

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 February 2009 (12.02.2009)

PCT

(10) International Publication Number
WO 2009/018657 A1

(51) International Patent Classification:

C07D 401/12 (2006.01) C07D 333/28 (2006.01)
A61K 31/13 (2006.01) C07D 401/14 (2006.01)
A61K 31/381 (2006.01) C07D 409/12 (2006.01)
A61K 31/44 (2006.01) C07D 413/12 (2006.01)
A61K 31/4427 (2006.01) C07D 413/14 (2006.01)
A61K 31/7056 (2006.01) C07D 417/12 (2006.01)
A61P 31/14 (2006.01) C07D 417/14 (2006.01)
C07D 231/14 (2006.01) C07D 471/04 (2006.01)
C07D 277/56 (2006.01)

H7S 2G5 (CA). RACOURT, Jean [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). STAMMERS, Timothy, A. [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA).

(21) International Application Number:

PCT/CA2008/001412

(22) International Filing Date: 31 July 2008 (31.07.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/953,701 3 August 2007 (03.08.2007) US

(71) Applicant (for all designated States except US):
BOEHRINGER INGELHEIM INTERNATIONAL
GMBH [DE/DE]; Binger Strasse 173, 55216 Ingelheim
(DE).

(74) Agent: LOOPER, Ywe, J.; c/o Boehringer Ingelheim (Canada) Ltd., 2100 Cunard Street, Laval, Québec H7S 2G5 (CA).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

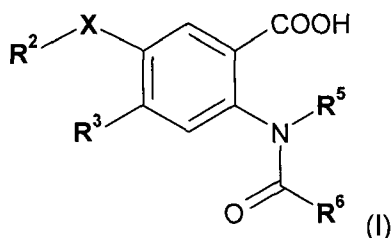
(72) Inventors; and

(75) Inventors/Applicants (for US only): BEAULIEU, Pierre, L. [CA/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). EDWARDS, Paul, J. [GB/CA]; 2100 Cunard Street, Laval, Québec H7S 2G5 (CA). POIRIER, Martin [CA/CA]; 2100 Cunard Street, Laval, Québec

Published:

— with international search report
— with sequence listing part of description published separately in electronic form and available upon request from the International Bureau

(54) Title: VIRAL POLYMERASE INHIBITORS



(57) Abstract: Compounds of formula I: wherein X, R², R³, R⁵ and R⁶ are defined herein, are useful as inhibitors of the hepatitis C virus NS5B polymerase.

WO 2009/018657 A1

VIRAL POLYMERASE INHIBITORS

RELATED APPLICATIONS

This application claims benefit of U.S. Serial No. 60/953701, filed August 3, 2007,
5 which is herein incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to compounds, compositions and methods for the
treatment of hepatitis C virus (HCV) infection. In particular, the present invention
10 provides novel inhibitors of the hepatitis C virus NS5B polymerase, pharmaceutical
compositions containing such compounds and methods for using these compounds
in the treatment of HCV infection.

BACKGROUND OF THE INVENTION

15 It is estimated that at least 130 million persons worldwide are infected with the
hepatitis C virus (HCV). Acute HCV infection progresses to chronic infection in a
high number of cases, and, in some infected individuals, chronic infection leads to
serious liver diseases such as cirrhosis and hepatocellular carcinoma.

20 Currently, standard treatment of chronic hepatitis C infection involves administration
of pegylated interferon-alpha in combination with ribavirin. However, this therapy is
not effective in reducing HCV RNA to undetectable levels in many infected patients
and is associated with often intolerable side effects such as fever and other
influenza-like symptoms, depression, thrombocytopenia and hemolytic anemia.

25 Furthermore, some HCV-infected patients have co-existing conditions which
contraindicate this treatment.

Therefore, a need exists for alternative treatments for hepatitis C viral infection. One
possible strategy to address this need is the development of effective antiviral
30 agents which inactivate viral or host cell factors which are essential for viral
replication.

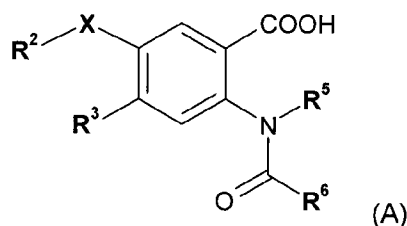
HCV is an enveloped positive strand RNA virus in the genus *Hepacivirus* in the
Flaviviridae family. The single strand HCV RNA genome is approximately 9500
35 nucleotides in length and has a single open reading frame (ORF), flanked by 5' and

3' non-translated regions. The HCV 5' non-translated region is 341 nucleotides in length and functions as an internal ribosome entry site for cap-independent translation initiation. The open reading frame encodes a single large polyprotein of about 3000 amino acids which is cleaved at multiple sites by cellular and viral proteases to produce the mature structural and non-structural (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) proteins. The viral NS2/3 protease cleaves at the NS2-NS3 junction; while the viral NS3 protease mediates the cleavages downstream of NS3, at the NS3-NS4A, NS4A-NS4B, NS4B-NS5A and NS5A-NS5B cleavage sites. The NS3 protein also exhibits nucleoside triphosphatase and RNA helicase activities. The NS4A protein acts as a cofactor for the NS3 protease and may also assist in the membrane localization of NS3 and other viral replicase components. Although NS4B and the NS5A phosphoprotein are also likely components of the replicase, their specific roles are unknown. The NS5B protein is the elongation subunit of the HCV replicase possessing RNA-dependent RNA polymerase (RdRp) activity.

The development of new and specific anti-HCV treatments is a high priority, and virus-specific functions essential for replication are the most attractive targets for drug development. The absence of RNA dependent RNA polymerases in mammals, and the fact that this enzyme appears to be essential to viral replication, would suggest that the NS5B polymerase is an ideal target for anti-HCV therapeutics. It has been recently demonstrated that mutations destroying NS5B activity abolish infectivity of RNA in a chimp model (Kolykhalov, A.A.; Mihalik, K.; Feinstone, S.M.; Rice, C.M.; 2000; *J. Virol.* **74**: 2046-2051).

25

WO 2007/087717 discloses compounds of the general formula (A):



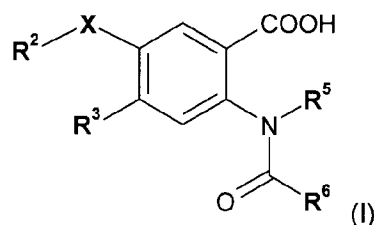
wherein R² is an optionally substituted aryl and R⁶ is an optionally substituted (C₅₋₇)cycloalkyl or aryl which are useful for the treatment of Hepatitis C virus infections.

30

SUMMARY OF THE INVENTION

The present invention provides a novel series of compounds having inhibitory activity against HCV polymerase. In particular compounds according to this invention inhibit RNA synthesis by the RNA dependent RNA polymerase of HCV, especially the enzyme NS5B encoded by HCV. A further advantage of compounds provided by this invention is their low to very low or even non-significant activity against other polymerases. Further objects of this invention arise for the one skilled in the art from the following description and the examples.

One aspect of the invention provides compounds of formula (I):



wherein:

X is selected from O and S;

R² is **Het** or aryl, optionally substituted with 1 to 5 **R²⁰** substituents, wherein **R²⁰** in each case is independently selected from:

a) halo, cyano or nitro;

b) **R⁷**, -C(=O)-**R⁷**, -C(=O)-O-**R⁷**, -O-**R⁷**, -S-**R⁷**, -SO-**R⁷**, -SO₂-**R⁷**, -(C₁₋₆)alkylene-**R⁷**, -(C₁₋₆)alkylene-C(=O)-**R⁷**,

-(C₁₋₆)alkylene-C(=O)-O-**R⁷**, -(C₁₋₆)alkylene-O-**R⁷**, -(C₁₋₆)alkylene-S-**R⁷**, -(C₁₋₆)alkylene-SO-**R⁷** or -(C₁₋₆)alkylene-SO₂-**R⁷**;

wherein **R⁷** is in each instance independently selected from H, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, aryl and **Het**;

wherein the (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₃₋₇)cycloalkyl and (C₁₋₆)alkylene are optionally substituted with 1 or 2 substituents each independently selected from -OH, -(C₁₋₆)alkyl, halo, -(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -O-(C₁₋₆)alkyl, cyano, COOH, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and -N((C₁₋₄)alkyl)₂;

and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3

substituents each independently selected from:

- 5
- i) halo, cyano, oxo, thioxo, imino, -OH, -O-(C₁₋₆)alkyl, -O-(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)haloalkyl, -C(=O)-(C₁₋₆)alkyl, -SO₂(C₁₋₆)alkyl, -C(=O)-NH₂, -C(=O)-NH(C₁₋₄)alkyl, -C(=O)-N((C₁₋₄)alkyl)₂, -C(=O)-NH(C₃₋₇)cycloalkyl, -C(=O)-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl, -N((C₁₋₄)alkyl)₂, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl or -NH-C(=O)(C₁₋₄)alkyl;
- 10
- ii) (C₁₋₆)alkyl optionally substituted with -OH, -O-(C₁₋₆)haloalkyl, or -O-(C₁₋₆)alkyl; and
- iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo or (C₁₋₆)alkyl; and
- 15
- c) -N(R⁸)R⁹, -C(=O)-N(R⁸)R⁹, -O-C(=O)-N(R⁸)R⁹, -SO₂-N(R⁸)R⁹, -(C₁₋₆)alkylene-N(R⁸)R⁹, -(C₁₋₆)alkylene-C(=O)-N(R⁸)R⁹, -(C₁₋₆)alkylene-O-C(=O)-N(R⁸)R⁹, or -(C₁₋₆)alkylene-SO₂-N(R⁸)R⁹; wherein the (C₁₋₆)alkylene is optionally substituted with 1 or 2 substituents each independently selected from -OH, -(C₁₋₆)alkyl, halo, -(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -O-(C₁₋₆)alkyl, cyano, COOH, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and -N((C₁₋₄)alkyl)₂;
- 20
- R⁸ is in each instance independently selected from H, (C₁₋₆)alkyl and (C₃₋₇)cycloalkyl; and
- R⁹ is in each instance independently selected from R⁷, -O-(C₁₋₆)alkyl, -(C₁₋₆)alkylene-R⁷, -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and -C(=O)N(R⁸)R⁷; wherein R⁷ and R⁸ are as defined above;
- 25
- or R⁸ and R⁹, together with the N to which they are attached, are linked to form a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂;
- 30
- wherein the heterocycle is optionally substituted with 1 to 3 substituents each independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, halo, oxo, -OH, SH, -O(C₁₋₆)alkyl, -S(C₁₋₆)alkyl,
- 35

(C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂,
 -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl
 and -NHC(=O)-(C₁₋₆)alkyl;

R³ is selected from H, halo, CN, (C₁₋₄)alkyl, -OH, -O-(C₁₋₄)alkyl, -S-(C₁₋₄)alkyl, -NH₂,
 5 -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and
 -N((C₁₋₄)alkyl)₂;

R⁵ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl- or **Het**; the (C₁₋₆)alkyl
 and **Het** each being optionally substituted with 1 to 4 substituents each
 independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, **Het**,
 10 -OH, -COOH, -C(=O)-(C₁₋₆)alkyl, -C(=O)-O-(C₁₋₆)alkyl, -SO₂(C₁₋₆)alkyl and
 -C(=O)-N(**R⁵¹**)**R⁵²**;

wherein **R⁵¹** is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl; and

R⁵² is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, **Het**, aryl-(C₁₋₃)alkyl- or
Het-(C₁₋₃)alkyl-;

15 wherein each of the (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, **Het**,
 aryl-(C₁₋₃)alkyl- and **Het**-(C₁₋₃)alkyl- are optionally substituted with 1 to
 3 substituents each independently selected from (C₁₋₆)alkyl,
 (C₁₋₆)haloalkyl, halo, oxo, -OH, -O(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₆)alkyl,
 -N((C₁₋₆)alkyl)₂, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl,
 20 -C(=O)(C₁₋₆)alkyl and -NHC(=O)-(C₁₋₆)alkyl;

wherein the (C₁₋₆)alkyl is optionally substituted with OH;
 or **R⁵¹** and **R⁵²**, together with the N to which they are attached, are linked to
 form a 4- to 7-membered heterocycle optionally further containing 1 to 3
 heteroatoms each independently selected from N, O and S, wherein each S
 25 heteroatom may, independently and where possible, exist in an oxidized
 state such that it is further bonded to one or two oxygen atoms to form the
 groups SO or SO₂;

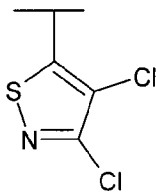
wherein the heterocycle is optionally substituted with 1 to 3
 substituents each independently selected from (C₁₋₆)alkyl,
 30 (C₁₋₆)haloalkyl, halo, oxo, -OH, -O(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₆)alkyl,
 -N((C₁₋₆)alkyl)₂, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl,
 -C(=O)(C₁₋₆)alkyl and -NHC(=O)-(C₁₋₆)alkyl;

wherein the (C₁₋₆)alkyl is optionally substituted with OH;

R⁶ is **Het**; being optionally substituted with 1 to 5 substituents each independently
 35 selected from halo, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -OH, -SH, -O-(C₁₋

₄alkyl, -S-(C₁₋₄)alkyl and -N(R⁸)R⁹; wherein R⁸ and R⁹ are as defined above; and
Het is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1
 to 4 heteroatoms each independently selected from O, N and S, or a 7- to
 14-membered saturated, unsaturated or aromatic heteropolycycle having
 5 wherever possible 1 to 5 heteroatoms, each independently selected from O,
 N and S; wherein each N heteroatom may, independently and where
 possible, exist in an oxidized state such that it is further bonded to an oxygen
 atom to form an N-oxide group and wherein each S heteroatom may,
 10 independently and where possible, exist in an oxidized state such that it is
 further bonded to one or two oxygen atoms to form the groups SO or SO₂;
 or a salt or ester thereof;

with the proviso that when X is O, R² is phenyl, R³ is H and R⁵ is H, then R⁶ is not



Another aspect of this invention provides a compound of formula (I), or a
 15 pharmaceutically acceptable salt or ester thereof, as a medicament.

Still another aspect of this invention provides a pharmaceutical composition
 comprising a therapeutically effective amount of a compound of formula (I) or a
 pharmaceutically acceptable salt or ester thereof; and one or more pharmaceutically
 20 acceptable carriers.

According to an embodiment of this aspect, the pharmaceutical composition
 according to this invention additionally comprises at least one other antiviral agent.

25 The invention also provides the use of a pharmaceutical composition as described
 hereinabove for the treatment of a hepatitis C viral infection in a mammal having or
 at risk of having the infection.

A further aspect of the invention involves a method of treating a hepatitis C viral
 30 infection in a mammal having or at risk of having the infection, the method
 comprising administering to the mammal a therapeutically effective amount of a

compound of formula (I), a pharmaceutically acceptable salt or ester thereof, or a composition thereof as described hereinabove.

Another aspect of the invention involves a method of treating a hepatitis C viral
5 infection in a mammal having or at risk of having the infection, the method
comprising administering to the mammal a therapeutically effective amount of a
combination of a compound of formula (I) or a pharmaceutically acceptable salt or
ester thereof, and at least one other antiviral agent; or a composition thereof.

10 Also within the scope of this invention is the use of a compound of formula (I) as
described herein, or a pharmaceutically acceptable salt or ester thereof, for the
treatment of a hepatitis C viral infection in a mammal having or at risk of having the
infection.

15 Another aspect of this invention provides the use of a compound of formula (I) as
described herein, or a pharmaceutically acceptable salt or ester thereof, for the
manufacture of a medicament for the treatment of a hepatitis C viral infection in a
mammal having or at risk of having the infection.

20 An additional aspect of this invention refers to an article of manufacture comprising a
composition effective to treat a hepatitis C viral infection; and packaging material
comprising a label which indicates that the composition can be used to treat infection
by the hepatitis C virus; wherein the composition comprises a compound of formula
(I) according to this invention or a pharmaceutically acceptable salt or ester thereof.

25

Still another aspect of this invention relates to a method of inhibiting the replication of
hepatitis C virus comprising exposing the virus to an effective amount of the
compound of formula (I), or a salt or ester thereof, under conditions where replication
of hepatitis C virus is inhibited.

30

Further included in the scope of the invention is the use of a compound of formula
(I), or a salt or ester thereof, to inhibit the replication of hepatitis C virus.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used herein, the following definitions apply unless otherwise noted:

- 5 The term “substituent”, as used herein and unless specified otherwise, is intended to mean an atom, radical or group which may be bonded to a carbon atom, a heteroatom or any other atom which may form part of a molecule or fragment thereof, which would otherwise be bonded to at least one hydrogen atom. Substituents contemplated in the context of a specific molecule or fragment thereof
- 10 are those which give rise to chemically stable compounds, such as are recognized by those skilled in the art.

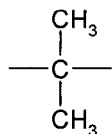
The term “(C_{1-n})alkyl” as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean acyclic, straight or branched

15 chain alkyl radicals containing from 1 to n carbon atoms. “(C₁₋₆)alkyl” includes, but is not limited to, methyl, ethyl, propyl (*n*-propyl), butyl (*n*-butyl), 1-methylethyl (*iso*-propyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), pentyl and hexyl. The abbreviation Me denotes a methyl group; Et denotes an ethyl group, Pr denotes a propyl group, iPr denotes a 1-methylethyl

20 group, Bu denotes a butyl group and tBu denotes a 1,1-dimethylethyl group.

The term “(C_{1-n})alkylene” as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean acyclic, straight or branched chain divalent alkyl radicals containing from 1 to n carbon atoms. “(C₁₋₆)alkylene”

25 includes, but is not limited to, -CH₂-, -CH₂CH₂-, $\begin{array}{c} \text{CH}_3 \\ | \\ \text{---C---} \\ | \\ \text{H} \end{array}$, $\begin{array}{c} \text{CH}_3 \\ | \\ \text{---CH---CH}_2\text{---} \end{array}$ and



The term “(C_{2-n})alkenyl”, as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an unsaturated, acyclic

30 straight or branched chain radical containing two to n carbon atoms, at least two of which are bonded to each other by a double bond. Examples of such radicals

include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl, and 1-butenyl. Unless specified otherwise, the term "(C_{2-n})alkenyl" is understood to encompass individual stereoisomers where possible, including but not limited to (*E*) and (*Z*) isomers, and mixtures thereof. When a (C_{2-n}) alkenyl group is substituted, it is
5 understood to be substituted on any carbon atom thereof which would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

10 The term "(C_{2-n})alkynyl", as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight or branched chain radical containing two to n carbon atoms, at least two of which are bonded to each other by a triple bond. Examples of such radicals include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, and 1-butyne. When a
15 (C_{2-n})alkynyl group is substituted, it is understood to be substituted on any carbon atom thereof which would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

20 The term "(C_{3-m})cycloalkyl" as used herein, wherein m is an integer, either alone or in combination with another radical, is intended to mean a cycloalkyl substituent containing from 3 to m carbon atoms and includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. When a (C_{3-m})cycloalkyl group is substituted, it is understood to be substituted on any carbon atom thereof which
25 would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "(C_{3-m})cycloalkyl-(C_{1-n})alkyl-" as used herein, wherein n and m are both
30 integers, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with a cycloalkyl radical containing from 3 to m carbon atoms as defined above. Examples of (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl- include, but are not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-
35 cyclopropylethyl, 2-cyclopropylethyl, 1-cyclobutylethyl, 2-cyclobutylethyl,

1-cyclopentylethyl, 2-cyclopentylethyl, 1-cyclohexylethyl and 2-cyclohexylethyl. When a (C_{3-m})cycloalkyl-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the cycloalkyl or the alkyl portion thereof or both, unless specified otherwise.

5

The term "aryl" as used herein, either alone or in combination with another radical, is intended to mean a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, 1-naphthyl, 2-naphthyl, tetrahydronaphthyl and dihydronaphthyl. When an aryl group is substituted, it is understood that substituents may be attached to any carbon atom thereof which would otherwise bear a hydrogen atom, unless specified otherwise.

15 The term "aryl-(C_{1-n})alkyl-" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with an aryl radical as defined above. Examples of aryl-(C_{1-n})alkyl- include, but are not limited to, phenylmethyl (benzyl), 1-phenylethyl, 2-phenylethyl and phenylpropyl. When an aryl-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the aryl or the alkyl portion thereof or both, unless specified otherwise.

The term "**Het**" as used herein, either alone or in combination with another radical, is intended to mean a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂, unless specified otherwise. When a **Het** group is substituted, it is understood that substituents may be attached to any carbon atom or heteroatom thereof which would otherwise bear a hydrogen atom, unless

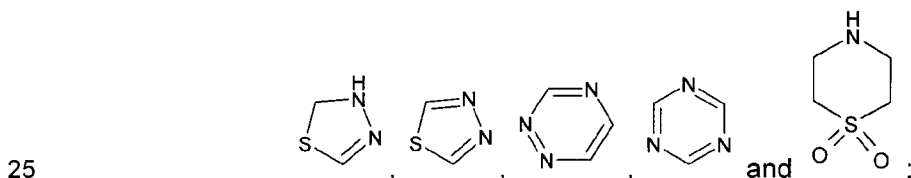
35

specified otherwise.

The term "**Het**-(C_{1-n})alkyl-" as used herein and unless specified otherwise, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with a **Het** substituent as defined above. Examples of **Het**-(C_{1-n})alkyl- include, but are not limited to, thienylmethyl, furylmethyl, piperidylethyl, 2-pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, quinolinylpropyl, and the like. When a **Het**-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the **Het** or the alkyl portion thereof or both, unless specified otherwise.

The term "heteroatom" as used herein is intended to mean O, S or N.

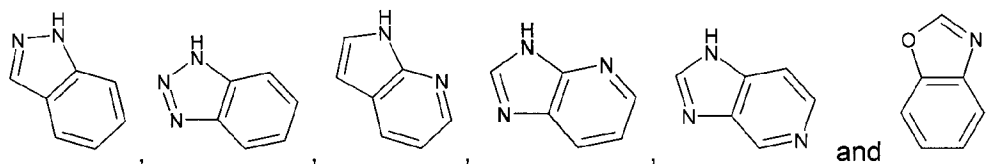
The term "heterocycle" as used herein and unless specified otherwise, either alone or in combination with another radical, is intended to mean a 4- to 7-membered saturated, unsaturated or aromatic heterocycle containing from 1 to 4 heteroatoms each independently selected from O, N and S; or a monovalent radical derived by removal of a hydrogen atom therefrom. Examples of such heterocycles include, but are not limited to, azetidine, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, thiazolidine, oxazolidine, pyrrole, thiophene, furan, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, triazole, tetrazole, piperidine, piperazine, azepine, diazepine, pyran, 1,4-dioxane, 4-morpholine, 4-thiomorpholine, pyridine, pyridine-N-oxide, pyridazine, pyrazine, pyrimidine, and the following heterocycles:



and saturated, unsaturated and aromatic derivatives thereof.

The term "heteropolycycle" as used herein and unless specified otherwise, either alone or in combination with another radical, is intended to mean a heterocycle as defined above fused to one or more other cycle, including a carbocycle, a heterocycle or any other cycle; or a monovalent radical derived by removal of a hydrogen atom therefrom. Examples of such heteropolycycles include, but are not

limited to, indole, isoindole, benzimidazole, benzothiophene, benzofuran, benzodioxole, benzothiazole, quinoline, isoquinoline, naphthyridine, and the following heteropolycycles:



5 and saturated, unsaturated and aromatic derivatives thereof.

The term "halo" as used herein is intended to mean a halogen substituent selected from fluoro, chloro, bromo or iodo.

10 The term "(C_{1-n})haloalkyl" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above wherein one or more hydrogen atoms are each replaced by a halo substituent. Examples of (C_{1-n})haloalkyl include but are not limited to chloromethyl, chloroethyl, dichloroethyl, bromomethyl, bromoethyl, dibromoethyl,
15 fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl and difluoroethyl.

The terms "-O-(C_{1-n})alkyl" or "(C_{1-n})alkoxy" as used herein interchangeably, wherein n is an integer, either alone or in combination with another radical, is intended to mean an oxygen atom further bonded to an alkyl radical having 1 to n carbon atoms as
20 defined above. Examples of -O-(C_{1-n})alkyl include but are not limited to methoxy (CH₃O-), ethoxy (CH₃CH₂O-), propoxy (CH₃CH₂CH₂O-), 1-methylethoxy (*iso*-propoxy; (CH₃)₂CH-O-) and 1,1-dimethylethoxy (*tert*-butoxy; (CH₃)₃C-O-). When an -O-(C_{1-n})alkyl radical is substituted, it is understood to be substituted on the (C_{1-n})alkyl portion thereof.

25

The terms "-S-(C_{1-n})alkyl" or "(C_{1-n})alkylthio" as used herein interchangeably, wherein n is an integer, either alone or in combination with another radical, is intended to mean an sulfur atom further bonded to an alkyl radical having 1 to n carbon atoms as defined above. Examples of -S-(C_{1-n})alkyl include but are not limited to methylthio
30 (CH₃S-), ethylthio (CH₃CH₂S-), propylthio (CH₃CH₂CH₂S-), 1-methylethylthio (*isopropyl*thio; (CH₃)₂CH-S-) and 1,1-dimethylethylthio (*tert*-butylthio; (CH₃)₃C-S-). When -S-(C_{1-n})alkyl radical, or an oxidized derivative thereof, such as an

-SO-(C_{1-n})alkyl radical or an -SO₂-(C_{1-n})alkyl radical, is substituted, each is understood to be substituted on the (C_{1-n})alkyl portion thereof.

The term "oxo" as used herein is intended to mean an oxygen atom attached to a carbon atom as a substituent by a double bond (=O).
5

The term "thioxo" as used herein is intended to mean a sulfur atom attached to a carbon atom as a substituent by a double bond (=S).


10 The term "imino" as used herein is intended to mean a NH group attached to a carbon atom as a substituent by a double bond (=NH).

The term "cyano" or "CN" as used herein is intended to mean a nitrogen atom attached to a carbon atom by a triple bond (C≡N).
15

The term "COOH" as used herein is intended to mean a carboxyl group (-C(=O)-OH). It is well known to one skilled in the art that carboxyl groups may be substituted by functional group equivalents. Examples of such functional group equivalents contemplated in this invention include, but are not limited to, esters, amides, imides,
20 boronic acids, phosphonic acids, phosphoric acids, tetrazoles, triazoles, N-acylsulfamides (RCONHSO₂NR₂), and N-acylsulfonamides (RCONHSO₂R).

The term "functional group equivalent" as used herein is intended to mean an atom or group that may replace another atom or group which has similar electronic,
25 hybridization or bonding properties.

The term "protecting group" as used herein is intended to mean protecting groups that can be used during synthetic transformation, including but not limited to
30 examples which are listed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981), and more recent editions thereof, herein incorporated by reference.

The following designation  is used in sub-formulas to indicate the bond which

is connected to the rest of the molecule as defined.

The term "salt thereof" as used herein is intended to mean any acid and/or base addition salt of a compound according to the invention, including but not limited to a
5 pharmaceutically acceptable salt thereof.

The term "pharmaceutically acceptable salt" as used herein is intended to mean a salt of a compound according to the invention which is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower
10 animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, generally water or oil-soluble or dispersible, and effective for their intended use. The term includes pharmaceutically-acceptable acid addition salts and pharmaceutically-acceptable base addition salts. Lists of suitable salts are found in, for example, S.M. Berge et al., J. Pharm. Sci.,
15 1977, 66, pp. 1-19, herein incorporated by reference.

The term "pharmaceutically-acceptable acid addition salt" as used herein is intended to mean those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with
20 inorganic acids including but not limited to hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, phosphoric acid and the like, and organic acids including but not limited to acetic acid, trifluoroacetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, butyric acid, camphoric acid, camphorsulfonic acid, cinnamic acid, citric acid, digluconic acid, ethanesulfonic acid,
25 glutamic acid, glycolic acid, glycerophosphoric acid, hemisulfic acid, hexanoic acid, formic acid, fumaric acid, 2-hydroxyethanesulfonic acid (isethionic acid), lactic acid, hydroxymaleic acid, malic acid, malonic acid, mandelic acid, mesitylenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid, nicotinic acid,
2-naphthalenesulfonic acid, oxalic acid, pamoic acid, pectinic acid, phenylacetic
30 acid, 3-phenylpropionic acid, pivalic acid, propionic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, sulfanilic acid, tartaric acid, p-toluenesulfonic acid, undecanoic acid and the like.

The term "pharmaceutically-acceptable base addition salt" as used herein is
35 intended to mean those salts which retain the biological effectiveness and properties

of the free acids and which are not biologically or otherwise undesirable, formed with inorganic bases including but not limited to ammonia or the hydroxide, carbonate, or bicarbonate of ammonium or a metal cation such as sodium, potassium, lithium, calcium, magnesium, iron, zinc, copper, manganese, aluminum and the like.

5 Particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically-acceptable organic nontoxic bases include but are not limited to salts of primary, secondary, and tertiary amines, quaternary amine compounds, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins, such as

10 methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-

15 ethylpiperidine, tetramethylammonium compounds, tetraethylammonium compounds, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, dibenzylamine, N,N-dibenzylphenethylamine, 1-ephedrine, N,N'-dibenzylethylenediamine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine,

20 trimethylamine, dicyclohexylamine, choline, and caffeine.

The term "ester thereof" as used herein is intended to mean any ester of a compound according to the invention in which any of the -COOH substituents of the molecule is replaced by a -COOR substituent, in which the **R** moiety of the ester is

25 any carbon-containing group which forms a stable ester moiety, including but not limited to alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, each of which being optionally further substituted. The term "ester thereof" includes but is not limited to pharmaceutically acceptable esters thereof.

30 The term "pharmaceutically acceptable ester" as used herein is intended to mean esters of the compound according to the invention in which any of the COOH substituents of the molecule are replaced by a -COOR substituent, in which the **R** moiety of the ester is selected from alkyl (including, but not limited to, methyl, ethyl, propyl, 1-methylethyl, 1,1-dimethylethyl, butyl); alkoxyalkyl (including, but not limited

35 to methoxymethyl); acyloxyalkyl (including, but not limited to acetoxymethyl); arylalkyl

(including, but not limited to, benzyl); aryloxyalkyl (including, but not limited to, phenoxyethyl); and aryl (including, but not limited to phenyl) optionally substituted with halogen, (C₁₋₄)alkyl or (C₁₋₄)alkoxy. Other suitable esters can be found in Design of Prodrugs, Bundgaard, H. Ed. Elsevier (1985), herein incorporated by reference.

5 Such pharmaceutically acceptable esters are usually hydrolyzed *in vivo* when injected into a mammal and transformed into the acid form of the compound according to the invention. With regard to the esters described above, unless otherwise specified, any alkyl moiety present preferably contains 1 to 16 carbon atoms, more preferably 1 to 6 carbon atoms. Any aryl moiety present in such esters

10 preferably comprises a phenyl group. In particular the esters may be a (C₁₋₁₆)alkyl ester, an unsubstituted benzyl ester or a benzyl ester substituted with at least one halogen, (C₁₋₆)alkyl, (C₁₋₆)alkoxy, nitro or trifluoromethyl.

The term "mammal" as used herein is intended to encompass humans, as well as

15 non-human mammals which are susceptible to infection by hepatitis C virus. Non-human mammals include but are not limited to domestic animals, such as cows, pigs, horses, dogs, cats, rabbits, rats and mice, and non-domestic animals.

The term "treatment" as used herein is intended to mean the administration of a

20 compound or composition according to the present invention to alleviate or eliminate symptoms of the hepatitis C disease and/or to reduce viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but before the appearance of symptoms of the disease, and/or prior to the

25 detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectable levels in the blood.

The term "antiviral agent" as used herein is intended to mean an agent that is effective to inhibit the formation and/or replication of a virus in a mammal, including

30 but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a mammal.

The term "therapeutically effective amount" means an amount of a compound according to the invention, which when administered to a patient in need thereof, is

35 sufficient to effect treatment for disease-states, conditions, or disorders for which the

compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue system, or patient that is sought by a researcher or clinician. The amount of a compound according to the invention which constitutes a therapeutically effective amount will vary depending on such factors as the

5 compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of the treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex and diet

10 of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

Preferred embodiments

15 In the following preferred embodiments, groups and substituents of the compounds according to this invention are described in detail.

X:

X-A: In one embodiment, **X** is O.

20 **X-B:** In another embodiment, **X** is S.

Any and each individual definition of **X** as set out herein may be combined with any and each individual definition of **R²**, **R²⁰**, **R³**, **R⁵** and **R⁶** as set out herein.

25 R²:

R²-A: In one embodiment, **R²** is **Het** or aryl, optionally substituted with 1 to 5 **R²⁰** substituents, wherein **R²⁰** is as defined herein.

R²-B: In another embodiment, **R²** is **Het** wherein **Het** is a 5- or 6-membered heterocycle containing 1 to 3 heteroatoms each independently selected from

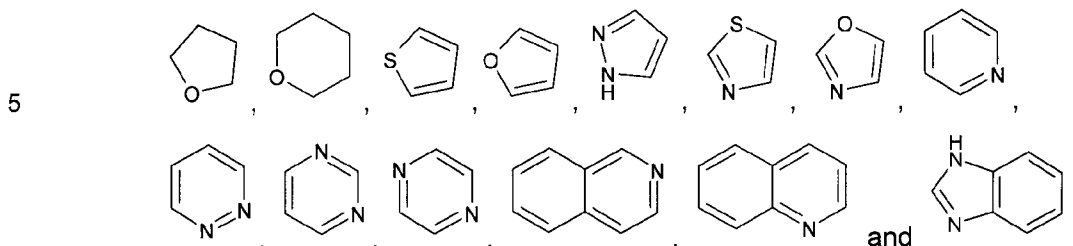
30 O, N and S, or a 9- or 10-membered bicyclic heteropolycycle containing 1 to 3 heteroatoms each independently selected from O, N and S; wherein **Het** is optionally substituted with 1 to 5 **R²⁰** substituents, wherein **R²⁰** is as defined herein.

R²-C: In another embodiment, **R²** is **Het** wherein **Het** is a 5- or 6-membered aromatic heterocycle containing 1 or 2 N heteroatoms, or a 9- or 10-

35

membered bicyclic heteropolycycle containing 1 or 2 N heteroatoms; wherein **Het** is optionally substituted with 1 to 3 R^{20} substituents, wherein R^{20} is as defined herein.

R²-D: In another embodiment, R^2 is **Het** selected from the following formulas:

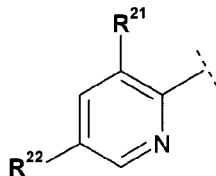


R²-E: In another embodiment, R^2 is **Het** of the formula:



wherein **Het** is optionally substituted with 1 to 3 R^{20} substituents, wherein R^{20} is as defined herein.

R²-F: In another embodiment, R^2 is of the formula:



15 wherein R^{21} is as defined:

R²¹-A: In this embodiment, R^{21} is selected from H, halo, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl and -O-(C₁₋₆)haloalkyl.

R²¹-B: In this embodiment, R^{21} is selected from H, Cl, Br, CH₃, CHF₂, CF₃, cyclopropyl, cyclobutyl and -OCF₃.

20 **R²¹-C:** In this embodiment, R^{21} is H, CHF₂ or CF₃.

R²¹-D: In this embodiment, R^{21} is H or CF₃.

R²¹-E: In this embodiment, R^{21} is CHF₂ or CF₃.

R²¹-F: In this embodiment, R^{21} is CF₃;

and R^{22} is R^{20} wherein R^{20} is as defined herein.

25

Any and each individual definition of R^{21} as set out herein may be combined

with any and each individual definition of X, R²⁰, R³, R⁵ and R⁶ as set out herein.

R^{2-G}: In another embodiment, R² is a group of the formula:

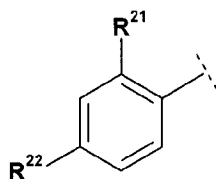


wherein R²² is R²⁰ wherein R²⁰ is as defined herein.

R^{2-H}: In another embodiment, R² is naphthyl or phenyl, the phenyl being optionally substituted with 1 to 5 R²⁰ wherein R²⁰ is as defined herein.

10 R^{2-I}: In yet another embodiment, R² is phenyl optionally substituted with 1 to 3 R²⁰ wherein R²⁰ is as defined herein.

R^{2-J}: In an alternative embodiment, R² is a group of formula:



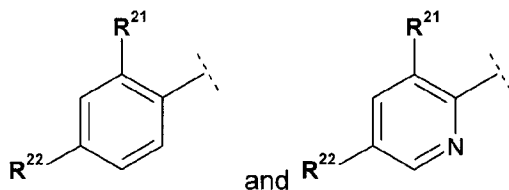
wherein R²¹ and R²² are as defined herein.

R^{2-K}: In another embodiment, R² is a group of the formula:



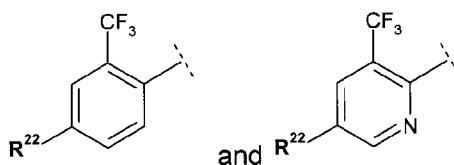
wherein R²² is R²⁰ wherein R²⁰ is as defined herein.

R^{2-L}: In yet another alternative embodiment, R² is selected from the group:



wherein R²¹ and R²² are as defined herein.

20 R^{2-M}: In yet another alternative embodiment, R² is selected from the group:



wherein R^{22} is as defined herein.

Any and each individual definition of R^2 as set out herein may be combined with any
 5 and each individual definition of X , R^{20} , R^3 , R^5 and R^6 as set out herein.

R^{20} -A:

R^{20} -A: In one embodiment, R^{20} is selected from:

- a) halo, cyano or nitro;
- 10 b) R^7 , $-C(=O)-R^7$, $-C(=O)-O-R^7$, $-O-R^7$, $-S-R^7$, $-SO-R^7$, $-SO_2-R^7$,
 $-(C_{1-6})$ alkylene- R^7 , $-(C_{1-6})$ alkylene- $C(=O)-R^7$,
 $-(C_{1-6})$ alkylene- $C(=O)-O-R^7$, $-(C_{1-6})$ alkylene- $O-R^7$, $-(C_{1-6})$ alkylene- $S-R^7$,
 $-(C_{1-6})$ alkylene- $SO-R^7$ or $-(C_{1-6})$ alkylene- SO_2-R^7 ;

wherein R^7 is in each instance independently selected from H,
 15 (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{2-6}) alkynyl, (C_{1-6}) haloalkyl, (C_{3-7}) cycloalkyl,
 aryl and **Het**;

wherein the (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{2-6}) alkynyl, (C_{3-7}) cycloalkyl and
 (C_{1-6}) alkylene are optionally substituted with 1 or 2 substituents each
 independently selected from $-OH$, $-(C_{1-6})$ alkyl, halo, $-(C_{1-6})$ haloalkyl,
 20 (C_{3-7}) cycloalkyl, $-O-(C_{1-6})$ alkyl, cyano, $COOH$, $-NH_2$, $-NH(C_{1-4})$ alkyl,
 $-NH(C_{3-7})$ cycloalkyl, $-N((C_{1-4})$ alkyl) (C_{3-7}) cycloalkyl and $-N((C_{1-4})$ alkyl) $_2$;
 and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3
 substituents each independently selected from:

- 25 i) halo, cyano, oxo, thioxo, imino, $-OH$, $-O-(C_{1-6})$ alkyl,
 $-O-(C_{1-6})$ haloalkyl, (C_{3-7}) cycloalkyl, (C_{1-6}) haloalkyl,
 $-C(=O)-(C_{1-6})$ alkyl, $-SO_2(C_{1-6})$ alkyl, $-C(=O)-NH_2$,
 $-C(=O)-NH(C_{1-4})$ alkyl, $-C(=O)-N((C_{1-4})$ alkyl) $_2$,
 $-C(=O)-NH(C_{3-7})$ cycloalkyl,
 30 $-C(=O)-N((C_{1-4})$ alkyl) (C_{3-7}) cycloalkyl, $-NH_2$, $-NH(C_{1-4})$ alkyl,
 $-N((C_{1-4})$ alkyl) $_2$, $-NH(C_{3-7})$ cycloalkyl,
 $-N((C_{1-4})$ alkyl) (C_{3-7}) cycloalkyl or $-NH-C(=O)(C_{1-4})$ alkyl;

- ii) (C₁₋₆)alkyl optionally substituted with -OH, -O-(C₁₋₆)haloalkyl, or -O-(C₁₋₆)alkyl; and
- iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally substituted with halo or (C₁₋₆)alkyl; and
- 5 c) -N(R⁸)R⁹, -C(=O)-N(R⁸)R⁹, -O-C(=O)-N(R⁸)R⁹, -SO₂-N(R⁸)R⁹, -(C₁₋₆)alkylene-N(R⁸)R⁹, -(C₁₋₆)alkylene-C(=O)-N(R⁸)R⁹, -(C₁₋₆)alkylene-O-C(=O)-N(R⁸)R⁹, or -(C₁₋₆)alkylene-SO₂-N(R⁸)R⁹; wherein the (C₁₋₆)alkylene is optionally substituted with 1 or 2 substituents each independently selected from -OH, -(C₁₋₆)alkyl, halo, -(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -O-(C₁₋₆)alkyl, cyano, COOH, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and -N((C₁₋₄)alkyl)₂;
- 10 R⁸ is in each instance independently selected from H, (C₁₋₆)alkyl and (C₃₋₇)cycloalkyl; and
- 15 R⁹ is in each instance independently selected from R⁷, -O-(C₁₋₆)alkyl, -(C₁₋₆)alkylene-R⁷, -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and -C(=O)N(R⁸)R⁷; wherein R⁷ and R⁸ are as defined above;
- or R⁸ and R⁹, together with the N to which they are attached, are linked to form a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂;
- 20 wherein the heterocycle is optionally substituted with 1 to 3 substituents each independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, halo, oxo, -OH, SH, -O(C₁₋₆)alkyl, -S(C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl and -NHC(=O)-(C₁₋₆)alkyl.
- 25
- 30 **R²⁰-B:** In another embodiment, R²⁰ is selected from:
- a) halo, cyano or nitro;
- b) R⁷, -(C₁₋₆)alkylene-R⁷, -C(=O)-R⁷, -O-R⁷, -C(=O)-O-R⁷, -(C₁₋₆)alkylene-O-R⁷, -S-R⁷, -SO₂-R⁷, -(C₁₋₆)alkylene-S-R⁷ or -(C₁₋₆)alkylene-SO₂-R⁷;
- 35 wherein R⁷ is in each instance independently selected from H,

(C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, aryl and **Het**; wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S, or **Het** is a 9- or 10-membered heteropolycycle containing 1 to 4 heteroatoms, each independently selected from N, O and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂; and wherein the (C₁₋₆)alkyl is optionally substituted with 1 or 2 substituents each independently selected from -OH, -O-(C₁₋₆)alkyl and COOH; and wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, cyano, oxo, imino, -OH, -O-(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -N((C₁₋₄)alkyl)₂, -NH-C(=O)(C₁₋₄)alkyl, (C₁₋₆)alkyl and **Het**, wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S; and

c) -N(R⁸)R⁹, -(C₁₋₆)alkylene-N(R⁸)R⁹ or -(C₁₋₆)alkylene-C(=O)-N(R⁸)R⁹ wherein R⁸ is in each instance independently selected from H and (C₁₋₆)alkyl; and R⁹ is in each instance independently selected from R⁷, -O-(C₁₋₆)alkyl, -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and -C(=O)N(R⁸)R⁷; wherein R⁷ and R⁸ are as defined above.

R²⁰-C: In another embodiment, R²⁰ is selected from:

b) R⁷, -(C₁₋₆)alkylene-R⁷, -C(=O)-R⁷, -(C₁₋₆)alkylene-O-R⁷, -SO₂-R⁷, -(C₁₋₆)alkylene-S-R⁷ or -(C₁₋₆)alkylene-SO₂-R⁷; wherein R⁷ is in each instance independently selected from H, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, aryl and **Het**; wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S, or **Het** is

a 9- or 10-membered heteropolycycle containing 1 to 4 heteroatoms, each independently selected from N, O and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂; and

wherein the (C₁₋₆)alkyl is optionally substituted with 1 or 2 substituents each independently selected from -OH, -O-(C₁₋₆)alkyl and COOH; and

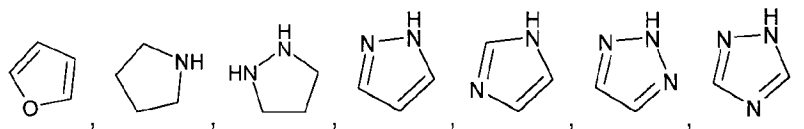
wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, cyano, oxo, imino, -OH, -O-(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -N((C₁₋₄)alkyl)₂, -NH-C(=O)(C₁₋₄)alkyl, (C₁₋₆)alkyl and **Het**, wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S; and

c) -(C₁₋₆)alkylene-N(R⁸)R⁹ or -(C₁₋₆)alkylene-C(=O)-N(R⁸)R⁹ wherein R⁸ is in each instance independently selected from H and (C₁₋₆)alkyl; and R⁹ is in each instance independently selected from R⁷, -O-(C₁₋₆)alkyl, -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and -C(=O)N(R⁸)R⁷; wherein R⁷ and R⁸ are as defined above.

R²⁰-D: In another embodiment, R²⁰ is selected from:

- a) halo or cyano;
 b) R⁷, -CH₂-R⁷, -C(=O)-R⁷, -CH₂-O-R⁷, -SO₂-R⁷, -CH₂-S-R⁷ or -CH₂-SO₂-R⁷;

wherein R⁷ is in each instance independently selected from H, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, phenyl and **Het**; wherein the **Het** is selected from:



- b) $-(C_{1-3})\text{alkylene-R}^7$, $-(C_{1-3})\text{alkylene-O-R}^7$, $-(C_{1-3})\text{alkylene-S-R}^7$ or $-(C_{1-3})\text{alkylene-SO}_2\text{-R}^7$;

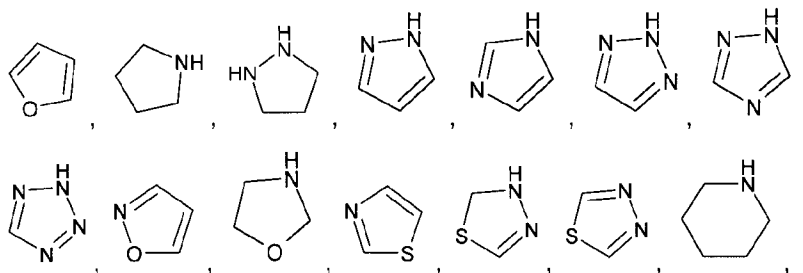
wherein R^7 is **Het**; wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S, or **Het** is a 9- or 10-membered heteropolycycle containing 1 to 4 heteroatoms, each independently selected from N, O and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂;

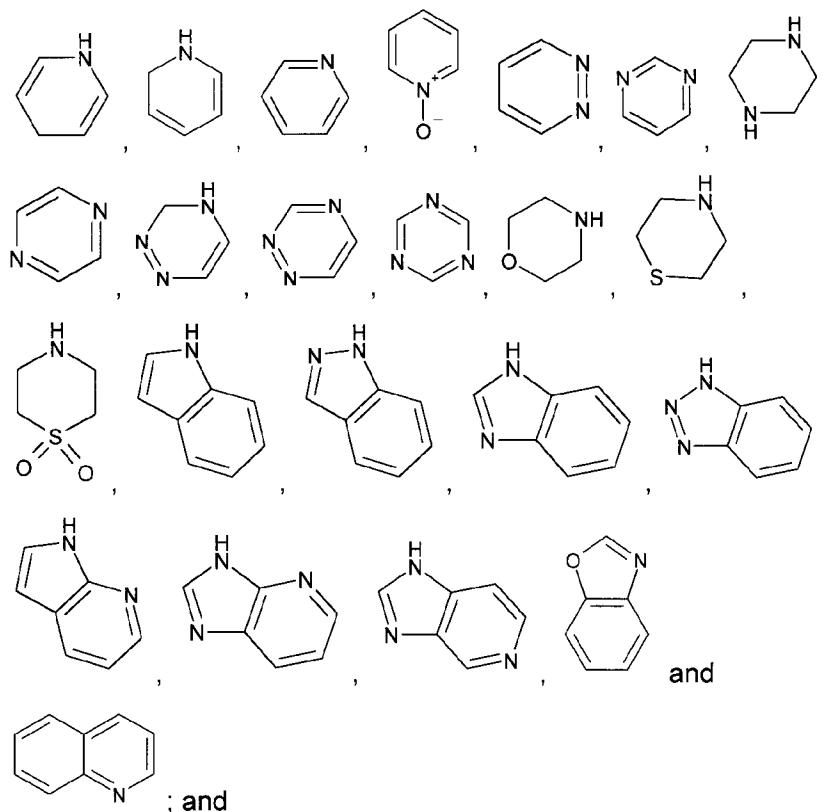
wherein the **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, cyano, oxo, imino, -OH, -O-(C₁₋₆)alkyl, -O-(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)₂, -NH-C(=O)(C₁₋₄)alkyl, (C₁₋₆)alkyl and **Het**, wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S; and

- c) $-(C_{1-3})\text{alkylene-N(R}^8)\text{R}^9$ wherein R^8 is in each instance independently selected from H, (C₁₋₆)alkyl and (C₃₋₇)cycloalkyl; and R^9 is R^7 wherein R^7 is as defined above.

R²⁰-F: In another embodiment, R^{20} is selected from:

- b) $-\text{CH}_2\text{-R}^7$, $-\text{CH}_2\text{CH}_2\text{-R}^7$, $-\text{CH}_2\text{-O-R}^7$, $-\text{CH}_2\text{-S-R}^7$ or $-\text{CH}_2\text{-SO}_2\text{-R}^7$; wherein R^7 is **Het**; wherein the **Het** is selected from:





5

wherein the **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, cyano, oxo, imino, -OH, -O-(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -N((C₁₋₄)alkyl)₂, -NH-C(=O)(C₁₋₄)alkyl and (C₁₋₆)alkyl; and

10 c) -CH₂-N(R⁸)R⁹ wherein R⁸ is in each instance independently selected from H and (C₁₋₆)alkyl; and R⁹ is R⁷ wherein R⁷ is as defined above.

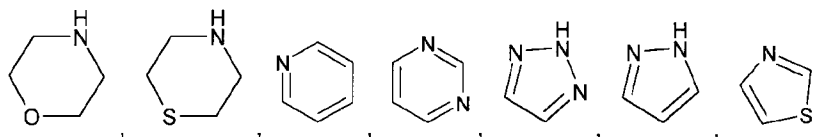
R²⁰-G: In another embodiment, R²⁰ is selected from:

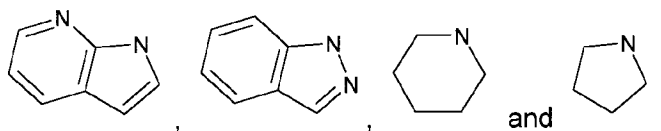
15

b) R⁷, -(C₁₋₆)alkylene-R⁷, -C(=O)-R⁷, -(C₁₋₆)alkylene-O-R⁷, -SO₂-R⁷, -(C₁₋₆)alkylene-S-R⁷ or -(C₁₋₆)alkylene-SO₂-R⁷;

wherein R⁷ is in each instance independently selected from H, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, aryl and **Het**; wherein the **Het** is selected from the group:

20





wherein the (C₁₋₆)alkyl is optionally substituted with 1 or 2 substituents each independently selected from -OH, -O-(C₁₋₆)alkyl and COOH; and

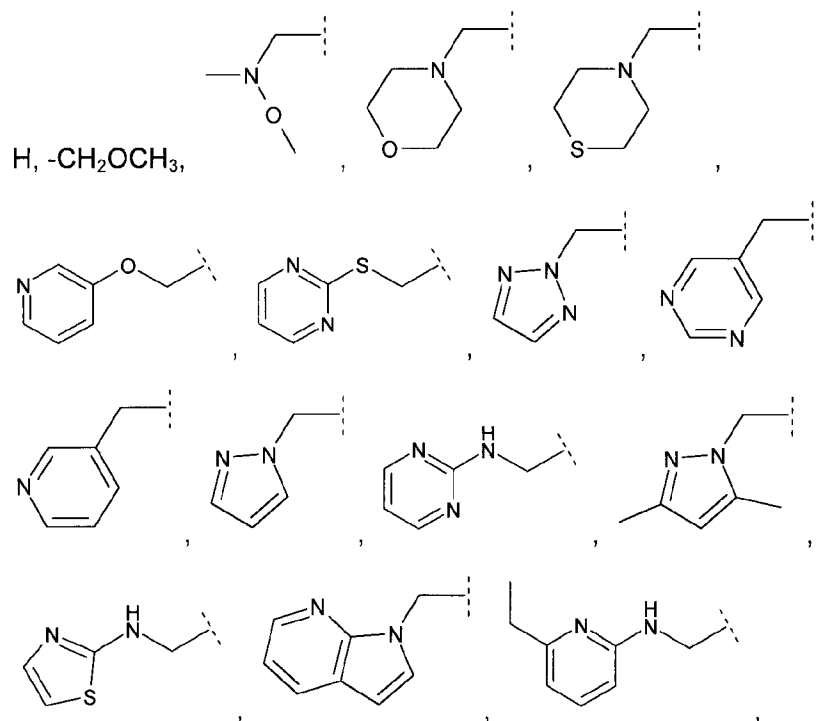
5 wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, cyano, oxo, imino, -OH, -O-(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -N((C₁₋₄)alkyl)₂, -NH-C(=O)(C₁₋₄)alkyl, (C₁₋₆)alkyl and **Het**, wherein the **Het** is a 5- or 6-

10 membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S; and

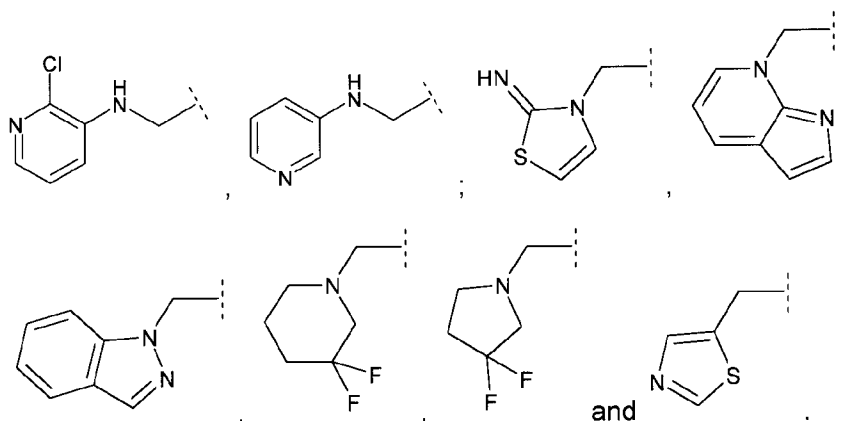
c) -(C₁₋₆)alkylene-N(R⁸)R⁹ or -(C₁₋₆)alkylene-C(=O)-N(R⁸)R⁹ wherein R⁸ is in each instance independently selected from H and (C₁₋₆)alkyl; and

15 R⁹ is in each instance independently selected from R⁷, -O-(C₁₋₆)alkyl, -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and -C(=O)N(R⁸)R⁷; wherein R⁷ and R⁸ are as defined above.

R²⁰-H: In another embodiment, R²⁰ is selected from:



20



R²⁰-I: In another embodiment, **R²⁰** is selected from:

- b) $-(C_{1-3})\text{alkylene-R}^7$, $-(C_{1-3})\text{alkylene-O-R}^7$, or $-(C_{1-3})\text{alkylene-S-R}^7$;
 5 wherein **R⁷** is **Het**; wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 3 nitrogen heteroatoms, or **Het** is a 9- or 10-membered heteropolycycle containing 1 to 4 nitrogen heteroatoms, wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group;
 10 wherein the **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, imino, -OH, -O-(C₁₋₆)alkyl, -O-(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)₂,
 15 -NH-C(=O)(C₁₋₄)alkyl, (C₁₋₆)alkyl and
- c) $-(C_{1-3})\text{alkylene-N(R}^8)\text{R}^9$ wherein
 20 **R⁸** is in each instance independently selected from H, (C₁₋₆)alkyl and (C₃₋₇)cycloalkyl; and
 R⁹ is **R⁷** wherein **R⁷** is as defined above.

20

Any and each individual definition of **R²⁰** as set out herein may be combined with any and each individual definition of **X**, **R²**, **R³**, **R⁵** and **R⁶** as set out herein.

R³:

- 25 **R³-A:** In one embodiment, **R³** is selected from H, halo, CN, (C₁₋₄)alkyl, -OH, -O-(C₁₋₄)alkyl, -S-(C₁₋₄)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and -N((C₁₋₄)alkyl)₂.

- R³-B:** In another embodiment, **R³** is selected from H, halo, CN, (C₁₋₄)alkyl, -O-(C₁₋₄)alkyl and -N((C₁₋₄)alkyl)₂.
- R³-C:** In another embodiment, **R³** is selected from H, halo and CN.
- R³-D:** In another embodiment, **R³** is selected from H, F, Cl and CN.
- 5 **R³-E:** In another embodiment, **R³** is selected from H and halo.
- R³-F:** In another embodiment, **R³** is selected from H, F and Cl.
- R³-G:** In another embodiment, **R³** is H or F.
- R³-H:** In another embodiment, **R³** is H.
- 10 Any and each individual definition of **R³** as set out herein may be combined with any and each individual definition of **X**, **R²⁰**, **R²**, **R⁵** and **R⁶** as set out herein.

R⁵:

- R⁵-A:** In one embodiment, **R⁵** is selected from H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl- or **Het**; the (C₁₋₆)alkyl and **Het** each being optionally substituted with 1 to 4 substituents each independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, **Het**, -OH, -COOH, -C(=O)-(C₁₋₆)alkyl, -C(=O)-O-(C₁₋₆)alkyl, -SO₂(C₁₋₆)alkyl and -C(=O)-N(**R⁵¹**)**R⁵²**;
- 15 wherein **R⁵¹** is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl; and
- 20 **R⁵²** is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, **Het**, aryl-(C₁₋₃)alkyl- or **Het**-(C₁₋₃)alkyl-;
- wherein each of the (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, **Het**, aryl-(C₁₋₃)alkyl- and **Het**-(C₁₋₃)alkyl- are optionally substituted with 1 to 3 substituents each independently selected from (C₁₋₆)alkyl,
- 25 (C₁₋₆)haloalkyl, halo, oxo, -OH, -O(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl and -NHC(=O)-(C₁₋₆)alkyl;
- wherein the (C₁₋₆)alkyl is optionally substituted with OH;
- or **R⁵¹** and **R⁵²**, together with the N to which they are attached, are linked to form a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂;
- 30

wherein the heterocycle is optionally substituted with 1 to 3 substituents each independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, halo, oxo, -OH, -O(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl and -NHC(=O)-(C₁₋₆)alkyl;

5

wherein the (C₁₋₆)alkyl is optionally substituted with OH.

R⁵-B: In one embodiment, **R⁵** is (C₁₋₆)alkyl.

R⁵-C: In another embodiment, **R⁵** is methyl or 1-methylethyl.

R⁵-D: In another embodiment, **R⁵** is 1-methylethyl.

10 **R⁵-E:** In another embodiment, **R⁵** is (C₁₋₄)alkyl substituted with (C₁₋₆)haloalkyl, **Het**, -COOH or -C(=O)-N(**R⁵¹**)**R⁵²**, wherein the **Het** is a 5- or 6-membered heterocycle containing from 1 to 4 N heteroatoms or **Het** is a 9- or 10-membered bicyclic heteropolycycle containing from 1 to 4 N heteroatoms; and wherein **R⁵¹** is H or (C₁₋₆)alkyl and **R⁵²** is selected from H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, **Het** and **Het**-(C₁₋₃)alkyl-;

15

wherein the (C₁₋₆)alkyl is optionally substituted with 1 or 2 substituents each independently selected from -O(C₁₋₆)alkyl and -N((C₁₋₆)alkyl)₂; and wherein the **Het** and the **Het** portion of **Het**-(C₁₋₃)alkyl- are each independently a 5- or 6-membered heterocycle containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein the **Het** and the **Het**-(C₁₋₃)alkyl- are each optionally substituted with 1 to 3 substituents each independently selected from halo, oxo, -OH, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, -(C=O)(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂ and -NH(C=O)(C₁₋₆)alkyl,

20

25

wherein the (C₁₋₆)alkyl is optionally substituted with OH; or **R⁵¹** and **R⁵²**, together with the N to which they are attached, are linked to form a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂;

30

wherein the heterocycle is optionally substituted with 1 to 3 substituents each independently selected from halo, oxo, -OH, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, -(C=O)(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂ and -NH(C=O)(C₁₋₆)alkyl,

35

wherein the (C₁₋₆)alkyl is optionally substituted with OH.

R⁵-F: In another embodiment, **R⁵** is (C₁₋₂)alkyl substituted with (C₁₋₆)haloalkyl or

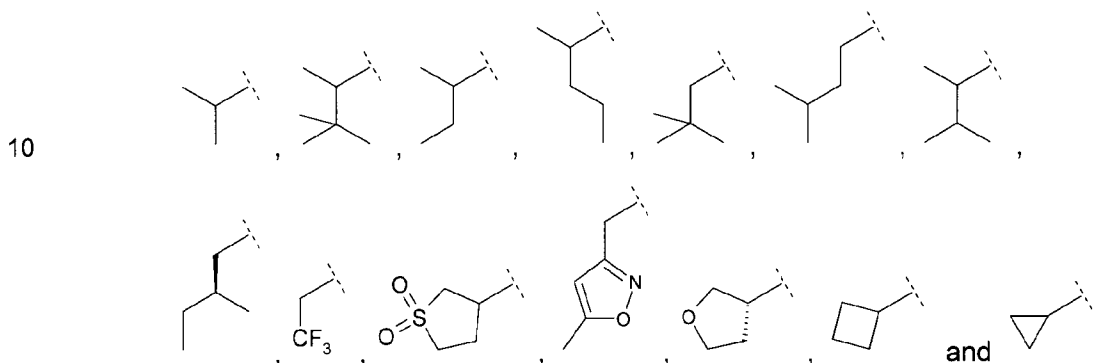
Het, wherein the **Het** is selected from ;

5 wherein the **Het** is optionally substituted with 1 or 2 substituents selected from (C₁₋₄)alkyl and -N((C₁₋₄)alkyl)₂.

R⁵-G: In another embodiment, **R⁵** is **Het**, (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl, optionally substituted with (C₁₋₆)haloalkyl.

R⁵-H: In another embodiment, **R⁵** is cyclopropyl or cyclobutyl.

R⁵-I: In another embodiment, **R⁵** is selected from:



R⁵-J: In another embodiment, **R⁵** is **Het** optionally substituted with 1 to 2 substituents each independently selected from (C₁₋₆)alkyl and (C₁₋₆)haloalkyl.

15 **R⁵-K:** In another embodiment, **R⁵** is (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl- or **Het**; the (C₁₋₆)alkyl and **Het** each being optionally substituted with 1 to 4 substituents each independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, **Het**, -OH, -COOH, -C(=O)-(C₁₋₆)alkyl, -C(=O)-O-(C₁₋₆)alkyl, -SO₂(C₁₋₆)alkyl and -C(=O)-N(**R⁵¹**)**R⁵²**;

20 wherein **R⁵¹** is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl; and

R⁵² is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, **Het**, aryl-(C₁₋₃)alkyl- or **Het**-(C₁₋₃)alkyl-;

25 wherein each of the (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, **Het**, aryl-(C₁₋₃)alkyl- and **Het**-(C₁₋₃)alkyl- are optionally substituted with 1 to 3 substituents each independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, halo, oxo, -OH, -O(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl and -NHC(=O)-(C₁₋₆)alkyl;

wherein the (C₁₋₆)alkyl is optionally substituted with OH;

or R^{51} and R^{52} , together with the N to which they are attached, are linked to form a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO_2 ;

5

wherein the heterocycle is optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, halo, oxo, $-OH$, $-O(C_{1-6})$ alkyl, $-NH_2$, $-NH(C_{1-6})$ alkyl, $-N((C_{1-6})alkyl)_2$, $-NH(C_{3-7})$ cycloalkyl, $-N((C_{1-4})alkyl)(C_{3-7})$ cycloalkyl, $-C(=O)(C_{1-6})$ alkyl and $-NHC(=O)-(C_{1-6})$ alkyl;

10

wherein the (C_{1-6}) alkyl is optionally substituted with OH.

Any and each individual definition of R^5 as set out herein may be combined with any and each individual definition of X, R^{20} , R^2 , R^3 and R^6 as set out herein.

15

R^6 :

R^6 -A: In an alternative embodiment, R^6 is **Het** optionally substituted with 1 to 5 substituents each independently selected from halo, (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7}) cycloalkyl, $-OH$, $-SH$, $-O-(C_{1-4})$ alkyl and $-S-(C_{1-4})$ alkyl.

20

R^6 -B: In another alternative embodiment, R^6 is **Het** optionally substituted with 1 to 3 substituents each independently selected from halo, $-OH$, (C_{1-4}) alkyl and (C_{1-4}) haloalkyl.

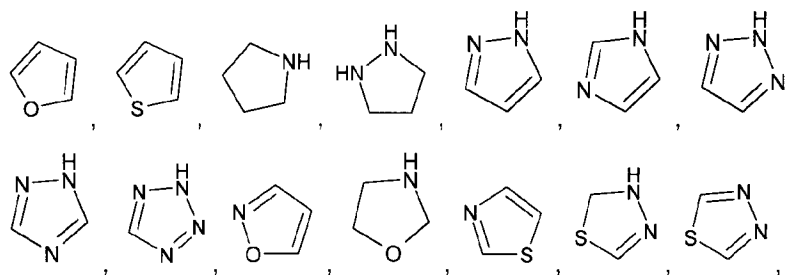
R^6 -C: In yet another alternative embodiment, R^6 is **Het** optionally substituted with 1 to 3 substituents each independently selected from F, Cl, Br, OH and methyl.

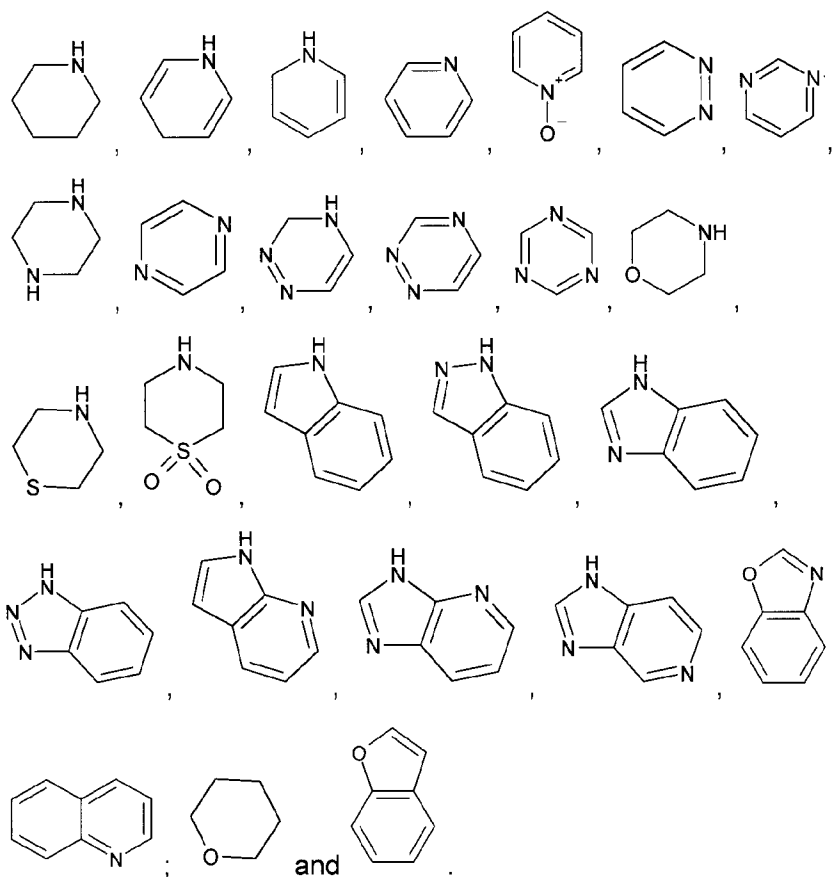
25

R^6 -D: In still another embodiment, R^6 is **Het** optionally substituted with 1 to 5 substituents each independently selected from halo, (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7}) cycloalkyl, $-OH$, $-SH$, $-O-(C_{1-4})$ alkyl and $-S-(C_{1-4})$ alkyl.

wherein the **Het** is selected from:

30

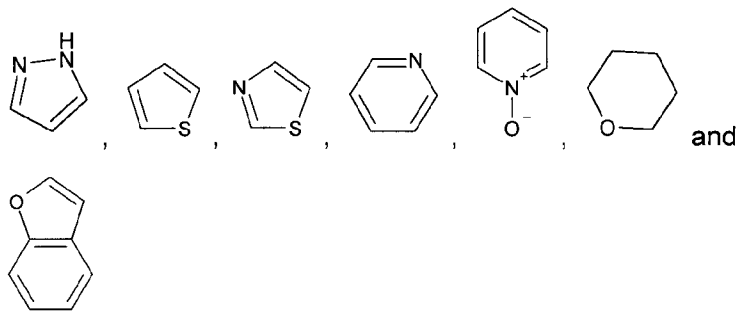




5

R⁶-E: In still another embodiment, **R⁶** is **Het** optionally substituted with 1 to 3 substituents each independently selected from halo, OH, (C₁₋₆)alkyl and (C₁₋₆)haloalkyl

wherein the **Het** is selected from:

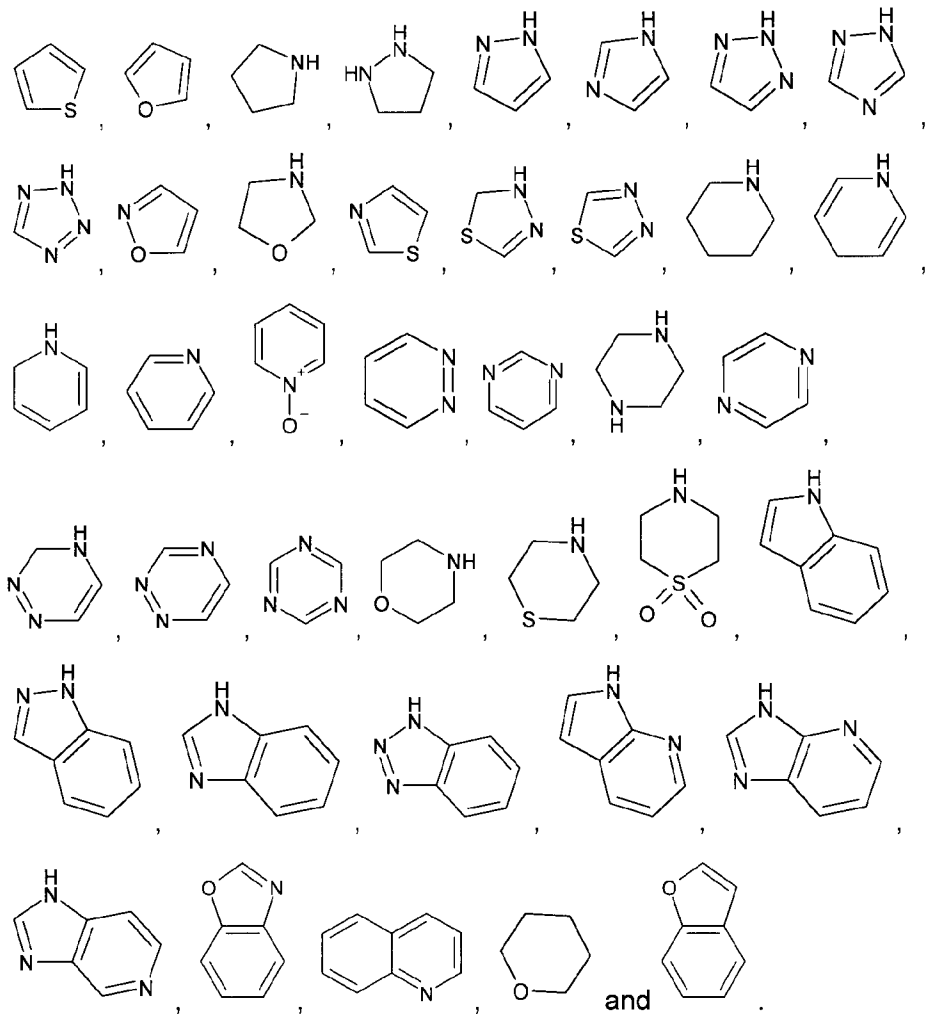


10

R⁶-F: In still another embodiment, **R⁶** is **Het** optionally substituted with 1 to 3 substituents each independently selected from halo, OH, (C₁₋₄)alkyl and (C₁₋₄)haloalkyl

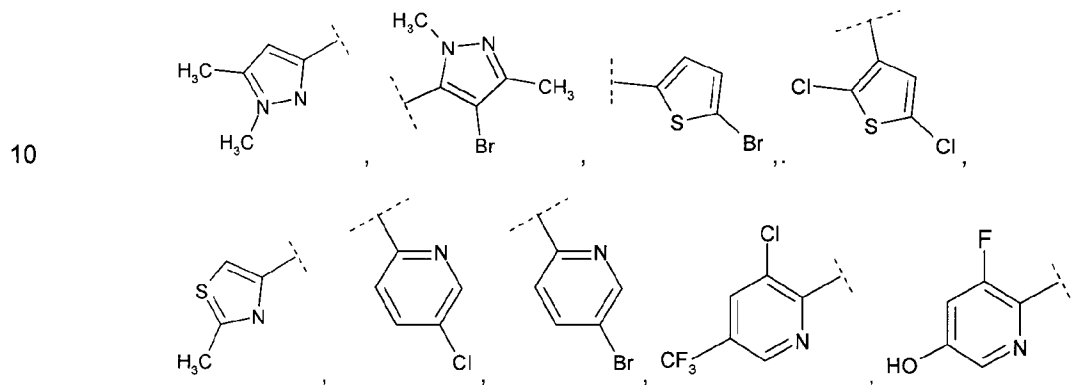
15

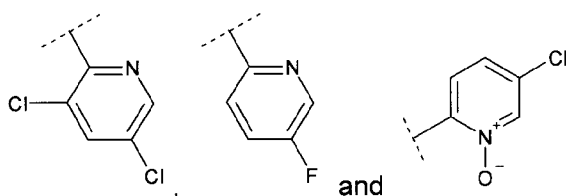
wherein the **Het** is selected from:



R⁶-G: In still another embodiment, R⁶ is Het,

wherein the Het is selected from:



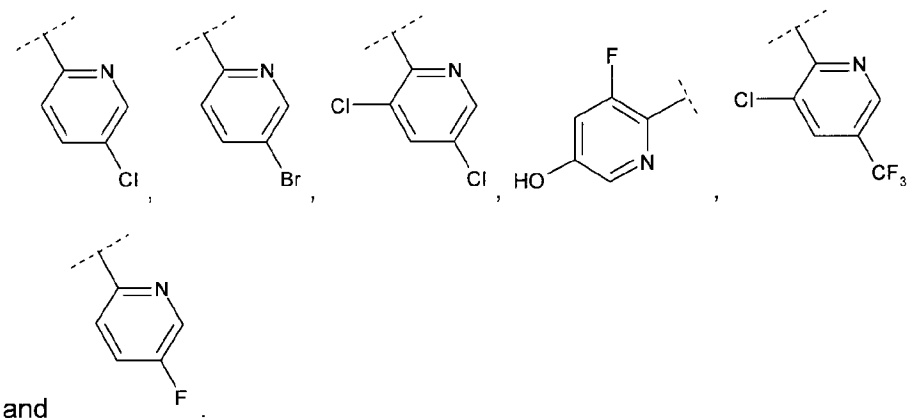


R⁶-H: In still another embodiment, **R⁶** is **Het** optionally substituted with 1 to 2 substituents each independently selected from halo, OH and (C₁₋₆)haloalkyl

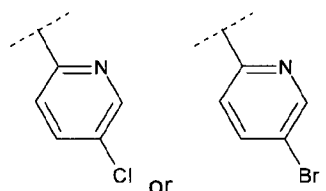


5

R⁶-I: In still another embodiment, **R⁶** is **Het**, wherein the **Het** is selected from:



10 **R⁶-J:** In still another embodiment, **R⁶** is



R⁶-K: In still another embodiment, **R⁶** is **Het**; being optionally substituted with 1 to 5 substituents each independently selected from halo, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -OH, -SH, -O-(C₁₋₄)alkyl, -S-(C₁₋₄)alkyl and -N(R⁸)R⁹; wherein R⁸ is selected from H, (C₁₋₆)alkyl and (C₃₋₇)cycloalkyl; and **R⁹** is **R⁷**; wherein **R⁷** is selected from H, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, aryl and **Het**;

15

wherein the (C₁₋₆)alkyl is optionally substituted with 1 or 2 substituents each independently selected from -OH, -O-(C₁₋₆)alkyl, cyano, COOH, -NH₂, -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl

and -N((C₁₋₄)alkyl)₂; and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from:

- 5
- i) halo, cyano, oxo, thioxo, imino, -OH, -O-(C₁₋₆)alkyl,
 -O-(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)haloalkyl,
 -C(=O)-(C₁₋₆)alkyl, -SO₂(C₁₋₆)alkyl, -C(=O)-NH₂,
 -C(=O)-NH(C₁₋₄)alkyl, -C(=O)-N((C₁₋₄)alkyl)₂,
 -C(=O)-NH(C₃₋₇)cycloalkyl,
 -C(=O)-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl,
 10 -N((C₁₋₄)alkyl)₂, -NH(C₃₋₇)cycloalkyl,
 -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl or -NH-C(=O)(C₁₋₄)alkyl;
- ii) (C₁₋₆)alkyl optionally substituted with -OH, -O-(C₁₋₆)haloalkyl,
 or -O-(C₁₋₆)alkyl; and
- iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally
 15 substituted with halo or (C₁₋₆)alkyl;
 or R⁸ and R⁹, together with the N to which they are attached,
 are linked to form a 4- to 7-membered heterocycle optionally further
 containing 1 to 3 heteroatoms each independently selected from N, O
 and S, wherein each S heteroatom may, independently and where
 20 possible, exist in an oxidized state such that it is further bonded to
 one or two oxygen atoms to form the groups SO or SO₂;
 wherein the heterocycle is optionally substituted with 1 to 3
 substituents each independently selected from (C₁₋₆)alkyl,
 (C₁₋₆)haloalkyl, halo, oxo, -OH, SH, -O(C₁₋₆)alkyl, -S(C₁₋₆)alkyl,
 25 (C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂,
 -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl and -NHC(=O)-(C₁₋₆)alkyl.

30 Any and each individual definition of R⁶ as set out herein may be combined with any
 and each individual definition of X, R², R²⁰, R³ and R⁵ as set out herein.

Examples of preferred subgeneric embodiments of the present invention are set
 forth in the following table, wherein each substituent group of each embodiment is
 defined according to the definitions set forth above:

35

Embodiment	X	R ²	R ²⁰	R ³	R ⁵	R ⁶
E-1	X-A	R ² -A	R ²⁰ -A	R ³ -A	R ⁵ -A	R ⁶ -B
E-2	X-A	R ² -A	R ²⁰ -E	R ³ -C	R ⁵ -A	R ⁶ -H
E-3	X-A	R ² -A	R ²⁰ -A	R ³ -A	R ⁵ -A	R ⁶ -B
E-4	X-A	R ² -A	R ²⁰ -E	R ³ -C	R ⁵ -A	R ⁶ -J
E-5	X-A	R ² -A	R ²⁰ -A	R ³ -A	R ⁵ -A	R ⁶ -J
E-6	X-A	R ² -A	R ²⁰ -A	R ³ -C	R ⁵ -A	R ⁶ -A
E-7	X-A	R ² -A	R ²⁰ -A	R ³ -A	R ⁵ -C	R ⁶ -I
E-8	X-A	R ² -B	R ²⁰ -E	R ³ -A	R ⁵ -A	R ⁶ -A
E-9	X-A	R ² -B	R ²⁰ -G	R ³ -A	R ⁵ -A	R ⁶ -J
E-10	X-A	R ² -B	R ²⁰ -A	R ³ -C	R ⁵ -A	R ⁶ -J
E-11	X-A	R ² -B	R ²⁰ -A	R ³ -A	R ⁵ -D	R ⁶ -A
E-12	X-A	R ² -F	R ²⁰ -E	R ³ -C	R ⁵ -G	R ⁶ -B
E-13	X-A	R ² -F	R ²⁰ -E	R ³ -A	R ⁵ -G	R ⁶ -J
E-14	X-A	R ² -F	R ²⁰ -A	R ³ -C	R ⁵ -D	R ⁶ -A
E-15	X-A	R ² -G	R ²⁰ -E	R ³ -C	R ⁵ -G	R ⁶ -B
E-16	X-A	R ² -G	R ²⁰ -E	R ³ -A	R ⁵ -G	R ⁶ -J
E-17	X-A	R ² -G	R ²⁰ -A	R ³ -C	R ⁵ -D	R ⁶ -A
E-18	X-A	R ² -J	R ²⁰ -E	R ³ -C	R ⁵ -G	R ⁶ -B
E-19	X-A	R ² -J	R ²⁰ -E	R ³ -A	R ⁵ -G	R ⁶ -J
E-20	X-A	R ² -J	R ²⁰ -A	R ³ -C	R ⁵ -D	R ⁶ -A
E-21	X-A	R ² -K	R ²⁰ -E	R ³ -C	R ⁵ -G	R ⁶ -B
E-22	X-A	R ² -K	R ²⁰ -E	R ³ -A	R ⁵ -G	R ⁶ -J
E-23	X-A	R ² -K	R ²⁰ -A	R ³ -C	R ⁵ -D	R ⁶ -A
E-24	X-A	R ² -L	R ²⁰ -A	R ³ -A	R ⁵ -A	R ⁶ -A
E-25	X-A	R ² -L	R ²⁰ -C	R ³ -A	R ⁵ -A	R ⁶ -A
E-26	X-A	R ² -L	R ²⁰ -C	R ³ -G	R ⁵ -G	R ⁶ -B
E-27	X-A	R ² -L	R ²⁰ -D	R ³ -D	R ⁵ -D	R ⁶ -J
E-28	X-A	R ² -L	R ²⁰ -D	R ³ -G	R ⁵ -G	R ⁶ -A
E-29	X-A	R ² -L	R ²⁰ -C	R ³ -B	R ⁵ -B	R ⁶ -B
E-30	X-A	R ² -L	R ²⁰ -D	R ³ -E	R ⁵ -E	R ⁶ -A
E-31	X-A	R ² -L	R ²⁰ -C	R ³ -G	R ⁵ -G	R ⁶ -B
E-32	X-A	R ² -L	R ²⁰ -A	R ³ -G	R ⁵ -G	R ⁶ -J
E-33	X-A	R ² -L	R ²⁰ -C	R ³ -D	R ⁵ -D	R ⁶ -H

Embodiment	X	R ²	R ²⁰	R ³	R ⁵	R ⁶
E-34	X-A	R ² -M	R ²⁰ -A	R ³ -A	R ⁵ -A	R ⁶ -A
E-35	X-A	R ² -M	R ²⁰ -C	R ³ -A	R ⁵ -A	R ⁶ -A
E-36	X-A	R ² -M	R ²⁰ -C	R ³ -G	R ⁵ -G	R ⁶ -B
E-37	X-A	R ² -M	R ²⁰ -D	R ³ -D	R ⁵ -D	R ⁶ -J
E-38	X-A	R ² -M	R ²⁰ -D	R ³ -G	R ⁵ -G	R ⁶ -A
E-39	X-A	R ² -M	R ²⁰ -C	R ³ -B	R ⁵ -B	R ⁶ -B
E-40	X-A	R ² -M	R ²⁰ -D	R ³ -E	R ⁵ -E	R ⁶ -A
E-41	X-A	R ² -M	R ²⁰ -C	R ³ -G	R ⁵ -G	R ⁶ -B
E-42	X-A	R ² -M	R ²⁰ -A	R ³ -G	R ⁵ -G	R ⁶ -J
E-43	X-A	R ² -M	R ²⁰ -C	R ³ -D	R ⁵ -D	R ⁶ -H
E-44	X-A	R ² -C	R ²⁰ -A	R ³ -F	R ⁵ -G	R ⁶ -D
E-45	X-A	R ² -C	R ²⁰ -C	R ³ -G	R ⁵ -C	R ⁶ -C
E-46	X-A	R ² -C	R ²⁰ -C	R ³ -G	R ⁵ -G	R ⁶ -B
E-47	X-A	R ² -C	R ²⁰ -A	R ³ -G	R ⁵ -G	R ⁶ -J
E-48	X-A	R ² -C	R ²⁰ -C	R ³ -D	R ⁵ -D	R ⁶ -H
E-49	X-A	R ² -C	R ²⁰ -G	R ³ -H	R ⁵ -H	R ⁶ -E
E-50	X-A	R ² -C	R ²⁰ -H	R ³ -H	R ⁵ -A	R ⁶ -G
E-51	X-A	R ² -C	R ²⁰ -J	R ³ -F	R ⁵ -I	R ⁶ -D
E-52	X-A	R ² -C	R ²⁰ -J	R ³ -D	R ⁵ -J	R ⁶ -B
E-53	X-A	R ² -D	R ²⁰ -D	R ³ -D	R ⁵ -D	R ⁶ -J
E-54	X-A	R ² -D	R ²⁰ -D	R ³ -G	R ⁵ -G	R ⁶ -A
E-55	X-A	R ² -D	R ²⁰ -C	R ³ -B	R ⁵ -B	R ⁶ -B
E-56	X-A	R ² -D	R ²⁰ -I	R ³ -H	R ⁵ -H	R ⁶ -B
E-57	X-A	R ² -D	R ²⁰ -G	R ³ -E	R ⁵ -J	R ⁶ -G
E-58	X-A	R ² -D	R ²⁰ -B	R ³ -D	R ⁵ -D	R ⁶ -D
E-59	X-A	R ² -D	R ²⁰ -D	R ³ -D	R ⁵ -D	R ⁶ -J
E-60	X-A	R ² -D	R ²⁰ -D	R ³ -D	R ⁵ -D	R ⁶ -C
E-61	X-A	R ² -D	R ²⁰ -C	R ³ -A	R ⁵ -H	R ⁶ -C
E-62	X-A	R ² -D	R ²⁰ -A	R ³ -C	R ⁵ -A	R ⁶ -F
E-63	X-A	R ² -D	R ²⁰ -C	R ³ -F	R ⁵ -J	R ⁶ -B
E-64	X-A	R ² -D	R ²⁰ -C	R ³ -E	R ⁵ -D	R ⁶ -A
E-65	X-A	R ² -E	R ²⁰ -C	R ³ -D	R ⁵ -D	R ⁶ -H
E-66	X-A	R ² -E	R ²⁰ -C	R ³ -G	R ⁵ -G	R ⁶ -B

Embodiment	X	R ²	R ²⁰	R ³	R ⁵	R ⁶
E-67	X-A	R ² -E	R ²⁰ -D	R ³ -D	R ⁵ -D	R ⁶ -J
E-68	X-A	R ² -E	R ²⁰ -D	R ³ -G	R ⁵ -G	R ⁶ -A
E-69	X-A	R ² -E	R ²⁰ -C	R ³ -B	R ⁵ -B	R ⁶ -B
E-70	X-A	R ² -E	R ²⁰ -D	R ³ -E	R ⁵ -E	R ⁶ -A
E-71	X-A	R ² -E	R ²⁰ -C	R ³ -G	R ⁵ -G	R ⁶ -B
E-72	X-A	R ² -H	R ²⁰ -A	R ³ -G	R ⁵ -G	R ⁶ -J
E-73	X-A	R ² -H	R ²⁰ -C	R ³ -D	R ⁵ -D	R ⁶ -H
E-74	X-A	R ² -H	R ²⁰ -G	R ³ -H	R ⁵ -H	R ⁶ -E
E-75	X-A	R ² -H	R ²⁰ -H	R ³ -H	R ⁵ -A	R ⁶ -G
E-76	X-A	R ² -H	R ²⁰ -J	R ³ -F	R ⁵ -I	R ⁶ -D
E-77	X-A	R ² -H	R ²⁰ -J	R ³ -D	R ⁵ -J	R ⁶ -B
E-78	X-A	R ² -I	R ²⁰ -C	R ³ -D	R ⁵ -D	R ⁶ -H
E-79	X-A	R ² -I	R ²⁰ -C	R ³ -G	R ⁵ -G	R ⁶ -B
E-80	X-A	R ² -I	R ²⁰ -D	R ³ -D	R ⁵ -D	R ⁶ -J
E-81	X-A	R ² -I	R ²⁰ -D	R ³ -G	R ⁵ -G	R ⁶ -A
E-82	X-A	R ² -I	R ²⁰ -C	R ³ -B	R ⁵ -B	R ⁶ -B
E-83	X-A	R ² -I	R ²⁰ -D	R ³ -E	R ⁵ -E	R ⁶ -A
E-84	X-A	R ² -I	R ²⁰ -A	R ³ -G	R ⁵ -G	R ⁶ -J
E-85	X-A	R ² -I	R ²⁰ -C	R ³ -D	R ⁵ -D	R ⁶ -H
E-86	X-B	R ² -A	R ²⁰ -A	R ³ -A	R ⁵ -A	R ⁶ -B
E-87	X-B	R ² -A	R ²⁰ -E	R ³ -C	R ⁵ -A	R ⁶ -H
E-88	X-B	R ² -A	R ²⁰ -A	R ³ -A	R ⁵ -A	R ⁶ -B
E-89	X-B	R ² -A	R ²⁰ -E	R ³ -C	R ⁵ -A	R ⁶ -J
E-90	X-B	R ² -F	R ²⁰ -E	R ³ -C	R ⁵ -G	R ⁶ -B
E-91	X-B	R ² -F	R ²⁰ -E	R ³ -A	R ⁵ -G	R ⁶ -J
E-92	X-B	R ² -F	R ²⁰ -A	R ³ -C	R ⁵ -D	R ⁶ -A
E-93	X-B	R ² -G	R ²⁰ -E	R ³ -C	R ⁵ -G	R ⁶ -B
E-94	X-B	R ² -G	R ²⁰ -E	R ³ -A	R ⁵ -G	R ⁶ -J
E-95	X-B	R ² -G	R ²⁰ -A	R ³ -C	R ⁵ -D	R ⁶ -A
E-96	X-B	R ² -J	R ²⁰ -E	R ³ -C	R ⁵ -G	R ⁶ -B
E-97	X-B	R ² -J	R ²⁰ -E	R ³ -A	R ⁵ -G	R ⁶ -J
E-98	X-B	R ² -J	R ²⁰ -A	R ³ -C	R ⁵ -D	R ⁶ -A
E-99	X-B	R ² -K	R ²⁰ -E	R ³ -C	R ⁵ -G	R ⁶ -B

Embodiment	X	R ²	R ²⁰	R ³	R ⁵	R ⁶
E-100	X-B	R ² -K	R ²⁰ -E	R ³ -A	R ⁵ -G	R ⁶ -J
E-101	X-B	R ² -K	R ²⁰ -A	R ³ -C	R ⁵ -D	R ⁶ -A
E-102	X-B	R ² -L	R ²⁰ -C	R ³ -G	R ⁵ -G	R ⁶ -B
E-103	X-B	R ² -L	R ²⁰ -D	R ³ -D	R ⁵ -D	R ⁶ -J
E-104	X-B	R ² -L	R ²⁰ -D	R ³ -G	R ⁵ -G	R ⁶ -A
E-105	X-B	R ² -L	R ²⁰ -C	R ³ -B	R ⁵ -B	R ⁶ -B
E-106	X-B	R ² -L	R ²⁰ -D	R ³ -E	R ⁵ -E	R ⁶ -A
E-107	X-B	R ² -L	R ²⁰ -C	R ³ -G	R ⁵ -G	R ⁶ -B
E-108	X-B	R ² -L	R ²⁰ -A	R ³ -G	R ⁵ -G	R ⁶ -J
E-109	X-B	R ² -L	R ²⁰ -C	R ³ -D	R ⁵ -D	R ⁶ -H
E-110	X-B	R ² -M	R ²⁰ -C	R ³ -G	R ⁵ -G	R ⁶ -B
E-111	X-B	R ² -M	R ²⁰ -D	R ³ -D	R ⁵ -D	R ⁶ -J
E-112	X-B	R ² -M	R ²⁰ -D	R ³ -G	R ⁵ -G	R ⁶ -A
E-113	X-B	R ² -M	R ²⁰ -C	R ³ -B	R ⁵ -B	R ⁶ -B
E-114	X-B	R ² -M	R ²⁰ -D	R ³ -E	R ⁵ -E	R ⁶ -A
E-115	X-B	R ² -M	R ²⁰ -C	R ³ -G	R ⁵ -G	R ⁶ -B
E-116	X-B	R ² -M	R ²⁰ -A	R ³ -G	R ⁵ -G	R ⁶ -J
E-117	X-B	R ² -M	R ²⁰ -C	R ³ -D	R ⁵ -D	R ⁶ -H

Examples of most preferred compounds according to this invention are each single compounds listed in the following Tables 1 and 2.

- 5 In general, all tautomeric and isomeric forms and mixtures thereof, for example, individual geometric isomers, stereoisomers, atropisomers, enantiomers, diastereomers, racemates, racemic or non-racemic mixtures of stereoisomers, mixtures of diastereomers, or mixtures of any of the foregoing forms of a chemical structure or compound is intended, unless the specific stereochemistry or isomeric form is specifically indicated in the compound name or structure.
- 10

It is well-known in the art that the biological and pharmacological activity of a compound is sensitive to the stereochemistry of the compound. Thus, for example, enantiomers often exhibit strikingly different biological activity including differences in pharmacokinetic properties, including metabolism, protein binding, and the like, and

15

pharmacological properties, including the type of activity displayed, the degree of activity, toxicity, and the like. Thus, one skilled in the art will appreciate that one enantiomer may be more active or may exhibit beneficial effects when enriched relative to the other enantiomer or when separated from the other enantiomer.

- 5 Additionally, one skilled in the art would know how to separate, enrich, or selectively prepare the enantiomers of the compounds of the present invention from this disclosure and the knowledge in the art.

Preparation of pure stereoisomers, e.g. enantiomers and diastereomers, or mixtures
10 of desired enantiomeric excess (ee) or enantiomeric purity, are accomplished by one or more of the many methods of (a) separation or resolution of enantiomers, or (b) enantioselective synthesis known to those of skill in the art, or a combination thereof. These resolution methods generally rely on chiral recognition and include, for example, chromatography using chiral stationary phases, enantioselective host-
15 guest complexation, resolution or synthesis using chiral auxiliaries, enantioselective synthesis, enzymatic and nonenzymatic kinetic resolution, or spontaneous enantioselective crystallization. Such methods are disclosed generally in *Chiral Separation Techniques: A Practical Approach* (2nd Ed.), G. Subramanian (ed.), Wiley-VCH, 2000; T.E. Beesley and R.P.W. Scott, *Chiral Chromatography*, John
20 Wiley & Sons, 1999; and Satinder Ahuja, *Chiral Separations by Chromatography*, Am. Chem. Soc., 2000, herein incorporated by reference. Furthermore, there are equally well-known methods for the quantitation of enantiomeric excess or purity, for example, GC, HPLC, CE, or NMR, and assignment of absolute configuration and conformation, for example, CD, ORD, X-ray crystallography, or NMR.

25

The compounds according to the present invention are inhibitors of the hepatitis C virus NS5B RNA-dependent RNA polymerase and thus may be used to inhibit replication of hepatitis C viral RNA.

- 30 A compound according to the present invention may also be used as a laboratory reagent or a research reagent. For example, a compound of the present invention may be used as positive control to validate assays, including but not limited to surrogate cell-based assays and *in vitro* or *in vivo* viral replication assays.

- 35 Compounds according to the present invention may also be used as probes to study

the hepatitis C virus NS5B polymerase, including but not limited to the mechanism of action of the polymerase, conformational changes undergone by the polymerase under various conditions and interactions with entities which bind to or otherwise interact with the polymerase.

5

Compounds of the invention used as probes may be labelled with a label which allows recognition either directly or indirectly of the compound such that it can be detected, measured and quantified. Labels contemplated for use with the compounds of the invention include, but are not limited to, fluorescent labels, chemiluminescent labels, colorimetric labels, enzymatic markers, radioactive isotopes, affinity tags and photoreactive groups.

Compounds of the invention used as probes may also be labelled with an affinity tag whose strong affinity for a receptor can be used to extract from a solution the entity to which the ligand is attached. Affinity tags include but are not limited to biotin or a derivative thereof, a histidine polypeptide, a polyarginine, an amylose sugar moiety or a defined epitope recognizable by a specific antibody.

Furthermore, compounds of the invention used as probes may be labelled with a photoreactive group which is transformed, upon activation by light, from an inert group to a reactive species, such as a free radical. Photoreactive groups include but are not limited to photoaffinity labels such as benzophenone and azide groups.

Furthermore, a compound according to the present invention may be used to treat or prevent viral contamination of materials and therefore reduce the risk of viral infection of laboratory or medical personnel or patients who come in contact with such materials (e.g. blood, tissue, surgical instruments and garments, laboratory instruments and garments, and blood collection apparatuses and materials).

30 **Pharmaceutical composition**

Compounds of the present invention may be administered to a mammal in need of treatment for hepatitis C viral infection as a pharmaceutical composition comprising a therapeutically effective amount of a compound according to the invention or a pharmaceutically acceptable salt or ester thereof; and one or more conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The specific

35

formulation of the composition is determined by the solubility and chemical nature of the compound, the chosen route of administration and standard pharmaceutical practice. The pharmaceutical composition according to the present invention may be administered orally or systemically.

5

For oral administration, the compound, or a pharmaceutically acceptable salt or ester thereof, can be formulated in any orally acceptable dosage form including but not limited to aqueous suspensions and solutions, capsules, powders, syrups, elixirs or tablets. For systemic administration, including but not limited to administration by subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, and intralesional injection or infusion techniques, it is preferred to use a solution of the compound, or a pharmaceutically acceptable salt or ester thereof, in a pharmaceutically acceptable sterile aqueous vehicle.

15

Pharmaceutically acceptable carriers, adjuvants, vehicles, excipients and additives as well as methods of formulating pharmaceutical compositions for various modes of administration are well-known to those of skill in the art and are described in pharmaceutical texts such as Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams & Wilkins, 2005; and L.V. Allen, N.G. Popovich and H.C. Ansel, Pharmaceutical Dosage Forms and Drug Delivery Systems, 8th ed., Lippincott Williams & Wilkins, 2004, herein incorporated by reference.

The dosage administered will vary depending upon known factors, including but not limited to the activity and pharmacodynamic characteristics of the specific compound employed and its mode, time and route of administration; the age, diet, gender, body weight and general health status of the recipient; the nature and extent of the symptoms; the severity and course of the infection; the kind of concurrent treatment; the frequency of treatment; the effect desired; and the judgment of the treating physician. In general, the compound is most desirably administered at a dosage level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

A daily dosage of active ingredient can be expected to be about 0.01 to about 200 milligrams per kilogram of body weight, with the preferred dose being about 0.1 to

about 50 mg/kg. Typically, the pharmaceutical composition of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to
5 produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

10 **Combination therapy**

Combination therapy is contemplated wherein a compound according to the invention, or a pharmaceutically acceptable salt or ester thereof, is co-administered with at least one additional antiviral agent. The additional agents may be combined with compounds of this invention to create a single dosage form. Alternatively these
15 additional agents may be separately administered, concurrently or sequentially, as part of a multiple dosage form.

When the pharmaceutical composition of this invention comprises a combination of a compound according to the invention, or a pharmaceutically acceptable salt or
20 ester thereof, and one or more additional antiviral agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen. In the case of a synergistic interaction between the compound of the invention and the additional antiviral agent or agents,
25 the dosage of any or all of the active agents in the combination may be reduced compared to the dosage normally administered in a monotherapy regimen.

Antiviral agents contemplated for use in such combination therapy include agents (compounds or biologicals) that are effective to inhibit the formation and/or
30 replication of a virus in a mammal, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a mammal. Such agents can be selected from another anti-HCV agent; an HIV inhibitor; an HAV inhibitor; and an HBV inhibitor.

35 Other anti-HCV agents include those agents that are effective for diminishing or

preventing the progression of hepatitis C related symptoms or disease. Such agents include but are not limited to immunomodulatory agents, inhibitors of HCV NS3 protease, other inhibitors of HCV polymerase, inhibitors of another target in the HCV life cycle and other anti-HCV agents, including but not limited to ribavirin,
5 amantadine, levovirin and viremagine.

Immunomodulatory agents include those agents (compounds or biologicals) that are effective to enhance or potentiate the immune system response in a mammal. Immunomodulatory agents include, but are not limited to, inosine monophosphate
10 dehydrogenase inhibitors such as VX-497 (merimepodib, Vertex Pharmaceuticals), class I interferons, class II interferons, consensus interferons, asialo-interferons pegylated interferons and conjugated interferons, including but not limited to interferons conjugated with other proteins including but not limited to human albumin. Class I interferons are a group of interferons that all bind to receptor type I,
15 including both naturally and synthetically produced class I interferons, while class II interferons all bind to receptor type II. Examples of class I interferons include, but are not limited to, α -, β -, δ -, ω -, and τ -interferons, while examples of class II interferons include, but are not limited to, γ -interferons.

20 Inhibitors of HCV NS3 protease include agents (compounds or biologicals) that are effective to inhibit the function of HCV NS3 protease in a mammal. Inhibitors of HCV NS3 protease include, but are not limited to, those compounds described in WO 99/07733, WO 99/07734, WO 00/09558, WO 00/09543, WO 00/59929, WO 03/064416, WO 03/064455, WO 03/064456, WO 2004/030670, WO 2004/037855,
25 WO 2004/039833, WO 2004/101602, WO 2004/101605, WO 2004/103996, WO 2005/028501, WO 2005/070955, WO 2006/000085, WO 2006/007700, WO 2006/007708, WO 2007/009227 (all by Boehringer Ingelheim), WO 02/060926, WO 03/053349, WO 03/099274, WO 03/099316, WO 2004/032827, WO 2004/043339, WO 2004/094452, WO 2005/046712, WO 2005/051410, WO 2005/054430 (all by
30 BMS), WO 2004/072243, WO 2004/093798, WO 2004/113365, WO 2005/010029 (all by Enanta), WO 2005/037214 (Intermune), WO 01/77113, WO 01/81325, WO 02/08187, WO 02/08198, WO 02/08244, WO 02/08256, WO 02/48172, WO 03/062228, WO 03/062265, WO 2005/021584, WO 2005/030796, WO 2005/058821, WO 2005/051980, WO 2005/085197, WO 2005/085242, WO
35 2005/085275, WO 2005/087721, WO 2005/087725, WO 2005/087730, WO

2005/087731, WO 2005/107745 and WO 2005/113581 (all by Schering), WO 2006/119061, WO 2007/016441, WO 2007/015855, WO 2007/015787 (all by Merck); and the candidates VX-950, ITMN-191 and SCH-503034.

- 5 Inhibitors of HCV polymerase include agents (compounds or biologicals) that are effective to inhibit the function of an HCV polymerase. Such inhibitors include, but are not limited to, non-nucleoside and nucleoside inhibitors of HCV NS5B polymerase. Examples of inhibitors of HCV polymerase include but are not limited to those compounds described in: WO 02/04425, WO 03/007945, WO 03/010140, WO
10 03/010141, WO 2004/064925, WO 2004/065367, WO 2005/080388, WO 2006/007693, WO 2007/019674, WO 2007/087717 (all by Boehringer Ingelheim), WO 01/47883 (Japan Tobacco), WO 03/000254 (Japan Tobacco), WO 03/026587 (BMS), WO 2004/087714 (IRBM), WO 2005/012288 (Genelabs), WO 2005/014543 (Japan Tobacco), WO 2005/049622 (Japan Tobacco), and WO 2005/121132
15 (Shionogi), WO 2005/080399 (Japan Tobacco), WO 2006/052013 (Japan Tobacco), WO 2006/119646 (Virochem Pharma), WO 2007/039146 (SmithKline Beecham), WO 2005/021568 (Biota), WO 2006/094347 (Biota) and the candidates HCV 796 (ViroPharma/Wyeth), R-1626, R-1656 and R-7128 (Roche), NM 283 (Idenix/Novartis), VCH-759 (Virochem), GSK625433 (GSK), GS9190 (Gilead), MK-
20 608 (Merck) and PF868554 (Pfizer).

Inhibitors of another target in the HCV life cycle include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of HCV other than by inhibiting the function of the HCV NS3 protease or HCV polymerase. Such
25 agents may interfere with either host or HCV viral mechanisms necessary for the formation and/or replication of HCV. Inhibitors of another target in the HCV life cycle include, but are not limited to, entry inhibitors, agents that inhibit a target selected from a helicase, a NS2/3 protease and an internal ribosome entry site (IRES) and agents that interfere with the function of other viral targets including but not limited to
30 an NS5A protein and an NS4B protein.

It can occur that a patient may be co-infected with hepatitis C virus and one or more other viruses, including but not limited to human immunodeficiency virus (HIV), hepatitis A virus (HAV) and hepatitis B virus (HBV). Thus also contemplated is
35 combination therapy to treat such co-infections by co-administering a compound

according to the present invention with at least one of an HIV inhibitor, an HAV inhibitor and an HBV inhibitor.

- HIV inhibitors include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of HIV. This includes but is not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HIV in a mammal. HIV inhibitors include, but are not limited to:
- NRTIs (nucleoside or nucleotide reverse transcriptase inhibitors; including but not limited to zidovudine, didanosine, zalcitabine, stavudine, lamivudine, emtricitabine, abacavir, and tenofovir);
 - NNRTIs (non-nucleoside reverse transcriptase inhibitors; including but not limited to nevirapine, delavirdine, efavirenz, etravirine, rilpivirine and BILR 355);
 - protease inhibitors (including but not limited to ritonavir, tipranavir, saquinavir, nelfinavir, indinavir, amprenavir, fosamprenavir, atazanavir, lopinavir, darunavir and brecanavir);
 - entry inhibitors including but not limited to
 - CCR5 antagonists (including but not limited to maraviroc (UK-427,857) and TAK-652),
 - CXCR4 antagonists (including but not limited to AMD-11070),
 - fusion inhibitors (including but not limited to enfuvirtide (T-20)) and
 - others (including but not limited to BMS-488043);
 - integrase inhibitors (including but not limited to MK-0518, c-1605, BMS-538158 and GS 9137);
 - TAT inhibitors;
 - maturation inhibitors (including but not limited to bevirimat (PA-457)); and
 - immunomodulating agents (including but not limited to levamisole).

HAV inhibitors include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of HAV. This includes but is not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HAV in a mammal. HAV inhibitors include but are not limited to Hepatitis A vaccines.

HBV inhibitors include agents (compounds or biologicals) that are effective to inhibit

the formation and/or replication of HBV in a mammal. This includes but is not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of HBV in a mammal. HBV inhibitors include, but are not limited to, agents that inhibit the HBV viral DNA polymerase and HBV vaccines.

5

Therefore, according to one embodiment, the pharmaceutical composition of this invention additionally comprises a therapeutically effective amount of one or more antiviral agents.

10 A further embodiment provides the pharmaceutical composition of this invention wherein the one or more antiviral agent comprises at least one other anti-HCV agent.

According to a more specific embodiment of the pharmaceutical composition of this invention, the at least one other anti-HCV agent comprises at least one

15 immunomodulatory agent.

According to another more specific embodiment of the pharmaceutical composition of this invention, the at least one other anti-HCV agent comprises at least one other inhibitor of HCV polymerase.

20

According to yet another more specific embodiment of the pharmaceutical composition of this invention, the at least one other anti-HCV agent comprises at least one inhibitor of HCV NS3 protease.

25 According to still another more specific embodiment of the pharmaceutical composition of this invention, the at least one other anti-HCV agent comprises at least one inhibitor of another target in the HCV life cycle.

30 All of the documents cited herein are incorporated in to the invention as a reference, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application.

EXAMPLES

Other features of the present invention will become apparent from the following non-limiting examples which illustrate, by way of example, the principles of the invention. As is well known to a person skilled in the art, reactions are performed in an inert atmosphere (including but not limited to nitrogen or argon) where necessary to protect reaction components from air or moisture. Temperatures are given in degrees Celsius (°C). Solution percentages and ratios express a volume to volume relationship, unless stated otherwise. Flash chromatography is carried out on silica gel (SiO₂) according to the procedure of W.C. Still *et al.*, J. Org. Chem., (1978), 43, 2923. Mass spectral analyses are recorded using electrospray mass spectrometry. Purification on a combiflash is performed using an Isco Combiflash (column cartridge SiO₂). Preparative HPLC is carried out under standard conditions using a SunFire™ Prep C18 OBD 5µM reverse phase column, 19 x 50 mm and a linear gradient (20 to 98%) employing 0.1%TFA/acetonitrile and 0.1%TFA/water as solvents. Compounds are isolated as TFA salts when applicable. Analytical HPLC is carried out under standard conditions using a Combiscreen™ ODS-AQ C18 reverse phase column, YMC, 50 x 4.6 mm i.d., 5 µM, 120 Å at 220 nM, elution with a linear gradient as described in the following table (Solvent A is 0.06% TFA in H₂O; solvent B is 0.06% TFA in CH₃CN):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	3.0	95	5
0.5	3.0	95	5
6.0	3.0	50	50
10.5	3.5	0	100

20

Abbreviations or symbols used herein include:

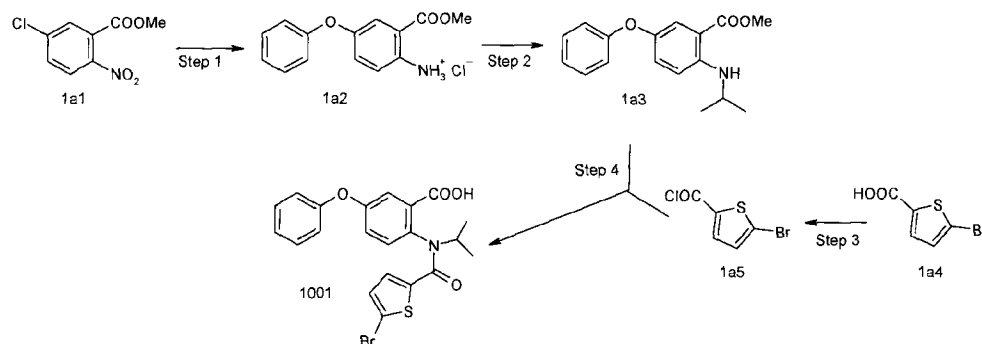
- Ac: acetyl;
- AcOH: acetic acid;
- 25 Bn: benzyl (phenylmethyl);
- Bu: butyl;
- n-BuLi: n-butyllithium;
- m-CPBA: *meta*-chloroperbenzoic acid;
- DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene;
- 30 DCE: dichloroethane;

- DCM: dichloromethane;
DIAD: diisopropyl azodicarboxylate;
DMAP: 4-dimethylaminopyridine;
DMF: *N,N*-dimethylformamide;
- 5 DMSO: dimethylsulfoxide;
EC₅₀: 50% effective concentration;
EDTA: ethylenediaminetetracetic acid;
Et: ethyl;
Et₃N: triethylamine;
- 10 Et₂O: diethyl ether;
EtOAc: ethyl acetate;
EtOH: ethanol;
HPLC: high performance liquid chromatography;
Hex: hexane;
- 15 IC₅₀: 50% inhibitory concentration;
LC-MS: liquid chromatography- mass spectrometry;
*i*Pr or *i*-Pr: 1-methylethyl (*iso*-propyl);
Me: methyl;
MeCN: acetonitrile;
- 20 MeI: iodomethane;
MeOH: methanol;
MS: mass spectrometry;
NaHB(OAc)₃: sodium triacetoxyborohydride;
NIS: N-iodosuccinamide;
- 25 NLIN: non-linear;
NMO: N-methylmorpholine N-oxide;
NMR: nuclear magnetic resonance spectroscopy;
Ph: phenyl;
Pr: propyl;
- 30 RT: room temperature (approximately 18°C to 25°C);
SAS: small-angle scattering;
SPA: scintillation proximity assay;
TCEP: tris(2-carboxyethyl)phosphine hydrochloride;
tert-butyl or *t*-butyl: 1,1-dimethylethyl;
- 35 TFA: trifluoroacetic acid;

THF: tetrahydrofuran;
TLC: thin layer chromatography.

EXAMPLE 1A

5 PREPARATION OF COMPOUND 1001



Step 1a:

To a mixture of phenol (5.0 g, 53 mmol) and methyl-5-chloro-2-nitrobenzoate **1a1** (7.6 g, 35 mmol) in DMSO (20 mL) is added anhydrous K_2CO_3 (7.3 g, 53 mmol). The mixture is heated to $90^\circ C$ and stirred 6 hours. The mixture is diluted in water then extracted with EtOAc (x 2). The combined organic extracts are washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure.

Step 1b:

The crude diarylether is diluted in MeOH and 10% $Pd(OH)_2/C$ (0.3 g) is added. The vessel is purged with H_2 then is stirred overnight under 1 atm of H_2 . The mixture is filtered through a pad of celite then is concentrated *in vacuo*. To a mixture of the crude aniline in anhydrous Et_2O (150 mL) is slowly added HCl (1 M in ether, 150 mL). The resulting solid hydrochloride salt **1a2** is collected by filtration and washed with excess ether and dried.

Step 2:

Reference: Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

25

To a mixture of aniline hydrochloride salt **1a2** (268 mg, 0.96 mmol) in anhydrous DCE (5 mL) is added 2-methoxypropene (0.37 mL, 3.8 mmol) followed by $NaHB(OAc)_3$ (407 mg, 1.9 mmol). The mixture is stirred overnight at room

temperature then is diluted in EtOAc and washed with saturated aqueous NaHCO₃ and brine. The organic phase is dried over MgSO₄, filtered then concentrated under reduced pressure. The resulting residue is subjected to flash chromatography to isolate isopropylaniline **1a3**.

5

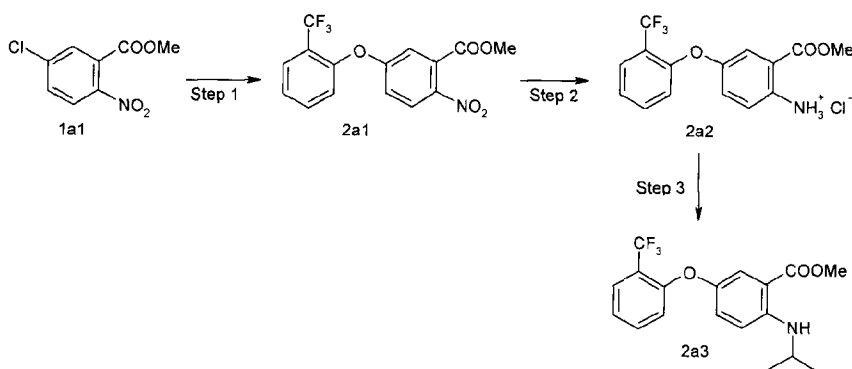
Step 3:

To a mixture of 5-bromo-2-thiophenecarboxylic acid **1a4** (56 mg, 0.27 mmol) and anhydrous CH₂Cl₂ (400 mL) is added a drop of anhydrous DMF followed by (COCl)₂ (2.0 M in DCM, 0.34 mL, 0.68 mmol). The mixture stirs 20 minutes at RT before
10 being concentrated under reduced pressure to yield the crude acid chloride **1a5**.

Step 4:

The crude acid chloride **1a5** is diluted in anhydrous pyridine (1 mL) and *i*-Pr-aniline **1a3** (50 mg, 0.18 mmol) is added. The mixture stirs overnight at RT. Aqueous
15 NaOH (10 N, 180 μL, 1.8 mmol) and water (180 μL) are added and the mixture stirs overnight at RT. The mixture is diluted in EtOAc and washed with 1N HCl and brine. The organic phase is dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is triturated in Et₂O and hexanes to provide compound **1001**.

20

EXAMPLE 2A**Preparation of intermediate 2a3****Step 1:**

25 The S_NAr reaction between 2-trifluoromethylphenol and methyl-5-chloro-2-nitrobenzoate **1a1** to form diarylether **2a1** is performed as described in example 1A step 1a.

Step 2:

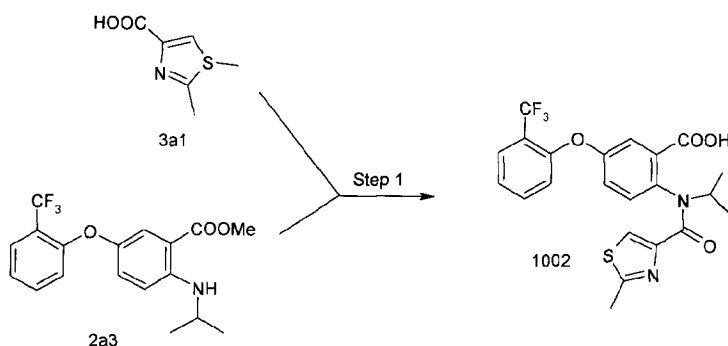
To a mixture of nitroarene **2a1** (780 mg, 2.3 mmol) in MeOH (20 mL) and AcOH (6 mL) is added iron powder (1.3 g, 23 mmol). The mixture is stirred for 30 minutes at
5 85 °C before being partitioned between EtOAc and saturated aqueous NaHCO₃.

The aqueous layer is separated and extracted again with EtOAc. The combined organic extracts are washed with water and brine. The organic phase is dried over MgSO₄, filtered, and then concentrated under reduced pressure.

To a mixture of the crude aniline in Et₂O and hexanes is added HCl (1.0 M in ether, 6 mL, 6 mmol). The resulting solid hydrochloride salt **2a2** is collected by filtration and washed with excess ether and dried.
10

Step 3:

Reductive amination to form *i*-Pr-aniline **2a3** is performed as described in example
15 1A step 2.

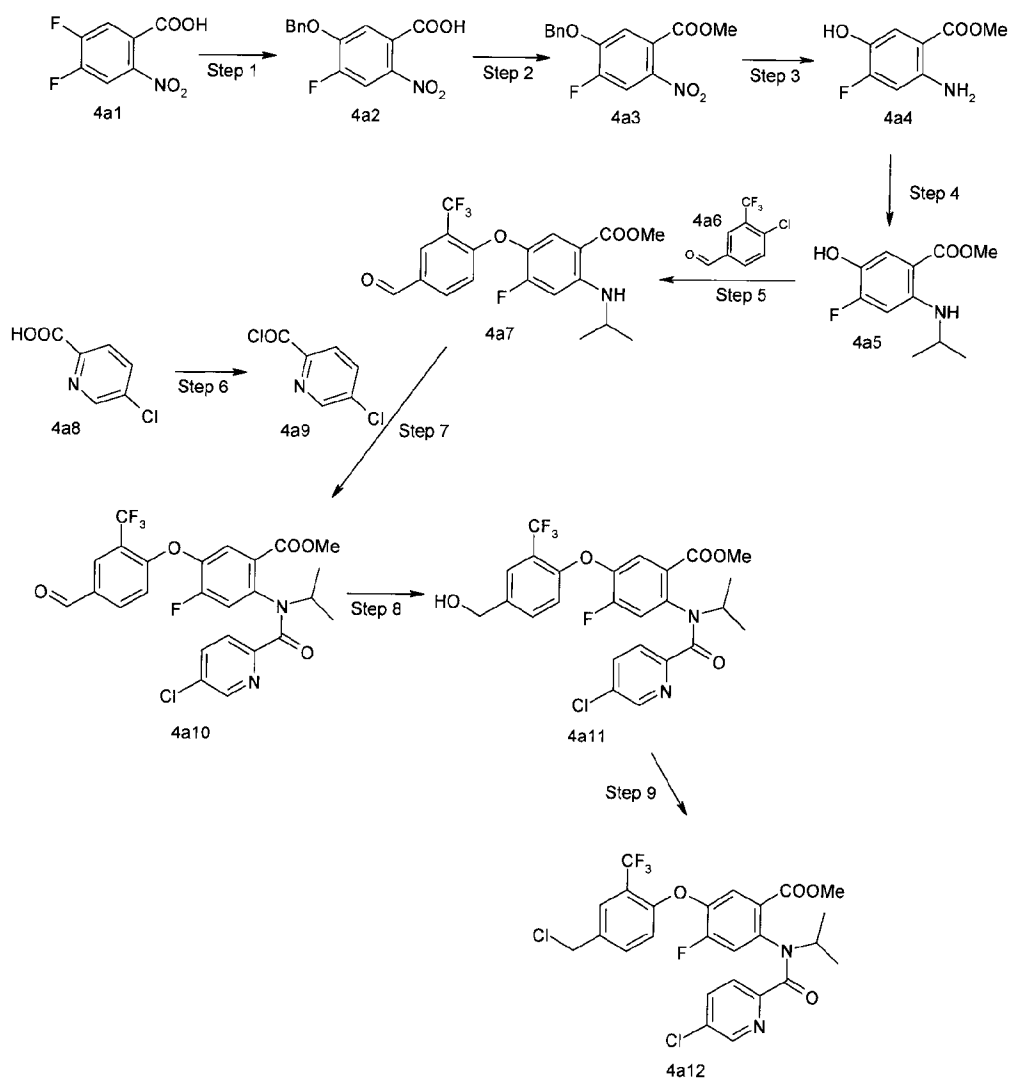
EXAMPLE 3A**Method A****20 Preparation of compound 1002**Step 1a:

To a mixture of 2-methyl-4-thiazolecarboxylic acid **3a1** (27 mg, 0.17 mmol) and anhydrous DCE (1 mL) is added triphosgene (22 mg, 0.08 mmol) and 2,4,6-collidine
25 (100 μL) and *i*-Pr-aniline **2a3** (35 mg, 0.10 mmol). The mixture is agitated on a J-Kem® orbital shaker (300 rpm) at 80°C overnight. The mixture is concentrated under reduced pressure using a Savant™ speed-vac. The residue is taken up in EtOAc and washed with saturated aqueous NaHCO₃ (x 2) and brine. The solvent is

removed under reduced pressure. The residue is taken up in DMSO then aqueous NaOH (10 N, 50 μ L, 0.5 mmol) and water (180 μ L) are added and the mixture is agitated on a J-Kem® orbital shaker (300 rpm) at RT overnight. The mixture is acidified with AcOH (200 μ L) then injected onto a preparative HPLC to isolate compound **1002**.

EXAMPLE 4A

Preparation of intermediate 4a12



10 Step 1:

4,5-difluoro-2-nitrobenzoic acid **4a1** (73 g, 359 mmol) is combined with anhydrous THF (2 L) under argon. Benzylalcohol (80.8 mL, 800 mmol) is added and the

mixture is chilled to 0°C. Sodiumbis(trimethylsilyl)amide (1.0 M in THF, 800 mL, 800 mmol) is added drop-wise. After stirring for one hour, the mixture is partitioned between saturated aqueous NH₄Cl and EtOAc. The organic phase is collected and dried over sodium sulfate. The mixture is filtered and concentrated. The resulting
5 solid **4a2** is washed with cold EtOAc and dried.

Step 2:

Carboxylic acid **4a2** (112.8 g, 384 mmol) is combined with anhydrous DMF (2 L). Potassium carbonate (108.1 g, 775 mmol) is added and the mixture is chilled to 0°C.
10 Iodomethane (110 g, 775 mmol) is added drop-wise and after 2 hours the reaction is quenched by the addition of saturated aqueous NH₄Cl. The aqueous solution is extracted with EtOAc (x 2). The combined organic extracts are then washed with water and brine before being dried with MgSO₄. Removal of solvent results in methyl ester **4a3**.

15

Step 3:

Benzylether **4a3** (56.7g, 186 mmol) is combined with MeOH (300 mL) and EtOAc (300 mL) in a Parr Bomb. The solution is degassed with Ar then Pearlman's catalyst (6 g) is added. The bomb is charged with 30 psi of H₂ and stirred at RT overnight.
20 The mixture is filtered and the solvent removed *in vacuo*. The residue is triturated with hexane to afford phenol **4a4**.

Step 4:

Reference: Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah,
25 R. D. *J. Org. Chem.* **1996**, *61*, 3849.

To a mixture of phenol **4a4** (5.00 g, 27 mmol) and DCM (200 mL) is added HCl (1.0 M in ether, 27 mL, 27 mmol). After stirring for 5 minutes at ambient temperature, 2-methoxypropene (3.8 mL, 40 mmol) is added followed by NaHB(OAc)₃ (11.4 g, 54
30 mmol). The mixture is stirred for 2 hours. The reaction mixture is diluted in EtOAc and washed with saturated aqueous NaHCO₃ and brine. The organic phase is dried with MgSO₄ then filtered. Silica gel is added to the solution then the solvent is removed under reduced pressure. The silica gel dry packed compound is purified by combiflash (5 to 30% EtOAc/Hex gradient) to isolate *i*-Pr-aniline **4a5**.

35

Step 5:

The coupling between *i*-Pr-aniline **4a5** and chloroarene **4a6** is performed under conditions described in example 1 step 1a. The crude product is purified by flash chromatography to afford diarylether **4a7**.

5

Step 6:

The conversion of acid **4a8** to acid chloride **4a9** is performed using the protocol described in example 1A step 3.

10 Step 7:

Diarylether **4a7** (4.96 g, 11.7 mmol) is combined with DCM (60 mL) and anhydrous pyridine (5.7 mL, 70.3 mmol). This mixture is transferred via cannula into a mixture of acid chloride **4a9** and DCM (60 mL). Finally, DMAP (0.29 g, 2.3 mmol) is added and the mixture is stirred under reflux for 20 hours. The reaction mixture is washed
15 with water, 0.5 N HCl and brine. The organic phase is dried with MgSO₄, and filtered followed by removal of the solvent under reduced pressure. The crude product is purified by flash chromatography to isolate amide **4a10**.

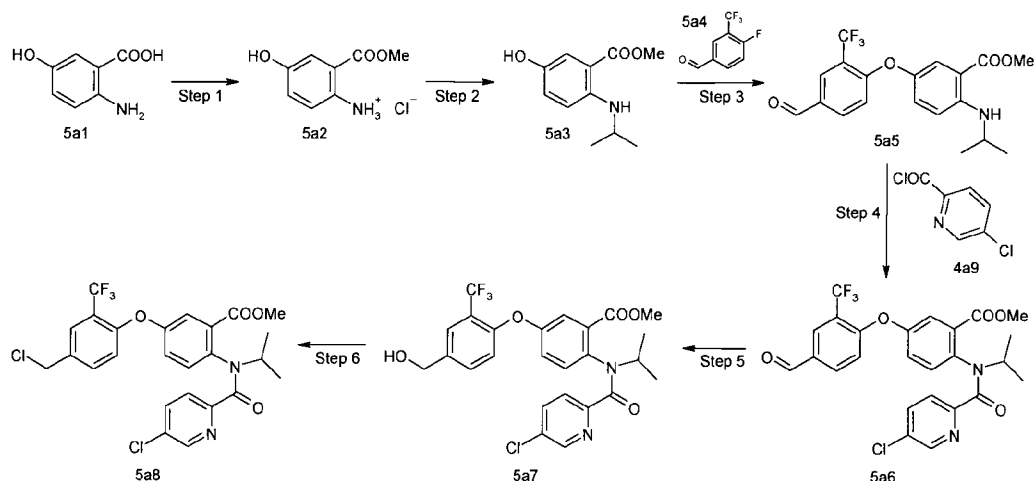
Step 8:

20 To a mixture of amide **4a10** (1.96 g, 3.6 mmol) in MeOH (20 mL) is added NaBH₄ (0.27 g, 7.3 mmol). The mixture is stirred at RT under an Ar atmosphere overnight. The mixture is diluted in EtOAc (100 ml) and washed with saturated aqueous NaHCO₃ and brine followed by drying over MgSO₄. Filtration and concentration affords alcohol **4a11** that is used without purification.

25

Step 9:

To a mixture of alcohol **4a11** (1.97 g, 3.6 mmol) in anhydrous DCM (50 mL) and anhydrous DMF (1 mL) is added SOCl₂ (0.86 g, 7.4 mmol) drop-wise. The mixture is stirred at RT for 1 hour. The mixture is diluted in EtOAc (100 mL) and washed with
30 saturated aqueous NaHCO₃ and brine, then dried over MgSO₄. After filtration and concentration *in vacuo* benzylchloride **4a12** is recovered.

EXAMPLE 5A**Preparation of intermediate 5a8****Step 1:**

To a mixture of 5-hydroxyanthranilic acid **5a1** (400 g, 2.6 mol) in MeOH (4 L) is added SOCl_2 (380 mL, 5.2 mol). The mixture is heated to reflux and stirred overnight before an additional portion of SOCl_2 is added (190 mL). The mixture is refluxed for 3 hours then allowed to cool to RT. The mixture is diluted in MeCN (6 L). The mixture is chilled to 10°C and stirred for 30 minutes. The resulting solid **5a2** is collected by filtration and washed with MeCN.

10

Step 2:

Introduction of the *i*-Pr-group to aniline hydrochloride salt **5a2** to generate **5a3** is performed as described in example 1A step 2.

Step 3:

The coupling between phenol **5a3** and fluoroarene **5a4** is performed under conditions described in example 1A step 1a. The crude product is purified by flash chromatography to afford diarylether **5a5**.

Step 4:

The coupling between diarylether **5a5** and acid chloride **4a9** to form amide **5a6** is performed under conditions described in example 4A step 7.

Step 5 & 6:

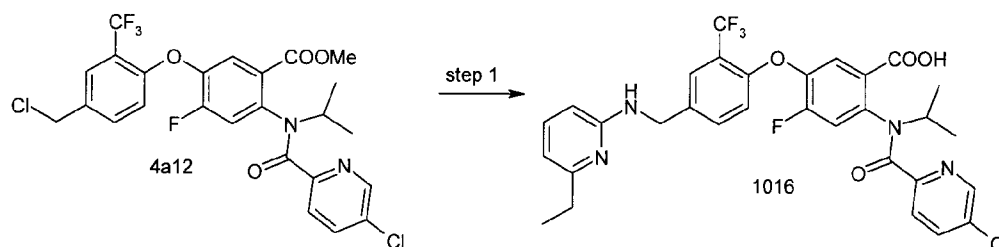
The conversion of amide **5a6** to alcohol **5a7** then to benzylchloride **5a8** is performed

using protocols described in example 4A steps 8 and 9. Final product **5a8** is purified by flash chromatography.

5 EXAMPLE 6A

Method B

Preparation of compound 1016



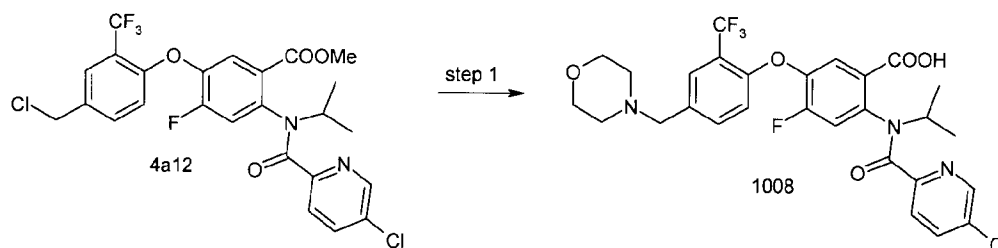
Step 1:

- 10 A mixture of benzylchloride **4a12** (56 mg, 0.1 mmol), 2-amino-6-ethylpyridine (18 mg, 0.15 mmol), Cs_2CO_3 (50 mg, 0.15 mmol), KI (6 mg, 0.04 mmol) and MgSO_4 (70 mg, 0.58 mmol) in DMF (1 mL) is agitated on a J-Kem® orbital shaker (300 rpm) at 70°C overnight. The mixture is cooled to ambient temperature, filtered and washed with DMSO (0.5 mL). Aqueous NaOH (5 N, 0.2 mL, 1.0 mmol) is added and the mixture is
- 15 agitated on a Bohdan orbital shaker (300 rpm) at RT for 2 hours. The mixture is acidified with AcOH, then purified by preparative HPLC to isolate compound **1016**.

EXAMPLE 7A

20 Method C

Preparation of compound 1008

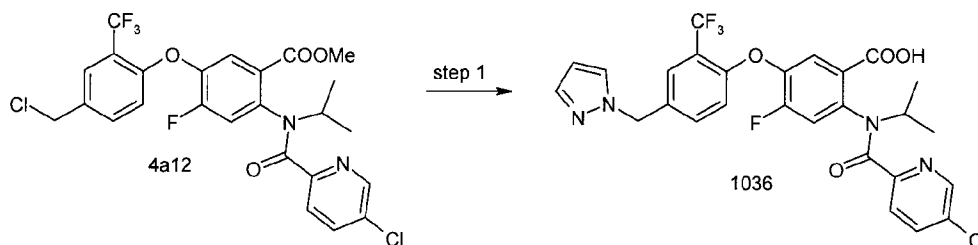


Step 1:

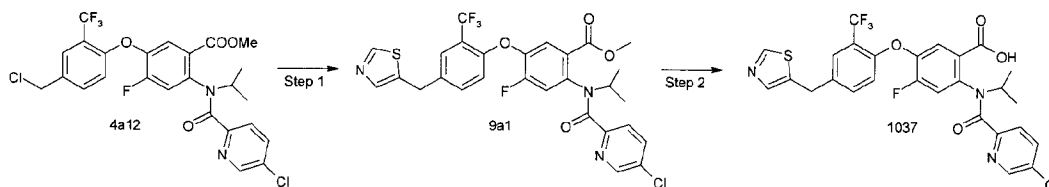
- 25 A mixture of intermediate **4a12** (56 mg, 0.1 mmol), morpholine (13 mg, 0.15 mmol) and Et_3N (0.025 mL, 0.18 mmol) in THF (2 mL) is agitated on a J-Kem® orbital shaker (300 rpm) at 70°C overnight. The mixture is concentrated under reduced

pressure using a Savant™ speed-vac and then taken up in DMSO (1 mL). Aqueous NaOH (5 N, 0.2 mL, 1.0 mmol) is added and the mixture is agitated on a Bohdan™ orbital shaker (300 rpm) at RT for 2 hours. The mixture is acidified with AcOH and purified by preparative HPLC to isolate compound **1008**.

5

EXAMPLE 8A**Preparation of compound 1036****Step 1:**

A mixture of benzylchloride **4a12** (40 mg, 0.07 mmol), pyrazole (5 mg, 0.07 mmol), K_2CO_3 (33 mg, 0.24 mmol), KI (4 mg, 0.02 mmol) in acetone (1 mL) is heated to 70°C and is stirred for 2 hours. The mixture is concentrated and the residue is taken-up in DMSO (1 mL). Aqueous NaOH (2.5 N, 0.4 mL, 1.0 mmol) is added and the mixture is heated to 50°C and is stirred for about 1 hour. The mixture is acidified with AcOH, then purified by preparative HPLC to isolate compound **1036**.

EXAMPLE 9A**METHOD D****Preparation of compound 1037****Step 1:**

To a degassed (N_2) mixture of benzylchloride **4a12** (84 mg, 0.15 mmol) in anhydrous DMF (2 mL) is added 5-tributylstannylthiazole (126 mg, 0.34 mmol) and $(Ph_3P)_4Pd$ (0) (17 mg, 0.02 mmol). The mixture is heated in a microwave at 120°C for 20

minutes. The mixture is diluted in EtOAc (50 ml) and washed with water and brine. The organic phase is dried over MgSO_4 , filtered and the solvent is removed under reduced pressure. The residue is subjected to flash chromatography (1:1 EtOAc/Hex) to isolate **9a1**.

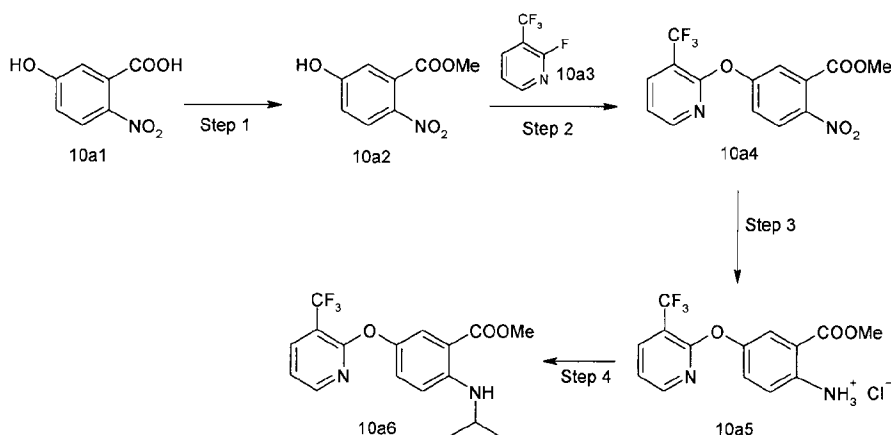
5

Step 2:

To a mixture of ester **9a1** (57 mg, 0.09 mmol) in DMSO (2 mL) and water (0.1 mL) is added aqueous LiOH (1 N, 100 μL , 0.1 mmol). The mixture is stirred overnight at RT.

More LiOH (1 N, 100 μL , 1.0 mmol) is added and stirring is continued for 1 hour.

10 The mixture is acidified with TFA, filtered then injected onto a preparative HPLC to isolate compound **1037**.

EXAMPLE 10A15 **Preparation of intermediate 10a6****Step 1:**

A mixture of carboxylic acid **10a1** (5.0 g, 27 mmol) and concentrated H_2SO_4 (4 mL) in MeOH (80 mL) is stirred at reflux for 12 hours. The mixture is concentrated under reduced pressure and poured onto a mixture of ice and saturated aqueous NaHCO_3 .

20 The aqueous mixture is acidified with citric acid and extracted twice with EtOAc. The combined organic extracts are washed with water and brine, dried with MgSO_4 , filtered, and concentrated under reduced pressure. Purification by flash chromatography (3:7 EtOAc/Hexane) affords ester **10a2**.

25 **Step 2:**

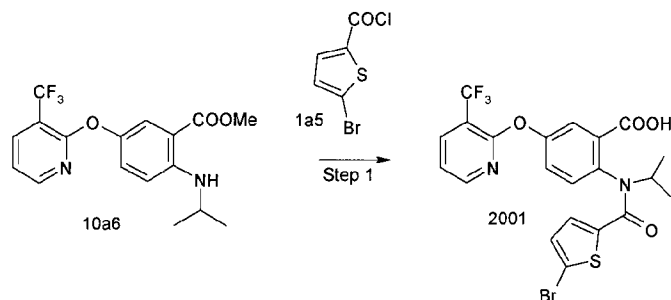
Compound **10a2** (10 g, 51 mmol), 2-fluoro-3-trifluoromethylpyridine **10a3** (10 g, 61 mmol) and K_2CO_3 (8.4 g, 61 mmol) are mixed in anhydrous DMSO (150 mL) at room temperature under an argon atmosphere. The mixture is stirred at 100°C overnight, cooled to room temperature and diluted with EtOAc (3 L). The organic phase is
5 washed with saturated NH_4Cl solution and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Addition of Et_2O and hexanes to the residue provides compound **10a4**; more compound **10a4** is obtained by concentrating the filtrate and purifying the residue by flash chromatography.

10 Step 3:

A mixture of compound **10a4** (12.5 g, 37 mmol), MeOH (600 mL) and Pd/C (1.4 g) is stirred at room temperature for 3.5 hours under H_2 (1 atm). The mixture is filtered through celite and rinsed with MeOH. The filtrate is concentrated and the residue is purified by flash chromatography (gradient; 1/4 to 2/3 EtOAc/Hexanes). A mixture of
15 the free aniline obtained and CH_2Cl_2 (250 mL) is cooled to 0°C and 2 M HCl in Et_2O (50 mL) is added. The mixture is stirred at room temperature for 1h and the hydrochloride salt **10a5** is collected by filtration, rinsed with Et_2O and air dried.

Step 4:

20 To a mixture of compound **10a5** (2.1 g, 5.9 mmol) and 2-methoxypropene (2.3 mL, 24 mmol) in CH_2Cl_2 is added $NaBH(OAc)_3$ (2.5 g, 12 mmol) portion-wise. The mixture is stirred at RT for 30 minutes, then diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic phase is dried with $MgSO_4$, filtered and concentrated under reduced pressure. Trituration of the residue in
25 hexanes/ether followed by filtration, washing (hexanes) and drying affords compound **10a6**.

EXAMPLE 11A**Method E****Preparation of compound 2001**5 **Step 1:**

To 5-bromothiophene-2-carbonyl chloride **1a5** (0.080 mmol) in an 8-mL vial is added a pyridine solution (0.5 mL) of the aniline **10a6** (20 mg, 0.056 mmol). The vial is agitated on a J-Kem® orbital shaker (250 rpm) at 80°C overnight and then concentrated. The residue is taken-up in dry pyridine (0.5 mL) containing DMAP (1.3

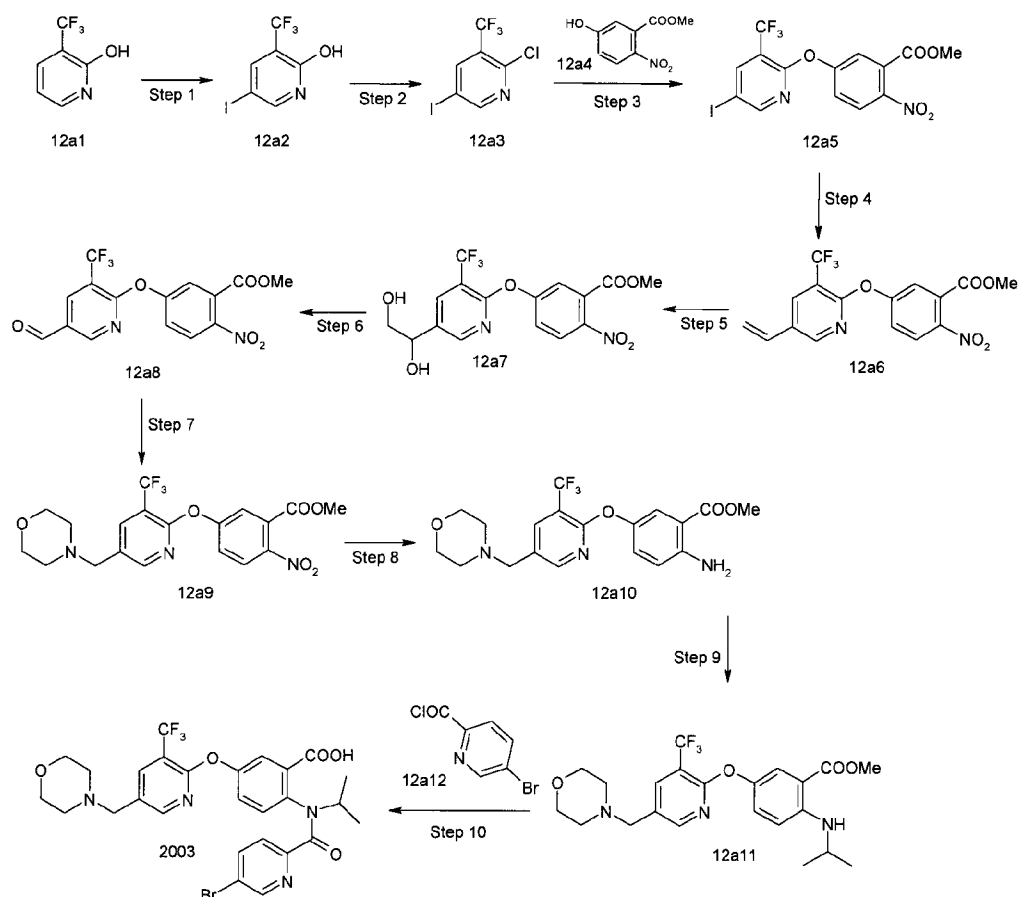
10 mg, 0.011 mmol) and treated again with 5-bromothiophene-2-carbonyl chloride (0.080 mmol). The reaction mixture is stirred overnight at 80°C. A third coupling reaction is performed at 60°C (0.08 mmol of acid chloride and 0.011 mmol of DMAP) as may be necessary in order to get a complete transformation to the desired amide.

After concentration, the crude amide is dissolved in dichloroethane (10 mL) and

15 treated with Wang resin (0.86 g, 0.95 mmol) and MP-carbonate (0.33 g, 0.95 mmol). The reaction mixture is agitated on a J-Kem® orbital shaker (250 rpm) at RT for 1hr, filtered and concentrated. The residue is then dissolved in DMSO (0.5 mL) and treated with water (50 µL) and a 10 N aqueous NaOH solution (50 µL). The reaction mixture is agitated on a Bohdan™ shaker at 450 rpm overnight at RT. Acetic acid

20 (200 µL) is added and the solution is injected onto a semi-preparative LC-MS (Column: Agilent SB-C18, 5µM, 21.2mm X 50mm; gradient: 5%-100% H₂O 0.06 % TFA / CH₃CN 0.06 % TFA; 30ml/min; 13.5min makeup: 25% H₂O 0.05% Ammonium Formate / 75% MeCN; 1ml/min). After lyophilization, **2001** is isolated.

25

EXAMPLE 12A**Preparation of compound 2003****Step 1:**

To a mixture of 2-hydroxy-3-(trifluoromethyl)pyridine **12a1** (39.01 g, 239 mmol) and anhydrous DMF (800 mL) under Ar is added *N*-iodosuccinimide (4.89 g, 244 mmol) and anhydrous K_2CO_3 (33.72 g, 244 mmol) and the mixture is allowed to stir at 60°C for about 3 hours. The mixture is cooled to ambient temperature, filtered and concentrated under reduced pressure. The residue is dissolved in DCM (1 L) and the organic phase is washed with brine. The aqueous phase is adjusted to pH 4 by the addition of 2 M HCl then extracted with DCM (1 L). The combined organic extracts are washed with brine (2 L) and dried over Na_2SO_4 . The mixture is concentrated to ~300 mL and cooled overnight in a fridge. The precipitated solid is removed by filtration and dried to provide aryl iodide **12a2**.

Step 2:

A mixture of compound **12a2** (115.7 g, 400 mmol) and $PhPOCl_2$ (668.6 g, 343 mmol)

under N₂ is stirred at 136°C overnight, then cooled to room temperature and added slowly to 3 L of crushed ice. The aqueous mixture is adjusted to pH 6 and filtered. The aqueous filtrate is extracted with DCM (3 L) then the organic phase is washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated to provide chloropyridine **12a3**.

Step 3:

The S_NAr reaction between methyl-5-hydroxy-2-nitrobenzoate **12a4** (synthesized from the corresponding benzoic acid using the conditions described example 5 step 1) and chloropyridine **12a3** to form ether **12a5** is performed in the conditions described in example 1A step 1.

Step 4:

To a degassed (Ar) mixture of compound **12a5** (1.05 g, 2.2 mmol) in anhydrous DMSO (25 mL) are added vinyltributyltin (890 μL, 3.0 mmol) and (PPh₃)₄Pd (254 mg, 0.22 mmol). The mixture is heated to 95°C for 1.5 hours. The reaction mixture is diluted in Et₂O/EtOAc (100 mL/150 mL) and washed with water and brine. The organic phase is dried over MgSO₄, filtered and the solvent is removed under reduced pressure. The residue is subjected to flash chromatography (5:1 Hexane/EtOAc) to isolate alkene **12a6**.

Step 5:

To a mixture of the alkene **12a6** (800 mg, 2.2 mmol) in acetone (710 mL) are added *tert*-BuOH (8 mL), water (5 mL), 4-*N*-methylmorpholineoxide monohydrate (60% solution in water, 565 μL, 3.3 mmol) and OsO₄ (2.5 wt % in *t*-BuOH, 365 μL). The mixture is stirred overnight at ambient temperature, then is concentrated and taken up in EtOAc (100 mL). The organic phase is washed with 1 N HCl, water, saturated aqueous NaHCO₃ and brine. The organic phase is dried over MgSO₄, filtered and the solvent is removed under reduced pressure. The residue is subjected to flash chromatography (1:2 Hexane/EtOAc) to isolate diol **12a7**.

Step 6:

Sodium periodate (460 mg, 2.2 mmol) is added to a mixture of the diol **12a7** (580 g, 1.4 mmol) in THF (10 mL) and water (5 mL). The mixture is stirred at RT overnight. The mixture is diluted with ether/EtOAc (50 mL/100 mL) then washed with water and

brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Crude aldehyde **12a8** is utilized in the next step without further purification.

Step 7:

- 5 To a mixture of the aldehyde **12a8** (510 mg, 1.4 mmol) in EtOH (6 mL) are added AcOH (87 μ L, 1.5 mmol) and morpholine (150 μ L, 1.7 mmol). The mixture is warmed to 50°C and is stirred for about 1 hour. The mixture is allowed to cool to RT and NaCNBH₃ (99 mg, 1.6 mmol) is added. The mixture is stirred at RT for about 2 hours. The mixture is diluted with ether/EtOAc (50 mL/100 mL) then washed with
- 10 saturated aqueous NaHCO₃, water and brine. The organic phase is dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is subjected to flash chromatography (1:2 Hexane/EtOAc) to isolate **12a9**.

Step 8:

- 15 Nitroarene **12a9** is reduced to aniline **12a10** using the procedure described in example 2A step 2. (note: HCl salt is not generated)

Step 9:

- To a mixture of aniline **12a10** (100 mg, 0.24 mmol) in DCM (5 mL) is added 2-methoxypropene (116 μ L, 1.2 mmol) followed by NaHB(OAc)₃ (258 mg, 1.2 mmol). The mixture is stirred overnight at RT then diluted in EtOAc and washed with saturated aqueous NaHCO₃, water and brine. The organic phase is dried over MgSO₄, filtered then concentrated under reduced pressure. Crude isopropylaniline **12a11** is utilized in the next step without further purification.

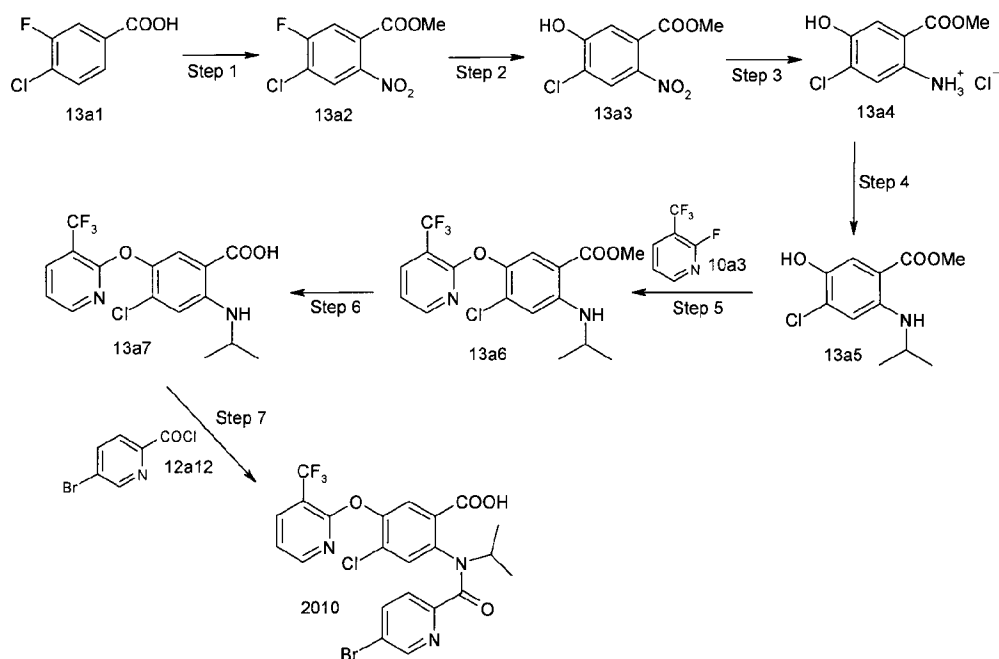
25

Step 10:

- Acid chloride **12a12** is formed from the corresponding carboxylic acid using the protocol described in example 1A step 3.
- To a mixture of *i*-Pr-aniline **12a11** (50 mg, 0.11 mmol) in anhydrous pyridine (3 mL) is added acid chloride **12a12** (0.55 mmol) and DMAP (13 mg, 0.11 mmol). The mixture is warmed to 80°C and stirs overnight. The mixture is diluted in EtOAc (50 mL) then washed with 10% citric acid, 1 N NaOH, water and brine. The organic phase is dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is taken-up in DMSO (2 mL), MeOH (1 mL) and water (0.2 mL) before

aqueous NaOH (10 N, 100 μ L, 1.0 mmol) is added. The mixture is stirred for 1 hour at RT before being acidified with TFA, filtered and injected onto a preparative HPLC to isolate compound **2003**.

5

EXAMPLE 13A**Preparation of compound 2010****Step 1:**

To a mixture of 4-chloro-3-fluorobenzoic acid **13a1** (2.00 g, 11.5 mmol) in concentrated H_2SO_4 (15 mL) chilled to 0°C is added NaNO_2 (1.16 g, 11.5 mmol) portion-wise. Once the addition of NaNO_2 is complete, the mixture is allowed to warm to RT and stirred overnight. The mixture is chilled to 0°C once again and MeOH (20 mL) is added carefully. The ice bath is removed and the mixture is heated to 100°C and stirred for about 4.5 hours. The mixture is carefully diluted into a water/ice mixture. The aqueous mixture is made basic by the addition of NaHCO_3 then is partitioned with EtOAc. The organic layer is separated then washed with water and brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Crude nitro-ester **13a2** is utilized without further purification.

Step 2:

Reference: Rogers, J. F.; Green D. M. *Tet. Lett.* **2002**, 43, 3585.

To a mixture of nitroarene **13a2** (2.57 g, 11.0 mmol) and 2-(methylsulfonyl)ethanol (1.82 g, 14.6 mmol) in anhydrous DMF (30 mL) under a N₂ atmosphere chilled to 0°C is added NaH (95%, 556 mg, 22.0 mmol). The mixture is stirred at 0°C for about 1
5 hour then stirred for 1 hour at RT. The reaction is quenched by the addition of 1 N aqueous HCl then partitioned with EtOAc. The organic phase is separated and washed with water. The organic phase is washed with 1 N NaOH (x 2). The combined aqueous washes are acidified with 1 N HCl then extracted with EtOAc (x 2). The combined organic extracts are dried over MgSO₄, filtered and concentrated
10 under reduced pressure. Crude phenol **13a3** is utilized without further purification.

Step 3:

To a mixture of nitroarene **13a3** (1.52 g, 6.6 mmol) in MeOH (15 mL) is added SnCl₂ (6.5 g, 33 mmol). The mixture is heated to reflux and stirs for 30 minutes. The
15 mixture is allowed to cool to RT then washed partitioned between EtOAc and saturated aqueous NaHCO₃. To the mixture is added celite (25 g) then the mixture is filtered. The organic phase is separated and washed with water and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is taken up in EtOAc then treated with HCl (1.0 N in ether, 8 mL, 8.0 mmol). Solid
20 aniline HCl salt **13a4** is recovered by filtration.

Step 4:

Introduction of the *i*-Pr-group to aniline hydrochloride salt **13a4** to generate **13a5** is performed as described in example 1A step 2.

25

Step 5:

The S_NAr reaction between phenol **13a5** and fluoropyridine **10a3** to form ether **13a6** is performed under the conditions described in example 1A step 1.

30 Step 6:

To a mixture of ester **13a6** (70 mg, 0.18 mmol) in THF (4 mL), MeOH (1 mL) and water (75 μL) is added NaOH (10 N, 90 μL, 0.90 mmol) and the mixture is stirred at RT overnight. The reaction is quenched by the addition of 0.5 N aqueous KHSO₄ then partitioned with EtOAc. The organic phase is separated and washed with water
35 and brine. The organic phase is dried over MgSO₄, filtered and concentrated under

reduced pressure. Crude anthranilic acid **13a7** is utilized without further purification.

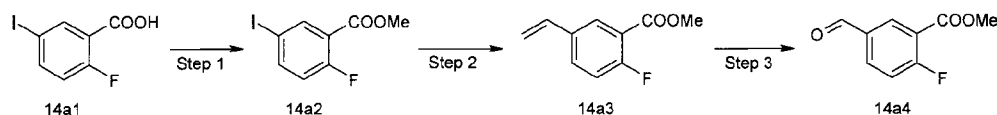
Step 7:

To a mixture of anthranilic acid **13a7** (53 mg, 0.14 mmol) in anhydrous DCE (2 mL) is added acid chloride **12a12** (44 mg, 0.27 mmol) and anhydrous pyridine (33 μ L, 0.41 mmol). The mixture is heated in a microwave oven at 150°C for 15 minutes. The mixture is diluted in DMSO (1 mL) and acidified with TFA before being partially concentrated and injected onto a preparative HPLC to isolate compound **2010**.

10

EXAMPLE 14A

Preparation of intermediate 14a4



Step 1:

To a stirring mixture of 2-iodo-5-fluorobenzoic acid **14a1** (25 g, 24 mmol) in MeCN (500 mL) and DMF (50 mL) chilled to -5 °C is added DBU (15.4 mL, 103 mmol) followed by the slow addition of MeI (8.8 mL, 141 mmol). The mixture is allowed to warm to RT and stirs overnight. The mixture is poured in water (1 L) then extracted with EtOAc (500 mL x 3). The combined organic extracts are washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude ester **14a2** is utilized without further purification.

20

Step 2:

To a mixture of iodoarene **14a2** (22.3 g, 79 mmol) in dioxane (200 mL) is added tributylvinyltin (20 mL, 68 mmol). The mixture is degassed (Ar) before (Ph₃P)₄Pd (2.4 g, 2.1 mmol) is added. The mixture is refluxed for about 1 hour then stirred at RT overnight. The mixture is concentrated under reduced pressure and the resulting residue is subjected to flash chromatography to isolate alkene **14a3**.

25

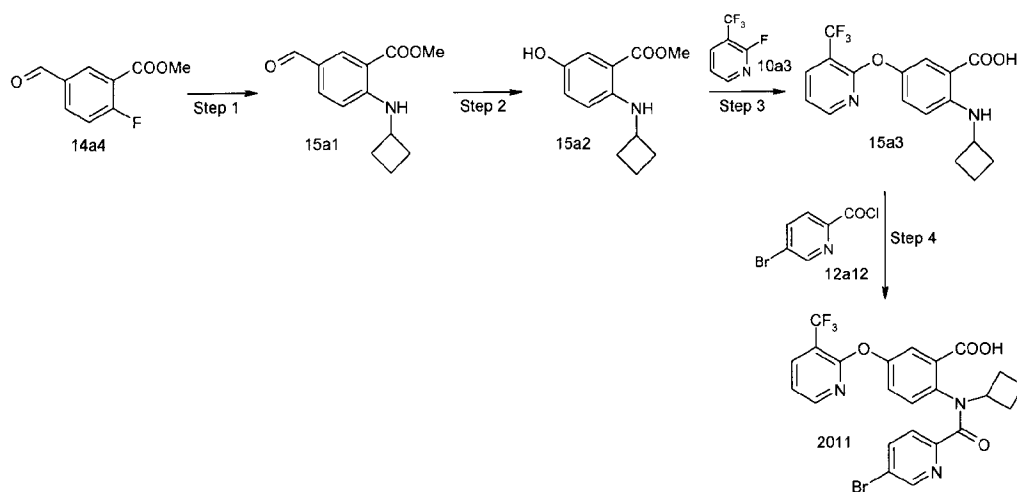
Step 3:

To a mixture of alkene **14a3** (9.6 g, 89 mmol) in THF (360 mL) and water (270 mL) is added OsO₄ (2.5% solution in *t*-BuOH, 5.4 mL) followed by the portion-wise addition of NaIO₄ (34 g, 160 mmol). The mixture is stirred for about 2 hours at RT before

30

being partially concentrated and diluted in EtOAc. The organic phase is washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue is subjected to flash chromatography to isolate aldehyde **14a4**.

5

EXAMPLE 15A**METHOD F****Preparation of compound 2011****Step 1:**

- 10 To an 8-mL vial are successively added K₂CO₃ (46 mg, 0.33 mmol), aldehyde **14a4** (50 mg, 0.275 mmol in 0.5 mL DMSO) and cyclobutylamine (98 mg, 1.4 mmol). The mixture is agitated on a J-Kem® orbital shaker (270 rpm) at 70°C overnight. Water (1 mL) and concentrated HCl (0.7 mL) are added to the mixture. The mixture is heated at 70°C for 3 hrs, extracted with EtOAc (2 mL) and washed three times with
- 15 water. After concentration the crude aniline **15a1** is obtained and used as such in the following transformation.

Step 2:

- To the crude amine **15a1** obtained above in methanol (1.5 mL in an 8-mL vial) at 2°C
- 20 are successively added hydrogen peroxide (43 μL of a 30% aqueous solution) and concentrated H₂SO₄ (20 μL). The mixture is agitated on a J-Kem® orbital shaker (290 rpm) at 2°C for 15 minutes and then a saturated aqueous solution of NaCl is added (2 mL). The mixture is extracted twice with EtOAc (2 mL and 1 mL) and the combined organic extracts are successively washed with water (1 mL) and brine (1

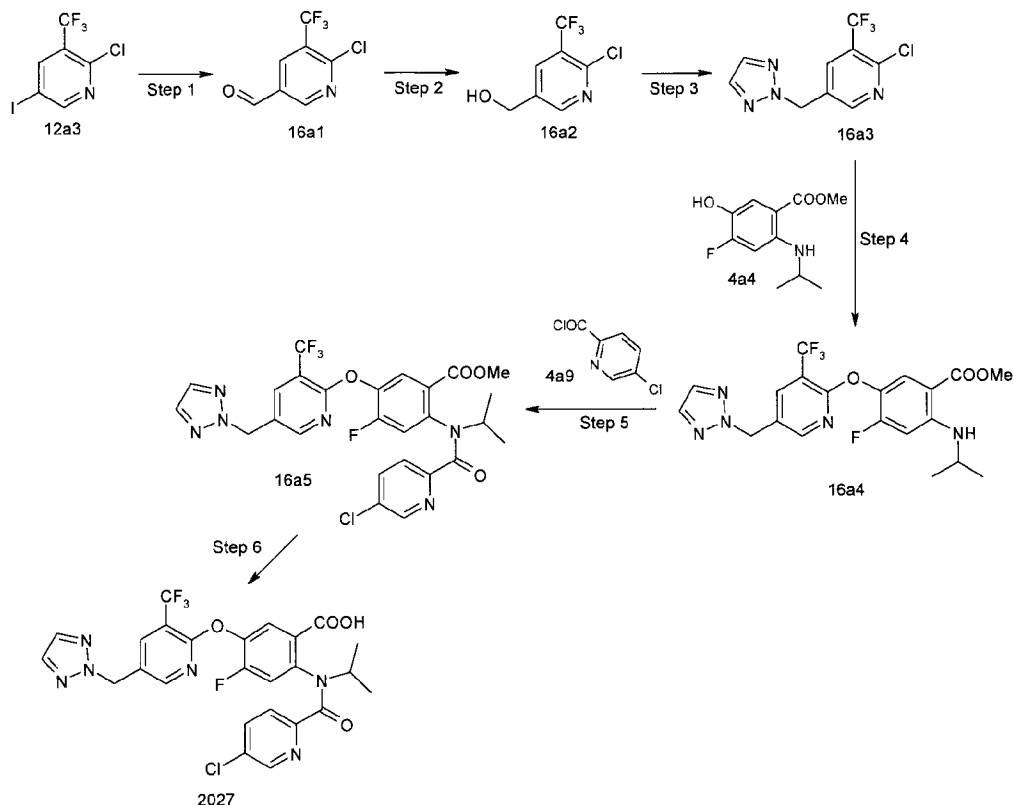
mL). The organic phase is dried with MgSO_4 , filtered and concentrated to afford the crude phenol **15a2** which is used as such in the following transformation.

Step 3:

- 5 To the crude phenol **15a2** obtained above in dry DMSO (0.5 mL) are successively added K_2CO_3 (133 mg, 0.96 mmol) and 2-fluoro-3-trifluoromethylpyridine **10a3** (40 μL , 0.33 mmol). The suspension is agitated overnight on a J-Kem® orbital shaker (290 rpm) at 85°C. Aqueous sodium hydroxide solution (5 N, 250 μL) is added at RT and the reaction mixture is agitated at 50°C for 3 hours. After acidification using a 1
- 10 N aq. KHSO_4 solution, the mixture is extracted three times with EtOAc. The combined organic extracts are successively washed with water and brine, dried over MgSO_4 and filtered. After concentration, the residue is dissolved in a mixture of DMSO and AcOH (1.5 mL) and purified by reverse phase preparative LC-MS. Conditions; column: Agilent SB-C18, 5 μM , 21.2mm X 50mm; gradient: 5% to 100%
- 15 H_2O 0.06 % TFA / CH_3CN 0.06 % TFA; flow: 30ml/min for 13.5min; makeup: 25% H_2O 0.05% Ammonium formate / 75% MeCN; 1ml/min. After lyophilization the desired compound **15a3** is isolated.

Step 4:

- 20 To a mixture of aniline **15a3** (11.1 mg, 0.032 mmol) in DCE (0.3 mL) is added acid chloride **12a12** (7.1 mg, 0.044 mmol) and pyridine (11.0 μL , 0.136mmol). The mixture is heated at 150°C for 15 minutes in a microwave. After concentration, the residue is dissolved in DMSO and AcOH, and purified by reverse phase preparative LC-MS. Conditions; column: Agilent SB-C18, 5 μM , 21.2mm X 50mm; gradient: 5%
- 25 to 100% H_2O 0.06 % TFA / CH_3CN 0.06 % TFA; flow: 30ml/min for 13.5min; makeup: 25% H_2O 0.05% Ammonium formate / 75% MeCN; 1ml/min. After lyophilization compound **2011** is isolated.

EXAMPLE 16A**Preparation of compound 2027****Step 1:**

Iodide **12a3** (10 g, 32.5 mmol) is combined with a 1:3 mixture of anhydrous THF and
 5 anhydrous toluene (100 mL) under an argon atmosphere. The mixture is cooled to -
 78 °C then *n*-BuLi (1.6 M in hexanes, 24 mL, 38.4 mmol) is added slowly by syringe
 over about 40 minutes. Stirring is continued for about 1 hour before ethylformate
 (3.2 mL, 39.7 mmol) in THF (10 mL) is added over a period of about 40 minutes.
 The mixture is stirred for about 1 hour before being quenched by the addition of 2 M
 10 HCl. The mixture is partitioned between EtOAc and saturated aqueous NaHCO₃.
 The organic phase is washed with brine and dried over Na₂SO₄. The mixture is
 filtered and concentrated under reduced pressure. Purification is performed by flash
 chromatography where the silica gel is pre-treated with 3% NEt₃ in hexanes then
 eluted with 1:1 EtOAc/Hex to isolate aldehyde **16a1**.

15

Step 2:

A mixture of aldehyde **16a1** (19 g, 81 mmol) in methanol (225 mL) is chilled to 0°C.
 Sodium borohydride (4.1 g, 109 mmol) is added portion-wise and the mixture is

stirred at 0°C for about 1.5 hours. Another portion of NaBH₄ (1 g) is added and the mixture is stirred for another 30 minutes. The reaction is quenched by the addition of NaHSO₄ (5% aqueous) then diluted in EtOAc (500 mL). The organic phase is separated then washed with water (500 mL) and brine. The organic phase is dried
5 over Na₂SO₄, filtered then concentrated under reduced pressure. The residue is subjected to flash chromatography (1:1 EtOAc/Hex) to isolate alcohol **16a2**.

Step 3:

Alcohol **16a2** (10.5 g, 48 mmol) is combined with triazole (3.42 g, 48 mmol) and
10 triphenylphosphine (14.3 g, 54 mmol) in anhydrous THF (500 mL). The mixture is chilled to 0°C and DIAD (10.6 mL, 54 mmol) is added drop-wise. Stirring continues at 0°C for about 1 hour before the mixture is allowed to warm to ambient temperature and is then stirred overnight. The mixture is diluted in EtOAc and washed with water (500 mL) and brine (500 mL) before being dried over Na₂SO₄. The solvents are
15 removed under reduced pressure and the residue is subject to flash chromatography (1:3 EtOAc/Hex) to afford benzylic triazole **16a3**.

Step 4:

Phenol **4a4** is coupled to chloropyridine **16a3** using reaction conditions described in
20 example 1A step 1a.

Step 5:

To a mixture of aniline **16a4** (445 mg, 0.98 mmol) in anhydrous DCE (10 mL) is added acid chloride **4a9** (249 mg, 1.4 mmol) and anhydrous pyridine (325 μL, 4.0
25 mmol). The mixture is heated in a microwave oven at 100°C for about 10 minutes twice. The mixture is diluted in EtOAc and washed with saturated aqueous NaHCO₃ (x 2) and brine. The organic phase is dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is subject to flash chromatography (2:3
EtOAc/Hex) to isolate amide **16a5**.

30

Step 6:

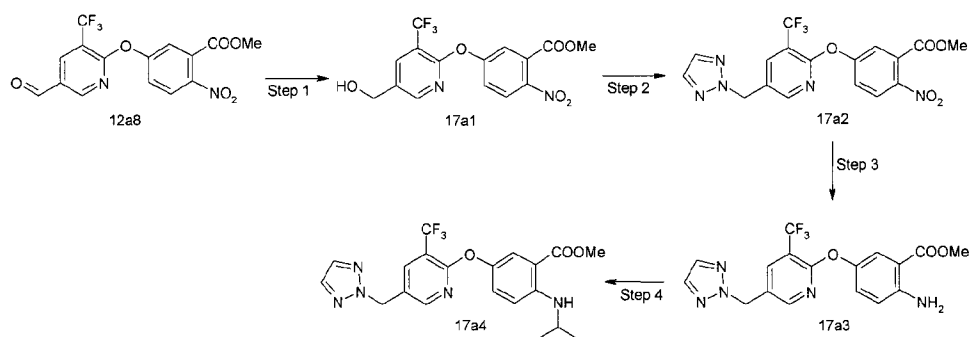
To a mixture of ester **16a5** (385 mg, 0.65 mmol) in DMSO (6 mL) is added aqueous NaOH (2.5 N, 1.8 mL, 4.5 mmol). The mixture stirs at RT for about 1 hour. The mixture is diluted in water then treated with AcOH. The resulting solid is recovered
35 by filtration then taken up in MeCN and water, frozen and lyophilized to provide

compound **2027**.

EXAMPLE 17A

5 METHOD G

Preparation of intermediate **17a4**



Step 1:

The conversion of aldehyde **12a8** to alcohol **17a1** is performed using protocol described in example 4A step 8.

10

Step 2:

Triazole **17a2** is prepared from alcohol **17a1** using protocol described in example 16A step 3.

15 Step 3:

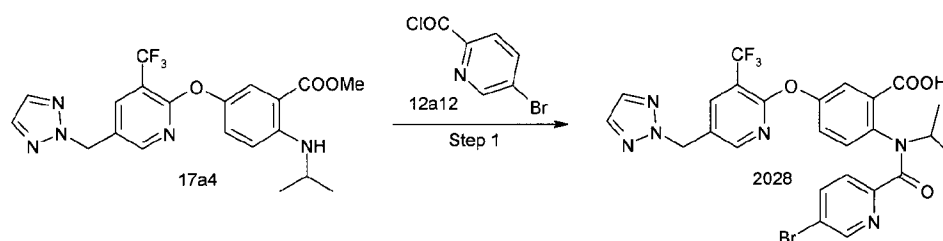
Nitroarene **17a2** (503 mg, 1.2 mmol) is dissolved in EtOAc (10mL) under a stream of nitrogen. Pd/C (100 mg) is added and the degassing is continued for about 2 minutes. Hydrogen is then bubbled through the mixture for about 5 minutes and then the mixture is stirred under hydrogen (1 atm) overnight at RT. The mixture is filtered through celite. The filtrate is concentrated and the residue is purified by combiflash (20% EtOAc/Hex to EtOAc) to yield aniline **17a3**.

20

Step 4:

Introduction of the *i*-Pr-group to aniline **17a3** to generate **17a4** is performed as described in example 4A step 4.

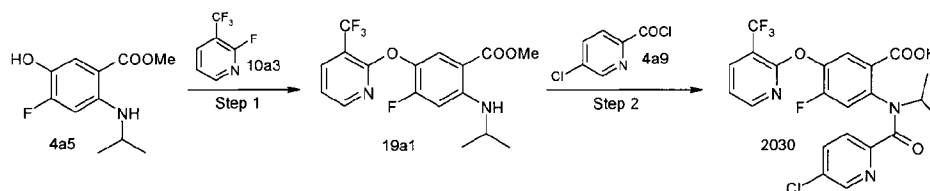
25

EXAMPLE 18A**METHOD G****Preparation of compound 2028**

5

Step 1:

To a mixture of aniline **17a4** (33 mg, 0.07 mmol) in anhydrous DCE (1 mL) is added acid chloride **12a12** (85mg, 0.39 mmol), DMAP (14 mg, 0.11 mmol) and anhydrous pyridine (30 μ L, 0.37 mmol). The mixture is heated in a microwave oven at 150°C for 15 minutes. The mixture is diluted in EtOAc and washed with saturated aqueous NaHCO₃ (x 3) and brine. The organic phase is dried over MgSO₄, filtered and concentrated. The residue is taken-up in THF (1 mL) and MeOH (0.5 mL) and NaOH (10 N, 100 μ L, 1.0 mmol) is added and the mixture stirs overnight at RT. The mixture is acidified with TFA before being filtered and injected onto a preparative HPLC to isolate compound **2028**.

EXAMPLE 19A**Preparation of compound 2030****Step 1:**

The coupling between phenol **4a5** and fluoropyridine **10a3** is performed under conditions described in example 1 step 1a. The crude product is purified by flash chromatography (1:9 EtOAc/Hex) to afford ether **19a1**.

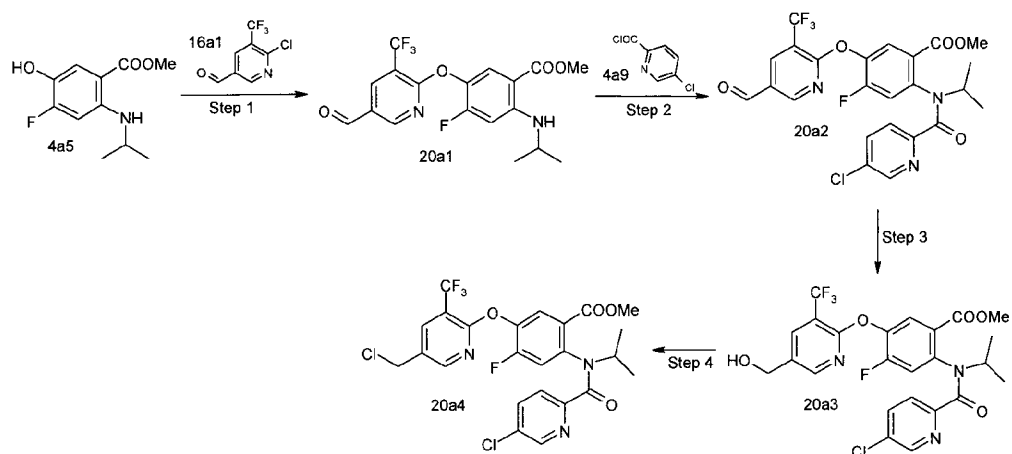
Step 2:

Coupling of aniline **19a1** to acid chloride **4a9**, followed by saponification to form

compound **2030** is performed as described in example 16A steps 5 & 6.

EXAMPLE 20A

5 Preparation of intermediate **20a4**



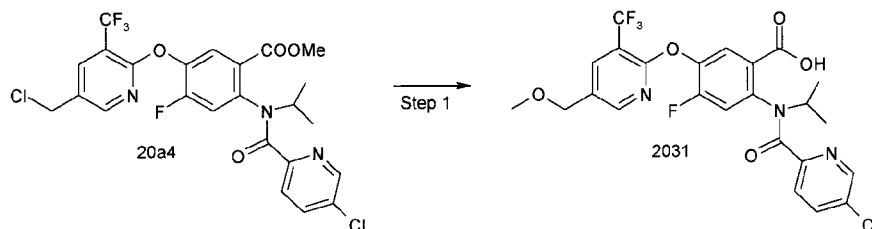
Steps 1-4:

The sequence demonstrated in example 4A steps 5 to 9 is used to provide intermediate **20a4**.

10

EXAMPLE 21A

Preparation of compound **2031**

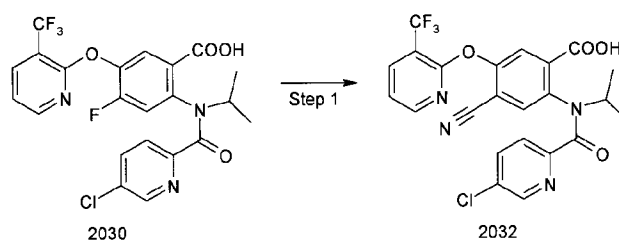


Step 1:

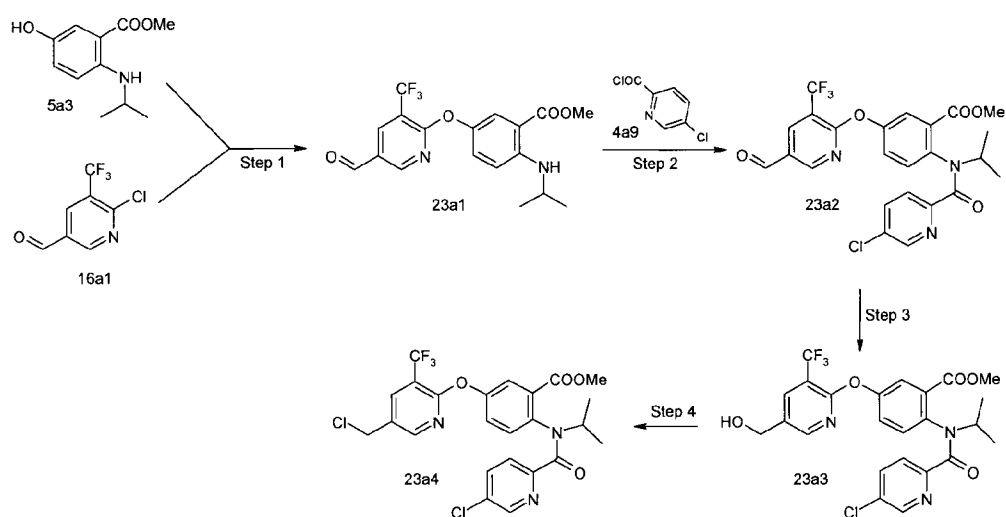
Sodium methoxide (25% in MeOH, 17 μ L, 0.08 mmol) is added to a mixture of benzyl chloride **20a4** (40 mg, 0.07 mmol) in MeOH (5 mL) then stirred at ambient temperature for about 16 hours. DMSO (1 mL) is added, followed by NaOH (2.5 N, 240 μ L, 0.6 mmol) and the mixture is stirred for about 1 hour at ambient temperature.

The mixture is acidified with AcOH, concentrated to 2 mL under reduced pressure, and injected into a preparative HPLC to isolated compound **2031**.

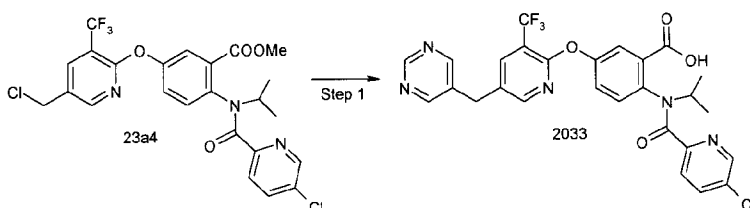
20

EXAMPLE 22A**METHOD H****Preparation of compound 2032****Step 1:**

- 5 To a mixture of compound 2030 (106 mg, 0.21 mmol) in DCM (5 mL) is added CH_2N_2 (solution in ether) until the characteristic yellow colour persists. The mixture is concentrated and the residue is taken-up in DMSO (1 mL) then NaCN (78 mg, 1.2 mmol) is added. The mixture is heated to 150°C for 20 minutes in a microwave oven until saponification of the ester is observed. The mixture is then injected onto the
- 10 preparative HPLC to isolate **2032**.

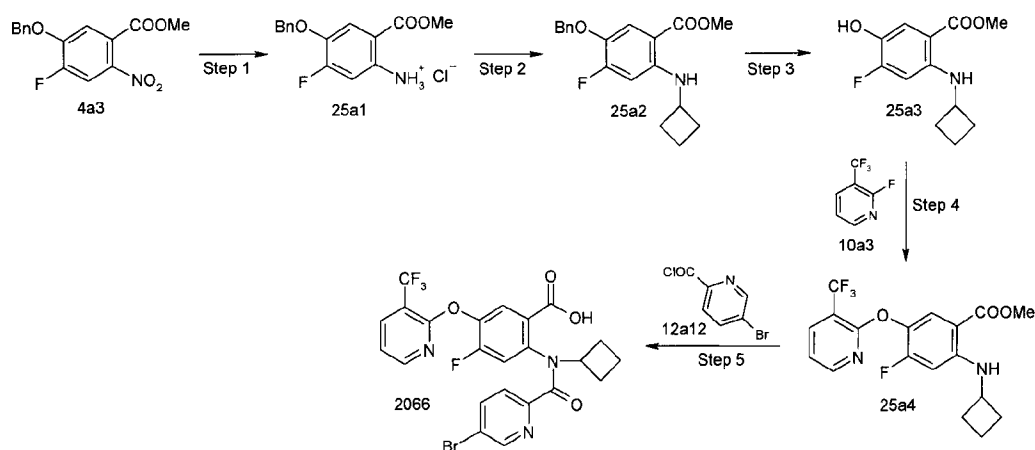
EXAMPLE 23A**Preparation of intermediate 23a4****Steps 1-4:**

The sequence demonstrated in example 4A steps 5 to 9 is used to provide intermediate **23a4**.

EXAMPLE 24A**METHOD F****Preparation of compound 2033****5 Step 1:**

Protocol adapted from: Nobre, S. M.; Monteiro, A. L. *Tet. Lett.* **2004**, *45*, 8225.

Triphenylphosphine (10 mg, 0.04 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), powdered K₃PO₄ (81 mg, 0.38 mmol), 5-pyrimidylboronic acid (35 mg, 0.28 mmol) and
 10 benzylchloride **23a4** (52 mg, 0.09 mmol) are combined in degassed (N₂) DMF (2.5 mL). The mixture is heated with stirring at 120°C for 20 minutes in a microwave oven. The mixture is diluted in DMSO (2 mL) / MeOH (1 mL) / water (0.3 mL) then NaOH (10 N, 350 μL, 3.5 mmol) is added. The mixture is stirred for about 1.5 hours at RT. The mixture is acidified with TFA, partially concentrated, filtered then injected
 15 onto a preparative HPLC to isolate compound **2033**.

EXAMPLE 25A**Preparation of compound 2066**

20

Step 1a:

The nitro intermediate **4a3** (63.8 g, 212 mmol) is diluted in THF (1 L). Aqueous

hydrochloric acid (1 M, 500 mL) is added followed by tin powder (55 g, 467 mmol). The mixture is stirred for about 2 hours at RT. The reaction mixture is then diluted in EtOAc and the pH of the mixture is adjusted to 7 by the addition of 1 N NaOH. The organic phase is separated then washed with water and brine. The organic phase is
5 then dried over NaSO₄ and solvent is removed to afford an aniline.

Step 1b:

The aniline (97.1 g, 377 mmol) is combined with anhydrous Et₂O (1 L) and the mixture is treated by the slow addition of HCl (2 M in ether, 2 L). The resulting
10 hydrochloride salt **25a1** is collected by filtration and washed with excess ether.

Step 2:

Reference: Apodacca, R.; Xiao, W. *Org. Lett.* **2001**, 3, 1745.

15 The HCl salt of **25a1** is converted to the free amine by washing a solution in EtOAc several times with saturated aqueous NaHCO₃. The organic phase is dried with MgSO₄, filtered and the solvent is removed under reduced pressure.

To a mixture of free base aniline **25a1** (275 mg, 1.0 mmol) in THF (5 mL) is added
20 cyclobutanone (150 μL, 2.0 mmol) followed by Bu₂SnCl₂ (15 mg, 0.05 mmol). The mixture is stirred for about 5 minutes at RT before phenylsilane (140 μL, 1.1 mmol) is added. The mixture is stirred for about 4 days at RT before dilution with saturated aqueous NaHCO₃ followed by extraction with EtOAc (x 2). The combined organic extracts are dried over MgSO₄, filtered and concentrated. The residue is subjected
25 to flash chromatography to provide cyclobutylaniline **25a2**.

Step 3:

To a mixture of benzylether **25a2** (265 mg, 0.8 mmol) in EtOH (5 mL) and EtOAc (2 mL) under a N₂ atmosphere is added 10% Pd/C (20 mg). The vessel is purged with
30 H₂ and is stirred at RT under 1 atm of H₂ overnight. The mixture is filtered through celite and the solvent is removed *in vacuo* to afford phenol **25a3**.

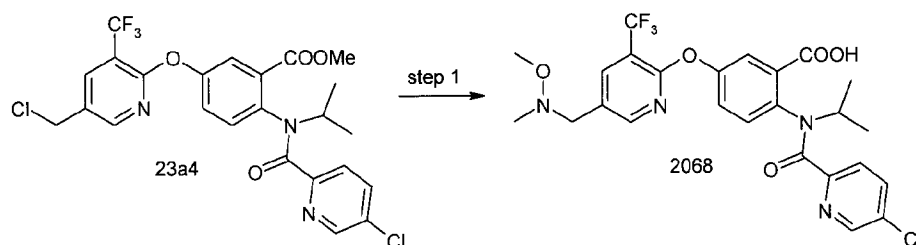
Step 4:

The S_NAr coupling of phenol **25a3** with fluoropyridine **10a3** to produce intermediate
35 **25a4** is performed as described in example 1A step 1.

Step 5:

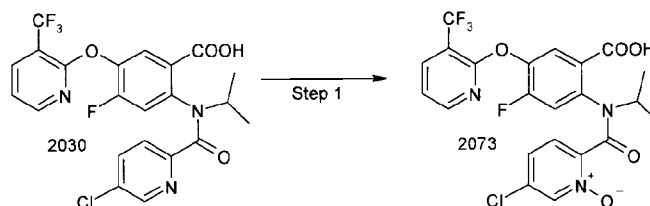
Aniline **25a4** is coupled to acid chloride **12a12** followed by saponification to prepared compound **2066** using the protocol described in example 18A step 1.

5

EXAMPLE 26A**Preparation of compound 2068****Step 1:**

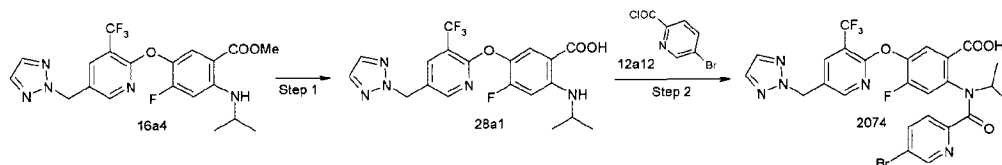
A mixture of benzylchloride **23a4** (50 mg, 0.09 mmol), *N,O*-dimethylhydroxylamine hydrochloride (13 mg, 0.14 mmol) and Et₃N (0.026 mL, 0.18 mmol) in DMF (1 mL) is stirred at 70°C overnight. After the mixture cools to RT, MeOH (0.5 mL) and LiOH·H₂O (39 mg, 0.9 mmol) are added and the mixture is stirred at RT overnight. The mixture is acidified with AcOH and then purified by preparative HPLC to isolate compound **2068**.

15

EXAMPLE 27A**Preparation of compound 2073****Step 1:**

To a mixture of compound **2030** (40 mg, 0.08 mmol) in DCM (1 mL) is added *m*-CPBA (19 mg, 0.09 mmol). The mixture is stirred overnight at RT. Another portion of *m*-CPBA is added and the mixture is stirred again for an additional day. The mixture is concentrated and the residue is taken-up in AcOH and then injected onto a preparative HPLC to isolate compound **2073**.

25

EXAMPLE 28A**METHOD J****5 Preparation of compound 2074****Step 1:**

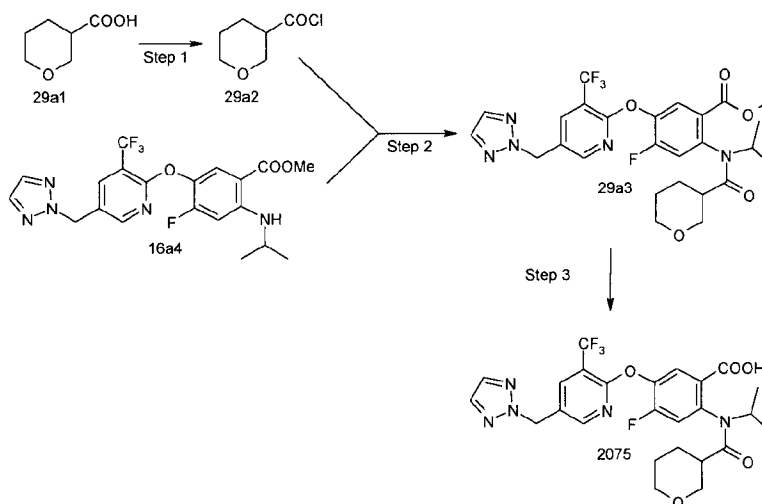
Saponification of ester **16a4** to acid **28a1** is performed as described in example 13A step 6.

10

Step 2:

Coupling of aniline **28a1** to acid chloride **12a12** to form compound **2074** is performed as described in example 13A step 7.

15

EXAMPLE 29A**METHOD K****Preparation of compound 2075****20 Step 1:**

Acid chloride **29a2** is prepared from acid **29a1** using the protocol described in example 1A step 3.

Step 2:

To a mixture of aniline **16a4** (90 mg, 0.20 mmol) in anhydrous DCE (2 mL) is added acid chloride **29a2** (208 mg, 1.4 mmol) and anhydrous pyridine (243 μ L, 3.0 mmol).

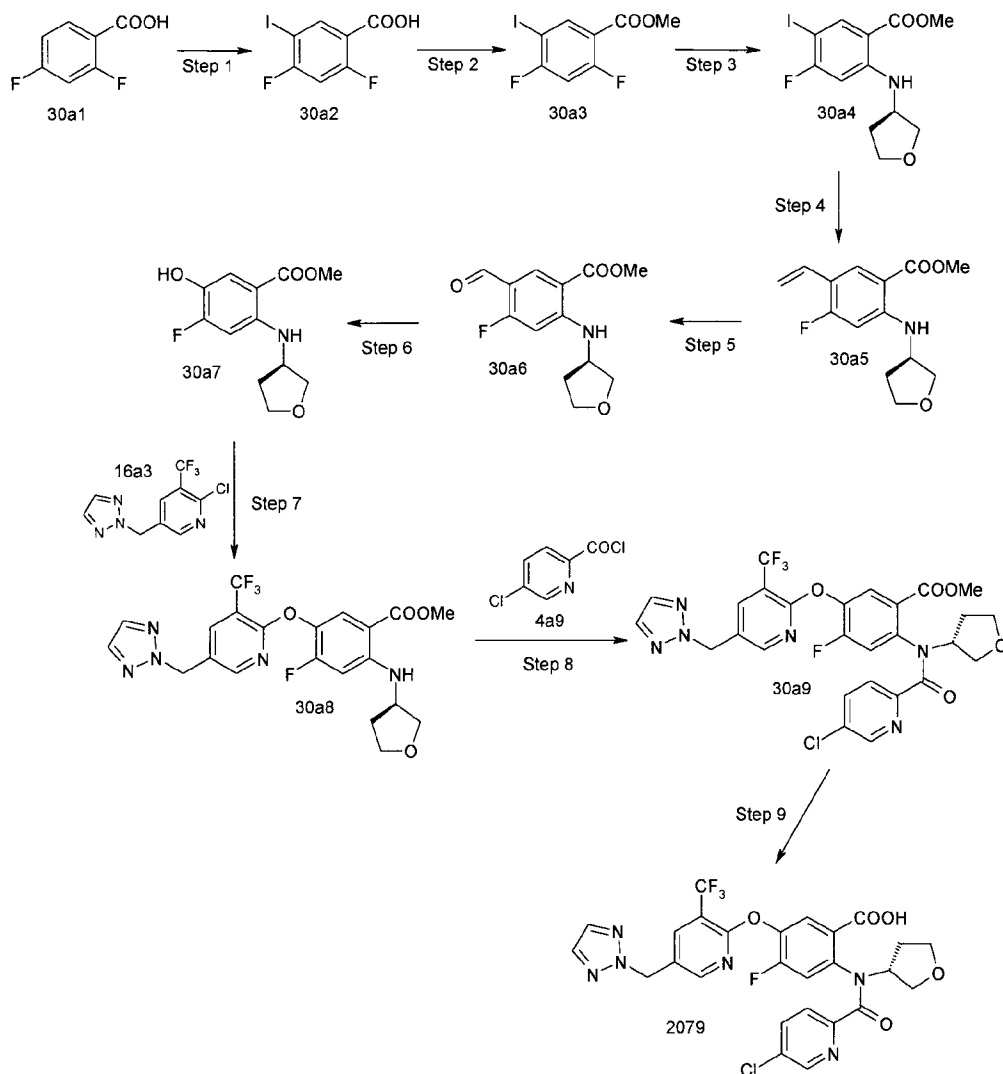
- 5 The mixture is heated in a microwave oven at 170°C for about 30 minutes. The mixture is diluted in EtOAc and washed with saturated aqueous NaHCO₃ and brine. The organic phase is dried over Na₂SO₄ and filtered. Silica gel is added to the filtrate and the mixture is concentrated. The silica gel dry-packed column is subjected to flash chromatography (30 to 90% EtOAc in Hex) to isolate amide **29a3**.

10

Step 2:

To a mixture of ester **29a3** (57 mg, 0.1 mmol) in THF (2 mL) and DMSO (0.5 mL) is added aqueous NaOH (5 N, 200 μ L, 1.0 mmol). The mixture is warmed to 50°C and is stirred for about 1 hour. The mixture is acidified with AcOH (0.5 mL) before being

- 15 filtered and injected onto a preparative HPLC to isolate compound **2075**.

EXAMPLE 30A**Preparation of compound 2079****Step 1:**

Reference: PCT/JP2005/009604

5

To a mixture of 2,4-difluorobenzoic acid **30a1** (5.00 g, 31.6 mmol) in concentrated H₂SO₄ (20 mL) chilled to -5°C is added NIS (6.83 g, 30.4 mmol) portion-wise. The mixture is allowed to warm to RT and stirred overnight. The mixture is poured over ice then diluted with 10% aqueous sodium sulfite. The resulting solid is collected by

10 filtration and washed with excess water (200 mL). The solid is taken-up in hot aqueous ethanol (50%) and the mixture is allowed to cool to RT (~1 hour), then chilled to 0°C. The solid **30a2** is recovered by filtration.

Step 2:

A mixture of acid **30a2** (37 g, 130 mmol) and concentrated H₂SO₄ (9 mL) in MeOH (200 mL) is heated to reflux and stirred overnight. The mixture is allowed to cool to
5 RT before being partially concentrated. The residue is diluted in EtOAc then washed with saturated aqueous NaHCO₃ (x 3) and brine. The organic phase is dried over Na₂SO₄, filtered and concentrated to afford methyl ester **30a3**.

Step 3:

10 To a mixture of difluoroarene **30a3** (1.00 g, 3.4 mmol) in DMF (30 mL) is added K₂CO₃ (700 mg, 5.0 mmol) and (*R*)-tetrahydrofuran-3-amine-HCl (415 mg, 3.4 mmol). The mixture is heated to about 75°C and stirred overnight. The mixture is partitioned between water and EtOAc. The organic phase is separated then washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄, filtered and
15 concentrated. The residue is subjected to flash chromatography (0 to 30% EtOAc in Hex) to isolate aniline **30a4**.

Step 4:

To a mixture of iodoarene **30a4** (413 mg, 1.1 mmol) in DMF (12 mL) is added
20 tributylvinyltin (396 µL, 1.4 mmol) and (Ph₃P)₄Pd (131 mg, 0.11 mmol). The mixture is degassed (Ar) before the vessel is sealed, then heated to about 110°C and stirred for about 2.5 hours. The mixture is allowed to cool to RT then is diluted in EtOAc and washed with saturated aqueous NaHCO₃ and brine. The organic phase is dried over Na₂SO₄, filtered and concentrated. The residue is subjected to flash
25 chromatography (0 to 30% EtOAc in Hex) to isolate alkene **30a5**.

Step 5a:

To a mixture of alkene **30a5** (287 mg, 1.1 mmol) in acetone (7 mL), *t*-BuOH (2 mL) and water (1.5 mL), chilled to 0°C, is added OsO₄ (2.5% solution in *t*-BuOH, 676 µL,
30 0.05 mmol) and NMO (190 mg, 1.6 mmol). The mixture is stirred for about 2 hours at 0°C before being poured into 10% aqueous Na₂S₂O₃. The aqueous mixture is extracted with EtOAc (x 2). The combined organic phases are washed with 10% aqueous Na₂S₂O₃ and brine, dried over Na₂SO₄, filtered and concentrated. The diol is utilized in the next step without further purification.

35

Step 5b:

The residue from above is taken-up in THF (4.5 mL) and water (4.5 mL). The resulting mixture is chilled to 0°C and NaIO₄ (34 g, 160 mmol) is added. The mixture stirs for 2 hours at 0°C before being diluted in saturated aqueous NaHCO₃. The aqueous mixture is extracted with EtOAc (x 2). The combined organic phases are washed with saturated aqueous NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated. The residue is subjected to flash chromatography (10 to 30% EtOAc in Hex) to isolate aldehyde **30a6**.

10 Step 6:

To a mixture of aldehyde **30a6** (206 mg, 0.77 mmol) in MeOH (1.5 mL), chilled to 0°C, is added concentrated H₂SO₄ (72 µL, 1.2 mmol) and hydrogen peroxide (30% aqueous solution, 131 µL, 1.2 mmol). The mixture is stirred at 0°C for 1.5 hour before the mixture is diluted in 10% aqueous KH₂PO₄. The aqueous mixture is extracted with Et₂O. The organic phase is washed with 10% aqueous KH₂PO₄ and brine (x 3). The combined aqueous phases are back-extracted with Et₂O and the organic phase is washed with 10% aqueous KH₂PO₄ and brine (x 3). The combined organic phases are dried over Na₂SO₄, filtered and concentrated. Crude phenol **30a7** is utilized in the next step without further purification.

20

Step 7:

To a mixture of phenol **30a7** (197 mg, 0.77 mmol) and chloropyridine **16a3** (203 mg, 0.77 mmol) in DMSO (3 mL) is added Cs₂CO₃ (376 mg, 1.2 mmol). The mixture is heated to 65°C and stirs for 1 hour. The mixture is diluted in saturated aqueous NaHCO₃ then extracted with EtOAc (x2). The combined organic extracts are washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue is subjected to flash chromatography (10 to 50% EtOAc in Hex) to isolate ether **30a8**.

30 Step 8:

To a mixture of aniline **30a8** (135 mg, 0.28 mmol) in anhydrous DCE (3 mL) is added acid chloride **4a9** (99 mg, 0.56 mmol), DMAP (3 mg, 0.03 mmol) and anhydrous pyridine (131 µL, 1.7 mmol). The mixture is heated in a microwave oven at 140°C for about 1 hour. The mixture is diluted in EtOAc and washed with 1 N HCl, water, saturated aqueous NaHCO₃ and brine. The organic phase is dried over Na₂SO₄,

35

filtered and concentrated. The residue is subjected to flash chromatography (20 to 100% EtOAc in Hex) to isolate ether **30a9**.

Step 9:

- 5 Ester **30a9** is converted to compound **2079** using conditions described in example 29A step 2.

EXAMPLE 31

Inhibition of NS5B RNA dependent RNA polymerase activity

- 10 Representative compounds of the invention are tested for inhibitory activity against the hepatitis C virus RNA dependent polymerase (NS5B), according to the protocol described below.

The HCV His-NS5B Δ 21 polymerase [**SEQ ID NO.1**] lacks the C-terminal 21 amino acids and is expressed with an N-terminal hexa-histidine tag from a pET-based
15 vector in *E. coli* strain JM109(DE3) and purified as described in McKercher et al., (2004) Nucleic Acids Res. **32**: 422-431. The homogeneous enzyme preparation is stored at -20°C in storage buffer (25 mM Tris/HCl pH 7.5, 300 mM NaCl, 5 mM DTT, 1 M EDTA and 30%(v/v) glycerol).

The purified His-NS5B Δ 21 polymerase is reconstituted in an assay that measures
20 the incorporation of ³H-UTP during the elongation of a biotin-oligo-(U)₁₂ RNA primer annealed to a homopolymeric poly(A) template. The test compound is added first, followed by the substrate, then the enzyme. At the end of the reaction, streptavidin scintillation proximity assay (SPA) beads are added and the radioactivity from the captured double-stranded RNA product is quantified on TopCount instrument
25 (Packard).

The components of the assay reaction are: 20 mM Tris-HCl pH 7.5, 1 mM TCEP, 1 mM EDTA, 5 mM MgCl₂, 0.01% w/v BSA, 5% v/v DMSO, 10 µg/mL Poly(A), 1 µg/mL Biotin-oligo-(U)₁₂, 333 nM UTP, 0.01 mCi/mL, (300 nM) ³H-UTP, 80 units/mL Rnasin, 12.5 nM His-NS5B Δ 21 polymerase and test inhibitor compound that is serially diluted
30 over a large concentration range. The assay is performed in 384-well plates with a 1.5 hour incubation at about 22°C, and then stopped with a solution of 0.5 M EDTA and the products captured with Streptavidin-coated beads. Following the addition of 6 M CsCl to the bottom of each well, the plate is left at room temperature for about 90 minutes before counting for 60 seconds on a TopCount. The calculated %
35 inhibition values are then used to determine IC₅₀, slope factor (n) and maximum

inhibition (I_{\max}) by the non-linear regression routine NLIN procedure of SAS.

EXAMPLE 32

Specificity of NS5B RNA dependent RNA polymerase inhibition

5 Representative compounds of the invention are tested for inhibitory activity against polio virus RNA dependent RNA polymerase and calf thymus DNA dependent RNA polymerase II as described in McKercher et al., (2004) Nucleic Acids Res. **32**: 422-431.

10 EXAMPLE 33

Cell-based luciferase reporter HCV RNA Replication Assay

Representative compounds of the invention are tested for activity as inhibitors of hepatitis C virus RNA replication in cells expressing a stable subgenomic HCV replicon, using the assay described in WO 2005/028501, herein incorporated by
15 reference.

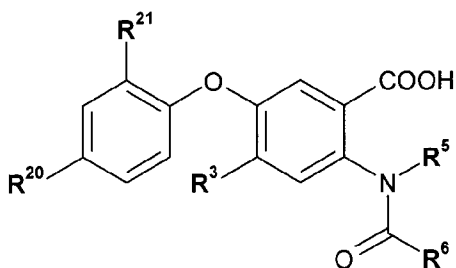
TABLES OF COMPOUNDS

The following tables list compounds representative of the invention. Representative compounds listed in Tables 1 and 2 below are tested in the assay of Example 31
20 and are found to have IC_{50} value below 30 μ M. Representative compounds listed in Tables 1 and 2 below are tested in the assay of Example 33 and are found to have a EC_{50} values below 30 μ M.

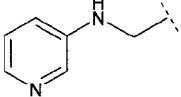

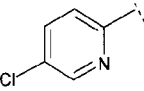
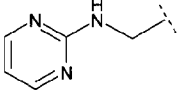

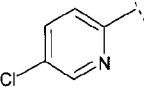
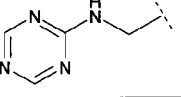

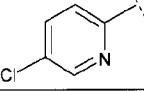
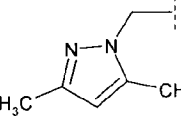

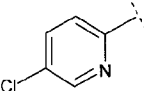
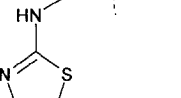

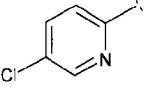
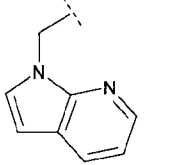

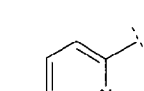
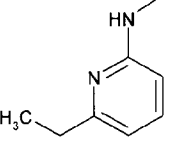

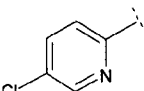
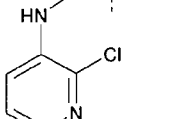

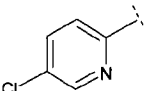
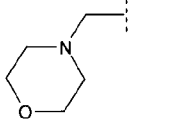

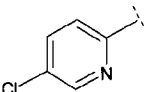
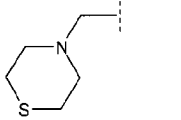

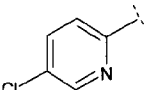
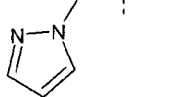

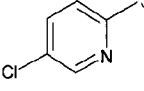
Retention times (t_R) for each compound are measured using the standard analytical HPLC conditions described in the Examples. As is well known to one skilled in the
25 art, retention time values are sensitive to the specific measurement conditions. Therefore, even if identical conditions of solvent, flow rate, linear gradient, and the like are used, the retention time values may vary when measured, for example, on different HPLC instruments. Even when measured on the same instrument, the values may vary when measured, for example, using different individual HPLC
30 columns, or, when measured on the same instrument and the same individual column, the values may vary, for example, between individual measurements taken on different occasions.

35

Table 1



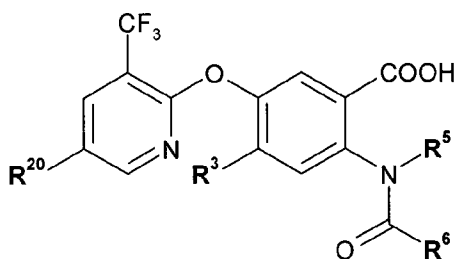
Cpd	R ²⁰	R ²¹	R ³	R ⁵	R ⁶	t _R (min)	m/z (MH) ⁺	Method
1001	H	H	H			6.6	462.1	EX 1A
1002	H	CF ₃	H			6.2	465.1	EX 3A A
1003	H	CF ₃	H			6	462.1	A
1004		CF ₃	F			5.1	604	B
1005		CF ₃	F			7.1	621	B
1006		CF ₃	H			4.8	586.1	B
1007		CF ₃	H			7.0	603	B
1008		CF ₃	F			4.5	596	EX 7A C
1009		CF ₃	F			4.8	612	C

Cpd	R ²⁰	R ²¹	R ³	R ⁵	R ⁶	t _R (min)	m/z (MH) ⁺	Method
1010		CF ₃	F			4.9	603	B
1011		CF ₃	F			5.5	604	B
1012		CF ₃	F			5.4	605	B
1013		CF ₃	F			6.5	605.1	B
1014		CF ₃	F			4.9	609	B
1015		CF ₃	F			6.9	627	B
1016		CF ₃	F			5.2	631.1	EX 6A B
1017		CF ₃	F			7.0	637	B
1018		CF ₃	H			4.3	578.1	C
1019		CF ₃	H			4.5	594.1	C
1020		CF ₃	H			6.3	559.1	B


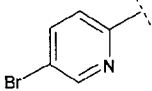

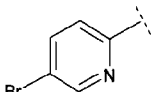

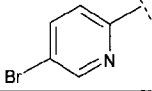

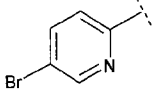

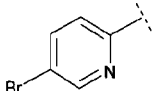

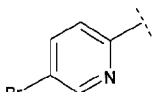

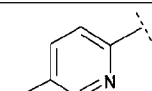

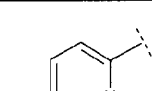

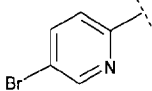

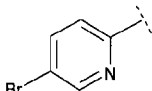
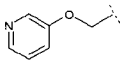

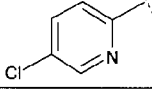
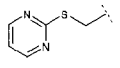

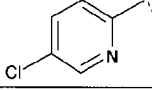
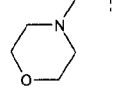

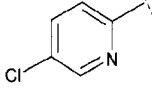
Cpd	R ²⁰	R ²¹	R ³	R ⁵	R ⁶	t _R (min)	m/z (MH) ⁺	Method
1021		CF ₃	H			4.6	585.1	B
1022		CF ₃	H			5.3	586.1	B
1023		CF ₃	H			5.1	587	B
1024		CF ₃	H			6.3	587.1	B
1025		CF ₃	H			4.7	591	B
1026		CF ₃	H			6.7	609.1	B
1027		CF ₃	H			7.2	609.1	B
1028		CF ₃	H			5.0	613.1	B
1029		CF ₃	H			6.9	619	B
1030		CF ₃	F			4.6	609	B

Cpd	R ²⁰	R ²¹	R ³	R ⁵	R ⁶	t _R (min)	m/z (MH) ⁺	Method
1031		CF ₃	F			4.9	627.1	B
1032		CF ₃	F			7.1	627	B
1033		CF ₃	H			4.4	591	B
1034		CF ₃	H			6.9	609.1	B
1035		CF ₃	H			4.6	609.1	B
1036		CF ₃	F			6.1	577.3	EX 8A
1037		CF ₃	F			6.7	594.1	EX 9A D

Table 2



Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	m/z (MH) ⁺	Method
2001	H	H			6.9	528.9	EX 11A E
2002	H	H			6.3	523.9	E
2003		H			4.3	623.1	EX 12A
2004	H	H			7	518.9	E
2005	H	H			6.4	541	E
2006	H	H			6.8	548	E
2007	H	H			6.5	514	E
2008	H	H			6.2	480	E
2009	H	H			5.4	480	E
2010	H	Cl			5.8	557.9	EX 13A

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	m/z (MH) ⁺	Method
2011	H	H			6.5	536	EX 15A F
2012	H	H			7.3	566	F
2013	H	H			6.7	538	F
2014	H	H			7.1	552	F
2015	H	H			6.8	564	F
2016	H	H			7.0	552	F
2017	H	H			6.8	538	F
2018	H	H			7.1	552	F
2019	H	H			5.6	600	F
2020	H	H			7.1	552	F
2021		F			4.8	605	B
2022		F			6.9	622	B
2023		F			4.4	597.1	C

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	m/z (MH) ⁺	Method
2024		F			4.6	613	C
2025	H	H			6.3	577	F
2026	H	H			6.1	522	F
2027		F			6.2	579.0	EX 16A
2028		H			6.6	605.0	EX 18A G
2029		H			6.5	561.1	G
2030	H	F			6.2	497.9	EX 19A
2031	-CH ₂ OCH ₃	F			6.3	542.0	EX 21A
2032	H	CN			5.9	505.0	EX 22A H
2033		H			5.1	572.1	EX 24A I
2034		F			5.3	590.1	I
2035		CN			5.9	586.1	H
2036		F			4.7	589.1	I

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	m/z (MH) ⁺	Method
2037		H			4.6	587.1	B
2038		H			6.7	604	B
2039		F			6.3	578	B
2040		F			4.6	604	B
2041		F			5.5	605	B
2042		F			5.9	605	B
2043		F			6.4	606.1	B
2044		F			4.7	610	B
2045		F			6.8	628	B
2046		F			7.2	628	B
2047		F			5.1	632.1	B
2048		F			6.8	638	B
2049		H			4.2	579.1	C
2050		H			4.3	595	C

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	m/z (MH) ⁺	Method
2051		H			6.0	560.1	B
2052		H			4.4	586.1	B
2053		H			5.1	587.1	B
2054		H			6.2	588.1	B
2055		H			4.5	592	B
2056		H			6.6	610.1	B
2057		H			7.0	610.1	B
2058		H			4.8	614.1	B
2059		H			6.6	620	B
2060		F			4.5	610.0	B
2061		F			4.7	628	B
2062		F			7.0	628	B
2063		H			4.3	592	B

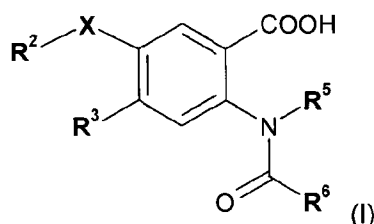
Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	m/z (MH) ⁺	Method
2064		H			4.5	610.1	B
2065		H			6.7	610.1	B
2066	H	F			7.1	556.0	EX 25A
2067		H			6.1	545.1	G
2068		H			5.4	552.1	EX 26A
2069		F			5.1	631.3	C
2070		F			5.1	617.3	C
2071		F			5.2	675.3	C
2072		F			5.2	661.3	C
2073	H	F			5.3	514.1	EX 27A
2074		F			6.5	625.1	EX 28A J
2075		F			6.1	552.1	EX 29A K
2076		F			6.5	595.1	D

Cpd	R ²⁰	R ³	R ⁵	R ⁶	t _R (min)	m/z (MH) ⁺	Method
2077		F			5.8	552.2	K
2078		F			5.7	584.2	J
2079		F			6.1	607.2	EX 30A
2080	H	H			7.1	552	F

All of the documents cited herein are incorporated into the application by reference, as if each of them is individually incorporated. Further, it would be appreciated that in the teachings of the invention, those skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application.

CLAIMS

1. A compound of formula (I):



5

wherein:

X is selected from O and S;

R² is **Het** or aryl, optionally substituted with 1 to 5 **R²⁰** substituents, wherein **R²⁰** in each case is independently selected from:

- 10 a) halo, cyano or nitro;
 b) **R⁷**, -C(=O)-**R⁷**, -C(=O)-O-**R⁷**, -O-**R⁷**, -S-**R⁷**, -SO-**R⁷**, -SO₂-**R⁷**,
 -(C₁₋₆)alkylene-**R⁷**, -(C₁₋₆)alkylene-C(=O)-**R⁷**,
 -(C₁₋₆)alkylene-C(=O)-O-**R⁷**, -(C₁₋₆)alkylene-O-**R⁷**, -(C₁₋₆)alkylene-S-**R⁷**,
 -(C₁₋₆)alkylene-SO-**R⁷** or -(C₁₋₆)alkylene-SO₂-**R⁷**;

15 wherein **R⁷** is in each instance independently selected from H,
 (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl,
 aryl and **Het**;

wherein the (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₂₋₆)alkynyl, (C₃₋₇)cycloalkyl and
 (C₁₋₆)alkylene are optionally substituted with 1 or 2 substituents each
 20 independently selected from -OH, -(C₁₋₆)alkyl, halo, -(C₁₋₆)haloalkyl,
 (C₃₋₇)cycloalkyl, -O-(C₁₋₆)alkyl, cyano, COOH, -NH₂, -NH(C₁₋₄)alkyl,
 -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and -N((C₁₋₄)alkyl)₂;
 and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3
 25 substituents each independently selected from:

- i) halo, cyano, oxo, thioxo, imino, -OH, -O-(C₁₋₆)alkyl,
 -O-(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, (C₁₋₆)haloalkyl,
 -C(=O)-(C₁₋₆)alkyl, -SO₂(C₁₋₆)alkyl, -C(=O)-NH₂,
 -C(=O)-NH(C₁₋₄)alkyl, -C(=O)-N((C₁₋₄)alkyl)₂,
 30 -C(=O)-NH(C₃₋₇)cycloalkyl,
 -C(=O)-N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl,

- N((C₁₋₄)alkyl)₂, -NH(C₃₋₇)cycloalkyl,
 -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl or -NH-C(=O)(C₁₋₄)alkyl;
- ii) (C₁₋₆)alkyl optionally substituted with -OH, -O-(C₁₋₆)haloalkyl,
 or -O-(C₁₋₆)alkyl; and
- 5 iii) aryl or **Het**, wherein each of the aryl and **Het** is optionally
 substituted with halo or (C₁₋₆)alkyl; and
- c) -N(R⁸)R⁹, -C(=O)-N(R⁸)R⁹, -O-C(=O)-N(R⁸)R⁹, -SO₂-N(R⁸)R⁹,
 -(C₁₋₆)alkylene-N(R⁸)R⁹, -(C₁₋₆)alkylene-C(=O)-N(R⁸)R⁹,
 -(C₁₋₆)alkylene-O-C(=O)-N(R⁸)R⁹, or -(C₁₋₆)alkylene-SO₂-N(R⁸)R⁹;
 10 wherein the (C₁₋₆)alkylene is optionally substituted with 1 or 2
 substituents each independently selected from -OH, -(C₁₋₆)alkyl, halo,
 -(C₁₋₆)haloalkyl (C₃₋₇)cycloalkyl, -O-(C₁₋₆)alkyl, cyano, COOH, -NH₂,
 -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and
 -N((C₁₋₄)alkyl)₂;
- 15 R⁸ is in each instance independently selected from H, (C₁₋₆)alkyl and
 (C₃₋₇)cycloalkyl; and
 R⁹ is in each instance independently selected from R⁷, -O-(C₁₋₆)alkyl,
 -(C₁₋₆)alkylene-R⁷, -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and
 -C(=O)N(R⁸)R⁷; wherein R⁷ and R⁸ are as defined above;
- 20 or R⁸ and R⁹, together with the N to which they are attached,
 are linked to form a 4- to 7-membered heterocycle optionally further
 containing 1 to 3 heteroatoms each independently selected from N, O
 and S, wherein each S heteroatom may, independently and where
 possible, exist in an oxidized state such that it is further bonded to
 25 one or two oxygen atoms to form the groups SO or SO₂;
 wherein the heterocycle is optionally substituted with 1 to 3
 substituents each independently selected from (C₁₋₆)alkyl,
 (C₁₋₆)haloalkyl, halo, oxo, -OH, SH, -O(C₁₋₆)alkyl, -S(C₁₋₆)alkyl,
 (C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂,
 30 -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl
 and -NHC(=O)-(C₁₋₆)alkyl;
- R³ is selected from H, halo, CN, (C₁₋₄)alkyl, -OH, -O-(C₁₋₄)alkyl, -S-(C₁₋₄)alkyl, -NH₂,
 -NH(C₁₋₄)alkyl, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl and
 -N((C₁₋₄)alkyl)₂;
- 35 R⁵ is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, (C₃₋₇)cycloalkyl-(C₁₋₆)alkyl- or **Het**; the (C₁₋₆)alkyl

and **Het** each being optionally substituted with 1 to 4 substituents each independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, **Het**, -OH, -COOH, -C(=O)-(C₁₋₆)alkyl, -C(=O)-O-(C₁₋₆)alkyl, -SO₂(C₁₋₆)alkyl and -C(=O)-N(R⁵¹)R⁵²;

5 wherein R⁵¹ is H, (C₁₋₆)alkyl or (C₃₋₇)cycloalkyl; and

R⁵² is H, (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, **Het**, aryl-(C₁₋₃)alkyl- or **Het**-(C₁₋₃)alkyl-;

wherein each of the (C₁₋₆)alkyl, (C₃₋₇)cycloalkyl, aryl, **Het**, aryl-(C₁₋₃)alkyl- and **Het**-(C₁₋₃)alkyl- are optionally substituted with 1 to 3 substituents each independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, halo, oxo, -OH, -O(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl and -NHC(=O)-(C₁₋₆)alkyl;

wherein the (C₁₋₆)alkyl is optionally substituted with OH; or R⁵¹ and R⁵², together with the N to which they are attached, are linked to form a 4- to 7-membered heterocycle optionally further containing 1 to 3 heteroatoms each independently selected from N, O and S, wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂;

wherein the heterocycle is optionally substituted with 1 to 3 substituents each independently selected from (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, halo, oxo, -OH, -O(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₆)alkyl, -N((C₁₋₆)alkyl)₂, -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -C(=O)(C₁₋₆)alkyl and -NHC(=O)-(C₁₋₆)alkyl;

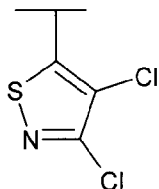
wherein the (C₁₋₆)alkyl is optionally substituted with OH;

R⁶ is **Het**; being optionally substituted with 1 to 5 substituents each independently selected from halo, (C₁₋₆)alkyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -OH, -SH, -O-(C₁₋₄)alkyl, -S-(C₁₋₄)alkyl and -N(R⁸)R⁹; wherein R⁸ and R⁹ are as defined above; and

30 **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen

atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂; or a salt or ester thereof;

5 with the proviso that when X is O, R² is phenyl, R³ is H and R⁵ is H, then R⁶ is not



2. The compound according to claim 1 wherein X is O.

10 3. The compound according to claim 1 wherein X is S.

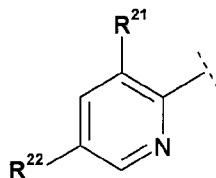
4. The compound according to any one of claims 1 to 3, wherein R² is **Het** wherein **Het** is a 5- or 6-membered aromatic heterocycle containing 1 or 2 N heteroatoms, or a 9- or 10-membered bicyclic heteropolycycle containing 1 or 2 N heteroatoms; wherein **Het** is optionally substituted with 1 to 3 R²⁰ substituents, wherein R²⁰ is as defined in claim 1.

5. The compound according to claim 4 wherein R² is **Het** of the formula:



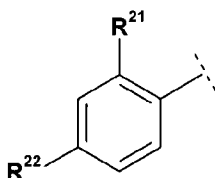
20 wherein **Het** is optionally substituted with 1 to 3 R²⁰ substituents, wherein R²⁰ is as defined in claim 1.

6. The compound according to claim 5 wherein R² is of the formula:



wherein R^{21} is selected from H, halo, (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7}) cycloalkyl and $-O-(C_{1-6})$ haloalkyl; and
and R^{22} is R^{20} wherein R^{20} is as defined in claim 1.

- 5 **7.** The compound according to claim 6 wherein R^{21} is CF_3
- 8.** The compound according to any one of claims 1 to 3 wherein R^2 is phenyl optionally substituted with 1 to 3 R^{20} wherein R^{20} is as defined in claim 1.
- 10 **9.** The compound according to claim 8 wherein R^2 is a group of formula:



wherein R^{21} is selected from H, halo, (C_{1-6}) alkyl, (C_{1-6}) haloalkyl, (C_{3-7}) cycloalkyl and $-O-(C_{1-6})$ haloalkyl; and
and R^{22} is R^{20} wherein R^{20} is as defined in claim 1.

15

- 10.** The compound according to claim 9 wherein R^{21} is CF_3 .
- 11.** The compound according to any one of claims 1 to 10 wherein R^{20} is selected from:

20

- a) halo, cyano or nitro;
- b) R^7 , $-(C_{1-6})$ alkylene- R^7 , $-C(=O)-R^7$, $-O-R^7$, $-C(=O)-O-R^7$, $-(C_{1-6})$ alkylene- $O-R^7$, $-S-R^7$, $-SO_2-R^7$, $-(C_{1-6})$ alkylene- $S-R^7$ or $-(C_{1-6})$ alkylene- SO_2-R^7 ;

25

wherein R^7 is in each instance independently selected from H, (C_{1-6}) alkyl, (C_{2-6}) alkenyl, (C_{1-6}) haloalkyl, (C_{3-7}) cycloalkyl, aryl and **Het**; wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S, or **Het** is a 9- or 10-membered heteropolycycle containing 1 to 4 heteroatoms, each independently selected from N, O and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form

30

an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to one or two oxygen atoms to form the groups SO or SO₂; and

5 wherein the (C₁₋₆)alkyl is optionally substituted with 1 or 2 substituents each independently selected from -OH, -O-(C₁₋₆)alkyl and COOH; and

wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, cyano, oxo, imino, -OH, -O-(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -N((C₁₋₄)alkyl)₂,
 10 -NH-C(=O)(C₁₋₄)alkyl, (C₁₋₆)alkyl and **Het**, wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S; and

c) -N(R⁸)R⁹, -(C₁₋₆)alkylene-N(R⁸)R⁹ or -(C₁₋₆)alkylene-C(=O)-N(R⁸)R⁹
 15 wherein

R⁸ is in each instance independently selected from H and (C₁₋₆)alkyl; and

R⁹ is in each instance independently selected from R⁷, -O-(C₁₋₆)alkyl, -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and -C(=O)N(R⁸)R⁷; wherein R⁷ and
 20 R⁸ are as defined above.

12. The compound according claim 11 wherein R²⁰ is selected from:

b) R⁷, -(C₁₋₆)alkylene-R⁷, -C(=O)-R⁷, -(C₁₋₆)alkylene-O-R⁷, -SO₂-R⁷,
 25 -(C₁₋₆)alkylene-S-R⁷ or -(C₁₋₆)alkylene-SO₂-R⁷;

wherein R⁷ is in each instance independently selected from H, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, aryl and **Het**; wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each independently selected from N, O and S, or **Het** is a 9- or 10-membered heteropolycycle containing 1 to 4 heteroatoms, each independently selected from N, O and S; wherein each N heteroatom may, independently and where possible, exist in an oxidized state such that it is further bonded to an oxygen atom to form an N-oxide group and wherein each S heteroatom may, independently and where possible, exist in an oxidized state such that
 30 it is further bonded to one or two oxygen atoms to form the groups SO
 35

or SO₂; and

wherein the (C₁₋₆)alkyl is optionally substituted with 1 or 2 substituents each independently selected from -OH, -O-(C₁₋₆)alkyl and COOH;

and

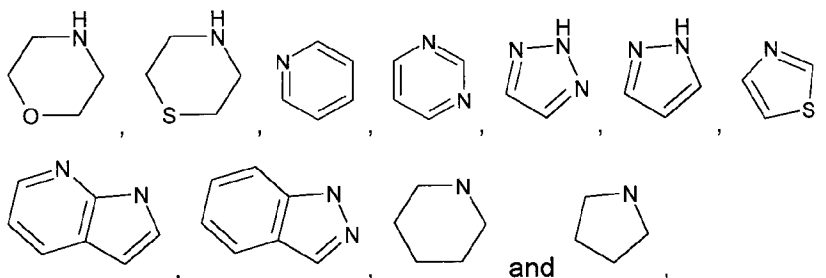
5 wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, cyano, oxo, imino, -OH, -O-(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -N((C₁₋₄)alkyl)₂, -NH-C(=O)(C₁₋₄)alkyl, (C₁₋₆)alkyl and **Het**, wherein the **Het** is a 5- or 6-membered heterocycle containing 1 to 4 heteroatoms, each
10 independently selected from N, O and S; and

c) -(C₁₋₆)alkylene-N(R⁸)R⁹ or -(C₁₋₆)alkylene-C(=O)-N(R⁸)R⁹ wherein R⁸ is in each instance independently selected from H and (C₁₋₆)alkyl;
and

15 R⁹ is in each instance independently selected from R⁷, -O-(C₁₋₆)alkyl, -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and -C(=O)N(R⁸)R⁷; wherein R⁷ and R⁸ are as defined above.

13. The compound according to claim 12 wherein R²⁰ is selected from:

20 b) R⁷, -(C₁₋₆)alkylene-R⁷, -C(=O)-R⁷, -(C₁₋₆)alkylene-O-R⁷, -SO₂-R⁷, -(C₁₋₆)alkylene-S-R⁷ or -(C₁₋₆)alkylene-SO₂-R⁷; wherein R⁷ is in each instance independently selected from H, (C₁₋₆)alkyl, (C₂₋₆)alkenyl, (C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, aryl and **Het**; wherein the **Het** is selected from the group:



wherein the (C₁₋₆)alkyl is optionally substituted with 1 or 2 substituents each independently selected from -OH, -O-(C₁₋₆)alkyl and COOH;
and

30 wherein each of the aryl and **Het** is optionally substituted with 1 to 3 substituents each independently selected from halo, cyano, oxo,

imino, -OH, -O-(C₁₋₆)alkyl, -NH₂, -NH(C₁₋₄)alkyl, -N((C₁₋₄)alkyl)₂,
 -NH-C(=O)(C₁₋₄)alkyl, (C₁₋₆)alkyl and **Het**, wherein the **Het** is a 5- or 6-
 membered heterocycle containing 1 to 4 heteroatoms, each
 independently selected from N, O and S; and

- 5 c) -(C₁₋₆)alkylene-N(R⁸)R⁹ or -(C₁₋₆)alkylene-C(=O)-N(R⁸)R⁹ wherein
 R⁸ is in each instance independently selected from H and (C₁₋₆)alkyl;
 and
 R⁹ is in each instance independently selected from R⁷, -O- (C₁₋₆)alkyl,
 -SO₂-R⁷, -C(=O)-R⁷, -C(=O)OR⁷ and -C(=O)N(R⁸)R⁷; wherein R⁷ and
 10 R⁸ are as defined above.

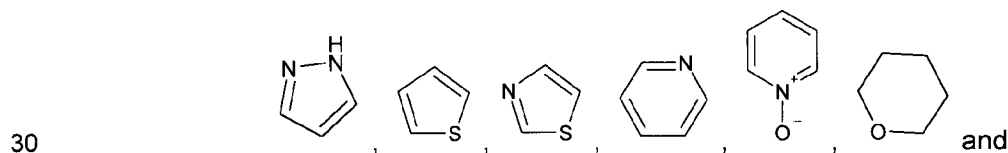
14. The compound according to any one of claims 1 to 10 wherein R²⁰ is
 selected from:

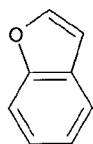
- 15 b) -(C₁₋₃)alkylene-R⁷, -(C₁₋₃)alkylene-O-R⁷, -(C₁₋₃)alkylene-S-R⁷ or
 -(C₁₋₃)alkylene-SO₂-R⁷;
 wherein R⁷ is **Het**; wherein the **Het** is a 5- or 6-membered heterocycle
 containing 1 to 4 heteroatoms, each independently selected from N,
 O and S, or **Het** is a 9- or 10-membered heteropolycycle containing 1
 to 4 heteroatoms, each independently selected from N, O and S;
 20 wherein each N heteroatom may, independently and where possible,
 exist in an oxidized state such that it is further bonded to an oxygen
 atom to form an N-oxide group and wherein each S heteroatom may,
 independently and where possible, exist in an oxidized state such that
 it is further bonded to one or two oxygen atoms to form the groups SO
 or SO₂;
 25 wherein the **Het** is optionally substituted with 1 to 3 substituents each
 independently selected from halo, cyano, oxo, imino, -OH,
 -O-(C₁₋₆)alkyl, -O-(C₁₋₆)haloalkyl, (C₃₋₇)cycloalkyl, -NH₂, -NH(C₁₋₄)alkyl,
 -NH(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)(C₃₋₇)cycloalkyl, -N((C₁₋₄)alkyl)₂,
 30 -NH-C(=O)(C₁₋₄)alkyl, (C₁₋₆)alkyl and **Het**, wherein the **Het** is a 5- or 6-
 membered heterocycle containing 1 to 4 heteroatoms, each
 independently selected from N, O and S; and
- c) -(C₁₋₃)alkylene-N(R⁸)R⁹ wherein
 R⁸ is in each instance independently selected from H, (C₁₋₆)alkyl and

(C₃₋₇)cycloalkyl; and
 R⁹ is R⁷ wherein R⁷ is as defined above.

15. The compound according to any one of claims 1 to 14 wherein R³ is selected
 5 from H, halo and CN.
16. The compound according to claim 15 wherein R³ is H, Cl, F or CN.
17. The compound according to claim 16 wherein R³ is H or F.
 10
18. A compound according to any one of claims 1 to 17 wherein R⁵ is Het,
 (C₃₋₇)cycloalkyl or (C₁₋₆)alkyl, optionally substituted with (C₁₋₆)haloalkyl
19. The compound according to claim 18 wherein R⁵ is (C₁₋₆)alkyl.
 15
20. The compound according to claim 19 wherein R⁵ is methyl or 1-methylethyl.
21. The compound according to claim 20 wherein R⁵ is 1-methylethyl.
- 20 22. The compound according to claim 18 wherein R⁵ is cyclopropyl or cyclobutyl.
23. The compound according to any one of claims 1 to 22 wherein R⁶ is Het
 optionally substituted with 1 to 3 substituents each independently selected
 from halo, -OH, (C₁₋₄)alkyl and (C₁₋₄)haloalkyl.
- 25 24. The compound according to claim 23 wherein R⁶ is Het optionally substituted
 with 1 to 3 substituents each independently selected from halo, OH, (C<sub>1-
 6</sub>)alkyl and (C₁₋₆)haloalkyl

wherein the Het is selected from:





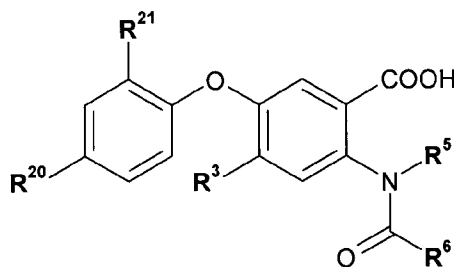
25. The compound according to claim 24 wherein R^6 is **Het** optionally substituted with 1 to 2 substituents each independently selected from halo, OH and

5

(C_{1-6})haloalkyl and wherein the **Het** is



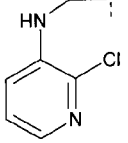

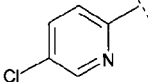
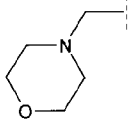

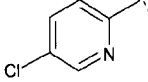
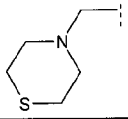

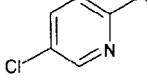
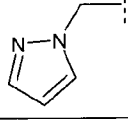

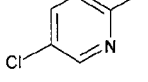
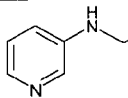

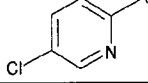
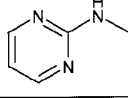

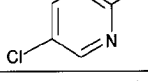
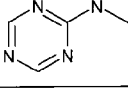

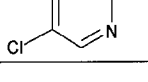
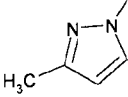

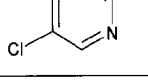
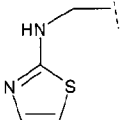

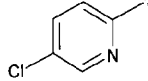
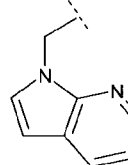

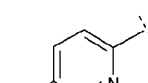
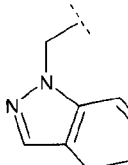

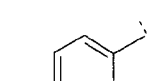
26. The compound according to claim 1 of the formula:



wherein R^{20} , R^{21} , R^3 , R^5 and R^6 are defined as:

R^{20}	R^{21}	R^3	R^5	R^6
H	H	H		
H	CF_3	H		
H	CF_3	H		
	CF_3	F		
	CF_3	F		

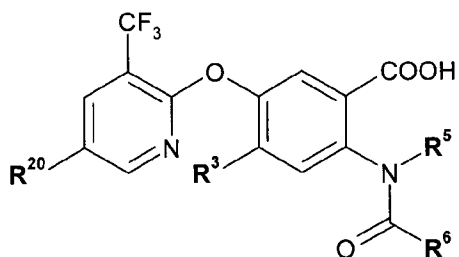
R ²⁰	R ²¹	R ³	R ⁵	R ⁶
	CF ₃	H		
	CF ₃	H		
	CF ₃	F		
	CF ₃	F		
	CF ₃	F		
	CF ₃	F		
	CF ₃	F		
	CF ₃	F		
	CF ₃	F		
	CF ₃	F		
	CF ₃	F		

R ²⁰	R ²¹	R ³	R ⁵	R ⁶
	CF ₃	F		
	CF ₃	H		
	CF ₃	H		
	CF ₃	H		
	CF ₃	H		
	CF ₃	H		
	CF ₃	H		
	CF ₃	H		
	CF ₃	H		
	CF ₃	H		
	CF ₃	H		

R ²⁰	R ²¹	R ³	R ⁵	R ⁶
	CF ₃	H		
	CF ₃	H		
	CF ₃	F		
	CF ₃	F		
	CF ₃	F		
	CF ₃	H		
	CF ₃	H		
	CF ₃	H		
	CF ₃	F		
	CF ₃	F		


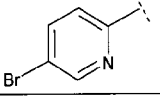

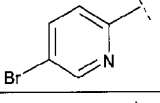

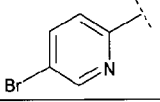

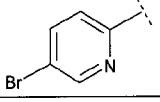
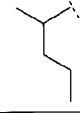
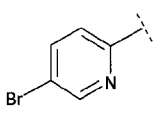

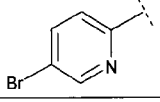

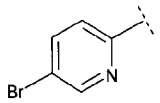

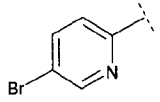
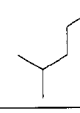
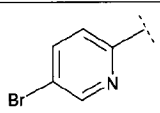
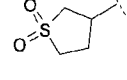
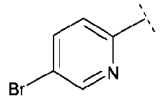
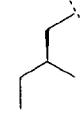
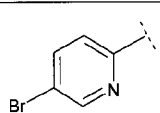
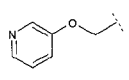

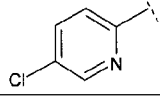
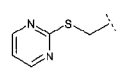

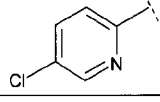
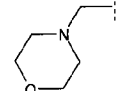

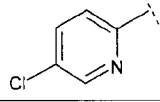
and

27. The compound according to claim 1 of the formula:



wherein R²⁰, R³, R⁵ and R⁶ are defined as:

R ²⁰	R ³	R ⁵	R ⁶
H	H		
H	H		
H	H		
H	H		
H	H		
H	H		
H	H		
H	H		

R ²⁰	R ³	R ⁵	R ⁶
H	Cl		
H	H		
H	H		
H	H		
H	H		
H	H		
H	H		
H	H		
H	H		
H	H		
H	H		
	F		
	F		
	F		

R ²⁰	R ³	R ⁵	R ⁶
	F		
-H	H		
-H	H		
	F		
	H		
	H		
H	F		
-CH ₂ OCH ₃	F		
H	CN		
	H		
	F		
	CN		
	F		

R ²⁰	R ³	R ⁵	R ⁶
	H		
	H		
	F		
	F		
	F		
	F		
	F		
	F		
	F		
	F		
	F		
	H		
	H		

R ²⁰	R ³	R ⁵	R ⁶
	H		
	H		
	H		
	H		
	H		
	H		
	H		
	H		
	H		
	F		
	F		
	F		
	H		

R ²⁰	R ³	R ⁵	R ⁶
	H		
	H		
H	F		
	H		
	H		
	F		
	F		
	F		
	F		
H	F		
	F		
	F		
	F		

R ²⁰	R ³	R ⁵	R ⁶
	F		
	F		
	F		
H	H		

28. The compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt or ester thereof, as a medicament.

5

29. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt or ester thereof; and one or more pharmaceutically acceptable carriers.

10

30. The pharmaceutical composition according to claim 29 additionally comprising at least one other antiviral agent.

31. The pharmaceutical composition according to claim 30, wherein the antiviral agent is selected from: ribavirin and amantadine.

15

32. The pharmaceutical composition according to claim 30 wherein the antiviral agent is an other anti-HCV agent.

33. The pharmaceutical composition according to claim 32, wherein the other anti-HCV agent is an immunomodulatory agent selected from α -, β -, δ - γ -, and ω -interferon.

20

34. The pharmaceutical composition according to claim 32, wherein the other anti-HCV agent is another inhibitor of HCV polymerase.
35. The pharmaceutical composition according to claim 32, wherein the other anti-HCV agent is an inhibitor of HCV NS3 protease.
- 5 36. The pharmaceutical composition according to claim 32, wherein the other anti-HCV agent is an inhibitor of another target in the HCV life cycle.
37. The pharmaceutical composition according to claim 36, wherein said inhibitor of another target in the HCV life cycle is an agent that inhibits a target selected from HCV helicase, HCV NS2/3 protease and HCV IRES.
- 10 38. Use of a pharmaceutical composition according to any one of claims 29 to 37 for the treatment of a hepatitis C viral infection in a mammal having or at risk of having the infection.
- 15 39. A method of treating a hepatitis C viral infection in a mammal having or at risk of having the infection, the method comprising administering to the mammal a therapeutically effective amount of a compound according to any one of claims 1 to 27, a pharmaceutically acceptable salt or ester thereof, or a composition according to any one of claims 29 to 37.
- 20 40. A method of treating a hepatitis C viral infection in a mammal having or at risk of having the infection, the method comprising administering to the mammal a therapeutically effective amount of a combination of a compound according to any one of claims 1 to 27 or a pharmaceutically acceptable salt or ester thereof, and at least one other antiviral agent; or a composition according to
- 25 any one of claims 29 to 37.
41. Use of a compound according to any one of claims 1 to 27, or a pharmaceutically acceptable salt or ester thereof, for the treatment of a
- 30 hepatitis C viral infection in a mammal having or at risk of having the infection.
42. Use of a compound according to any one of claims 1 to 27, or a

pharmaceutically acceptable salt or ester thereof, for the manufacture of a medicament for the treatment of a hepatitis C viral infection in a mammal having or at risk of having the infection.

- 5 **43.** An article of manufacture comprising a composition effective to treat a hepatitis C viral infection; and packaging material comprising a label which indicates that the composition can be used to treat infection by the hepatitis C virus; wherein the composition comprises a compound according to any one of claims 1 to 27 or a pharmaceutically acceptable salt or ester thereof.
- 10
- 44.** A method of inhibiting the replication of hepatitis C virus comprising exposing the virus to an effective amount of the compound according to any one of claims 1 to 27, or a salt or ester thereof, under conditions where replication of hepatitis C virus is inhibited.
- 15
- 45.** Use of a compound according to any one of claims 1 to 27, or a salt or ester thereof, to inhibit the replication of hepatitis C virus.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2008/001412

A. CLASSIFICATION OF SUBJECT MATTER

IPC: *C07D 401/12* (2006.01) , *A61K 31/13* (2006.01) , *A61K 31/381* (2006.01) , *A61K 31/44* (2006.01) ,
A61K 31/4427 (2006.01) , *A61K 31/7056* (2006.01) (more IPCs on the last page)
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)
IPC⁸: C07D, A61K, A61P (see box A for sub-class)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN CAPlus (chemical structure search), Delphion (IPC + keywords = hepatitis C virus, viral infection, NS5B inhibitors, polymerase),
Canadian Patent Database (IPC + keywords)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/04425 A2 (Beaulieu et al.) 17 January 2002 (17-01-2002) *entire document*	1-45
A	WO 03/010140 A2 (Beaulieu et al.) 6 February 2003 (06-02-2003) *entire document*	1-45
A	WO 07/014922 A1 (Raboisson et al.) 8 February 2007 (08-02-2007) *entire document*	1-45
P, A	WO 07/087717 (Coulombe et al.) 9 August 2007 (09-08-2007) *entire document*	1-45

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search

Date of mailing of the international search report

21 October 2008 (21-10-2008)

23 October 2008 (23-10-2008)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001-819-953-2476

Authorized officer
Tung Siu 819- 934-6735

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2008/001412

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. Claim Nos. : 39-40
because they relate to subject matter not required to be searched by this Authority, namely :

Claims 39-40 are directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. However, this Authority has carried out a search based on the alleged effects or purposes/uses of the product defined in claims 39-40.
2. Claim Nos. :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :
3. Claim Nos. :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2008/001412

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO0204425	17-01-2002	AT346049T T	15-12-2006
		AU7225801 A	21-01-2002
		CA2412718 A1	17-01-2002
		CA2439176 A1	12-09-2002
		DE60124718D D1	04-01-2007
		DE60124718T T2	13-09-2007
		EP1301487 A2	16-04-2003
		EP1370682 A2	17-12-2003
		ES2276803T T3	01-07-2007
		HU0400039 A2	28-04-2004
		IL157280D D0	19-02-2004
		JP2004502761T T	29-01-2004
		JP2004520839T T	15-07-2004
		MXPA02012906 A	30-07-2004
		MXPA03007760 A	16-03-2004
		NZ528644 A	27-05-2005
		US6448281 B1	10-09-2002
		US6479508 B1	12-11-2002
		US6794404 B2	21-09-2004
		US2004110126 A1	10-06-2004
		US2004224955 A1	11-11-2004
UY26818 A1	31-01-2002		
WO02070739 A2	12-09-2002		
WO03010140	06-02-2003	AT382348T T	15-01-2008
		AT382605T T	15-01-2008
		AU2002313410B B2	11-09-2008
		AU2002355150B B2	07-08-2008
		BR0211360 A	13-07-2004
		BR0211477 A	17-08-2004
		CA2449180 A1	06-02-2003
		CA2450033 A1	06-02-2003
		CN1558759 A	29-12-2004
		CN1610546 A	27-04-2005
		DE60224400D D1	14-02-2008
		DE60224401D D1	14-02-2008
		DK1414441T T3	13-05-2008
		DK1414797T T3	13-05-2008
		EP1414441 A2	06-05-2004
		EP1414797 A2	06-05-2004
		EP1891950 A1	27-02-2008
		EP1891951 A1	27-02-2008
		ES2299588T T3	01-06-2008
		ES2299591T T3	01-06-2008
		HR20040072 A2	30-06-2004
		HR20040073 A2	30-06-2004
		HU0401784 A2	28-12-2004
		HU0402065 A2	28-02-2005
		IL159545D D0	01-06-2004
		IL159649D D0	01-06-2004
		JP2004537564T T	16-12-2004
		JP2005504030T T	10-02-2005
		MXPA04000729 A	25-06-2004
		MXPA04000731 A	25-06-2004
		NO20040322 A	26-02-2004
NZ531229 A	31-03-2006		
NZ531267 A	24-02-2006		
PL368357 A1	21-03-2005		
PL372125 A1	11-07-2005		

-/-- continued on extra sheet

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/CA2008/001412

Continuation of Patent Family Annex:

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO03010140	06-02-2003	SI1414441T T1	30-06-2008
		SI1414797T T1	30-06-2008
		US7141574 B2	28-11-2006
		US7157486 B2	02-01-2007
		US2006160798 A1	20-07-2006
		US2006293306 A1	28-12-2006
		UY27397 A1	28-02-2003
		WO03010141 A2	06-02-2003
		YU6904 A	17-08-2006
		YU7004 A	15-12-2006
		ZA200400122 A	03-11-2004
		ZA200400240 A	01-11-2004
WO2007014922	08-02-2007	AR055360 A1	22-08-2007
		AU2006274861 A1	08-02-2007
		CA2617096 A1	08-02-2007
		EP1919898 A1	14-05-2008
		KR20080039938 A	07-05-2008
WO2007087717	09-08-2007	AR059292 A1	26-03-2008
		AU2007211789 A1	09-08-2007
		US2007219176 A1	20-09-2007
		UY30127 A1	28-09-2007

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2008/001412

A61P 31/14 (2006.01), *C07D 231/14* (2006.01), *C07D 277/56* (2006.01), *C07D 333/28* (2006.01),
C07D 401/14 (2006.01), *C07D 409/12* (2006.01), *C07D 413/12* (2006.01), *C07D 413/14* (2006.01),
C07D 417/12 (2006.01), *C07D 417/14* (2006.01), *C07D 471/04* (2006.01)