, $-S(O)_m-$, $-C(=NR^{23})-$, $-C(=NOR^{29})-$, $-C(N\text{-}N\text{-}(R^{25})_2)-$, $-C(N\text{-}NR^{27}C(=O)N\text{-}(R^{27})_2)-$ and $-C(Z\text{-}R^{28})_2-$;

m is 0, 1, or 2;

R^{23} is selected from the group consisting of hydrogen, lower alkyl, aryl, substituted aryl, arylalkyl and substituted arylalkyl;

R^{29} is selected from the group consisting of hydrogen, lower alkyl, aryl, substituted aryl, arylalkyl and substituted arylalkyl;

each R^{25} is independently selected from the group consisting of hydrogen, lower alkyl, aryl, substituted aryl, arylalkyl and substituted arylalkyl;

each R^{27} is independently selected from the group consisting of hydrogen, lower alkyl, aryl, substituted aryl, arylalkyl and substituted arylalkyl;

each Z is independently -O- or -S-;

each R^{28} is independently selected from the group consisting of lower alkyl, aryl, substituted aryl, arylalkyl and substituted arylalkyl or alternatively, the two R^{18}'s taken together with the heteroatoms to which they are bonded form a 5, 6 or 7 membered cycloheteroalkyl;

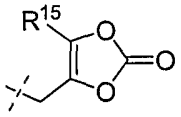
G is selected from the group consisting of aryl, substituted aryl, arylalkyl, substituted arylalkyl, heteroaryl, substituted heteroaryl, cycloheteroalkyl and substituted cycloheteroalkyl; and

each R^{20} is, independently of the other, selected from the group consisting of -OH, -SH, -CN, -C(O)H, $-NO_2$, halo, fluoro, chloro, bromo, iodo, lower alkyl, substituted lower alkyl, lower heteroalkyl, substituted lower heteroalkyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, lower haloalkyl,

monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower alkylthio, substituted lower alkylthio, lower alkoxy, substituted lower alkoxy, methoxy, substituted methoxy, lower heteroalkoxy, substituted lower heteroalkoxy, cycloalkoxy, substituted cycloalkoxy, cycloheteroalkoxy, substituted cycloheteroalkoxy, lower haloalkoxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, amino, lower di- or monoalkylamino, substituted lower di- or monoalkylamino, aryl, substituted aryl, aryloxy, substituted aryloxy, phenoxy, substituted phenoxy, arylalkyl, substituted arylalkyl, arylalkyloxy, substituted arylalkyloxy, benzyl, benzyloxy, heteroaryl, substituted heteroaryl, heteroaryloxy, substituted heteroaryloxy, heteroarylalkyl, substituted heteroarylalkyl, heteroarylalkyloxy, substituted heteroarylalkyloxy, carboxyl, lower alkoxycarbonyl, substituted lower alkoxycarbonyl, aryloxycarbonyl, substituted aryloxycarbonyl, arylalkyloxycarbonyl, substituted arylalkyloxycarbonyl, carbamate, substituted carbamate, carbamoyl, substituted carbamoyl, thiocarbamoyl, substituted thiocarbamoyl, ureas, substituted ureas, thioureas, substituted thioureas, sulfamoyl, substituted sulfamoyl and a group of the formula -L-R^{14}, where "L" is a linker and R^{14} is cycloalkyl, substituted cycloalkyl, cycloheteroalkyl or substituted cycloheteroalkyl;

provided that when R^{11} is hydrogen or lower alkyl, then R^{12} is not hydrogen.

2. The compound according to claim 1, wherein s is 1, R^{12} is -H, and R^{11} is a group of the formula

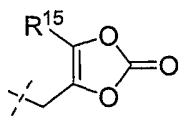


wherein R^{15} is -CH_2-OR^{30}.

3. The compound according to claim 2, wherein R^{30} is a sugar moiety.

4. The compound according to claim 1, wherein s is 0.

5. The compound according to claim 4, wherein R^{12} is -H, R^{11} is a group of the formula



wherein R^{15} is lower alkyl, arylalkyl, aryl, cycloheteroalkyl, cycloalkyl, or -CH_2-OR^{30}.

6. The compound according to claim 5, wherein R^{15} is piperidyl, pyrrolidinyl, t-butyl, benzyl, cyclobutyl or propyl.

7. The compound according to claim 6, wherein R^{15} is $-CH_2-OR^{30}$.

8. The compound according to claim 7, wherein R^{30} is a sugar moiety.

9. The compound according to claim 1, wherein s is 0 and R^{11} is selected from the group consisting of hydrogen or $-(CHR^{10})_n$-J-G, wherein n is 0, 1 or 2, J is $-(CH_2)_{1-3}$-, -C(O)-, -O- or-O-$(CH_2)_{1-3}$-,and G is substituted aryl, cycloheteroalkyl, substituted cycloheteroalkyl or heteroaryl.

10. The compound according to claim 9, wherein R^{11} is hydrogen.

11. The compound according to claim 9, wherein G is pyrrolidinyl, morpholinyl or imidazolyl.

12. The compound according to claim 9, wherein G is phenyl substituted with methoxy, -chloro, fluoro, CH_2-P(O)(OR^b)(OR^b), -O-P(O)(OR^b)(OR^b), methyl, -O-C(O)-NH-R^b, -$NR^bC(O)OR^b$, ethyl-piperazinyl, piperazinyl, t-butyl-O-C-(O)-piperazinyl, -O-$(CH_2)_{0-4}$-R^b,or -$C(O)OR^b$, wherein R^b is -H, propyl, t-butyl, ethyl, or morpholinyl.

13. The compound according to claim 1, wherein
s is 0;
each X is chloro, and R^{12} is selected from the group consisting of hydrogen, $-C(O)OR^{16}$, $-C(O)R^{17}$ and $-P(O)(OR^{18})OR^{19}$;
R^{16} is lower alkyl, arylalkyl, substituted cycloalkyl, or cycloalkyl;
R^{17} is selected from the group consisting of lower alkyl, $-N(R^c)_2$, or N-morpholino;
each R^c is independently hydrogen, alkyl, hydroxyalkyl, C_0-C_6 alkyl-cycloheteroalkyl, or heteroarylalkyl; and
R^{18} and R^{19} are independently H or lower alkyl.

14. The compound according to claim 13, wherein R^{12} is $-P(O)(OR^{18})OR^{19}$.

15. The compound according to claim 14, wherein R^{18} and R^{19} are both -H, ethyl or propyl.

16. The compound according to claim 13, wherein R^{12} is $-C(O)OR^{16}$.

17. The compound according to claim 16, wherein R^{16} is adamantane methyl, propyl, $-CH_2$-phenyl, t-butyl, cyclohexyl, or cyclohexyl substituted with methyl, propyl, or pentyl.

18. The compound according to claim 13, wherein R^{12} is $-C(O)R^{17}$.

19. The compound according to claim 18, wherein R^{17} is methyl, N-morpholino, or $-N(R^c)_2$.

20. The compound according to claim 19, wherein each R^c is independently hydrogen, $-(CH_2)_3$-morpholinyl, $-CH_2$-pyridinyl or $-(CH_2)_2$-OH.

21. The compound of claim 1, wherein s is 0 and A is phenyl substituted with at least two R^{20} groups selected from the group consisting of halo, lower alkoxy, carboxyl, lower haloalkyl, cycloalkyl, lower alkoxycarbonyl and $-L-R^{14}$, wherein "L" is a -O- and R^{14} is cycloheteroalkyl or substituted cycloheteroalkyl.

22. The compound of claim 21, wherein A represents a phenyl ring substituted at the 2- and 6-positions with the same or different R^{20} substituent.

23. The compound of claim 22, wherein one R^{20} is halo and the other R^{20} is lower alkoxy, lower haloalkyl or cycloalkyl.

24. The compound of claim 23 wherein one R^{20} is chloro and the other R^{20} is methoxy, $-CF_3$, or cyclopropyl.

25. The compound of claim 22, wherein one R^{20} is halo and the other R^{20} is carboxyl or lower alkoxycarbonyl.

26. The compound of claim 25, wherein one R^{20} is chloro and the other R^{20} is methoxycarbonyl.

27. The compound of claim 22 wherein one R^{20} is halo and the other R^{20} is $-O-R^{14}$, wherein R^{14} is morpholinyl or morpholinyl substituted with -C(O)-O-t-butyl or $-C(O)-CH_3$.

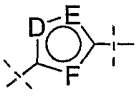
28. The compound of claim 1, wherein s is 0 and A represents a pyrid-2-yl ring substituted at the 3-position with an R^{20} substituent, a pyrid-3-yl ring substituted at the 2- and 4-positions with the same or different R^{20} substituents or a pyrid-4-yl ring substituted at the 3- and 5-positions with the same or different R^{20} substituents.

29. The compound according to claim 28, wherein each R^{20} is independently selected from the group consisting of halo, lower dialkylamino and $-L-R^{14}$, wherein "L" is a -O- and R^{14} is cycloheteroalkyl.

30. The compound according to claim 29, wherein each R^{20} is independently selected from the group consisting of chloro, $-N(CH_3)_2$, and $-O-R^{14}$, wherein R^{14} is morpholinyl.

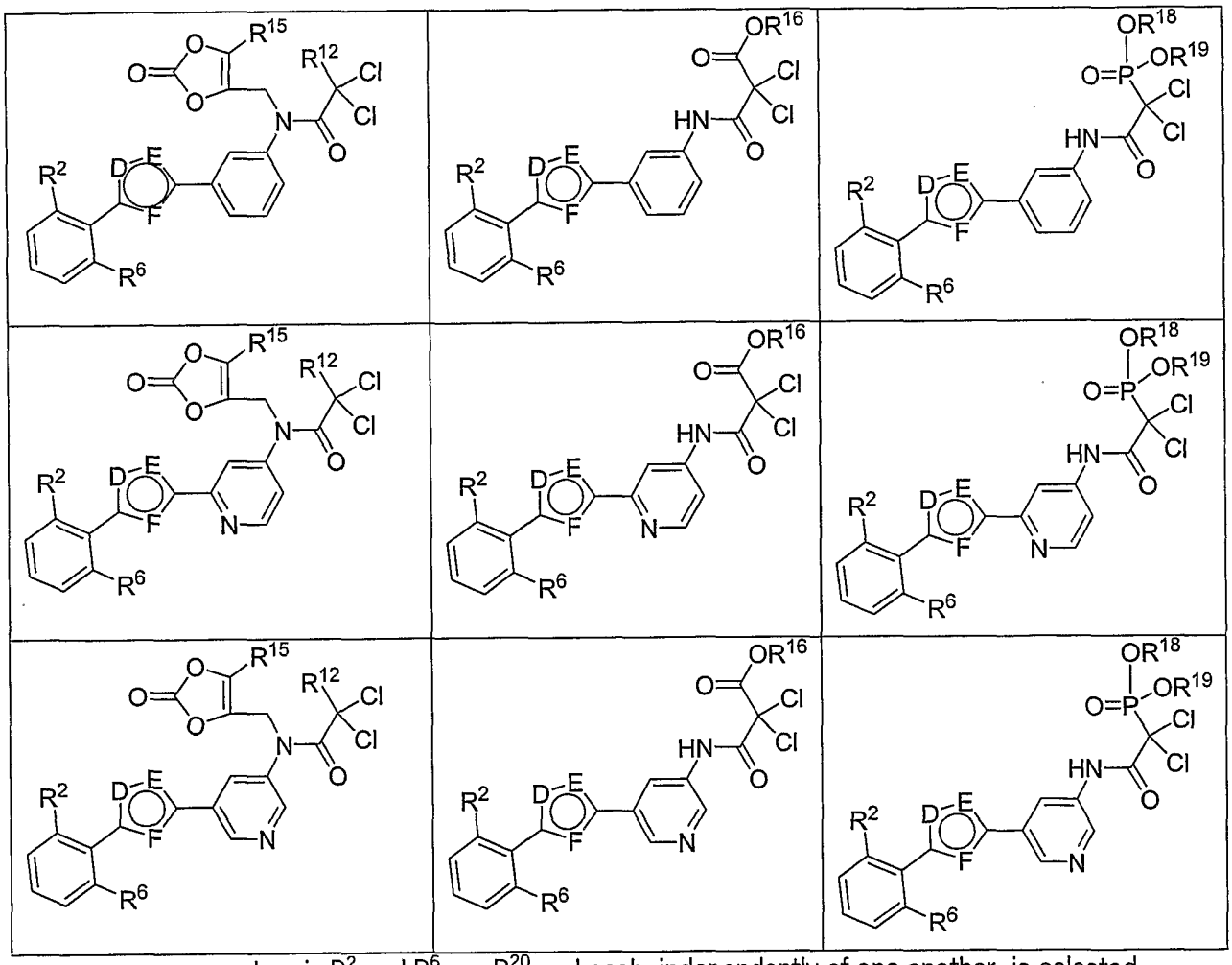
31. The compound according to claim 1, wherein s is 0 and C represents a phenyl ring, a pyrid-2-yl ring or a pyrid-3-yl ring.

32. The compound of claim 1, wherein s is 0 and B represents a isoxazolyl, pyrazolyl, oxadiazolyl or triazolyl ring.

33. The compound of claim 1, wherein s is 0 and B is  , where D, E and F are each, independently of one another, selected from N, O and CH, provided that at least two of D, E and F are other than CH and D and E are not both simultaneously O.

34. The compound of claim 1, wherein s is 0 and each X is -Cl.

35. The compound of claim 34, wherein is selected from the group consisting of:



wherein R^2 and R^6 are R^{20} and each, independently of one another, is selected from the group consisting of -OH, $-NO_2$, halo, fluoro, chloro, bromo, iodo, lower alkyl, methyl, lower heteroalkyl, (C_3-C_6) cycloalkyl, 5- or 6-membered cycloheteroalkyl, N-morpholinyl, N-methyl-N-piperazinyl, N-piperadinyl, substituted N-piperadinyl,

4-(N-piperadinyl)-N-piperadinyl, 4-amino-N-piperadinyl, lower alkoxy, methoxy, ethoxy, lower alkylthio, methylthio, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower haloalkyloxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, aryl, phenyl, arylalkyl, benzyl, aryloxy, phenoxy, arylalkyloxy, benzyloxy, 5- or 6-membered heteroaryl, lower alkyloxycarbonyl, sulfamoyl and -L-R^{14}, where L is -$(CH_2)_{1-3}$- or -O-$(CH_2)_{1-3}$- and R^{14} is a 5- or 6-membered cycloheteroalkyl or N-morpholinyl.

36. The compound of claim 35, wherein R^2 and R^6 are each, independently of one another, selected from the group consisting of chloro, bromo, iodo and fluoro.

37. The compound of claim 35, wherein D is O, E is N and F is CH.

38. The compound of claim 35, wherein D is N, E is O and F is CH.

39. The compound according to claim 35, wherein R^{12} is -H and R^{15} is lower alkyl, arylalkyl, aryl, cycloheteroalkyl, cycloalkyl, or a sugar moiety.

40. The compound according to claim 39, wherein R^{15} is piperidyl, pyrrolidinyl, t-butyl, benzyl, cyclobutyl or propyl.

41. The compound according to claim 35, wherein R^{16} is lower alkyl or cycloalkyl.

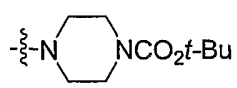
42. The compound according to claim 41, wherein R^{16} is t-butyl or adamantane.

43. The compound according to claim 35, wherein R^{18} is -H or lower alkyl and R^{19} is H or lower alkyl.

44. The compound according to claim 43, wherein R^{18} and R^{19} are both -H, ethyl or propyl.

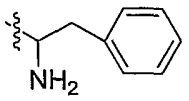
45. The compound according to claims 1, wherein s is 0 and G is aryl or substituted aryl.

46. The compound according to claims 45, wherein G is phenyl substituted with one or more groups selected from hydrogen, -F, -Cl, -OMe, -CO_2H, -CO_2*t*-Bu, -CH_2CO_2Et, methyl -OC(O)CH_3, -OC(O)$CH_2N(CH_3)_2$, -OC(O)$CH_2N(CH_3)$Boc, -OC(O)$CH_2NH(CH_3)$, or



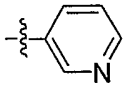
47. The compound according to claims 1, wherein s is 0 and G is substituted arylalkyl.

48. The compound according to claim 47, wherein G is



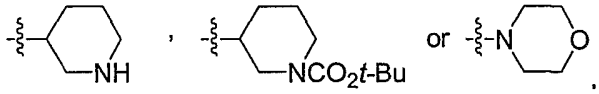
49. The compound according to claims 1, wherein s is 0 and G is heteroaryl.

50. The compound according to claim 49, wherein G is



51. The compound according to claims 1, wherein s is 0 and G is cycloheteroalkyl or substituted cycloheteroalkyl.

52. The compound according to claim 51, wherein G is



53. The compound of claim 1, wherein when administered to a cell comprising a hepatitis C virion, the compound inhibits HCV replication and/or proliferation and has an IC_{50} of 10 μM or less, as measured in an *in vitro* assay.

54. The compound of claim 1 which is selected from the group consisting of those provided in Tables 1 through 13.

55. A composition comprising a pharmaceutically acceptable vehicle and a compound according to any one of Claims 1-54.

56. A method of inhibiting replication and/or proliferation of a hepatitis C ("HC") virion, comprising the step of contacting an HC virion with an amount of a compound according to any one of Claims 1-55 effective to inhibit replication and/or proliferation of the HC virion.

57. The method of claim 56 which is practiced *in vitro*.

58. The method of claim 56 which is practiced *in vivo*.

59. A method of treating or preventing an HCV infection, comprising the step of administering to a subject an amount of a compound according to any one of Claims 1-54 effective to treat or prevent an HCV infection.

60. The method of claim 59, wherein the subject is a human.

61. The method of claim 59, wherein the compound is administered in an amount of about 0.1 mg/kg/day to 200 mg/kg/day.

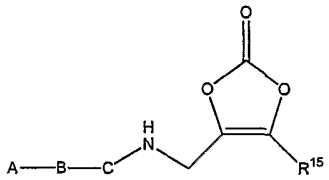
62. The method of claim 59, wherein the compound is administered in an amount of about 10 mg/kg/day to 100 mg/kg/day.

63. The method of claim 59, wherein the compound is administered orally, intravenously or subcutaneously.

64. The method of claim 59, which is practiced therapeutically in a subject having an HCV infection.

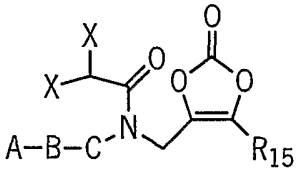
65. The method of claim 59, which is practiced prophylactically in a subject at risk of developing an HCV infection.

66. An intermediate compound useful for synthesizing substituted heterocycle compounds, said intermediate compound having a structure defined by structural formula (IV):



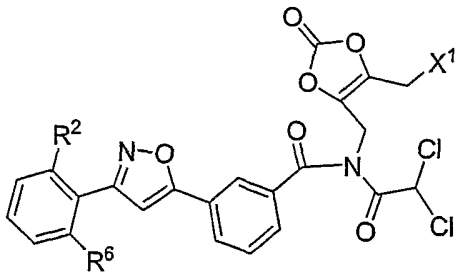
wherein A, B, C and R^{15} are as defined in claim 1.

67. A method of synthesizing a heterocycle compound according to structural formula (XI):



wherein A, B, C, X and R^{15} are as defined in claim 1, comprising dihaloacetylating a compound according to claim 28, thereby yielding a compound according to structural formula (XI).

68. A compound according to claim 1 of the formula (XII)



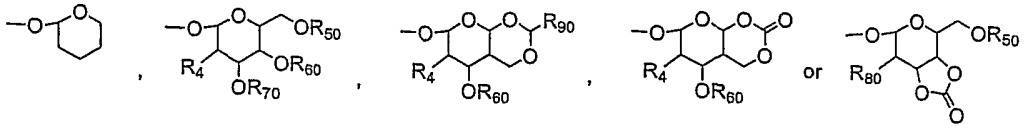
wherein

X^1 is hydroxyl, C_1-C_6 alkoxy, C_1-C_6 hydroxyalkoxy, C_1-C_6 alkoxy-C_1-C_6 alkoxy, poly-C_1-C_6 alkoxy or a sugar moiety; and

R^2 and R^6 are R^{20} and each, independently of one another, is selected from the group consisting of -OH, -NO_2, halo, fluoro, chloro, bromo, iodo, lower alkyl, methyl, lower heteroalkyl, (C_3-C_6) cycloalkyl, 5- or 6-membered cycloheteroalkyl, N-morpholinyl, N-methyl-N-piperazinyl, N-piperadinyl, substituted N-piperadinyl, 4-(N-piperadinyl)-N-piperadinyl, 4-amino-N-piperadinyl, lower alkoxy, methoxy, ethoxy, lower alkylthio, methylthio, lower haloalkyl, monohalomethyl, dihalomethyl, trihalomethyl, trifluoromethyl, lower haloalkyloxy, monohalomethoxy, dihalomethoxy, trihalomethoxy, trifluoromethoxy, aryl, phenyl, arylalkyl, benzyl, aryloxy, phenoxy, arylalkyloxy, benzyloxy, 5- or 6-membered heteroaryl, lower alkyloxycarbonyl, sulfamoyl and -L-R^{14}, where L is -$(CH_2)_{1-3}$- or -O-$(CH_2)_{1-3}$- and R^{14} is a 5- or 6-membered cycloheteroalkyl or N-morpholinyl.

69. The compound of claim 68 wherein R^2 and R^6 are each, independently of one another, selected from the group consisting of chloro, bromo, iodo and fluoro.

70. A compound according to claim 68, wherein X^1 is a substituted or unsubstituted tetrahydropyran or 6-(hydroxymethyl)-tetrahydro-2H-pyran-2,4,5-triol, hexahydropyrano[2,3-d][1,3]dioxine-5,7-diol or 5,7-dihydroxy-hexahydropyrano[2,3-d][1,3]dioxin-2-one, 6-hydroxy-4-(hydroxymethyl)-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-2-one, or any one of the following structures:

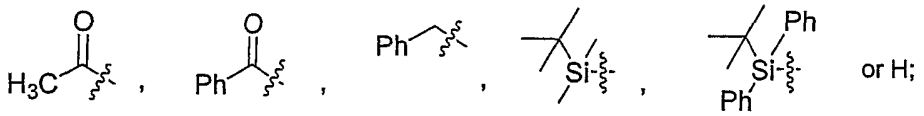


wherein R_{50}, R_{60} and R_{70} are independently C_1-C_6 alkyl, C_0-C_6 alkylaryl, acyl, C_0-C_6 alkyl-C(=O)-aryl, C_0-C_6 alkyl-C(=O)-C_1-C_6 alkyl, acetyl, benzoyl, benzyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, hydrogen, or -$Si(R_{100})_3$, wherein each R_{100} is

the same or different and is C_1-C_6 alkyl or C_0-C_6 alkylaryl; R_{80} is C_1-C_6 alkyl, methyl or hydrogen; and R_{90} is -H, or any alkyl chain or aryl group or substituted aryl group.

71. A compound according to claim 70, wherein

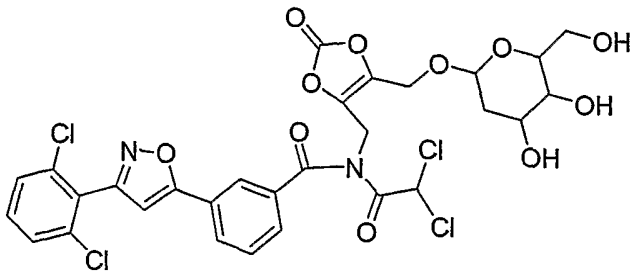
R_{50}, R_{60} and R_{70} are independently



R_{80} is -H or -CH_3; and

R_{90} is C_1-C_6 alkyl, aryl or substituted aryl.

72. A compound according to claim 68 that is



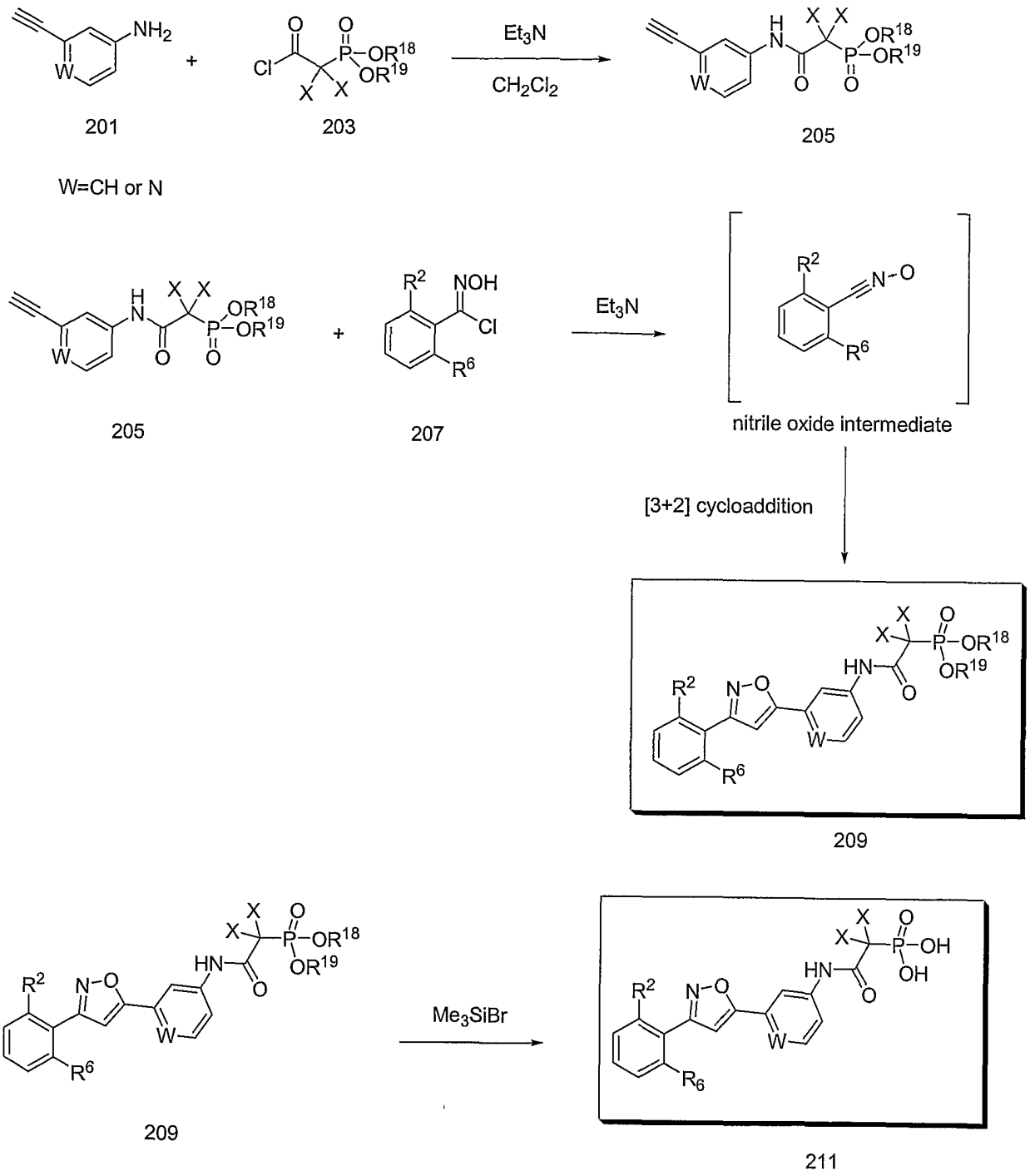

Et3N
CH2Cl2
201
203
205
W=CH or N
Et3N
205
207
nitrile oxide intermediate
[3+2] cycloaddition
209
Me3SiBr
209
211

Fig. 1

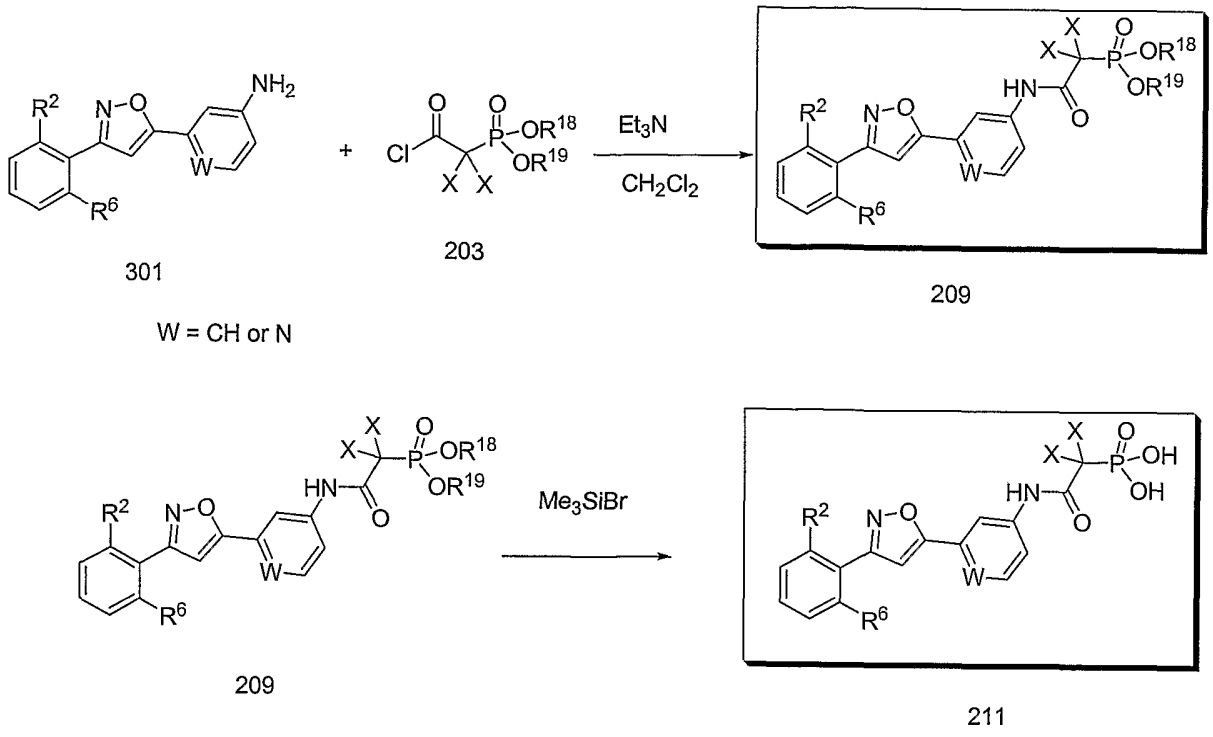

R2
N-O
NH2
W
R6
301
W = CH or N
Cl
O
P
OR18
OR19
X
203
Et3N
CH2Cl2
209
HN
Me3SiBr
OH
211

Fig. 2

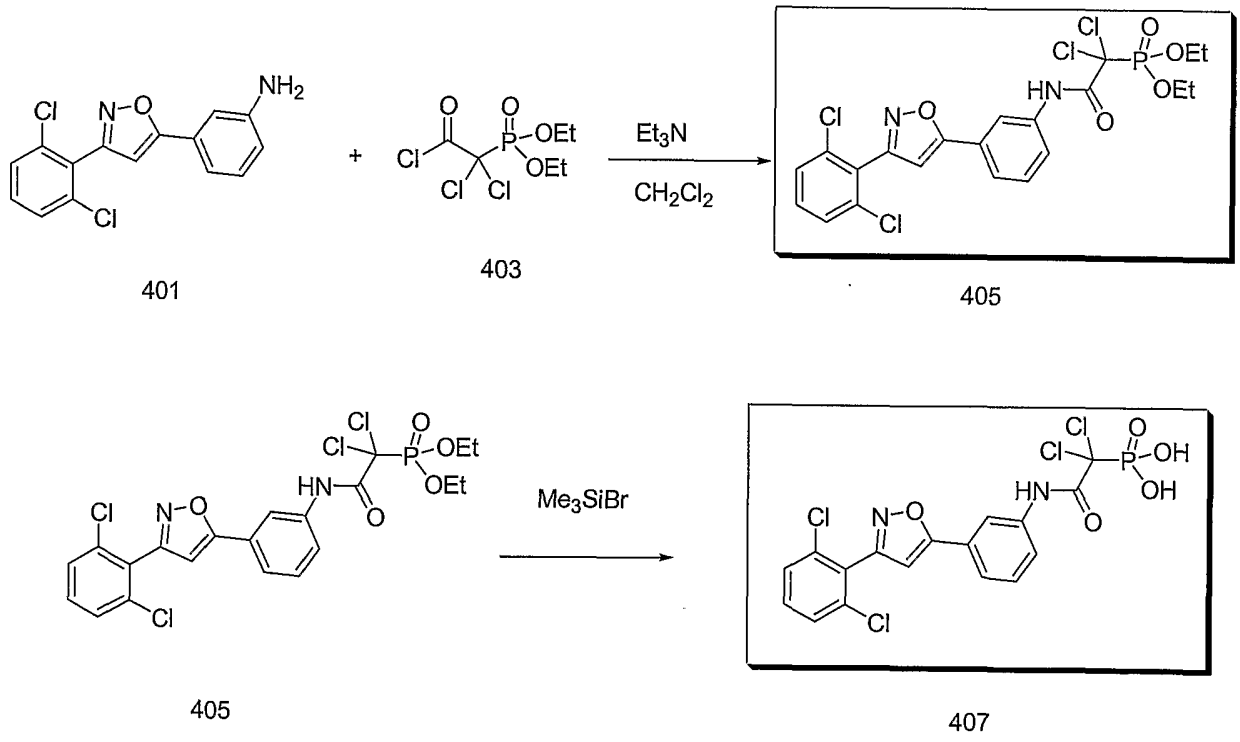

Cl
N-O
NH2
401
403
Et3N
CH2Cl2
OEt
405
HN
Me3SiBr
OH
407

Fig. 3

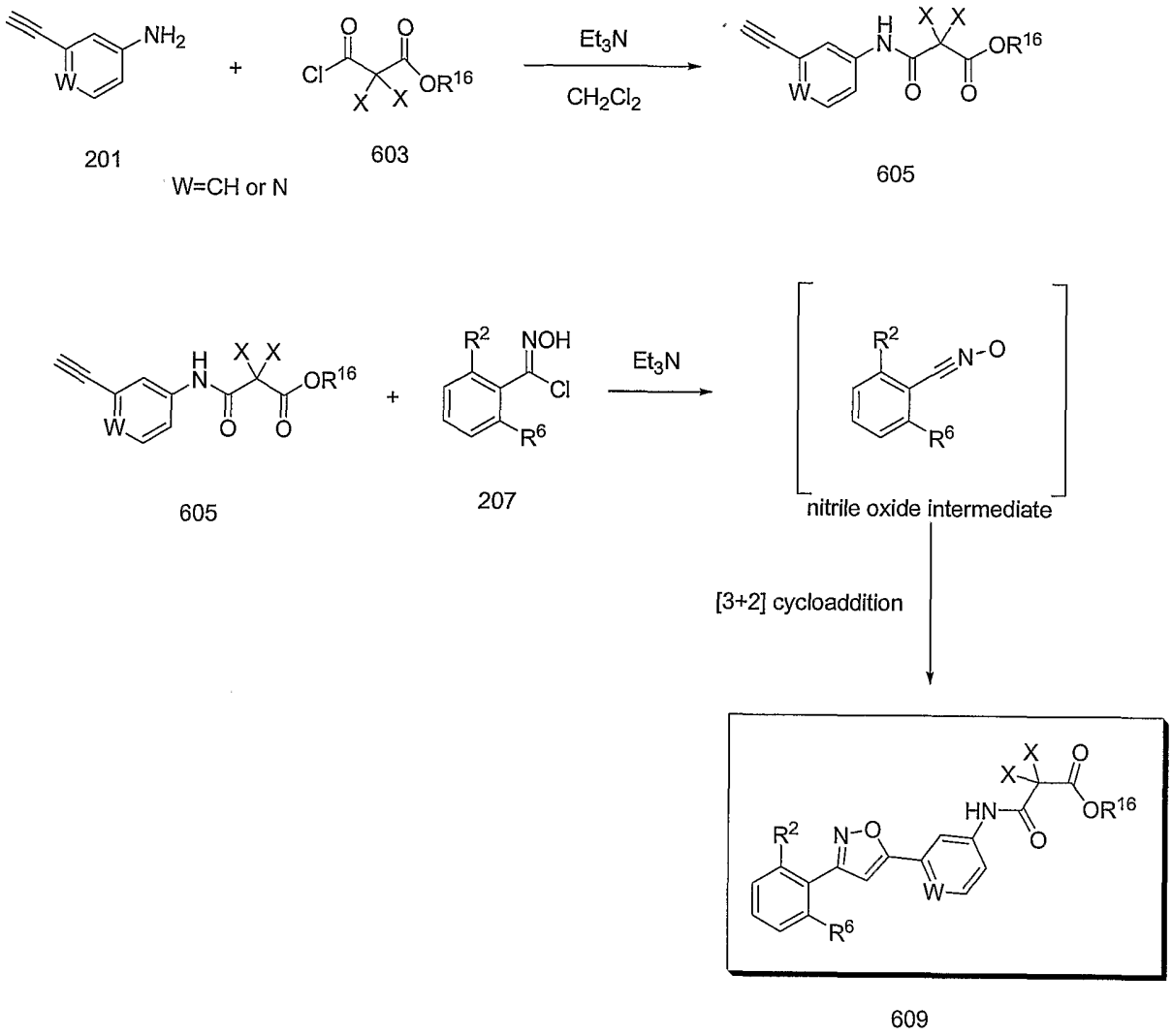

Et3N
CH2Cl2
201
603
605
W=CH or N
Et3N
605
207
nitrile oxide intermediate
[3+2] cycloaddition
609

Fig. 4

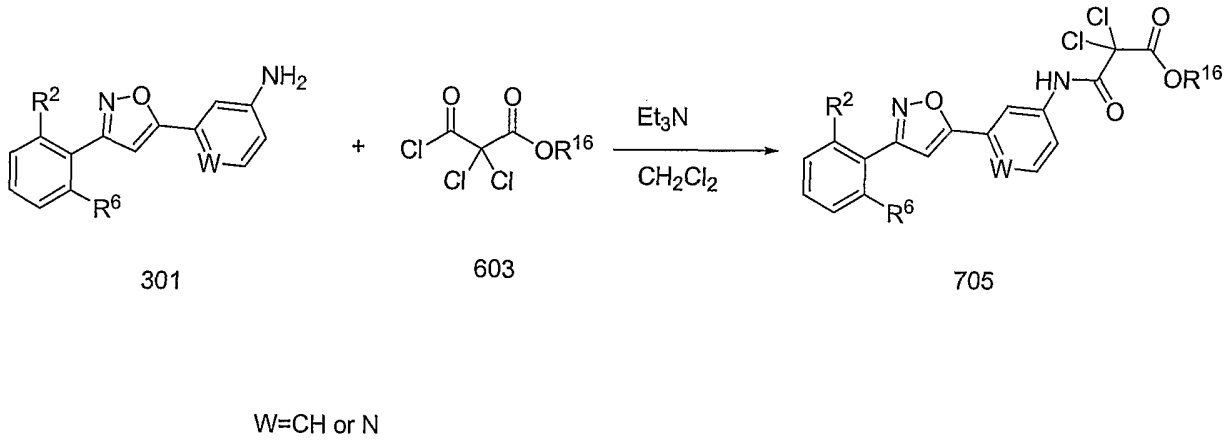

Et3N
CH2Cl2
301
603
705
W=CH or N

Fig. 5

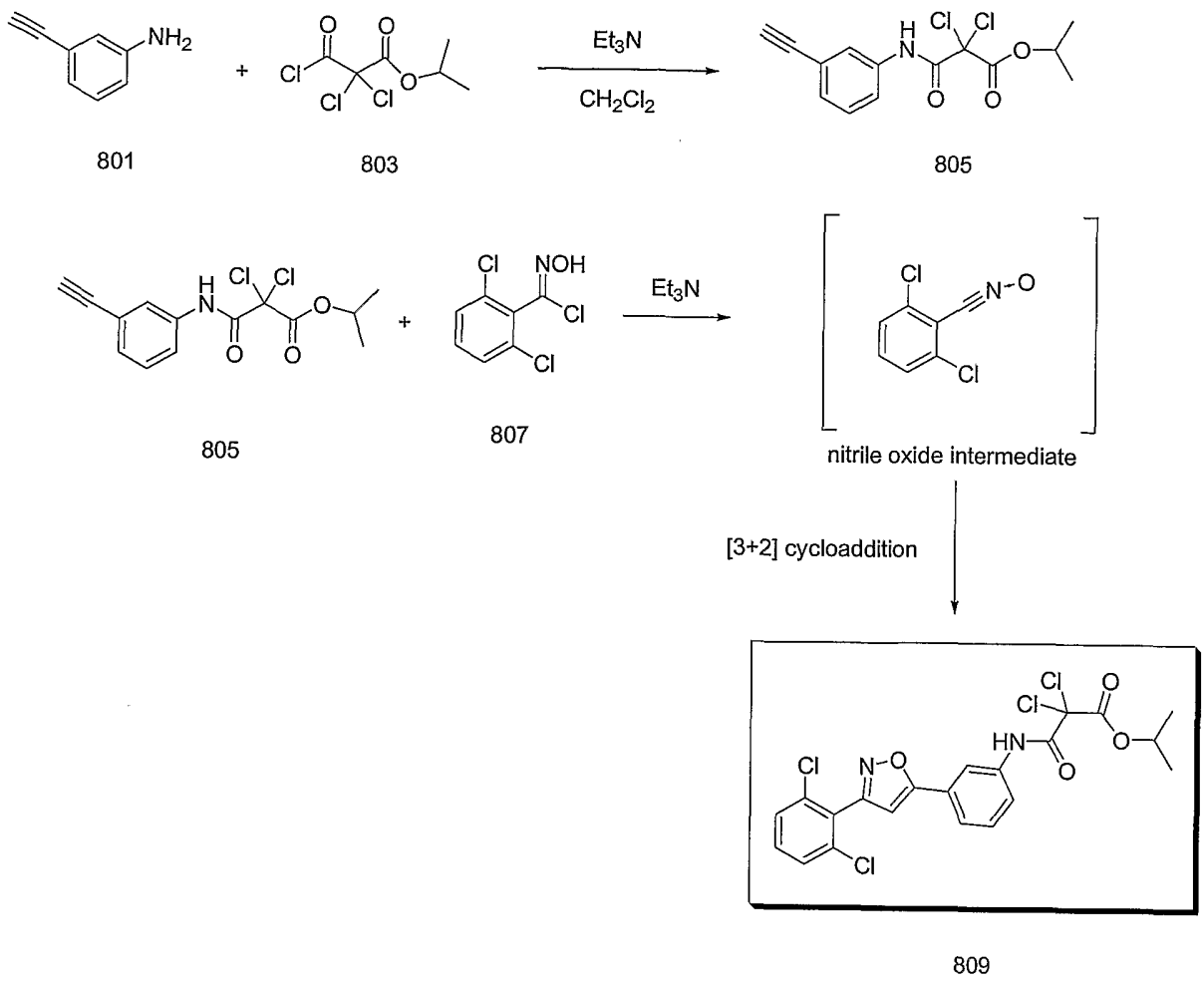

Et3N
CH2Cl2
801
803
805
805
807
Et3N
nitrile oxide intermediate
[3+2] cycloaddition
809

Fig. 6

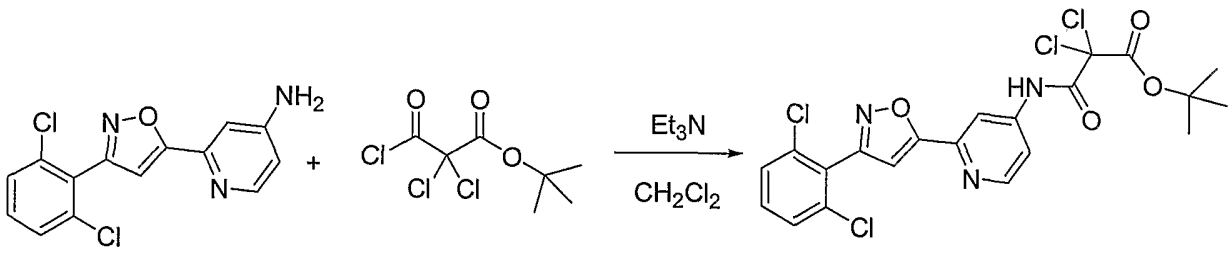
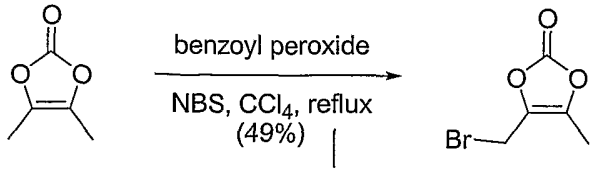
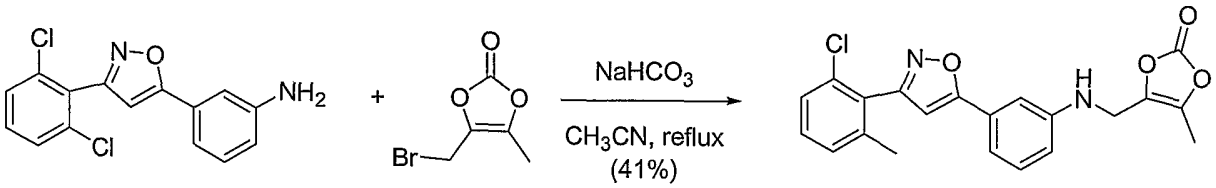

Et3N
CH2Cl2
501
503
505

Fig. 7

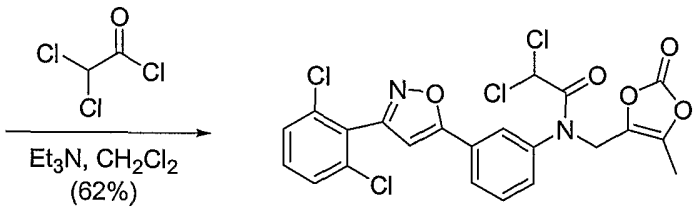


903

Fig. 8A



401 903 905



907

Fig. 8B

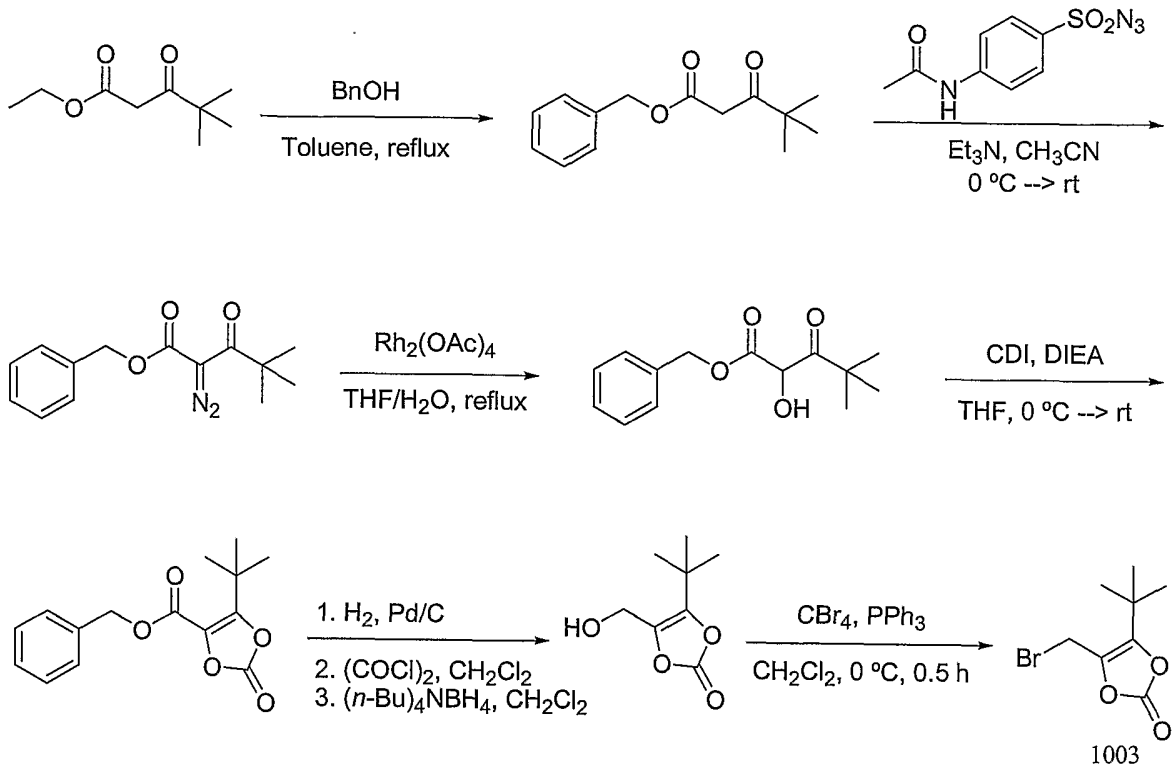

BnOH
Toluene, reflux
SO_2N_3
Et_3N, CH_3CN
0 °C --> rt
$Rh_2(OAc)_4$
THF/H_2O, reflux
CDI, DIEA
THF, 0 °C --> rt
1. H_2, Pd/C
2. $(COCl)_2$, CH_2Cl_2
3. $(n\text{-}Bu)_4NBH_4$, CH_2Cl_2
CBr_4, PPh_3
CH_2Cl_2, 0 °C, 0.5 h
1003

Fig. 9A

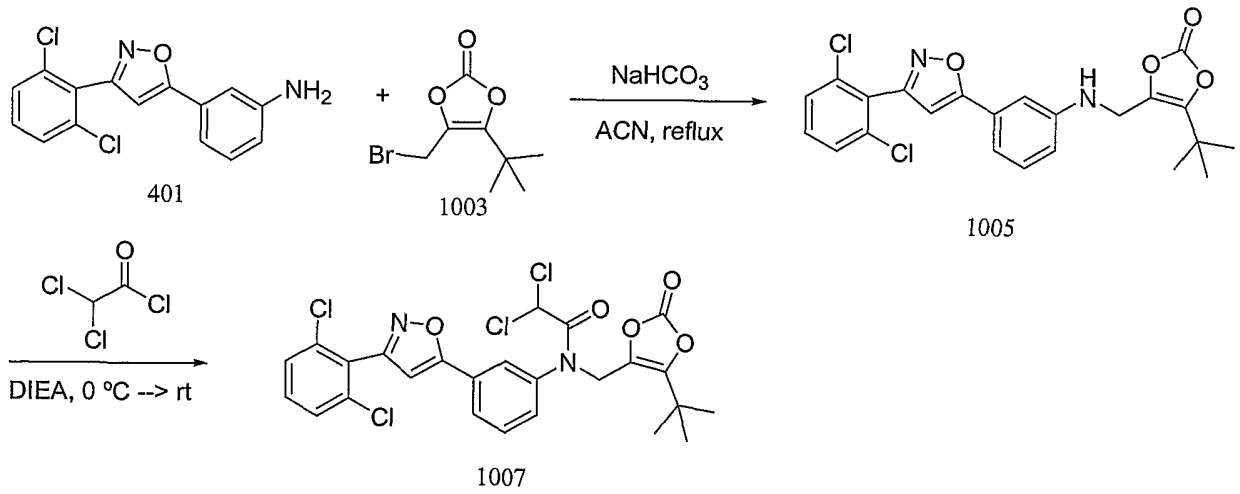
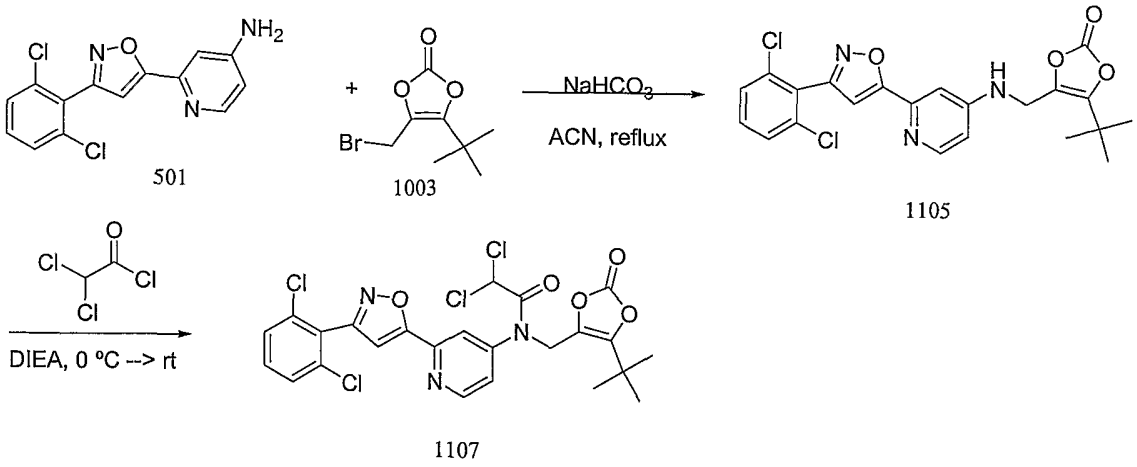
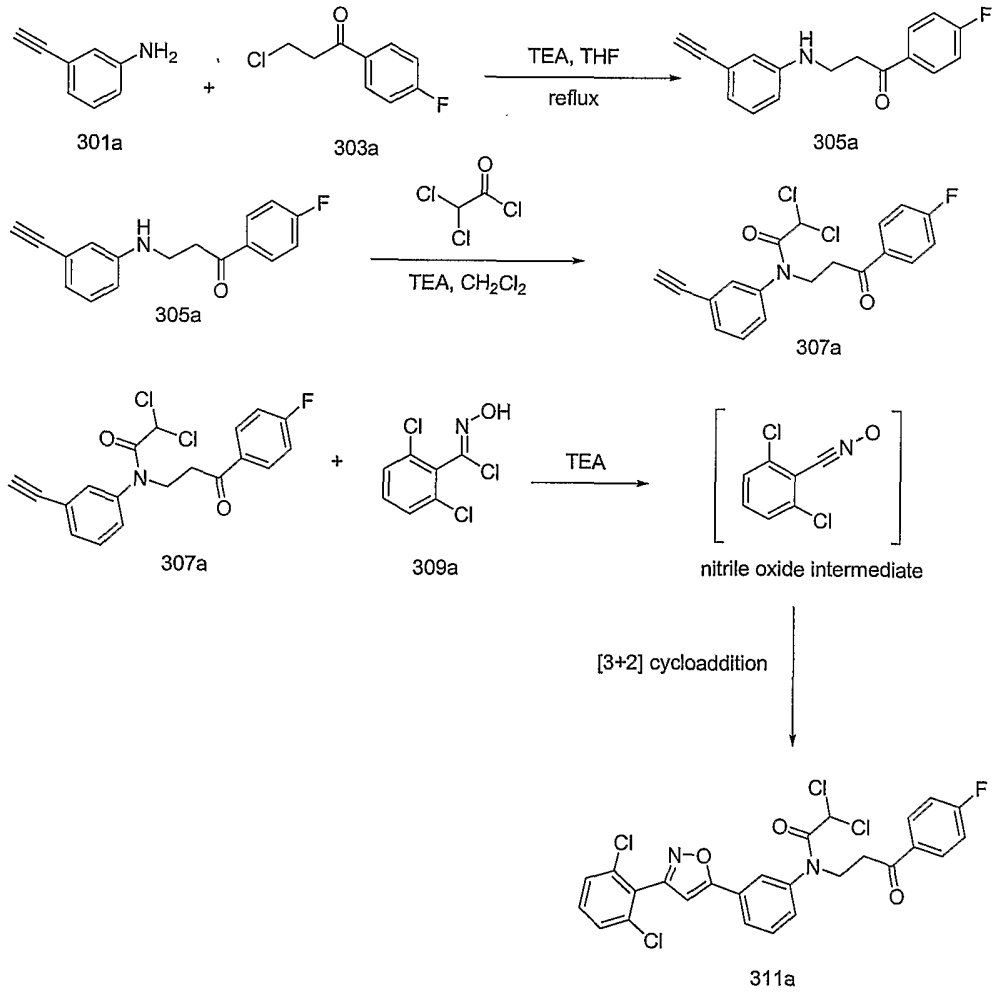

401
1003
$NaHCO_3$
ACN, reflux
1005
DIEA, 0 °C --> rt
1007

Fig. 9B



501 1003 1105 1107

Fig. 10



301a 303a 305a 305a 307a 307a 309a 311a

Fig. 11

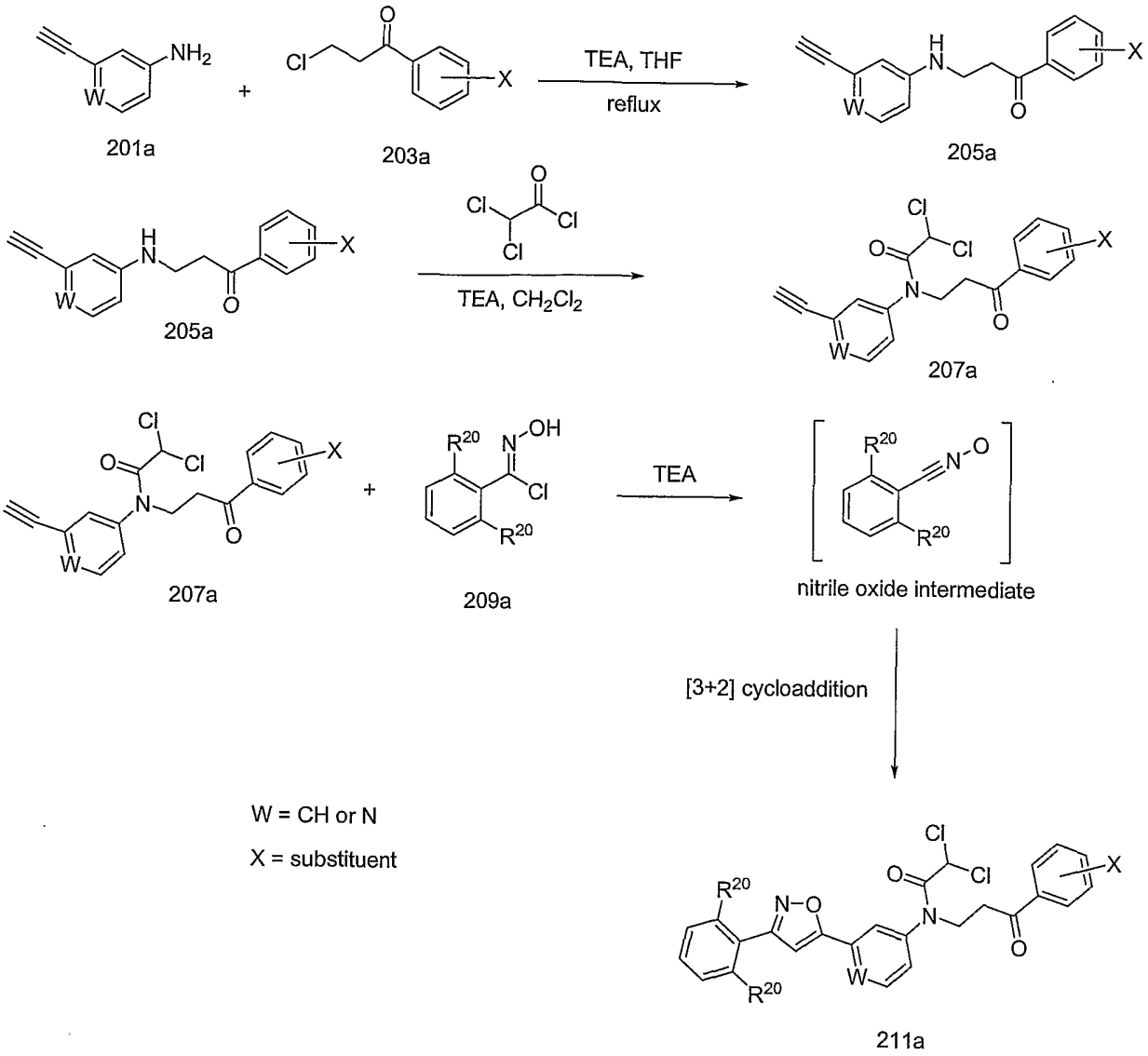

NH2
W
201a
Cl
O
X
203a
TEA, THF
reflux
H
N
O
205a
TEA, CH2Cl2
Cl
Cl
207a
R20
N-OH
209a
TEA
nitrile oxide intermediate
[3+2] cycloaddition
W = CH or N
X = substituent
N-O
211a

Fig. 12

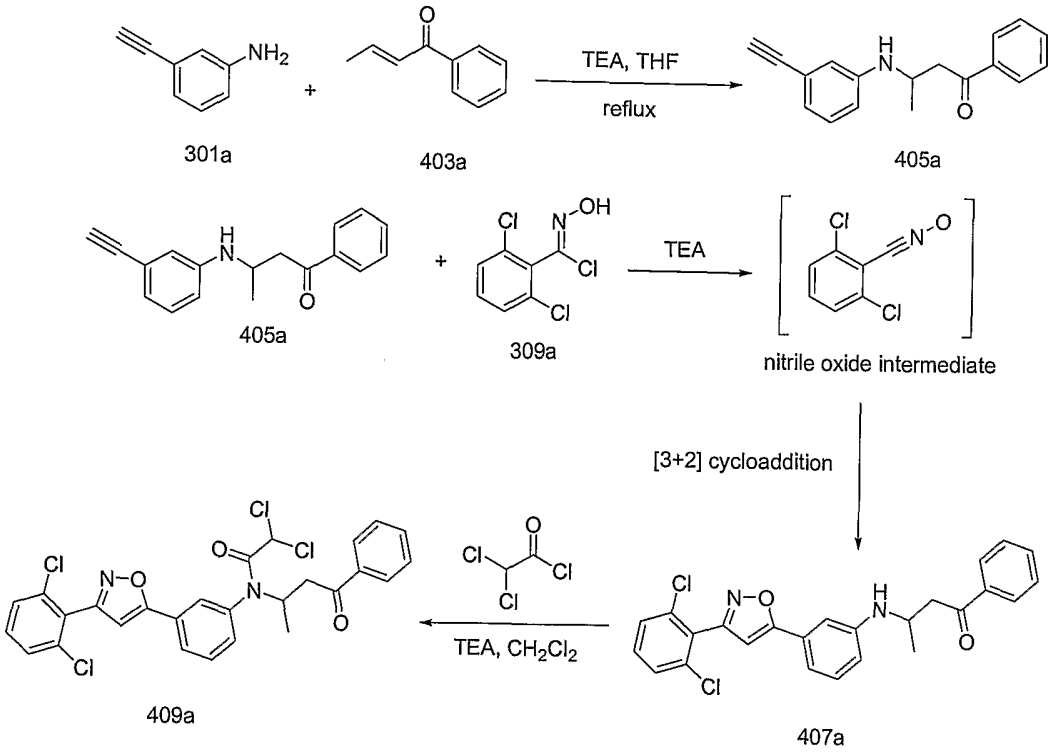

TEA, THF
reflux
301a
403a
405a
405a
309a
TEA
nitrile oxide intermediate
[3+2] cycloaddition
TEA, CH2Cl2
409a
407a

Fig. 13

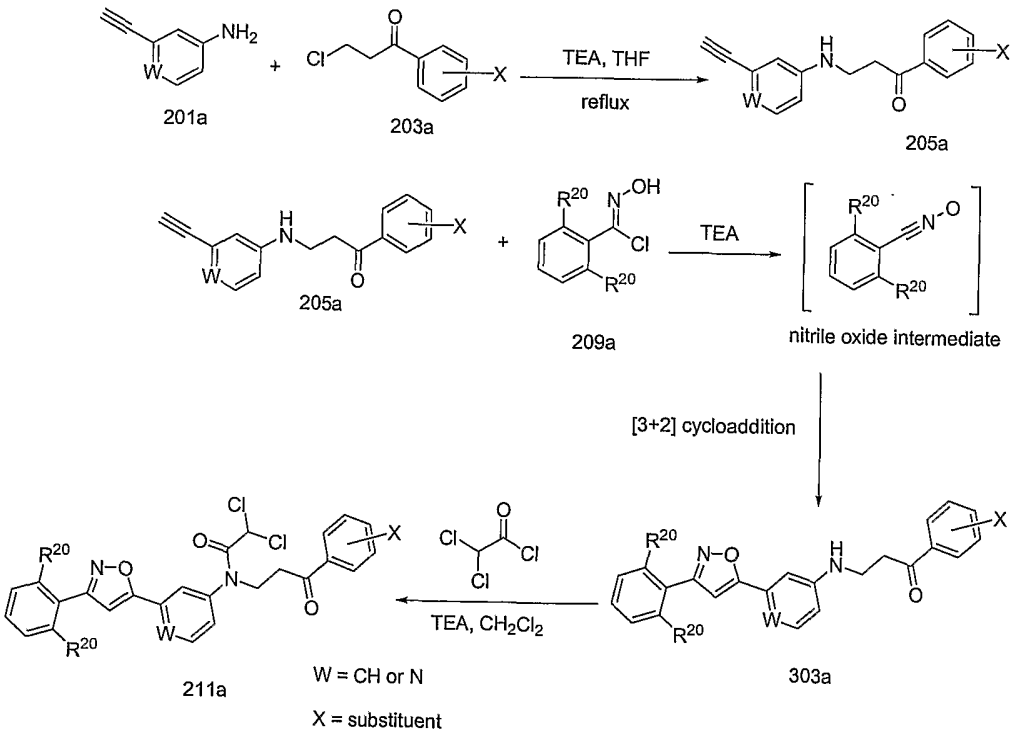
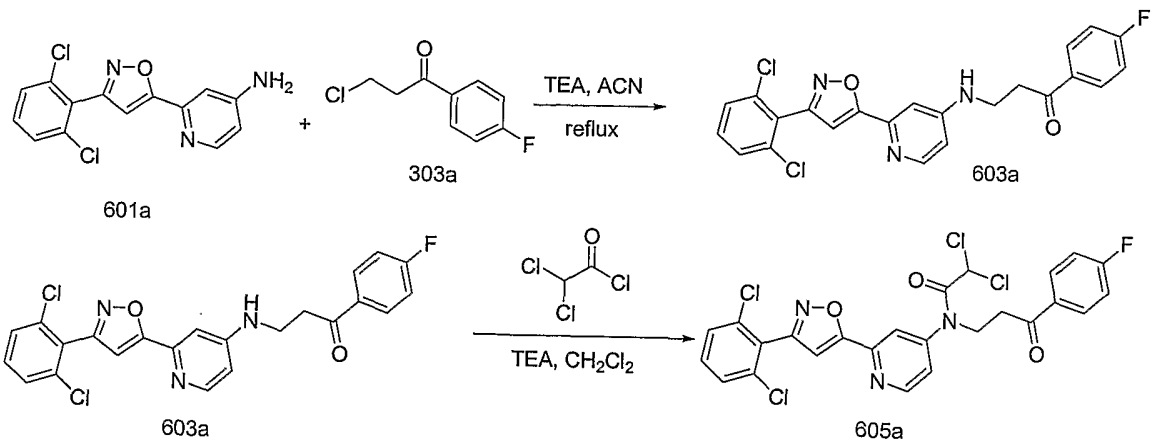
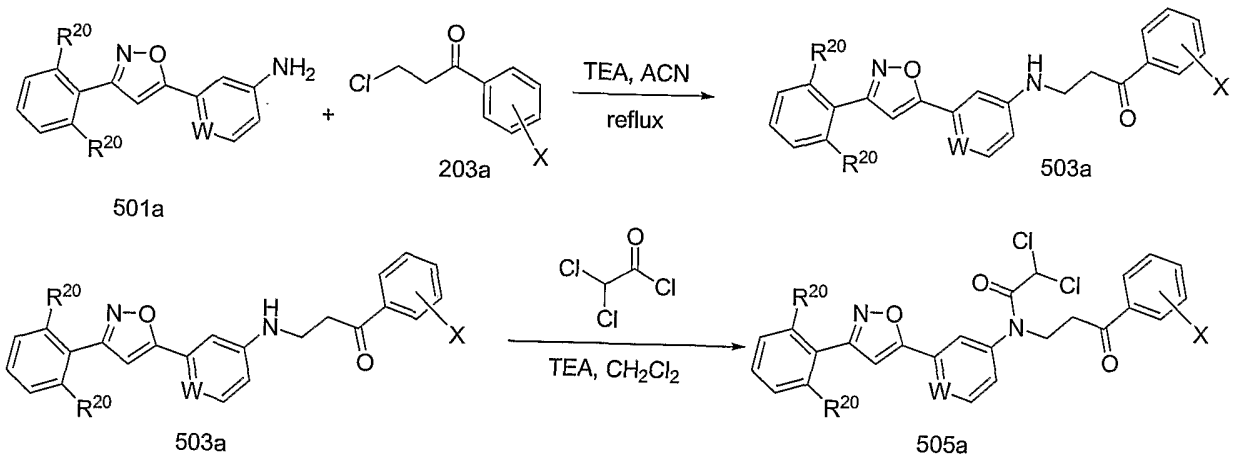

TEA, THF
reflux
201a
203a
205a
205a
209a
TEA
nitrile oxide intermediate
[3+2] cycloaddition
TEA, CH2Cl2
211a
303a
W = CH or N
X = substituent

Fig. 14



601a 303a 603a 603a 605a

Fig. 15



501a 203a 503a 503a 505a

W = CH or N

X is a substituent

Fig. 16

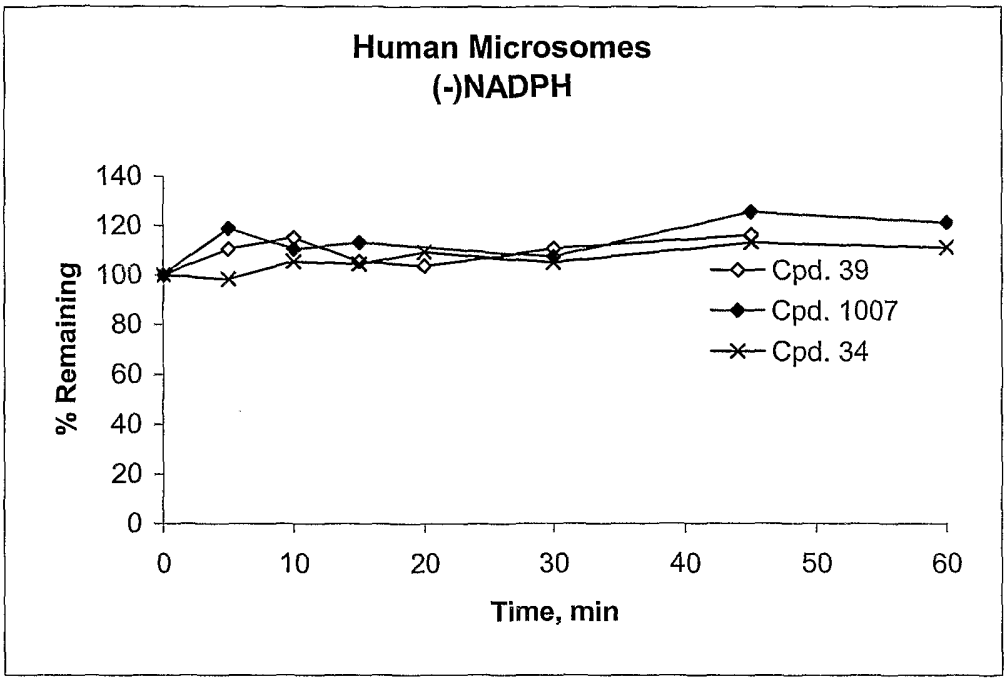


Fig. 17A

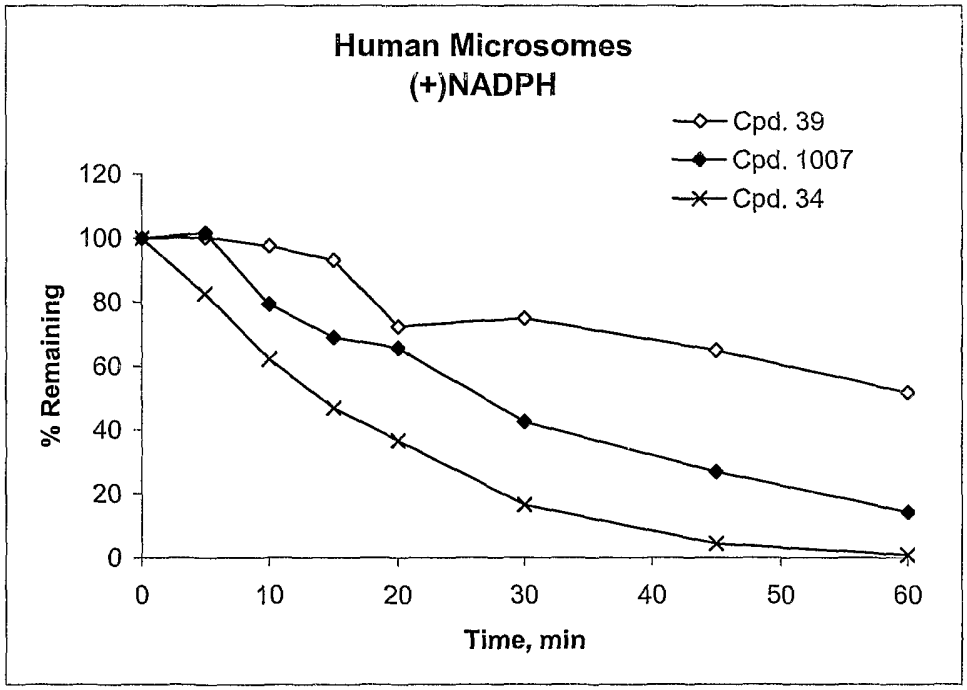


Fig. 17B

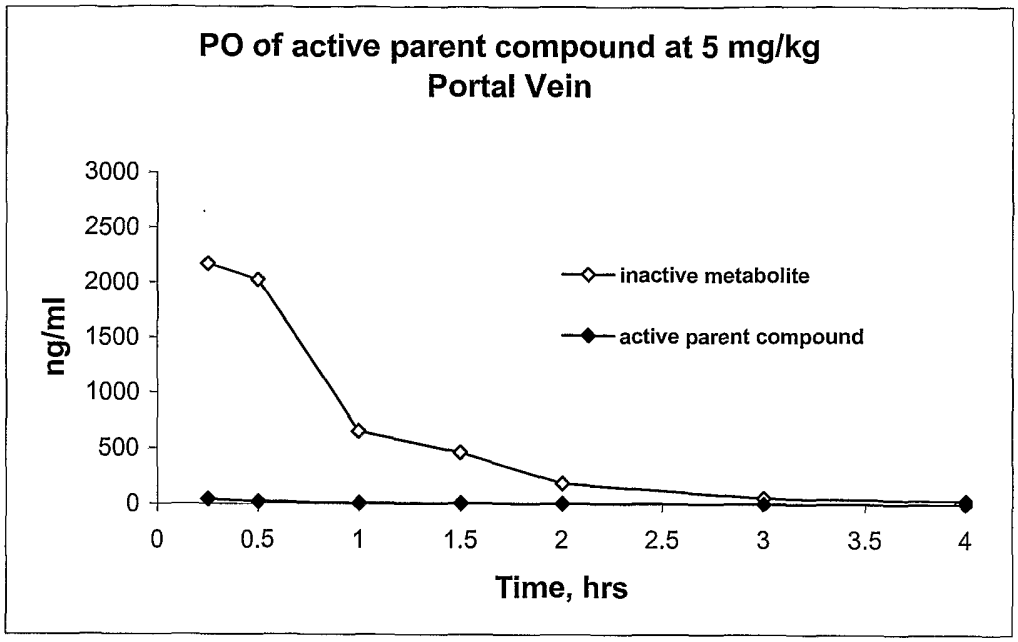


Fig. 18A

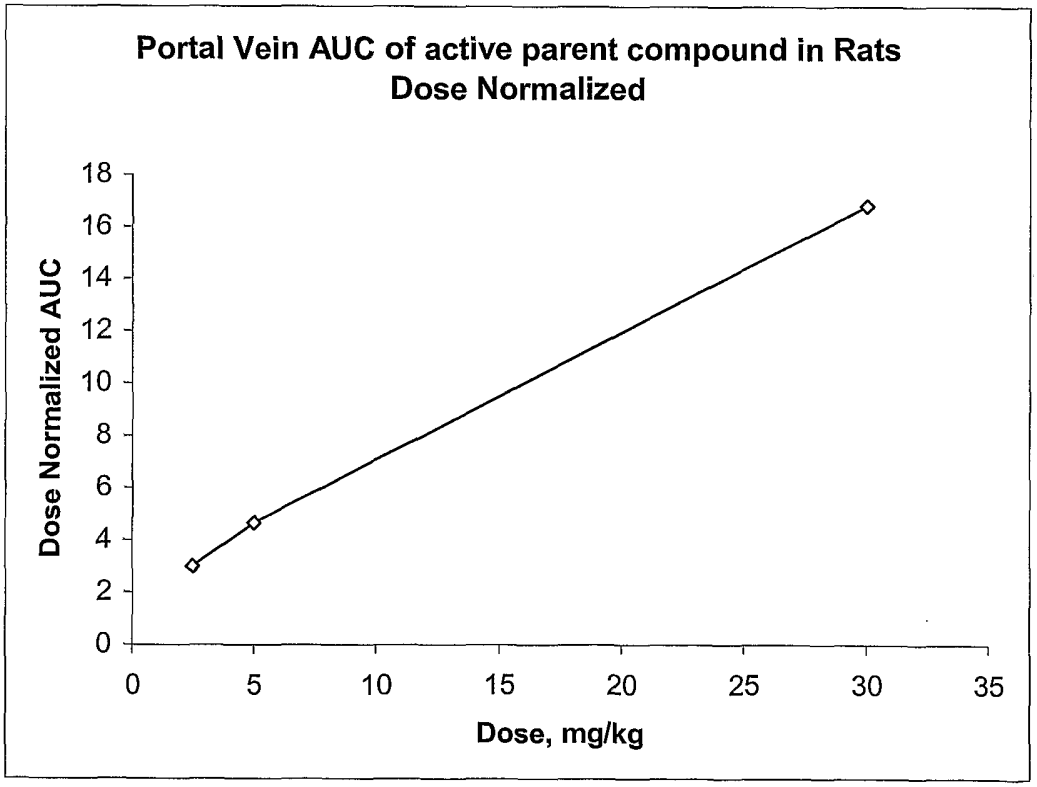


Fig. 18B

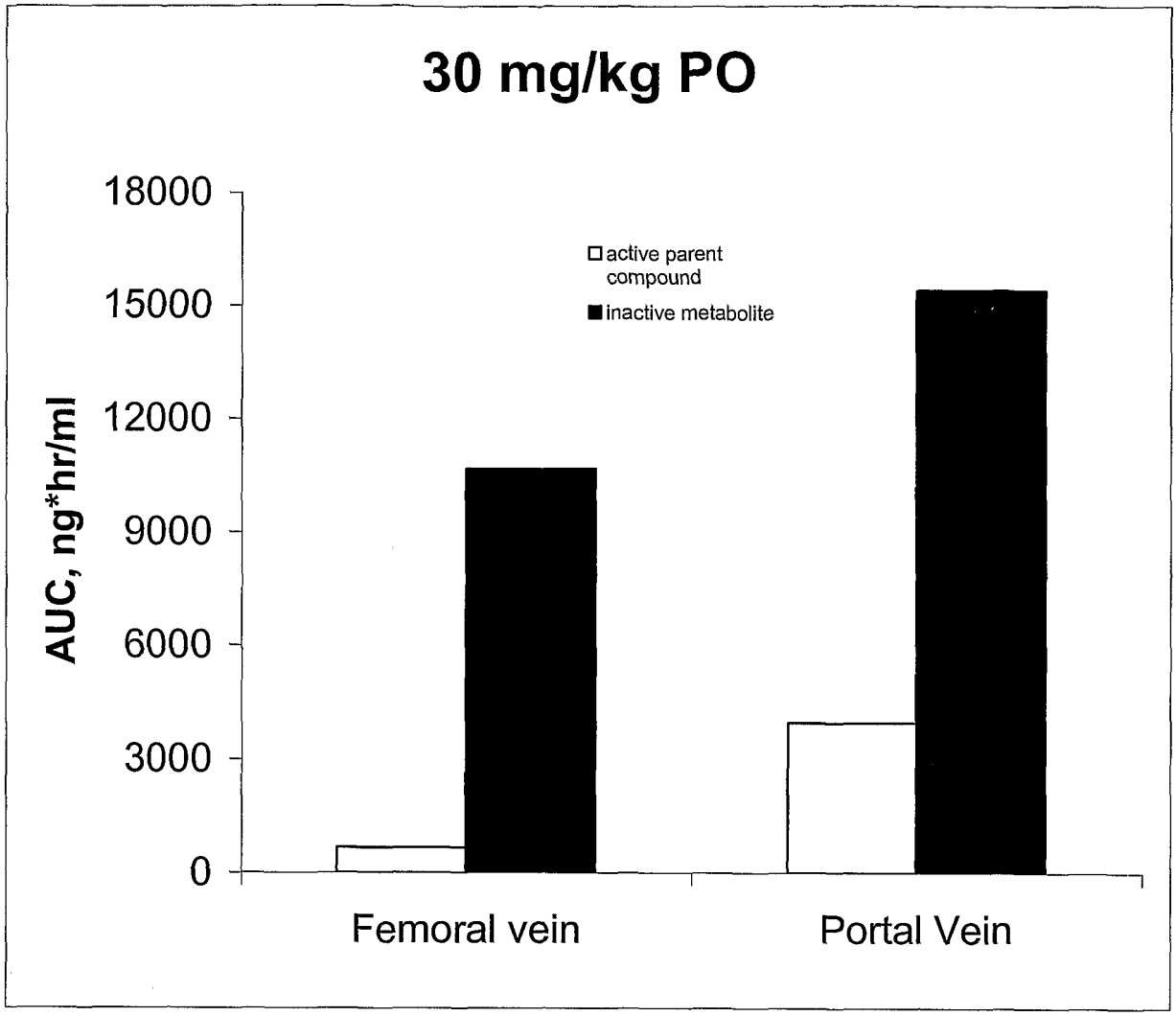

30 mg/kg PO
AUC, ng*hr/ml
18000
15000
12000
9000
6000
3000
0
active parent compound
inactive metabolite
Femoral vein
Portal Vein

Fig. 19

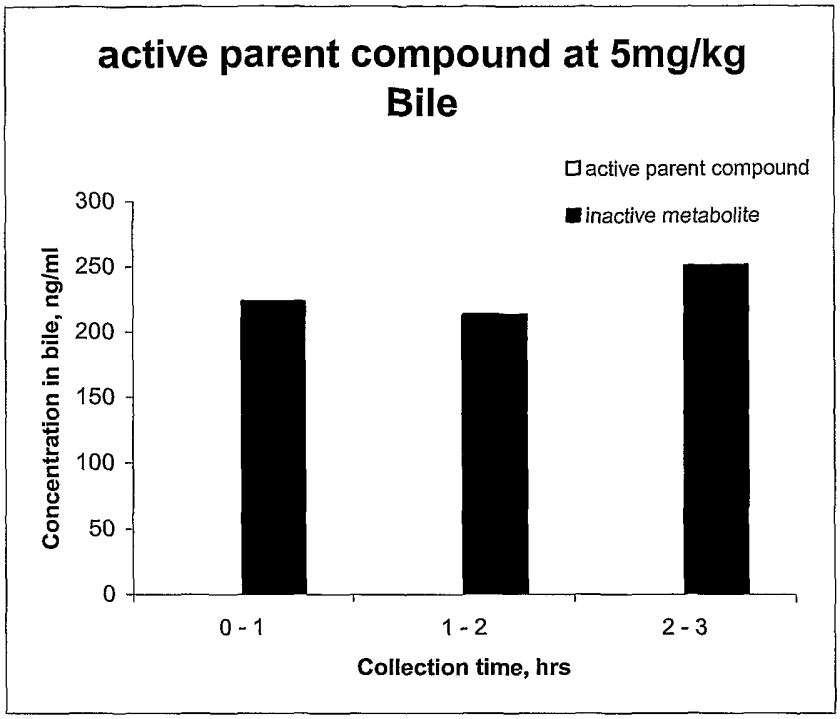


Fig. 20A

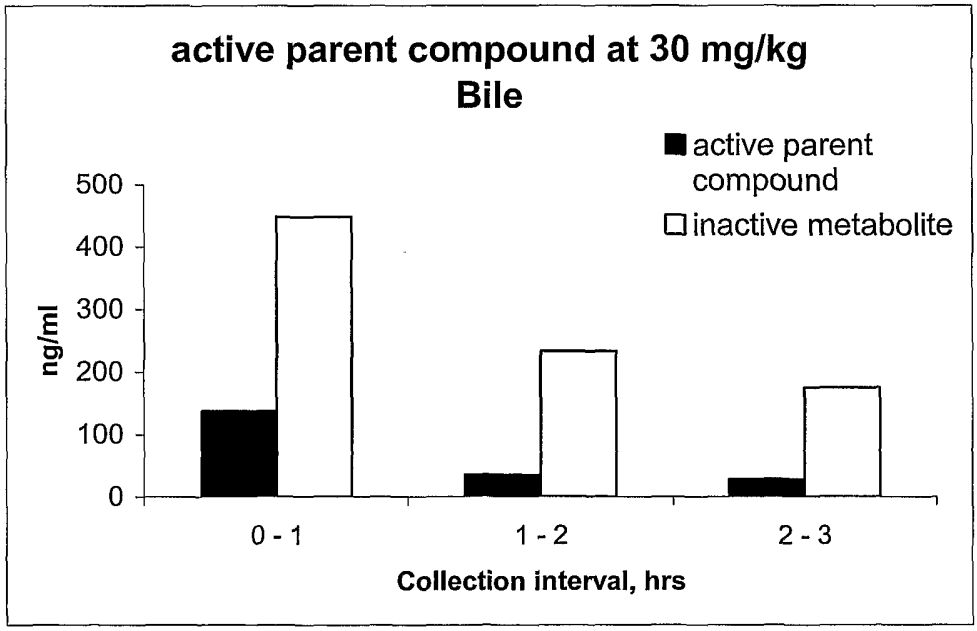


Fig. 20B

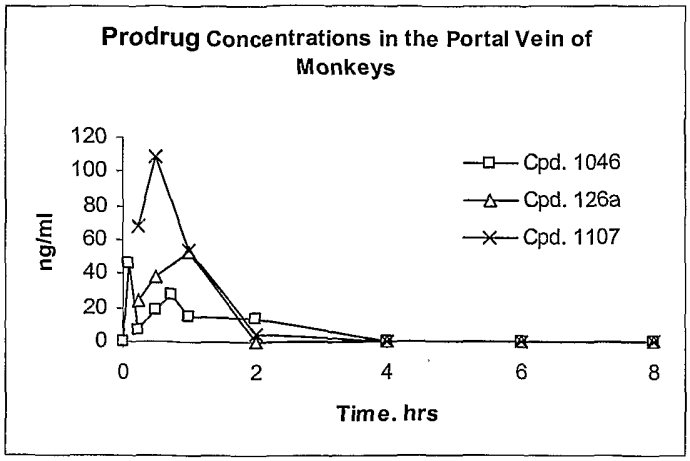


Fig. 21A

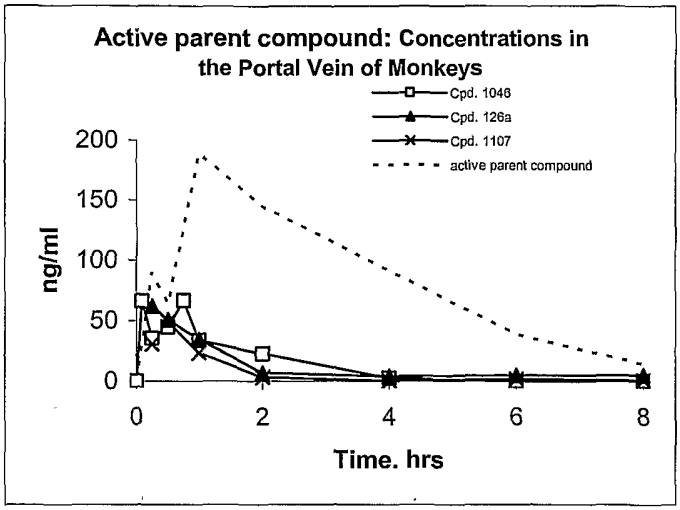


Fig. 21B

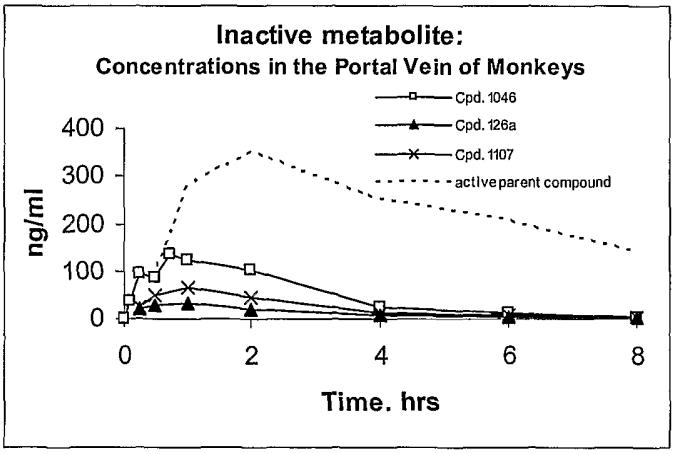


Fig. 21C

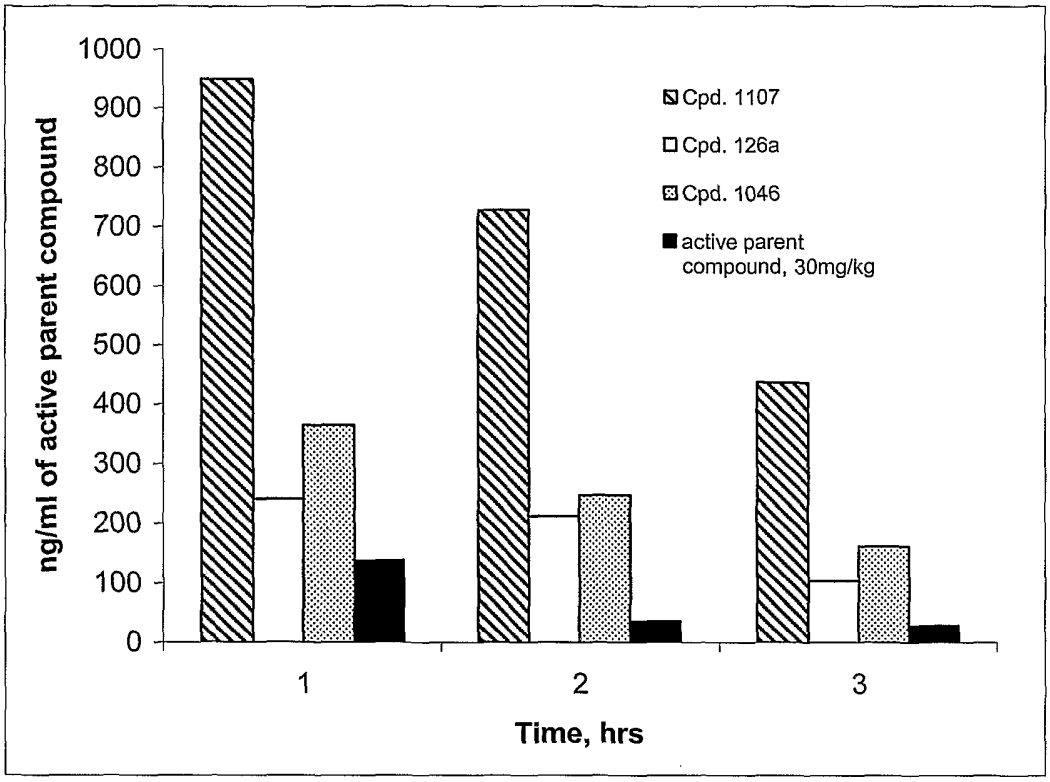

1000
900
800
700
600
500
400
300
200
100
0
ng/ml of active parent compound
Cpd. 1107
Cpd. 126a
Cpd. 1046
active parent compound, 30mg/kg
1
2
3
Time, hrs

Fig. 22

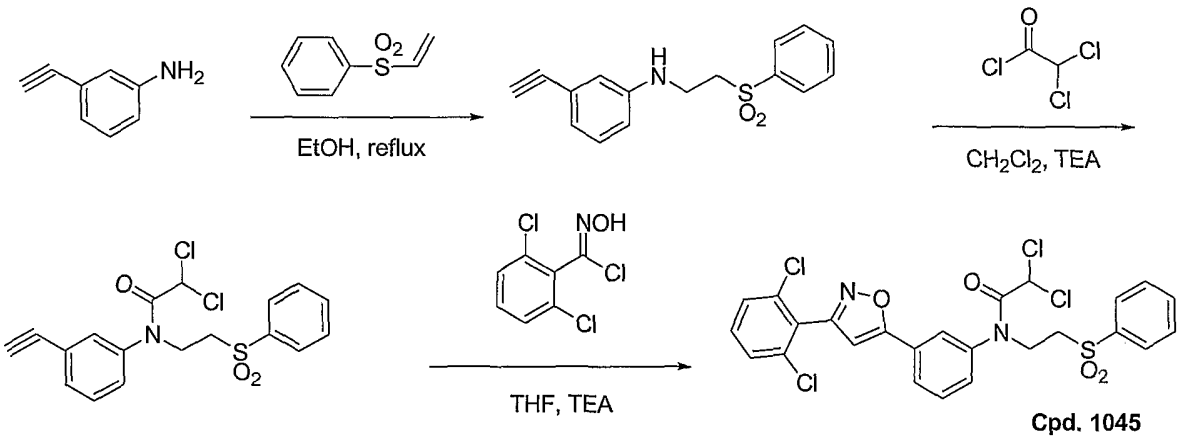

NH2
O2
S
EtOH, reflux
H
N
S
O2
O
Cl
Cl
Cl
CH2Cl2, TEA
Cl
O
N
Cl
S
O2
Cl
NOH
Cl
Cl
THF, TEA
N-O
Cpd. 1045

Fig. 23

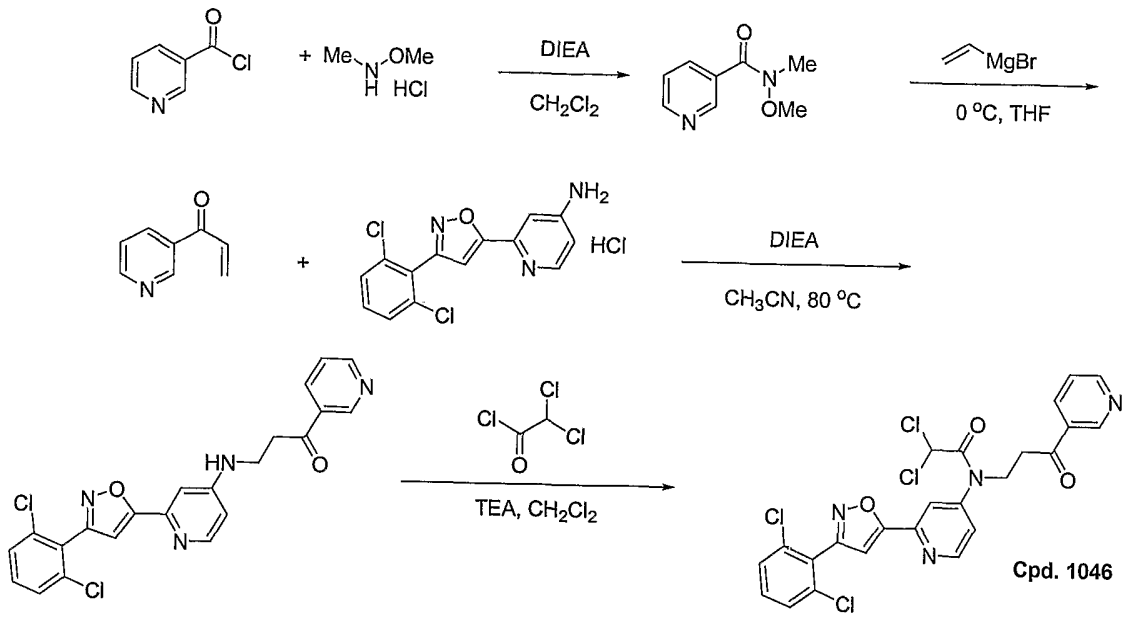

DIEA
CH_2Cl_2
MgBr
0 °C, THF
HCl
DIEA
CH_3CN, 80 °C
TEA, CH_2Cl_2
Cpd. 1046

Fig. 24

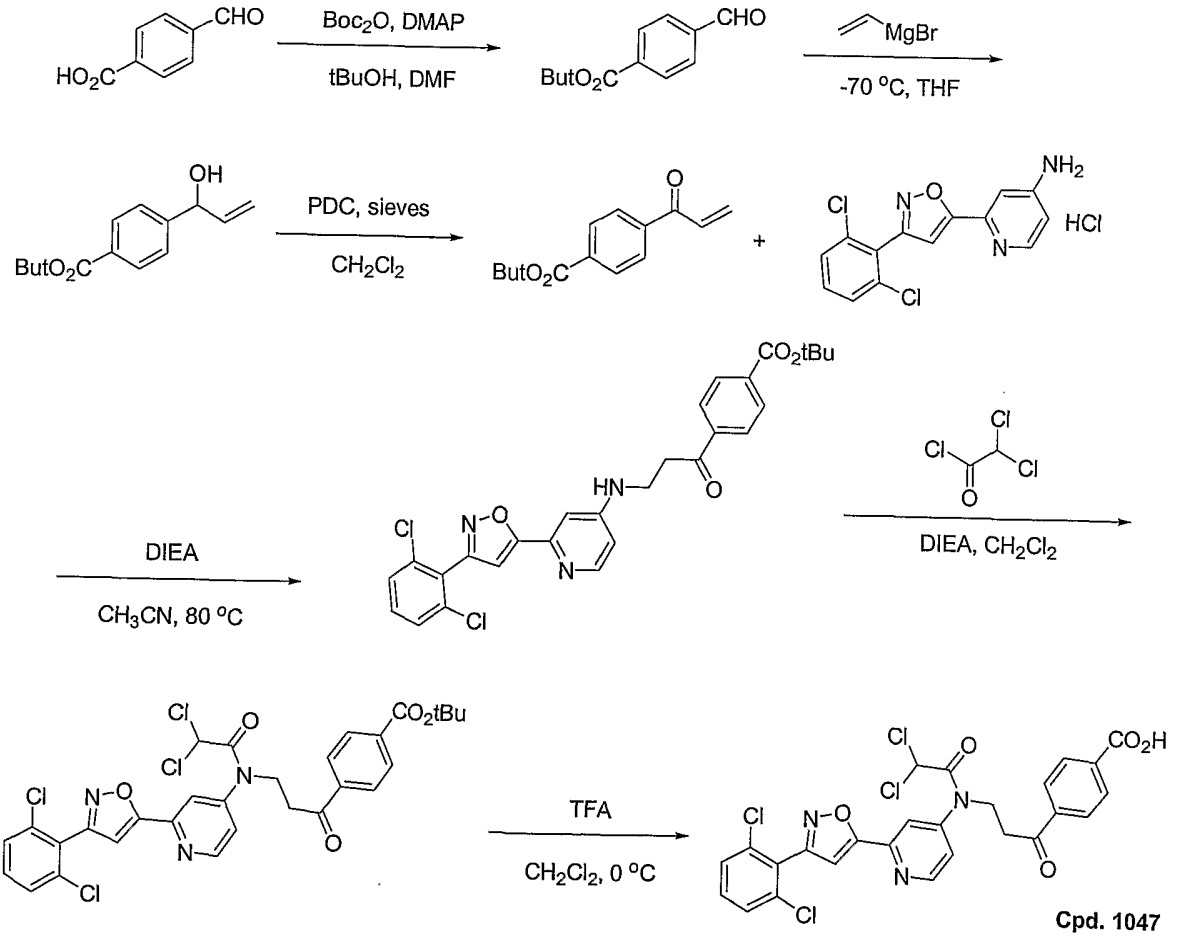

Boc_2O, DMAP
tBuOH, DMF
MgBr
-70 °C, THF
PDC, sieves
CH_2Cl_2
HCl
DIEA
CH_3CN, 80 °C
DIEA, CH_2Cl_2
TFA
CH_2Cl_2, 0 °C
Cpd. 1047

Fig. 25

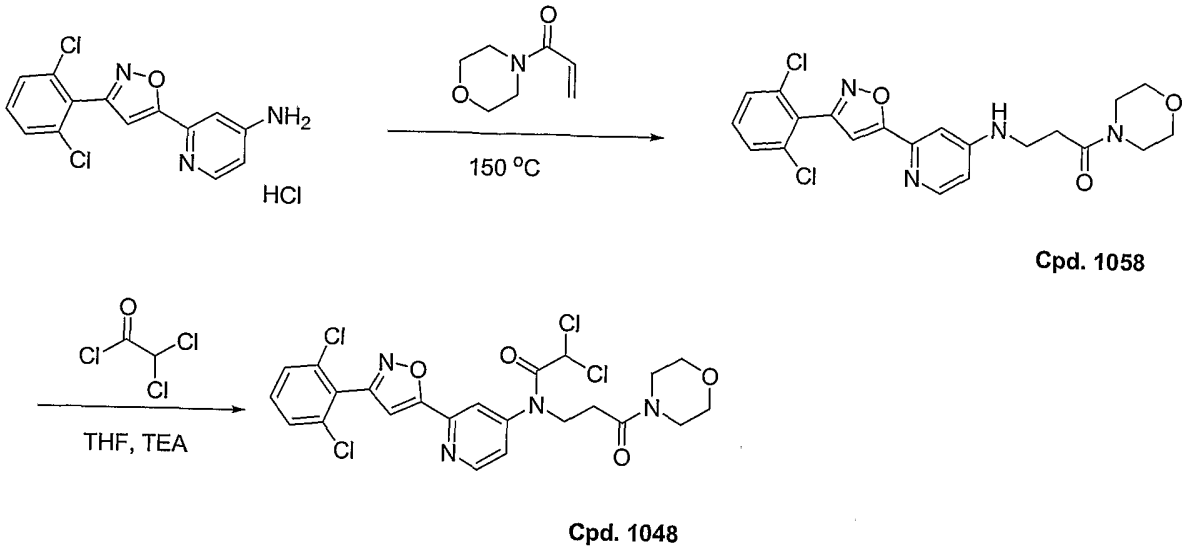

Cl
N
O
NH2
Cl
N
HCl
O
N
O
150 °C
Cl
N
O
H
N
N
O
O
Cpd. 1058
O
Cl
Cl
Cl
THF, TEA
Cl
N
O
Cl
Cl
N
N
O
O
Cpd. 1048

Fig. 26

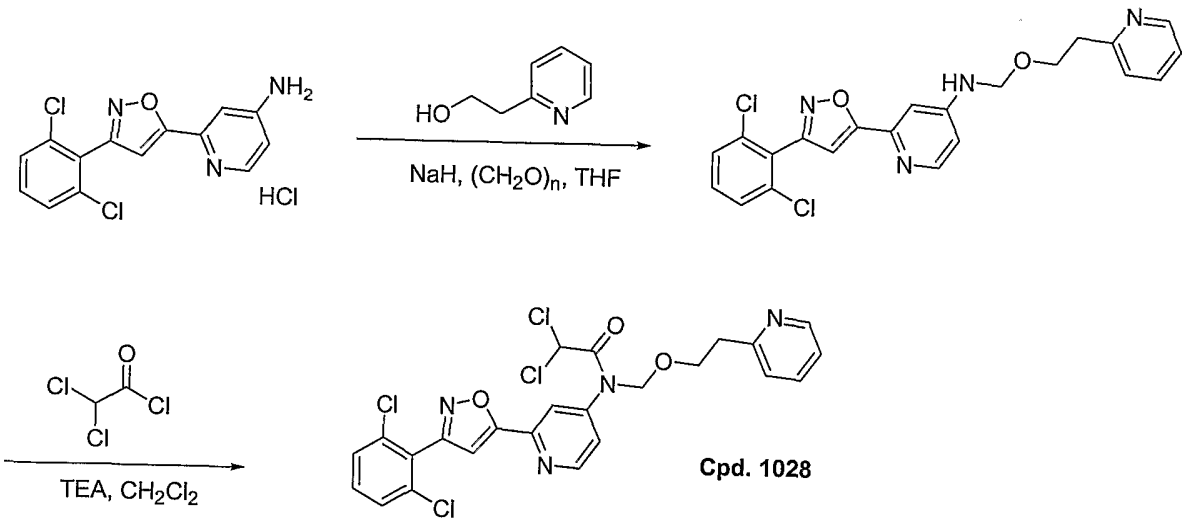

Cl
N
O
NH2
Cl
N
HCl
HO
N
NaH, (CH2O)n, THF
N
HN
O
Cl
N
O
N
Cl
O
Cl
Cl
Cl
TEA, CH2Cl2
Cl
Cl
O
N
O
N
Cl
N
Cpd. 1028

Fig. 27

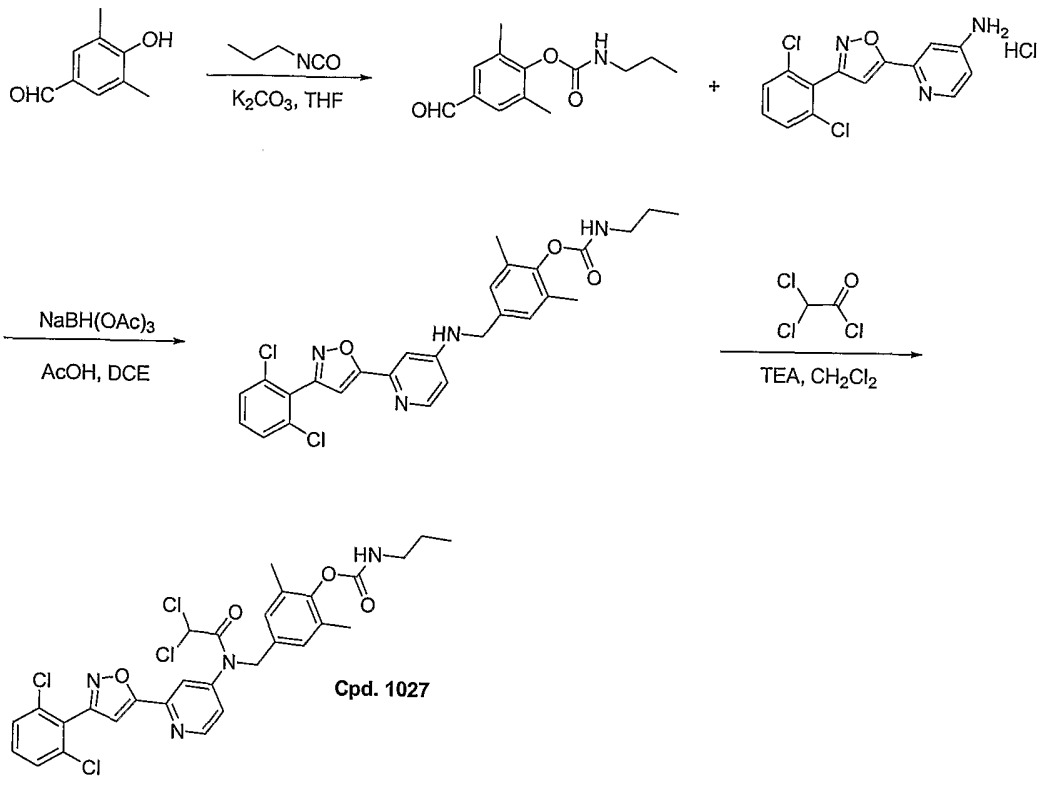

OH
OHC
NCO
K_2CO_3, THF
H
N
O
O
OHC
+
Cl
N-O
NH_2
HCl
N
Cl
$NaBH(OAc)_3$
AcOH, DCE
HN
O
O
HN
Cl
N-O
N
Cl
Cl
Cl
O
Cl
TEA, CH_2Cl_2
HN
O
O
Cl
Cl
O
N
Cl
N-O
N
Cl
Cpd. 1027

Fig. 28

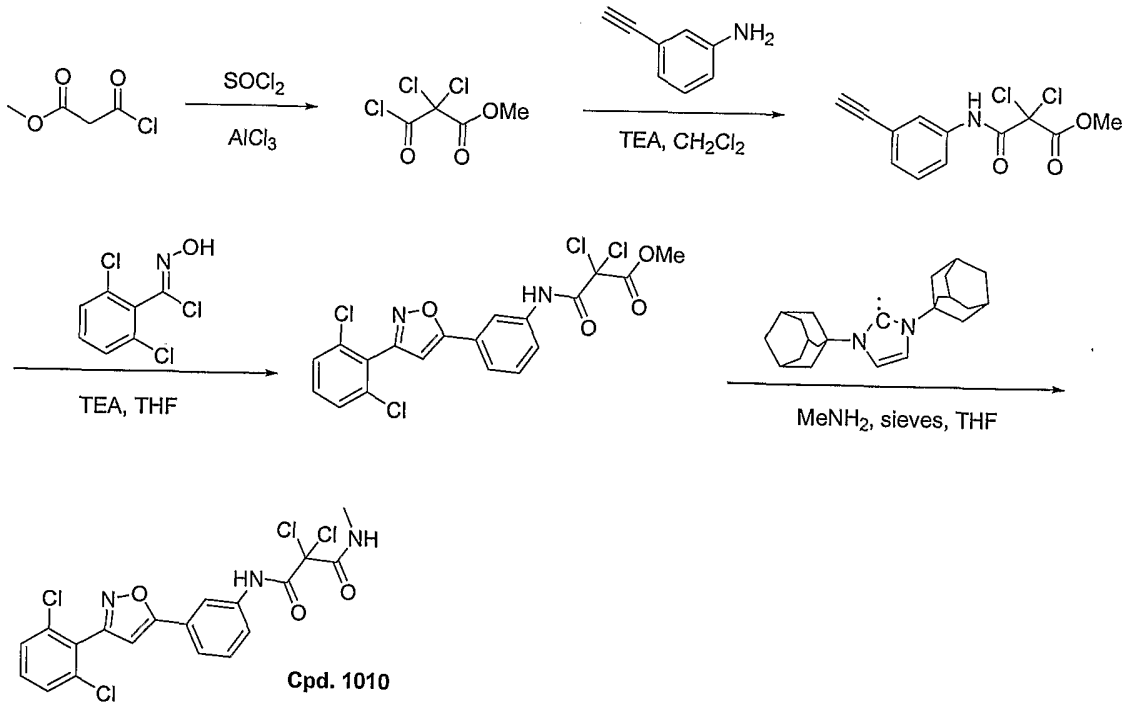
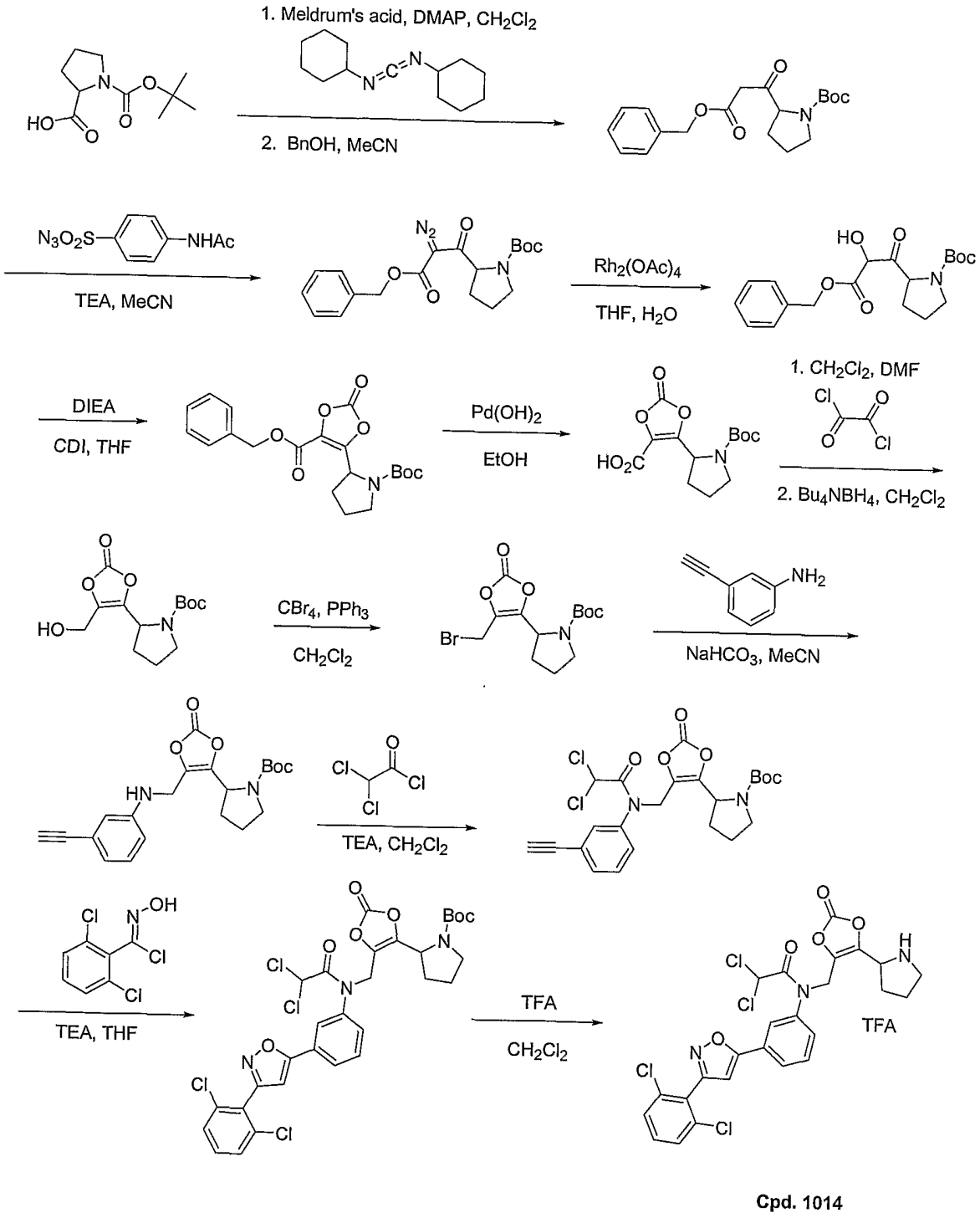

O
O
O
Cl
$SOCl_2$
$AlCl_3$
Cl
Cl
Cl
O
O
OMe
NH_2
TEA, CH_2Cl_2
H
N
Cl
Cl
O
O
OMe
Cl
N-OH
Cl
Cl
TEA, THF
Cl
Cl
OMe
HN
O
Cl
N-O
Cl
$MeNH_2$, sieves, THF
Cl
Cl
NH
HN
O
O
Cl
N-O
Cl
Cpd. 1010

Fig. 29



Cpd. 1014

Fig. 30

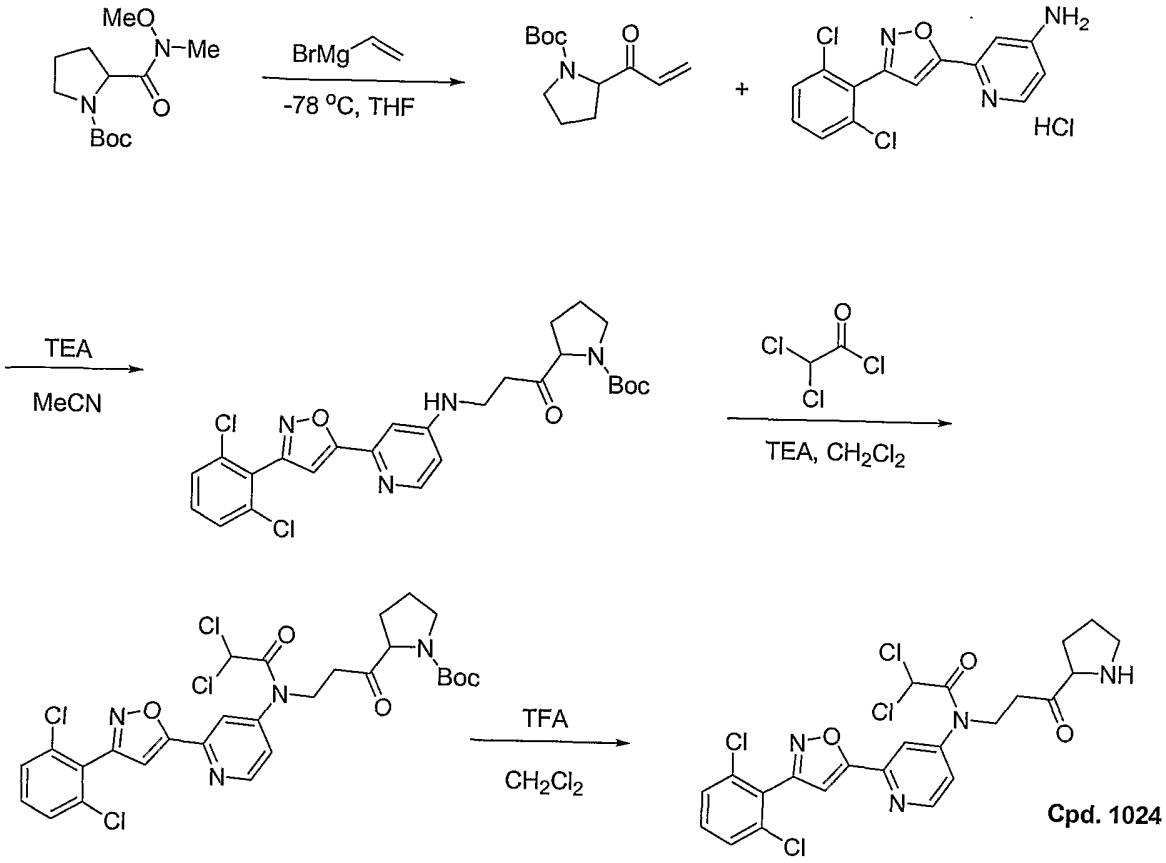

MeO
N–Me
O
N
Boc
BrMg
-78 °C, THF
Boc
N
O
+
Cl
N–O
NH2
N
Cl
HCl
TEA
MeCN
Cl
N–O
HN
N
Boc
O
Cl
N
Cl
O
Cl
Cl
TEA, CH2Cl2
Cl
Cl
O
N
Boc
O
Cl
N–O
N
Cl
TFA
CH2Cl2
Cl
Cl
O
N
NH
O
Cl
N–O
N
Cl
Cpd. 1024

Fig. 31

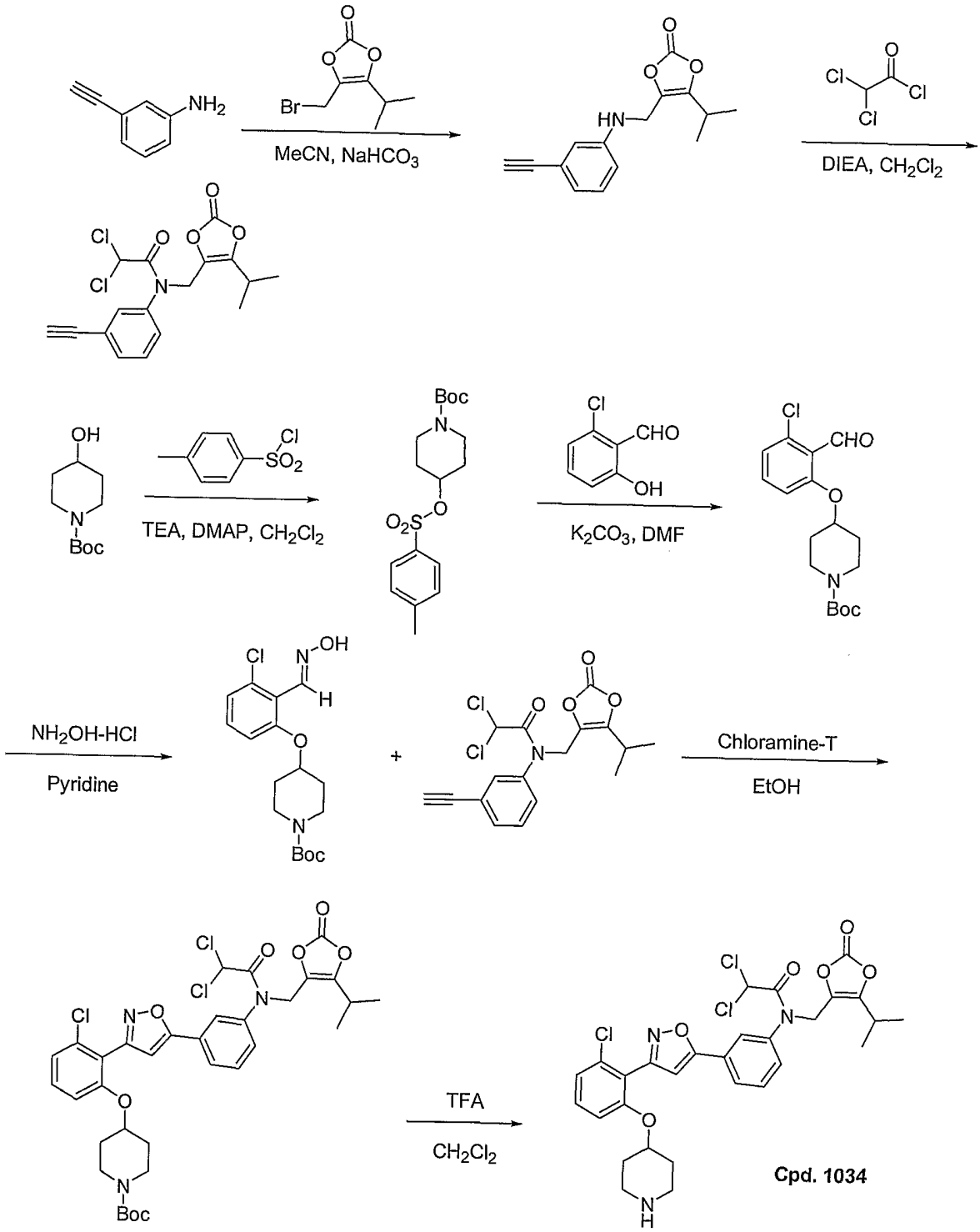

MeCN, NaHCO3
DIEA, CH2Cl2
TEA, DMAP, CH2Cl2
K2CO3, DMF
NH2OH-HCl
Pyridine
Chloramine-T
EtOH
TFA
CH2Cl2
Cpd. 1034

Fig. 32

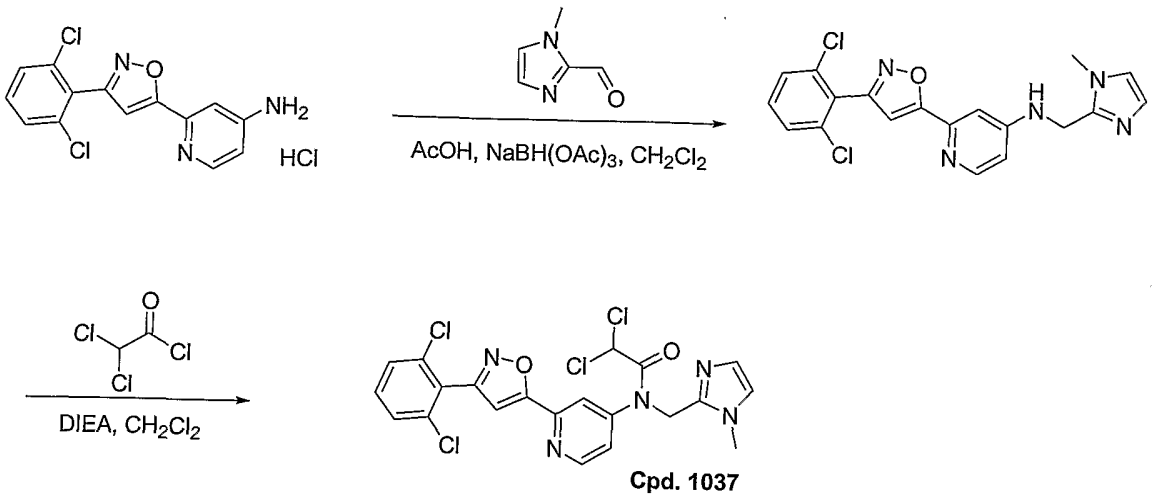

AcOH, NaBH(OAc)3, CH2Cl2
DIEA, CH2Cl2
Cpd. 1037

Fig 33

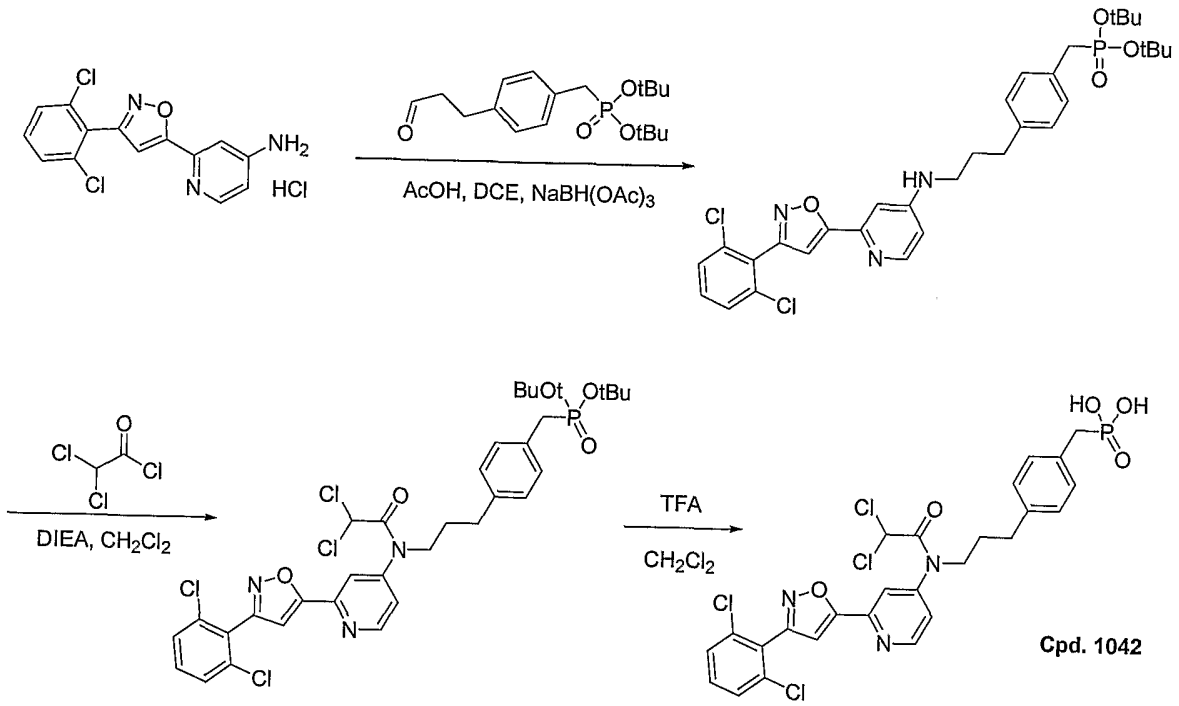

AcOH, DCE, NaBH(OAc)3
DIEA, CH2Cl2
TFA
CH2Cl2
Cpd. 1042

Fig. 34

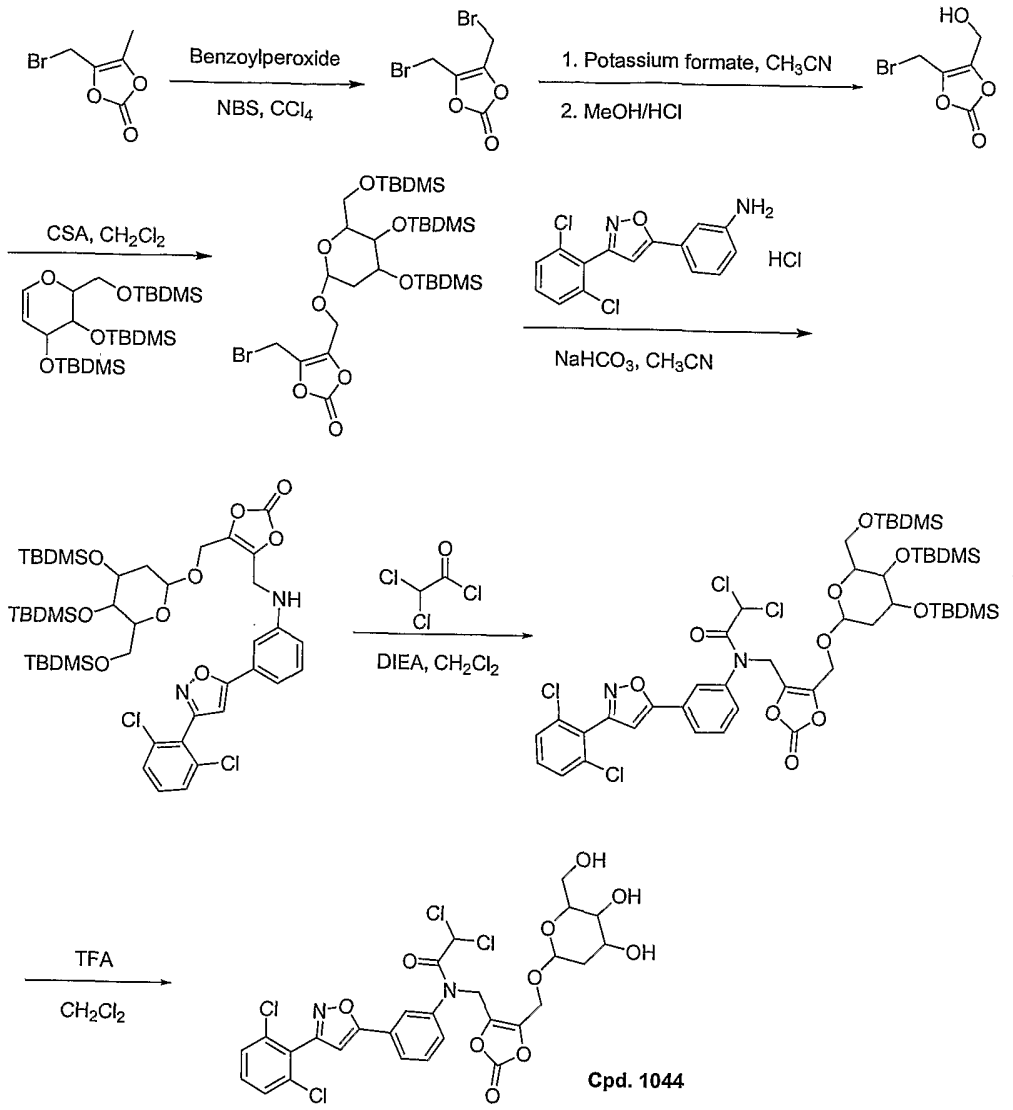

Benzoylperoxide
NBS, CCl4
1. Potassium formate, CH3CN
2. MeOH/HCl
CSA, CH2Cl2
NaHCO3, CH3CN
HCl
DIEA, CH2Cl2
TFA
CH2Cl2
Cpd. 1044

Fig. 35

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/009909

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D261/08 C07D413/04 A61K31/4439 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 A61K A61P

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/018463 A (RIGEL PHARMACEUTICALS, INC; SINGH, RAJINDER; GOFF, DANE; PARTRIDGE, JO) 4 March 2004 (2004-03-04) the whole document	1-72
A	WO 03/040112 A (RIGEL PHARMACEUTICALS, INC; SINGH, RAJINDER; GOFF, DANE; LU, HENRY; IS) 15 May 2003 (2003-05-15) the whole document	1-72
P,X	WO 2004/099164 A (RIGEL PHARMACEUTICALS, INC; SINGH, RAJINDER; GOFF, DANE; PARTRIDGE, JO) 18 November 2004 (2004-11-18) examples 608,609	1-72

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

☒ Patent family members are listed in annex.

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"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	Date of mailing of the international search report
24 June 2005	01/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Lauro, P

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/009909

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004018463 A	04-03-2004	US 2004127497 A1	01-07-2004
		AU 2003262831 A1	11-03-2004
		CA 2494164 A1	04-03-2004
		EP 1530569 A2	18-05-2005
		WO 2004018463 A2	04-03-2004
WO 03040112 A	15-05-2003	BR 0206266 A	30-12-2003
		CA 2465189 A1	15-05-2003
		CN 1585756 A	23-02-2005
		EP 1451162 A1	01-09-2004
		JP 2005511604 T	28-04-2005
		WO 03040112 A1	15-05-2003
		US 2003165561 A1	04-09-2003
		US 2004236112 A1	25-11-2004
WO 2004099164 A	18-11-2004	US 2004266840 A1	30-12-2004
		WO 2004099164 A1	18-11-2004