(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 December 2011 (08.12.2011)

PCT

(10) International Publication Number
WO 2011/151652 A1

(51) International Patent Classification:
C07D 243/26 (2006.01) *A61K 31/5513* (2006.01)
C07D 401/12 (2006.01) *A61P 31/14* (2006.01)

(21) International Application Number:
PCT/GB2011/051048

(22) International Filing Date:
3 June 2011 (03.06.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/351,012 3 June 2010 (03.06.2010) US

(71) Applicant *(for all designated States except US)*: **ARROW THERAPEUTICS LIMITED** [GB/GB]; 2 Kingdom Street, London, Greater London W2 6BD (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BARNES, Michael, Christopher, Stratton** [GB/GB]; c/o AstraZeneca R&D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **FLACK, Stephen, Sean** [GB/GB]; c/o AstraZeneca R&D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **FRASER, Ian** [GB/GB]; c/o AstraZeneca R&D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **LUMLEY, James, Andrew** [GB/GB]; c/o AstraZeneca R&D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **PANG, Pui Shan** [GB/GB]; c/o AstraZeneca R&D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **SPENCER, Keith, Charles** [GB/GB]; c/o AstraZeneca R&D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

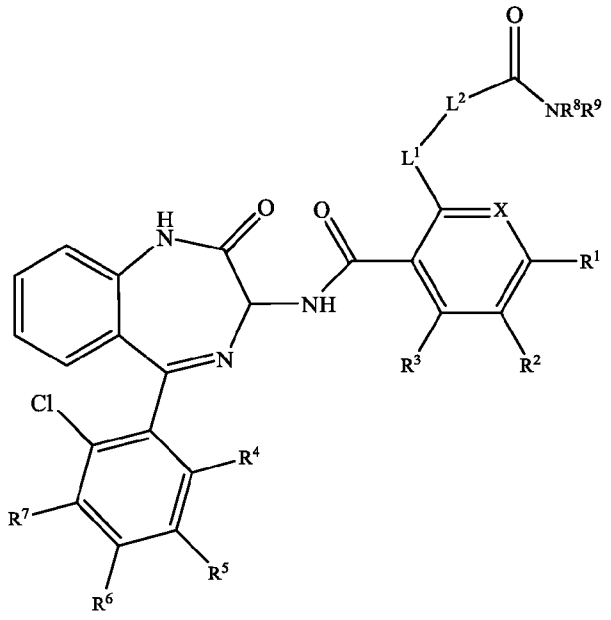
(74) Agent: **ASTRAZENECA INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

(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, CL, 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, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,

[Continued on next page]

(54) Title: BENZODIAZEPINE COMPOUNDS USEFUL FOR THE TREATMENT OF HEPATITIS C



(I)

(57) Abstract: The invention concerns benzodiazepine derivatives of Formula (I): wherein X, L^1, L^2, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 are as defined in the description. The present invention also relates to processes for the preparation of such compounds, pharmaceutical compositions containing them and their use in the treatment or prophylaxis of hepatitis C virus infection.

WO 2011/151652 A1

SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

BENZODIAZEPINE COMPOUNDS USEFUL FOR THE TREATMENT OF HEPATITIS C

Introduction

The present invention relates to a series of benzodiazepine derivatives and, in particular, it relates to a series of benzodiazepine derivatives which are inhibitors of the hepatitis C virus (HCV) Polymerase enzyme and are therefore active against HCV infection. This invention also relates to methods for the preparation of such benzodiazepine derivatives and novel intermediates in the preparation thereof, to pharmaceutical compositions containing such benzodiazepine derivatives, to the use of such benzodiazepine derivatives in the preparation of medicines and to the use of such benzodiazepine derivatives in the treatment of HCV infection.

Background

Hepatitis C virus is a member of the *Flaviviridae* family of viruses and HCV infection is the leading cause of chronic liver disease worldwide. An estimated 170 million people are infected with HCV worldwide. Following the initial acute infection, a majority of infected individuals develop chronic hepatitis, which can progress to liver fibrosis, cirrhosis, end-stage liver disease and hepatocellular carcinoma. Liver cirrhosis due to HCV infection is the principal cause of liver transplantation.

There are six major HCV genotypes and more than 50 subtypes, with HCV type 1 being the predominant genotype in the US and Europe. HCV has a positive-sense, single-stranded RNA genome that encodes a single polyproptein which undergoes posttranslational cleavage to provide ten viral proteins, including viral structural proteins (envelope glycoproteins E1 and E2, and the core nucleocapsid protein), non-structural proteins (helicase, polymerase and protease) and other proteins of unknown function. Replication of the viral genome is mediated by the RNA-dependent RNA polymerase.

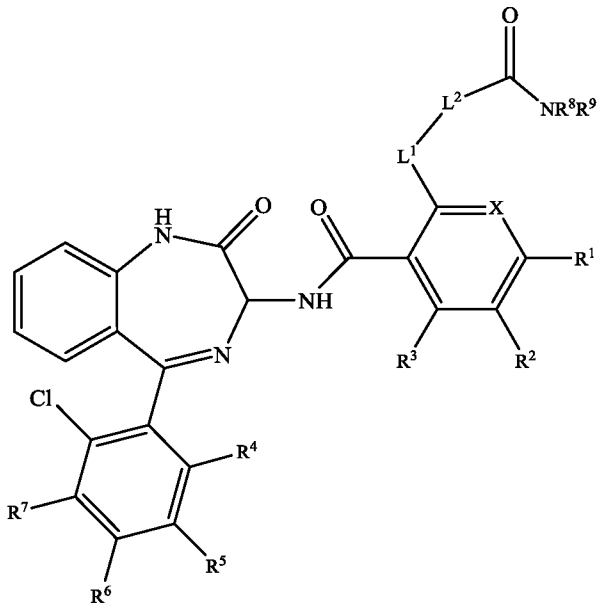
The current standard of care for HCV infection is treatment with interferon-alpha in combination with ribavirin. However, such therapy is only partially effective and may cause significant, undesirable side effects.

An alternative strategy for the treatment of HCV infection is the targeting of HCV polymerase with small molecular weight inhibitors. For example, WO 07/034127 discloses a series of benzodiazepine derivatives that are inhibitors of the HCV polymerase. Nonetheless, there is still a requirement for alternative HCV polymerase inhibitors which

differ by virtue of their chemical structure and may have superior potency against HCV Polymerase and/or advantageous physical properties and/or favourable toxicity profiles and/or favourable metabolic profiles in comparison with other known HCV Polymerase inhibitors.

Description of the Invention

A further series of HCV Polymerase inhibitors is described herein. According to a first aspect of the present invention there is therefore provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein:

L^1 represents O or NR^{10}, wherein R^{10} represents hydrogen, (1-6C)alkyl, acetyl, trifluoromethyl or trifluoromethylcarbonyl;

L^2 represents $-(CR^{11}R^{12})_n-$, wherein n represents 1, 2, 3, 4 ,5 or 6 and R^{11} and R^{12} independently represent hydrogen or (1-3C)alkyl;

X represents CH or N;

R^1 represents hydrogen or fluoro;

R^2 represents hydrogen, halogeno, (1-6C)alkyl, (1-6C)alkoxy, formyl, (2-6C)alkanoyl, trifluoromethyl or trifluoromethoxy;

R^3 represents hydrogen, (1-6C)alkyl or halogeno;

R^4 represents hydrogen, halogeno, (1-6C)alkyl, (1-6C)alkoxy, halogeno-(1-6C)alkyl, halogeno-(1-6C)alkoxy, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (2-6C)alkanoyl, or $-(CH_2)_p-NR^{13}R^{14}$, wherein p represents 0, 1 or 2 and R^{13} and R^{14} independently represent

hydrogen or (1-3C)alkyl, or R^{13} and R^{14} are joined so as to form a 4, 5, 6 or 7 membered heterocyclic ring which optionally comprises, in addition to the nitrogen atom to which R^{13} and R^{14} are attached, 1 or 2 further heteroatoms independently selected from O, N or S, and wherein said heterocyclic ring is optionally substituted with 1, 2 or 3 substituents independently selected from R^{15};

R^5 represents hydrogen, (1-6C)alkyl or halogeno;

R^6 represents hydrogen, halogeno, (1-6C)alkyl, (1-6C)alkoxy, halogeno-(1-6C)alkyl or halogeno-(1-6C)alkoxy;

R^7 represents hydrogen, (1-6C)alkyl, (1-6C)alkoxy, halogeno, trifluoromethyl or trifluoromethoxy;

R^8 represents hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, aryl, a 5 or 6 membered monocyclic heteroaryl ring which comprises 1, 2, 3 or 4 ring heteroatoms independently selected from O, N or S, or a 9 or 10 membered bicyclic heteroaryl ring which comprises 1, 2, 3, 4 or 5 ring heteroatoms independently selected from O, N or S, wherein said aryl, monocyclic heteroaryl or bicyclic heteroaryl ring is optionally substituted with 1, 2 or 3 substituents independently selected from R^{15};

R^9 represents hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl or (1-6C)alkylsulfonyl,

or R^8 and R^9 are joined so as to form a 4, 5, 6 or 7 membered heterocyclic ring which optionally comprises, in addition to the nitrogen atom to which R^8 and R^9 are attached, 1 or 2 further heteroatoms independently selected from O, N or S, and wherein said heterocyclic ring is optionally substituted with 1, 2 or 3 substituents independently selected from R^{15}; and

R^{15} represents halogeno, (1-6C)alkyl, (1-6C)alkoxy, halogeno-(1-6C)alkyl, halogeno-(1-6C)alkoxy, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (2-6C)alkanoyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, sulfamoyl, N-(1-6C)alkylsulfamoyl, N,N-di[(1-6C)alkyl]sulfamoyl, (1-6C)alkylsulfonylamino, (1-6C)alkylsulfonyl-N-(1-6C)alkylamino, aryl, a 5 or 6 membered monocyclic heteroaryl ring which comprises 1, 2, 3 or 4 ring heteroatoms independently selected from O, N or S, a 9 or 10 membered bicyclic heteroaryl ring which comprises 1, 2, 3, 4 or 5 ring heteroatoms independently selected from O, N or S, or $-(CH_2)_q-NR^{16}R^{17}$, wherein q represents 0, 1, 2, 3 or 4 and R^{16} and R^{17} independently represent hydrogen, (1-6C)alkyl or cyclopropyl, or R^{16} and R^{17} are joined so as to form a 4, 5, 6 or 7 membered heterocyclic ring which optionally comprises, in addition to the nitrogen

atom to which R^{16} and R^{17} are attached, 1 or 2 further heteroatoms independently selected from O, N or S.

The term "halogeno" is used herein to denote fluoro, chloro, bromo and iodo.

The term "(1-6C)alkyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length which may be straight-chained or branched. However, references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *tert*-butyl are specific for the branched chain version only. For example, "(1-6C)alkyl" includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, *tert*-pentyl, hexyl and isohexyl. The terms "(1-3C)alkyl" and (1-2C)alkyl" are to be construed accordingly.

The term "(1-6C) alkoxy" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to oxygen. For example, "(1-6C) alkoxy" includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentoxy and hexoxy.

The term "(1-6C)alkoxy-(1-6C)alkyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked via oxygen to another saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched. For example, "(1-6C)alkoxy-(1-6C)alkyl" includes, but is not limited to, methoxyethyl, methoxypropyl, ethoxypropyl, propoxyethyl and butoxypropyl.

The term "(2-6C)alkanoyl" is intended to mean a saturated carbon chain of 1 to 5 carbon atoms in length, which may be straight-chained or branched, linked to carbonyl. For example, "(2-6C)alkanoyl" includes acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl and hexanoyl.

The term "(1-6C)alkylsulfonyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to sulfur dioxide. For example, "(1-6C)alkylsulfonyl" includes, but is not limited to, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, *tert*-butylsulfonyl, pentylsulfonyl and hexylsulfonyl.

The term "(1-6C)alkylsulfinyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to sulfur oxide. For example, "(1-6C)alkylsulfinyl" includes, but is not limited to, methylsulfinyl,

ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, butylsulfinyl, isobutylsulfinyl, *tert*-butylsulfinyl, pentylsulfinyl and hexylsulfinyl.

The term "(1-6C)alkylthio" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, linked to sulfur. For example, "(1-6C)alkylsulfinyl" includes, but is not limited to, methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, *tert*-butylthio, pentylthio and hexylthio.

The term "halogeno-(1-6C)alkyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, wherein at least one of the hydrogen atoms has been replaced by a halogeno atom. For example, "halogeno-(1-6C)alkyl" includes, but is not limited to, difluoromethyl, trifluoromethyl, chloro(difluoro)methyl, difluoroethyl and difluoropropyl.

The term "halogeno-(1-6C)alkoxy" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, wherein at least one of the hydrogen atoms has been replaced by a halogeno atom, linked to oxygen. For example, "halogeno-(1-6C)alkoxy" includes, but is not limited to, difluoromethoxy, trifluoromethoxy, chloro(difluoro)methoxy, difluoroethoxy and difluoropropoxy.

The term "hydroxy-(1-6C)alkyl" is intended to mean a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched, wherein at least one of the hydrogen atoms has been replaced by a hydroxy group. For example, "hydroxy-(1-6C)alkyl" includes, but is not limited to, hydroxymethyl, dihydroxyethyl and dihydroxypropyl.

A sulfamoyl group is a group H_2N-SO_2-.

The term "N-(1-6C)alkylsulfamoyl" is intended to mean a sulfamoyl group wherein one of the hydrogen atoms of the amino group has been replaced by a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched. For example, "N-(1-6C)alkylsulfamoyl" includes, but is not limited to, methylaminosulfonyl, ethylaminosulfonyl and isopropylaminosulfonyl.

The term "N,N-di(1-6C)alkylsulfamoyl" is intended to mean a sulfamoyl group wherein both of the hydrogen atoms of the amino group have been replaced by a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched. For example, "N,N-di[(1-6C)alkyl]sulfamoyl" includes, but is not limited to, dimethylaminosulfonyl, diethylaminosulfonyl and *N*-ethyl-*N*-methylaminosulfonyl.

A "(1-6C)alkylsulfonylamino" group is a group (1-6C)alkyl-$S(O)_2$-N(H)-, wherein the (1-6C)alkyl group is a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched. For example, "(1-6C)alkylsulfonylamino" includes, but is not limited to, mesylamino, ethylsulfonylamino and isopropylsulfonylamino.

A "(1-6C)alkylsulfonyl-N-(1-6C)alkylamino" group is a group (1-6C)alkyl-$S(O)_2$-[N(1-6C)alkyl]-, wherein each (1-6C)alkyl group is independently a saturated carbon chain of 1 to 6 carbon atoms in length, which may be straight-chained or branched. For example, "N-(1-6C)alkyl-(1-6C)alkylsulfonylamino" includes, but is not limited to, mesyl-*N*-(methyl)amino, ethylsulphonyl-*N*-(isopropyl)amino and isopropylsulphonyl-*N*-(ethyl)amino.

The term "aryl" is intended to mean phenyl or naphthyl.

Unless stated otherwise, the term "5 or 6 membered monocyclic heteroaryl ring" is intended to mean a 5 or 6 membered, totally unsaturated and/or aromatic monocyclic ring which comprises 1, 2, 3 or 4 heteroatoms independently selected from nitrogen, oxygen or sulfur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is possible, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. Examples of 5 or 6 membered monocyclic heteroaryl rings include, but are not limited to, pyrrolyl, furanyl, imidazolyl, triazolyl, tetrazolyl, pyrazinyl, pyrazolyl, pyrimidinyl, pyridazinyl, pyridinyl, pyrrolyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl, thiadiazolyl, 1,2,4-triazolyl and thiophenyl.

Unless stated otherwise, the term "9 or 10 membered bicyclic heteroaryl ring" is intended to mean a 9 or 10 membered, totally unsaturated and/or aromatic bicyclic ring which comprises 1, 2, 3, 4 or 5 heteroatoms independently selected from nitrogen, oxygen or sulfur, linked via ring carbon atoms or ring nitrogen atoms where a bond from a nitrogen is possible. Examples of 9 or 10 membered bicyclic heteroaryl rings include, but are not limited to, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl or naphthyridinyl.

The term "(3-7C)cycloalkyl" is intended to mean a saturated carbon 3 to 7 membered ring. Examples of (3-7C)cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or bicyclo[2.2.1]heptyl.

Where reference is made herein to R^8 and R^9, to R^{13} and R^{14} or to R^{16} and R^{17} joining so as to form a 4, 5, 6 or 7 membered heterocyclic ring which optionally comprises, in addition to the nitrogen atom to which they are attached, 1 or 2 one or more additional heteroatoms independently selected from O, N or S, the ring so formed suitably contains 1 or 2 additional heteroatoms and, more suitably contains 1 additional heteroatom, representative examples of which are listed above. For example, the ring so formed may be selected from azetidin-1-yl, pyrrolidin-1-yl, pyrazolidin-1-yl, piperidin-1-yl, morpholin-4-yl and piperazin-1-yl.

It is to be understood that, insofar as compounds of Formula (I) defined above exist in optically active or racemic forms by virtue of the asymmetric carbon atom, the invention includes in its definition any such optically active or racemic form which possesses the property of HCV Polymerase inhibitory activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Racemic compounds and racemic intermediates thereof are drawn herein as flat structures whereas stereospecific compounds and stereospecific intermediates thereof are drawn with the appropriate stereochemistry indicated.

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

L^1 represents O or NR^{10}, wherein R^{10} represents hydrogen or (1-6C)alkyl, particularly wherein R^{10} represents hydrogen or (1-2C)alkyl.

L^1 represents O.

L^2 represents $-(CR^{11}R^{12})_n-$, wherein n represents 1, 2 or 3 (particularly wherein n represents 1), and R^{11} and R^{12} independently represent hydrogen or (1-2C)alkyl. For example, L^2 may represent $-CH_2-$.

X represents N.

R^1 represents hydrogen.

R^2 represents halogeno,particularly fluoro.

R^3 represents hydrogen.

R^4 represents halogeno or (1-6C)alkoxy, particularly halogeno or (1-2C)alkoxy. For example, R^4 may represent chloro, methoxy or ethoxy.

R^5 represents hydrogen.

R^6 represents halogeno, for example chloro.

R^7 represents hydrogen.

R^8 represents hydrogen, (1-6C)alkyl or (3-7C)cycloalkyl.

R^9 represents hydrogen, (1-6C)alkyl or (3-7C)cycloalkyl.

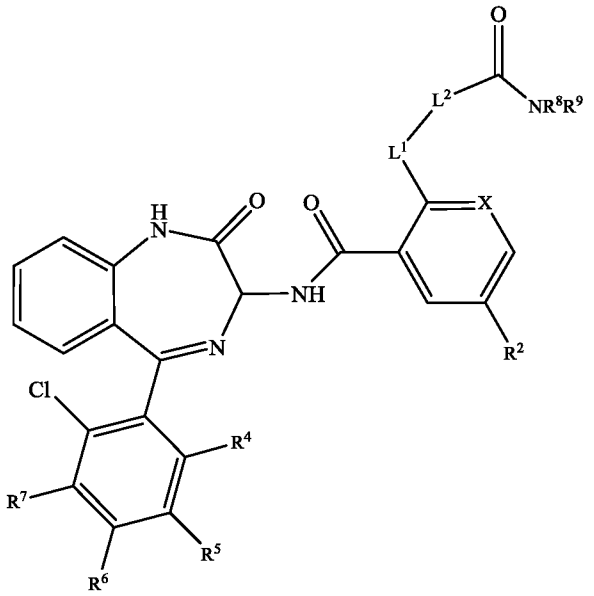
In a further aspect of the invention, R^1 and R^3 are both hydrogen and R^2 represents halogeno (particularly fluoro).

In a further aspect of the invention, R^5 and R^7 are both hydrogen, R^4 represents halogeno, (1-6C)alkyl, (1-6C)alkoxy, halogeno-(1-6C)alkyl, halogeno-(1-6C)alkoxy, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (2-6C)alkanoyl or $-(CH_2)_p-NR^{13}R^{14}$, wherein p represents 0, 1 or 2 and R^{13} and R^{14} independently represent hydrogen or (1-3C)alkyl, or R^{13} and R^{14} are joined so as to form a 4, 5, 6 or 7 membered heterocyclic ring which optionally comprises, in addition to the nitrogen atom to which R^{13} and R^{14} are attached, 1 or 2 further heteroatoms independently selected from O, N or S, and wherein said heterocyclic ring is optionally substituted with 1, 2 or 3 substituents selected from R^{15} as herein defined; and R^6 represents halogeno, (1-6C)alkyl, (1-6C)alkoxy, halogeno-(1-6C)alkyl or halogeno-(1-6C)alkoxy.

In a further aspect of the invention, R^5 and R^7 are both hydrogen, R^4 represents halogeno, or (1-6C)alkoxy; and R^6 represents halogeno (particularly chloro).

In a further aspect of the invention, R^1, R^3, R^5 and R^7 are all hydrogen; R^2 represents halogeno (particularly fluoro); R^4 represents halogeno or (1-6C)alkoxy; and R^6 represents halogeno (particularly chloro).

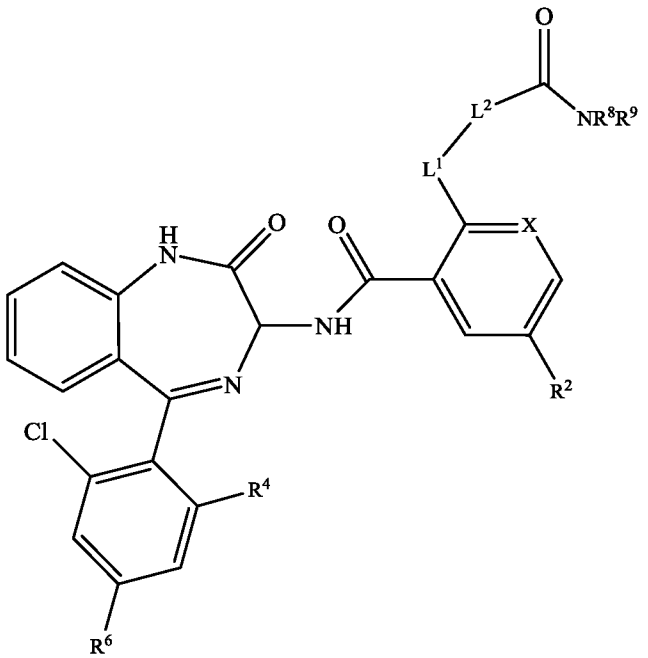
In a further aspect of the invention, the compound of Formula (I) has the configuration shown in Formula (IA):



(IA)

wherein L^1, L^2, X, R^2, R^4 R^5, R^6, R^7, R^8 and R^9 are as hereinbefore defined. For the avoidance of doubt, in the Formula (IA), R^1 and R^3 as shown in the Formula (I) are both hydrogen.

In a further aspect of the invention, the compound of Formula (I) has the configuration shown in Formula (IB):



(IB)

wherein L^1, L^2, X, R^2, R^4, R^6, R^8 and R^9 are as hereinbefore defined. For the avoidance of doubt, in the Formula (IA), R^1, R^3, R^5 and R^7 as shown in the Formula (I) are all hydrogen.

Reference herein to a compound of Formula (I) should be understood to refer equally to a compound of Formula (I), (IA) or (IB).

It is to be understood that certain compounds of Formula (I) above may exist in unsolvated forms as well as solvated forms, such as, for example, hydrated forms. It is to be understood that the present invention encompasses all such solvated forms that possess HCV Polymerase inhibitory activity.

It is also to be understood that certain compounds of Formula (I) above may exist in crystalline form and exhibit polymorphism. The present invention encompasses all such polymorphic forms which possess HCV Polymerase inhibitory activity.

In an aspect of the present invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in crystalline form.

Particular novel compounds of Formula (I) include, but are not limited to, the following compounds:

2-(2-amino-2-oxoethoxy)-5-fluoro-N-(2-oxo-5-(2,4,6-trichlorophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)nicotinamide;

2-(2-amino-2-oxoethoxy)-N-(5-(2,4-dichloro-6-methoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide;

2-(2-amino-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide;

2-(2-(ethylamino)-2-oxoethoxy)-5-fluoro-N-(2-oxo-5-(2,4,6-trichlorophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)nicotinamide;

N-(5-(2,4-dichloro-6-methoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(2-(ethylamino)-2-oxoethoxy)-5-fluoronicotinamide;

N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(2-(ethylamino)-2-oxoethoxy)-5-fluoronicotinamide;

2-(2-(cyclopropylamino)-2-oxoethoxy)-5-fluoro-N-(2-oxo-5-(2,4,6-trichlorophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)nicotinamide;

2-(2-(cyclopropylamino)-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide;

2-(2-(diethylamino)-2-oxoethoxy)-5-fluoro-N-(2-oxo-5-(2,4,6-trichlorophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)nicotinamide;
N-(5-(2,4-dichloro-6-methoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(2-(diethylamino)-2-oxoethoxy)-5-fluoronicotinamide;
N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(2-(diethylamino)-2-oxoethoxy)-5-fluoronicotinamide;
and pharmaceutically acceptable salts thereof.

Further particular novel compounds of Formula (I) include, but are not limited to, the following compounds:
(S)-2-(2-amino-2-oxoethoxy)-5-fluoro-N-(2-oxo-5-(2,4,6-trichlorophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)nicotinamide;
(R)-2-(2-amino-2-oxoethoxy)-5-fluoro-N-(2-oxo-5-(2,4,6-trichlorophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)nicotinamide;
(S)-2-(2-amino-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide;
(R)-2-(2-amino-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide;
(S)-2-(2-(cyclopropylamino)-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide;
and pharmaceutically acceptable salts thereof.

A particular novel compound of Formula (I) is 2-(2-amino-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide and pharmaceutically acceptable salts thereof.

A particular novel compound of Formula (I) is (S)-2-(2-amino-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide and pharmaceutically acceptable salts thereof.

A suitable pharmaceutically acceptable salt of a compound of Formula (I) is, for example, where the compound is sufficiently basic, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulfonate or *p*-toluenesulfonate salt. There may be more than one anion depending on the number of charged functions and the valency of the anions. Other pharmaceutically

acceptable salts, as well as pro-drugs such as pharmaceutically acceptable esters and pharmaceutically acceptable amides may be prepared using conventional methods.

For example, the compounds of the invention may be administered in the form of a pro-drug, that is a compound that is broken down in the human or animal body to release a compound of the invention. A pro-drug may be used to alter the physical properties and/or the pharmacokinetic properties of a compound of the invention. A pro-drug can be formed when the compound of the invention contains a suitable group or substituent to which a property-modifying group can be attached. Examples of pro-drugs include *in vivo* cleavable amide derivatives that may be formed at an amino group in a compound of Formula (I).

Accordingly, the present invention includes those compounds of Formula (I) as hereinbefore defined when made available by organic synthesis and when made available within the human or animal body by way of cleavage of a pro-drug thereof. Accordingly, the present invention includes those compounds of Formula (I) that are produced by organic synthetic means and also such compounds that are produced in the human or animal body by way of metabolism of a precursor compound, that is a compound of Formula (I) may be a synthetically-produced compound or a metabolically-produced compound.

A suitable pharmaceutically acceptable pro-drug of a compound of Formula (I) is one that is based on reasonable medical judgement as being suitable for administration to the human or animal body without undesirable pharmacological activities and without undue toxicity.

Various forms of pro-drug have been described, for example in the following documents:

a) Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) Design of Pro-drugs, edited by H. Bundgaard, (Elsevier, 1985);

c) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Pro-drugs", by H. Bundgaard p. 113-191 (1991);

d) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

e) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988);

f) N. Kakeya, *et al.*, Chem. Pharm. Bull., 32, 692 (1984);

g) T. Higuchi and V. Stella, "Pro-Drugs as Novel Delivery Systems", A.C.S. Symposium

Series, Volume 14; and

h) E. Roche (editor), "Bioreversible Carriers in Drug Design", Pergamon Press, 1987.

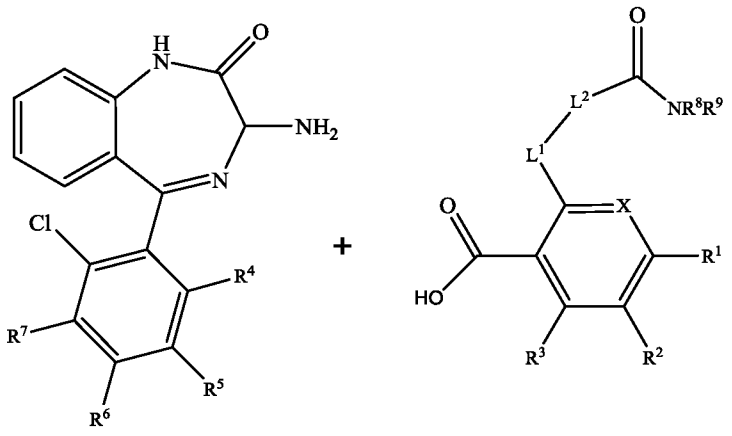
A suitable pharmaceutically acceptable pro-drug of a compound of Formula (I) that possesses an amino group is, for example, an *in vivo* cleavable amide derivative thereof. Suitable pharmaceutically acceptable amides from an amino group include, for example an amide formed with C_{2-10} alkanoyl groups such as an acetyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl groups.

The *in vivo* effects of a compound of Formula (I) may be exerted in part by one or more metabolites that are formed within the human or animal body after administration of a compound of Formula (I). As stated hereinbefore, the *in vivo* effects of a compound of Formula (I) may also be exerted by way of metabolism of a precursor compound (a pro-drug).

Preparation of Compounds of Formula (I)

Certain processes for the synthesis of compounds of Formula (I) as hereinbefore defined are provided as a further feature of the invention. Thus, according to a further aspect of the invention there is provided a process for the preparation of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, which comprises a process (a) or (b):

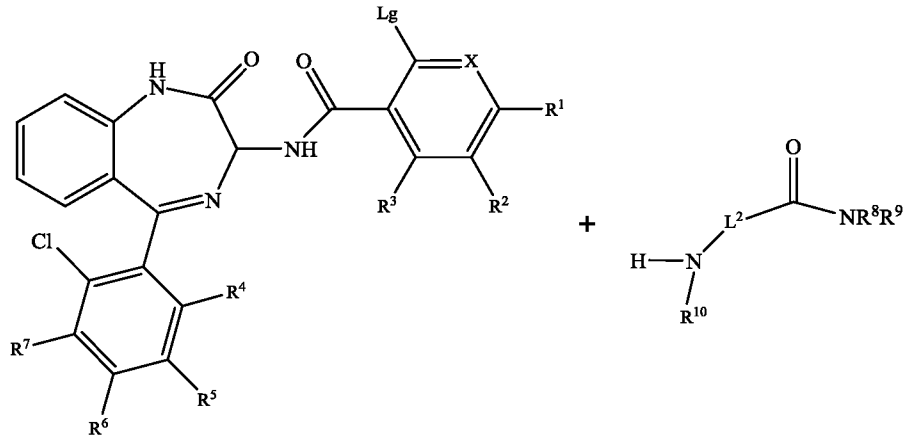
(a) reaction of a compound of Formula (II), or a salt thereof, with a compound of Formula (III), or a reactive derivative thereof, in the presence of a suitable coupling agent and a suitable base:



(II) (III)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, L^1, L^2 and X are as defined for Formula (I) except that any functional group is protected if necessary; or

(b) when L^1 represents NR^{10}, reaction of a compound of Formula (IV) with an amine of Formula (V):



(IV) (V)

wherein Lg represents a suitable leaving group and R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, L^2 and X are as defined for Formula (I), except that any functional group is protected if necessary;

and thereafter, if necessary:

(i) converting a compound of Formula (I) into another compound of Formula (I);

(ii) removing any protecting groups;

(iii) separating a racemic mixture into separate enantiomers; and/or

(iv) preparing a pharmaceutically acceptable salt thereof.

In process (a), a compound of Formula (II) may be reacted with a compound of Formula (III) in the presence of a suitable coupling agent, for example O-(1H-benzotriazol-1-yl)-N,N,N',N',-tetramethyluronium hexafluorophosphate (HBTU), optionally in the presence of a suitable base, for example triethylamine (TEA), a suitable solvent, for example *N,N*-dimethylformamide (DMF), and at a suitable temperature, for example room temperature.

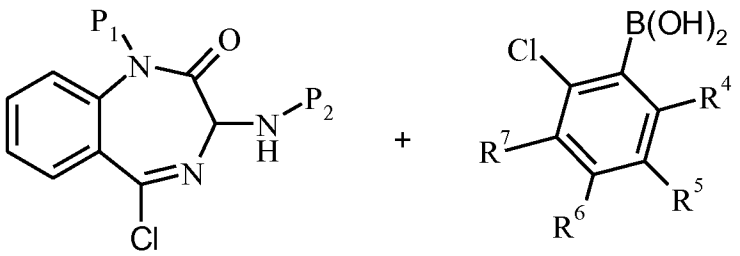
By the term "reactive derivative" of the compound of the Formula (III) is meant a carboxylic acid derivative that will react with the compound of Formula (II) to give the corresponding amide. A suitable reactive derivative of a compound of the Formula (III) would be readily determined by persons skilled in the art. For example, the reactive derivative may be an acyl halide, for example an acyl chloride formed by the reaction of the compound of Formula (III) and an inorganic acid chloride, for example thionyl chloride.

In process (b), a compound of Formula (IV) wherein Lg represents a suitable leaving group, for example fluoro, chloro, bromo, iodo, mesylate or tosylate, may be reacted with an

amine of Formula (V) in a suitable solvent, for example a 4:1 mixture of 1,4-dioxane in water, by heating to a suitable temperature, for example 100 to 200°C, more suitably about 160°C, using a suitable heat source, for example microwave radiation.

Intermediate compounds (II), (III), (IV) and (V) may be prepared using suitable procedures known in the art.

For example, compounds of Formula (II) may be prepared by reacting a compound of Formula (VI) with a compound of Formula (VII) in the presence of silver and a suitable catalyst wherein P_1 and P_2 represent suitable protecting groups:



(VI) (VII)

wherein R^4, R^5, R^6 and R^7 are as defined for Formula (I), except that any functional group is protected if necessary, and thereafter removing the protecting groups (i.e. including P_1 and P_2).

A compound of Formula (VI) wherein P_1 and P_2 represent suitable protecting groups, for example p-methoxybenzyl (PMB) and *tert*-butyloxycarbonyl respectively, may be reacted with a compound of Formula (VII) in a suitable solvent, for example THF, in the presence of silver, for example Ag_2CO_3, a suitable catalyst, for example tetrakis(triphenylphosphine)palladium(0), and optionally in the presence of a suitable base, for example K_2CO_3, by heating to a suitable temperature, for example reflux temperature.

A process for the preparation of compounds of Formula (I) may comprise converting a compound of Formula (I) into another compound of Formula (I) using standard chemical reactions well-known to those skilled in the art to produce another compound of the invention. Chemical conversions of this type are well known to those skilled in the art and may include functional group interconversions such as hydrolysis, hydrogenation, hydrogenolysis, oxidation or reduction, and/or further functionalisation by standard reactions such as amide or metal-catalysed coupling, or nucleophilic displacement reactions. Examples of such

conversions are described, for instance, in *Comprehensive Organic Chemistry*, Volume 2, p3, D. Barton and D. Ollis Eds, Pergamon, 1979, *Comprehensive Functional Group Transformations,* A.R. Katritzky, O. Meth-Cohn, and C.W. Rees Eds., Pergamon, 1995, and by various authors in *Houben-Weyl, Methods of Organic Chemistry*, Verlag Chemie, various years, and references therein.

It will be appreciated by a person skilled in the art that it may be necessary/desirable to protect any sensitive groups in the compounds in some of the processes/ reactions mentioned herein. The instances where protection is necessary or desirable, and suitable methods for providing such protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see P.G.M. Wuts and T.W. Green, *Protective Groups in Organic Synthesis*, 4th Edition, John Wiley and Sons, 2002). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

Any protecting groups utilised in the processes described herein may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule. The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

For example, in process (a) described above, a suitable protecting group for the ring nitrogen of the benzodiazepine would be p-methoxybenzyl. Once the reaction described in process (a) is complete, the p-methoxybenzyl can be removed, for example by treating with aluminium trichloride or cerium(IV) ammonium nitrate.

A process for the manufacture of compounds of Formula (I) in the form of a single enantiomer may comprise separating a racemic compound of the invention into separate enantiomers.

Examples of suitable methods for separating the enantiomers of a racemic compound are well known to those skilled in the art and include chromatography using a suitable chiral stationary phase; or conversion of a racemic mixture into diastereomeric derivatives,

separation of the mixture of diastereomeric derivatives into two single diastereomers, and regeneration of a separate single enantiomer from each separate single diastereomer; or selective chemical reaction of one of the enantiomers of a racemic compound (kinetic resolution) using a diastereoselective reaction catalysed by a microbiological agent or an enzyme.

Alternatively, compounds of the invention in the form of a single enantiomer may be prepared by using chiral starting materials to carry out one of the processes described above.

Alternatively, compounds of the invention in the form of a single enantiomer may be prepared by using a dynamic kinetic resolution method, such as the method described herein.

Biological Assays

The ability of compounds to inhibit HCV Polymerase activity and replication of an HCV replicon was assessed using the assays described below.

(a) HCV polymerase enzyme assay

Compounds were tested for inhibition of HCV polymerase using a radiometric [^{33}P]-UTP incorporation assay and a biotinylated U_{13}:PolyA primer:template RNA substrate.

Recombinant HCV polymerase (BK strain) was expressed and purified from *E. coli* with a 21 amino acid C-terminal deletion and a His_6-tag. The general assay buffer consisted of 20 mM Tris (pH 7.5), 25 mM KCl, 5 mM $MgCl_2$, 3 mM DTT, 0.5 mg/ml BSA, 0.01% Tween20. The standard reaction, in 96 well plates, contained 10 µl of diluted compound, 50 µl of substrate and 40 µl of enzyme. Compounds, supplied as 10 mM stocks in DMSO, were diluted initially in neat DMSO, and subsequently buffer was added to give a DMSO concentration of 30%; 10 µl of this was added to the assay plate to give a final concentration in the 100 µl assay of 3% DMSO. The biotinylated U_{13}:PolyA RNA substrate was pre-annealed with 40 µM 5′-biotinylated U_{13} (Dharmacon) and 213 µg/ml PolyA (Amersham Biosciences) in water incubated at 70°C for 5 minutes before being cooled on ice. Substrate (50 µl) was added in buffer to give a final concentration in the 100 µl assay of 125 nM biotinylated U_{13}:0.63 µg/ml PolyA and 200 nM UTP with 0.4 µCi [^{33}P]-UTP per well (Perkin Elmer). The reaction was initiated by the addition of 40 µl of enzyme in buffer to give 100 nM final concentration. The reaction was incubated at 25°C for 100 minutes and then stopped by addition of 100 µl of 100 mM EDTA. The samples were then transferred to 96 well Streptavidin-coated FlashPlates (Perkin Elmer) and incubated at room temperature for ~1 hour to allow binding to occur. The plates were then washed three times with phosphate-

buffered saline containing 0.05% Tween20 in an automated plate washer to remove unincorporated [^{33}P]-UTP, and then counted in a Packard TopCount Scintillation Counter.

Each plate included a set of positive controls (no compound, maximum signal) and negative controls (no enzyme, minimum signal) and in each run at least one reference compound was included to validate the assay. The IC_{50}, concentration required to inhibit the enzyme activity by 50%, was calculated using an 8-point IC_{50} curve and fitted using the program XLfit (IDBS).

(b) HCV replicon assay

Cells used:

HCV replicon cells Huh 9B (ReBlikon), containing the firefly luciferase – ubiquitin – neomycin phosphotransferase fusion protein and EMCV-IRES driven HCV polyprotein with cell culture adaptive mutations.

Cell culture conditions:

Cells were cultured at 37 °C in a 5% CO_2 environment and split twice a week on seeding at 2 x 10^6 cells/flask on day 1 and 1 x 10^6 3 days later. G418 at 0.5mg/ml was added to the culture medium but not the assay medium.

The culture medium consisted of DMEM with 4500g/l glucose and glutamax (Gibco 61965-026) supplemented with 1 x non-essential amino acids (Invitrogen 11140-035), penicillin (100 IU/ml) / streptomycin (100 µg/ml) (Invitrogen 15140-122), FCS (10%, 50ml) and 1 mg/ml G418 (Invitrogen 10131-027) & 10 % Australian foetal calf serum (Invitrogen 10099-141).

Assay procedure:

A flask of cells was trypsinised and a cell count carried out. Cells were diluted to 100,000 cells/ml and 100 µl of this used to seed one opaque white 96-well plate (for the replicon assay) and one flat-bottomed clear plate (for the tox assay) for every five compounds to be tested for IC_{50}. Wells G12 and H12 were left empty in the clear plate as the blank. Plates were then incubated at 37°C in a 5% CO_2 environment for 24 h.

On the following day compound dilutions are made up in medium at twice their desired final concentration in a clear round bottomed plate. All dilutions have a final DMSO concentration of 1%.

Once the dilution plate had been made up, controls and compounds were transferred to the assay plates (containing the cells) at 100 µl /well in duplicate wells.
Exception: no compound was added to wells A1 and A2 of either plate and 100 µl of 1% DMSO was added to these instead. Plates were then incubated at 37 °C with 5% CO_2 for 72h.

At the end of the incubation time, the cells in the white plate were harvested by washing in PBS (100µL per well) and gently tapping dry before addition of 20µL per well of lysis buffer (25mM tris-phosphate, 8mM $MgCl_2$, 1mM DTT, 1% Triton X-100, 15% glycerol. pH to 7.8 using KH_2PO_4 prior to triton and glycerol addition. Substrate was prepared: 23.5mM beetle luciferin (Promega E1603), 26mM ATP (Sigma O-2060) in 100nM Tris buffer pH 7.8 aliquoted and stored at –80 °C was thawed and diluted 1:50 in luciferase assay buffer (20mM Tricine (Sigma T-0377), 1.07mM magnesium carbonate hydroxide (Sigma M-5671), 0.1mM EDTA (Sigma E-5134), 2.67mM $MgSO_4$ (BDH 101514Y), 33.3mM dithiothreitol (Sigma 150460) pH 7.8).

The M injector of the microplate luminometer (Lmax, Molecular Devices) was primed with 5 x 300 µl injections of the diluted substrate. After 5-60 min incubation in lysis buffer at room temperature, a plate was inserted into the luminometer and 100 µl luciferase assay reagent was added by the injector on the luminometer. The signal was measured using a 1 second delay followed by a 4 second measurement programme. The IC_{50}, the concentration of the drug required for reducing the replicon level by 50% in relation to the untreated cell control value, can be calculated from the plot of the percentage reduction of the luciferase activity vs. drug concentration.

The clear plate was stained with 100 µl 0.5% methylene blue in 50% ethanol at room temperature for 1h, followed by solvation of the absorbed methylene blue in 100µl per well of 1% lauroylsarcosine. Absorbance of the plate was measured on a microplate spectrophotometer (Molecular Devices) and the absorbance for each concentration of compound expressed as a proportion of the relative DMSO control. The TD_{50}, the concentration of drug required to reduce the total cell area by 50% relative to the DMSO controls, can be calculated by plotting the absorbance at 620 nm minus background against drug concentration.

Results

When tested in assays (a) and (b) described above, all of the compounds of the Examples gave IC_{50} values for HCV polymerase inhibitory activity and/or reduction of replicon levels of less than 10 μM (micromolar), indicating that the compounds of the invention are expected to possess useful therapeutic properties. The IC_{50} values so obtained are shown in the following Table:

Example Number	HCV 1b Polymerase Assay Value IC_{50}(μM)	Replicon Assay Value IC_{50} (μM)
1	0.108	0.077
2	0.303	0.056
3	0.144	0.032
4	0.289	0.382
5	0.524	0.114
6	0.196	0.061
7	0.312	0.085
8	0.178	0.116
9	0.347	0.059
10	1.320	0.062
11	0.673	1.310
12	0.107	0.095
13	0.296	0.263
14	0.060	0.039
15	0.852	0.568
16	0.090	0.056

Pharmaceutical Compositions and Methods of Treatment Comprising Compounds of Formula (I)

The compounds of Formula (I), and pharmaceutically acceptable salts thereof, as hereinbefore defined may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the Formula (I) compound/salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are

described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

The compounds of the invention may be administered in a variety of dosage forms. Thus, they can be administered orally, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. The compounds of the invention may also be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

The compounds of the invention are typically formulated for administration with a pharmaceutically acceptable carrier or diluent. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The compound of Formula (I), or pharamaceutically acceptable salt thereof, as hereinbefore defined will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg/m^2 body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The compounds of Formula (I) and their pharmaceutically acceptable salts as hereinbefore defined have activity as pharmaceuticals, in particular as antiviral agents and especially as agents for the treatment of Flaviviridae infections. More particularly, the compounds of Formula (I) and their pharmaceutically acceptable salts may be used in the treatment of hepatitis C virus infection.

Thus, the present invention provides a compound of Formula (I), or a pharmaceutically-acceptable salt thereof, as hereinbefore defined for use in therapy.

The present invention further provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined for use as a medicament.

The present invention further provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a further aspect, the present invention provides a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined for use in the treatment or prophylaxis of hepatitis C virus infection.

In a further aspect, the present invention provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for use in the treatment or prophylaxis of hepatitis C virus.

In a further aspect, the present invention provides a method of treating, or reducing the risk of, hepatitis C virus infection in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, HCV infection. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

The compounds of the invention may also be administered in conjunction with other compounds used for the treatment of viral infections. Thus, the invention further relates to combination therapies for the treatment of a viral infection, particularly infection by hepatitis C virus, wherein a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined or a pharmaceutical composition or formulation comprising a compound of Formula (I), is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents.

In particular the compounds of the invention may be administered in conjunction with one or more further active ingredients that are selected from:

(a) a HCV protease inhibitor, for example IDX-320, MK-5172, IDX-320, BMS-650032, ACH-2684, ACH-1625,BI-1335, TMC435350, MK7009, ITMN-191, BILN-2061, VX-950, BILN-2065, BMS-605339, VX-500 and SCH 503034;

(b) a HCV polymerase inhibitor, for example ABT-333, ABT-072, IDX-184, ANA598, VX-222, PSI-938, PSI-7977, R-7128, MK-0608, VCH759, PF-868554, GS9190, NM283, valopicitabine, PSI-6130, XTL-2125, NM-107, R7128 (R4048), GSK625433, R803, R-1626, BILB-1941, HCV-796, JTK-109 and JTK-003, benzimidazole derivatives, benzo- 1,2,4-thiadiazine derivatives, phenylalanine derivatives,;

(c) a HCV helicase inhibitor;

(d) an immunomodulatory agent, for example α-, β-, and γ- interferons such as rIFN-α 2b, rIFN-α 2ba, consensus IFN-α (infergen), feron, reaferon, intermax α, rIFN-β, infergen + actimmune, IFN-omega with DUROS, albuferon, locteron, Rebif, Oral IFN-α, IFN-α 2b XL, AVI-005, pegylated-infergen, pegylated derivatized interferon-α compounds such as pegylated rIFN-α 2b, pegylated rIFN-α 2a, pegylated IFN- β, compounds that stimulate the synthesis of interferon in cells, interleukins, Toll like receptor (TLR) agonists, compounds that enhance the development of type 1 helper T cell response and thymosin;

(e) a HCV NS5a inhibitor such as A-831 and A-689, PPI-461 or BMS-790052;

(f) other antiviral agents, for example ribavirin, ribavirin analogs such as rebetol, copegus and viramidine (taribavirin), amantadine, and telbivudine, inhibitors of internal ribosome entry, alpha-glucosidase 1 inhibitors such as MX-3253 (celgosivir) and UT-231B, hepatoprotectants such as IDN- 6556, ME-3738, LB-84451 and MitoQ, broad-spectrum viral inhibitors, such as IMPDH inhibitors (e.g., mycophenolic acid and derivatives thereof, and VX-497, VX-148, and/or VX-944); and

(g) other drugs for treating HCV such as zadaxin, nitazoxanide, BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA-971, NOV-205, tarvacin, EHC-18, NIM811, DEBIO-025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, and Oglufanide.

In one aspect of the invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in combination with one or more further active ingredients that are selected from a HCV protease inhibitor, a HCV

polymerase inhibitor, a HCV helicase inhibitor, an interferon, ribavirin and a HCV NS5a inhibitor for use in the treatment of HCV infection.

In one aspect of the invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in combination with one or more further active ingredients that are selected from a HCV protease inhibitor, a HCV polymerase inhibitor, a HCV helicase inhibitor, an interferon, ribavirin and a HCV NS5a inhibitor in the manufacture of a medicament for use in the treatment of HCV infection.

In one aspect of the invention, there is provided a method for the treatment of HCV infection in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in combination with one or more further active ingredients that are selected from a HCV protease inhibitor, a HCV polymerase inhibitor, a HCV helicase inhibitor, an interferon, ribavirin and a HCV NS5a inhibitor.

In one aspect of the invention, there is provided a pharmaceutical composition which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in combination with one or more further active ingredients that are selected from a HCV protease inhibitor, a HCV polymerase inhibitor, a HCV helicase inhibitor, an interferon, ribavirin and a HCV NS5a inhibitor and in association with a pharmaceutically acceptable diluents or carrier.

In one aspect of the invention, there is provided a pharmaceutical composition which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in combination with one or more further active ingredients that are selected from a HCV protease inhibitor, a HCV polymerase inhibitor, a HCV helicase inhibitor, an interferon, ribavirin and a HCV NS5a inhibitor and in association with a pharmaceutically acceptable diluents or carrier for use in the treatment of HCV infection.

In one aspect of the invention, there is provided a kit which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in combination with one or more further active ingredients that are selected from a HCV protease inhibitor, a HCV polymerase inhibitor, a HCV helicase inhibitor, an interferon, ribavirin and a HCV NS5a inhibitor.

In one aspect of the invention, there is provided a kit which comprises (a) a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in a first

unit dosage form, (b) one or more further active ingredients that are selected from a HCV protease inhibitor, a HCV polymerase inhibitor, a HCV helicase inhibitor, an interferon, ribavirin and a HCV NS5a inhibitor in a second unit dosage form and (c) container means for containing said first and second dosage forms.

In one embodiment of the invention, there is provided a therapeutic combination which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined and one or more further active ingredients that are selected from a HCV protease inhibitor, a HCV polymerase inhibitor, a HCV helicase inhibitor, an interferon, ribavirin and a HCV NS5a inhibitor.

In one embodiment of the invention, there is provided a combination product which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined and one or more further active ingredients that are selected from a HCV protease inhibitor, a HCV polymerase inhibitor, a HCV helicase inhibitor, an interferon, ribavirin and a HCV NS5a inhibitor.

In one aspect of the invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in combination with an interferon, ribavirin and VX950 (also known as Telaprevir, (1*S*,3a*R*,6a*S*)-2-[(2*S*)-2-[[(2*S*)-2-Cyclohexyl-2-(pyrazine-2-carbonylamino)acetyl]amino]-3,3-dimethylbutanoyl]-*N*-[(3*S*)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1*H*-cyclopenta[c]pyrrole-1-carboxamide or (3S,3aS,6aR)-2-[(2S)-2-[[(2S)-2-cyclohexyl-2-(pyrazine-2-carbonylamino)acetyl]amino]-3,3-dimethyl-butanoyl]-N-[(1S)-1-[2-(cyclopropylamino)-2-oxo-acetyl]butyl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-3-carboxamide).

In one aspect of the invention, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in combination with an interferon, ribavirin and VX950 in the manufacture of a medicament for use in the treatment of HCV infection.

In one aspect of the invention, there is provided a method for the treatment of HCV infection in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in combination with an interferon, ribavirin and VX950.

In one aspect of the invention, there is provided a pharmaceutical composition which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as

hereinbefore defined in combination with one or more further active ingredients that are selected from an interferon, ribavirin and VX950 and in association with a pharmaceutically acceptable diluents or carrier.

In one aspect of the invention, there is provided a pharmaceutical composition which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in combination with an interferon, ribavirin and VX950 and in association with a pharmaceutically acceptable diluents or carrier for use in the treatment of HCV infection.

In one aspect of the invention, there is provided a kit which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in combination with an interferon, ribavirin and VX950.

In one aspect of the invention, there is provided a kit which comprises (a) a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in a first unit dosage form, (b) an interferon, ribavirin and VX950 in a second unit dosage form and (c) container means for containing said first and second dosage forms.

In another embodiment of the invention, there is provided a therapeutic combination which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined and an interferon, ribavirin and VX950.

In another embodiment of the invention, there is provided a combination product which comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined and an interferon, ribavirin and VX950.

Examples of interferon that may be used include PEGASYS (Peginterferon alfa-2a) and PegIntron (Peginterferon alfa-2b).

The term "therapeutic combination" as referred to in this description is intended to mean any combination of the specified pharmaceutical agents that produces a therapeutic effect upon administration.

The term "combination product" as referred to in this description is intended to mean any product that comprises a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined and another specified pharmaceutical agent or agents and includes, but is not limited to, an individual pharmaceutical preparation comprising both a compound of Formula (I) and another specified pharmaceutical agent or agents (i.e. a combined preparation), a kit of parts comprising pharmaceutical preparations of a compound

of Formula (I) and another specified pharmaceutical agent or agents as individual or separate preparations, storage means for pharmaceutical preparations of a compound of Formula (I) and another specified pharmaceutical agent or agents as either individual or separate preparations and/or means for dispensing pharmaceutical preparations of a compound of Formula (I) and another specified pharmaceutical agent or agents as either individual or separate preparations, wherein the term "individual pharmaceutical preparation" or "individual preparations" is intended to mean a single pharmaceutical preparation which comprises both a compound of Formula (I) and another specified pharmaceutical agent or agents and wherein the term "separate preparations" is intended to mean two or more different pharmaceutical preparations one of which comprises a compound of Formula (I) and the others of which each comprise another specified pharmaceutical agent.

In another aspect of the invention, there is provided a therapeutic combination or a combination product comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined and one or more further active ingredients that are selected from a HCV protease inhibitor, a HCV polymerase inhibitor, a HCV helicase inhibitor, an interferon, ribavirin and a HCV NS5a inhibitor, for use in the treatment of hepatitis C virus infection.

In one embodiment of the invention, there is provided a therapeutic combination or a combination product comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined and an interferon, ribavirin and VX950, for use in the treatment of hepatitis C virus infection.

In another aspect, the present invention provides the use of a therapeutic combination or a combination product comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined and one or more further active ingredients that are selected from a HCV protease inhibitor, a HCV polymerase inhibitor, a HCV helicase inhibitor, an interferon, ribavirin and a HCV NS5a inhibitor, in the manufacture of a medicament for the treatment of hepatitis C virus infection.

In one embodiment, the present invention provides the use of a therapeutic combination or a combination product comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined and an interferon, ribavirin and VX950, in the manufacture of a medicament for the treatment of hepatitis C virus infection.

Examples

The present invention will now be further explained by reference to the following illustrative examples in which, generally:

(i) temperatures are given in degrees Celsius (°C); unless stated otherwise, operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18 to 25°C;

(ii) Organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (1-750mbar) with a bath temperature up to 60°C;

(iii) chromatography means flash chromatography on silica gel;

(iv) in general, the course of reactions was followed by analytical LC-MS, and reaction times where given are for illustration only.

(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane, determined at 250MHz, using perdeuterio dimethyl sulphoxide (d_6-DMSO) as solvent, unless otherwise stated; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; coupling constants, *J*, are reported in Hz;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) LC-MS was carried out using one of four methods:

1. (QC Method 1)

Liquid Chromatograph : Agilent 1200 series, with PDA detector, scan range 190-400nm.
Mass spectrometer : Agilent MSD 6120 operating in electrospray ionisation mode with +ve/ -ve ion switching.

LC Conditions

Mobile phase A : 0.1% Formic acid in water
Mobile phase B : 0.1% Formic acid in acetonitrile

Gradient

Time (mins)	%B
0	5
0.5	95
1.45	95

Flow rate : 1.5ml/min.

Column : Varian Pursuit Ultra 3 C18 30mm x 2.1mm

Column temp : 50C

2. (QC Method 2)

Liquid Chromatograph : Agilent 1200 series, with PDA detector, scan range 190-400nm.

Mass spectrometer : Agilent MSD 6120 operating in electrospray ionisation mode with +ve/ -ve ion switching.

LC Conditions

Mobile phase A : 0.1% formic acid in water

Mobile phase B : 0.1% formic acid in acetonitrile

Gradient

Time (mins)	%B
1	5
4	95
4.9	95
5	5

Flow rate : 1.0ml/min.

Column : Varian Pursuit Ultra 3 C18 50mm x 2.1mm

Column temp : 50C

3. (QC Method 3)

Liquid Chromatograph : Waters Acquity UPLC, with PDA detector, (scan range 190-400nm) and ELSD.

Mass spectrometer : Waters SQD operating in electrospray ionisation mode with +ve/ -ve ion switching.

LC Conditions

Mobile phase A : 0.1% formic acid in water

Mobile phase B : 0.1% formic acid in acetonitrile

Gradient

Time (mins)	%B
0	1
0.1	1
5	95
5.3	95

Flow rate : 0.6 ml/min

Column : Waters Acquity UPLC BEH C18 50mm x 2.1mm 1.7um

Column temp : 50C

4. (QC Method 4)

Liquid Chromatograph : Agilent 1200 series, with PDA detector, scan range 190-400nm.

Mass spectrometer : Agilent MSD 6120 operating in electrospray ionisation mode with +ve/-ve ion switching.

LC Conditions

Mobile phase A : 0.1% Formic acid in water

Mobile phase B : 0.1% Formic acid in acetonitrile

Gradient

Time (mins)	%B
0	2
0.3	2
2	95
2.45	95

Flow rate : 1.5ml/min.

Column : Varian Pursuit Ultra 3 C18 30mm x 2.1mm

Column temp : 50C

(x) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulfur atom have not been resolved;

(xi) all microwave reactions were carried out in a CEM Discover® microwave synthesiser;

(xii) Preparative high performance liquid chromatography (HPLC) was carried out using the following conditions, unless otherwise stated:

Liquid Chromatograph : Waters 600 pump, W2700 Sample Manager, W996 PDA detector

Mass spectrometer : Waters ZQ operating in electrospray ionisation mode.

LC Conditions

Mobile phase A : 0.1% formic acid in water

Mobile phase B : 0.1% formic acid in acetonitrile

Gradient

Time (mins.)	%B
2	5
15	75
16	100
18	100

Flow rate: 20 ml/min

Column: Gemini C18 50mm x 21.2mm 5um 110A Axia (Phenomenex Ltd)

(xiii) Chiral LC analysis was carried out using the below method, unless otherwise stated:

Column: 10 x 250 mm CHIRALPAK® IA

Mobile phase: 80% (10% DCM in EtOH) in i-hexane

Flow rate: 1.0 ml/min

Detection: UV 254nm

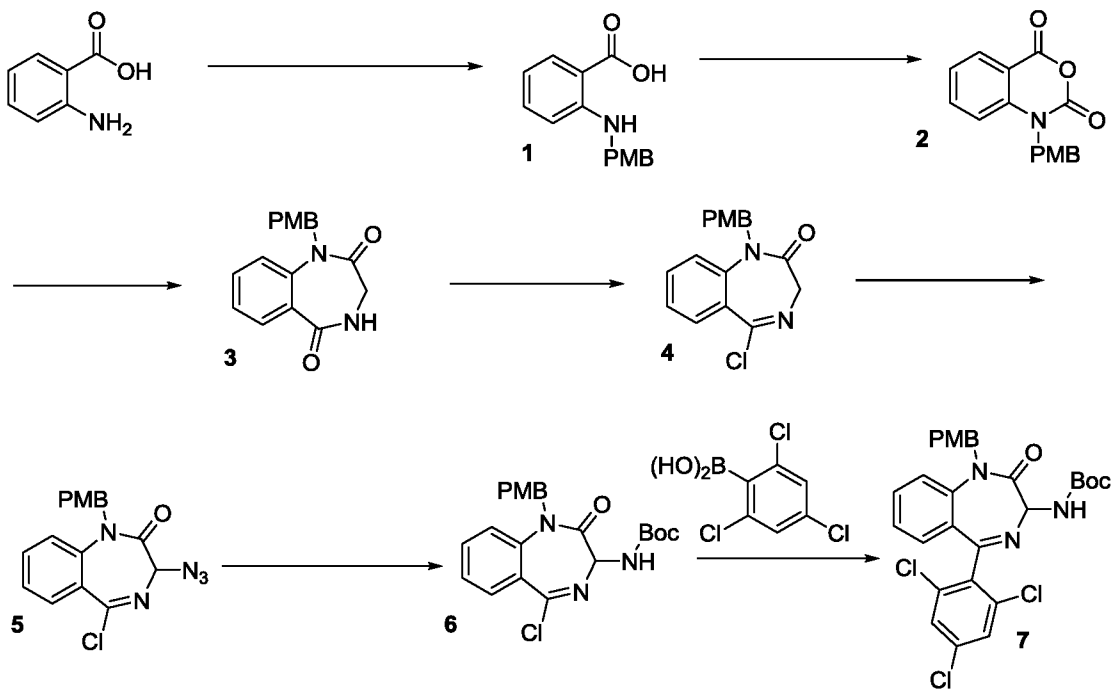
Temperature: 20°C

(xiii) the following abbreviations have been used herein, where necessary:

CAN	Cerium(IV) ammonium nitrate
DCM	Dichloromethane
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulphoxide
Ether	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
FCC	Flash column chromatography
HBTU	O-(1H-benzotriazol-1-yl)-N,N,N',N',-tetramethyluronium hexafluorophosphate

MeOH	Methanol
MsCl	Methanesulphonyl chloride
PE	Petroleum ether
PMB	p-Methoxybenzyl
^{i}PrOAc	Isopropyl acetate
R_t	Retention time
RT	Room temperature
TBME	*tert*-butylmethylether
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
min	minutes
h	hours
d	days

Synthesis of intermediates



2-(4-Methoxy-benzylamino)benzoic acid (1)

A 60L-reactor was set under inert atmosphere and charged with 2-aminobenzoic acid (3.00kg, 21.90 mol) and dichloromethane (55 L). 4-Methoxybenzaldehyde (3.60 kg, 26.50 mol) and acetic acid (0.67 L) were added. The resulting suspension was heated to 40 °C. At a temperature of 37 °C a clear solution was obtained. After stirring at 40 °C for 30 min the solution was cooled to 5 °C and sodium triacetoxyhydroborate (9.83 kg, 46.0 mol) was added in portions (caution: addition is very exothermic, efficient cooling is necessary). After complete addition the reaction was warmed to room temperature and stirred at that temperature over night (16 h). Water (35 L) and THF (5 L) were added and the biphasic mixture was transferred into a 100 L-separating vessel. The phase separation was insufficient at this point. The distinguishable organic layer was separated and the residual biphasic mixture was filtered through Celite Hyflo (1 kg). The filtrate showed excellent phase separation. The rest of the organic layer was separated and the aqueous layer was extracted with dichloromethane (5 L). The combined organic layers were washed with water (10 L), evaporated to dryness (16 mbar, 50 °C). TBME (10 L) was added to the solid and the suspension was stirred at room temperature for 2 h. The obtained yellow solid was filtered off, washed with TBME (4 L) and dried at 40 °C / 20 mbar for 12 h. The title compound was isolated as a yellow solid in 90 % yield (5.04 kg, >99 a/a% purity).

NMR δ 7.89 (1H, dd, *J* 7.9, 1.6), 7.23-7.33 (3H, m), 6.89 (2H, m), 6.68 (1H, d, *J* 7.9Hz), 6.54 (1H, m), 4.34 (2H, s), 3.72 (3H, s);
MS (m/e) 256 $[M-H]^-$, R_t 0.92min (QC Method 1)

1-(4-Methoxy-benzyl)-1H-benzo[d][1,3]oxazine-2,4-dione (2)

A 30L-reactor was set under inert atmosphere and charged with 2-(4-methoxybenzylamino)benzoic acid (**1**) (1.64 kg, 6.37 mol) and THF (16 L). The resulting yellow solution was cooled to 15 °C and bis(trichloromethyl)carbonate (0.69 kg, 2.33 mol) was added in portions within 45 min (addition is exothermic). Upon addition a white solid starts to precipitate. After complete addition the obtained white suspension is stirred at room temperature over night (16 h). The suspension was concentrated to dryness on a rotavap (50 °C) and TBME (14 L) was added to the residue. The resulting suspension was stirred at 50 °C for 10 min and then cooled to room temperature within 2 h. The obtained solid was

filtered off, washed with TBME (4 L) and dried at 40 °C / 20 mbar for 12 h. The title compound was isolated as a white solid in 99 % yield (1.78 kg, 99a/a% purity).

NMR δ 8.01 (1H, dd, *J* 8.2, 1.9), 7.74 (1H, m), 7.25-7.37 (3H, m), 6.88 (2H, m), 5.21 (2H, s), 3.70 (3H, s);
MS (m/e) No MI observed, R_t 2.8min (QC Method 2)

1-(4-Methoxy-benzyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-one (3)

A 60L-reactor was set under inert atmosphere and charged with 1-(4-methoxybenzyl)-1HBenzo[d][1,3]oxazine-2,4-dione **(2)** (6.43 kg, 22.70 mol) and acetic acid (46 L). To the resulting white suspension, glycine (4.02 kg, 53.50 mol) was added and the mixture was heated to 92 °C within 3 h (caution: upon heating a strong gas evolution was observed). At a temperature of 90 °C a clear solution was obtained. The mixture was stirred at 92 °C for 24 h. The reaction was cooled to 20 °C and the acetic acid was evaporated on a rotavap (50 °C). Residual acetic acid was removed by co-evaporation with toluene (2 x 5 L). The residue was dissolved in ethyl acetate (8 L). This solution was added within 30 min to sodium hydroxide solution (2 M, 40 L) with vigorous stirring. The resulting precipitate was filtered off and washed with water (2 x 8 L) and ethyl acetate (2 x 5 L). The title compound was obtained after drying at 40 °C / 20 mbar for 12 h in 79 % yield (5.41 kg, 97a/a% purity).

NMR δ 8.78 (1H, t, *J* 6.0), 7.65 (1H, dd, *J* 7.6, 1.3), 7.45-7.58 (2H, m), 7.28 (1H, ddd, *J* 8.2, 6.3, 1.9), 7.04 (2H, d, *J* 8.4), 6.81 (2H, d, *J* 8.4), 5.27 (1H, d, *J* 15.6), 4.88 (1H, d, *J* 15.6), 3.69 (3H, s);
MS (m/e) 297 $[M+H]^+$, R_t 0.71min (QC Method 1)

5-Chloro-1-(4-methoxy-benzyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one (4)

A 40L-reactor was set under inert atmosphere and charged with 1-(4-methoxybenzyl)3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione **(3)** (2.10 kg, 7.1 mol), toluene (21 L) and N,Ndimethylaniline (2.69 L, 21.3 mol). To the resulting suspension phosphoryl trichloride (660 mL, 7.2 mol) was added within 15 min. The obtained yellow suspension was heated to 110 °C and stirred at this temperature over night (16 h). The mixture was cooled to 25 °C and slowly added into a solution of potassium carbonate (7 kg) in water (25 L) and ice (5 kg) with

stirring. The pH of the mixture stayed >12 at all times. The resulting biphasic mixture was transferred into a 100 L-separating vessel. The organic layer was separated and the aqueous layer was extracted with toluene (5 L). The combined organic layers were dried over sodium sulphate and the solvent was evaporated on a rotavap (50 °C). To the crude product, heptanes (3 L) was added and the resulting suspension was stirred at room temperature on a rotavap for 20 min. The solvent was decanted off and this procedure was repeated for a second time. The next day, the isolated solid was combined with the product which had crystallized from the combined heptane solutions after storage over night. The obtained solid was dissolved in ethyl acetate (5 L) on a rotavap (50 °C). After cooling to room temperature the solution was filtered through 2.5 kg of silica gel. The silica gel was washed with ethyl acetate (25 L) and the collected solution was evaporated to dryness under reduced pressure (50 °C). TBME (2 L) was added to the residue and the suspension was stirred at room temperature over night (16 h). The suspension was cooled to 0 °C and stirred for 2 h at that temperature. The solid was filtered off, washed with ice-cold TBME (3 x 500 mL) and dried at 30 °C/20 mbar until constant weight (12 h). The title compound was isolated as an off-white solid in 75 % yield (1.69 kg, >95a/a% purity).

NMR δ 7.71 (1H, dd, *J* 8.5, 0.9), 7.54-7.64 (2H, m), 7.27-7.35 (1H, m), 6.96 (2H, d, *J* 8.6), 6.79 (2H, d, *J* 8.6), 5.28 (1H, d, *J* 15.6), 4.88 (1H, d, *J* 15.6), 4.45 (1H, d, *J* 10.7), 3.86 (1H, d, *J* 10.7), 3.66 (3H, s);
MS (m/e) 315 $[M+H]^+$, R_t 0.90min (QC Method 1)

3-Azido-5-chloro-1-(4-methoxy-benzyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one (5)

Potassium t-butoxide (0.66 kg, 5.90 mol) was dissolved in 2-Methyl-Tetrahydrofuran (6.3 L) under argon. 3A Molecular Sieve (300 g) was added. 2,4,6-triisopropylbenzenesulfonyl azide (1.86 kg, 5.17 mol) was dissolved in 2-Methyl-Tetrahydrofuran (4.00 L) under argon. 3A Molecular Sieves (300 g) was added. Both solutions were stored for 12h at rt. A 30L-glass reactor was set under inert atmosphere. 5-chloro-1-(4-methoxy-benzyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one **(4)** (1.58 kg, 4.92 mol) was loaded into the reactor and 2-Methyl-Tetrahydrofuran (9.5 L) was added. The Suspension was cooled to -40°C. The dry solution of potassium tert-butoxide was added via dropping funnel keeping the temperature between -40°C and -50°C. A red solution was formed during addition. The reaction mixture

was stirred for 1h between -40°C and -50°C. Next, the dry solution of 2,4,6-triisopropylbenzenesulfonyl azide was added via dropping funnel keeping the temperature between -40°C and -50°C. The mixture was stirred for 2.5h at -40°C. Acetic acid (2.26 L, 39.4 mol) was added via dropping funnel keeping temperature below -20°C. Reaction mixture turned into an orange suspension. The reaction was warmed up to RT and finally warmed to 30°C for 36h (until full consumption of intermediate triazene). The mixture was cooled to rt and transferred to 50L extraction vessel. 10kg ice was added to the organic layer and 4N NaOH (6.8L) was added slowly under stirring. Then saturated $NaHCO_3$ solution (8L) was added slowly under stirring until pH=8. The phases were separated and the organic layer was washed again with sat. NaHCO3-solution (4L) and brine (5L). Phases were separated and organic phase was dried with Na_2SO_4, filtered and concentrated to approx 10L volume. The concentrate crystallized. Solid was filtered off, washed with EtOAc (1L) and dried to give the title compound (0.74 kg, >98a/a%purity, 40%). The mother liquor was concentrated to dryness and the residue was recrystallised again from EtOAc (2.0L). Another crop of product could be obtained after filtration/drying (0.36 kg, 90a/a% purity, 19%).

NMR δ 7.75 (1H, dd, *J* 8.5, 0.9), 7.62-7.68 (2H, m), 7.32-7.40 (1H, m), 6.96 (2H, d, *J* 8.6), 6.80 (2H, d, *J* 8.6), 5.33 (1H, d, *J* 15.5), 4.98 (1H, s), 4.95 (1H, d, *J* 16.4), 3.66 (3H, s);
MS (m/e) No MI observed, R_t 1.02min (QC Method 1)

[5-Chloro-1-(4-methoxy-benzyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester (6)

A 50L-autoclave was loaded with 3-azido-5-chloro-1-(4-methoxy-benzyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one **(5)** (1.0 kg, 2.81 mol, 1.0 eq), di-*tert*-butyl dicarbonate (0.98 kg, 4.50 mol, 1.5 eq). Dioxane (12 L) was added in order to dissolve all solids. platinum (IV) oxide (70 g, 7 wt%) was added and autoclave was pressurized with hydrogen (10 bar). After 1h, pressure was released and autoclave was again repressurised with hydrogen (10bar). This procedure was repeated a second time after 2h. After 3h, reaction was filtered over a pressure nutsche and filtrate was treated with Norit Supra Eur A (200 g) for 45min at 45°C. The suspension was concentrated at 50°C/16mbar and the residue was redissolved in EtOAc (7 L). The suspension was filtered over a plug of Celite hyflo and the filter cake was rinsed with EtOAc (10 L). The filtrate was evaporated to dryness and the crude product was recrystallised

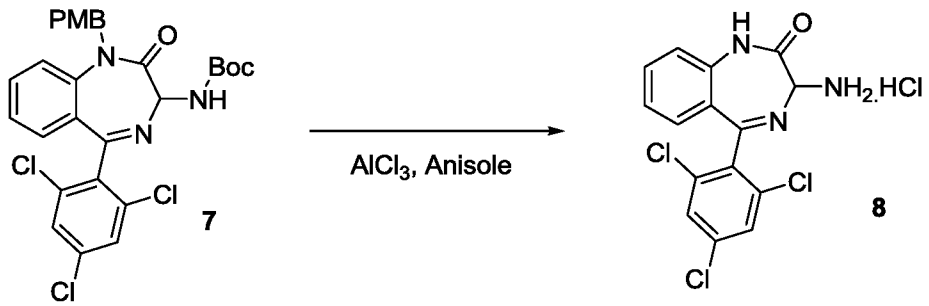
from EtOAc/heptanes (4 L, 1:1). The title compound was obtained as pale yellow solid in 82% yield (1.04 kg, 99a/a% purity).

NMR δ 7.98 (1H, d, *J* 8.8), 7.75 (1H, d, *J* 7.9), 7.62-7.71 (2H, m), 7.33-7.41 (1H, m), 6.92 (2H, d, *J* 8.5), 6.78 (2H, d, *J* 8.5), 5.37 (1H, d, *J* 15.5), 5.09 (1H, d, *J* 8.5), 4.89 (1H, d, *J* 15.5), 3.65 (3H, s), 1.37 (9H, s);
MS (m/e) 330 $[(M\text{-}Boc)+H]^+$, R_t 1.06min (QC Method 1)

[1-(4-Methoxy-benzyl)-2-oxo-5-(2,4,6-trichloro-phenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester (7)

A suspension of [5-chloro-1-(4-methoxy-benzyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester **(6)** (4.3g, 10mmol), 2,4,6-trichlorophenyl boroninc acid (4.3g, 19mmol), tetrakis(triphenylphospine)palladium (0) (4.6g, 4mmol), K_2CO_3 (3.0g, 21mmol) and Ag_2CO_3 (8.6g, 31mmol) in THF (120ml) was heated at reflux for 72 h. The reaction mixture was cooled and filtered through celite®. The filtrate was reduced onto silica and column chromatography (SiO_2; PE→3:2 PE:ether) gave a partially pure sample. Further chromatograph (SiO_2; 19:1 DCM:MeOH) gave the title compound; (1.3g, 2.2mmol).

NMR δ 7.96 (1H, d, *J* 8.5), 7.77 (1H, d, *J* 8.2), 7.59-7.71 (2H, m), 7.05-7.30 (4H, m), 6.80 (2H, d, *J* 8.5), 5.04-5.25 (3H, m), 3.67 (3H, s), 1.38 (9H, s);
MS (m/e) 576 $[M+H]^+$, R_t 1.23min (QC Method 1)

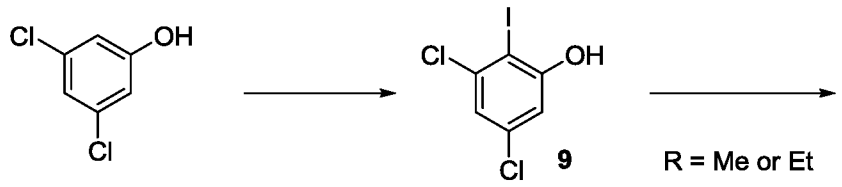


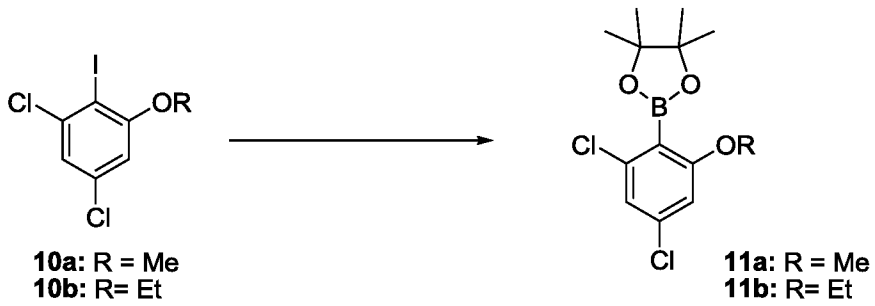
3-Amino-5-(2,4,6-trichloro-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one hydrochloride (8)

A solution of [1-(4-methoxy-benzyl)-2-oxo-5-(2,4,6-trichloro-phenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester **(7)** (1.7g, 3mmol) in anhydrous anisole (25ml) was treated with aluminium trichloride (4.0g, 30mmol) and then heated at 70°C for 4 h. The reaction mixture was cooled to RT, diluted with EtOAc (200ml) and basified with saturated K_2CO_3 solution. The resulting slurry was filtered through Celite® and the organics separated, dried and concentrated. The resulting residue was taken into DCM (50ml) and stirred for 2 h with 2M HCl (50ml). The resulting precipitate was filtered off and dried under vacuum to give the title compound; (0.82g, 2.3mmol).

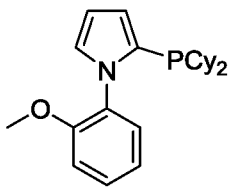
NMR δ 11.54 (1H, s), 9.09 (3H, br, s), 7.95 (1H, d, *J* 1.9), 7.77 (1H, d, *J* 1.9), 7.59-7.72 (1H, m), 7.34 (1H, d, *J* 7.9), 7.14-7.26 (2H, m), 5.27 (1H, s);

MS (m/e) 356 $[M+H]^+$, R_t 0.69min (QC Method 1)





CataCXiumPOMeCy =



3,5-Dichloro-2-iodophenol (9)

A 30L-reactor was set under inert atmosphere. Iodine (2.72 kg, 10.74 mol) was dissolved in toluene (19 L) and stirred until full dissolution (3-4h) at ambient temperature. A 63L-reactor was set under inert atmosphere. Toluene (8 L) was fed into the reactor followed by addition of sodium hydride (60%, 0.859 kg, 21.47 mol). The suspension was cooled to 0-5°C and a solution of 3,5-dichlorophenol (1.75 kg, 10.74 mol) in toluene (8.75 L) was added during 1.5h keeping the internal temperature <10°C. After complete addition, the mixture was further stirred for 45 min. The iodine-solution was added over the course of 2 h keeping internal temperature below 10 °C. After 2 h, the conversion was 96% (HPLC) and reaction was quenched by slow addition (20 min) of 2N HCl (8 L) keeping the internal temperature <15°C. The layers were separated and the aqueous phase was extracted with TBME (5 L). The organic phases were combined and washed with 10% $Na_2S_2O_3$-solution (2x 8 L), brine (8 L). The organic phase was dried over Na_2SO_4, filtered and concentrated. The crude product was recrystallized from heptanes (7.5 L, 60°C to 0°C). The solids were filtered off and dried at 40 °C / 50 mbar for 48 h to give the title compound (**9**) in 82% yield (2.70 kg, 94a/a% purity).

NMR ($CDCl_3$) δ 7.14 (1H, d, *J* 2.2), 6.97 (1H, d, *J* 2.2), 5.68 (1H, br s);
MS (m/e) 287 $[M-H]^-$, R_t 0.98min (QC Method 1)

1,5-Dichloro-2-iodo-3-methoxybenzene (10a)

To the crude material from the preparation of 3,5-dichloro-2-iodophenol (**9**) in DMF (300ml) was added Cs_2CO_3 (63.7g, 196mmol) and MeI (14.4ml, 231mmol). After 16 h, the reaction mixture was filtered over Celite®, concentrated, and then partitioned between EtOAc and 2M HCl. Separation of the organic phase and concentration provided an oil, which was triturated from PE to provide the title compound as a pale yellow solid; (32g, 57%).

NMR ($CDCl_3$) δ 7.19 (1H, d, *J* 2.2), 6.74 (1H, d, *J* 2.2), 3.95 (3H, s);
MS (m/e) No MI observed, R_t 1.15 min (QC Method 1).

1,5-Dichloro-2-iodo-3-ethoxybenzene (10b)

A 30L-reactor was set under inert atmosphere and a scrubber was loaded with 4N NaOH/EtOH. 3,5-dichloro-2-iodophenol (**9**) (3.34 kg, 11.5 mol) was dissolved in DMF (12

L). K_2CO_3 (2.39 kg, 17.3 mol) was added and the mixture was heated to 50°C. At an internal temperature of 50°C, iodoethane (1.02L, 12.7 mol) was added during 30 min keeping internal temperature at 50-55°C. The mixture was stirred for another 30 min before reaction was allowed to equilibrate to ambient temperature. Celite Hyflo (2 kg) was added to the stirred mixture and after 0.5 h the mixture was filtered over a Celite Hyflo pad (1 kg). The filter cake was rinsed with DMF (2 L). The filtrate was concentrated at 45 °C / 16 mbar. The residue was partitioned between heptanes (20 L) and water (8 L). After phase separation, the organic phase was further washed with water (8 L) and brine (8 L). All aqueous phases were back extracted with heptanes (5 L). The organic phases were combined and dried over Na_2SO_4. The filtrate was evaporated and the crude product was re-crystallized from heptanes (4 L, 60°C to 0°C). The title compound (**10b)** was obtained as off-white solid in 85% yield (3.13kg, 99a/a% purity).

NMR ($CDCl_3$) δ 7.12 (1H, d, *J* 2.1), 6.66 (1H, d, *J* 2.1), 4.10 (2H, q, *J* 7.0), 1.53 (3H, t, *J* 7.0)

2-(2,4-Dichloro-6-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11a)

To a solution of 1,5-dichloro-2-iodo-3-methoxybenzene **(10a)** (21.0g, 69.3mmol) in THF (250ml) was sequentially added CuI (1.32g, 6.9mmol) and NaH (60% dispersion in mineral oil, 4.2g, 104mmol), followed by a slow addition of pinacolborane (15.1ml, 104mmol). The resulting suspension was stirred at room temperature for 16 h under a N_2 atmosphere, and then quenched with saturated NH_4Cl (250ml). After 20 min, the reaction mixture was extracted with EtOAc (×3), dried and then filtered over Celite®. Concentrated and purification by column chromatography (SiO_2; EtOAc:PE 0:1→1:9) to afford the title boronate as a white solid; (15.1g, 72%).

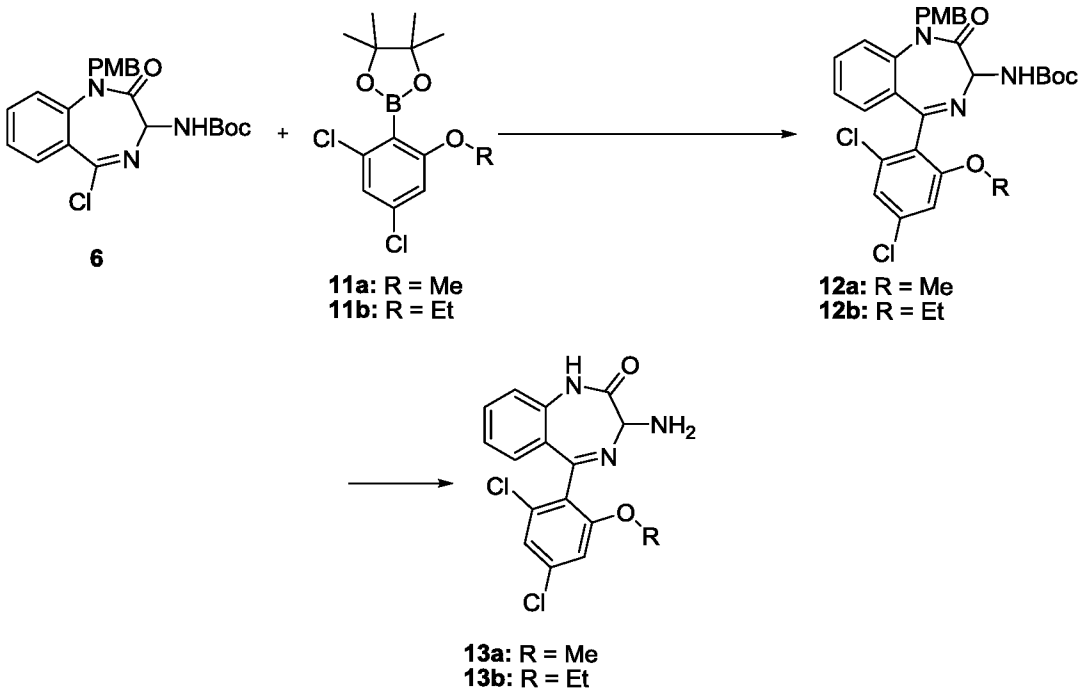
NMR ($CDCl_3$) 6.87 (1H, d, *J* 1.6), 6.63 (1H, d, *J* 1.6), 3.37 (3H, s), 1.32 (12H, s);
MS (m/e) No MI observed, R_t 1.17min (QC Method 1)

2-(2,4-Dichloro-6-ethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (11b)

Dry dioxane (1.5 L) was degassed by passing a flow of argon through the solvent for 30 min. CataCXiumPOMeCy (45.9 g, 124 mmol) and $Pd(OAc)_2$ (13.95 g, 62.2 mmol) were added and the mixture was stirred for 45 min to give a bright orange solution. A 30L-reactor was set

under inert atmosphere and charged with 1,5-dichloro-3-ethoxy-2-iodobenzene (**10b**) (1.97 kg, 6.22 mol) in dioxane (18 L). Triethylamine (2.58 L, 18.6 mol) was added and the mixture was cooled to 10°C. The mixture was degassed by passing a flow of argon through the solution for 1 h. To the dark solution 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.35 kg, 10.6 mol) was rapidly added. Some gas evolution but no significant exotherm could be observed. A flow of argon was again passed through the solution for 10 min. The clear yellow solution formed was heated to 80°C (internal temperature) and the catalyst solution was added via cannula within 10 min. The reaction was kept at this temperature for 5 h before cooling to ambient. The mixture was concentrated at 45 °C / 20 mbar and the residue was re-dissolved in DCM (12 L). The mixture was filtered over a plug of Hyflo (1 kg). The filtrate was washed with water (2 x 5 L), brine (2 L). All aqueous phases were combined and back-extracted with DCM (3 L). The organic phases were combined and dried over Na_2SO_4. The filtrate was concentrated until crystallisation started. The crystallisation was completed by addition of heptanes (5 L). Further 2 L solvent were distilled off. The thick suspension was stirred at 45 °C for 45 min and then cooled to 0 °C for 1 h. The solid was filtered off and rinsed with cold heptanes. The title compound **4** was obtained after drying at 40 °C / 15mbar for 12 h in 85% yield (1.65 kg, >97a/a% purity).

NMR ($CDCl_3$) δ 6.96 (1H, d, *J* 1.6), 6.70 (1H, d, *J* 1.6), 4.00 (2H, q, *J* 7.0), 1.45-1.38 (3H, m), 1.42 (12H, s);
MS (m/e) No MI observed, R_t 1.22min (QC Method 1)



***tert*-Butyl 5-(2,4-dichloro-6-methoxyphenyl)-1-(4-methoxybenzyl)-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-ylcarbamate (12a)**

A solution of [5-chloro-1-(4-methoxy-benzyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester **(6)** (16.0g, 37mmol), 2-(2,4-dichloro-6-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **(11a)** (13.0g, 43mmol) and $Pd(PPh_3)_4$ (3.7g, 3.2mmol) in 1,2-dimethoxyethane (120ml) and saturated Na_2CO_3 (60ml) were heated at 100 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with water, extracted with EtOAc (×3), and dried. Concentration and trituration with ether provided the title compound as a white solid. (11.8g) Concentration of the mother liquor followed by purification by column chromatography (SiO_2; EtOAc:PE 0:1→2:3) provided a further crop of the desired product as a white solid; (7.5g, combined mass 19.3g, total yield 91%).

NMR δ 8.01-7.80 (0.3H, m), 7.70-7.44 (1.7H, m), 7.41-7.04 (6H, m), 6.92-6.77 (2H, m), 5.25-4.95 (2H, m), 3.86 (1.7H, s), 3.70 (1.3H, s), 3.69 (1.7H, s), 3.35 (1.3H, s), 1.38 (7.8H, s), 1.31 (1.2H, s);

MS (m/e) 570 $[M+H]^+$, R_t 1.19min (QC Method 1)

***tert*-Butyl 5-(2,4-dichloro-6-ethoxyphenyl)-1-(4-methoxybenzyl)-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-ylcarbamate (12b)**

A 30L-glass reactor was set under inert atmosphere. 1,2-dimethoxyethane (15 L) and 2N Na_2CO_3-solution (7 L, 14.0 mol, 3.1 eq) were added. 2-(2,4-dichloro-6-ethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**11b**) (1.59 kg, 5.0 mol, 1.1 eq) and [5-chloro-1-(4-methoxy-benzyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl]-carbamic acid tert-butyl ester (**6**) (1.96 kg, 4.56 mol, 1.0 eq) were dissolved in the mixture. A flow of argon was passed through the biphasic mixture for 45min. $Pd(PPh_3)_4$ (0.16 kg, 0.14 mol, 3 mol%) was added and mixture was heated to 80°C (internal temperature). After 3h, reaction was cooled to rt and transferred to extraction vessel. Organic phase was diluted with EtOAc (4 L). Phases were separated and the organic phase was washed with water (5 L) and brine (5 L). The aqueous phases were back extracted with EtOAc (2 L). The organic phases were combined, dried with Na_2SO_4, filtered and evaporated. The crude product was recrystallised from EtOAc (4 L). The title compound was isolated as a white solid in 77% yield (2.0 kg, 99a/a% purity).

NMR δ 7.90-7.78 (0.4H, m), 7.71-7.50 (1.1H, m), 7.39-7.05 (6.4H, m), 6.96-6.77 (2.1H, m), 5.43-5.09 (1.8H, m), 4.61 (0.2H, d, *J* 15.8), 4.23-4.01 (0.8H, m), 3.84-3.65 (1.2H, m), 3.74 (1.2H, s), 3.68 (1.8H, s), 1.39 (9H, s), 1.20 (1.8H, t, *J* 7.0), 0.78 (1.2H, t, *J* 7.0);
MS (m/e) 584 $[M+H]^+$, R_t 1.23min (QC Method 1)

3-Amino-5-(2,4-dichloro-6-methoxyphenyl)-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one (13a)

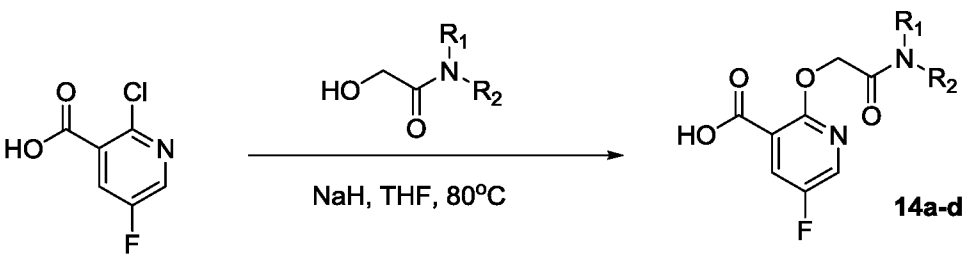
To *tert*-butyl 5-(2,4-dichloro-6-methoxyphenyl)-1-(4-methoxybenzyl)-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-ylcarbamate **(12a)** (4.0g, 7.0mmol) in anisole (30ml) was added $AlCl_3$ (4.6g, 34.8mmol) and the solution heated to 70 °C under N_2 for 16 h. Upon cooling to room temperature, the reaction mixture was slowly added to saturated $NaHCO_3$ (200ml). Celite® was added to the suspension, which was then filtered over Celite®, washing with copious quantities of a mixture of EtOAc and acetone. The aqueous phase from the filtrate was subsequently removed, and the organic materials were extracted with EtOAc (×2). The combined organic extracts were dried, concentrated and triturated with ether to provide the title compound as a pale yellow powder. (2.0g, 81%).

NMR δ 10.77 (1H, br s), 7.53-7.44 (1H, m), 7.35 (0.3H, d, *J* 1.6), 7.30 (0.7H, d, *J* 1.6), 7.20-7.02 (4H, m), 4.27 (1H, m), 3.91 (2H, m), 3.50 (1H, m);
MS (m/e) 350 $[M+H]^+$, R_t 0.62min (QC Method 1).

3-Amino-5-(2,4-dichloro-6-ethoxyphenyl)-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one (13b)

To *tert*-butyl 5-(2,4-dichloro-6-ethoxyphenyl)-1-(4-methoxybenzyl)-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-ylcarbamate **(12b)** (3.4g, 5.8mmol) in anisole (30ml) was added $AlCl_3$ (3.8g, 28.8mmol) and the solution heated to 70 °C under N_2 for 16 h. Upon cooling to room temperature, the reaction mixture was slowly added to saturated $NaHCO_3$ (200ml). Celite® was added to the suspension, which was then filtered over Celite®, washing with copious quantities of a mixture of EtOAc and acetone. The aqueous phase from the filtrate was subsequently removed, and the organic materials were extracted with EtOAc (×2). The combined organic extracts were dried, concentrated and triturated with ether to provide the title compound as a pale grey powder. (1.5g, 71%).

NMR δ 10.81 (0.6H, s), 10.77 (0.4H, s), 7.53-7.42 (1H, m), 7.34-7.27 (1H, m), 7.21-7.04 (4H, m), 4.30-4.12 (1.8H, m), 3.91-3.75 (0.6H, m), 3.70-3.54 (0.6H, m), 1.28 (1.2H, t, *J* 7.0), 0.81 (1.8H, t, *J* 7.0);
MS (m/e) 364 $[M+H]^+$, R_t 0.65min (QC Method 1).



2-(2-Amino-2-oxoethoxy)-5-fluoronicotinic acid (14a)

A suspension of 2-chloro-5-fluoronicotinic acid (5.95g, 33.9mmol) and glycolamide (5.0g, 66.6mmol) in anhydrous THF (400ml) was cooled in an ice-bath and treated portionwise with sodium hydride (60% dispersion in mineral oil, 7.8g, 195mmol). On completion of addition, the resulting slurry was stirred, under N_2, at 80°C for 72hr. The reaction mixture was cooled and poured into ice-cooled 2M HCl. The aqueous was adjusted to ~pH11 and washed with

ether. The aqueous was adjusted to pH 1 with conc. HCl and the resulting precipitate collected by filtration. Washing sequentially with water and ether afforded the title compound as a white solid; (4.64g, 21.7mmol).

NMR δ 8.32 (1H, d, *J* 3.2), 8.06 (1H, dd, *J* 3.2, 8.2), 7.36 (2H, br, s), 4.73 (2H, s);
MS (m/e) 215 $[M+H]^+$, R_t 0.86min (QC Method 4)

2-(2-(Ethylamino)-2-oxoethoxy)-5-fluoronicotinic acid (14b)

A solution of 2-chloro-5-fluoronicotinic acid (2.50g, 14.2mmol) and N-ethyl-2-hydroxyacetamide (1.95g, 18.9mmol) in anhydrous THF (200ml) was treated with NaH (60% dispersion in oil, 2.30g, 57.5mmol) and the resulting suspension heated at 75°C overnight. On cooling, the reaction mixture was diluted with water and washed with ether. The aqueous was acidified with conc. HCl and extracted with DCM. The organics were dried and reduced onto silica. Purification by column chromatography (SiO_2; DCM:MeOH 1:0→19:1) followed by trituration with ether gave the title compound as a white solid (0.24g, 1.0mmol).

NMR δ 8.34 (1H, d, *J* 3.2), 8.06 (1H, dd, *J* 2.8, 7.9), 7.99 (1H, br, t *J* 4.7), 4.76 (2H, s), 3.18-3.05 (2H, m), 1.01 (1H, t, *J* 7.0);
MS (m/e) 243 $[M+H]^+$, R_t 1.03min (QC Method 4)

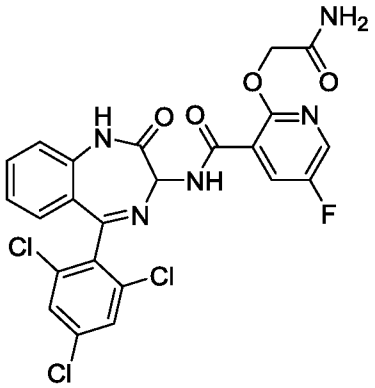
2-(2-(Cyclopropylamino)-2-oxoethoxy)-5-fluoronicotinic acid (14c)

Preparation analogous to **14b**, using N-cyclopropyl-2-hydroxyacetamide.
MS (m/e) 255 $[M+H]^+$, R_t 1.07min (QC Method 4)

2-(2-(Diethylamino)-2-oxoethoxy)-5-fluoronicotinic acid (14d)

Preparation analogous to **14b**, using N,N-diethyl-2-hydroxyacetamide.
MS (m/e) 271 $[M+H]^+$, R_t 1.26min (QC Method 4)

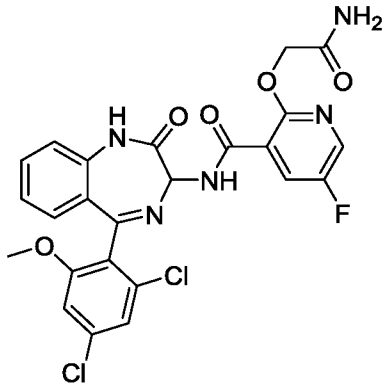
Example 1: 2-(2-Amino-2-oxoethoxy)-5-fluoro-N-(2-oxo-5-(2,4,6-trichlorophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)nicotinamide



A solution of 2-(2-amino-2-oxoethoxy)-5-fluoronicotinic acid (**14a)** (60mg, 0.28mmol), HBTU (130mg, 0.34mmol) and TEA (80μL, 0.57mmol) in DMF (3ml) was treated with 3-amino-5-(2,4,6-trichloro-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one hydrochloride **(8)** (100mg, 0.25mmol) and stirred for 24 h. The reaction mixture was diluted with water and the resulting precipitate collected by filtration. This was dissolved into DCM and reduced onto silica. Purification by column chromatography (SiO_2; DCM:EtOH:NH_3 1:0:0 → 200:8:1) gave the title compound.

NMR δ 11.26 (1H, br, s), 9.67 (1H, d, *J* 7.3), 8.33 (1H, d, *J* 3.2), 8.06 (1H, dd, *J* 8.2, 2.8), 7.91 (1H, d, *J* 1.9), 7.74 (1H, d, *J* 1.9), 7.68-7.57 (2H, m), 7.34-7.29 (2H, m), 7.26-7.15 (2H, m), 5.56 (1H, d, *J* 7.5), 4.85 (2H, d, *J* 1.3);
MS (m/e) 550/552 $[M+H]^+$, R_t 2.54min (QC Method 2)

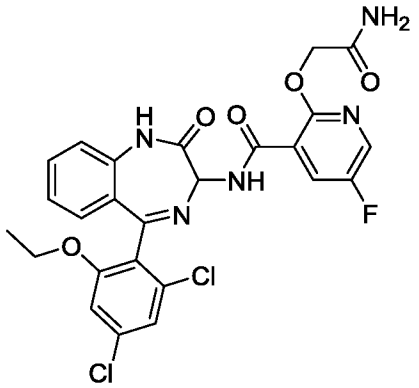
Example 2: 2-(2-Amino-2-oxoethoxy)-N-(5-(2,4-dichloro-6-methoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide



Preparation analogous to **Example 1**, using 3-amino-5-(2,4-dichloro-6-methoxyphenyl)-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one **(13a)** and 2-(2-amino-2-oxoethoxy)-5-fluoronicotinic acid (**14a**).

NMR δ 11.16 (0.6H, br, s), 11.14 (0.4H, br, s), 9.62 (1H, d, *J* 7.6), 8.34 (1H, d, *J* 3.2), 8.10-8.01 (1H, m), 7.66-7.55 (2H, m), 7.40-7.03 (6H, m), 5.49 (1H, d, *J* 7.6), 4.86 (0.8H, s), 4.85 (1.2H, s), 3.92 (1.8H, s), 3.54 (1.2H, s);
MS (m/e) 546 $[M+H]^+$, R_t 2.45min (QC Method 2)

Example 3: 2-(2-Amino-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide

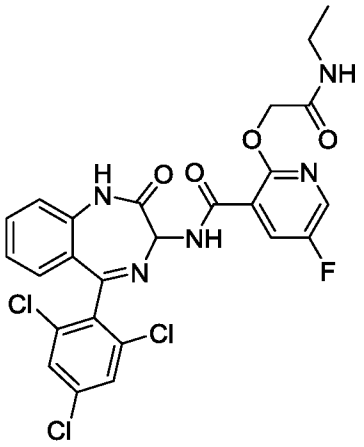


A solution of 2-(2-amino-2-oxoethoxy)-5-fluoronicotinic acid (**14a**) (60mg, 0.28mmol), HBTU (130mg, 0.34mmol) and TEA (80µl, 0.57mmol) in DMF (3ml) was treated with 3-

amino-5-(2,4-dichloro-6-ethoxyphenyl)-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one **(13b)** (100mg, 0.25mmol) and stirred for 24 h. The reaction mixture was diluted with water and the resulting precipitate collected by filtration. This was dissolved into DCM and reduced onto silica. Purification by column chromatography (SiO_2; DCM:EtOH:NH_3 1:0:0 → 200:8:1) gave the title compound.

NMR δ 11.16 (1H, br, s), 9.60 (1H, d, *J* 7.6), 8.34 (1H, d, *J* 3.2), 8.08-7.99 (1H, m), 7.62-7.52 (2H, m), 7.35-7.09 (6H, m), 5.50 (0.6H, d, *J* 7.6), 5.49 (0.4H, d, *J* 7.6), 4.85 (2H, br, s), 4.27-4.07 (0.8H, m), 3.91-3.79 (0.6H, m), 3.71-3.59 (0.6H, m), 1.26 (1.2H, t, *J* 7.0), 0.83 (1.8H, t, *J* 7.0);
MS (m/e) 560 $[M+H]^+$, R_t 2.62min (QC Method 2)

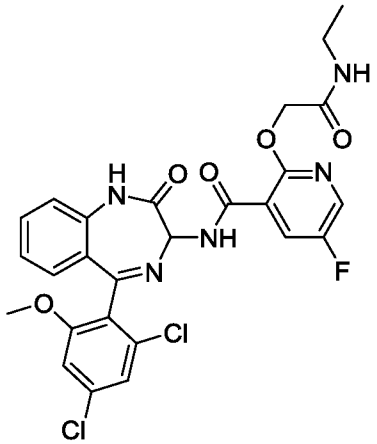
Example 4: 2-(2-(Ethylamino)-2-oxoethoxy)-5-fluoro-N-(2-oxo-5-(2,4,6-trichlorophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)nicotinamide



Preparation analogous to **Example 1**, using 3-amino-5-(2,4,6-trichloro-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one hydrochloride **(8)** and 2-(2-(ethylamino)-2-oxoethoxy)-5-fluoronicotinic acid **(14b)**.

NMR δ 11.29 (1H, br, s), 9.64 (1H, d, *J* 7.6), 8.34 (1H, d, *J* 3.2), 8.09-8.02 (2H, m), 7.92 (1H, d, *J* 1.9), 7.75 (1H, d, *J* 1.9), 7.69-7.59 (1H, m), 7.32 (1H, d, *J* 7.9), 7.26-7.16 (2H, m), 5.56 (1H, d, *J* 7.6), 4.84 (2H, s), 3.14-3.02 (2H, m), 0.96 (3H, t, *J* 7.3);
MS (m/e) 578/580 $[M+H]^+$, R_t 2.77min (QC Method 2)

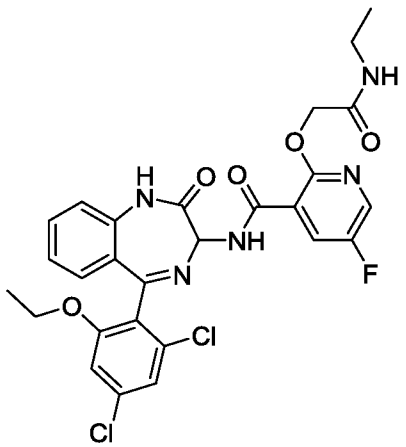
Example 5: N-(5-(2,4-Dichloro-6-methoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(2-(ethylamino)-2-oxoethoxy)-5-fluoronicotinamide



Preparation analogous to **Example 1**, using 3-amino-5-(2,4-dichloro-6-methoxyphenyl)-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one **(13a)** and 2-(2-(ethylamino)-2-oxoethoxy)-5-fluoronicotinic acid (**14b)**.

NMR δ 11.19 (0.6H, br, s), 11.16 (0.4H, br, s), 9.58 (0.6H, d, *J* 7.6), 9.57 (0.4H, d, *J* 7.6), 8.34 (0.4H, d, *J* 2.8), 8.33 (0.6H, d, *J* 3.2), 8.09-7.98 (2H, m), 7.63-7.54 (1H, m), 7.37 (0.4H, d, *J* 1.6), 7.34 (0.6H, d, *J* 1.6), 7.28 (1H, d, *J* 8.2), 7.24-7.13 (3H, m), 5.50 (0.4H, d, *J* 7.6), 5.49 (0.6H, d, *J* 7.6), 4.84 (0.8H, s), 4.81 (1.2H, s), 3.91 (1.8H, s), 3.53 (1.2H, s), 3.14-3.01 (2H, m), 0.96 (3H, t, *J* 7.3);
MS (m/e) 574 $[M+H]^+$, R_t 2.67min (QC Method 2)

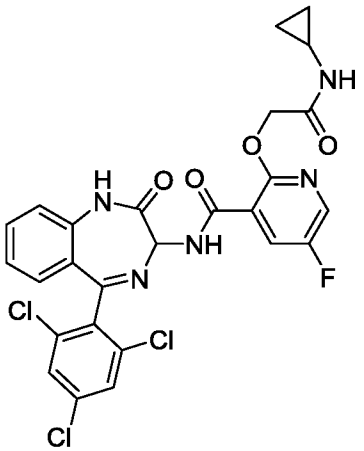
Example 6: N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(2-(ethylamino)-2-oxoethoxy)-5-fluoronicotinamide



Preparation analogous to **Example 1**, using 3-amino-5-(2,4-dichloro-6-ethoxyphenyl)-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one **(13b)** and 2-(2-(ethylamino)-2-oxoethoxy)-5-fluoronicotinic acid **(14b)**.

NMR δ 11.20 (1H, br, s), 9.58 (1H, d, *J* 7.6), 8.35 (1H, d, *J* 2.8), 8.10-7.99 (2H, m), 7.63-7.54 (1H, m), 7.38-7.26 (2H, m), 7.24-7.10 (3H, m), 5.52 (0.6H, d, *J* 7.6), 5.51 (0.4H, d, *J* 7.6), 4.85 (2H, s), 4.32-4.08 (0.8H, m), 3.93-3.80 (0.6H, m), 3.74-3.62 (0.6H, m), 3.16-3.02 (2H, m), 1.27 (1.2H, t, *J* 7.0), 0.97 (3H, t, *J* 7.3), 0.86 (1.8H, t, *J* 7.0);
MS (m/e) 588 $[M+H]^+$, R_t 2.85min (QC Method 2)

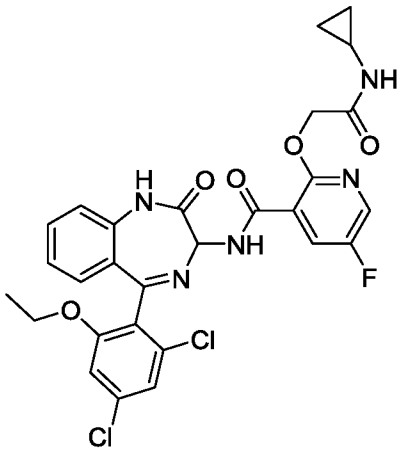
Example 7: 2-(2-(Cyclopropylamino)-2-oxoethoxy)-5-fluoro-N-(2-oxo-5-(2,4,6-trichlorophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)nicotinamide



Preparation analogous to **Example 1**, using 3-amino-5-(2,4,6-trichloro-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one hydrochloride **(8)** and 2-(2-(cyclopropylamino)-2-oxoethoxy)-5-fluoronicotinic acid **(14c)**.

NMR δ 11.28 (1H, br, s), 9.59 (1H, d, *J* 7.6), 8.33 (1H, d, *J* 2.8), 8.13 (1H, d, *J* 3.8), 8.07 (1H, dd, *J* 3.2, 8.5), 7.91 (1H, d, *J* 1.9), 7.73 (1H, d, *J* 1.9), 7.67-7.59 (1H, m), 7.32 (1H, d, *J* 7.9), 7.26-7.15 (2H, m), 5.56 (1H, d, *J* 7.6), 4.84 (2H, s), 2.67-2.54 (1H, m), 0.60-0.51 (2H, m), 0.42-0.33 (2H, m);
MS (m/e) 590/592 $[M+H]^+$, R_t 2.96min (QC Method 3)

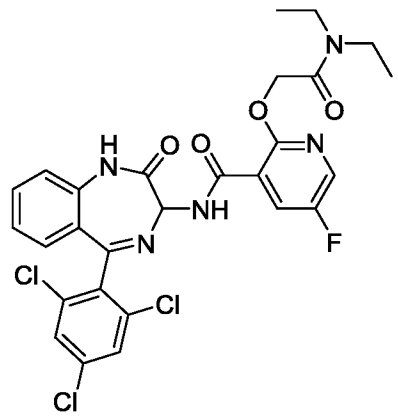
Example 8: 2-(2-(Cyclopropylamino)-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide



Preparation analogous to **Example 1**, using 3-amino-5-(2,4-dichloro-6-ethoxyphenyl)-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one (**13b)** and 2-(2-(cyclopropylamino)-2-oxoethoxy)-5-fluoronicotinic acid (**14c)**.

NMR δ 11.18 (1H, br, s), 9.54 (0.6H, d, *J* 7.6), 9.53 (0.4H, d, *J* 7.6), 8.34 (1H, d, *J* 3.2), 8.13 (1H, d, *J* 4.1), 8.09-8.00 (1H, m), 7.62-7.52 (1H, m), 7.34 (0.6H, d, *J* 1.9), 7.31 (0.4H, d, *J* 1.9), 7.27 (1H, d, *J* 7.9), 7.22-7.09 (3H, m), 5.50 (0.6H, d, *J* 7.3), 5.48 (0.4H, *J* 7.6), 4.84 (2H, s), 4.30-4.08 (0.8H, m), 3.93-3.79 (0.6H, m), 3.73-3.59 (0.6H, m), 2.66-2.55 (1H, m), 1.26 (1.2H, t, *J* 7.0), 0.85 (1.8H, t, *J* 7.0), 0.60-0.50 (2H, m), 0.43-0.34 (2H, m);
MS (m/e) 600/602 $[M+H]^+$, R_t 3.04min (QC Method 3)

Example 9: 2-(2-(Diethylamino)-2-oxoethoxy)-5-fluoro-N-(2-oxo-5-(2,4,6-trichlorophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)nicotinamide

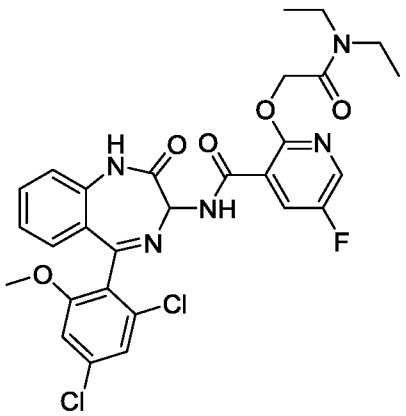


Preparation analogous to **Example 1**, using 3-amino-5-(2,4,6-trichloro-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one hydrochloride **(8)** and 2-(2-(diethylamino)-2-oxoethoxy)-5-fluoronicotinic acid **(14d)**.

NMR δ 11.24 (1H, br, s), 9.60 (1H, d, *J* 7.6), 8.34 (1H, d, *J* 3.2), 8.11 (1H, d, *J* 3.2, 8.5), 7.90 (1H, d, *J* 1.9), 7.74 (1H, d, *J* 1.9), 7.66-7.58 (1H, m), 7.30 (1H, d, *J* 7.9), 7.26-7.15 (2H, m), 5.54 (1H, d, *J* 7.3), 5.35 (1H, d, *J* 14.8), 5.24 (1H, d, *J* 14.8), 3.39-3.19 (4H, m), 1.18 (3H, t, *J* 7.0), 0.98 (3H, t, *J* 7.0);

MS (m/e) 606/608 $[M+H]^+$, R_t 3.05min (QC Method 2)

Example 10: N-(5-(2,4-Dichloro-6-methoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(2-(diethylamino)-2-oxoethoxy)-5-fluoronicotinamide

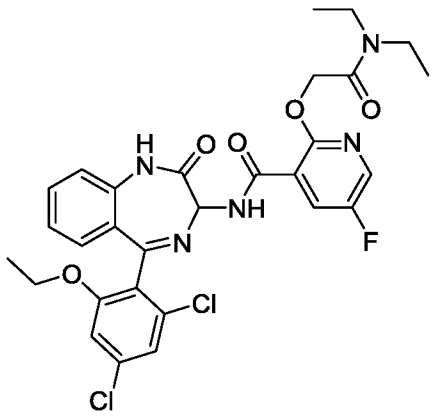


Preparation analogous to **Example 1**, using 3-amino-5-(2,4-dichloro-6-methoxyphenyl)-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one (**13a)** and 2-(2-(diethylamino)-2-oxoethoxy)-5-fluoronicotinic acid (**14d)**.

NMR δ 11.14 (0.6H, br, s), 11.11 (0.4H, br, s), 9.55 (0.4H, d, *J* 7.6), 9.46 (0.6H, d, *J* 7.6), 8.34 (1H, d, *J* 3.2), 8.14-8.06 (1H, m), 7.62-7.53 (1H, m), 7.36 (0.4H, d, *J* 1.9), 7.33 (0.6H, d, *J* 1.9), 7.30-7.12 (4H, m), 5.50 (1H, d, *J* 7.3), 5.34 (1H, d, *J* 14.8), 5.24 (1H, d, *J* 15.1), 3.91 (1.8H, s), 3.53 (1.2H, s), 3.38-3.18 (4H, m), 1.17 (3H, t, *J* 7.0), 0.98 (3H, t, *J* 7.0);

MS (m/e) 602 $[M+H]^+$, R_t 2.92min (QC Method 2)

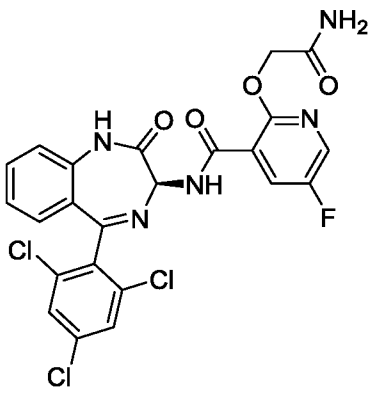
Example 11: N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-(2-(diethylamino)-2-oxoethoxy)-5-fluoronicotinamide



Preparation analogous to **Example 1**, using 3-amino-5-(2,4-dichloro-6-ethoxyphenyl)-1*H*-benzo[*e*][1,4]diazepin-2(3*H*)-one (**13b**) and 2-(2-(diethylamino)-2-oxoethoxy)-5-fluoronicotinic acid (**14d**).

NMR δ 11.14 (0.6H, br, s), 11.12 (0.4H, br, s), 9.55 (0.6H, d, *J* 7.6), 9.50 (0.4H, d, *J* 7.9), 8.34 (1H, d, *J* 3.2), 8.13-8.05 (1H, m), 7.61-7.52 (1H, m), 7.33 (0.6H, d, *J* 1.9), 7.31 (0.4H, d, *J* 1.9), 7.26 (1H, d, *J* 7.9), 7.21-7.09 (3H, m), 5.51 (0.6H, d, *J* 7.6), 5.49 (0.4H, d, *J* 7.3), 5.39-5.21 (2H, m), 4.30-4.09 (0.8H, m), 3.93-3.81 (0.6H, m), 3.71-3.58 (0.6H, m), 3.39-3.18 (4H, m), 1.26 (1.2H, t, *J* 7.0), 1.18 (3H, t, *J* 7.0), 0.98 (3H, t, *J* 7.0), 0.83 (1.8H, t, *J* 7.0);
MS (m/e) 616 $[M+H]^+$, R_t 3.09min (QC Method 2)

Example 12: (S)-2-(2-Amino-2-oxoethoxy)-5-fluoro-N-(2-oxo-5-(2,4,6-trichlorophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)nicotinamide



Prepared from **Example 1**, using preparative HPLC:

Column: 10 x 250 mm CHIRALPAK® IA

Mobile phase: 90% EtOH in i-hexane

Flow rate: 1.0 ml/min

Detection: UV 254nm

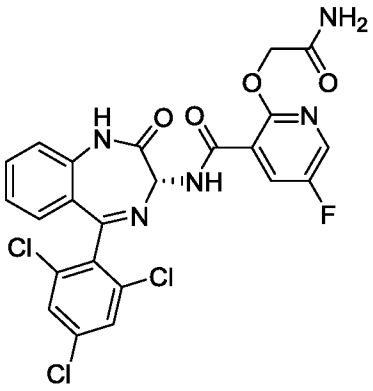
Temperature: 20°C

Enantiomer R_t: 35.37min

NMR δ 11.26 (1H, br, s), 9.67 (1H, d, *J* 7.3), 8.33 (1H, d, *J* 3.2), 8.06 (1H, dd, *J* 8.2, 2.8), 7.91 (1H, d, *J* 1.9), 7.74 (1H, d, *J* 1.9), 7.68-7.57 (2H, m), 7.34-7.29 (2H, m), 7.26-7.15 (2H, m), 5.56 (1H, d, *J* 7.5), 4.85 (2H, s);

MS (m/e) 550/552 $[M+H]^+$, R_t 2.52min (QC Method 2)

Example 13: (R)-2-(2-Amino-2-oxoethoxy)-5-fluoro-N-(2-oxo-5-(2,4,6-trichlorophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)nicotinamide



Prepared from **Example 1**, using preparative HPLC:

Column: 10 x 250 mm CHIRALPAK® IA

Mobile phase: 90% EtOH in i-hexane

Flow rate: 1.0 ml/min

Detection: UV 254nm

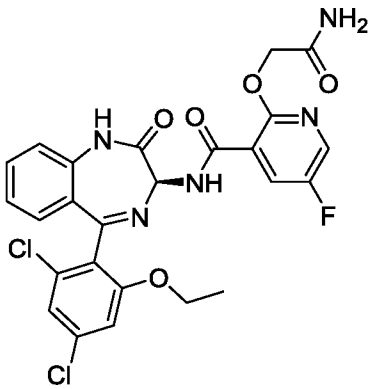
Temperature: 20°C

Enantiomer R_t: 28.30min

NMR δ 11.26 (1H, br, s), 9.67 (1H, d, *J* 7.3), 8.33 (1H, d, *J* 3.2), 8.06 (1H, dd, *J* 8.2, 2.8), 7.91 (1H, d, *J* 1.9), 7.74 (1H, d, *J* 1.9), 7.68-7.57 (2H, m), 7.34-7.29 (2H, m), 7.26-7.15 (2H, m), 5.56 (1H, d, *J* 7.5), 4.85 (2H, s);

MS (m/e) 550/552 $[M+H]^+$, R_t 2.52min (QC Method 2)

Example 14: (S)-2-(2-Amino-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide



Method A: Prepared from **Example 3**, using preparative HPLC:

Column: 10 x 250 mm CHIRALPAK® IA

Mobile phase: 80% (10% DCM in EtOH) in i-hexane

Flow rate: 1.0 ml/min

Detection: UV 254nm

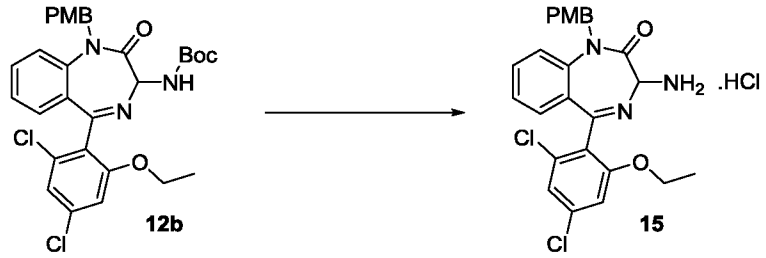
Temperature: 20°C

Enantiomer R_t: 31.17min

NMR δ 11.18 (0.6H, br, s), 11.15 (0.4H, br, s), 9.61 (1H, d, *J* 7.9), 8.34 (1H, d, *J* 3.2), 8.09-7.99 (1H, m), 7.62-7.53 (2H, m), 7.35-7.30 (2H, m), 7.27 (1H, d, *J* 7.9), 7.22-7.09 (3H, m), 5.50 (0.6H, d, *J* 7.3), 5.48 (0.4H, d, *J* 7.3), 4.85 (2H, s), 4.27-4.07 (0.8H, m), 3.91-3.79 (0.6H, m), 3.71-3.59 (0.6H, m), 1.26 (1.2H, t, *J* 7.0), 0.83 (1.8H, t, *J* 7.0);

MS (m/e) 560 $[M+H]^+$, R_t 2.60min (QC Method 2)

Method B: Preparation of enatiomers via a dynamic kinetic resolution

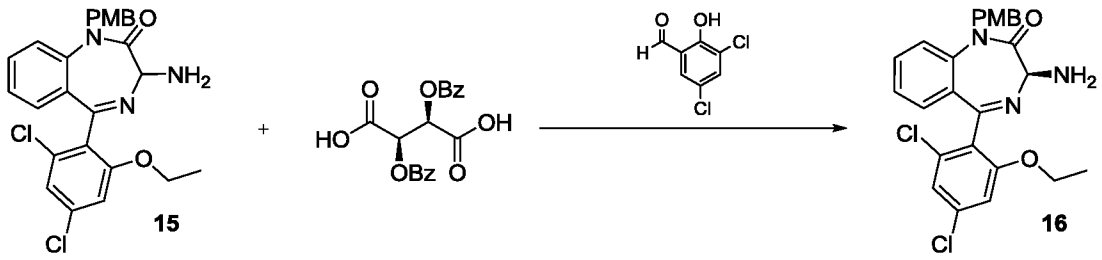


3-Amino-5-(2,4-dichloro-6-ethoxyphenyl)-1-(4-methoxybenzyl)-1H-benzo[e][1,4]diazepin-2(3H)-one (15)

30L-reactor was set under Argon and loaded with *tert*-butyl 5-(2,4-dichloro-6-ethoxyphenyl)-1-(4-methoxybenzyl)-2-oxo-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-ylcarbamate **(12b)** (2.46 kg, 4.21 mol, 1.0 eq). Dioxane (11 L) was added and the mixture was stirred until all solids went into solution. The mixture was cooled to 18°C and 4N HCl in Dioxane (8.55 L, 34.2 mol, 8.0 eq) was added during 20min, maintaining internal temperature between 18° and 23°C. The mixture was stirred at 23°C for 12h. A white yellowish suspension was formed and TBME (8 L) was added in order to complete precipitation. The suspension was stirred for 1h before the solid was filtered off and washed with TBME (4 L). The colourless solid was dried for 48h (40°C/50mbar) to give the title compound as a dioxane adduct in 92% yield (2.66 kg, 1:1 adduct, 99a/a% purity).

NMR ($CDCl_3$) δ 7.51-7.10 (7H, m), 7.00-6.73 (3H, m), 5.69 (0.5H, d, *J* 15.3), 5.40 (0.5H, d, *J* 15.3), 4.81 (0.5H, d, *J* 15.3), 4.76 (0.5H, s), 4.71 (0.5H, s), 4.40 (0.5H, d, *J* 15.3), 4.17 (1H, q, *J* 7.0), 3.89-3.70 (4H, m), 2.45 (2H, br s), 1.43 (1.5H, t, *J* 7.0), 1.04 (1.5H, t, *J* 7.0);

MS (m/e) 484 $[M+H]^+$, R_t 0.74min (QC Method 1)

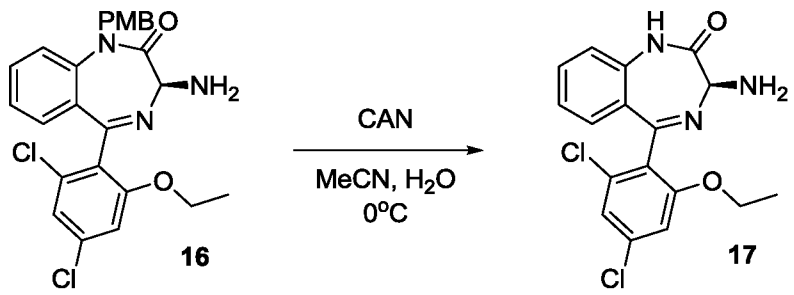


(S)-3-Amino-5-(2,4-dichloro-6-ethoxyphenyl)-1-(4-methoxybenzyl)-1H-benzo[e][1,4]diazepin-2(3H)-one (16)

3-amino-5-(2,4-dichloro-6-ethoxyphenyl)-1-(4-methoxybenzyl)-1H-benzo[e][1,4]diazepin-2(3H)-one hydrochloride **(15)** (20 g, 31.5 mmol) was partitioned between DCM (200mL) and 8% $NaHCO_3$-solution (200 mL). The DCM Phase was washed once more with 8% $NaHCO_3$ solution (200 mL). DCM Phase was dried over Na_2SO_4, filtered and evaporated to give a white solid. The free base (14.1 g, approx 5% dioxane) was suspended in isopropylacetate (220 mL) and (–)-2,3-dibenzoyl-L-tartaric acid (11.28 g, 31.5 mmol) and 3,5-dichlorosalicylaldehyde (0.30 g, 1.6 mmol) were added. The yellow suspension was heated to 70°C for 3h. The thick suspension was cooled to rt overnight. The solid was filtered off and rinsed with iPrOAc (100mL). The colourless solid was dried at hgh vacuum for 2h. The solid was partitioned between TBME/1N NaOH (300mL, 1:1). The organic phase was washed with 1N NaOH (100ml) and brine (100mL). The organic phase was dried (Na_2SO_4), filtered and evaporated to give a colourless solid in 69% yield (10.2g, 99a/a% purity, 96.7% ee).

Chiral LC: Enantiomer R_t: 34.57min

MS (m/e) 484 $[M+H]^+$, R_t 0.74min (QC Method 1)



(S)-3-Amino-5-(2,4-dichloro-6-ethoxyphenyl)-1H-benzo[e][1,4]diazepin-2(3H)-one (17)

To a suspension of (S)-3-amino-5-(2,4-dichloro-6-ethoxyphenyl)-1-(4-methoxybenzyl)-1H-benzo[e][1,4]diazepin-2(3H)-one **(16)** (4.5g, 9.3mmol) in MeCN (60ml) at 0°C was added a solution of CAN (25.5g, 46.5mmol) in H_2O (20ml). The solution was maintained at 0°C for 5h, and then water and EtOAc were added. The products were extracted with EtOAc (×3),

washed with water (×3) and brine, and then dried. Concentration followed by trituration from ether provided the product as a pale orange solid (3.8 g, ~85% pure) which was used without further purification.

(S)-2-(2-Amino-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide (Example 14)

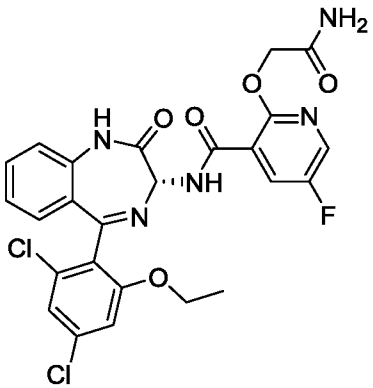
To a mixture of 2-(2-amino-2-oxoethoxy)-5-fluoronicotinic acid (**14a)** (2.19g, 10.2mmol) and HBTU (3.9g, 10.2mmol) in DCM (30ml) was added TEA (3.9ml, 27.8mmol). After 5 min, (S)-3-amino-5-(2,4-dichloro-6-ethoxyphenyl)-1H-benzo[e][1,4]diazepin-2(3H)-one **(17)** and DCM (20ml) was added. After 5h, water was added and the products were collected by filtration, which were then washed with ether. The products were absorbed onto silica gel and purified by column chromatographies (SiO_2; MeOH:DCM 1:99→1:24, and then C18; MeCN:H_2O 3:7→4:1) afforded the title compound as a white solid; (1.4g, 2.50mmol).

Chiral LC: Enantiomer R_t: 31.17min

NMR δ 11.18 (0.6H, br, s), 11.15 (0.4H, br, s), 9.61 (1H, d, *J* 7.9), 8.34 (1H, d, *J* 3.2), 8.09-7.99 (1H, m), 7.62-7.53 (2H, m), 7.35-7.30 (2H, m), 7.27 (1H, d, *J* 7.9), 7.22-7.09 (3H, m), 5.50 (0.6H, d, *J* 7.3), 5.48 (0.4H, d, *J* 7.3), 4.85 (2H, s), 4.27-4.07 (0.8H, m), 3.91-3.79 (0.6H, m), 3.71-3.59 (0.6H, m), 1.26 (1.2H, t, *J* 7.0), 0.83 (1.8H, t, *J* 7.0);

MS (m/e) 560 $[M+H]^+$, R_t 2.60min (QC Method 2)

Example 15: (R)-2-(2-Amino-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide



Prepared from **Example 3**, using preparative HPLC:

Column: 10 x 250 mm CHIRALPAK® IA

Mobile phase: 80% (10% DCM in EtOH) in i-hexane

Flow rate: 1.0 ml/min

Detection: UV 254nm

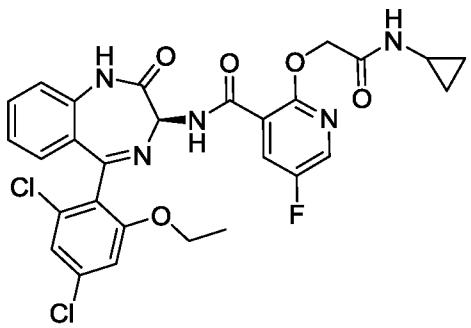
Temperature: 20°C

Enantiomer R_t: 22.33min

NMR δ 11.18 (0.6H, br, s), 11.15 (0.4H, br, s), 9.61 (1H, d, *J* 7.9), 8.34 (1H, d, *J* 3.2), 8.09-7.99 (1H, m), 7.62-7.53 (2H, m), 7.35-7.30 (2H, m), 7.27 (1H, d, *J* 7.9), 7.22-7.09 (3H, m), 5.50 (0.6H, d, *J* 7.3), 5.48 (0.4H, d, *J* 7.3), 4.85 (2H, s), 4.27-4.07 (0.8H, m), 3.91-3.79 (0.6H, m), 3.71-3.59 (0.6H, m), 1.26 (1.2H, t, *J* 7.0), 0.83 (1.8H, t, *J* 7.0);

MS (m/e) 560 $[M+H]^+$, R_t 2.60min (QC Method 2)

Example 16: (S)-2-(2-(Cyclopropylamino)-2-oxoethoxy)-N-(5-(2,4-dichloro-6-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-fluoronicotinamide



To a mixture of 2-(2-(cyclopropylamino)-2-oxoethoxy)-5-fluoronicotinic acid (**14c**) (67mg, 0.26mmol) and HBTU (0.10g, 0.26mmol) in DCM (1ml) was added TEA (61µl, 0.44mmol). After 5 min, (S)-3-amino-5-(2,4-dichloro-6-ethoxyphenyl)-1H-benzo[e][1,4]diazepin-2(3H)-one (**17**) (67mg, 0.18mmol) and DCM (1ml) was added. After 2h, water was added and the products were extracted into DCM (×3) and dried. Concentration and purification by column chromatography (SiO_2; MeOH:DCM 0:1→1:19) afforded the title compound as a white solid; (0.065g, 0.11mmol).

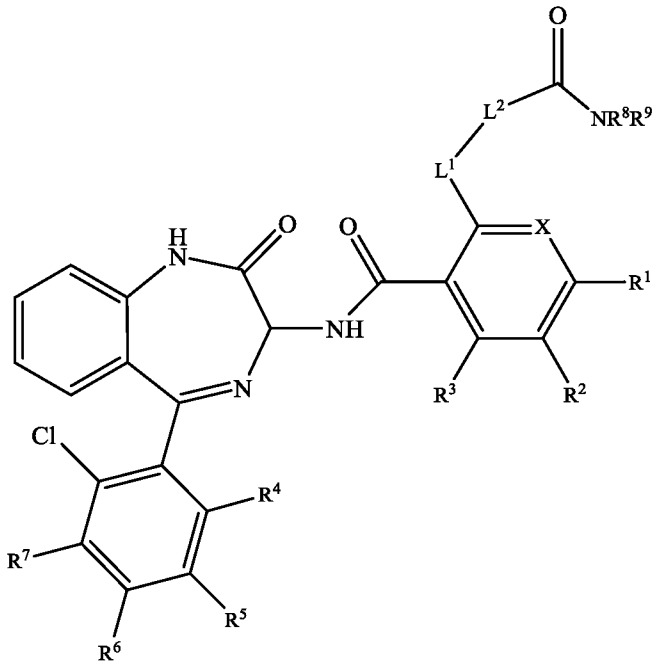
Chiral LC: Enantiomer R_t: 34.79min

NMR δ 11.18 (1H, br, s), 9.54 (0.6H, d, *J* 7.6), 9.53 (0.4H, d, *J* 7.6), 8.34 (1H, d, *J* 3.2), 8.13 (1H, d, *J* 4.1), 8.09-8.00 (1H, m), 7.62-7.52 (1H, m), 7.34 (0.6H, d, *J* 1.9), 7.31 (0.4H, d, *J* 1.9), 7.27 (1H, d, *J* 7.9), 7.22-7.09 (3H, m), 5.50 (0.6H, d, *J* 7.3), 5.48 (0.4H, *J* 7.6), 4.84 (2H, s), 4.30-4.08 (0.8H, m), 3.93-3.79 (0.6H, m), 3.73-3.59 (0.6H, m), 2.66-2.55 (1H, m), 1.26 (1.2H, t, *J* 7.0), 0.85 (1.8H, t, *J* 7.0), 0.60-0.50 (2H, m), 0.43-0.34 (2H, m);

MS (m/e) 600/602 $[M+H]^+$, R_t 3.04min (QC Method 3)

Claims

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein:

L^1 represents O or NR^{10}, wherein R^{10} represents hydrogen, (1-6C)alkyl, acetyl, trifluoromethyl or trifluoromethylcarbonyl;

L^2 represents $-(CR^{11}R^{12})_n-$, wherein n represents 1, 2, 3, 4 ,5 or 6 and R^{11} and R^{12} independently represent hydrogen or (1-3C)alkyl;

X represents CH or N;

R^1 represents hydrogen or fluoro;

R^2 represents hydrogen, halogeno, (1-6C)alkyl, (1-6C)alkoxy, formyl, (2-6C)alkanoyl, trifluoromethyl or trifluoromethoxy;

R^3 represents hydrogen, (1-6C)alkyl or halogeno;

R^4 represents hydrogen, halogeno, (1-6C)alkyl, (1-6C)alkoxy, halogeno-(1-6C)alkyl, halogeno-(1-6C)alkoxy, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (2-6C)alkanoyl, or $-(CH_2)_p-NR^{13}R^{14}$, wherein p represents 0, 1 or 2 and R^{13} and R^{14} independently represent hydrogen or (1-3C)alkyl, or R^{13} and R^{14} are joined so as to form a 4, 5, 6 or 7 membered heterocyclic ring which optionally comprises, in addition to the nitrogen atom to which R^{13}

and R^{14} are attached, 1 or 2 further heteroatoms independently selected from O, N or S, and wherein said heterocyclic ring is optionally substituted with 1, 2 or 3 substituents independently selected from R^{15};

R^5 represents hydrogen, (1-6C)alkyl or halogeno;

R^6 represents hydrogen, halogeno, (1-6C)alkyl, (1-6C)alkoxy, halogeno-(1-6C)alkyl or halogeno-(1-6C)alkoxy;

R^7 represents hydrogen, (1-6C)alkyl, (1-6C)alkoxy, halogeno, trifluoromethyl or trifluoromethoxy;

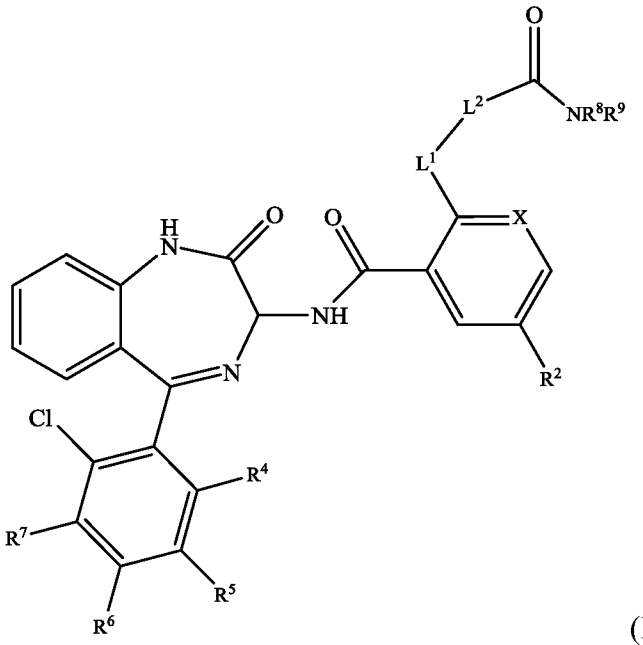
R^8 represents hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, aryl, a 5 or 6 membered monocyclic heteroaryl ring which comprises 1, 2, 3 or 4 ring heteroatoms independently selected from O, N or S, or a 9 or 10 membered bicyclic heteroaryl ring which comprises 1, 2, 3, 4 or 5 ring heteroatoms independently selected from O, N or S, wherein said aryl, monocyclic heteroaryl or bicyclic heteroaryl ring is optionally substituted with 1, 2 or 3 substituents independently selected from R^{15};

R^9 represents hydrogen, (1-6C)alkyl, (3-7C)cycloalkyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl or (1-6C)alkylsulfonyl,

or R^8 and R^9 are joined so as to form a 4, 5, 6 or 7 membered heterocyclic ring which optionally comprises, in addition to the nitrogen atom to which R^8 and R^9 are attached, 1 or 2 further heteroatoms independently selected from O, N or S, and wherein said heterocyclic ring is optionally substituted with 1, 2 or 3 substituents independently selected from R^{15}; and

R^{15} represents halogeno, (1-6C)alkyl, (1-6C)alkoxy, halogeno-(1-6C)alkyl, halogeno-(1-6C)alkoxy, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, (2-6C)alkanoyl, (1-6C)alkylthio, (1-6C)alkylsulfinyl, (1-6C)alkylsulfonyl, sulfamoyl, N-(1-6C)alkylsulfamoyl, N,N-di[(1-6C)alkyl]sulfamoyl, (1-6C)alkylsulfonylamino, (1-6C)alkylsulfonyl-N-(1-6C)alkylamino, aryl, a 5 or 6 membered monocyclic heteroaryl ring which comprises 1, 2, 3 or 4 ring heteroatoms independently selected from O, N or S, a 9 or 10 membered bicyclic heteroaryl ring which comprises 1, 2, 3, 4 or 5 ring heteroatoms independently selected from O, N or S, or $-(CH_2)_q-NR^{16}R^{17}$, wherein q represents 0, 1, 2, 3 or 4 and R^{16} and R^{17} independently represent hydrogen, (1-6C)alkyl or cyclopropyl, or R^{16} and R^{17} are joined so as to form a 4, 5, 6 or 7 membered heterocyclic ring which optionally comprises, in addition to the nitrogen atom to which R^{16} and R^{17} are attached, 1 or 2 further heteroatoms independently selected from O, N or S.

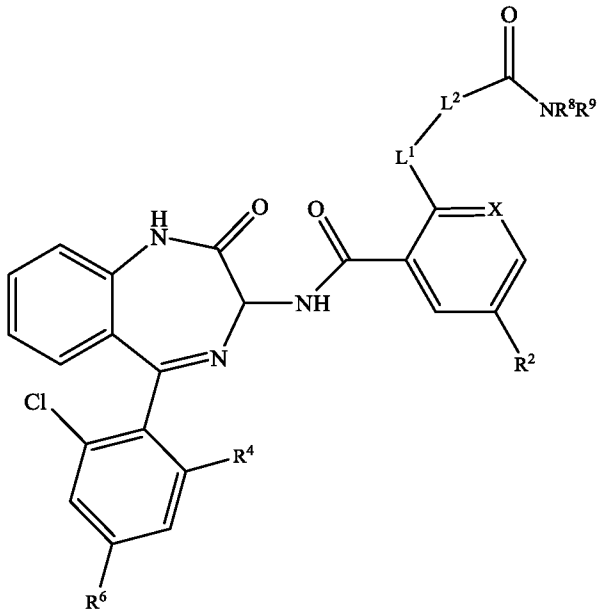
2. A compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) has the configuration shown in Formula (IA):



(IA)

wherein L^1, L^2, A, X, R^2, R^4 R^5, R^6 and R^7 are as defined as Claim 1.

3. A compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound of Formula (I) has the configuration shown in Formula (IB):



(IB)

wherein L^1, L^2, A, X, R^2, R^4 and R^6 are as defined in Claim 1.

4. A compound according to any one of Claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R^2 represents halogeno.

5. A compound according to any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^4 represents halogeno or (1-6C)alkoxy.

6. A compound according to any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^6 represents halogeno.

7. A compound according to any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein L^1 represents O.

8. A compound according to any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein L^2 represents $-(CR^{11}R^{12})_n-$, wherein n represents 1, 2 or 3, and R^{11} and R^{12} independently represent hydrogen or (1-2C)alkyl.

9. A compound according to any one of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein R^8 represents hydrogen, (1-6C)alkyl or (3-7C)cycloalkyl.

10. A compound according to any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^9 represents hydrogen, (1-6C)alkyl or (3-7C)cycloalkyl.

11. A compound according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein X represents N.

12. A compound according to Claim 1 which is selected from Examples 1 to 16 and pharmaceutically acceptable salts thereof.

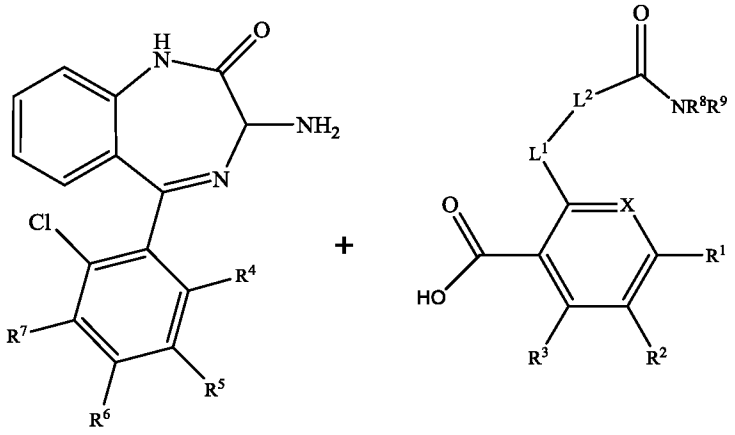
13. A pharmaceutical composition which comprises a compound according to any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable diluent or carrier.

14. A compound according to any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use as a medicament.

15. A compound according to any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, for use in the treatment of HCV infection.

16. A process for the preparation of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, which comprises a process (a) or (b):

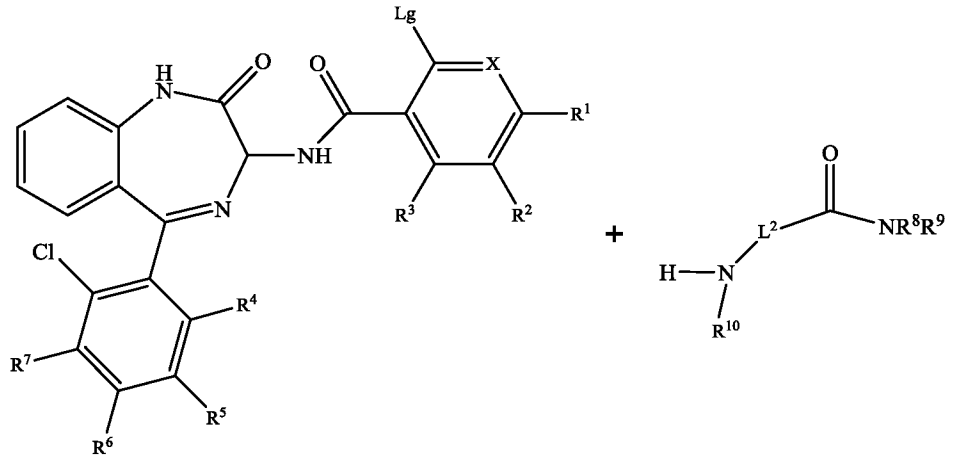
(a) reaction of a compound of Formula (II), or a salt thereof, with a compound of Formula (III) in the presence of a suitable coupling agent and a suitable base:



(II) (III)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, L^1, L^2 and X are as defined for formula (I) in Claim 1 except that any functional group is protected if necessary; or

(b) when L^1 represents NR^{10}, reaction of a compound of Formula (IV) with an amine of Formula (V):



(IV) (V)

wherein Lg represents a suitable leaving group and R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} and L^2 are as defined for formula (I) in Claim 1, except that any functional group is protected if necessary;

and thereafter, if necessary:

(i) converting a compound of Formula (I) into another compound of Formula (I);

(ii) removing any protecting groups;

(iii) separating a racemic mixture into separate enantiomers; and/or

(iv) preparing a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2011/051048

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D243/26 C07D401/12 A61K31/5513 A61P31/14
ADD.

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)
C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/034127 A1 (ARROW THERAPEUTICS LTD [GB]; DENNISON HELENA [GB]; WARNE JUSTIN [GB];) 29 March 2007 (2007-03-29) page 1, line 3 - line 5 page 17; compound (Ib') page 25, line 1 - line 3 -----	1-16

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

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 August 2011	18/08/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hoepfner, Wolfgang

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2011/051048

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007034127 A1	29-03-2007	AU 2005336627 A1	29-03-2007
		BR PI0520554 A2	13-06-2009
		CA 2622592 A1	29-03-2007
		CN 101267825 A	17-09-2008
		EP 1928465 A1	11-06-2008
		JP 2009508830 A	05-03-2009
		US 2009318427 A1	24-12-2009