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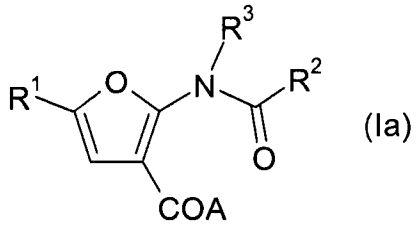
(54) Title: FURAN DERIVATIVES AND THEIR USE AS ANTIVIRAL AGENTS



(Ia)

(57) Abstract: Anti-viral agents of compounds of Formula (Ia) : wherein A, R^1, R^2 and R^3 are as defined in the specification, processes for their preparation and their use in HCV treatment are provided.

WO 2007/147794 A1

FURAN DERIVATIVES AND THEIR USE AS ANTIVIRAL AGENTS

FIELD OF THE INVENTION

The present invention relates to novel 3-carboxy furan derivatives useful as anti-viral agents. Specifically, the present invention involves novel inhibitors of Hepatitis C Virus (HCV) replication.

BACKGROUND OF THE INVENTION

Infection with HCV is a major cause of human liver disease throughout the world. In the US, an estimated 4.5 million Americans are chronically infected with HCV. Although only 30% of acute infections are symptomatic, greater than 85% of infected individuals develop chronic, persistent infection. Treatment costs for HCV infection have been estimated at $5.46 billion for the US in 1997. Worldwide over 200 million people are estimated to be infected chronically. HCV infection is responsible for 40-60% of all chronic liver disease and 30% of all liver transplants. Chronic HCV infection accounts for 30% of all cirrhosis, end-stage liver disease, and liver cancer in the U.S. The CDC estimates that the number of deaths due to HCV will minimally increase to 38,000/year by the year 2010.

Due to the high degree of variability in the viral surface antigens, existence of multiple viral genotypes, and demonstrated specificity of immunity, the development of a successful vaccine in the near future is unlikely. Alpha-interferon (alone or in combination with ribavirin) has been widely used since its approval for treatment of chronic HCV infection. However, adverse side effects are commonly associated with this treatment: flu-like symptoms, leukopenia, thrombocytopenia, depression from interferon, as well as anemia induced by ribavirin (Lindsay, K.L. (1997) Hepatology 26 (suppl 1): 71S-77S). This therapy remains less effective against infections caused by HCV genotype 1 (which constitutes ~75% of all HCV infections in the developed markets) compared to infections caused by the other 5 major HCV genotypes. Unfortunately, only ~50-80% of the patients respond to this treatment (measured by a reduction in serum HCV RNA levels and normalization of liver enzymes) and, of responders, 50-70% relapse within 6 months of cessation of treatment. Recently, with the introduction of pegylated interferon (Peg-IFN), both initial and sustained response rates have improved substantially, and combination treatment of Peg-IFN with ribavirin constitutes the gold standard for therapy. However, the side effects associated with combination therapy and the impaired response in patients with genotype 1 present opportunities for improvement in the management of this disease.

First identified by molecular cloning in 1989 (Choo, Q-L et al (1989) Science 244:359-362), HCV is now widely accepted as the most common causative agent of post-transfusion non A, non-B hepatitis (NANBH) (Kuo, G et al (1989) Science 244:362-364). Due to its genome structure and sequence homology, this virus was assigned as a new genus in the *Flaviviridae* family. Like the other members of the *Flaviviridae,* such as flaviviruses (e.g. yellow fever virus and Dengue virus types 1-4) and pestiviruses (e.g. bovine viral diarrhea

virus, border disease virus, and classic swine fever virus) (Choo, Q-L et al (1989) Science 244:359-362; Miller, R.H. and R.H. Purcell (1990) Proc. Natl. Acad. Sci. USA 87:2057-2061), HCV is an enveloped virus containing a single strand RNA molecule of positive polarity. The HCV genome is approximately 9.6 kilobases (kb) with a long, highly conserved, noncapped 5' nontranslated region (NTR) of approximately 340 bases which functions as an internal ribosome entry site (IRES) (Wang CY et al 'An RNA pseudoknot is an essential structural element of the internal ribosome entry site located within the hepatitis C virus 5' noncoding region' RNA- A Publication of the RNA Society. 1(5): 526-537, 1995 Jul.). This element is followed by a region which encodes a single long open reading frame (ORF) encoding a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins.

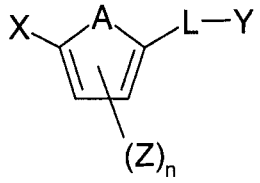
Upon entry into the cytoplasm of the cell, this RNA is directly translated into a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins. This large polypeptide is subsequently processed into the individual structural and nonstructural proteins by a combination of host and virally-encoded proteinases (Rice, C.M. (1996) in B.N. Fields, D.M.Knipe and P.M. Howley (eds) Virology 2nd Edition, p931-960; Raven Press, N.Y.). Following the termination codon at the end of the long ORF, there is a 3' NTR which roughly consists of three regions: an ~ 40 base region which is poorly conserved among various genotypes, a variable length poly(U)/polypyrimidine tract, and a highly conserved 98 base element also called the "3' X-tail" (Kolykhalov, A. et al (1996) J. Virology 70:3363-3371; Tanaka, T. et al (1995) Biochem Biophys. Res. Commun. 215:744-749; Tanaka, T. et al (1996) J. Virology 70:3307-3312; Yamada, N. et al (1996) Virology 223:255-261). The 3' NTR is predicted to form a stable secondary structure which is essential for HCV growth in chimps and is believed to function in the initiation and regulation of viral RNA replication.

The NS5B protein (591 amino acids, 65 kDa) of HCV (Behrens, S.E. et al (1996) EMBO J. 15:12-22), encodes an RNA-dependent RNA polymerase (RdRp) activity and contains canonical motifs present in other RNA viral polymerases. The NS5B protein is fairly well conserved both intra-typically (~95-98% amino acid (aa) identity across 1b isolates) and inter-typically (~85% aa identity between genotype 1a and 1b isolates). The essentiality of the HCV NS5B RdRp activity for the generation of infectious progeny virions has been formally proven in chimpanzees (A. A. Kolykhalov *et al.*. (2000) Journal of Virology, 74(4): 2046-2051). Thus, inhibition of NS5B RdRp activity (inhibition of RNA replication) is predicted to be useful to treat HCV infection.

Based on the foregoing, there exists a significant need to identify synthetic or biological compounds for their ability to inhibit replication of HCV.

PCT publication numbers WO2005/009954 and WO2005/009539 generically disclose a range of compounds, including certain 3-carboxy furan compounds, having calcium ion-

release-activated calcium ion channel modulating properties and immunosuppressive and anti-inflammatory activity. The compounds disclosed have the formula (I)



(I)

wherein

X is an optionally substituted phenyl, 4H-[1,2,4]triazol-4-yl, pyridyl or indolizinyl;

Y is an optionally substituted cycloalkyl, cycloalkenyl, heterocyclyl, aryl or heteroaryl;

A is –O-, -$S(O)_p$-, -NH-, -NZ-, -CH=CH-, -CZ=CH-, -CH=CZ-, -N=CH-, -N=CZ-, -CH=N-, -CZ=N-, or an N-oxide of -N=CH-, -N=CZ-, -CH=N-, -CZ=N-;

each Z is independently selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl or heteroaralkyl, each optionally substituted; or a haloalkyl, -$C(O)NR^1R^2$, -$NR^4C(O)R^5$, halo, -OR^4, cyano, nitro, haloalkyl, -$C(O)R^4$, -NR^1R^2, -SR^4, -$C(O)OR^4$, -$OC(O)R^4$, -$NR^4C(O)NR^1R^2$, -$OC(O)NR^1R^2$, -$NR^4C(O)OR^5$, -$S(O)_pR^4$, OR –$S(O)_pNR^1R^2$;

L is a linker selected from a covalent bond, -$NRCH_2$-, CH_2NR-, -C(O)-, -NR-C(O)-, -C(O)-NR-, -OC(O)-, -C(O)O-, -C(S)-, -NR-C(S)-, -C(S)-NR-;

each R is independently selected from –H, an alkyl, acetyl, tert-butoxycarbonyl, benzyloxycarbonyl;

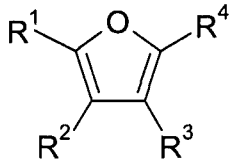
R^1 and R^2 are independently H, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl or heteroaralkyl, each optionally substituted; or R^1 and R^2 together with the nitrogen to which they are attached is optionally substituted heterocyclyl or heteroaryl;

R^4 and R5 are independently H, or alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, heteroaryl, aralkyl or heteroaralkyl, each optionally substituted;

n is 0 or an integer from 1 to 4; and

p is 0, 1 or 2.

PCT publication number WO2004/110357 generically discloses a range of compounds, including certain 3-carboxy furan compounds, having phosphodiesterase 6 delta (PDE6D) modulating activity. The compounds disclosed have the formula (III)



(III)

wherein

R^1, R^2, R^3, and R^4 are independently selected from the group consisting of hydrogen, halogen, alkyl, cycloalkyl, aryl, heteroaryl, $NR^5C(O)R^7$, $C(O)NR^5R^6$, $C(O)R^7$ and $C(O)OR^7$, wherein R^5, R^6 and R^7 are independently selected to be hydrogen, lower alkyl, cycloalkyl or aryl, and where R^5, R^6, and R^7 together can optionally form a 3, 4, 5, 6 or 7 membered ring optionally having one or more degrees of substitution.

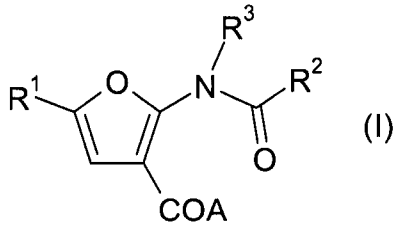
Surprisingly, it has now been found that compounds according to the present invention, generically disclosed in WO2004/110357, WO2005/009954 and WO2005/009539, and having a specific substitution pattern, are inhibitors of HCV polymerase.

SUMMARY OF THE INVENTION

The present invention involves novel 3-carboxy furan compounds represented hereinbelow, pharmaceutical compositions comprising such compounds and use of the compounds in treating viral infection, especially HCV infection.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides the use of a compound of Formula (I) :



(I)

wherein:

A represents hydroxy;

R^1 represents $-R^X-R^Y$;

R^X represents phenyl (optionally substituted by halo, methyl, ethyl, methoxy or trifluoromethyl) or a 5- or 6-membered heteroaryl bonded through a ring carbon atom to the carbon atom of the furan;

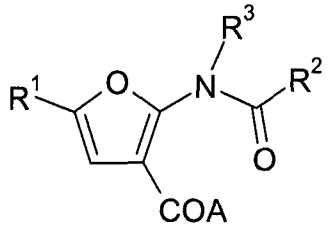
R^Y represents H, halo, or heteroaryl (optionally substituted by one or more substituents selected from $-C_{1-4}$alkyl, halo, hydroxy and $-NH_2$), wherein when R^X is phenyl or a 6-membered heteroaryl, then R^Y is bonded in the *para*-position;

R^2 represents $-C_{5-7}$cycloalkyl (optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl (unsubstituted), $-CF_3$, $-CF_2H$, $-CFH_2$, hydroxy and fluoro) or phenyl (optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl, $-CF_3$ and halo);

R^3 represents linear or branched $-C_{1-6}$alkyl (optionally substituted by one or more substituents selected from 5- or 6-membered heteroaryl and 5- or 6-membered heterocyclyl), linear or branched $-C_{2-6}$alkyl (optionally substituted by one or more substituents selected from methoxy, ethoxy and fluoro), or $-C_{3-6}$cycloalkyl, pyranyl or tetrahydrofuranyl (each of which may be optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl, fluoro and methoxy), or $-CH_2CF_3$, or $-CH_2$cyclopropyl;

or salts, solvates or esters thereof in the manufacture of a medicament for the treatment and/or prophylaxis of viral infection, particularly HCV infection.

The present invention also provides a compound of Formula (I) represented by Formula (Ia) :



(Ia)

wherein:

A represents hydroxy;

R^1 represents $-R^X-R^Y$;

R^X represents phenyl (optionally substituted by halo, methyl, ethyl, methoxy or trifluoromethyl) or 5- or 6-membered heteroaryl bonded through a ring carbon atom to the carbon atom of the furan;

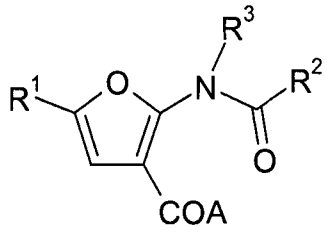
R^Y represents heteroaryl (optionally substituted by one or more substituents selected from $-C_{1-4}$alkyl, halo, hydroxy and $-NH_2$), wherein when R^X is phenyl or 6-membered heteroaryl, then R^Y is bonded in the *para*-position;

R^2 represents $-C_{5-7}$cycloalkyl (optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl, $-CF_3$, $-CF_2H$, $-CFH_2$, hydroxy and fluoro) or phenyl (optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl, $-CF_3$ and halo);

R^3 represents linear or branched $-C_{1-6}$alkyl (optionally substituted by one or more substituents selected from 5- or 6-membered heteroaryl and 5- or 6-membered heterocyclyl), linear or branched $-C_{2-6}$alkyl (optionally substituted by one or more substituents selected from methoxy, ethoxy and fluoro), or $-C_{3-6}$cycloalkyl, pyranyl or tetrahydrofuranyl (each of which may be optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl, fluoro and methoxy), or $-CH_2CF_3$ or $-CH_2$cyclopropyl;

or salts, solvates or esters thereof.

The present invention also provides the use of a compound of Formula (Ib) :



(Ib)

wherein:

A represents hydroxy;

R^1 represents $-R^X-R^Y$;

R^X represents phenyl (optionally substituted by halo, methyl, ethyl, methoxy or trifluoromethyl) or a 5- or 6-membered heteroaryl bonded through a ring carbon atom to the carbon atom of the furan;

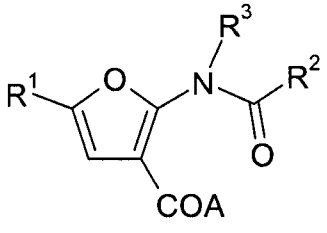
R^Y represents H, halo, or heteroaryl (optionally substituted by one or more substituents selected from $-C_{1-4}$alkyl, halo, hydroxy and $-NH_2$), wherein when R^X is phenyl or a 6-membered heteroaryl, then R^Y is bonded in the *para*-position;

R^2 represents $-C_{5-7}$cycloalkyl (optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl (unsubstituted), $-CF_3$, $-CF_2H$, $-CFH_2$, hydroxy and fluoro) or phenyl (optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl, $-CF_3$ and halo);

R^3 represents linear or branched $-C_{1-6}$alkyl (optionally substituted by one or more substituents selected from $-C_2-C_6$ alkoxy, 5- or 6-membered heteroaryl and 5- or 6-membered heterocyclyl), or $-C_{3-6}$cycloalkyl, pyranyl or tetrahydrofuranyl (each of which may be optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl, fluoro and methoxy), or $-CH_2CF_3$, or $-CH_2$cyclopropyl;

or salts, solvates or esters thereof in the manufacture of a medicament for the treatment and/or prophylaxis of viral infection, particularly HCV infection.

The present invention also provides a compound of Formula (I) represented by Formula (Ic) :



(Ic)

wherein:

A represents hydroxy;

R^1 represents $-R^X-R^Y$;

R^X represents phenyl (optionally substituted by halo, methyl, ethyl, methoxy or trifluoromethyl) or 5- or 6-membered heteroaryl bonded through a ring carbon atom to the carbon atom of the furan;

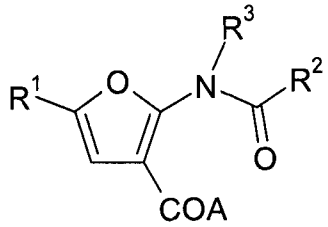
R^Y represents heteroaryl (optionally substituted by one or more substituents selected from $-C_{1-4}$alkyl, halo, hydroxy and $-NH_2$), wherein when R^X is phenyl or 6-membered heteroaryl, then R^Y is bonded in the *para*-position;

R^2 represents $-C_{5-7}$cycloalkyl (optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl, $-CF_3$, $-CF_2H$, $-CFH_2$, hydroxy and fluoro) or phenyl (optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl, $-CF_3$ and halo);

R^3 represents linear or branched $-C_{1-6}$alkyl (optionally substituted by one or more substituents selected from $-C_2$-C_6 alkoxy, 5- or 6-membered heteroaryl and 5- or 6-membered heterocyclyl), or $-C_{3-6}$cycloalkyl, pyranyl or tetrahydrofuranyl (each of which may be optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl, fluoro and methoxy), or $-CH_2CF_3$ or $-CH_2$cyclopropyl;

or salts, solvates or esters thereof.

The present invention provides the use of a compound of Formula (Id) :



(Id)

wherein:

A represents hydroxy;

R^1 represents $-R^X-R^Y$;

R^X represents phenyl (optionally substituted by halo, methyl, ethyl, methoxy or trifluoromethyl) or a 5 or 6-membered heteroaryl bonded through a ring carbon atom to the carbon atom of the furan;

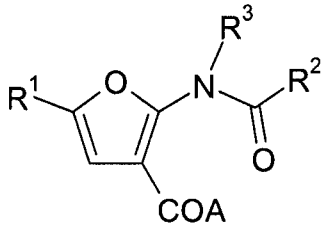
R^Y represents H, halo, or heteroaryl optionally substituted by one or more substituents selected from $-C_{1-4}$alkyl, halo, hydroxy or $-NH_2$, wherein when R^X is phenyl or a 6-membered heteroaryl, then R^Y is bonded in the *para*-position;

R^2 represents C_{5-7}cycloalkyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl, CF_3, hydroxy or halo) or phenyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl, CF_3 or halo);

R^3 represents linear or branched -C_{1-6}alkyl (optionally substituted by one or more substituents selected from methoxy, ethoxy, or a 5 or 6-membered heteroaryl or heterocyclyl), or -C_{3-6}cycloalkyl, pyranyl or furanyl (each of which may be optionally substituted by one or more substituents selected from -C_{1-2}alkyl, fluoro or methoxy);

and salts, solvates and esters thereof in the manufacture of a medicament for the treatment and/or prophylaxis of viral infection, particularly HCV infection.

The present invention also provides a compound of Formula (I) represented by Formula (Ie) :



(Ie)

wherein:

A represents hydroxy;

R^1 represents -R^X-R^Y;

R^X represents phenyl (optionally substituted by halo, methyl, ethyl, methoxy or trifluoromethyl) or a 5 or 6-membered heteroaryl bonded through a ring carbon atom to the carbon atom of the furan;

R^Y represents heteroaryl optionally substituted by one or more substituents selected from -C_{1-4}alkyl, halo, hydroxy or $-NH_2$, wherein when R^X is phenyl or a 6-membered heteroaryl, then R^Y is bonded in the *para*-position;

R^2 represents C_{5-7}cycloalkyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl, CF_3, hydroxy or halo) or phenyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl, CF_3 or halo);

R^3 represents linear or branched -C_{1-6}alkyl (optionally substituted by one or more substituents selected from methoxy, ethoxy, or a 5 or 6-membered heteroaryl or heterocyclyl), or -C_{3-6}cycloalkyl, pyranyl or furanyl (each of which may be optionally substituted by one or more substituents selected from -C_{1-2}alkyl, fluoro or methoxy);

and salts, solvates and esters thereof.

There is provided as a further aspect of the present invention a compound of Formula (I) or pharmaceutically acceptable salts, solvates or esters thereof for use in human or veterinary medical therapy, particularly in the treatment or prophylaxis of viral infection, particularly flavivirus infection, for example HCV infection.

It will be appreciated that reference herein to therapy and/or treatment includes, but is not limited to prevention, retardation, prophylaxis, therapy and cure of the disease. It will further be appreciated that references herein to treatment or prophylaxis of HCV infection include treatment or prophylaxis of HCV-associated disease such as liver fibrosis, cirrhosis and hepatocellular carcinoma.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with viral infection, particularly HCV infection, which method comprises administering to said human or animal subject an effective amount of a compound of Formula (I) or pharmaceutically acceptable salts, solvates or esters thereof.

According to another aspect of the invention, there is provided the use of a compound of Formula (I) or pharmaceutically acceptable salts, solvates or esters thereof in the manufacture of a medicament for the treatment and/or prophylaxis of viral infection, particularly HCV infection.

It will be appreciated that the compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic, diastereoisomeric, and optically active forms. All of these racemic compounds, enantiomers and diastereoisomers are contemplated to be within the scope of the present invention.

In one aspect, R^X represents phenyl optionally substituted by halo, methyl, methoxy or trifluoromethyl. In a further aspect, R^X represents phenyl optionally substituted by halo or methyl. In a further aspect, R^X represents unsubstituted phenyl.

In one aspect, R^Y represents bicyclic heteroaryl optionally substituted by one or more substituents selected from -C_{1-4}alkyl, halo, hydroxy or –NH_2, wherein when R^X is phenyl or a 6-membered heteroaryl, then R^Y is bonded in the *para*-position. In a further aspect, R^Y represents unsubstituted bicyclic heteroaryl.

In a further aspect, R^Y represents furo[3,2-*b*]pyridin-2-yl, pyrazolo[1,5-*a*]pyrimidin-2-yl, imidazo[1,2-*a*]pyridin-2-yl, imidazo[2,1-*b*][1,3]thiazol-6-yl, 7-amino-5-methylpyrazolo[1,5-*a*]pyrimidin-2-yl, 5-methylpyrazolo-[1,5-*a*]pyrimidin-2-yl, 7-aminopyrazolo[1,5-*a*]pyrimidin-2-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl, furo[2,3-b]pyridin-5-yl, 1,3-benzoxazol-2-yl, 5-amino-1,3-benzoxazol-2-yl, [1,3]oxazolo[5,4-b]pyridin-2-yl, or furo[3,2-*c*]pyridin-2-yl.

In a further aspect, R^Y represents furo[3,2-*b*]pyridin-2-yl, pyrazolo[1,5-*a*]pyrimidin-2-yl, imidazo[1,2-*a*]pyridin-2-yl, imidazo[2,1-*b*][1,3]thiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl or 1,3-benzoxazol-2-yl. In a further aspect, R^Y represents furo[3,2-*b*]pyridin-2-yl or pyrazolo[1,5-*a*]pyrimidin-2-yl.

In one aspect, R^Y represents furo[3,2-*b*]pyridin-2-yl, imidazo[1,2-*a*]pyridin-2-yl, 1,3-benzoxazol-2-yl or [1,3]oxazolo[4,5-b]pyridin-2-yl. In a further aspect, R^Y represents furo[3,2-*b*]pyridin-2-yl, imidazo[1,2-*a*]pyridin-2-yl, or [1,3]oxazolo[4,5-b]pyridin-2-yl. In a further aspect, R^Y represents furo[3,2-*b*]pyridin-2-yl.

In a further aspect, R^Y represents H or halo. In a further aspect, R^Y represents H or bromo.

In one aspect, R^2 represents -C_6cycloalkyl (optionally substituted by one or more C_{1-2}alkyl substituents) or $-CF_3$. In a further aspect, R^2 represents -C_6cycloalkyl (optionally substituted by one or more C_{1-2}alkyl substituents). In a further aspect, R^2 represents *trans*-4-methylcyclohexyl or *trans*-4-(trifluoromethyl)cyclohexyl. In a further aspect, R^2 represents *trans*-4-methylcyclohexyl.

In one aspect, R^3 represents 1-methylethyl, tetrahydrofuran-2-yl or (methyloxy)ethyl. In a further aspect, R^3 represents 1-methylethyl.

In one aspect, A represents hydroxy; R^X represents phenyl optionally substituted by halo, methyl, methoxy or trifluoromethyl; R^Y represents bicyclic heteroaryl optionally substituted by one or more substituents selected from -C_{1-4}alkyl, halo, hydroxy or $-NH_2$, wherein when R^X is phenyl or a 6-membered heteroaryl, then R^Y is bonded in the *para*-position; R^2 represents -C_6cycloalkyl optionally substituted by one or more C_{1-2}alkyl substituents; and R^3 represents 1-methylethyl, tetrahydrofuran-2-yl or (methyloxy)ethyl.

In another aspect, A represents hydroxy; R^X represents unsubstituted phenyl; R^Y represents furo[3,2-*b*]pyridin-2-yl, pyrazolo[1,5-*a*]pyrimidin-2-yl, imidazo[1,2-*a*]pyridin-2-yl, imidazo[2,1-*b*][1,3]thiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl or 1,3-benzoxazol-2-yl; R^2 represents *trans*-4-methylcyclohexyl or *trans*-4-(trifluoromethyl)cyclohexyl; and R^3 represents 1-methylethyl, tetrahydrofuran-2-yl or (methyloxy)ethyl.

In a further aspect, A represents hydroxy; R^X represents unsubstituted phenyl; R^Y represents furo[3,2-*b*]pyridin-2-yl or pyrazolo[1,5-*a*]pyrimidin-2-yl; R^2 represents *trans*-4-methylcyclohexyl or *trans*-4-(trifluoromethyl)cyclohexyl; and R^3 represents 1-methylethyl, tetrahydrofuran-2-yl or (methyloxy)ethyl.

In another aspect, A represents hydroxy; R^X represents unsubstituted phenyl; R^Y represents furo[3,2-*b*]pyridin-2-yl, imidazo[1,2-*a*]pyridin-2-yl, or [1,3]oxazolo[4,5-b]pyridin-2-yl; R^2 represents *trans*-4-methylcyclohexyl; and R^3 represents 1-methylethyl.

It is to be understood that the present invention covers all combinations of aspects, suitable, convenient and preferred groups described herein.

As used herein, the term "compounds of the invention" means the compounds according to Formula I and the salts, solvates and esters thereof. The term "a compound of the invention" means any one of the compounds of the invention as defined above.

As used herein, "acetyl" refers to $-C(O)CH_3$.

As used herein unless otherwise specified, "alkyl" refers to an optionally substituted hydrocarbon group. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or unsaturated. Where the alkyl group is linear or branched, examples of such groups include methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl or hexyl and the like. Where the alkyl hydrocarbon group is unsaturated, it will be understood that there will be a minimum of 2 carbon atoms in the group, for example an alkenyl or alkynyl group. Where the alkyl hydrocarbon group is cyclic, it will be understood that there will be a minimum of 3 carbon atoms in the group. In one aspect, alkyl moieties are saturated. In one aspect, alkyl moieties are $-C_{1-4}$alkyl. Unless otherwise stated, optional substituents include $-C_{1-6}$alkyl (unsubstituted), $=CH(CH_2)_tH$, fluoro, $-CF_3$, $-OR^E$, $-SR^E$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-CO_2H$, $-CO_2R^D$, $-NR^BR^C$, $-NR^AC(O)R^D$, $-NR^ACO_2R^D$, $-NR^AC(O)NR^FR^G$, $-SO_2NR^FR^G$, $-SO_2R^D$, nitro, cyano, oxo, aryl, heteroaryl and heterocyclyl.

As used herein, the term "alkenyl" refers to a linear or branched hydrocarbon group containing one or more carbon-carbon double bonds. In one aspect the alkenyl group has from 2 to 6 carbon atoms. Examples of such groups include ethenyl, propenyl, butenyl, pentenyl or hexenyl and the like.

As used herein, the term "alkynyl" refers to a linear or branched hydrocarbon group containing one or more carbon-carbon triple bonds. In one aspect the alkynyl group has from 2 to 6 carbon atoms. Examples of such groups include ethynyl, propynyl, butynyl, pentynyl or hexynyl and the like.

As used herein unless otherwise specified, "cycloalkyl" refers to an optionally substituted, cyclic hydrocarbon group. The hydrocarbon group may be saturated or partially unsaturated, monocyclic or bridged bicyclic. Where the cycloalkyl group is saturated, examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl and the like. Where the cycloalkyl group is partially unsaturated, examples of such groups include cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl or cyclooctenyl and the like. In one aspect, the cycloalkyl group has from 5 to 7 carbon atoms. In one aspect, cycloalkyl moieties are cyclohexenyl, cyclopentenyl and cyclohexyl. Unless otherwise stated, the cycloalkyl group may be substituted by one or more optional substituents including $-C_{1-6}$alkyl

(unsubstituted), $=CH(CH_2)_tH$, fluoro, $-CF_3$, $-OR^E$, $-SR^E$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-CO_2H$, $-CO_2R^D$, $-NR^BR^C$, $-NR^AC(O)R^D$, $-NR^ACO_2R^D$, $-NR^AC(O)NR^FR^G$, $-SO_2NR^FR^G$, $-SO_2R^D$, nitro, cyano, oxo, phenyl and heterocyclyl.

As used herein, the term " alkoxy" refers to an -O-alkyl group wherein alkyl is saturated but otherwise as defined herein. Examples of such groups include methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy and the like.

As used herein unless otherwise specified, "aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. "Aryl" includes carbocyclic aryl and biaryl groups, all of which may be optionally substituted. In one aspect, "aryl" moieties contain 6-10 carbon atoms. In one aspect, "aryl" moieties are unsubstituted, monosubstituted, disubstituted or trisubstituted phenyl. In one aspect, unless otherwise stated, "aryl" substituents are selected from the group consisting of $-C_{1-6}$alkyl, halo, $-OR^E$, $-SR^E$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-CO_2H$, $-CO_2R^D$, $-NR^BR^C$, $-NR^AC(O)R^D$, $-NR^ACO_2R^D$, $-NR^AC(O)NR^FR^G$, $-SO_2NR^FR^G$, $-SO_2R^D$, nitro, cyano, heterocyclyl, $-CF_3$, $-OCF_3$ and phenyl.

As used herein, "carbonyl" refers to -C(O)-.

As used herein, "cyano" refers to -CN.

As used herein, "halogen" or "halo" refer to a fluorine, chlorine, bromine or iodine atom. References to "fluoro", "chloro", "bromo" or "iodo" should be construed accordingly.

As used herein, unless otherwise specified, "heteroaryl" refers to an optionally substituted, 5, 6, 8, 9 or 10 membered, aromatic group comprising one to four heteroatoms selected from N, O and S, with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. In one aspect, "heteroaryl" moieties are unsubstituted, monosubstituted, disubstituted or trisubstituted (where applicable) pyridine, pyrazine, thiazole, thiophene, oxadiazole, oxazole, pyrimidine, pyridazine, benzodioxole, benzofuran, benzodioxin, indole, benzimidazole, benzofuran, indole, indazole, isoindole, benzothiophene, benzothiazole, benzoxazole, benzisoxazole, benzisothiazole, benzotriazole, furopyridine, furopyrimidine, furopyridazine, furopyrazine, furotriazine, pyrrolopyridine, pyrrolopyrimidine, pyrrolopyridazine, pyrrolopyrazine, pyrrolotriazine, thienopyridine, thienopyrimidine, thienopyridazine, thienopyrazine, thienotriazine, thiazolopyridine, thiazolopyrimidine, thiazolopyridazine, thiazolopyrazine, thiazolotriazine, oxazolopyridine, oxazolopyrimidine, oxazolopyridazine, oxazolopyrazine, oxazolotriazine, imidazopyridine, imidazopyrimidine, imidazopyridazine, imidazopyrazine, imidazotriazine, pyrazolopyridine, pyrazolopyrimidine, pyrazolopyridazine, pyrazolopyrazine, pyrazolotriazine, triazolopyridine, triazolopyrimidine, triazolopyridazine, triazolopyrazine, quinoline, naphthyridine, quinoxaline, quinazoline, isoquinoline, cinnoline, pyridopyridazine, pyridopyrimidine, pyridopyrazine,

pyrazinopyrazine, pteridine, pyrazinopyridazine, pyrimidopyridazine, pyrimidopyrimidine, imidazothiazole, thiazolooxazole. All isomers of the above heteroaryls are within the scope of this invention. Each heteroaryl group may be attached at any ring carbon or may be attached through nitrogen when the nitrogen is part of a 5-membered ring. In one aspect, unless otherwise stated, "heteroaryl" substituents are selected from the group consisting of $-C_{1-6}$alkyl, halo, $-OR^E$, $-SR^E$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-CO_2R^D$, $-NR^BR^C$, $-NR^AC(O)R^D$, $-NR^ACO_2R^D$, $-NR^AC(O)NR^FR^G$, $-SO_2NR^FR^G$, $-SO_2R^D$, oxo, nitro, cyano, heterocyclyl, $-CF_3$ and phenyl.

As used herein unless otherwise specified, "heterocyclic" and "heterocyclyl" refer to an optionally substituted, 5 or 6 membered, saturated or partially unsaturated, cyclic group containing 1 or 2 heteroatoms selected from N, optionally substituted by hydrogen, $-C_{1-6}$alkyl, $-C(O)R^D$, $-C(O)NR^BR^C$, -C(O)OH, $-SO_2R^D$, aryl or heteroaryl; O; and S, optionally substituted by one or two oxygen atoms. Ring carbon atoms may be optionally substituted by $-C_{1-6}$alkyl, $-OR^A$, $-C(O)R^D$, or $-SO_2R^D$. In one aspect, unless otherwise stated, "heterocyclic" moieties are unsubstituted or monosubstituted tetrahydro-2H-pyran-4-yl, piperidinyl and tetrahydrofuran-3-yl.

As used herein, "nitro" refers to $-NO_2$.

As used herein, "oxo" refers to =O.

As used herein, "Et" refers to "ethyl", "iPr" refers to "isopropyl", "Me" refers to "methyl", "OBn" refers to "benzyloxy", and "Ph" refers to "phenyl".

R^A represents hydrogen or $-C_{1-6}$alkyl.

R^B and R^C independently represent hydrogen, $-C_{1-6}$alkyl, aryl, heterocyclyl or heteroaryl; or R^B and R^C together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group.

R^D is selected from the group consisting of $-C_{1-6}$alkyl, aryl, heterocyclyl, heteroaryl, arylalkyl, and heteroarylalkyl.

R^E represents hydrogen, $-C_{1-6}$alkyl, arylalkyl, heteroarylalkyl, aryl, heterocyclyl or heteroaryl.

R^F and R^G are independently selected from the group consisting of hydrogen, $-C_{1-6}$alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or R^F and R^G together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group.

In a further aspect, the present invention provides a compound chosen from the group consisting of:

5-{4-(Furo[3,2-*b*]pyridin-2-yl)phenyl}-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid;
5-{4-(Imidazo[1,2-a]pyridin-2-yl)phenyl}-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid;
5-[4-(1,3-Benzoxazol-2-yl)phenyl]-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid;
2-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-{4-([1,3]oxazolo[4,5-b]pyridin-2-yl)phenyl}-3-furancarboxylic acid;
2-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-3-furancarboxylic acid;
5-(4-Pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-(tetrahydro-3-furanyl{[*trans*-4-(trifluoromethyl)cyclohexyl]carbonyl}amino)-3-furancarboxylic acid;
5-(4-Furo[3,2-*b*]pyridin-2-ylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylic acid;
5-(4-Furo[3,2-*b*]pyridin-2-ylphenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylic acid;
2-{[(*trans*-4-Methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-3-furancarboxylic acid;
5-(4-Imidazo[2,1-*b*][1,3]thiazol-6-ylphenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylic acid;
5-(4-Imidazo[2,1-*b*][1,3]thiazol-6-ylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid;
2-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-3-furancarboxylic acid;
5-(4-Imidazo[2,1-*b*][1,3]thiazol-6-ylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylic acid; and
2-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-5-(4-[1,3]oxazolo[4,5-*b*]pyridin-2-ylphenyl)-3-furancarboxylic acid,

and salts, solvates and esters, and individual enantiomers thereof where appropriate.

Also included in the present invention are pharmaceutically acceptable salt complexes. The present invention also covers the pharmaceutically acceptable salts of the compounds of Formula (I). Suitable pharmaceutically acceptable salts of the compounds of Formula (I) include acid salts, for example sodium, potassium, calcium, magnesium and tetraalkylammonium and the like, or mono- or di- basic salts with the appropriate acid for example organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids and the like.

The present invention also relates to solvates of the compounds of Formula (I), for example hydrates.

The present invention also relates to pharmaceutically acceptable esters of the compounds of Formula (I), for example carboxylic acid esters -COOR, in which R is selected from straight or branched chain alkyl, for example n-propyl, n-butyl, alkoxyalkyl (e.g. methoxymethyl), aralkyl (e.g. benzyl), aryloxyalkyl (e.g. phenoxymethyl), aryl (e.g. phenyl optionally substituted by halogen, -C_{1-4}alkyl or -C_{1-4}alkoxy or amino); or for example -$CH_2OC(O)R'$ or -CH_2OCO_2R' in which R' is alkyl (e.g. R' is *t*-butyl). Unless otherwise specified, any alkyl moiety present in such esters preferably contains 1 to 18 carbon atoms, particularly 1 to 4 carbon atoms. Any aryl moiety present in such esters preferably comprises a phenyl group.

In one aspect, the compounds of Formulae (Ia), (1b) or (1c) are in the form of the parent compound, a salt or a solvate.

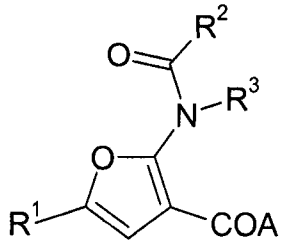
As used herein, the term "pharmaceutically acceptable" used in relation to an ingredient (active ingredient such as an active ingredient, a salt thereof or an excipient) which may be included in a pharmaceutical formulation for administration to a patient, refers to that ingredient being acceptable in the sense of being compatible with any other ingredients present in the pharmaceutical formulation and not being deleterious to the recipient thereof.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

It will further be appreciated that certain compounds of the present invention may exist in different tautomeric forms. All tautomers are contemplated to be within the scope of the present invention.

PROCESSES

Compounds of Formula (I) in which A is hydroxy may be prepared from a compound of Formula (II)



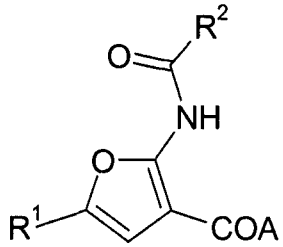
(II)

in which A is a protected hydroxy group, for example an alkoxy, benzyloxy or silyloxy group and R^1, R^2, and R^3 are as defined above for Formula (I). For example when A is methoxy or ethoxy, and R^1, R^2 and R^3 are as defined above for Formula (I), by treatment with an appropriate base, for example aqueous sodium hydroxide or lithium hydroxide, optionally in a suitable solvent such as methanol, ethanol, tetrahydrofuran or combinations thereof. Suitably, the temperature is in the range 20 to 100°C. Alternatively, when A is methoxy or ethoxy and R^1, R^2 and R^3 are as defined above for Formula (I), by treatment with lithium iodide in a suitable solvent such as pyridine, lutidine or collidine, suitably in the temperature range 100-170°C.

For example when A is *tert*-butoxy, and R^1, R^2 and R^3 are as defined above for Formula (I), by treatment with an appropriate acid, for example trifluoroacetic acid. Suitably, the reaction is carried out in a solvent, for example dichloromethane. Suitably, the temperature is in the range 0 to 50°C, for example 15 to 30°C.

For example when A is silyloxy, and R^1, R^2 and R^3 are as defined above for Formula (I), by treatment with a suitable fluoride source for example tetrabutylammonium fluoride. The reaction is carried out in a suitable solvent, for example tetrahydrofuran. Suitably, the temperature is in the range 0 to 50°C, for example 15 to 30°C.

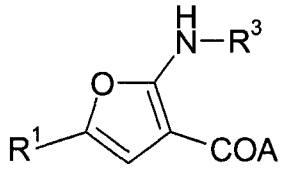
Compounds of Formula (II) may be prepared by reaction of a compound of Formula (III)



(III)

in which A is an alkoxy, benzyloxy or silyloxy group, and R^1 and R^2 are as defined above for Formula (I); with a suitable alkylating agent R^3-X in which X is a halo atom such as chloro, bromo or iodo, or X is a sulphonate ester such as methanesulfonate, and R^3 is as defined above for Formula (I), in a suitable solvent such as dimethylformamide or dichloromethane, in the presence of a suitable base, such as triethylamine or sodium hydride. The reaction may optionally be carried out under nitrogen. Suitably, the temperature is in the range -78 to 50°C.

Compounds of Formula (II) may also be prepared by reaction of a compound of Formula (IV)

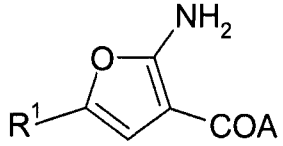


(IV)

in which A is an alkoxy, benzyloxy or silyloxy group, with a suitable acylating agent, for example R^2-C(O)-Y, wherein Y is a halo atom, such as chloro or bromo, and R^2 is as defined above for Formula (I). The reaction may be carried out in a suitable solvent, for example dichloromethane or 1,2-dichloroethane, optionally in the presence of a suitable base, for

example pyridine or triethylamine. A phosphine such as triphenylphosphine may optionally be used in place of the base. Suitably, the temperature is in the range 40 to 90°C.

Compounds of Formula (III) may be prepared by reaction of a compound of Formula (V)

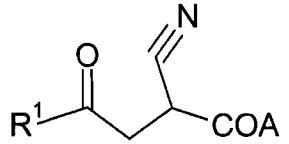


(V)

in which A is an alkoxy, benzyloxy or silyloxy group, with a suitable acylating agent, for example R^2-C(O)-Y, wherein Y is a halo atom, such as chloro or bromo, and R^2 is as defined above for Formula (I). The reaction may be carried out in a suitable solvent, for example dichloromethane or 1,2-dichloroethane, optionally in the presence of a suitable base, for example pyridine or triethylamine. A phosphine such as triphenylphosphine may optionally be used in place of the base. The reaction may optionally be carried out under nitrogen. Suitably, the temperature is in the range 0 to 60°C.

Compounds of Formula (IV) may be prepared by reaction of a compound of Formula (V) in which A is an alkoxy, benzyloxy or silyloxy group, by treatment with a suitable vinyl ether, or a suitable aldehyde or a suitable ketone, in the presence of a suitable acid, such as acetic acid, and a suitable reducing agent, such as sodium triacetoxyborohydride, in a suitable solvent, such as dichloromethane. Alternatively, compounds of Formula (IV) may be prepared from compounds of Formula (V) in which A is an alkoxy, benzyloxy or silyloxy, by treatment with a suitable alkylating agent R^3-X where X is a halo atom such as chloro, bromo or iodo, or X is a sulphonate ester such as methanesulfonate, in suitable solvent, such as dimethylformamide, in the presence of a suitable base, such as triethylamine.

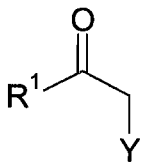
Compounds of Formula (V) may be prepared by treatment of a compound of Formula (VI)



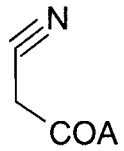
(VI)

in which A is an alkoxy, benzyloxy or silyloxy group, and R^1 is as defined above for Formula (I), with a suitable acid, for example trifluoroacetic acid. The reaction is carried out in a suitable solvent such as dichloromethane at a temperature in the range 0-30°C.

Compounds of Formula (VI) may be prepared by reaction of a compound of Formula (VII)



(VII)



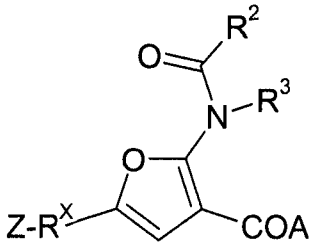
(VIII)

in which R^1 is as defined above for Formula (I) and Y is a halo atom such as chloro, bromo or iodo, with a compound of Formula (VIII) in which A is an alkoxy, benzyloxy or silyloxy group.

The reaction is carried out in suitable solvent, such as dimethylformamide, in the presence of a suitable base, such as diethylamine.

Compounds of Formula (VII) and (VIII) are commercially available or known in the art.

Compounds of Formula (I) in which A is hydroxy, or (II) in which A is an alkoxy, benzyloxy or silyloxy group, may be prepared by reaction of a compound of Formula (IX)



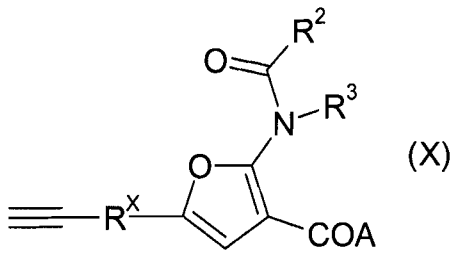
(IX)

in which Z represents a halo atom, such as chloro, bromo or iodo, and R^X, R^2, R^3 are as defined above for Formula (I), and A is hydroxy or an alkoxy, benzyloxy or silyloxy group, by reaction with a suitable heteroaryl boronic acid, R^Y-boronic acid, in which R^Y is as defined above for Formula (I), in the presence of a palladium catalyst such as palladium (II) acetate, a reagent such as 2-dicyclohexylphosphino-2'(N,N-dimethylamino)-biphenyl, and an additional reagent such as caesium fluoride, in a suitable solvent, such as 1,4-dioxane. Alternatively the R^Y boronic acid or boronic ester may be reacted in the presence of a palladium catalyst such as tetrakis(triphenylphosphine) palladium(0), a reagent such as sodium carbonate, is a suitable solvent such as dimethoxymethane or ethanol, preferably at a temperature in the range 50-85°C. Alternatively, for coupling the boronic acids or esters methods well known in the art may be employed, see, for example, Chemical Communications (2005) 38, 4759-4763, Angew Chemie Int Ed (2005) 44, 4442-4489, Tetrahedron (2002) 58, 9633-9695, Synthesis (2004) 2419-2440.

R^Y-Boronic acids are commercially available or may be prepared by analogy to methods provided in Organometallics (1983) 2, 1316, Chem Revs. (1995) 95, 2457, Journal of Org Chem (2004) 69, 1999, SynLett (2004) (5), 892, Bioorg Med Chem (2005) 13, 2305, Tetrahedron Letters (2004) 44, 9359 and Tetrahedron Letters (2005) 45, 6657.

Compounds of Formula (IX) are compounds of Formula (II) where R^1 in Formula (II) represents $-R^X-R^Y$ and R^Y represents halo. Thus, compounds of Formula (IX) may be prepared according to processes previously described for Formula (II).

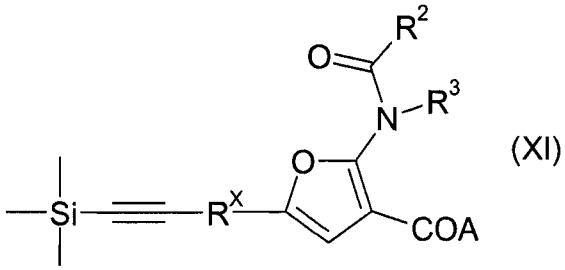
Compounds of Formula (I) or (II) in which R^1 represents a $-R^X$-(furopyridine), may be prepared by treatment of a compound of Formula (X)


(X)

in which R^2, R^3 and A are as defined above for Formula (II), with a suitable pyridine (the pyridine being substituted with adjacent hydroxy and iodo groups), with a suitable catalyst such as bis(triphenylphosphine)palladium (II) chloride and copper (I) iodide, in the presence of a suitable base, such as triethylamine, optionally in an additional suitable solvent, such as DMF. Suitably the temperature is in the range 50-80°C. For examples of furopyridine synthesis see Bioorganic and Medicinal Chemistry Letters (2002) 12, 1399, Synthesis (1986) 749.

Compounds of Formula (I) or (II) in which R^1 represents a -R^X-(pyrrolopyridine), may be prepared by treatment of a compound of Formula (X) in which R^2, R^3 and A are as defined above for Formula (II), with an appropriate pyridine (the pyridine being substituted by adjacent amino and iodo groups), in the presence of a suitable catalyst such as bis(triphenylphosphine)palladium (II) chloride and copper (I) iodide, in a suitable solvent such as triethylamine. Suitably the temperature is in the range 50-80°C. For examples of pyrrolopyridine synthesis see Heterocycles (1986) 24, 31, Tetrahedron (2003) 59, 1571, Synlett (1992) 515.

Compounds of Formula (X) in which A is an alkoxy, benzyloxy or silyloxy group and R^X, R^2 and R^3 are as defined above for Formula (I) may be prepared by desilylation of a compound of Formula (XI)

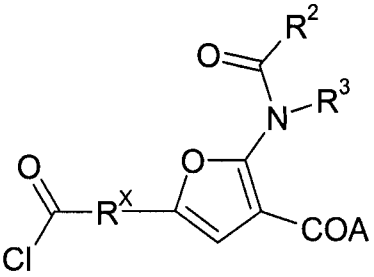

(XI)

in which R^X, R^2, and R^3 are as defined above for Formula (I), and A is an alkoxy, benzyloxy or silyloxy group, by reaction with a suitable base such as potassium carbonate in a suitable solvent such as ethanol or by treatment with a suitable fluoride source for example tetrabutylammonium fluoride in a suitable solvent such as tetrahydrofuran. The reaction may optionally be carried out under nitrogen. Suitably, the temperature is in the range 0 to 30°C.

Compounds of Formula (XI) in which A is an alkoxy, benzyloxy or silyloxy group, may be prepared by reaction of a compound of Formula (IX) in which Z represents a halo atom, such as chloro, bromo or iodo, and R^X, R^2, R^3 are as defined above for Formula (I), and A is an

alkoxy, benzyloxy or silyloxy group, by reaction with trimethylsilylacetylene in the presence of a palladium catalyst such as bis(triphenylphosphine)palladium (II) chloride and copper (I) iodide, a reagent such as triethylamine, in a suitable solvent such as tetrahydrofuran, suitably at a temperature in the range 50-75°C. The reaction may optionally be carried out under nitrogen.

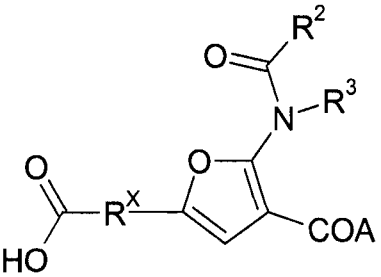
Compounds of Formula (II) in which R^1 represents a -R^X-(1,3-benzoxazol-2-yl), may be prepared by reaction of a compound of Formula (XII)



(XII)

in which A is an alkoxy, benzyloxy or silyloxy group and R^X, R^2 and R^3 are as defined above for Formula (I) with 2-aminophenol in a suitable solvent such as 1,4-dioxane. The reaction is suitably carried out at elevated temperature by heating in a microwave reactor at a temperature in the range 150 to 210°C.

Compounds of Formula (XII) in which in which R^X, R^2 and R^3 are as defined above for Formula (I), and A is an alkoxy, benzyloxy or silyloxy group, may be prepared by reaction of a compound of Formula (XIII)



(XIII)

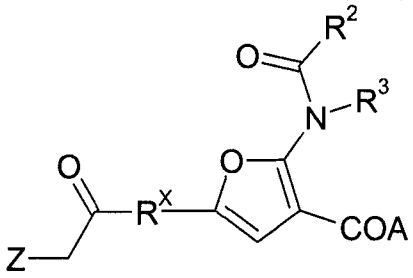
in which R^X, R^2 and R^3 are as defined above for Formula (I), and A is an alkoxy, benzyloxy or silyloxy group by reacting with a reagent such as oxalyl choride or thionyl chloride in a suitable solvent such as dichloromethane. A catalyst such as diethylformamide may optionally be used. The reaction may optionally be carried out under nitrogen. Suitably, the temperature is in the range 0 to 30°C.

Compounds of Formula (II) in which R^1 represents a -R^X-(oxazolopyridine) may be prepared by reacting a compound of Formula (XIII) with an appropriate pyridine derivative (the pyridine being substituted with adjacent amino and hydroxyl groups), in the presence of an acid such as polyphosphoric acid at temperatures in the range 180-200°C (see for example J. Med. Chem. (1978) 21, 1158). Alternatively, the acid chloride (XII) may be reacted with an appropriate pyridine (the pyridine being substituted with adjacent amino and hydroxyl groups) in a microwave reactor at elevated temperature, for example 150-210°C, in a

suitable solvent such as 1,4-dioxane (see for example Tetrahedron Letters (2003) 44, 175). Compounds of Formula (II) in which R^1 represents -R^X-(oxazolopyridine) may also be prepared by reacting a compound of Formula (XIII) with an appropriate pyridine (the pyridine being substituted with adjacent amino and hydroxyl groups) using a suitable coupling agent such as HATU, and then in a second step cyclised using an appropriate reagent such as phosphorous oxychloride.

Compounds of Formula (XIII) in which A is an alkoxy, benzyloxy or silyloxy group, may be prepared by reaction of a compound of Formula (IX) in which Z represents a halo atom, such as chloro, bromo or iodo, or a trifluoromethanesulphonate group and R^X, R^2, R^3 are as defined above for Formula (I), and A is an alkoxy, benzyloxy or silyloxy group, by reaction with carbon monoxide and water in the presence of a suitable palladium catalyst such as palladium (II) acetate or bis-diphenylphosphinoferrocene or combinations thereof, in the presence of a suitable base such as triethylamine, in a suitable solvent such as DMF. Suitably, the temperature is in the range 50 to 80°C.

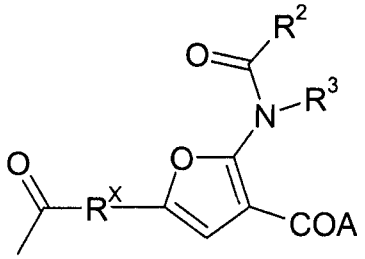
Compounds of Formula (I) or (II) in which R^1 represents a -R^X-(imidazo[1,2-a]pyridine), may be prepared by treatment of a compound of Formula (XIV)



(XIV)

in which R^X, R^2 and R^3 are as defined above for Formula (I), A is an alkoxy, benzyloxy or silyloxy group and Z represents a halo atom, such as chloro, bromo or iodo, with 2-aminopyridine. The reaction is carried out in a suitable solvent, for example dimethoxyethane. Suitably, the temperature is in the range to 50 to 80°C.

Compounds of Formula (XIV) in which in which R^X, R^2 and R^3 are as defined above for Formula (I), and A is an alkoxy, benzyloxy or silyloxy group, may be prepared by reaction of a compound of Formula (XV)



(XV)

in which R^X, R^2 and R^3 are as defined above for Formula (I), and A is an alkoxy, benzyloxy or silyloxy group, with a halogenating agent, for example bromine, in a suitable solvent, such as

chloroform. The reaction may optionally be carried out under nitrogen. Suitably, the temperature is in the range 0 to 30°C.

Alternatively, compounds of Formula (XIV) can also be prepared from compounds of Formula (XV) by first reacting with an appropriate silylating agent, such as trimethylsilyl triflate, in the presence of a suitable base, such as 2,6-lutidine, in an appropriate solvent, for example dichloromethane, followed by the addition of a suitable halogenating agent, for example N-bromosuccinamide. It can be appreciated that these steps can be performed separately or combined as above. Suitably, the temperature is in the range 0 to 30°C. The reaction may optionally be carried out under nitrogen.

Compounds of Formula (XV) in which in which R^X, R^2 and R^3 are as defined above for Formula (I), and A is an alkoxy, benzyloxy or silyloxy group, may be prepared by reaction of a compound of Formula (XII) in which R^X, R^2 and R^3 are as defined above for Formula (I), and A is an alkoxy, benzyloxy or silyloxy group by treating with methylzinc chloride in a suitable solvent, for example tetrahydrofuran. The reaction may optionally be carried out under nitrogen. Suitably, the temperature is in the range -10 to 30°C.

Alternatively compounds of Formula (XV) can be prepared from compounds of Formula (IX) in which Z represents a halo atom, such as chloro, bromo or iodo, and R^X, R^2, R^3 are as defined above for Formula (I), and A is hydroxy or an alkoxy, benzyloxy or silyloxy group, by treatment with a suitable vinyl ether such as butylethenyl ether and a suitable catalyst such as palladium (II) acetate and 1,3-bis(diphenylphosphino)propane in the presence of 1-butyl-3-methylimidazolium tetrafluoroborate and a suitable base such as diisopropylamine in a suitable solvent for example, dimethyl sulphoxide followed by work-up with a suitable acid such as hydrochloric acid. The reaction is carried out under nitrogen and suitably the temperature is in the range 100 to 130°C.

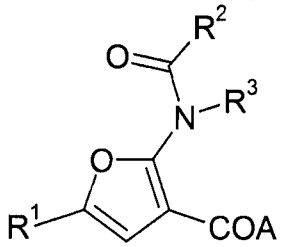
Compounds of Formula (I) or (II) in which R^1 represents phenyl substituted by a 4-imidazo[1,2-a]pyridine, may be prepared by analogy to methods described in Tetrahedron Letters (2001) 42, 3077.

Compounds of Formula (I) or (II) in which R^1 represents a 4-(1H-benzimidazol-2-yl)phenyl derivative may be prepared by analogy to methods described in J. Heterocyclic Chem. (1994) 31, 957.

Compounds of Formula (I) or (II) in which R^1 represents a 4-(1,3-benzoxazol-2-yl)phenyl derivative may be prepared by analogy to methods described in Tetrahedron Letters (2003) 44, 175.

Compounds of Formula (I) or (II) in which R^1 represents a 4-(1,3-benzothiazol-2-yl)phenyl derivative may be prepared by analogy to methods described in Tetrahedron Letters (2003) 44, 175 or Synth. Commun. (1990) 20, 3379.

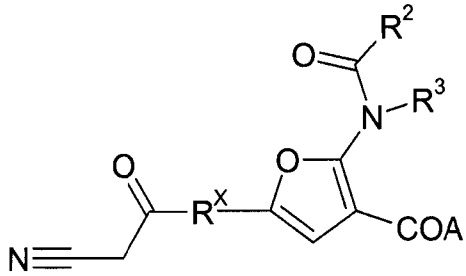
Compounds of Formula (I) or (II) in which R^1 represents a 4-(pyrazolopyrimidine)phenyl, may be prepared by treating a compound of Formula (II)'



(II)'

in which R^1 represents 4-(phenyl)-1H-pyrazole-5-amine with 1,1,3,3-tetramethoxypropane in a suitable solvent, such as acetic acid, suitably the temperature is in the range 90-110°C.

Compounds of Formula (II)' in which R^1 represents 4-(phenyl)-1H-pyrazole-5-amine may be prepared by treating a compound of Formula (XVI)



(XVI)

in which R^X, R^2 and R^3 are as defined above for Formula (I) and A is an alkoxy, benzyloxy or silyloxy group, with hydrazine, such as hydrazone hydrate, in the presence of a suitable acid such acetic acid in a suitable solvent for example ethanol. Suitably, the temperature is in the range 50 to 80°C. The reaction may optionally be carried out under nitrogen.

Compounds of Formula (XVI) in which R^X, R^2 and R^3 are as defined above for Formula (I) and A is an alkoxy, benzyloxy or silyloxy group may be prepared by treating a compound of Formula (XIV) in which R^X, R^2 and R^3 are as defined above for Formula (I) and A is an alkoxy, benzyloxy or silyloxy group and Z represents a halo atom, such as chloro, bromo or iodo, with a suitable cyanide such as sodium cyanide or potassium cyanide in a suitable solvent for example ethanol. Suitably, the temperature is in the range 0 to 30°C. The reaction may optionally be carried out under nitrogen.

Compounds of Formula (I) or (II) in which R^1 represents a 4-(thiazolopyridine)phenyl, may be prepared by reacting a compound of Formula (II)' in which R^1 represents 4-phenyl-COCl with an appropriate pyridine (the pyridine being substituted with adjacent amino and chloro

groups), in the presence of a suitable base such as pyridine, and then in a second step cyclised using a reagent such as Lawesson's reagent in a suitable solvent such as DMPU, at a suitable temperature such as 90-110°C.

Compounds of Formula (I) or (II) in which R^1 represents a 4-(thiazolopyridine)phenyl, may also be prepared by reacting a compound of Formula (II)' in which R^1 represents 4-carboxyphenyl with an appropriate pyridine (the pyridine being substituted with adjacent amino and thiol groups), in the presence of an acid such as polyphosphoric acid at temperatures in the range 180-200°C (see for example J. Med. Chem. (1978) 21, 1158). Alternatively, the acid chloride of the 4-carboxyphenyl may be reacted with an appropriate pyridine (the pyridine being substituted with adjacent amino and thiol groups), in a microwave reactor in a suitable solvent such as 1,4-dioxane (see for example Tetrahedron Letters (2003) 44, 175). In another alternative the 4-carboxyphenyl compound may be reacted with an appropriate pyridine (the pyridine being substituted with adjacent amino and thiol groups), using a suitable coupling agent such as HATU, and then in a second step cyclised using an appropriate reagent such as phosphorous oxychloride.

Suitable methods for the preparation of compounds with the above discussed R^Y derivatives may be found in the chemical literature, for example those described in Comprehensive Heterocyclic Chemistry, Edited by A.R. Katritzky and C.W. Rees, Pergamon 1984, and Heterocyclic Chemistry, Edited by J.A. Joules and K. Mills, 4th Ed, Blackwell Science.

Esters of compounds of Formula (I), in which A is -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, may also be prepared by esterification of a compound of Formula (I) in which A is hydroxy by standard literature procedures for esterification.

The various general methods described above may be useful for the introduction of the desired groups at any stage in the stepwise formation of the required compound, and it will be appreciated that these general methods can be combined in different ways in such multi-stage processes. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product.

It will be appreciated that compounds of Formula (I), (II), (II)', (III), (IV), (V), (VI), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV) which exist as diastereoisomers may optionally be separated by techniques well known in the art, for example by column chromatography or recrystallisation. For example, the formation of an ester using a chiral alcohol, separation of the resulting diastereoisomers, and subsequent hydrolysis of the ester to yield the individual enantiomeric acid of Formula (I), (II), (II)', (III), (IV), (V), (VI), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV).

It will be appreciated that racemic compounds of Formula (I), (II), (II)', (III), (IV), (V), (VI), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV) may be optionally resolved into their individual enantiomers. Such resolutions may conveniently be accomplished by standard methods known in the art. For example, a racemic compound of Formula (I), (II), (II)', (III), (IV), (V), (VI), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV) may be resolved by chiral preparative HPLC. Alternatively, racemic compounds of Formula (I), (II), (II)', (III), (IV), (V), (VI), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV) which contain an appropriate acidic or basic group, such as a carboxylic acid group or amine group may be resolved by standard diastereoisomeric salt formation with a chiral base or acid reagent respectively as appropriate. Such techniques are well established in the art. For example, a racemic basic compound may be resolved by treatment with a chiral acid such as (R)-(-)-1,1'-binaphthyl-2,2'-diyl-hydrogen phosphate or (-)-di-O,O'-p-tolyl-L-tartaric acid, in a suitable solvent, for example isopropanol. The free enantiomer may then be obtained by treating the salt with a suitable base, for example triethylamine, in a suitable solvent, for example methyl *tert*-butyl ether. Alternatively, racemic acid compounds may be resolved using a chiral base, for example (S)-alpha methylbenzylamine, (S)-alpha phenylethylamine, (1S, 2S)-(+)-2-amino-1-phenyl-1,3-propane-diol, (-) ephidrine, quinine, brucine. Individual enantiomers of Formula (I), (II), (II)', (III), (IV), (V), (VI), (IX), (X), (XI), (XII), (XIII), (XIV) and (XV) may then be progressed to an enantiomeric compound of Formula (I) by the chemistry described above in respect of racemic compounds.

With appropriate manipulation and protection of any chemical functionality, synthesis of compounds of Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section. Suitable protecting groups can be found, but are not restricted to, those found in T W Greene and P G M Wuts 'Protective Groups in Organic Synthesis', 3rd Ed (1999), J Wiley and Sons.

EXAMPLES

ABBREVIATIONS

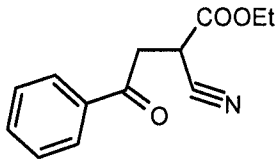
AcOH	acetic acid
CO	carbon monoxide
DCE	1,2-dichloroethane
DCM	dichloromethane
DEF	N,N-diethylformamide
DME	1,2-dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
DPPP	1,3-Bis(diphenylphosphino)propane
EtOH	ethanol
h	hours
HCl	hydrochloric acid

HPLC	high pressure liquid chromatography
ISCO Companion	Automated flash chromatography equipment with fraction analysis by UV absorption available from Presearch.
KHMDS	potassium hexamethyldisilazide
MDAP HPLC	reverse phase HPLC on a C_{18} column using a two-solvent gradient elution with (A) water containing formic acid (0.1%) and (B) acetonitrile-water (95:5 v/v) containing formic acid (0.05%) as the eluents, and analysis of the fractions by electrospray mass spectroscopy.
MeCN	acetonitrile
mins	minutes
NBS	*N*-Bromosuccinimide
NH_2 SPE	aminopropyl capped silca ion-exchange solid phase extraction cartridge
SPE	solid phase extraction column
THF	tetrahydrofuran

All mass spectroscopy was performed using electrospray as the method of ionisation.

Intermediate 1

Ethyl 2-cyano-4-oxo-4-phenylbutanoate



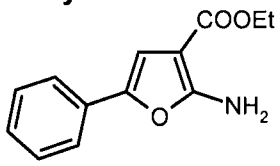
To 2-bromo-acetophenone (2g) was added dry DMF (5 mL), ethyl cyanoacetate (1.13 g) and diethylamine (2.2 g) dropwise at room temperature under nitrogen and the reaction stirred for 3 h. The reaction was then poured into water and extracted with DCM, passed through a hydrophobic frit and the organic phase concentrated. This was purified by ISCO companion silica chromatography, eluting with a gradient of ethyl acetate in cyclohexane (5-100%) to give the title compound.

MS calcd for $(C_{13}H_{13}NO_3 + H)^+$: 232

MS found (electrospray): $(M+H)^+ = 232$

Intermediate 2

Ethyl 2-amino-5-phenyl-3-furancarboxylate



Trifluoroacetic acid (5 mL) was added in one portion to Intermediate 1 (260 mg) in DCM (5 mL) at room temperature. The reaction was stirred for 2 h and the solvents removed under

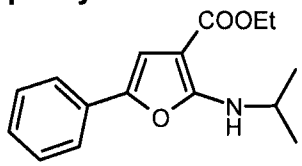
vacuum. The residue was partitioned between DCM and saturated sodium bicarbonate solution and passed through a hydrophobic frit. The organics were then concentrated to give an oil. This was purified by ISCO companion silica chromatography, eluting with a gradient of ethyl acetate in cyclohexane (5-100%) to give the title compound.

MS calcd for $(C_{13}H_{13}NO_3 + H)^+$: 232

MS found (electrospray): $(M+H)^+ = 232$

Intermediate 3

Ethyl 2-[(1-methylethyl)amino]-5-phenyl-3-furancarboxylate



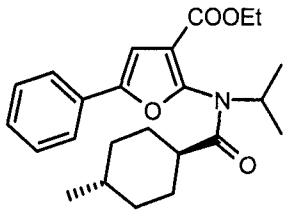
To Intermediate 2 (260 mg) in dry DCM (4.2 mL) was added 2-methoxypropene (0.32 g) and acetic acid slowly (0.27 g), followed by sodium triacetoxyborohydride (477 mg) added portion wise. The mixture was stirred at room temperature under nitrogen for 24 h. The reaction was neutralised by slowly adding sodium bicarbonate solution and extracted with DCM. The organics were dried through a hydrophobic frit and concentrated to give the title compound.

MS calcd for $(C_{16}H_{19}NO_3 + H)^+$: 274

MS found (electrospray): $(M+H)^+ = 274$

Intermediate 4

Ethyl 2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-phenyl-3-furancarboxylate



To Intermediate 3 (240 mg) in dry DCM (3.8 mL) was added *trans*-4-methylcyclohexanecarbonyl chloride[1] (210 mg) slowly and then triethylamine (88 mg). The reaction was heated at 45°C under nitrogen for 24 h. The reaction was then cooled and partitioned between DCM and 2N HCl solution. The organics were dried through a hydrophobic frit and concentrated. This residue was purified by ISCO companion silica chromatography, eluting with a gradient of ethyl acetate in cyclohexane (0-50%). The product was further purified by NH_2 SPE chromatography eluting with 1,4-dioxane gave the title compound.

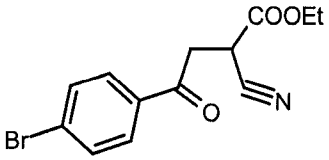
MS calcd for $(C_{24}H_{31}NO_4 + H)^+$: 398

MS found (electrospray): $(M+H)^+ = 398$

Ref 1: WO 2004/052885

Intermediate 5

Ethyl 4-(4-bromophenyl)-2-cyano-4-oxobutanoate



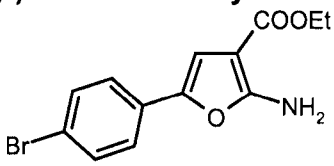
To 2-bromo-1-(4-bromophenyl)ethanone (20 g) was added dry DMF (50 mL), ethyl cyanoacetate (8.1 g) and diethylamine (15.8 g) slowly dropwise with stirring under nitrogen, maintaining the temperature below 40°C. The reaction was stirred for 2 h. The reaction was then diluted with DCM (500 mL), poured into water and washed with 2N HCl. The organic phase was then passed through a hydrophobic frit and concentrated to give the title compound.

MS calcd for $(C_{13}H_{12}NBrO_3 + H)^+$: 310/312

MS found (electrospray): $(M+H)^+ = 310/312$

Intermediate 6

Ethyl 2-amino-5-(4-bromophenyl)-3-furancarboxylate



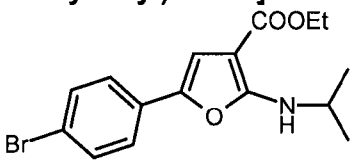
Trifluoroacetic acid (200 mL) was added in one portion to Intermediate 5 (18.2 g) in DCM (200 mL) at room temperature. The reaction was stirred for 16 h and the solvents removed under vacuum. The residue was partitioned between DCM and saturated sodium bicarbonate solution and passed through a hydrophobic frit. The organics were then concentrated to give an oil which was purified by ISCO companion silica chromatography, eluting with a gradient of ethyl acetate in cyclohexane (5-100%) to give the title compound.

MS calcd for $(C_{13}H_{12}BrNO_3 + H)^+$: 310/312

MS found (electrospray): $(M+H)^+ = 310/312$

Intermediate 7

Ethyl 5-(4-bromophenyl)-2-[(1-methylethyl)amino]-3-furancarboxylate

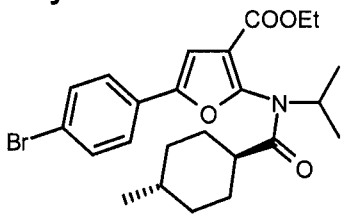


To Intermediate 6 (7 g) in dry DCM (110 mL) was added 2-methoxypropene (6.5 g) and acetic acid slowly (5.4 g), followed by sodium triacetoxyborohydride (9.56 g) added portion wise. The mixture was stirred at room temperature under nitrogen for 48 h. The reaction was neutralised by slowly adding saturated sodium bicarbonate solution and extracted with DCM. The organics were dried through a hydrophobic frit and concentrated. This was purified by ISCO companion silica chromatography, eluting with a gradient of ethyl acetate in cyclohexane (5-50%) to give the title compound.

MS calcd for $(C_{16}H_{18}NBrO_3+ H)^+$: 352/354
MS found (electrospray): $(M+H)^+$ = 352/354

Intermediate 8

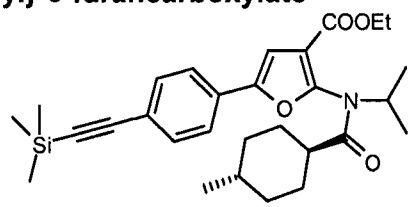
Ethyl 5-(4-bromophenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate



To ethyl 5-(4-bromophenyl)-2-[(1-methylethyl)amino]-3-furancarboxylate (4.1 g, a synthesis of which is described as Intermediate 7) in dry DCE (39 mL) was added *trans*-4-methylcyclohexanecarbonyl chloride[1] (2.24 g). The reaction was heated at reflux under nitrogen for 48 h. Further acid chloride (0.9 g) was added and the reaction continued for 24 h. The reaction was then cooled, quenched with saturated sodium bicarbonate solution, extracted with DCM, dried through a hydrophobic frit and concentrated. This was purified by ISCO companion silica chromatography, eluting with a gradient of ethyl acetate in cyclohexane (5-30%) to give the title compound.
MS calcd for $(C_{24}H_{30}NBrO_4 + H)^+$: 476/478
MS found (electrospray): $(M+H)^+$ = 476/478
Ref 1: WO 2004/052885

Intermediate 9

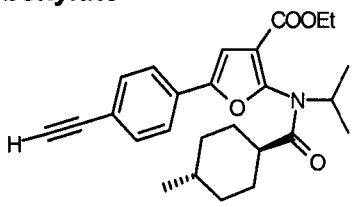
Ethyl 2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-{4-[(trimethylsilyl)ethynyl]phenyl}-3-furancarboxylate



Ethyl 5-(4-bromophenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate (0.4 g, a synthesis of which is described as Intermediate 8), copper (I) iodide (8 mg), $Pd(PPh_3)_2Cl_2$ (29 mg), trimethylsilyl acetylene (148 mg) and triethylamine (0.4 mL) were mixed in dry THF (2 mL). The stirred solution was degassed and placed under a nitrogen atmosphere, then heated at 55°C for 2 h. The reaction was cooled and diluted with DCM, filtered and concentrated. This was purified by ISCO companion silica chromatography eluting with a gradient of ethyl acetate in cyclohexane (0% to 50%) to give the title compound
MS calcd for $(C_{29}H_{39}NO_4Si+ H)^+$: 494
MS found (electrospray): $(M+H)^+$ = 494

Intermediate 10

Ethyl 5-(4-ethynylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate



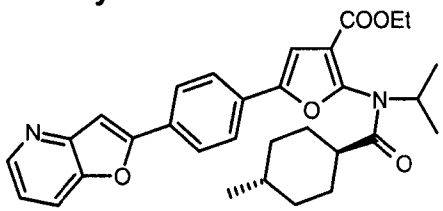
Intermediate 9 (270 mg) and potassium carbonate (38 mg) were stirred in ethanol (5.4 mL) under nitrogen for 72 h. The reaction mixture was partitioned between saturated sodium bicarbonate solution and DCM, passed through a hydrophobic frit and the organic phase concentrated. This was purified by ISCO companion silica chromatography, eluting with a gradient of ethyl acetate in cyclohexane (0 to 50%) to give the title compound.

MS calcd for $(C_{26}H_{31}NO_4 + H)^+$: 422

MS found (electrospray): $(M+H)^+ = 422$

Intermediate 11

Ethyl 5-{(4-furo[3,2-*b*]pyridin-2-yl)phenyl}-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate



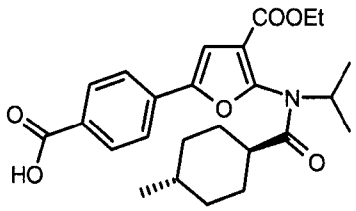
To Intermediate 10 (78 mg) was added 2-iodo-3-hydroxypyridine (40.8 mg), bis(triphenylphosphine)palladium dichloride (13 mg), copper (I) iodide (3.5 mg) and triethylamine (1.2 mL). The reaction was stirred at 70°C, under nitrogen, for 16 h. The reaction was cooled, partitioned between saturated sodium bicarbonate solution and DCM,, passed through a hydrophobic and then concentrated. The crude product was dissolved in DCM, filtered and purified by ISCO companion silica chromatography eluting with a gradient of ethyl acetate in cyclohexane (0% to 100%) to give the title compound.

MS calcd for $(C_{31}H_{34}N_2O_5 + H)^+$: 515

MS found (electrospray): $(M+H)^+ = 515$

Intermediate 12

4-{4-[(Ethyloxy)carbonyl]-5-[[(trans-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-furanyl}benzoic acid



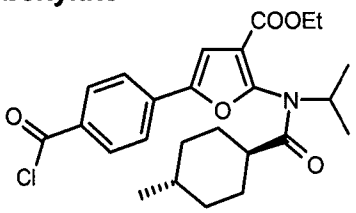
Carbon monoxide gas was gently bubbled through a DMF (20 mL) solution of ethyl 5-(4-bromophenyl)-2-[[(*trans*-4methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate (2 g, a synthesis of which is described as Intermediate 8), water (1.51 mL), palladium (II) acetate (57 mg), bis-diphenylphosphinoferrocene (280 mg) and triethylamine (1.2 mL). The reaction was then stirred at 60°C under a carbon monoxide atmosphere for 16 h. The reaction was cooled, partitioned between ethyl acetate and 2N hydrochloric acid. The organic phase was then washed with brine, passed through a hydrophobic frit and concentrated. The crude product was dissolved in a minimal amount of 1,4-dioxane and loaded onto a 70g NH_2 SPE cartridge that had been conditioned with 1,4-dioxane. The cartridge was washed with 1,4-dioxane (~300 mL) and then eluted with acetic acid:1,4-dioxane (1:9) to give the title compound.

MS calcd for $(C_{25}H_{31}NO_6 + H)^+$: 442

MS found (electrospray): $(M+H)^+ = 442$

Intermediate 13

Ethyl 5-[4-(chlorocarbonyl)phenyl]-2-[[(trans-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate



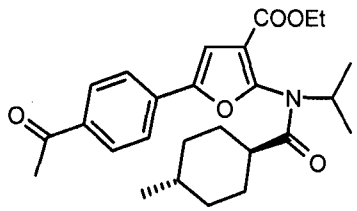
To Intermediate 12 (0.91 g) was added dry DCM (12 mL), N,N-diethylformamide (1 drop) and oxalyl chloride (0.26 g). The reaction was stirred under a nitrogen atmosphere for 16 h. The solvent was removed and DCM (12 mL), N,N-diethylformamide (1 drop) and oxalyl chloride (0.26 g) added and the mixture stirred for 16 h. The solvent was removed to give the title compound.

MS calcd for $(C_{25}H_{30}ClNO_5 + H)^+$: 461

MS found (electrospray): $(M+H)^+ = 441$ (as NH_2 amide – ammonia added to MS sample)

Intermediate 14

Ethyl 5-(4-acetylphenyl)-2-[[(trans-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate



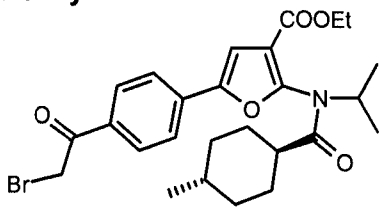
To Intermediate 13 (100 mg) in dry THF (1 mL) at 0°C, under a nitrogen atmosphere, was added 2M methyl zinc chloride in THF (0.163 mL). The reaction was then stirred at 0°C for 15 mins, then room temperature for 1 h. The reaction was quenched with saturated ammonium chloride, extracted with DCM and separated with a hydrophobic frit. The organic phase was concentrated and purified by a 12 g silica ISCO Companion flash column eluted with 0-50% ethyl acetate in cyclohexane to give the title compound.

MS calcd for $(C_{26}H_{33}NO_5 + H)^+$: 440

MS found (electrospray): $(M+H)^+ = 440$

Intermediate 15

Ethyl 5-[4-(bromoacetyl)phenyl]-2-[[(trans-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate



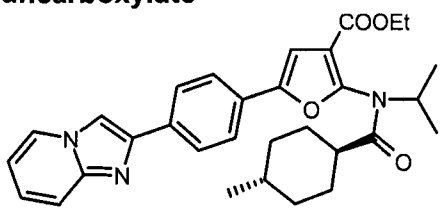
To Intermediate 14 (62 mg) was added chloroform (6 mL) and bromine (0.22 g). The reaction was stirred at room temperature for 20 mins, quenched with sodium thiosulphate solution and extracted with DCM. This was separated with a hydrophobic frit and the organics concentrated to give the title compound.

MS calcd for $(C_{26}BrH_{32}NO_5 + H)^+$: 518/20

MS found (electrospray): $(M+H)^+ = 518/20$

Intermediate 16

Ethyl 5-{(4-imidazo[1,2-a]pyridin-2-yl)phenyl}-2-[[(trans-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate



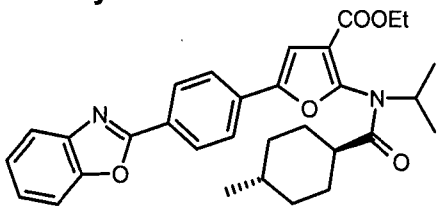
To Intermediate 15 (66 mg) was added 1,2-dimethoxyethane (1 mL) and 2-aminopyridine (12 mg). The reaction was stirred at 60°C, under a nitrogen atmosphere, for 4 h. The solvent was then evaporated and the crude material was purified by 12 g silica ISCO Companion flash column eluting with 0-100% ethyl acetate in cyclohexane to give the title compound.

MS calcd for $(C_{31}H_{35}N_3O_4 + H)^+$: 514

MS found (electrospray): $(M+H)^+ = 514$

Intermediate 17

Ethyl 5-[4-(1,3-benzoxazol-2-yl)phenyl]-2-[[(trans-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate



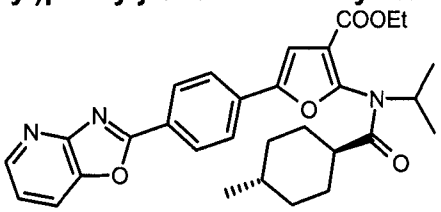
A reaction vial was charged with Intermediate 13 (350 mg), 1,4-dioxane (1.75 mL) and 2-aminophenol (84 mg). The reaction was then heated in a microwave reactor at 200°C for 1 h. The reaction was cooled, diluted with DCM and purified by 80 g silica ISCO Companion flash column eluting with 0-50% ethyl acetate in cyclohexane to give the title compound.

MS calcd for $(C_{31}H_{34}N_2O_5 + H)^+$: 515

MS found (electrospray): $(M+H)^+ = 515$

Intermediate 18

Ethyl 2-[[(trans-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-{(4-[1,3]oxazolo[4,5-b]pyridin-2-yl)phenyl}-3-furancarboxylate



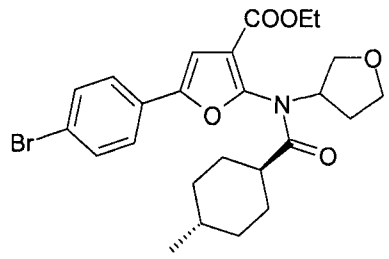
A reaction vial was charged with Intermediate 13 (350 mg), 1,4-dioxane (1.75 mL) and 2-amino-3-hydroxypyridine (85 mg). The reaction was then heated in a microwave reactor at 200°C for 1 h. The reaction was cooled, diluted with DCM and purified by 80 g silica ISCO Companion flash column eluting with 5-70% ethyl acetate in cyclohexane. This material was then further purified by 43 g reverse phase C18 ISCO Companion flash column eluting with 40-95% acetonitrile (0.05% formic acid) in water (0.1% formic acid) to give the title compound.

MS calcd for $(C_{30}H_{33}N_3O_5 + H)^+$: 516

MS found (electrospray): $(M+H)^+ = 516$

Intermediate 19

Ethyl 5-(4-bromophenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate



A solution of 3-hydroxytetrahydrofuran (1.92 mL) and pyridine (2.59 mL) in dry DCM (100 mL) was cooled to -10°C. Triflic anhydride (4.62 mL) was added dropwise via syringe and the resulting mixture was stirred at -10°C under nitrogen for 1.5 h.

A solution of ethyl 5-(4-bromophenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl]amino}-3-furancarboxylate (3.98 g, a synthesis of which is described as Intermediate 51) in dry THF (80 mL) and dry DMF (10 mL) was cooled to -78°C. KHMDS (24 mL, 0.5M solution in toluene) was added dropwise via syringe, and the reaction mixture was stirred at -78°C under nitrogen for 30 mins.

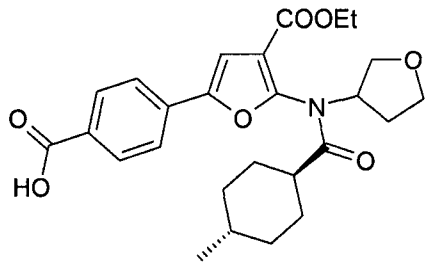
The triflate solution (prepared above) was allowed to warm to room temperature, was washed with 2M HCl and the layers were separated using a hydrophobic frit. The organics were passed through a silica SPE cartridge and the fractions were transferred to a dropping funnel. The solution was then added dropwise to the KHMDS reaction mixture. The reaction was stirred at -78°C under nitrogen for 1 h, then at -10°C for 2.5 h. The reaction was quenched with saturated sodium bicarbonate solution and the organics were extracted with EtOAc. The layers were separated and the organic phase was washed with brine. The organics were dried over sodium sulphate, were filtered using a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 5-55% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{25}H_{30}BrNO_5 + H)^+$: 504/506

MS found (electrospray): $(M+H)^+$ = 504/506

Intermediate 20

4-{4-[(Ethyloxy)carbonyl]-5-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-2-furanyl}benzoic acid



CO gas was bubbled through a stirred solution of ethyl 5-(4-bromophenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate (9.16 g, a synthesis of which is described as Intermediate 19), palladium (II) acetate (245 mg), dppf (1.16 g) and triethylamine (10.1 mL) in DMF (92 mL) and water (6.5 mL) for 20 mins. The reaction mixture was stirred at 60°C under a CO atmosphere for 1.25 h. CO gas was

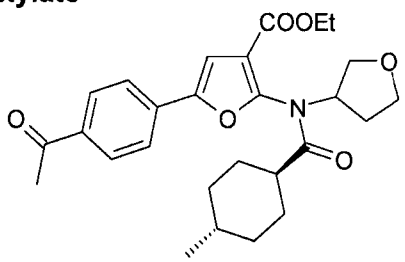
bubbled through the solution for a further 10 mins and the reaction was stirred at 60°C under a CO atmosphere for 2 h (a little more CO bubbled through after 1 h). The reaction mixture was then allowed to cool to room temperature and was partitioned between 2M HCl and EtOAc. The organics were separated, dried using a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by NH_2 SPE cartridge, eluting with 10% AcOH in 1,4-dioxane to give the title compound.

MS calcd for $(C_{26}H_{31}NO_7 + H)^+$: 470

MS found (electrospray): $(M+H)^+ = 470$

Intermediate 21

Ethyl 5-(4-acetylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate



To Intermediate 20 (6.97 g) were added dry DCM (104 mL), 1 drop DEF and oxalyl chloride (2.82 g), with care. The reaction was stirred at room temperature under nitrogen for 16 h and was evaporated *in vacuo* to give ethyl 5-[4-(chlorocarbonyl)phenyl]-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate.

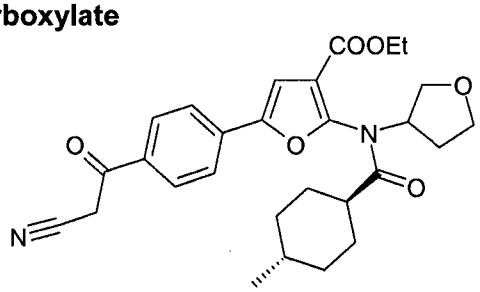
To ethyl 5-[4-(chlorocarbonyl)phenyl]-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate (6.5 g, prepared above) was added dry THF (100 mL) and the mixture was cooled to 0°C under nitrogen. Methyl zinc chloride (10.01 mL, 2M in THF) was added and the reaction was stirred for 10 mins. The reaction was quenched with saturated ammonium chloride, and was partitioned with DCM. The organics were separated using a hydrophobic frit and were evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 20-80% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{27}H_{33}NO_6 + H)^+$: 468

MS found (electrospray): $(M+H)^+ = 468$

Intermediate 22

Ethyl 5-[4-(cyanoacetyl)phenyl]-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate



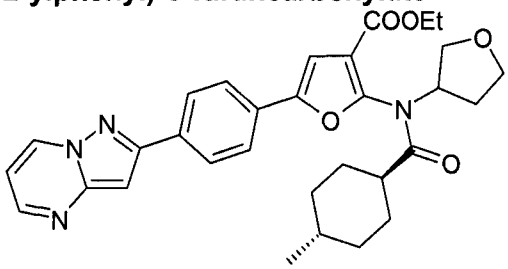
To Intermediate 21 (1 g) in dry DCM (20 mL) at 0°C under nitrogen was added 2,6-lutidine (0.46 g) and trimethylsilyl triflate (0.475 g). After 30 mins a further portion of trimethylsilyl triflate (0.158 g) was added and the reaction was stirred for 10 mins. NBS (0.38 g) was added and the reaction was stirred for 15 mins. The reaction was partitioned between 2N HCl and DCM, the organics were separated using a hydrophobic frit and evaporated *in vacuo*. The residue was dissolved in EtOH (13 mL) and potassium cyanide (0.42 g) in water (4.2 mL) was added. The reaction was stirred at room temperature under nitrogen for 2 h. The EtOH was removed and the residue was diluted with water. The solution was adjusted to ~pH 3 with AcOH and was partitioned with EtOAc. The layers were separated and the organics were passed through a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 20-100% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{28}H_{32}N_2O_6 + H)^+$: 493

MS found (electrospray): $(M+H)^+ = 493$

Intermediate 23

Ethyl 2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-3-furancarboxylate



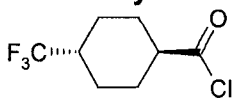
To Intermediate 22 (0.67 g) was added EtOH (13 mL), AcOH (0.67 mL) and hydrazine monohydrate (72 mg). The reaction was stirred for 2 h at 70°C under nitrogen. The solvent was evaporated *in vacuo* and to the residue was added AcOH (6.7 mL) and 1,1,3,3-tetrakis(methyloxy)propane (0.27 g). The reaction mixture was stirred at 110°C for 3 h. The solvent was evaporated *in vacuo* and the residue was purified by ISCO Companion silica chromatography, eluting with a gradient 20-80% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{31}H_{34}N_4O_5 + H)^+$: 543

MS found (electrospray): $(M+H)^+ = 543$

Intermediate 24

***trans*-4-(Trifluoromethyl)cyclohexanecarbonyl chloride**



Oxalyl chloride (4.59 mL) was added dropwise to a solution of *trans*-4-(trifluoromethyl)cyclohexanecarboxylic acid[1] (6.85 g) in dry DCM (100 mL) at room temperature under nitrogen. After 10 mins an effervescence was observed and the reaction

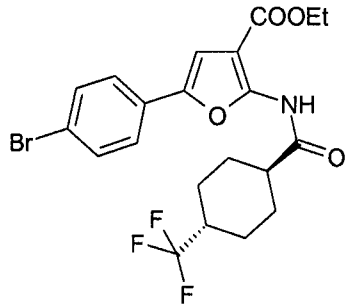
was stirred at room temperature overnight. The solvent was evaporated *in vacuo* to give the title compound.

^{1}H NMR (d_6-DMSO) δ 2.38-2.19 (2H, m), 1.92 (4H, dd), 1.44-1.22 (4H, m).

Ref 1: DE 39 30 119 (A1)

Intermediate 25

Ethyl 5-(4-bromophenyl)-2-({[*trans*-4-(trifluoromethyl)cyclohexyl]carbonyl}amino)-3-furancarboxylate



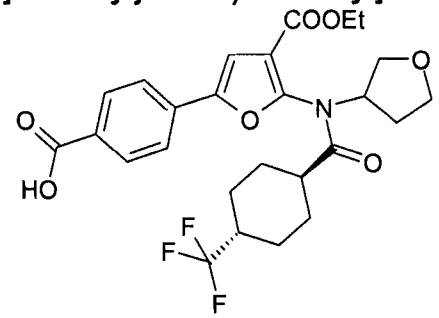
To a solution of ethyl 2-amino-5-(4-bromophenyl)-3-furancarboxylate (3.9 g, a synthesis of which is described as Intermediate 6) in dry DCM (62 mL) was added triethylamine (1.4 g) and *trans*-4-(trifluoromethyl)cyclohexanecarbonyl chloride (2.84 g, a synthesis of which is described as Intermediate 24). The reaction was stirred at room temperature for 16 h, then at 45°C for 16 h. A further portion of *trans*-4-(trifluoromethyl)cyclohexanecarbonyl chloride (1 g, a synthesis of which is described as Intermediate 24) was added and stirring was continued at 45°C for 16 h. The reaction was cooled, partitioned between 2N HCl and DCM, separated using a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-50% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{21}H_{21}BrF_3NO_4 + H)^+$: 488/490

MS found (electrospray): $(M+H)^+$ = 488/490

Intermediate 26

4-[4-[(Ethyloxy)carbonyl]-5-(tetrahydro-3-furanyl{[*trans*-4-(trifluoromethyl)cyclohexyl]carbonyl}amino)-2-furanyl]benzoic acid



To 3-hydroxytetrahydrofuran (1.82 g) was added dry DCM (78 mL) and pyridine (2.2 g). The solution was cooled to -10°C under nitrogen, then triflic anhydride (6.75 g) was added and

the reaction was stirred for 1.5 h. The reaction was partitioned between 2N HCl and was separated using a hydrophobic frit. The organics were passed through a silica SPE cartridge to give the triflate solution.

In a separate flask, KHMDS (20.8 mL, 0.5M in toluene) was added to a solution of Intermediate 25 (3.9 g) in dry DMF (9.75 mL) and dry THF (78 mL), at -78°C under nitrogen. The reaction was stirred for 1 h, then the triflate solution (prepared above) was added. The reaction was stirred at -78°C for 1 h, then at 0°C for 2 h. The reaction was quenched with saturated sodium bicarbonate solution and was extracted with EtOAc. The organic phase was washed with brine, passed through a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-50% EtOAc in cyclohexane to give ethyl 5-(4-bromophenyl)-2-(tetrahydro-3-furanyl{[*trans*-4-(trifluoromethyl)cyclohexyl]carbonyl}amino)-3-furancarboxylate.

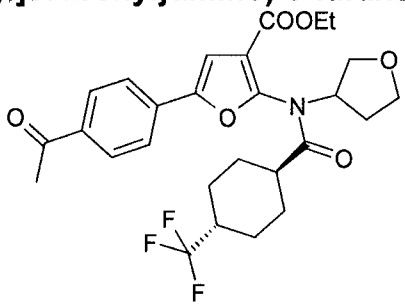
CO gas was bubbled through a solution of ethyl 5-(4-bromophenyl)-2-(tetrahydro-3-furanyl{[*trans*-4-(trifluoromethyl)cyclohexyl]carbonyl}amino)-3-furancarboxylate (1.6 g, prepared above), triethylamine (0.58 g), palladium(II) acetate (39 mg), Dppf (191 mg) and water (1.03 g) in DMF (16 mL). The reaction was stirred at 60°C under a CO atmosphere for 16 h. The reaction was cooled, partitioned between EtOAc and 2N HCl and was separated. The organics were passed through a hydrophobic frit and were evaporated *in vacuo*. The crude material was purified by NH_2 SPE cartridge to give the title compound.

MS calcd for $(C_{26}H_{28}F_3NO_7 + H)^+$: 524

MS found (electrospray): $(M+H)^+ = 524$

Intermediate 27

Ethyl 5-(4-acetylphenyl)-2-(tetrahydro-3-furanyl{[*trans*-4-(trifluoromethyl)cyclohexyl]carbonyl}amino)-3-furancarboxylate



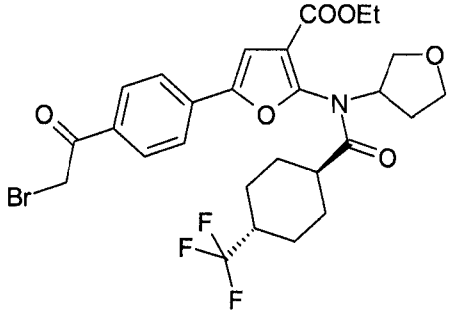
To Intermediate 26 (1.2g) was added dry DCM (18 mL), DEF (1 drop) and oxalyl chloride (0.44 g). The reaction was stirred at room temperature under nitrogen for 16 h. The solvent was removed, dry THF (18 mL) was added and the mixture was cooled in an ice bath under nitrogen. Methylzinc chloride (1.72 mL, 2M in THF) was added and the reaction was stirred at room temperature for 1.5 h. The reaction was quenched with saturated ammonium chloride, extracted with DCM and passed through a hydrophobic frit. The organics were evaporated *in vacuo* and the crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-100% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{27}H_{30}F_3NO_6 + H)^+$: 522

MS found (electrospray): $(M+H)^+ = 522$

Intermediate 28

Ethyl 5-[4-(bromoacetyl)phenyl]-2-(tetrahydro-3-furanyl{[*trans*-4-(trifluoromethyl)cyclohexyl]carbonyl}amino)-3-furancarboxylate



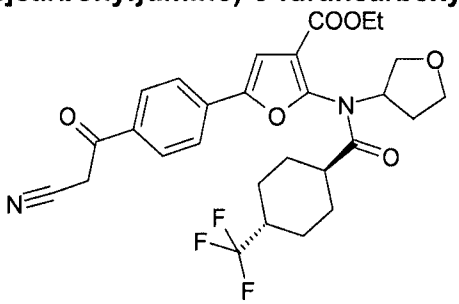
To Intermediate 27 (0.69 g) was added dry chloroform (27.6 mL) and bromine (2.1 g). The reaction was stirred at room temperature for 20 mins and was quenched with 5% sodium thiosulphate solution. The mixture was extracted with chloroform and was passed through a hydrophobic frit. The organics were evaporated *in vacuo* to give the title compound.

MS calcd for $(C_{27}H_{29}BrF_3NO_6 + H)^+$: 600/602

MS found (electrospray): $(M+H)^+ = 600/602$

Intermediate 29

Ethyl 5-[4-(cyanoacetyl)phenyl]-2-(tetrahydro-3-furanyl{[*trans*-4-(trifluoromethyl)cyclohexyl]carbonyl}amino)-3-furancarboxylate



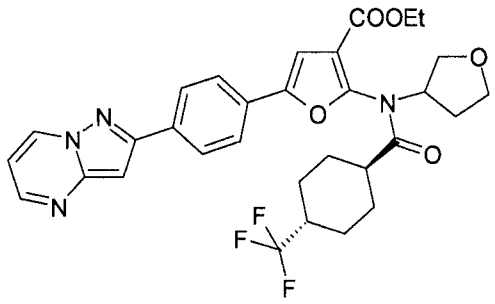
To Intermediate 28 (600 mg) was added EtOH (6 mL), followed by potassium cyanide (195 mg) in water (2 mL). The reaction was stirred at room temperature for 2 h. The EtOH was removed, the residue was diluted with water and was adjusted to pH3 with glacial acetic acid. The mixture was extracted with DCM, then EtOAc. The combined organics were passed through a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-100% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{28}H_{29}F_3N_2O_6 + H)^+$: 547

MS found (electrospray): $(M+H)^+ = 547$

Intermediate 30

Ethyl 5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-(tetrahydro-3-furanyl{[*trans*-4-(trifluoromethyl)cyclohexyl]carbonyl}amino)-3-furancarboxylate



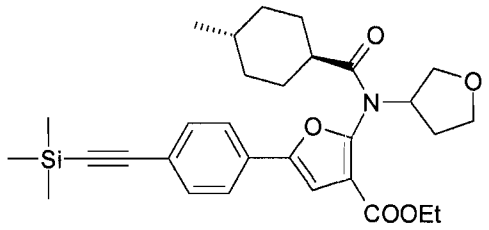
To Intermediate 29 (45 mg) was added EtOH (0.9mL), AcOH (0.045 mL) and hydrazine monohydrate (4.3 mg). The reaction was stirred at 70°C for 2 h under nitrogen. The reaction was cooled and evaporated *in vacuo*. To the residue was added AcOH (0.5 mL) and 1,1,3,3-tetrakis(methyloxy)propane (16 mg). The reaction was stirred at 110°C for 2 h and was then cooled and evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-110% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{31}H_{31}F_3N_4O_5 + H)^+$: 597

MS found (electrospray): $(M+H)^+ = 597$

Intermediate 31

Ethyl 2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-5-{4-[(trimethylsilyl)ethynyl]phenyl}-3-furancarboxylate



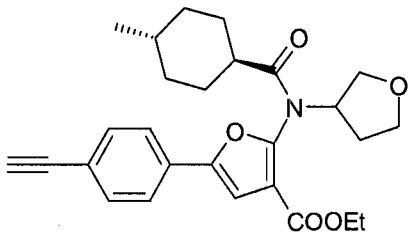
To a stirred solution of ethyl 5-(4-bromophenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate (1.8 g, a synthesis of which is described as Intermediate 19) in dry THF (9 mL) was added triethylamine (1.8 mL), copper(I) iodide (34mg), (trimethylsilyl)acetylene (0.908 mL) and dichlorobis(triphenylphosphine)palladium (II) (125 mg). The reaction mixture was stirred at 55°C for 2 h, under nitrogen. The reaction was cooled, diluted with DCM, filtered using a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-50% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{30}H_{39}NO_5Si + H)^+$: 522

MS found (electrospray): $(M+H)^+ = 522$

Intermediate 32

Ethyl 5-(4-ethynylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate



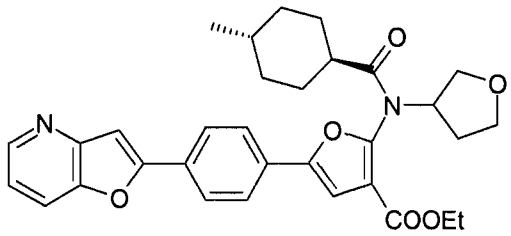
To a solution of Intermediate 31 (888 mg) in EtOH (18 mL) was added potassium carbonate (118 mg) and the reaction was stirred at room temperature, under nitrogen for 3 h. The mixture was partitioned between saturated sodium bicarbonate solution and DCM, and the layers were separated using a hydrophobic frit. The organics were evaporated *in vacuo* to give the title compound.

MS calcd for $(C_{27}H_{31}NO_5 + H)^+$: 450

MS found (electrospray): $(M+H)^+ = 450$

Intermediate 33

Ethyl 5-(4-furo[3,2-*b*]pyridin-2-ylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate



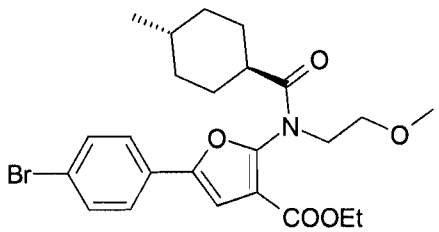
A mixture of Intermediate 32 (228 mg), 2-iodo-3-hydroxypyridine (112 mg), copper(I) iodide (10 mg), dichlorobis(triphenylphosphine)palladium (II) (36 mg) and triethylamine (3.5 mL) were stirred and heated in a Reacti-vial at 70°C for 17 h. The reaction was cooled, partitioned between saturated sodium bicarbonate solution and DCM, separated using a hydrophobic frit and the organics were evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-100% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{32}H_{34}N_2O_6 + H)^+$: 543

MS found (electrospray): $(M+H)^+ = 543$

Intermediate 34

Ethyl 5-(4-bromophenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylate



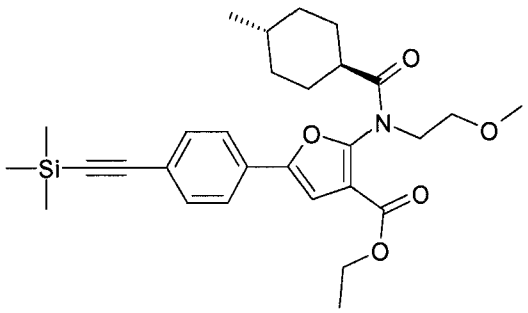
A solution of ethyl 5-(4-bromophenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl]amino}-3-furancarboxylate (5 g, a synthesis if which is described as Intermediate 51) in dry DMF (100 mL) was stirred under nitrogen with cooling for 15 mins. Sodium hydride (0.92 g, 60% dispersion in oil) was added portion-wise. The reaction was left to stir under nitrogen for 2h. 2-Bromoethylmethyl ether (11.2 mL) was added and the reaction was left to stir overnight. The reaction mixture was treated with 2N HCl (2 mL) and was evaporated *in vacuo*. The residue was partitioned between 2N HCl and DCM, the organics were separated using a hydrophobic frit and were evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 5-100% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{24}H_{30}BrNO_5 + H)^+$: 492/494

MS found (electrospray): $(M+H)^+$ = 492/494

Intermediate 35

Ethyl 2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-5-{4-[(trimethylsilyl)ethynyl]phenyl}-3-furancarboxylate



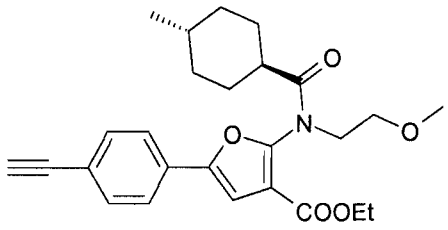
To a stirred solution of Intermediate 34 (0.9 g) in dry THF (5 mL) was added triethylamine (0.9 mL), copper(I) iodide (17 mg), (trimethylsilyl)acetylene (0.4 mL) and dichlorobis(triphenylphosphine)palladium (II) (61 mg). The reaction mixture was stirred at 55°C for 2 h. A further portion of (trimethylsilyl)acetylene (0.4 mL) was added and the reaction was heated overnight at room temperature under nitrogen. The reaction was cooled and DCM was added. The solution was filtered using a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 5-50% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{29}H_{39}NO_5Si + H)^+$: 510

MS found (electrospray): $(M+H)^+$ = 510

Intermediate 36

Ethyl 5-(4-ethynylphenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylate



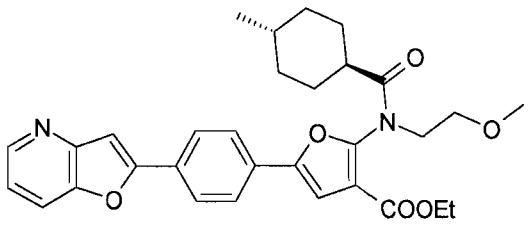
To a solution of Intermediate 35 (0.45 g) in EtOH (10 mL) was added potassium carbonate (60 mg). The reaction mixture was stirred at room temperature under nitrogen for 3 h. The mixture was partitioned between saturated sodium bicarbonate solution and DCM, the layers were separated using a hydrophobic frit and the organics were evaporated *in vacuo* to give the title compound.

MS calcd for $(C_{26}H_{31}NO_5 + H)^+$: 438

MS found (electrospray): $(M+H)^+ = 438$

Intermediate 37

Ethyl 5-(4-furo[3,2-*b*]pyridin-2-ylphenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylate



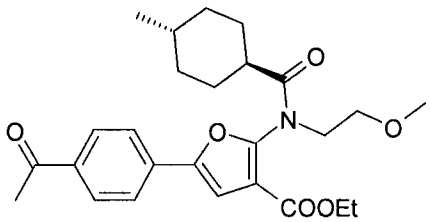
A mixture of Intermediate 36 (220 mg), 2-iodo-3-hydroxypyridine (112 mg), copper(I) iodide (10 mg), dichlorobis(triphenylphosphine)palladium (II) (36 mg) and triethylamine (3.5 mL) were heated in a Reacti-vial at 70°C overnight. The reaction was cooled to room temperature, partitioned between saturated sodium bicarbonate solution and DCM, separated using a hydrophobic frit and the organics were evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-100% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{31}H_{34}N_2O_6 + H)^+$: 531

MS found (electrospray): $(M+H)^+ = 531$

Intermediate 38

Ethyl 5-(4-acetylphenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylate



A solution of ethyl 5-(4-bromophenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylate (6 g, a synthesis of which is described as

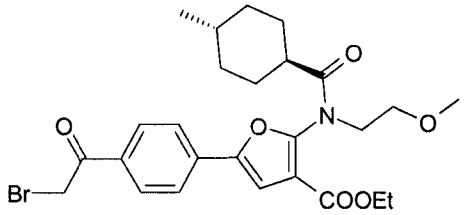
Intermediate 34), palladium (II) acetate (138 mg), DPPP (0.5 g) and 1-butyl-3-methylimidazolium tetrafluoroborate (1.25 mL) in dry DMSO (25 mL) was de-gassed by bubbling nitrogen through for 10 mins. Butylethenyl ether (4.91 g) and diisopropylamine (2.98 g) were added and the reaction was stirred under nitrogen at 115°C for 18 h. The mixture was cooled and 2N HCl (60 mL) was added. This mixture was stirred for 15 mins, then DCM (100 mL) was added and was stirred for 15 mins. The phases were separated using a hydrophobic frit and the organics were evaporated *in vacuo*. The crude material was purified by silica Biotage cartridge, eluting with 1:1 EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{26}H_{33}NO_6 + H)^+$: 456

MS found (electrospray): $(M+H)^+ = 456$

Intermediate 39

Ethyl 5-[4-(bromoacetyl)phenyl]-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylate



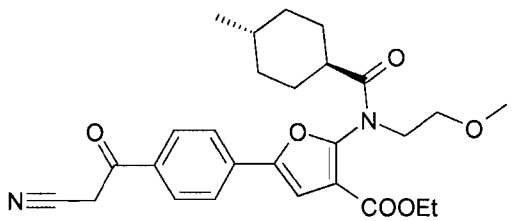
To a solution of Intermediate 38 (1.6 g) in dry chloroform (70 mL) was added bromine (1.8 mL). The reaction mixture was stirred at room temperature for 9 mins and was quenched with 15% sodium thiosulphate solution. The organics were separated, washed again with 15% sodium thiosulphate solution, separated using a hydrophobic frit and evaporated *in vacuo* to give the title compound.

MS calcd for $(C_{26}H_{32}BrNO_6 + H)^+$: 534/536

MS found (electrospray): $(M+H)^+ = 534/536$

Intermediate 40

Ethyl 5-[4-(cyanoacetyl)phenyl]-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylate



To a solution of Intermediate 39 (1.8 g) in EtOH (32 mL) was added potassium cyanide (0.68 g) in water (6 mL). The reaction was stirred at room temperature for 2 h. The EtOH was evaporated *in vacuo* and the residue was diluted with water and adjusted to pH3 with glacial acetic acid. The aqueous was extracted with DCM and the organics were passed through a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by ISCO

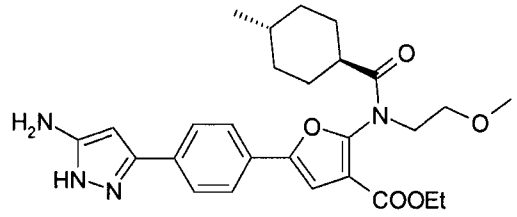
Companion silica chromatography, eluting with a gradient 0-100% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{27}H_{32}N_2O_6 + H)^+$: 481

MS found (electrospray): $(M+H)^+ = 481$

Intermediate 41

Ethyl 5-[4-(5-amino-1*H*-pyrazol-3-yl)phenyl]-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylate



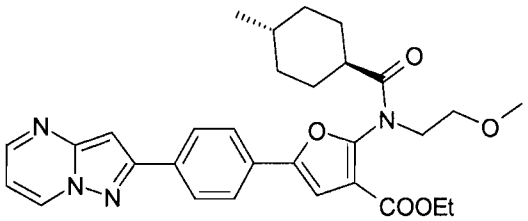
A solution of Intermediate 40 (0.18 g) in EtOH (2 mL) was treated with glacial acetic acid (0.08 mL). Hydrazine monohydrate (0.024 mL) was added and the mixture was heated at 70°C for 2 h. The EtOH was removed *in vacuo* and the residue was partitioned between DCM and saturated sodium bicarbonate solution. The organics were separated using a hydrophobic frit and evaporated *in vacuo* to give the title compound.

MS calcd for $(C_{27}H_{34}N_4O_5 + H)^+$: 495

MS found (electrospray): $(M+H)^+ = 495$

Intermediate 42

Ethyl 2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-3-furancarboxylate



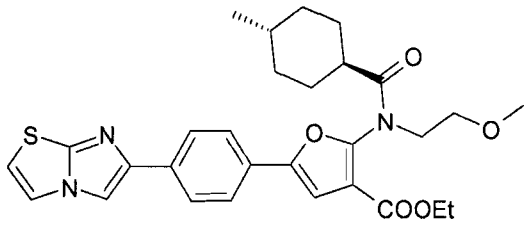
A solution of Intermediate 41 (188 mg) in AcOH (1.5 mL) was treated with 1,1,3,3-tetrakis(methyloxy)propane (0.077 mL). The reaction was heated at 110°C for 1.5 h and was then cooled and evaporated *in vacuo*. The residue was partitioned between DCM and saturated sodium bicarbonate solution. The organics were separated using a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 5-100% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{30}H_{34}N_4O_5 + H)^+$: 531

MS found (electrospray): $(M+H)^+ = 531$

Intermediate 43

Ethyl 5-(4-imidazo[2,1-*b*][1,3]thiazol-6-ylphenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylate



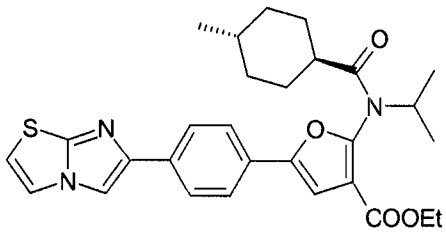
To a solution of ethyl 5-[4-(bromoacetyl)phenyl]-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylate (0.55 g, a synthesis of which is described as Intermediate 39) in ethylene glycol (10 mL) was added 2-aminothiazole (200 mg). The reaction was heated at 60°C under nitrogen overnight and was evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-100% EtOAc in hexane to give the title compound.

MS calcd for $(C_{29}H_{33}N_3O_5S + H)^+$: 536

MS found (electrospray): $(M+H)^+ = 536$

Intermediate 44

Ethyl 5-(4-imidazo[2,1-*b*][1,3]thiazol-6-ylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate



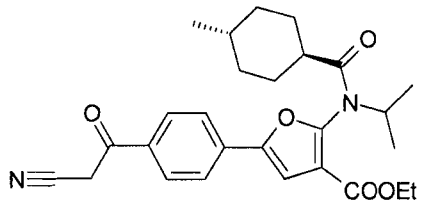
To a solution of ethyl 5-[4-(bromoacetyl)phenyl]-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate (724 mg, a synthesis of which is described as Intermediate 15) in DME (11 mL) was added 2-aminothiazole (256 mg). The reaction was stirred at 60°C under nitrogen for 18 h and was evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-100% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{29}H_{33}N_3O_4S + H)^+$: 520

MS found (electrospray): $(M+H)^+ = 520$

Intermediate 45

Ethyl 5-[4-(cyanoacetyl)phenyl]-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate



To a solution of ethyl 5-[4-(bromoacetyl)phenyl]-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate (670 mg, a synthesis of which is described as

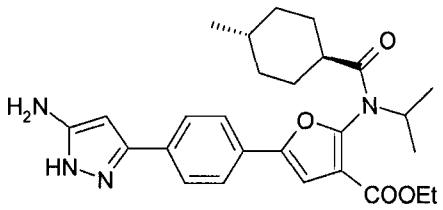
Intermediate 15) in EtOH (6 mL) was added a solution of potassium cyanide (252 mg) in water (2 mL). The mixture was stirred at room temperature for 3 h, then the EtOH was evaporated *in vacuo*. The residue was diluted with water (10 mL) and the glacial acetic acid was added until pH3 was obtained. The mixture was extracted with DCM, the layers were separated using a hydrophobic frit and the organics evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 3-100% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{27}H_{32}N_2O_5 + H)^+$: 465

MS found (electrospray): $(M+H)^+ = 465$

Intermediate 46

Ethyl 5-[4-(5-amino-1*H*-pyrazol-3-yl)phenyl]-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate



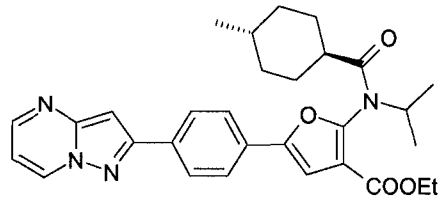
A solution of Intermediate 45 (189 mg) was dissolved in EtOH (2 mL) and was treated with glacial acetic acid (0.08 mL). Hydrazine monohydrate (0.024 mL) was added and the mixture was heated at 70°C for 18 h. The EtOH was evaporated *in vacuo* and the residue was partitioned between saturated sodium bicarbonate solution and DCM. The organics were separated using a hydrophobic frit and were evaporated *in vacuo* to give the title compound.

MS calcd for $(C_{27}H_{34}N_4O_4 + H)^+$: 479

MS found (electrospray): $(M+H)^+ = 479$

Intermediate 47

Ethyl 2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-3-furancarboxylate



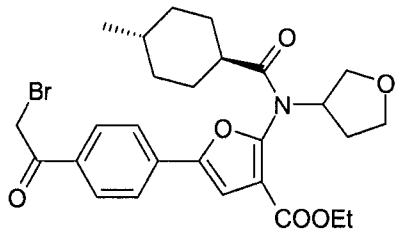
A solution of Intermediate 46 (186 mg) in AcOH (1.5 mL) was treated with 1,1,3,3-tetrakis(methyloxy)propane (0.077 mL). The reaction was heated at 110°C for 1.5 h and was evaporated *in vacuo*. The residue was partitioned between DCM and saturated sodium bicarbonate solution. The organics were separated using a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 3-100% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{30}H_{34}N_4O_4 + H)^+$: 515

MS found (electrospray): $(M+H)^+ = 515$

Intermediate 48

Ethyl 5-[4-(bromoacetyl)phenyl]-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate



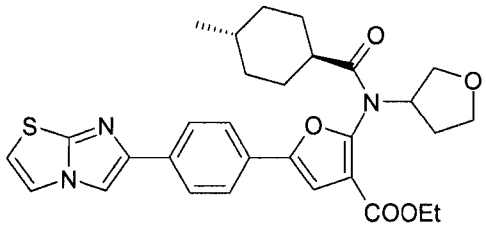
To a solution of ethyl 5-(4-acetylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate (857 mg, a synthesis of which is described as Intermediate 21) in dry chloroform (35 mL) was added a solution of bromine (0.92 mL) in dry chloroform (7.85 mL). The reaction was stirred at room temperature under nitrogen for 10 mins. The reaction was quenched with 5% sodium thiosulphate solution and the organics were extracted with DCM. The layers were separated using a hydrophobic frit and the organics were evaporated *in vacuo* to give the title compound.

MS calcd for $(C_{27}H_{32}BrNO_6 + H)^+$: 546/548

MS found (electrospray): $(M+H)^+ = 546/548$

Intermediate 49

Ethyl 5-(4-imidazo[2,1-*b*][1,3]thiazol-6-ylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate



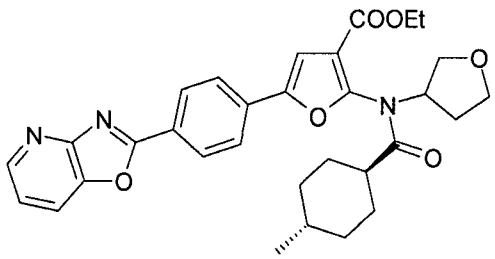
To a solution of Intermediate 48 (239 mg) in DME (3.6 mL) was added 2-aminothiazole (88 mg). The reaction was heated at 60°C and stirred under nitrogen for 18 h. The solvent was evaporated *in vacuo* and the crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-100% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{30}H_{33}N_3O_5S + H)^+$: 548

MS found (electrospray): $(M+H)^+ = 548$

Intermediate 50

Ethyl 2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-5-(4-[1,3]oxazolo[4,5-*b*]pyridin-2-ylphenyl)-3-furancarboxylate



To Intermediate 20 (6.97 g) were added dry DCM (104 mL), DEF (1 drop) and oxalyl chloride (2.82 g), with care. The reaction was stirred at room temperature under nitrogen for 16 h and was evaporated *in vacuo* to give ethyl 5-[4-(chlorocarbonyl)phenyl]-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate.

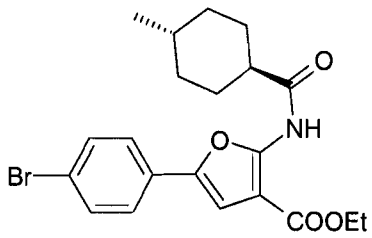
A mixture of ethyl 5-[4-(chlorocarbonyl)phenyl]-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylate (0.5 g, prepared above) and 2-amino-3-hydroxypyridine (112 mg) in dry 1,4-dioxane (2.5 mL) was heated in a microwave at 200°C for 2 h. The reaction was diluted with DMSO (2.5 mL) and was purified by reverse phase ISCO Companion chromatography, using a C18 cartridge, eluting with a gradient 40-96% MeCN in water to give the title compound.

MS calcd for $(C_{31}H_{33}N_3O_6 + H)^+$: 544

MS found (electrospray): $(M+H)^+ = 544$

Intermediate 51

Ethyl 5-(4-bromophenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl]amino}-3-furancarboxylate



To a solution of ethyl 2-amino-5-(4-bromophenyl)-3-furancarboxylate (20 g, a synthesis of which is described as Intermediate 6) in dry DCM (300 mL) was added *trans*-4-methylcyclohexanecarbonyl chloride[1] (15.4 g) in DCM (50 mL) dropwise. After the addition was complete the reaction was heated at 45°C for 16 h. The mixture was partitioned between 2N HCl and DCM, and the DCM was separated, passed through a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by silica Biotage cartridge, eluting with 5% EtOAc/cyclohexane to give the title compound.

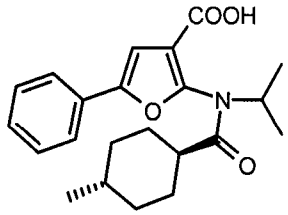
MS calcd for $(C_{21}H_{24}BrNO_4 + H)^+$: 434/436

MS found (electrospray): $(M+H)^+ = 434/436$

Ref 1: WO 2004/052885

Example 1

2-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-phenyl-3-furancarboxylic acid



Intermediate 4 (210 mg) was dissolved in THF (2 mL) and ethanol (2 mL). 2N Lithium hydroxide solution (2 mL) was added and the mixture stirred at room temperature for 24 h. The reaction was then quenched with 2N HCl, extracted with DCM, passed through a hydrophobic frit and the organics concentrated. The residue was then purified by ISCO companion C_{18} chromatography eluting with water (0.1% formic acid) then a gradient of 40-80% acetonitrile (containing 0.05% formic acid) to give the title compound.

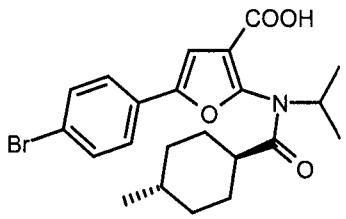
MS calcd for $(C_{22}H_{27}NO_4 + H)^+$: 370

MS found (electrospray): $(M+H)^+ = 370$

^1H NMR (MeOD): δ. 7.69 (2H, d), 7.44 (2H, t), 7.34 (1H, t), 7.13 (1H, s), 4.76 (1H, m), 2.16 (1H, tt), 1.85-1.27 (10H, br. m), 1.05 (3H, d), 0.785 (3H, d), 0.76-0.54 (2H, m), carboxylic acid proton not seen.

Example 2

5-(4-Bromophenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid



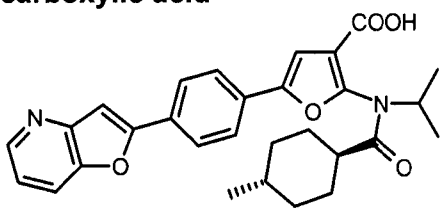
Ethyl 5-(4-bromophenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylate (12 mg, a synthesis of which is described as Intermediate 8) was dissolved in THF (1 mL) and ethanol (1 mL). 2N Lithium hydroxide solution (1 mL) was added and the mixture stirred at room temperature for 16 h. The reaction was then quenched with 2N HCl, extracted with DCM, passed through a hydrophobic frit and the organics concentrated to give the title compound.

MS calcd for $(C_{22}H_{26}NBrO_4 + H)^+$: 448/450

MS found (electrospray): $(M+H)^+ = 448/450$

Example 3

5-{4-(Furo[3,2-*b*]pyridin-2-yl)phenyl}-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid



Intermediate 11 (32 mg) was dissolved in THF (1 mL) and ethanol (1 mL). 2N Lithium hydroxide solution (1 mL) was added and the mixture stirred at room temperature for 16 h. The reaction was then quenched with 2N HCl, extracted with DCM, passed through a hydrophobic frit and the organics concentrated. Purification by NH_2 SPE chromatography eluting with 1,4-dioxane, followed by 6% AcOH in 1,4-dioxane gave the title compound.

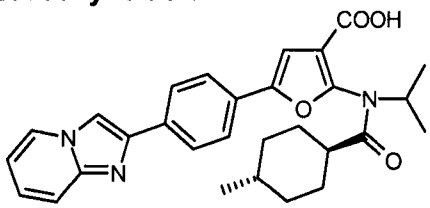
MS calcd for $(C_{29}H_{30}N_2O_5+ H)^+$: 487

MS found (electrospray): $(M+H)^+ = 487$

^1H NMR (MeOD): δ 8.47 (1H, dd), 8.06 (2H, d), 8.0 (1H, d), 7.85 (2H, d), 7.42 (1H, s), 7.36 (1H, dd), 7.25 (1H, s), 4.77 (1H, m), 2.22 (1H, tt), 1.9-1.20 (10H, br. m), 1.075 (3H, d), 0.785 (3H, d), 0.76-0.6 (2H, m), carboxylic acid proton not seen.

Example 4

5-{4-(Imidazo[1,2-a]pyridin-2-yl)phenyl}-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid



Intermediate 16 (19 mg) was dissolved in THF (1 mL) and ethanol (1 mL). 2N Lithium hydroxide solution (1 mL) was added and the mixture stirred at room temperature for 16 h. The reaction was then neutralised with 2N HCl and extracted with ethyl acetate. The phases were separated and the organic phase passed through a hydrophobic frit and concentrated to give the title compound.

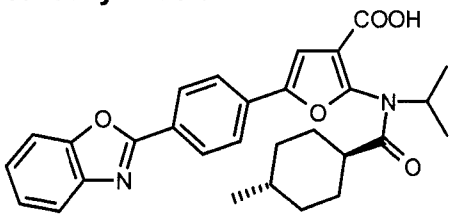
MS calcd for $(C_{29}H_{31}N_3O_4+ H)^+$: 486

MS found (electrospray): $(M+H)^+ = 486$

^1H NMR (MeOD) : δ 8.42 (1H, d), 8.26 (1H, s), 8.0 (2H, d), 7.75 (2H, d), 7.55 (1H, d), 7.32 (1H, dd), 7.13 (1H, s), 6.92 (1H, t), 4.76 (1H, m), 2.75 (1H, m), 1.90 (1H, br), 1.75 (1H, br), 1.64 (2H, br), 1.52 (1H, br), 1.40 (1H, br), 1.30 (4H, br), 1.10 (3H, br. d), 0.78 (3H, d), 0.68 (2H, br) carboxylic acid proton not seen.

Example 5

5-[4-(1,3-Benzoxazol-2-yl)phenyl]-2-[[(trans-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid



Intermediate 17 (180 mg) was dissolved in THF (2 mL) and ethanol (2 mL). 2N Lithium hydroxide solution (2 mL) was added and the mixture stirred at room temperature for 16 h. The reaction was then neutralised with 2N HCl and extracted with ethyl acetate. The phases

were separated and the organic phase was washed with brine passed through a hydrophobic frit and concentrated to give the title compound.

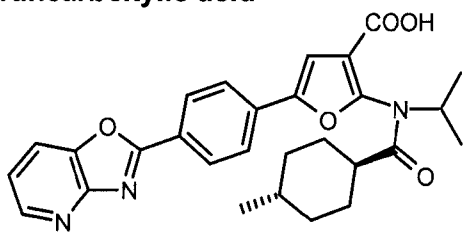
MS calcd for $(C_{29}H_{30}N_2O_5+ H)^+$: 487

MS found (electrospray): $(M+H)^+ = 487$

^1H NMR (MeOD) : δ 8.3 (2H, d), 7.9 (2H, d), 7.72 (2H, m), 7.41 (2H, m), 7.28 (1H, s), 4.76 (1H, m), 2.3 (1H, m), 1.95 (1H, br), 1.73 (1H, br), 1.65 (2H, br), 1.54 (1H, br), 1.38 (1H, br), 1.26 (4H, br), 1.08 (3H, br), 0.78 (3H, d), 0.68 (2H, br) carboxylic acid proton not seen.

Example 6

2-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-{4-([1,3]oxazolo[4,5-b]pyridin-2-yl)phenyl}-3-furancarboxylic acid



Intermediate 18 (56 mg) was dissolved in THF (1 mL) and ethanol (1 mL). 2N Lithium hydroxide solution (0.055 mL) was added and the mixture stirred at room temperature for 16 h. Further 2N lithium hydroxide (0.028 mL) was added and stirred for a further 5 h. The reaction was then neutralised with 2N HCl and partitioned between ethyl acetate and water. The phases were separated and the organic phase passed through a hydrophobic frit and concentrated. The crude material was purified by 13 g reverse phase C18 ISCO Companion flash column eluting with 40-95% acetonitrile (0.05% formic acid) in water (0.1% formic acid) to give the title compound.

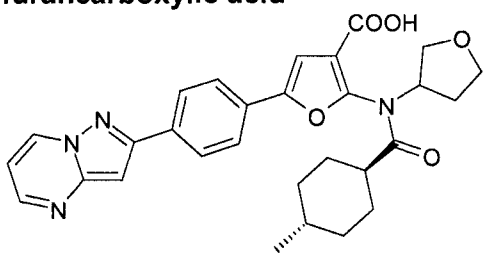
MS calcd for $(C_{28}H_{29}N_3O_5+ H)^+$: 488

MS found (electrospray): $(M+H)^+ = 488$

^1H NMR (MeOH) : δ 8.52 (1H, s), 8.38 (2H, d), 8.14 (1H, s), 7.95 (2H, d), 7.48 (1H, m), 7.40 (1H, s), 4.78 (1H, m), 2.15 (1H, br), 1.88-1.50 (5H, br), 1.42 (1H, br), 1.30 (4H, br), 1.08 (3H, br), 0.78 (3H, d), 0.67 (2H, br) carboxylic acid proton not seen.

Example 7

2-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-3-furancarboxylic acid

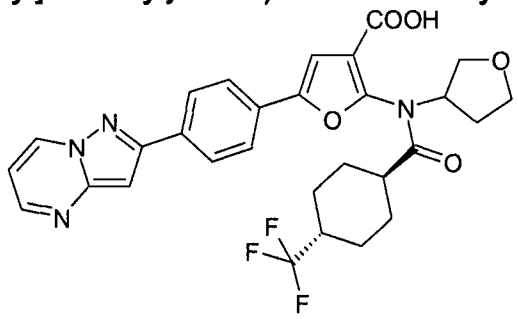


To Intermediate 23 (0.40 g) was added THF (4 mL), EtOH (4 mL) and 2M lithium hydroxide (4 mL). The reaction was stirred at room temperature for 16 h. The mixture was acidified with 2N HCl to ~pH 1-3, and was then partitioned between DCM and water. The organics

were separated using a hydrophobic frit and the organic phase was evaporated *in vacuo* to give the title compound.
MS calcd for $(C_{29}H_{30}N_4O_5 + H)^+$: 515
MS found (electrospray): $(M+H)^+ = 515$

Example 8

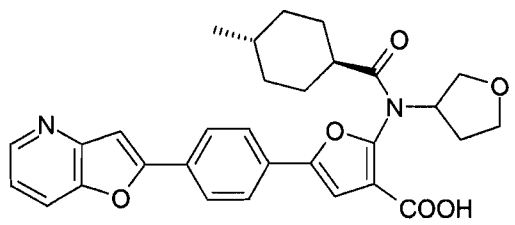
5-(4-Pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-(tetrahydro-3-furanyl{[*trans*-4-(trifluoromethyl)cyclohexyl]carbonyl}amino)-3-furancarboxylic acid



To Intermediate 30 (22 mg) was added THF (1 mL), EtOH (1 mL) and 2M lithium hydroxide solution (1 mL). The reaction was stirred at room temperature for 16 h. The reaction was adjusted to pH 5 with 2N HCl and was extracted with DCM. The organics were separated using a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by reverse phase ISCO Companion chromatography, using a C18 cartridge, eluting with a gradient 40-100% MeCN in water to give the title compound.
MS calcd for $(C_{29}H_{27}F_3N_4O_5 + H)^+$: 569
MS found (electrospray): $(M+H)^+ = 569$
^1H NMR (CD_3OD) δ 8.93 (1H, d), 8.50 (1H, dd), 8.12 (2H, d), 7.84 (2H, d), 7.27 (1H, s), 7.11 (1H, s), 7.00 (1H, dd), 5.14-4.96 (1H, m), 4.05-3.61 (5H, m), 2.42-1.82 (7H, m), 1.69-1.42 (2H, m), 1.23-0.99 (2H, m), carboxylic acid proton not seen.

Example 9

5-(4-Furo[3,2-*b*]pyridin-2-ylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylic acid

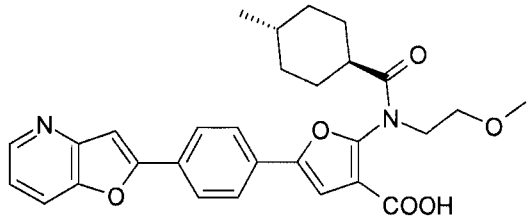


To a stirred solution of Intermediate 33 (142 mg) in EtOH (5 mL) and THF (5 mL) was added 2M lithium hydroxide solution (4 mL). The reaction mixture was stirred at room temperature for 18 h, and was then neutralised with 2M HCl (4 mL). The mixture was partitioned between water and DCM, was stirred and separated using a hydrophobic frit. The organics were evaporated *in vacuo*. The crude material was purified by reverse phase ISCO Companion

chromatography, using a C18 cartridge, eluting with a gradient 40-95% MeCN in water. The material was freeze-dried from 1,4-dioxane to give the title compound.
MS calcd for $(C_{30}H_{30}N_2O_6 + H)^+$: 515
MS found (electrospray): $(M+H)^+$ = 515

Example 10

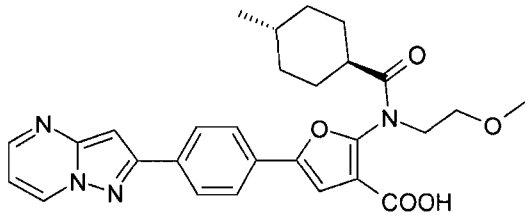
5-(4-Furo[3,2-*b*]pyridin-2-ylphenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylic acid



To a stirred solution of Intermediate 37 (100 mg) in EtOH (5 mL) and THF (5 mL) was added 2M lithium hydroxide solution (4 mL). The reaction mixture was stirred overnight and was then neutralised with 2M HCl (4 mL). The mixture was partitioned between water and DCM. The layers were separated, the organics were passed through a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by reverse phase MDAP HPLC to give the title compound.
MS calcd for $(C_{29}H_{30}N_2O_6 + H)^+$: 503
MS found (electrospray): $(M+H)^+$ = 503
^{1}H NMR ($CDCl_3$) δ 8.57 (1H, dd), 8.01 (2H, d), 7.87 (1H, d), 7.80 (2H, d), 7.39 (1H, s), 7.30 (1H, dd), 7.18 (1H, d), 4.02 (2H, br), 3.64 (2H, t), 3.31 (3H, s), 2.24-2.13 (1H, t), 1.91-1.80 (2H, m), 1.74-1.54 (4H, m), 1.43-1.28 (1H, m), 0.85-0.68 (5H, m), carboxylic acid proton not seen.

Example 11

2-{[(*trans*-4-Methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-3-furancarboxylic acid

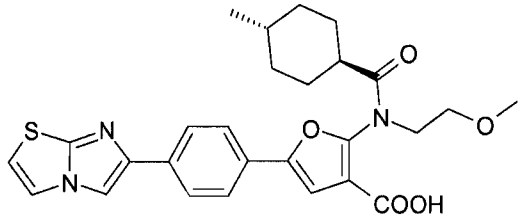


A solution of Intermediate 42 (0.07 g) in THF (1 mL) and EtOH (1 mL) was treated with 2N sodium hydroxide solution (0.5 mL) and the mixture was stirred at room temperature for 18 h. The mixture was acidified with 2N HCl and was extracted with DCM. The DCM layer was separated using a hydrophobic frit and was evaporated *in vacuo*. The crude material was purified by reverse phase MDAP HPLC to give the title compound.
MS calcd for $(C_{28}H_{30}N_4O_5 + H)^+$: 503
MS found (electrospray): $(M+H)^+$ = 503

^{1}H NMR ($CDCl_3$) δ 8.72 (1H, d), 8.50 (1H, dd), 8.07 (2H, d), 7.76 (2H, d), 7.11 (1H, s), 7.04 (1H, s), 6.84 (1H, dd), 3.98 (2H, t), 3.64 (2H, t), 3.32 (3H, s), 2.18-2.06 (1H. m), 1.85-1.74(2H, m), 1.72-1.48 (4H, m), 1.40-1.27 (1H, m), 0.83-0.67 (5H, m), carboxylic acid proton not seen.

Example 12

5-(4-Imidazo[2,1-*b*][1,3]thiazol-6-ylphenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylic acid



To a solution of Intermediate 43 (0.2 g) in THF (10 mL) and EtOH (10 mL) was added 2M lithium hydroxide (10 mL). The reaction was stirred at room temperature for 16 h and was acidified using 2M HCl. The mixture was partitioned between water and DCM and was stirred and separated. The organics were dried using a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by MDAP HPLC to give the title compound.

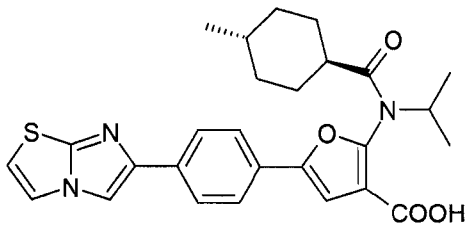
MS calcd for $(C_{27}H_{29}N_3O_5S + H)^+$: 508

MS found (electrospray): $(M+H)^+$ = 508

^{1}H NMR ($CDCl_3$) δ 7.88 (2H, d), 7.80 (1H, s), 7.71 (2H, d), 7.47 (1H, d), 7.07 (1H, s), 6.88 (1H, d), 3.97 (2H, t), 3.63 (2H, t), 3.31 (3H, s), 2.20-2.08 (1H, t), 1.86-1.75 (2H, m), 1.71-1.49(4H, m), 1.39-1.27 (1H, m), 0.82-0.68 (5H, m), carboxylic acid proton not seen.

Example 13

5-(4-Imidazo[2,1-*b*][1,3]thiazol-6-ylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid



To a solution of Intermediate 44 (111 mg) in THF (4 mL) and EtOH (4 mL) was added 2M lithium hydroxide solution (4 mL), and the reaction was stirred at room temperature for 20 h. 2M HCl was added and the mixture was partitioned between water and DCM. The layers were separated using a hydrophobic frit, and the organics were evaporated *in vacuo*. The crude material was purified by reverse phase ISCO Companion chromatography, using a C18 cartridge, eluting with a gradient 40-95% MeCN in water to give the title compound.

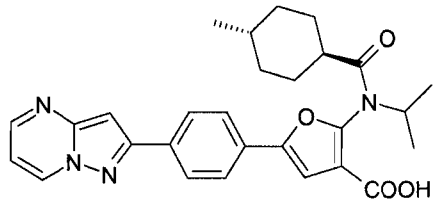
MS calcd for $(C_{27}H_{29}N_3O_4S + H)^+$: 492

MS found (electrospray): $(M+H)^+$ = 492

^{1}H NMR (d_6-DMSO) δ 13.04 (1H, br), 8.30 (1H, s), 7.97-7.90 (3H, m), 7.77 (2H, d), 7.33-7.28 (2H, m), 4.69 (1H, quintet), 2.04 (1H, t), 1.72-1.12 (10H, m), 0.96 (3H, d), 0.80-0.54 (5H, m).

Example 14

2-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-3-furancarboxylic acid



To a solution of Intermediate 47 (147 mg) in THF (2 mL) and EtOH (2 mL) was added 2N sodium hydroxide solution (1mL). The mixture was stirred at room temperature for 24 h. The mixture was acidified with 2N HCl and was extracted with DCM. The organic layer was separated using a hydrophobic frit and was evaporated *in vacuo*. The crude material was purified by reverse phase ISCO Companion chromatography, using a C18 cartridge, eluting with a gradient 40-95% MeCN (0.05% formic acid) in water (0.1% formic acid) to give the title compound.

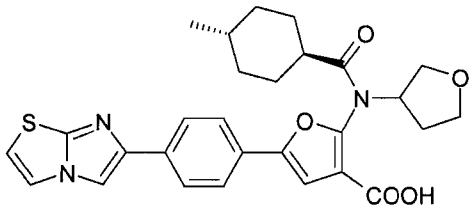
MS calcd for $(C_{28}H_{30}N_4O_4 + H)^+$: 487

MS found (electrospray): $(M+H)^+$ = 487

^{1}H NMR ($CDCl_3$) δ 8.76 (1H, dd), 8.51 (1H, dd), 8.09 (2H, d), 7.79 (2H, d), 7.16 (1H, s), 7.06 (1H, s), 6.86 (1H, dd), 4.93 (1H, quintet), 2.12 (1H, t), 1.84-1.60 (5H, m), 1.55-1.43 (1H, m), 1.39-1.24 (4H, m), 1.15-1.03 (3H, m), 0.83-0.64 (5H, m), carboxylic acid proton not seen.

Example 15

5-(4-Imidazo[2,1-*b*][1,3]thiazol-6-ylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylic acid



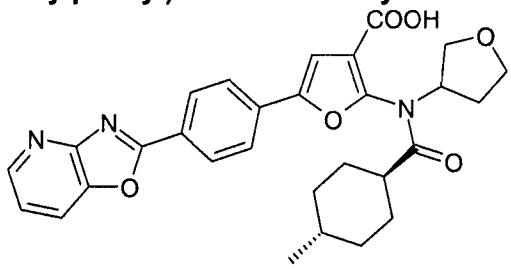
Intermediate 49 (38 mg) was dissolved in THF (2 mL) and EtOH (2 mL). 2M Lithium hydroxide solution (2 mL) was added and the reaction was stirred at room temperature for 16 h. The mixture was neutralised using 2M HCl (2 mL) and was partitioned between water and DCM. The layers were stirred and separated using a hydrophobic frit. The organic phase was evaporated *in vacuo* and the crude material was purified by reverse phase ISCO Companion chromatography, using a C18 cartridge. The material was freeze-dried from 1,4-dioxane to give the title compound.

MS calcd for $(C_{28}H_{29}N_3O_5S + H)^+$: 520

MS found (electrospray): $(M+H)^+$ = 520

Example 16

2-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-5-(4-[1,3]oxazolo[4,5-*b*]pyridin-2-ylphenyl)-3-furancarboxylic acid



To Intermediate 50 (71 mg) was added dry pyridine (0.7 mL) and lithium iodide (171 mg). The reaction was heated in a Reacti-vial for 3 days at 120°C. The reaction was cooled and evaporated *in vacuo*. The crude material was purified by reverse phase ISCO Companion chromatography, using a C18 cartridge, eluting with a gradient 40-90% MeCN in water. The material was purified further by MDAP HPLC and was freeze-dried to give the title compound.

MS calcd for $(C_{29}H_{29}N_3O_6 + H)^+$: 516

MS found (electrospray): $(M+H)^+ = 516$

The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in therapy, comprising a compound of Formula (I) or a pharmaceutically acceptable salt or solvate thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.

The compounds of the present invention can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical, transdermal, or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets and liquid preparations such as syrups, elixirs and concentrated drops.

Alternatively, injection (parenteral administration) may be used, e.g., intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the chemical entities of the invention are formulated in liquid solutions, preferably, in pharmaceutically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the chemical entities may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives.

In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.

The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound (IC_{50}) potency, (EC_{50}) efficacy, and the biological half-life (of the compound), the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art.

Amounts administered also depend on the routes of administration and the degree of oral bioavailability. For example, for compounds with low oral bioavailability, relatively higher doses will have to be administered. Oral administration is a preferred method of administration of the present compounds.

Preferably the composition is in unit dosage form. For oral application, for example, a tablet, or capsule may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be administered. In each case, dosing is such that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/Kg, for example from 0.1 to 50 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes contains suitably from 0.01 mg to 100 mg/Kg, of a compound of Formula(I). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, for example once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

Compounds of Formula (I) which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil. olive oil, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions

may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional non-CFC propellant such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

ASSAYS

The potential for chemical entities of the invention to inhibit NS5B wildtype HCV polymerase activity, genotype 1b, may be demonstrated, for example, using the following *in vitro* assay:

In Vitro Detection of inhibitors of HCV RNA-dependent RNA Polymerase Activity

Incorporation of [^{33}P]-GMP into RNA was followed by absorption of the biotin labelled RNA polymer by streptavidin containing SPA beads. A synthetic template consisting of biotinylated 13mer-oligoG hybridised to polyrC was used as a homopolymer substrate.

Reaction Conditions were 0.5 μM [^{33}P]-GTP (20 Ci/mMol), 1 mM Dithiothreitol, 20 mM $MgCl_2$, 5mM $MnCl_2$, 20 mM Tris-HCl, pH7.5, 1.6 μg/mL polyC/0.256 μM biotinylated oligoG13, 10% glycerol, 0.01% NP-40, 0.2 u/μL RNasin and 50 mM NaCl.

HCV RNA Polymerase (Recombinant full-length NS5B (Lohmann et al, J. Virol. 71 (11), 1997, 8416. 'Biochemical properties of hepatitis C virus NS5B RNA-dependent RNA polymerase and identification of amino acid sequence motifs essential for enzymatic activity') expressed in baculovirus and purified to homogeneity) was added to 4 nM final concentration.

5x concentrated assay buffer mix was prepared using 1M $MnCl_2$ (0.25 mL), glycerol (2.5mL), 10% NP-40 (0.025 mL) and Water (7.225 mL), *Total* 10 mL.

2x concentrated enzyme buffer contained 1M-Tris-HCl, pH7.5 (0.4 mL), 5M NaCl (0.2 mL), 1M-$MgCl_2$ (0.4 mL), glycerol (1 mL), 10% NP-40 (10 μL), 1M DTT (20 μL) and water (7.97 mL), *Total* 10 mL.

Substrate Mix was prepared using 5x Concentrated assay Buffer mix (4μL), [^{33}P]-GTP (10 μCi/μL, 0.02μL), 25 μM GTP (0.4 μL), 40 u/μL RNasin (0.1 μL), 20 μg/mL polyrC/biotinylated-oligorG (1.6 μL), and Water (3.94 μL), *Total* 10 μL.

Enzyme Mix was prepared by adding 1mg/ml full-length NS5B polymerase (1.5 μL) to 2.81mL 2x-concentrated enzyme buffer.

The Assay was set up using compound (1μL), Substrate Mix (10 μL), and Enzyme Mix (added last to start reaction) (10 μL), *Total* 21 μL.

The reaction was performed in a U-bottomed, white, 96-well plate. The reaction was mixed on a plate-shaker, after addition of the Enzyme, and incubated for 1h at 22°C. After this time, the reaction was stopped by addition of 40 μL 1.875 mg/ml streptavidin SPA beads in 0.1 M EDTA. The beads were incubated with the reaction mixture for 1h at 22°C after which 120 μL 0.1 M EDTA in PBS was added. The plate was sealed, mixed centrifuged and incorporated radioactivity determined by counting in a Trilux (Wallac) or Topcount (Packard) Scintillation Counter.

After subtraction of background levels without enzyme, any reduction in the amount of radioactivity incorporated in the presence of a compound, compared to that in the absence, was taken as a measure of the level of inhibition. Ten concentrations of compounds were tested in three- or fivefold dilutions. From the counts, percentage of inhibition at highest concentration tested or IC_{50}s for the compounds were calculated using GraFit 3, GraFit 4 or GraFit 5 software packages or a data evaluation macro for Excel based on XLFit Software (IDBS).

The exemplified compounds had an IC_{50} of <10μM in the above described assay. In one aspect, compounds have an IC_{50} of <2μM. Accordingly, the compounds of the invention are of potential therapeutic benefit in the treatment and prophylaxis of HCV. Accordingly, the compounds of the present invention are of great potential therapeutic benefit in the treatment and prophylaxis of HCV.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example immune therapies (eg. Interferon, such as Interferon alfa-2a (Roferon-A; Hoffmann-La Roche), inteferon alpha-2b (Intron-A; Schering-Plough), interferon alfacon-1 (Infergen; Intermune), peginterferon alpha-2b (Peg-Intron; Schering-Plough) or peginterferon alpha-2a (Pegasys; Hoffmann-La Roche)), therapeutic vaccines, antifibrotic agents, anti-inflammatory agents such as corticosteroids or

NSAIDs, bronchodilators such as beta-2 adrenergic agonists and xanthines (e.g. theophylline), mucolytic agents, anti-muscarinics, anti-leukotrienes, inhibitors of cell adhesion (e.g. ICAM antagonists), anti-oxidants (eg N-acetylcysteine), cytokine agonists, cytokine antagonists, lung surfactants and/or antimicrobial, anti-viral agents (eg ribavirin and amantidine), and anti-HCV agents (eg HCV NS3 protease inhibitors or HCV NS5b polymerase inhibitors). The compositions according to the invention may also be used in combination with gene replacement therapy.

The invention thus provides, in a further aspect, a combination comprising a compound of Formula (I) together with at least one other therapeutically active agent, especially Interferon, ribavirin and/or an additional anti-HCV agent.

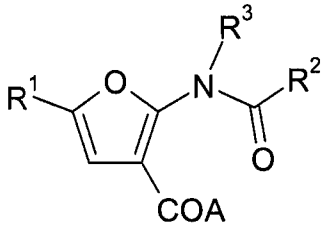
The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof represent a further aspect of the invention.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

Claims

1. A compound of Formula (Ia) :



(Ia)

wherein:

A represents hydroxy;

R^1 represents $-R^X-R^Y$;

R^X represents phenyl (optionally substituted by halo, methyl, ethyl, methoxy or trifluoromethyl) or 5- or 6-membered heteroaryl bonded through a ring carbon atom to the carbon atom of the furan;

R^Y represents heteroaryl (optionally substituted by one or more substituents selected from $-C_{1-4}$alkyl, halo, hydroxy and $-NH_2$), wherein when R^X is phenyl or 6-membered heteroaryl, then R^Y is bonded in the *para*-position;

R^2 represents $-C_{5-7}$cycloalkyl (optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl (unsubstituted), $-CF_3$, $-CF_2H$, $-CFH_2$, hydroxy and fluoro) or phenyl (optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl, $-CF_3$ and halo);

R^3 represents linear or branched $-C_{1-6}$alkyl (optionally substituted by one or more substituents selected from 5- or 6-membered heteroaryl and 5- or 6-membered heterocyclyl), linear or branched $-C_{2-6}$alkyl (optionally substituted by one or more substituents selected from methoxy, ethoxy and fluoro), or $-C_{3-6}$cycloalkyl, pyranyl or tetrahydrofuranyl (each of which may be optionally substituted by one or more substituents selected from $-C_{1-2}$alkyl, fluoro and methoxy), or $-CH_2CF_3$ or $-CH_2$cyclopropyl;

or salts, solvates or esters thereof.

2. A compound as claimed in Claim 1 chosen from the group consisting of:
5-{4-(Furo[3,2-*b*]pyridin-2-yl)phenyl}-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid;
5-{4-(Imidazo[1,2-a]pyridin-2-yl)phenyl}-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid;

5-[4-(1,3-Benzoxazol-2-yl)phenyl]-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid;
2-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-{4-([1,3]oxazolo[4,5-b]pyridin-2-yl)phenyl}-3-furancarboxylic acid;
2-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-3-furancarboxylic acid;
5-(4-Pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-(tetrahydro-3-furanyl{[*trans*-4-(trifluoromethyl)cyclohexyl]carbonyl}amino)-3-furancarboxylic acid;
5-(4-Furo[3,2-*b*]pyridin-2-ylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylic acid;
5-(4-Furo[3,2-*b*]pyridin-2-ylphenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylic acid;
2-{[(*trans*-4-Methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-3-furancarboxylic acid;
5-(4-Imidazo[2,1-*b*][1,3]thiazol-6-ylphenyl)-2-{[(*trans*-4-methylcyclohexyl)carbonyl][2-(methyloxy)ethyl]amino}-3-furancarboxylic acid;
5-(4-Imidazo[2,1-*b*][1,3]thiazol-6-ylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-3-furancarboxylic acid;
2-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-3-furancarboxylic acid;
5-(4-Imidazo[2,1-*b*][1,3]thiazol-6-ylphenyl)-2-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-3-furancarboxylic acid; and
2-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-5-(4-[1,3]oxazolo[4,5-*b*]pyridin-2-ylphenyl)-3-furancarboxylic acid,

and salts, solvates and esters thereof.

3. A compound as claimed in Claim 1, wherein R^X represents phenyl optionally substituted by halo, methyl, methoxy or trifluoromethyl.

4. A compound as claimed in Claim 1 or 3, wherein R^Y represents furo[3,2-*b*]pyridin-2-yl, pyrazolo[1,5-*a*]pyrimidin-2-yl, imidazo[1,2-*a*]pyridin-2-yl, imidazo[2,1-*b*][1,3]thiazol-6-yl, [1,3]oxazolo[4,5-*b*]pyridin-2-yl or 1,3-benzoxazol-2-yl.

5. A compound as claimed in Claim 1, 3 or 4, wherein R^2 represents *trans*-4-methylcyclohexyl or *trans*-4-(trifluoromethyl)cyclohexyl.

6. A compound as claimed in Claim 1, 3, 4 or 5, wherein R^3 represents 1-methylethyl, tetrahydrofuranyl or (methyloxy)ethyl.

7. A compound as claimed in Claim 1 wherein A represents hydroxy; R^X represents phenyl optionally substituted by halo, methyl, methoxy or trifluoromethyl; R^Y represents

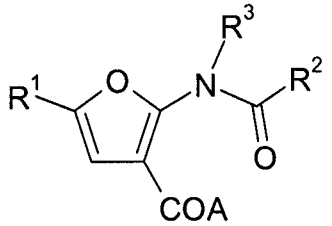
bicyclic heteroaryl optionally substituted by one or more substituents selected from -C_{1-4}alkyl, halo, hydroxy or $-NH_2$, wherein when R^X is phenyl or a 6-membered heteroaryl, then R^Y is bonded in the *para*-position; R^2 represents -C_6cycloalkyl optionally substituted by one or more C_{1-2}alkyl substituents; and R^3 represents 1-methylethyl, tetrahydrofuran-2-yl or (methyloxy)ethyl.

8. A compound as claimed in Claim 1 or Claim 7 wherein A represents hydroxy; R^X represents unsubstituted phenyl; R^Y represents furo[3,2-*b*]pyridin-2-yl, pyrazolo[1,5-*a*]pyrimidin-2-yl, imidazo[1,2-*a*]pyridin-2-yl, imidazo[2,1-*b*][1,3]thiazol-6-yl, [1,3]oxazolo[4,5-b]pyridin-2-yl or 1,3-benzoxazol-2-yl; R^2 represents *trans*-4-methylcyclohexyl or *trans*-4-(trifluoromethyl)cyclohexyl; and R^3 represents 1-methylethyl, tetrahydrofuran-2-yl or (methyloxy)ethyl.

9. A compound as claimed in Claims 1, 7 or 8 wherein A represents hydroxy; R^X represents unsubstituted phenyl; R^Y represents furo[3,2-*b*]pyridin-2-yl or pyrazolo[1,5-*a*]pyrimidin-2-yl; R^2 represents *trans*-4-methylcyclohexyl or *trans*-4-(trifluoromethyl)cyclohexyl; and R^3 represents 1-methylethyl, tetrahydrofuran-2-yl or (methyloxy)ethyl.

10. A compound as claimed in Claims 1, 7, 8 or 9 wherein A represents hydroxy; R^X represents unsubstituted phenyl; R^Y represents furo[3,2-*b*]pyridin-2-yl, imidazo[1,2-*a*]pyridin-2-yl, or [1,3]oxazolo[4,5-b]pyridin-2-yl; R^2 represents *trans*-4-methylcyclohexyl; and R^3 represents 1-methylethyl.

11. A method of treating or preventing viral infection which comprises administering to a subject in need thereof, an effective amount of a compound of Formula (I) :



(I)

wherein:

A represents hydroxy;

R^1 represents -R^X-R^Y;

R^X represents phenyl (optionally substituted by halo, methyl, ethyl, methoxy or trifluoromethyl) or a 5- or 6-membered heteroaryl bonded through a ring carbon atom to the carbon atom of the furan;

R^Y represents H, halo, or heteroaryl (optionally substituted by one or more substituents selected from -C_{1-4}alkyl, halo, hydroxy and $-NH_2$), wherein when R^X is phenyl or a 6-membered heteroaryl, then R^Y is bonded in the *para*-position;

R^2 represents -C_{5-7}cycloalkyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl (unsubstituted), $-CF_3$, $-CF_2H$, $-CFH_2$, hydroxy and fluoro) or phenyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl, $-CF_3$ and halo);

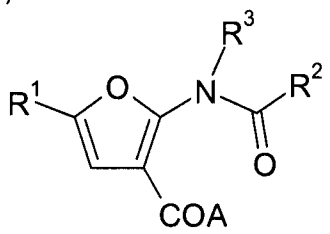
R^3 represents linear or branched -C_{1-6}alkyl (optionally substituted by one or more substituents selected from -C_2-C_6 alkoxy, 5- or 6-membered heteroaryl and 5- or 6-membered heterocyclyl), or -C_{3-6}cycloalkyl, pyranyl or tetrahydrofuranyl (each of which may be optionally substituted by one or more substituents selected from -C_{1-2}alkyl, fluoro and methoxy), or $-CH_2CF_3$, or $-CH_2$cyclopropyl;

or salts, solvates or esters thereof

12. A method as claimed in claim 11 which involves inhibiting HCV replication.

13. A method as claimed in claim 11 or 12 in which the compound is administered in an oral dosage form.

14. A compound of Formula (I) :



(I)

wherein:

A represents hydroxy;

R^1 represents -R^X-R^Y;

R^X represents phenyl (optionally substituted by halo, methyl, ethyl, methoxy or trifluoromethyl) or a 5- or 6-membered heteroaryl bonded through a ring carbon atom to the carbon atom of the furan;

R^Y represents H, halo, or heteroaryl (optionally substituted by one or more substituents selected from -C_{1-4}alkyl, halo, hydroxy and $-NH_2$), wherein when R^X is phenyl or a 6-membered heteroaryl, then R^Y is bonded in the *para*-position;

R^2 represents -C_{5-7}cycloalkyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl (unsubstituted), -CF_3, -CF_2H, -CFH_2, hydroxy and fluoro) or phenyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl, -CF_3 and halo);

R^3 represents linear or branched -C_{1-6}alkyl (optionally substituted by one or more substituents selected from -C_2-C_6 alkoxy, 5- or 6-membered heteroaryl and 5- or 6-membered heterocyclyl), or -C_{3-6}cycloalkyl, pyranyl or tetrahydrofuranyl (each of which may be optionally substituted by one or more substituents selected from -C_{1-2}alkyl, fluoro and methoxy), or –CH_2CF_3, or –CH_2cyclopropyl;

or salts, solvates or esters thereof, for use in medical therapy.

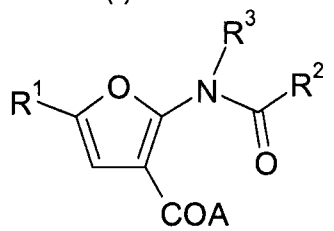
15. A compound as claimed in claim 14 wherein the medical therapy is the treatment of viral infection.

16. A compound as claimed in claim 15 wherein the viral infection is HCV.

17. A pharmaceutical formulation comprising a compound chosen from compounds of Formula (Ia) and pharmaceutically acceptable salts, solvates and esters thereof as defined in claim 1 in conjunction with at least one pharmaceutically acceptable diluent or carrier.

18. A pharmaceutical formulation as claimed in claim 17, wherein the formulation is presented in oral form.

19. Use of a compound of Formula (I) :



(I)

wherein:

A represents hydroxy;

R^1 represents -R^X-R^Y;

R^X represents phenyl (optionally substituted by halo, methyl, ethyl, methoxy or trifluoromethyl) or a 5- or 6-membered heteroaryl bonded through a ring carbon atom to the carbon atom of the furan;

R^Y represents H, halo, or heteroaryl (optionally substituted by one or more substituents selected from -C_{1-4}alkyl, halo, hydroxy and $-NH_2$), wherein when R^X is phenyl or a 6-membered heteroaryl, then R^Y is bonded in the *para*-position;

R^2 represents -C_{5-7}cycloalkyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl (unsubstituted), -CF_3, -CF_2H, -CFH_2, hydroxy and fluoro) or phenyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl, -CF_3 and halo);

R^3 represents linear or branched -C_{1-6}alkyl (optionally substituted by one or more substituents selected from -C_2-C_6 alkoxy, 5- or 6-membered heteroaryl and 5- or 6-membered heterocyclyl), or -C_{3-6}cycloalkyl, pyranyl or tetrahydrofuranyl (each of which may be optionally substituted by one or more substituents selected from -C_{1-2}alkyl, fluoro and methoxy), or $-CH_2CF_3$, or $-CH_2$cyclopropyl;

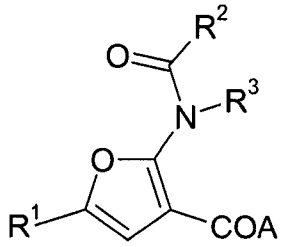
or salts, solvates or esters thereof, in the manufacture of a medicament for the treatment and/or prophylaxis of viral infection.

20. Use as claimed in Claim 19 wherein the viral infection is HCV.

21. A combination comprising a compound of Formula (Ia) as defined in Claim 1, together with at least one other therapeutically active agent.

22. A combination as claimed in Claim 21, wherein the other therapeutically active agent is selected from Interferon, ribavirin and/or an additional anti-HCV agent.

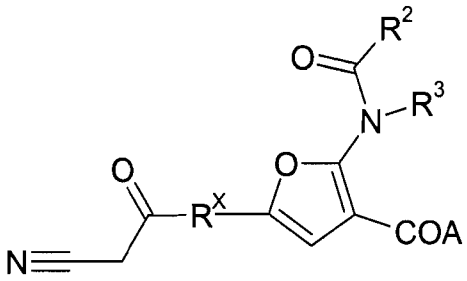
23. A process for the preparation of a compound of Formula (I) or Formula (II) as defined in Claim 1, comprising treatment of a compound of Formula (II)



(II)

in which A is a protected hydroxy group and R^1, R^2, and R^3 are as defined for Claim 1, with a base.

24. A process for the preparation of a compound of Formula (I) or Formula (II) in which R^1 represents a 4-(pyrazolopyrimidine)phenyl and R^2, R^3 and A are as defined in Claim 1, comprising treatment of a compound of Formula (XVI)



(XVI)

in which R^X, R^2 and R^3 are as defined in Claim 1 and A is an alkoxy, benzyloxy or silyloxy group, with (i) hydrazine in the presence of an acid, followed by (ii) treatment with 1,1,3,3-tetramethoxypropane.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/055991

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D307/68 A61K31/341 C07D471/04 C07D493/04 A61P31/00
C07D413/10 C07D498/04 C07D513/04 A61K31/4355 A61K31/437
A61K31/421 A61K31/429

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 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, 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.
Y	WO 2005/063734 A (BAYER HEALTHCARE AG [DE]; THEDE KAI [DE]; WUNBERG TOBIAS [DE]; LOWINGE) 14 July 2005 (2005-07-14) page 1, lines 2-5 pages 36-49; examples 6a,7a-10a,15a-22a,28a,32a,35a-38a page 85 - page 94; examples 1-6,11-17,19--22,25,28-30 claims 1-15 ----- -/--	1-24

[X] Further documents are listed in the continuation of Box C.

[X] 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
5 September 2007	12/09/2007

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/055991

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PFEFFERKORN J A ET AL: "Inhibitors of HCV NS5B polymerase. Part 1: Evaluation of the southern region of (2Z)-2-(benzoylamino)-3-(5-phenyl-2-furyl) acrylic acid" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 15, no. 10, 16 May 2005 (2005-05-16), pages 2481-2486, XP004877709 ISSN: 0960-894X page 2481; figure 1 page 2843; tables 1,2	1-24
A	WO 2005/092863 A (GLAXO GROUP LTD [GB]; BRAVI GIANPAOLO [GB]; CORFIELD JOHN ANDREW [GB];) 6 October 2005 (2005-10-06) page 1, lines 4-6 page 94 - page 95; examples 8,10,17-26,29,31,32,34,36,38,39,48-51,53 page 100 - page 108; examples 87-90,108 claims 1-13	1-24
A	WO 2005/009539 A (SYNTA PHARMACEUTICALS CORP [US]; XIE YU [US]; HOLMQVIST MATS [US]; MAH) 3 February 2005 (2005-02-03) cited in the application pages 3-5	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/055991

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

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

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

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

Remark on Protest

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

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/055991

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005063734 A	14-07-2005	CA 2550428 A1	14-07-2005
		DE 10359791 A1	21-07-2005
		EP 1694665 A2	30-08-2006
		US 2007099929 A1	03-05-2007
WO 2005092863 A	06-10-2005	AR 051349 A1	10-01-2007
		EP 1730116 A1	13-12-2006
		US 2007167507 A1	19-07-2007
WO 2005009539 A	03-02-2005	AU 2004259024 A1	03-02-2005
		AU 2004259347 A1	03-02-2005
		BR PI0412257 A	03-10-2006
		BR PI0412805 A	26-09-2006
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		CA 2533598 A1	03-02-2005
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		JP 2007501186 T	25-01-2007
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		KR 20060058092 A	29-05-2006
		KR 20060066711 A	16-06-2006
		MX PA06000836 A	04-05-2006
		MX PA06000837 A	04-05-2006
		WO 2005009954 A2	03-02-2005