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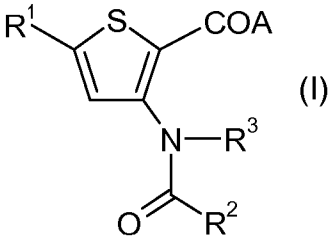
(54) **Title:** 3-CARBONYLAMINOTHIOPHENE-2-CARBOXYLIC ACIDS AS HEPATITIS C VIRUS INHIBITORS



(I)

(57) **Abstract:** The present invention relates to novel 2-carboxy thiophene compounds of the formula (I): and salts thereof, to pharmaceutical compositions containing them and their use in medicine, as anti-viral agents. Specifically, the present invention relates to compounds as inhibitors of Hepatitis C Virus (HCV) replication.

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3-CARBONYLAMINOTHIOPHENE-2-CARBOXYLIC ACIDS AS HEPATITIS C VIRUS INHIBITORS

FIELD OF THE INVENTION

The present invention relates to novel 2-carboxy thiophene 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.

Although the predominant HCV genotype worldwide is genotype 1, this itself has two main subtypes, denoted 1a and 1b. As seen from entries into the Los Alamos HCV database (www.hcv.lanl.gov) (Table 1) there are regional differences in the distribution of these subtypes: while genotype 1a is most abundant in the United States, the majority of

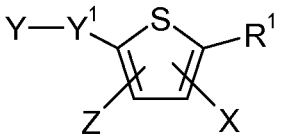
sequences in Europe and Japan are from genotype 1b.

Table 1

% of sequences in the database	World	USA	Europe	Japan
Genotype 1	71.8	87.8	75.9	80.2
Genotype 1a	28.4	66.4	21.7	1.6
Genotype 1b	43.4	21.4	54.2	78.6

Based on the foregoing, there exists a significant need to identify synthetic or biological compounds for their ability to inhibit replication of both genotype 1a and genotype 1b of HCV.

PCT publication number WO2002/100851 generically discloses certain compounds, including certain 2-carboxy thiophene compounds, having HCV inhibitory activity. The data provided relates to an HCV polymerase assay utilising the 1b genotype. The compounds disclosed have the formula (I)



(I)

wherein

X is chosen from $–N(R^3)M(R^2)$ or $–JN(R^2)(R^3)$;

M is chosen from $–SO_2$-, -SO-, -S-, -C(O)-, -C(S)-, $-CH_2C(O)N(R^4)$-, $-CH_2C(S)N(R^{15})$-, $-CH(R^{15})$-, $-C(=N(R^8))$-, or a bond;

R^4 is C_{1-6}alkyl;

R^8 is chosen from H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, C_{6-14}aryl, C_{3-12}heterocycle, C_{3-12}heteroaralkyl, C_{6-16}aralkyl;

R^{15} is chosen from H or C_{1-6}alkyl;

J is chosen from $–C(W)$-, $-C(R^6)$-, -S-, -S(O)-, or $-SO_2$-;

W is chosen from O, S or NR^7;

R^7 is chosen from H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, C_{6-14}aryl, C_{3-12}heterocycle, C_{3-12}heteroaralkyl, C_{6-16}aralkyl;

R^6 is chosen from H, C_{1-12}alkyl, C_{6-14}aryl, or C_{6-16}aralkyl;

Y^1 is chosen from a bond, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl;

Y is chosen from $COOR^{16}$, $COCOOR^5$, $P(O)OR^aOR^b$, $S(O)OR^5$, $S(O)_2OR^5$, tetrazole, $CON(R^9)CH(R^5)COOR^5$, $CONR^{10}R^{11}$, $CON(R^9)$-SO_2-R^5, $CONR^9OH$, or halogen;

R^9, R^5,R^{10} and R^{11} are each independently chosen from H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, C_{3-12}heterocycle, C_{3-18}heteroaralkyl, C_{6-18}aralkyl;

or R^{10} and R^{11} are taken together with the nitrogen to form a 3 to 10 membered heterocycle;

R^a and R^b are each independently chosen from H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, C_{6-14}aryl, C_{3-12}heterocycle, C_{3-18}heteroaralkyl, C_{6-18}aralkyl;

or R^a and R^b are taken together with the oxygens to form a 5 to 10 membered heterocycle;
R^{16} is chosen from H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, C_{6-14}aryl, C_{3-12}heterocycle, C_{3-18}heteroaralkyl, C_{6-18}aralkyl; provided that R^{16} is other than methyl or ethyl;
R^1 is chosen from C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, C_{6-14}aryl, C_{3-12}heterocycle, C_{3-18}heteroaralkyl, C_{6-18}aralkyl;
R^2 is chosen from C_{1-12}alkyl, C_{2-12}alkynyl, C_{6-14}aryl, C_{3-12}heterocycle, C_{3-18}heteroaralkyl, C_{6-18}aralkyl;
R^3 is chosen from H, C_{1-12}alkyl, C_{2-12}alkenyl, C_{2-12}alkynyl, C_{6-14}aryl, C_{3-12}heterocycle, C_{3-18}heteroaralkyl, C_{6-18}aralkyl;
Z is chosen from H, halogen, or C_{1-6}alkyl.

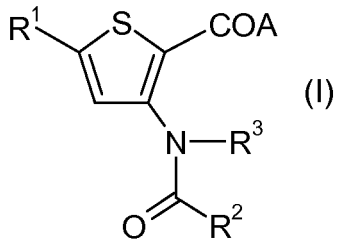
Surprisingly, it has now been found that compounds according to the present invention, generically disclosed in WO2002/100851, and having a specific substitution pattern, exhibit improved properties over those compounds specifically disclosed in WO2002/100851.

SUMMARY OF THE INVENTION

The present invention involves novel 2-carboxy thiophene 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 a compound of Formula (I) :



(I)

wherein:

A represents hydroxy;

R^1 represents $-R^xR^y$;

R^X represents phenyl (optionally substituted at one of the *meta*-positions to the thiophene by chloro, fluoro, methyl, ethyl, $-CF_3$, -OMe, $-NH_2$ or –OH); thienyl (optionally substituted by chloro, fluoro, methyl, ethyl, $-CF_3$ or –OMe) bonded through a ring carbon atom to the carbon atom of the thiophene; or pyridyl wherein the N atom is positioned at the *meta*-position to the

thiophene (optionally substituted at the other *meta*-position to the thiophene by chloro, fluoro, methyl, ethyl, -CF_3, -OMe, -NH_2 or –OH);

R^Y represents optionally substituted 8-, 9- or 10-membered bicyclic heteroaryl, bonded such that when R^X is phenyl or pyridyl, the R^Y group is attached to R^x in the *para*-position to the thiophene;

R^2 represents -C_{5-7}cycloalkyl (optionally substituted by one or more substituents independently selected from -C_{1-2}alkyl (optionally substituted with one or more fluoro substituents), and –OH) or C_6cycloalkenyl;

R^3 represents linear or branched –C_{2-6}alkyl substituted by one or more fluoro substituents, or –$(CH_2)_mC_{3-6}$cycloalkyl substituted by one or more fluoro substituents;

m represents 0 or 1;

or a salt thereof.

The compounds of the present invention exhibit improved potency against the replication of HCV (1a and 1b genotypes), and therefore have the potential to achieve greater efficacy in man. High potency in both genotypes is considered to be advantageous.

There is provided as a further aspect of the present invention a compound chosen from compounds of Formula (I) or a pharmaceutically acceptable salt 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 a pharmaceutically acceptable salt thereof.

According to another aspect of the invention, there is provided the use of a compound of Formula (I) or a pharmaceutically acceptable salt 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 unsubstituted phenyl or unsubstituted thienyl.

In one aspect, R^Y represents optionally substituted 8- or 9-membered 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, 5-amino-1,3-benzoxazol-2-yl, [1,3]oxazolo[5,4-b]pyridin-2-yl, furo[3,2-*c*]pyridin-2-yl, 4-amino-1,3-benzoxazol-2-yl, pyrazolo[1,5-*a*]pyrimidin-5-yl, 7-hydroxy-1-benzofuran-2-yl, 7-hydroxy-1,3-benzoxazol-2-yl, pyrazolo[1,5-*b*]pyridazin-2-yl, 6-aminoimidazo[1,2-*a*]pyridin-2-yl, 1*H*-benzimidazol-5-yl, 5-amino-1-benzofuran-2-yl, 6-amino-1-benzofuran-2-yl, 6-amino-1,3-benzoxazol-2-yl, 1,3-benzoxazol-2-yl, 1*H*-indol-5-yl or 1*H*-indol-6-yl, all of which may be optionally substituted.

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 or 7-aminopyrazolo[1,5-*a*]pyrimidin-2-yl, all of which may be optionally substituted.

In a further aspect, R^Y represents furo[3,2-*b*]pyridin-2-yl, pyrazolo[1,5-*a*]pyrimidin-2-yl or imidazo[1,2-*a*]pyridin-2-yl, all of which may be optionally substituted. In a further aspect, R^Y represents optionally substituted pyrazolo[1,5-a]pyrimidinyl. In a further aspect, R^Y represents unsubstituted pyrazolo[1,5-a]pyrimidinyl.

In one aspect, R^2 represents C_6cycloalkyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl optionally substituted with one or more fluoro groups) or cyclohex-3-en-1-yl. In a further aspect, R^2 represents -C_6cycloalkyl (optionally substituted by methyl or trifluoromethyl). In a further aspect, R^2 represents *trans*-4-methylcyclohexyl.

In one aspect, R^3 represents $-CH_2CHF_2$ or $-CH_2CF_3$.

In one aspect, R^X represents unsubstituted phenyl or unsubstituted thienyl; R^Y represents optionally substituted 8- or 9-membered bicyclic heteroaryl group; R^2 represents -C_6cycloalkyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl optionally substituted with one or more fluoro groups); and R^3 represents $-CH_2CHF_2$ or $-CH_2CF_3$.

In a further aspect, R^X represents unsubstituted phenyl or unsubstituted thienyl; R^Y represents unsubstituted pyrazolo[1,5-a]pyrimidinyl; R^2 represents *trans*-4-methylcyclohexyl;

and R^3 represents $-CH_2CHF_2$ or $-CH_2CF_3$.

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

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

As used herein unless otherwise specified, the term 'alkyl' as used herein refers to a linear or branched saturated hydrocarbon group having the stated number of carbon atoms. For example, 'C_{1-6}alkyl' has from 1 to 6 carbon atoms. 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. In one aspect, alkyl moieties are $-C_{1-4}$alkyl. Unless otherwise stated, the alkyl group may be substituted by one or more optional substituents independently selected from the group consisting of $-C_{1-6}$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, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclyl, wherein t is an integer from 0 to 3 and R^A-R^G are as defined below.

As used herein unless otherwise specified, the term 'alkenyl' refers to a linear or branched hydrocarbon group containing one or more carbon-carbon double bonds and having the stated number of carbon atoms. For example, 'C_{2-6}alkenyl' has from 2 to 6 carbon atoms. Examples of such groups include ethenyl, propenyl, butenyl, pentenyl or hexenyl and the like. Unless otherwise stated, the alkenyl group may be substituted by one or more optional substituents independently selected from the group consisting of $-C_{1-6}$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, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclyl, wherein t is an integer from 0 to 3 and R^A-R^G are as defined below.

As used herein unless otherwise specified, the term 'alkynyl' refers to a linear or branched hydrocarbon group containing one or more carbon-carbon triple bonds and having the stated number of carbon atoms. For example, 'C_{2-6}alkenyl' has from 2 to 6 carbon atoms. Examples of such groups include ethynyl, propynyl, butynyl, pentynyl or hexynyl and the like. Unless otherwise stated, the alkynyl group may be substituted by one or more optional substituents independently selected from the group consisting of $-C_{1-6}$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, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted heterocyclyl, wherein t is an integer from 0 to 3 and R^A-R^G are as defined below.

As used herein unless otherwise specified, the term 'cycloalkyl' refers to a saturated

monocyclic hydrocarbon ring having the stated number of carbon atoms. For example, 'C_{3-8}cycloalkyl' has from 3 to 8 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl and the like. Unless otherwise stated, the cycloalkyl group may be substituted by one or more optional substituents independently selected from the group consisting of -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, optionally substituted phenyl and optionally substituted heterocyclyl, wherein t is an integer from 0 to 3 and R^A-R^G are as defined below.

The term 'cycloalkenyl' as used herein refers to an unsaturated non-aromatic monocyclic hydrocarbon ring of 3 to 8 carbon atoms containing one or more carbon-carbon double bonds and having the stated number of carbon atoms. For example, 'C_{3-8}cycloalkyl' has from 3 to 8 carbon atoms. Examples of such groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl or cyclooctenyl and the like. Unless otherwise stated, the cycloalkyl group may be substituted by one or more optional substituents independently selected from the group consisting of -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, optionally substituted phenyl and optionally substituted heterocyclyl, wherein t is an integer from 0 to 3 and R^A-R^G are as defined below.

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

The term 'aryl' as used herein refers to a C_{6-12}monocyclic or bicyclic hydrocarbon ring wherein at least one ring is aromatic. Examples of such groups include phenyl, naphthyl or tetrahydronaphthalenyl and the like. In one aspect, 'aryl' moieties contain 6-10 carbon atoms. In one aspect, 'aryl' moieties are unsubstituted, monosubstituted, disubstituted or trisubstituted phenyl. Unless otherwise stated, the aryl group may be substituted by one or more optional substituents independently selected from the group consisting of -C_{1-6}alkyl unsubstituted), 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, optionally substituted heterocyclyl, -CF_3, -OCF_3 and optionally substituted phenyl, wherein R^A-R^G are as defined below. In another aspect, the 'aryl' group may be substituted by -C_{1-6}alkyl (unsubstituted), 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 (unsubstituted), -CF_3, -OCF_3 and phenyl (unsubstituted), wherein R^A-R^G are as defined below. In another aspect, the 'aryl' group is unsubstituted.

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

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

As used herein, the terms 'halogen', hal 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, the term 'heteroaryl' refers to a 5-6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur, with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. As used herein, unless otherwise specified, the term 'bicyclic heteroaryl' as used herein refers to a fused 8-10 membered bicyclic aromatic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur, 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, including 'bicyclic heteroaryl' substituents, are independently selected from the group consisting of -C_{1-6}alkyl (unsubstituted), 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, optionally substituted heterocyclyl, -CF_3 and optionally substituted phenyl, wherein R^A–R^G are as defined below. In another aspect, 'heteroaryl' subsituents including 'bicyclic heteroaryl' substituents are independently selected from the group consisting of -C_{1-6}alkyl (unsubstituted), 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 (unsubstituted), -CF_3 and phenyl (unsubstituted), wherein R^A–R^G are as defined below. In

another aspect, 'heteroaryl' including 'bicyclic heteroaryl' is unsubstituted.

The term 'heterocyclyl' refers to a 4-7 membered monocyclic ring or a fused 8-12 membered bicyclic ring, each of which may be saturated or partially unsaturated containing 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur, wherein N atoms may be 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 and S atoms may be 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. Examples of such monocyclic rings include pyrrolidinyl, azetidinyl, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl, azepanyl and the like. Examples of such bicyclic rings include indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1*H*-3-benzazepine, tetrahydroisoquinolinyl and the like.

In one aspect, the term 'heterocyclyl' refers to a 4-7 membered monocyclic ring or a fused 8-12 membered bicyclic ring, each of which may be saturated or partially unsaturated containing 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur, wherein N atoms may be optionally substituted by hydrogen, -C_{1-6}alkyl (unsubstituted), -$C(O)R^D$, -$C(O)NR^BR^C$, -C(O)OH, -SO_2R^D, aryl (unsubstituted) or heteroaryl (unsubstituted) and S atoms may be optionally substituted by one or two oxygen atoms. Ring carbon atoms may be optionally substituted by -C_{1-6}alkyl (unsubstituted), -OR^A, -$C(O)R^D$, or -SO_2R^D. Examples of such monocyclic rings include pyrrolidinyl, azetidinyl, pyrazolidinyl, oxazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, dioxolanyl, dioxanyl, oxathiolanyl, oxathianyl, dithianyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydropyranyl, tetrahydropyridinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, diazepanyl, azepanyl and the like. Examples of such bicyclic rings include indolinyl, isoindolinyl, benzopyranyl, quinuclidinyl, 2,3,4,5-tetrahydro-1*H*-3-benzazepine, tetrahydroisoquinolinyl and the like.

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 is selected from the group consisting of hydrogen or optionally substituted -C_{1-6}alkyl. In one aspect, R^A is selected from the group consisting of hydrogen or -C_{1-6}alkyl.

R^B and R^C are independently selected from the group consisting of hydrogen and -C_{1-6}alkyl,

aryl, heterocyclyl and heteroaryl, all of which may be optionally substituted; 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, for example piperidine, piperazine, morpholine or pyrrolidine. In one aspect, R^B and R^C are independently selected from the group consisting of hydrogen and -C_{1-6}alkyl, aryl, heterocyclyl and 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, for example piperidine, piperazine, morpholine or pyrrolidine.

R^D is selected from the group consisting of -C_{1-6}alkyl, aryl, heterocyclyl, heteroaryl, arylalkyl, and heteroarylalkyl, all of which may be optionally substituted. In one, aspect R^D is selected from the group consisting of -C_{1-6}alkyl, aryl, heterocyclyl, heteroaryl, arylalkyl, and heteroarylalkyl.

R^E is selected from the group consisting of hydrogen, -C_{1-6}alkyl, arylalkyl, heteroarylalkyl, aryl, heterocyclyl and heteroaryl, all of which may be optionally substituted. In one aspect, R^E is selected from the group consisting of hydrogen, -C_{1-6}alkyl, arylalkyl, heteroarylalkyl, aryl, heterocyclyl and heteroaryl.

R^F and R^G are independently selected from the group consisting of hydrogen and -C_{1-6}alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl, all of which may be optionally substituted; 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 one aspect, R^F and R^G are independently selected from the group consisting of hydrogen and -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.

For the avoidance of doubt, the term “independently” means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

In a further aspect, the present invention provides a compound chosen from the group consisting of:
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylate;
4-[[(*trans*-4-Methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5'-pyrazolo[1,5-*a*]pyrimidin-2-yl-2,2'-bithiophene-5-carboxylic acid;
4-{(2,2-Difluoroethyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-5'-pyrazolo[1,5-*a*]pyrimidin-2-yl-2,2'-bithiophene-5-carboxylic acid; and
3-{(2,2-Difluoroethyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylic acid
or a salt thereof.

In a further aspect, the present invention provides the compound Ammonium 3-[[(*trans*-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylate.

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 solvates of the salts of compounds of the Formula (I). Solvates of the compounds of Formula (I) and solvates of the salts of the compounds of Formula (I) are included within the scope of the present invention.

As used herein, the term “solvate” refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Most preferably the solvent used is water and the solvate may also be referred to as a hydrate.

Solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the solvent is pharmaceutically acceptable. However, solvates having non-pharmaceutically acceptable solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts.

The present invention also relates to esters of the compounds of Formula (I). Esters of the compounds of Formula (I) are included within the scope of the present invention. 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 optionally substituted 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 suitably contains 1 to 18 carbon atoms,

particularly 1 to 4 carbon atoms. Any aryl moiety present in such esters suitably comprises a phenyl group.

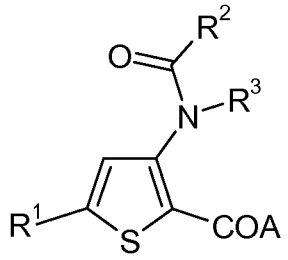
As used herein, the term "pharmaceutically acceptable" used in relation to an ingredient (active ingredient such as an active ingredient, a salt thereof or an excipient) which may be included in a pharmaceutical formulation for administration to a patient, refers to that ingredient being acceptable in 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)



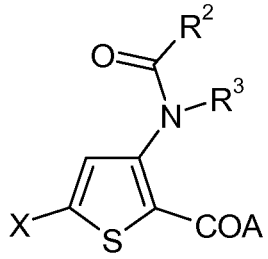
(II)

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 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.

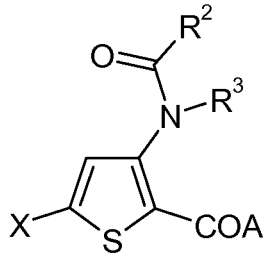
Compounds of Formula (I) in which A is hydroxy, or compounds of Formula (II) in which A is an alkoxy, benzyloxy or silyloxy group and R^1, R^2 and R^3 are as defined above for Formula (I), may be prepared by reaction of a compound of Formula (III)



(III)

in which A is hydroxy or an alkoxy, benzyloxy or silyloxy group, R^2 and R^3 are as defined above for Formula (I), and X is a halogen such as bromide or iodide; with a suitable boronic acid R^1-$B(OH)_2$ or boronate ester R^1-B(OR')(OR''), in which R^1 is as defined above for Formula (I) and R' and R'' are independently C_{1-6}alkyl or R' and R'' together with the carbon atoms to which they are attached form a ring optionally substituted by C_{1-6}alkyl, such as a pinacol ester, in the presence of a palladium catalyst such as tetrakistriphenyl phosphine palladium(0) or bis-[(diphenylphosphino)-ferrocene]-palladium(II) chloride, in the presence of a suitable base such as sodium carbonate, in a suitable solvent such as DMF, dioxane or dimethyoxyethane, or combinations thereof, optionally in the presence of water, at a temperature in the range 50-100°C, optionally under an inert atmosphere.

Compounds of Formula (I) in which A is hydroxy, or compounds of Formula (II) in which A is an alkoxy, benzyloxy or silyloxy group and R^1, R^2 and R^3 are as defined above for Formula (I), may be prepared by reaction of a compound of Formula (III)'

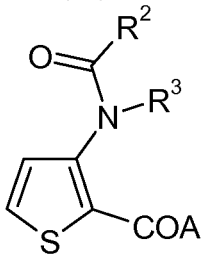


(III)'

in which A is hydroxy or an alkoxy, benzyloxy or silyloxy group, R^2 and R^3 are as defined above for Formula (I), and X is a suitable boronic acid -$B(OH)_2$ or boronate ester -B(OR')(OR''), in which R' and R'' are independently C_{1-6}alkyl or R' and R'' together with the carbon atoms to which they are attached form a ring optionally substituted by C_{1-6}alkyl, such as a pinacol ester, with R^1-Hal wherein R^1 is as defined above for Formula (I) and Hal is a halogen such as bromide or iodide, in the presence of a palladium catalyst such as tetrakistriphenyl phosphine palladium(0) or bis-[(diphenylphosphino)-ferrocene]-palladium(II) chloride, in the presence of a suitable base such as sodium carbonate, in a suitable solvent such as DMF, dioxane or dimethyoxyethane, or combinations thereof, optionally in the

presence of water, at a temperature in the range 50-100°C, optionally under an inert atmosphere.

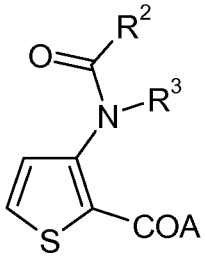
Compounds of Formula (III) in which A is an alkoxy, benzyloxy or silyloxy group, R^2 and R^3 are as defined above for Formula (I) and X is a halogen such as bromide or iodide, may be prepared from compounds of Formula (IV)



(IV)

in which A is an alkoxy, benzyloxy or silyloxy, and R^2 and R^3 are as defined above for Formula (I), by treatment with a suitable base such as lithium diisopropylamide and a halogen source such as iodine in a suitable solvent such as tetrahydrofuran, heptane, ethylbenzene or combinations thereof and at a temperature in the range -78°C to -20°C.

Compounds of Formula (III)' in which A is an alkoxy, benzyloxy or silyloxy group and X is a suitable boronic acid $-B(OH)_2$ or boronate ester -B(OR')(OR''), in which R' and R'' are independently C_{1-6}alkyl or R' and R'' together with the carbon atoms to which they are attached form a ring optionally substituted by C_{1-6}alkyl, such as a pinacol ester, may be prepared from compounds of Formula (IV)



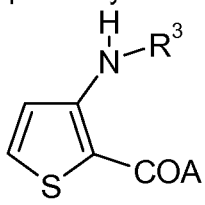
(IV)

in which A is an alkoxy, benzyloxy or silyloxy, and R^2 and R^3 are as defined above for Formula (I), by treatment with a suitable base such as lithium diisopropylamide and a boronate such as $B(OR)_3$ wherein R is an alkyl group, for example methyl, in a suitable solvent such as tetrahydrofuran, heptane, ethylbenzene or combinations thereof, and at a temperature in the range -78°C to -20°C.

Compounds of Formula (III) in which A is hydroxy, R^2 and R^3 are as defined above for Formula (I), and X is a halogen such as bromide or iodide, may be prepared from compounds of Formula (III) in which A is an alkoxy, benyloxy or silyloxy group, R^2 and R^3 are as defined above for Formula (I), and X is a halogen such as bromide or iodide, for example by treatment with an appropriate base, acid or fluoride source as described in relation to the preparation of compounds of Formula (I) from compounds of Formula (II).

Compounds of Formula (IV), in which A is an alkoxy, benzyloxy or silyloxy group and R^2 and

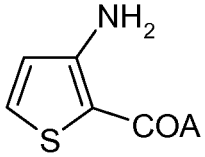
R^3 are as defined above may be prepared by reaction of a compound of Formula (V)



(V)

in which A an alkoxy, benzyloxy or silyloxy group, and R^3 is as defined above for Formula (I), with a suitable acylating agent, for example R^2-C(O)-Y, wherein Y is a halo atom, for example 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 dichloroethane, and optionally in the presence of a suitable base, for example pyridine or triethylamine. The reaction may be carried out at a suitable temperature, for example in the range 20°C to 80°C and optionally under an inert atmosphere. A phosphine such as triphenylphosphine may optionally be used in place of the base.

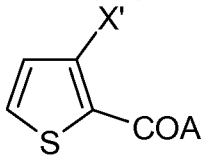
Compounds of Formula (V), in which A is an alkoxy, benzyloxy or silyloxy group and R^3 is as defined above for Formula (I), may be prepared by reaction of a compound of Formula (VI)



(VI)

in which A 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 (V), in which A is an alkoxy, benzyloxy or silyloxy group and R^3 is as defined above for Formula (I), may be prepared from compounds of Formula (VI) in which A is an alkoxy, benzyloxy or silyloxy are as defined above for Formula (I), by treatment with a suitable alkylating agent R^3-X' where X' is a halo group such as chloride, bromide or iodide, or X' is a sulphonate ester such as methanesulfonate or trifluoromethanesulphonate, in suitable solvent such as dimethylformamide in the presence of a suitable base such as triethylamine.

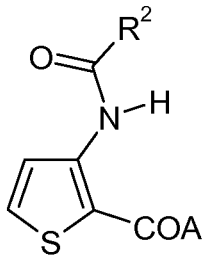
Compounds of Formula (V) may also be prepared by reacting a compound of Formula (VII)



(VII)

in which A is an alkoxy, benzyloxy or silyloxy group and X' is a halo group such as bromo, with an amine R^3-NH_2 in the presence of a palladium catalyst such as tris(dibenzylidenacetone)dipalladium in the presence of a reagent such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) and a base such as caesium carbonate, in a suitable solvent such as toluene and in a suitable temperature range such as 80-120°C.

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

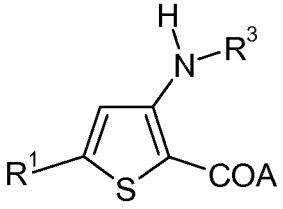


(VIII)

in which A an alkoxy, benzyloxy or silyloxy group, and R^2 is 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 or trifluoromethanesulphonate, and R^3 is as defined above for Formula (I), in a suitable solvent such as dimethylformamide, in the presence of a suitable base such as sodium hydride optionally in the presence of triethylamine.

Compounds of Formula (VIII), in which A is an alkoxy, benzyloxy or silyloxy group and R^2 is as defined above for Formula (I), may be prepared by reaction of a compound of Formula (VI) in which A an alkoxy, benzyloxy or silyloxy group, with a suitable acylating agent, for example R^2-C(O)-Y, wherein Y is a halo atom, for example 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, 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.

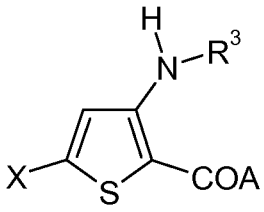
Compounds of Formula (II), in which A is an alkoxy, benzyloxy or silyloxy group and R^1, R^2 and R^3 are as defined above for Formula (I), may also be prepared by reaction of a compound of Formula (IX)



(IX)

in which A an alkoxy, benzyloxy or silyloxy group, and R^1 and R^3 are as defined above for Formula (I), with a suitable acylating agent, for example R^2-C(O)-Y, wherein Y is a halo atom, for example 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 dichloroethane, optionally in the presence of a suitable base, for example pyridine or triethylamine. The reaction may be carried out at a suitable temperature, for example in the range 20°C to 100°C. A phosphine such as triphenylphosphine may optionally be used in place of the base.

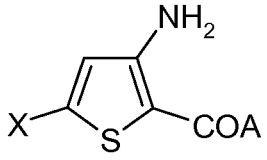
Compounds of Formula (IX) in which A is an alkoxy, benzyloxy or silyloxy group and R^1 and R^3 are as defined above for Formula (I), may also be prepared by reaction of a compound of Formula (X)



(X)

in which X is a halogen such as bromide or iodide, A is an alkoxy, benzyloxy or silyloxy group and R^3 is as defined above for Formula (I), with a suitable boronic acid R^1-$B(OH)_2$ or boronate ester R^1-B(OR')(OR''), in which R' and R'' are independently C_{1-6}alkyl or R' and R'' together with the carbon atoms to which they are attached form a ring optionally substituted by C_{1-6}alkyl, such as a pinacol ester, in the presence of a palladium catalyst such as tetrakistriphenyl phosphine palladium(0) or bis-[(diphenylphosphino)-ferrocene]-palladium(II) chloride, in the presence of a suitable base such as sodium carbonate, in a suitable solvent such as DMF, dioxane or dimethyoxyethane, or combinations thereof, optionally in the presence of water, at a temperature in the range 50-100°C, optionally under an inert atmosphere.

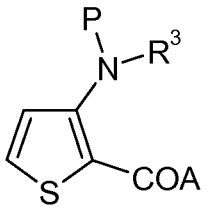
Compounds of Formula (X) in which A is an alkoxy, benzyloxy or silyloxy group, R^3 is as defined above for Formula (I) and X is a halogen such as bromide or iodide, may be prepared by reaction of a compound of Formula (XI)



(XI)

in which A is an alkoxy, benzyloxy or silyloxy group and X is a halogen such as bromide or iodide, by treatment with a suitable vinyl ether, 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 (X), in which A is an alkoxy, benzyloxy or silyloxy group and X is a halogen such as bromide or iodide, may be prepared from compounds of Formula (XI) in which A is an alkoxy, benzyloxy or silyloxy, and X is a halogen such as bromide or iodide, by treatment with a suitable alkylating agent R^3-X' where X' is a halo group such as chloride, bromide or iodide, or X' is a sulphonate ester such as methanesulfonate or trifluoromethanesulphonate, and R^3 is as defined above for Formula (I), in suitable solvent such as dimethylformamide in the presence of a suitable base such as triethylamine.

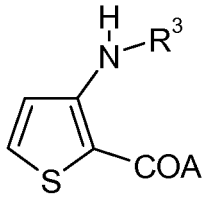
Compounds of Formula (X) in which A is an alkoxy, benzyloxy or silyloxy group, R^3 is as defined above for Formula (I) and X is a halogen such as bromide or iodide, may be prepared by reaction of a compound of Formula (XI)'



(XI)'

wherein P is $-COCF_3$ or $-CO_2{}^tBu$ and R^3 is as defined above for Formula (I), by treatment with a halogen source, for example iodine, in a suitable solvent such as THF, heptane, ethylbenzene, or combinations thereof, in the presence of a suitable base such as LDA, at a suitable temperature for example -78 to -20°C, optionally in an inert atmosphere, and thereafter removing the protecting group P, for example with hydrochloric acid when P is $CO_2{}^tBu$ or with aqueous sodium carbonate solution when P is $COCF_3$.

Compounds of Formula (XI)' in which P is $-COCF_3$ and R^3 is as defined above for Formula (I), may be prepared from a compound of Formula (V)

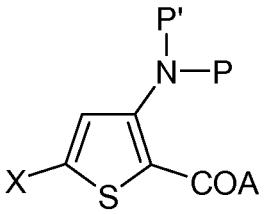


(V)

in which A an alkoxy, benzyloxy or silyloxy group, and R^3 is as defined above for Formula (I), in treatment with trifluoroacetic anhydride in a suitable solvent such as diethylether.

Compounds of Formula (XI)' in which P is CO_2tBu and R^3 is as defined above for Formula (I), may be prepared from a compound of Formula (V), by treatment with di-tert-butyl dicarbonate in a suitable solvent such as ether, acetonitrile or acetone, optionally in the presence of a catalyst such as DMAP and a base such as triethylamine.

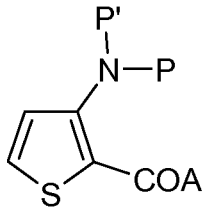
Compounds of Formula (XI), in which A is an alkoxy, benzyloxy or silyloxy group and X is a halogen such as iodide, may be prepared from a compound of Formula (XII)



(XII)

in which P is a suitable protecting group such as $-COCF_3$ or $-CO_2{}^tBu$ and P' is hydrogen or a suitable protecting group such as $-CO_2{}^tBu$. For example, when P is $-COCF_3$ and P' is hydrogen, by treatment with a suitable base such as aqueous potassium carbonate optionally in the presence of an alcohol such as methanol, or when P is $-CO_2{}^tBu$ and P' is hydrogen or $-CO_2{}^tBu$, by treatment with a suitable acid such as hydrochloric acid or trifluoroacetic acid in a suitable solvent such as dioxane or dichloromethane.

Compounds of Formula (XII), in which A is an alkoxy, benzyloxy or silyloxy group, X is a halo atom such as iodide and P is a suitable protecting group such as $-COCF_3$ and P' is hydrogen, or P is $-CO_2{}^tBu$ and P' is hydrogen or $-CO_2{}^tBu$, may be prepared by reaction of a compound of Formula (XIII)

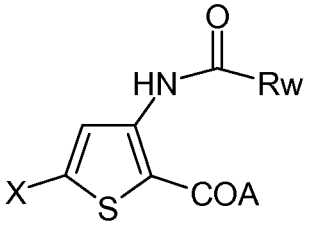


(XIII)

in which A is an alkoxy, benzyloxy or silyloxy group, P is a suitable protecting group such as $-COCF_3$ and P' is hydrogen, or P is $-CO_2{}^tBu$ and P' is hydrogen or $-CO_2{}^tBu$, with a suitable base such as lithium diisopropylamide and a halogen source such as iodine, in a suitable solvent such as tetrahydrofuran, and at a temperature in the range -78°C to -20°C.

Compounds of Formula (XIII), in which A is an alkoxy, benzyloxy or silyloxy group and P and P' are as described above for Formula (XII), may be prepared by treating compounds of Formula (VI) with trifluoroacetic anhydride or di-tert-butyl dicarbonate in a suitable solvent such as ether, acetonitrile or acetone, optionally in the presence of a catalyst such as DMAP and a base such as triethylamine.

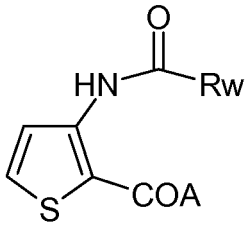
Compounds of Formula (X), in which A is an alkoxy, benzyloxy or silyloxy group, R^3 is as defined above for Formula (I) and X is a halogen such as bromide or iodide, may also be prepared by reaction of a compound of Formula (XIV)



(XIV)

in which A is an alkoxy, benzyloxy or silyloxy group, X is a halogen such as bromide or iodide and Rw is $-CF_3$, $-CF_2H$ or $-CH_2F$, by treatment with a reducing agent such as sodium borohydride in the presence of an acid such as acetic acid, in a suitable solvent such as dioxane and at a temperature in the range 0-25°C.

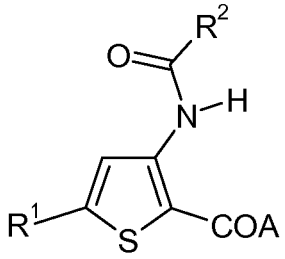
Compounds of Formula (V), in which A is an alkoxy, benzyloxy or silyloxy group, R^3 is as defined above for Formula (I) and X is a halogen such as bromide or iodide, may also be prepared by reaction of a compound of Formula (XIV)'



(XIV)'

in which A is an alkoxy, benzyloxy or silyloxy group, X is a halogen such as bromide or iodide and Rw is $-CF_3$, $-CF_2H$ or $-CH_2F$, by treatment with a reducing agent such as sodium borohydride in the presence of an acid such as acetic acid, in a suitable solvent such as dioxane and at a temperature in the range 0-25°C.

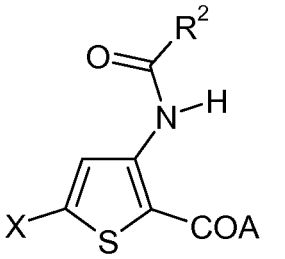
Compounds of Formula (II), in which A is an alkoxy, benzyloxy or silyloxy group and R^1, R^2 and R^3 are as defined above for Formula (I), may also be prepared from compounds of Formula (XV)



(XV)

in which A is an alkoxy, benzyloxy or silyloxy, and R^1 and R^2 are as defined above for Formula (I), by treatment with a suitable alkylating agent R^3-X' where X' is a halo group such as chloride, bromide or iodide, or X' is a sulphonate ester such as methanesulfonate or trifluoromethylsulphonate, and R^3 is as defined above for Formula (I), in a suitable solvent such as dimethylformamide in the presence of a suitable base such as triethylamine or sodium hydride or combinations thereof.

Compounds of Formula (XV), in which A is an alkoxy, benzyloxy or silyloxy group and R^1 and R^2 are as defined above for Formula (I), may also be prepared from compounds of Formula (XVI)



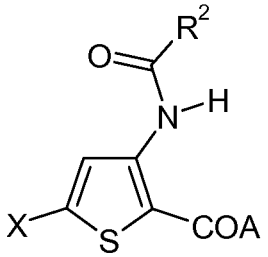
(XVI)

in which A is an alkoxy, benzyloxy or silyloxy, R^2 is as defined above for Formula (I) and X is a halogen such as bromide or iodide, by treatment with a suitable boronic acid R^1-$B(OH)_2$ or boronate ester R^1-B(OR')(OR''), in which R' and R'' are independently C_{1-6}alkyl or R' and R'' together with the carbon atoms to which they are attached form a ring optionally substituted by C_{1-6}alkyl, such as a pinacol ester, in the presence of a palladium catalyst such as tetrakistriphenyl phosphine palladium(0) or bis-[(diphenylphosphino)-ferrocene]-palladium(II) chloride, in the presence of a suitable base such as sodium carbonate, in a suitable solvent such as DMF, dioxane or dimethyoxyethane, or combinations thereof, optionally in the presence of water, at a temperature in the range 50-100°C, optionally under an inert atmosphere.

Compounds of Formula (XVI), in which A is an alkoxy, benzyloxy or silyloxy group, R^2 is as

defined above for Formula (I) and X is a halogen such as bromide or iodide, may be prepared from compounds of Formula (XI) in which A is an alkoxy, benzyloxy or silyloxy, and X is a halogen such as bromide or iodide, by treatment with a suitable acylating agent, for example R^2-C(O)-Y, wherein Y is a halo atom, for example 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 dichloroethane, optionally in the presence of a suitable base, for example pyridine or triethylamine. The reaction may be carried out at a suitable temperature, for example in the range 20°C to 100°C. A phosphine such as triphenylphosphine may optionally be used in place of the base.

Compounds of Formula (III) in which A is an alkoxy, benzyloxy or silyloxy group, R^2 and R^3 are as defined above for Formula (I) and X is a halogen such as bromide or iodide, may also be prepared from compounds of Formula (XVI)



(XVI)

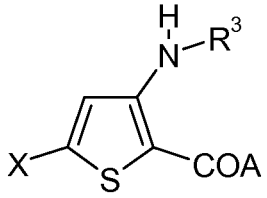
in which A is an alkoxy, benzyloxy or silyloxy, X is a halogen such as bromide or iodide and R^2 is as defined above for Formula (I), by treatment with a suitable alkylating agent R^3-X' where X' is a halo group such as chloride, bromide or iodide, or X' is a sulphonate ester such as methanesulphonate or trifluoromethanesulphonate, and R^3 is as defined above for Formula (I), in suitable solvent such as dimethylformamide in the presence of a suitable base such as triethylamine or sodium hydride or combinations thereof.

Compounds of Formula (III) in which A is an alkoxy, benzyloxy or silyloxy group, X is a halogen such as bromide or iodide and R^2 and R^3 are as defined above for Formula (I), may also be prepared by reaction of a compound of Formula (X), in which A an alkoxy, benzyloxy or silyloxy group, R^3 is as defined above for Formula (I) and X is a halogen such as bromide or iodide, with a suitable acylating agent, for example R^2-C(O)-Y, wherein Y is a halo atom, for example 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, 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.

Compounds of Formula (X), in which A is an alkoxy, benzyloxy or silyloxy group, R^3 is as defined above and X is a suitable halogen such as bromide or iodide, may also be prepared by reaction of a compound of Formula (V) in which A an alkoxy, benzyloxy or silyloxy group, and R^3 is as defined above for Formula (I), by treatment with a suitable base such as lithium diisopropylamide and a halogen source such as iodine in a suitable solvent such as tetrahydrofuran, heptane, ethylbenzene or mixtures thereof and at a temperature in the

range -78°C to -20°C.

Compounds of Formula (III)' in which A is an alkoxy, benzyloxy or silyloxy group, R^3 is as defined above for Formula (I) and X is a suitable boronic acid -$B(OH)_2$ or boronate ester -B(OR')(OR''), in which R' and R'' are independently C_{1-6}alkyl or R' and R'' together with the carbon atoms to which they are attached form a ring optionally substituted by C_{1-6}alkyl, such as a pinacol ester, may also be prepared by reaction of a compound of Formula (XVI)'



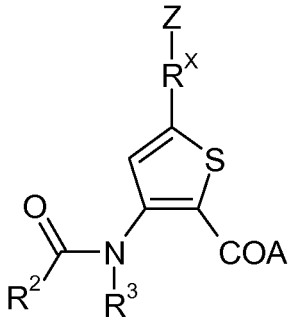
(XVI)'

in which A an alkoxy, benzyloxy or silyloxy group, and R^3 is as defined above for Formula (I) and X is a suitable boronate ester -B(OR')(OR''), in which R' and R'' are independently C_{1-6}alkyl or R' and R'' together with the carbon atoms to which they are attached form a ring optionally substituted by C_{1-6}alkyl, such as a pinacol ester, with a suitable acylating agent, for example R^2-C(O)-Y, wherein Y is a halo atom, for example 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, 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.

Compounds of Formula (XVI)', in which A is an alkoxy, benzyloxy or silyloxy group, R^3 is as defined above and X is a suitable boronic acid -$B(OH)_2$ or boronate ester -B(OR')(OR''), in which R' and R'' are independently C_{1-6}alkyl or R' and R'' together with the carbon atoms to which they are attached form a ring optionally substituted by C_{1-6}alkyl, such as a pinacol ester, may also be prepared by reaction of a compound of Formula (V) in which A an alkoxy, benzyloxy or silyloxy group, and R^3 is as defined above for Formula (I), by treatment with a suitable base such as lithium diisopropylamide and a boronate source such as $B(OR)_3$ wherein R is an alkyl group, for example methyl, in a suitable solvent such as tetrahydrofuran, and at a temperature in the range -78°C to -20°C.

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

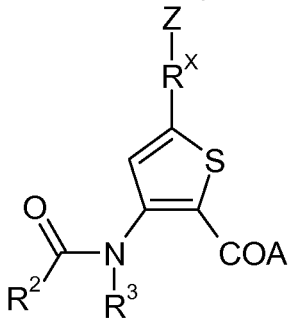
Compounds of Formula (I) in which A is hydroxy, or compounds of Formula (II) in which A is an alkoxy, benzyloxy or silyloxy group, and R^1, R^2 and R^3 are as defined above for Formula (I), may be prepared by reaction of a compound of Formula (II)'



(II)'

in which Z represents a halo substituent, and R^X, R^2, R^3, and A are as defined for Formula (II), by reaction with a suitable heteroaryl boronic acid R^Y-boronic acid wherein 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 dioxane.

Compounds of Formula (I) in which A is hydroxy, or compounds of Formula (II) in which A is an alkoxy, benzyloxy or silyloxy group and R^1, R^2 and R^3 are as defined above for Formula (I), may also be prepared by reaction of a compound of Formula (II)'



(II)'

in which Z represents $B(OH)_2$, and R^X, R^2, R^3 and A are as defined for Formula (II), by reaction with a suitable heteroaryl halide R^Y-hal, in which suitably the halide is bromo or iodo, 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 dioxane.

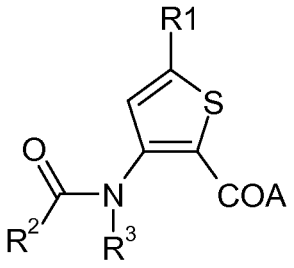
Compounds of Formula (II)' in which Z is halo and R^X, R^2, R^3 and A are as defined for Formula (II), may be prepared by reaction of a compound of Formula (III) wherein A is an alkoxy, benzyloxy or silyloxy group, R^2 and R^3 are as defined above for Formula (I), and X is halo such as bromo or iodo, with a boronic acid of Formula Z-R^X-boronic acid wherein Z is halo and R^x is as defined above for Formula (I) under the conditions described above for the preparation of compounds of Formula (I) and (II) from compounds of Formula (III) and R^Y-R^X-boronic acid.

Compounds of Formula (II)', in which Z is $-B(OH)_2$, may be prepared by reaction of a compound of Formula (III), in which A is an alkoxy, benzyloxy or silyloxy group, R^2 and R^3 are as defined above for Formula (I) and X is halo such as bromo or iodo, with a compound of Formula Z-R^X-$B(OH)_2$, wherein R^x is as described above for Formula (I) and Z is $-B(OH)_2$,

under the conditions described above for the preparation of compounds of Formula (I) and (II) from (III) and R^1-boronic acid.

Boronic acids Z-R^X-boronic acid, R^Y-R^X-boronic acid and R^Y-boronic acid 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 (I) or (II) in which R^1 represents a 4-(furopyridine)phenyl and R^2, R^3 and A are as defined above for Formula (II), may be prepared by treatment of a compound of Formula (II)''



(II)"

in which R^1 represents a 4-ethynylphenyl derivative, and 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 a suitable solvent such as triethylamine or 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 4-(pyrrolopyridine)phenyl and R^2, R^3 and A are as defined above for Formula (II), may be prepared by treatment of a compound of Formula (II)'' in which R^1 represents 4-ethynylphenyl and 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 (I) or (II) in which R^1 represents phenyl substituted by a 4-imidazo[1,2-a]pyridine-2-yl and R^2, R^3 and A are as defined above for Formula (II), 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 5-(pyrazolopyrimidine)-2-thienyl and R^2, R^3 and A are as defined above for Formula (II), may be prepared by treating a compound of Formula (II)'' in which R^1 represents 3-(thienyl)-1H-pyrazole-5-amine and R^2,

R^3 and A are as defined above for Formula (II) 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 (I) or (II) in which R^1 represents a 4-(pyrazolopyrimidine)phenyl and R^2, R^3 and A are as defined above for Formula (II), may be prepared by treating a compound of Formula (II)'' in which R^1 represents 4-(phenyl)-1H-pyrazole-5-amine and R^2, R^3 and A are as defined above for Formula (II) with 1,1,3,3-tetramethoxypropane in a suitable solvent such as acetic acid; suitably the temperature is in the range 90-110°C.

Suitable methods for the preparation of compounds incorporating 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.

Compounds of Formula R^Y-R^X-$B(OR')_2$ or R^Y-$B(OR')_2$ for use in the preparation of compounds of Formula (II) are available commercially or may be prepared from compounds of Formula (II) R^Y-R^X-hal or R^Y-hal by methods well known in the art.

Compounds of Formula R^Y-R^X-hal or R^Y-hal for use in the preparation of compounds of Formula (II) are available commercially or may be prepared by methods well known in the art. Some examples of heteroaryl halide preparation are given below (but are not limited to these examples).

A 2-(4-bromophenyl)imidazo[1,2-a]pyridine derivative may be prepared by analogy to methods described in Tetrahedron Letters (2001) 42, 3077.

A 4-(furopyridine)phenyl bromide, may be prepared by treatment of a 4-ethynylphenyl bromide 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 a suitable solvent such as triethylamine or 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.

A 4-(pyrazolopyrimidine)phenyl bromide may be prepared by treating a 3-(4-bromophenyl)-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.

A 2-(5-bromo-2-thienyl)pyrazolo[1,5-a]pyrimidine may be prepared by treating a 3-(5-bromo-2-thienyl)-1H-pyrazol-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.

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.

It will be appreciated that compounds of Formula (I), (II), (III), (III)', (IV), (V), (VIII), (IX), (X), (XV) and (XVI) 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), (III), (III)', (IV), (V), (VIII), (IX), (X), (XV) and (XVI).

It will be appreciated that racemic compounds of Formula (I), (II), (III), (III)', (IV), (V), (VIII), (IX), (X), (XV) and (XVI) 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), (III), (III)', (IV), (V), (VIII), (IX), (X), (XV) and (XVI) may be resolved by chiral preparative HPLC. Alternatively, racemic compounds of Formula (I), (II), (III), (III)', (IV), (V), (VIII), (IX), (X), (XV) and (XVI) 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 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), (III), (III)', (IV), (V), (VIII), (IX), (X), (XV) and/or (XVI) 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
Calcd	calculated
DCE	1,2-dichloroethane
DCM	dichloromethane
DEF	*N,N*-diethylformamide
DMF	*N,N*-dimethylformamide
DME	1,2-dimethoxyethane
EtOAc	ethyl acetate
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.
LDA	lithium diisopropylamide
MeCN	acetonitrile
MeOH	methanol
mins	minutes
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.
NH2 SPE	aminopropyl capped silica ion-exchange solid phase extraction cartridge
OASIS HLB cartridge	sample extraction cartridge available from Waters
$PdCl_2$(dppf)	[1,1'-bis(diphenylphosphino)ferrocene]dichloro-palladium(II)
SPE	silica packed solid phase extraction column
TFA	trifluoroacetic acid
THF	tetrahydrofuran

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

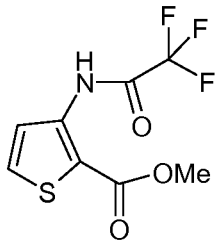
Regardless of how the preparation of compounds are represented in the present specification no inference can be drawn that particular batches (or mixtures of two or more batches) of intermediates were used in the next stage of the preparation. The examples and intermediates are intended to illustrate the synthetic routes suitable for preparation of the same, to assist the skilled persons understanding of the present invention.

Proton Nuclear Magnetic Resonance (1H NMR) spectra were recorded either on Varian

instruments at 400 MHz, or on a Bruker instrument at 400 MHz. Chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The NMR spectra were recorded at a temperature ranging from 15 to 25 °C.

Intermediate 1

Methyl 3-[(trifluoroacetyl)amino]-2-thiophenecarboxylate

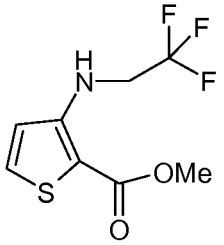


To a stirred solution of methyl 3-amino-2-thiophenecarboxylate (10.1 g) and triethylamine (8.04 mL) in DCM (100 mL) at 0°C was added trifluoroacetic anhydride (9.98 mL) dropwise over 0.25 hours. The reaction mixture was allowed to warm to room temperature and was left to stand for 5 days. The mixture was evaporated *in vacuo* and the residue was partitioned between sodium bicarbonate solution and DCM. The organics were separated using a hydrophobic frit and were evaporated *in vacuo* to give the title compound.

^{1}H NMR ($CDCl_3$) δ 11.20 (1H, br, s), 8.08 (1H, d), 7.58 (1H, d), 3.95 (3H, s).

Intermediate 2

Methyl 3-[(2,2,2-trifluoroethyl)amino]-2-thiophenecarboxylate



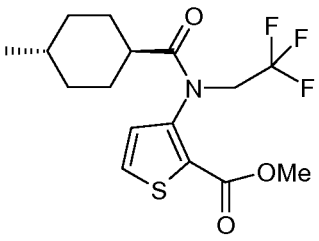
To a stirred suspension of sodium borohydride (1.89 g) and methyl 3-[(trifluoroacetyl)amino]-2-thiophenecarboxylate (Intermediate 1) (2.53 g) in dioxane (20 mL) was added a solution of acetic acid (3.0 g) in dioxane (10 mL) over a period of 10 mins, at 10°C. The mixture was stirred under reflux for 2 hours. The reaction was evaporated *in vacuo* and the residue was partitioned between water and DCM. The organic phase was separated using a hydrophobic frit and was evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 5-65% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_8H_8F_3NO_2S + H)^+$: 240

MS found (electrospray): $(M+H)^+ = 240$

Intermediate 3

Methyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-2-thiophenecarboxylate



To a stirred solution of methyl 3-[(2,2,2-trifluoroethyl)amino]-2-thiophenecarboxylate (Intermediate 2) (0.54 g) in 1,2-dichloroethane (25 mL) was added *trans*-4-methylcyclohexanecarbonyl chloride[1] (540 mg) and the mixture was heated at reflux for 17 hours. A further portion of *trans*-4-methylcyclohexanecarbonyl chloride[1] (540 mg) in 1,2-dichloroethane (5 mL) was added and the mixture was heated at reflux for 3 days. The mixture was cooled and evaporated *in vacuo*. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-65% EtOAc in cyclohexane. The material was partitioned between DCM and saturated sodium bicarbonate solution and was stirred overnight. The organics were separated using a hydrophobic frit and evaporated *in vacuo* to give the title compound.

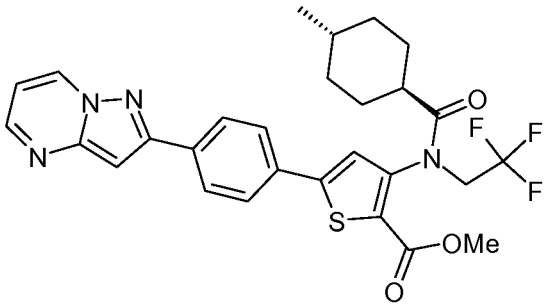
MS calcd for $(C_{16}H_{20}F_3NO_3S + H)^+$: 364

MS found (electrospray): $(M+H)^+ = 364$

Ref 1: WO 2004/052885.

Intermediate 4

Methyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylate



A solution of LDA (1.8M solution in THF/heptane/ethyl benzene, 3.46 mL) was cooled to -78°C under nitrogen. A solution of methyl 3-[[(trans-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-2-thiophenecarboxylate (Intermediate 3) (0.76 g) in dry THF (7 mL) was added dropwise over 0.5 h, keeping the temperature below -70°C. The mixture was stirred

for 2 h, then a solution of iodine (1.06 g) in dry THF (7 mL) was added dropwise over 0.5 hours, keeping the temperature below -65°C. The reaction was stirred for 2 hours, and was then allowed to warm to -50°C. Saturated ammonium chloride solution and sodium thiosulphate solution (2 g in 10 mL water) were added dropwise with rapid stirring and the mixture was allowed to warm to room temperature. The mixture was diluted with EtOAc and water. The organics were separated, washed with water (x 2) and dried over sodium sulphate, before being evaporated *in vacuo* to give crude methyl 5-iodo-3-[[(*trans*-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-2-thiophenecarboxylate.

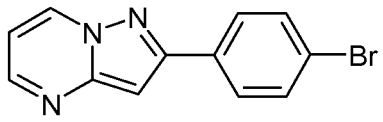
A mixture of the crude methyl 5-iodo-3-[[(*trans*-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-2-thiophenecarboxylate, 2N sodium carbonate solution (3.3 mL), tetrakis(triphenylphosphine)palladium (0) (200 mg) and 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazolo[1,5-a]pyrimidine (Intermediate 6) (580 mg) in DMF (12 mL) was heated at 100°C under nitrogen for 3 hours. The reaction was evaporated *in vacuo* and the residue was partitioned between DCM and water. The organics were separated using a hydrophobic frit and concentrated *in vacuo* (to 5-10 mL volume). The crude solution was purified by ISCO Companion silica chromatography, eluting with a gradient 0-60% EtOAc in cyclohexane. The material was purified further by MDAP HPLC to give the title compound.

MS calcd for $(C_{28}H_{27}F_3N_4O_3S + H)^+$: 557

MS found (electrospray): $(M+H)^+$ = 557

Intermediate 5

2-(4-Bromophenyl)pyrazolo[1,5-*a*]pyrimidine



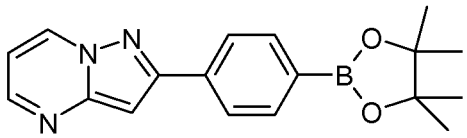
A solution of 5-(4-bromophenyl)-2H-pyrazol-3-ylamine (20.2 g, 84.8 mmol) in glacial acetic acid (300 mL) was treated with 1,1,3,3-tetramethoxypropane (15.4 mL, 93.3 mmol) and the mixture heated to around 110°C over approximately 25 mins. Further heating was continued at 110°C for 60 mins, then the temperature was cooled to around 40°C over 90 mins. The resulting solid was filtered off, washed with water and dried at 40°C under vacuum to give the title compound.

MS calcd for $(C_{28}H_8BrN_3 + H)^+$: 275/277

MS found (electrospray): $(M+H)^+$ = 275/277

Intermediate 6

2-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazolo[1,5-*a*]pyrimidine



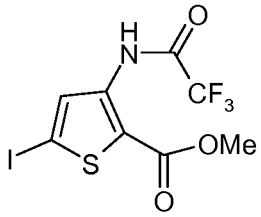
A mixture of 2-(4-bromophenyl)pyrazolo[1,5-a]pyrimidine (Intermediate 5) (7.0 g, 25.4 mmol), bis(pinacolato)diboron (9.2 g, 38.3 mmol), potassium acetate (7.52 g, 76.6 mmol) and $PdCl_2(dppf)$ (1.38 g, 1.69 mmol) in dry dioxane (120 mL) was heated under reflux under nitrogen for 90 mins. The solvent was evaporated, and the residue partitioned between DCM and water. The aqueous layer was separated and washed twice with DCM. The combined organic fractions were dried (Na_2SO_4), evaporated *in vacuo* and purified by ISCO Companion silica chromatography, eluting with a gradient 0-20% EtOAc in cyclohexane, to give the title compound.

MS calcd for $(C_{18}H_{20}BN_3O_2 + H)^+$: 322

MS found (electrospray): $(M+H)^+ = 322$

Intermediate 7

Methyl 5-iodo-3-[(trifluoroacetyl)amino]-2-thiophenecarboxylate



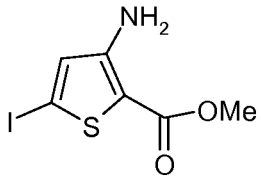
To a solution of LDA (2M in THF, 26 mL) was added THF (80 mL) at -78 °C under nitrogen, followed by a solution of methyl 3-[(trifluoroacetyl)amino]-2-thiophenecarboxylate (Intermediate 1) (4 g, 2.59 mmol) in THF (60 mL) via syringe over 30 mins. After complete addition, the mixture was left for 15 mins, then iodine (4g, 15.8 mmol) in THF (40 mL) was added via syringe over 30 mins at -78°C. The mixture was quenched by the addition of ammonium chloride, then ethyl acetate added at room temperature. The organic fraction was separated, washed with sodium thiosulphate solution (50%) and brine, the organic layer was dried (Na_2SO_4) and evaporated. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-20% ethyl acetate in cyclohexane to give the title compound. Further quantities were obtained by collecting the early eluting fractions and further purification by ISCO Companion silica chromatography, eluting with a gradient 0-10% ethyl acetate in cyclohexane to give the title compound.

MS calcd for $(C_8H_5F_3INO_2S - H)^-$: 378

MS found (electrospray): $(M+H)^- = 378$

Intermediate 8

Methyl 3-amino-5-iodo-2-thiophenecarboxylate



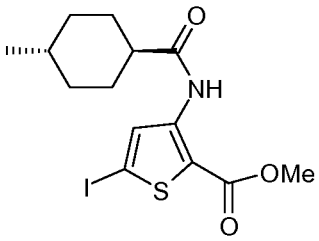
A mixture of methyl 5-iodo-3-[(trifluoroacetyl)amino]-2-thiophenecarboxylate (Intermediate 7) (0.98 g, 2.59 mmol) and potassium carbonate (1.8 g, 13 mmol) in methanol (60 mL) and water (6 mL) was stirred at room temperature for 18 h. The solvent was evaporated and partitioned between water (30 mL) and DCM (50 mL), then passed through a hydrophobic frit and the organic fraction evaporated. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient of 0-20% ethyl acetate in cyclohexane to give the title compound. Further quantities were obtained by collecting the early eluting fractions and further purification by ISCO Companion silica chromatography, eluting with a gradient 0-50% DCM in cyclohexane.

MS calcd for $(C_6H_6INO_2S + H)^+$: 284

MS found (electrospray): $(M+H)^+ = 284$

Intermediate 9

Methyl 5-iodo-3-{[(*trans*-4-methylcyclohexyl)carbonyl]amino}-2-thiophenecarboxylate



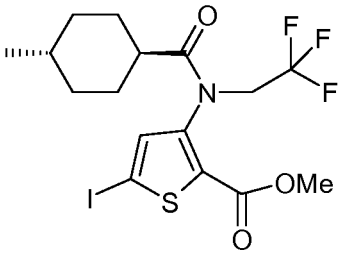
To a mixture of methyl 3-amino-5-iodo-2-thiophenecarboxylate (Intermediate 8) (0.54 g) in DCE (25 mL) was added *trans*-4-methylcyclohexanecarbonyl chloride[1] (910 mg, 5.7 mmol) and the mixture heated under reflux under nitrogen for 3 h. The mixture was cooled, water (20 mL) was added, and after stirring for 5 mins, the mixture was passed through a hydrophobic frit. The aqueous layer was extracted twice with DCM, the organic fractions combined, dried (hydrophobic frit) and evaporated. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-50% DCM in cyclohexane to give the title compound.

MS calcd for $(C_{14}H_{18}INO_3S + H)^+$: 408

MS found (electrospray): $(M+H)^+ = 408$

Intermediate 10

Methyl 5-iodo-3-[[(*trans*-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-2-thiophenecarboxylate



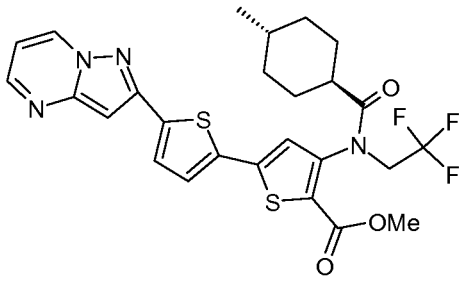
A mixture of methyl 5-iodo-3-{[(trans-4-methylcyclohexyl)carbonyl]amino}-2-thiophenecarboxylate (Intermediate 9) (150 mg) and sodium hydride (18 mg, 0.44 mmol) in dry DMF (0.5 mL) was stirred over an ice bath under nitrogen for 30 mins. 2,2,2-Trifluoroethyl triflate (0.08 mL, 0.55 mmol) was added and the mixture heated at 70°C for 5 hours. A further aliquot of 2,2,2-trifluoroethyl triflate (0.08 mL, 0.55 mmol) was added and the mixture heated for 16 hours. The mixture was poured into citric acid solution (10 mL), ethyl acetate added and the mixture stirred for approximately 15 mins. The aqueous layer was separated, extracted with ethyl acetate, the organic fractions combined, dried (hydrophobic frit) and evaporated. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-20% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{16}H_{19}F_3INO_3S + H)^+$: 490

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

Intermediate 11

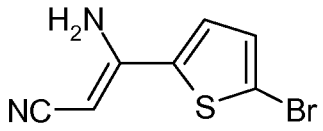
Methyl 4-[[(*trans*-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5'-pyrazolo[1,5-*a*]pyrimidin-2-yl-2,2'-bithiophene-5-carboxylate



A mixture of methyl 5-iodo-3-[[(trans-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-2-thiophenecarboxylate (Intermediate 10) (67 mg, 0.14 mmol), 2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]pyrazolo[1,5-a]pyrimidine (Intermediate 16) (54 mg, 0.16 mmol), sodium carbonate (44 mg, 0.41 mmol) and $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) in dioxane (2 mL) and water (0.5 mL) was heated in a microwave at 300 W and 100°C for 10 mins. The solvent was evaporated, and the residue taken into water and extracted twice with ethyl acetate. The combined organic fractions were dried using a hydrophobic frit, evaporated *in vacuo* and purified by ISCO Companion silica chromatography, eluting with a

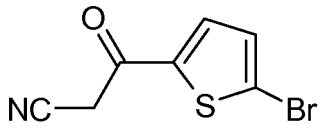
gradient 0-100% EtOAc in cyclohexane, to give the title compound.
MS calcd for $(C_{26}H_{25}F_3N_4O_3S_2 + H)^+$: 563
MS found (electrospray): $(M+H)^+$ = 563

Intermediate 12
(2E,*Z*)-3-Amino-3-(5-bromo-2-thienyl)-2-propenenitrile



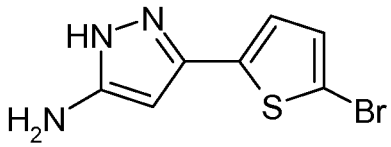
To a solution of 5-bromothiophene-2-carbonitrile (10.0 g, 53.2 mmol) in dry MeCN (5.56 mL) and dry toluene (200 mL) under nitrogen was added potassium *tert*-butoxide (17.9 g, 159.6 mmol) in four equal portions over 45 mins. After 3 hours, diethyl ether (150 mL) and saturated sodium carbonate solution (150 mL) were added and the mixture stirred vigorously for 10 mins. The organic layer was extracted with more ether (2 x 50 mL), the combined organics were dried (hydrophobic frit) and evaporated to give the title compound.
MS calcd for $(C_7H_5BrN_2S - H)^-$: 228/230
MS found (electrospray): $(M-H)^-$ = 228/230

Intermediate 13
3-(5-Bromo-2-thienyl)-3-oxopropanenitrile



To a solution of (2E,Z)-3-amino-3-(5-bromo-2-thienyl)-2-propenenitrile (Intermediate 12) (12.91 g, 56 mmol) in chloroform (400 mL) was added hydrochloric acid (5N, 150 mL) and the mixture stirred overnight. The mixture was then passed through a hydrophobic frit and evaporated to give the title compound.
MS calcd for $(C_7H_4BrNOS - H)^-$: 229/231
MS found (electrospray): $(M-H)^-$ = 229/231

Intermediate 14
3-(5-Bromo-2-thienyl)-1*H*-pyrazol-5-amine



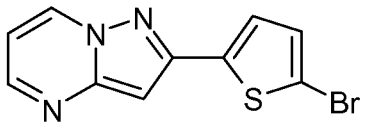
To a solution of 3-(5-bromo-2-thienyl)-3-oxopropanenitrile (Intermediate 13) (11.6 g, 50.6 mmol) in acetic acid (12 mL) and ethanol (100 mL) was added hydrazine monohydrate (4.9 mL, 101 mmol) and the mixture heated at 70°C under nitrogen for 2 hours. The cooled solution was poured into sodium bicarbonate solution (500 mL), DCM (200 mL) was added, and the mixture stirred vigorously and then passed through a hydrophobic frit. The aqueous layer was extracted with DCM (150 mL and 100 mL), the organic fractions combined, washed with water (100 mL), dried (hydrophobic frit) and evaporated to give the title compound.

MS calcd for $(C_7H_6BrN_3S+ H)^+$: 244/246

MS found (electrospray): $(M+H)^+$ = 244/246

Intermediate 15

2-(5-Bromo-2-thienyl)pyrazolo[1,5-*a*]pyrimidine



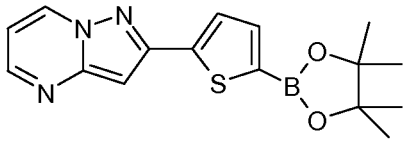
To a solution of 3-(5-Bromo-2-thienyl)-1H-pyrazol-5-amine (Intermediate 14) (10.5 g, 43 mmol) in acetic acid (120 mL) was added 1,1,3,3-tetramethoxypropane (8.54 mL, 52 mmol) and the mixture heated at 110°C under nitrogen for 16 hours, then evaporated to dryness. The residue was dissolved in $CHCl_3$ (200 mL), neutralised with sodium bicarbonate solution (300 mL) and the layers separated. The aqueous layer was extracted with $CHCl_3$ (2 x 100 mL), the organic fractions combined, dried (hydrophobic frit) and evaporated. Vigorous stirring in methanol and filtration afforded the title compound. Purification of the filtrate using SPE silica chromatography, eluting with a gradient of ethyl acetate in cyclohexane, followed by trituration of the obtained crude product with methanol afforded more of the title compound.

MS calcd for $(C_{10}H_6BrN_3S+ H)^+$: 281/283

MS found (electrospray): $(M+H)^+$ = 281/283

Intermediate 16

2-[5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]pyrazolo[1,5-*a*]pyrimidine



To a mixture of 2-(5-bromo-2-thienyl)pyrazolo[1,5-a]pyrimidine (Intermediate 15) (7.0 g, 25.4 mmol), bis(pinacoloto)diboron (1.0 g, 6.07 mmol), and potassium acetate (1.05 g, 10.7 mmol) in dry DMF (20 mL) was added $PdCl_2$(dppf) (145 mg, 0.178 mmol) and the mixture heated at

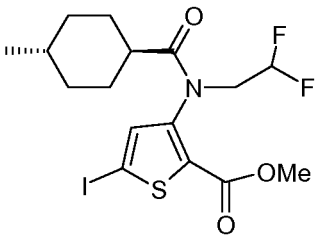
100°C under nitrogen for 2 hours. The solvent was evaporated, the residue partitioned between ethyl acetate (100 mL) and water (100 mL), and a resulting solid removed by filtration. The combined organic fractions were dried (Na_2SO_4), evaporated *in vacuo,* dissolved in DCM (approx 5 mL) and purified by SPE silica chromatography, eluting with cyclohexane followed by a gradient of EtOAc in cyclohexane, to give the title compound.

MS calcd for $(C_{16}H_{18}BN_3O_2S+ H)^+$: 328

MS found (electrospray): $(M+H)^+$ = 328

Intermediate 17

Methyl 3-{(2,2-difluoroethyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-5-iodo-2-thiophenecarboxylate



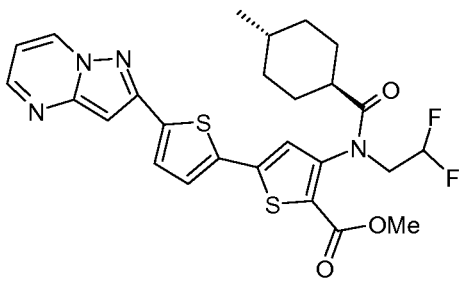
A mixture of methyl 5-iodo-3-{[(trans-4-methylcyclohexyl)carbonyl]amino}-2-thiophenecarboxylate (Intermediate 9) (468 mg, 1.15 mmol) and sodium hydride (69 mg, 1.72 mmol) in dry DMF (1.5 mL) was stirred over an ice bath under nitrogen for 1 hour. 2,2,-Difluoroethyl triflate (368 mg, 1.72 mmol) was added and the mixture heated at 70°C under nitrogen for 2 hours, then stirred at room temperature for 18 hours. The mixture was poured into citric acid solution (15 mL), extracted with ethyl acetate (2 x 20 mL), separated, dried (hydrophobic frit) and evaporated. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-20% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{16}H_{20}F_2INO_3S + H)^+$: 472

MS found (electrospray): $(M+H)^+$ = 472

Intermediate 18

Methyl 4-{(2,2-difluoroethyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-5'-pyrazolo[1,5-*a*]pyrimidin-2-yl-2,2'-bithiophene-5-carboxylate



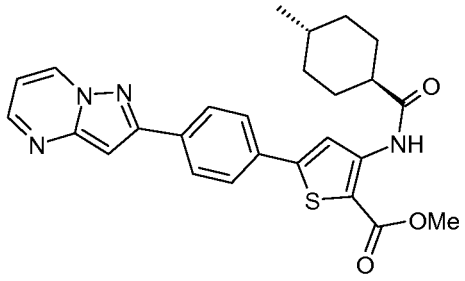
A mixture of methyl 3-{(2,2-difluoroethyl)[(trans-4-methylcyclohexyl)carbonyl]amino}-5-iodo-2-thiophenecarboxylate (Intermediate 17) (90 mg, 0.19 mmol), 2-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]pyrazolo[1,5-a]pyrimidine (Intermediate 16) (75 mg, 0.23 mmol), sodium carbonate (61 mg, 0.57 mmol) and $Pd(PPh_3)_4$ (22 mg, 0.02 mmol) in dioxane (1.5 mL) and water (0.5 mL) was heated in a microwave at 300 W and 100°C for 10 mins. The solvent was evaporated, and the residue portioned between water and DCM. The organic fraction was dried using a hydrophobic frit, evaporated *in vacuo* and purified by ISCO Companion silica chromatography, eluting with a gradient 0-100% EtOAc in cyclohexane, to give the title compound.

MS calcd for $(C_{26}H_{26}F_2N_4O_3S_2 + H)^+$: 545

MS found (electrospray): $(M+H)^+$ = 545

Intermediate 19

Methyl 3-{[(*trans*-4-methylcyclohexyl)carbonyl]amino}-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylate



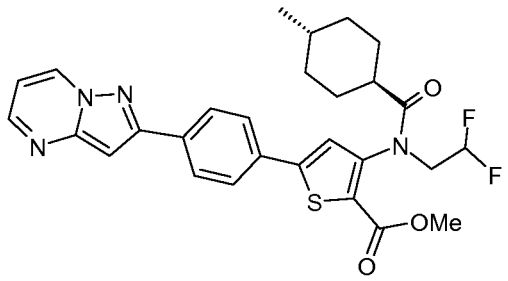
A solution of methyl 5-iodo-3-{[(trans-4-methylcyclohexyl)carbonyl]amino}-2-thiophenecarboxylate (Intermediate 9) (1.5 g, 3.7 mmol), 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazolo[1,5-a]pyrimidine (Intermediate 6) (1.42 g, 4.4 mmol), sodium carbonate (1.17 g, 11.1 mmol) and $Pd(PPh_3)_4$ (0.21 g, 0.18 mmol) in dioxane (30 mL) and water (10 mL) was heated in a microwave at 90°C for 24 hours. The solvent was evaporated, and the residue partitioned between water and ethyl acetate, filtered through a celite pad, and the organic layer separated. The aqueous fraction was extracted twice with ethyl acetate. The combined organic fractions were dried using a hydrophobic frit, evaporated *in vacuo* and purified by ISCO Companion silica chromatography, eluting with a gradient 0-100% EtOAc in cyclohexane, to give the title compound.

MS calcd for $(C_{26}H_{26}N_4O_3S + H)^+$: 475

MS found (electrospray): $(M+H)^+$ = 475

Intermediate 20

Methyl 3-{(2,2-difluoroethyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylate



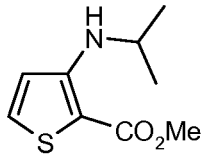
A mixture of Methyl 3-{[(trans-4-methylcyclohexyl)carbonyl]amino}-5-(4-pyrazolo[1,5-a]pyrimidin-2-ylphenyl)-2-thiophenecarboxylate (Intermediate 19) (121 mg, 0.26 mmol) and sodium hydride (7.4 mg, 0.31 mmol) in dry DMF (1.5 mL) was stirred over an ice bath under nitrogen for 90 mins. 2,2-Difluoroethyl triflate (109 mg, 0.51 mmol) was added and the mixture heated at 70°C for 5 hours. A further aliquot 2,2,2-trifluoroethyl triflate (0.08 mL, 0.55 mmol) was added and the mixture heated at 70°C for 18 h. The mixture was poured into citric acid solution (10 mL), ethyl acetate (15 mL) added and the mixture stirred for approximately 20 mins. The aqueous layer was separated, extracted with ethyl acetate, the organic fractions combined, washed with brine (10 mL), dried (hydrophobic frit) and evaporated. The crude material was purified by ISCO Companion silica chromatography, eluting with a gradient 0-30% EtOAc in cyclohexane to give the title compound.

MS calcd for $(C_{28}H_{28}F_2N_4O_3S + H)^+$: 539

MS found (electrospray): $(M+H)^+$ = 539

Intermediate 21

Methyl 3-[(1-methylethyl)amino]-2-thiophenecarboxylate



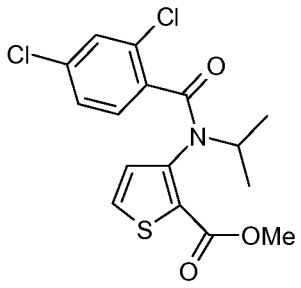
2-Methoxypropene (9.18 mL) was added to a solution of methyl 3-amino-2-thiophene carboxylate (5 g) in dry DCM (100 mL) at room temperature under nitrogen. Glacial acetic acid (5.6 mL) was added slowly. Sodium triacetoxyborohydride (10.12g) was then added in portions over 30 min. The resulting opaque solution was then left to stir at room temperature for 24 hours. The mixture was poured into 8% sodium bicarbonate solution (300 mL), the layers were separated and the DCM layer washed further with bicarbonate solution (2 x 100 mL), dried (hydrophobic frit) and evaporated to give the title compound.

MS calcd for $(C_9H_{13}NO_2S + H)^+$: 200

MS found (electrospray): $(M+H)^+$ =200

Intermediate 22

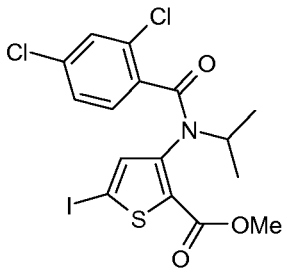
Methyl 3-[[(2,4-dichlorophenyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylate



To a solution of methyl 3-[(1-methylethyl)amino]-2-thiophenecarboxylate (5 g, a synthesis of which is described as Intermediate 21) in pyridine (45 mL) was added 2,4-dichlorobenzoyl chloride (5.3 mL) under nitrogen. The mixture was heated at 70°C overnight under nitrogen. The reaction was partitioned between EtOAc and saturated sodium bicarbonate solution, and the organics were separated and washed with brine. The organics were dried over sodium sulphate and evaporated *in vacuo*. The crude material was purified by silica Biotage cartridge, eluting with 15% EtOAc in cyclohexane to give the title compound.
MS calcd for $(C_{16}H_{15}NO_3SCl_2 + H)^+$: 372/374/376
MS found (electrospray): $(M+H)^+$ = 372/374/376

Intermediate 23

Methyl 3-[[(2,4-dichlorophenyl)carbonyl](1-methylethyl)amino]-5-iodo-2-thiophenecarboxylate

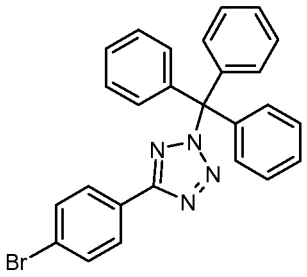


n-Butyllithium (3.49 mL, 1.6M solution in hexanes) was added dropwise to a solution of diisopropylamine (0.781 mL) in THF (5 mL) at 0°C under nitrogen. The solution was cooled to -78°C and a solution of methyl 3-[[(2,4-dichlorophenyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylate (Intermediate 22) (1.036 g) in THF (5 mL) was added dropwise, maintaining an internal temperature below -65°C. The reaction was left to stir for 30 mins. A solution of iodine (0.846 g) in THF (5 mL) was added dropwise, maintaining the internal temperature below -65°C. The reaction was left to stir for 1.5 hours. The reaction was quenched with saturated ammonium chloride (10 mL) and was allowed to warm to room temperature. EtOAc (40 mL) was added and the layers were separated. The organics were washed with 5% sodium thiosulphate solution (3 x 30 mL), water (30 mL) and 2N HCl (20 mL), and were then dried over sodium sulphate and evaporated *in vacuo*. The crude material was purified by silica SPE cartridge, eluting with a gradient 0-100% DCM in

cyclohexane, followed by 1-5% MeOH in DCM to give the title compound.
MS calcd for $(C_{16}H_{14}Cl_2INO_3S + H)^+$: 498/500/502
MS found (electrospray): $(M+H)^+$ = 498/500/502

Intermediate 24

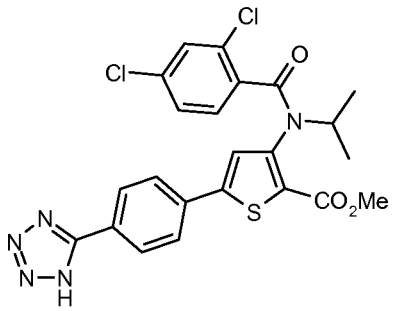
5-(4-Bromophenyl)-2-(triphenylmethyl)-2*H*-tetrazole



A mixture of 5-(4-bromophenyl)-1*H*-tetrazole (2 g), trityl chloride (2.47 g), tetrabutyl ammonium bromide (130 mg) and 2N sodium hydroxide solution (4.79 mL) in DCM (15 mL) was stirred vigorously at room temperature for 3 hours. The mixture was diluted with DCM (50 mL) and water (30 mL). The layers were separated and the aqueous extracted further with DCM (3 x 20 mL). The combined organic fractions were dried using a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by silica SPE cartridge, eluting with DCM to give the title compound.
^{1}H NMR ($CDCl_3$) δ 8.05 (2H, d), 7.6 (2H, d), 7.4-7.1 (15H, m).

Intermediate 25

Methyl 3-[[(2,4-dichlorophenyl)carbonyl](1-methylethyl)amino]-5-[4-(1*H*-tetrazol-5-yl)phenyl]-2-thiophenecarboxylate



n-Butyl lithium (2.94 mL, 1.6M solution in hexanes) was added dropwise to a solution of 5-(4-bromophenyl)-2-(triphenylmethyl)-2*H*-tetrazole (2.0 g, a synthesis of which is described as Intermediate 24) in THF (25 mL) at -78°C under nitrogen. The mixture was stirred at -78°C under nitrogen for 45 mins. Trimethoxyborate (0.669 mL) in THF (3 mL) was added dropwise, maintaining the internal temp at -78°C. This was stirred at -78°C for 30 mins then

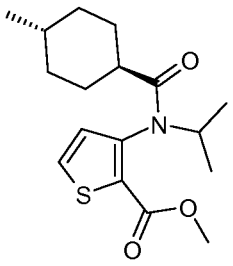
allowed to warm to room temperature and stirred for a further 45 mins. Water (30 mL) was added slowly and the mixture extracted with EtOAc (2 x 40 mL), dried over sodium sulphate and evaporated *in vacuo*. The material was triturated with diethyl ether (40 mL) and the resulting solid was filtered off. Tetrakis(triphenylphosphine)palladium (0) (23 mg) was added to a mixture of methyl 3-[[(2,4-dichlorophenyl)carbonyl](1-methylethyl)amino]-5-iodo-2-thiophenecarboxylate (200 mg, a synthesis of which is described as Intermediate 23) and the solid (prepared above) (185 mg) in dioxane (3 mL) and 2N sodium carbonate solution (1 mL). The mixture was heated to 100°C under nitrogen for 4 hours. The reaction was allowed to cool and the solvent evaporated, acidified with 2N HCl and the phases separated using a hydrophobic frit. This was evaporated and the crude material was purified by silica SPE cartridge, eluting with a gradient 0-30% EtOAc in cyclohexane, followed by a gradient EtOAc to MeCN to acetone to MeOH. These latter fractions were combined and evaporated, dissolved in MeOH and applied to a NH_2 SPE cartridge. Elution was with MeOH (5 x column volumes) then 10% acetic acid/MeOH (5 x column volumes). The acetic acid/MeOH fractions were combined and evaporated *in vacuo* to give the title compound.

MS calcd for $(C_{23}H_{19}Cl_2N_5O_3S + H)^+$: 516/518/520

MS found (electrospray): $(M+H)^+$ = 516/518/520

Intermediate 26

Methyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylate



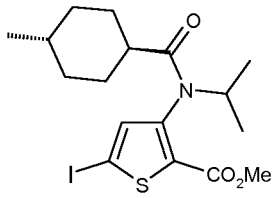
To a solution of methyl 3-[(1-methylethyl)amino]-2-thiophenecarboxylate (6.45 g, a synthesis of which is described as Intermediate 21) in DCE (100 mL) was added *trans*-4-methylcyclohexanecarbonyl chloride[1] (5.9 g) and the reaction was heated at 85°C overnight. A further portion of *trans*-4-methylcyclohexanecarbonyl chloride[1] (3 g) was added and the reaction was heated at 85°C for 24 hours. The reaction was quenched with saturated sodium bicarbonate solution. The organics were separated and the aqueous layer was extracted with DCM (x 3). The combined organics were dried by passing through a hydrophobic frit and were evaporated *in vacuo*. The crude material was triturated with heptane, filtered and dried under vacuum to give the title compound.

MS calcd for $(C_{17}H_{25}NO_3S + H)^+$: 324

MS found (electrospray): $(M+H)^+$ = 324

Intermediate 27

Methyl 5-iodo-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylate



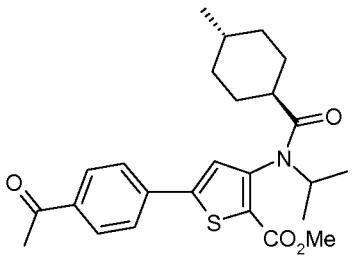
A solution of methyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylate (Intermediate 26) (10.5 g) in dry THF (100 mL) was added dropwise at -77°C under nitrogen to a 2M solution of LDA in THF/heptane/ethyl benzene (48.4 mL) maintaining an internal temperature <-70°C. The dropping funnel was washed through with dry THF (10 mL) and stirring continued at -77°C for 2.5 hours. A solution of iodine (16.5 g) in dry THF (100 mL) was added dropwise to the stirred reaction mixture maintaining an internal temperature <-70°C, then the dropping funnel was washed through with dry THF (10 mL). After stirring under nitrogen at -77°C for 1.5 hours, the reaction mixture was quenched by addition of saturated ammonium chloride solution and warmed to 0°C. The mixture was diluted with 5% sodium thiosulfate solution, then the organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4), filtered and evaporated. The crude product was purified by flash chromatography over silica gel (Biotage) eluting with cyclohexane / EtOAc (10:1) to give the title compound.

MS calcd for $(C_{17}H_{24}NIO_3S + H)^+$: 450

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

Intermediate 28

Methyl 5-(4-acetylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylate



A mixture of (4-acetylphenyl)boronic acid (66 mg), methyl 5-iodo-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylate (150 mg, a synthesis of which is described as Intermediate 27), 2N sodium carbonate solution (0.7 mL) and tetrakis(triphenylphosphine)palladium (0) (39 mg) in DMF (3 mL) was heated at 100°C under nitrogen atmosphere, in a Reactivial for 90 minutes. The DMF was evaporated *in vacuo* and the residue partitioned between DCM and water. The DCM layer was separated

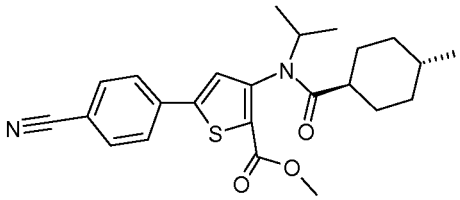
using a hydrophobic frit and concentrated. The residue was purified by ISCO Companion silica chromatography, eluting with a gradient of EtOAc in cyclohexane (0% to 30%) to give the title compound.

MS calcd for $(C_{25}H_{31}NO_4S+ H)^+$: 442

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

Intermediate 29

Methyl 5-(4-cyanophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylate



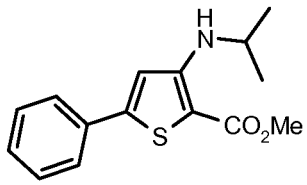
A mixture of (4-cyanophenyl)boronic acid (59 mg), methyl 5-iodo-3-[[(trans-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylate (Intermediate 27) (150 mg), 2N sodium carbonate solution (0.7 mL) and tetrakis(triphenylphosphine)palladium (0) (39 mg) in DMF (3 mL) was heated at 100°C under nitrogen atmosphere, in a Reactivial for 90 minutes. The DMF was evaporated under vacuum and the residue partitioned between DCM and water. The DCM layer was separated using a hydrophobic frit and concentrated. The residue was purified by ISCO Companion silica chromatography, eluting with a gradient of EtOAc in cyclohexane (0% to 30%) to give the title compound.

MS calcd for $(C_{24}H_{28}N_2O_3S+ H)^+$: 425

MS found (electrospray): $(M+H)^+ = 425$

Intermediate 30

Methyl 3-[(1-methylethyl)amino]-5-phenyl-2-thiophenecarboxylate

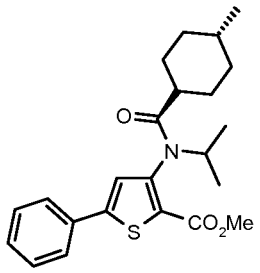


To a solution of 3-amino-5-phenyl-thiophene-2-carboxylic acid methyl ester (4.92 g, 21.1 mmol) in DCM (110 mL) was added 2-methoxypropene (8.23 mL, 84.4 mmol), acetic acid (4.83 mL, 84.4 mmol) and sodium triacetoxyborohydride (8.94 g, 42.2 mmol) and the mixture stirred overnight. Ethyl acetate and water were added, the aqueous phase adjusted to pH7 using sodium bicarbonate and then extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over sodium sulphate. The crude product was

purified by silica chromatography using a Flashmaster Personal apparatus (Argonaut) eluting with DCM / cyclohexane (1:4) to give the title compound.
MS calcd for $(C_{15}H_{17}NO_2S+ H)^+$: 276
MS found (electrospray): $(M+H)^+$ =276

Intermediate 31

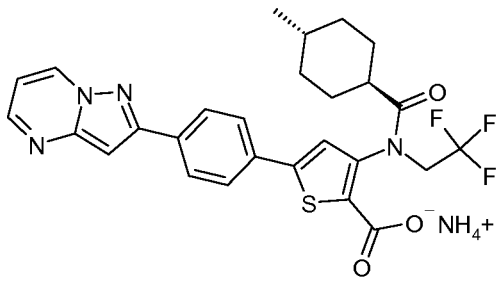
Methyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-phenyl-2-thiophenecarboxylate



To methyl 3-[(1-methylethyl)amino]-5-phenyl-2-thiophenecarboxylate (Intermediate 30) (500 mg, 1.82 mmol) in DCM (4 mL) was added *trans*-4-methylcyclohexanecarbonyl chloride[1] (350 mg, 2.18 mmol) followed by triphenylphosphine (500 mg, 1.91 mmol) and the solution stirred at 45°C for 18 hours. After cooling, it was diluted with ethyl acetate (40 mL) and saturated sodium bicarbonate solution (40 mL). The aqueous phase was washed with ethyl acetate (2 x 40 mL), the combined organic fractions were dried (Na_2SO_4) and concentrated. The residue was purified by chromatography over silica using a Flashmaster Personal apparatus (Argonaut) eluting with ethyl acetate / cyclohexane (5:95) to give the title compound.
MS calcd for $(C_{23}H_{29}NO_3S+ H)^+$: 400
MS found (electrospray): $(M+H)^+$ =400

Example 1

Ammonium 3-[[(*trans*-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylate



To a solution of methyl 3-[[(trans-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5-

(4-pyrazolo[1,5-a]pyrimidin-2-ylphenyl)-2-thiophenecarboxylate (Intermediate 4) (20 mg) in THF (1 mL) and ethanol (1 mL) was added 2N sodium hydroxide solution (0.5 mL) and the mixture was stirred for 18 hours . The mixture was evaporated *in vacuo* and the residue was partitioned between 2N HCl and DCM. The organics were separated using a hydrophobic frit and evaporated *in vacuo*. The crude material was purified by reverse phase using a Supelco ABZ + plus 100 x 21.2 mm, 5 µm column with a flow rate 20 mL/min, 2 injections of 0.5 mL each, eluting with a gradient of 45-100% MeCN (containing 0.05% formic acid) in water (containing 0.1% formic acid). The material obtained was taken into chloroform/MeOH/0.88 ammonia mixture (30:15:3) and was evaporated *in vacuo* to give the title compound.

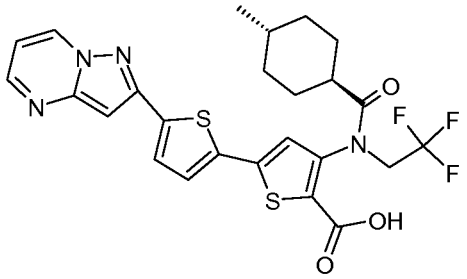
MS calcd for $(C_{27}H_{25}F_3N_4O_3S + H)^+$: 543

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

^{1}H NMR (d_6-DMSO) δ 9.16 (1H, d), 8.56 (1H, d), 8.14 (2H, d), 7.90 (2H, d), 7.67 (1H, s), 7.33 (1H, s), 7.19 (3H, br), 7.07 (1H, dd), 4.86-4.69 (1H, m), 4.22-4.07 (1H, m), 2.27-2.16 (1H, m), 1.82-1.69 (1H, m), 1.65-1.50 (3H, m), 1.46-1.15 (4H, m), 0.75 (3H, d), 0.71-0.57 (2H, m), ammonium protons not seen.

Example 2

4-[[(*trans*-4-Methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5'-pyrazolo[1,5-*a*]pyrimidin-2-yl-2,2'-bithiophene-5-carboxylic acid



To a solution of methyl 4-[[(trans-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5'-pyrazolo[1,5-a]pyrimidin-2-yl-2,2'-bithiophene-5-carboxylate (Intermediate 11) (63 mg) in THF (2 mL) and methanol (2 mL) was added 2N sodium hydroxide solution (1 mL) and the mixture was stirred for 20 hours. The mixture was evaporated *in vacuo*, taken into water (10 mL), acidified with 2N hydrochloric acid and extracted with ethyl acetate (15 mL x 2). The organic layers were combined, dried using a hydrophobic frit, evaporated and purified by MDAP HPLC to give the title compound.

MS calcd for $(C_{25}H_{23}F_3N_4O_3S_2 + H)^+$: 549

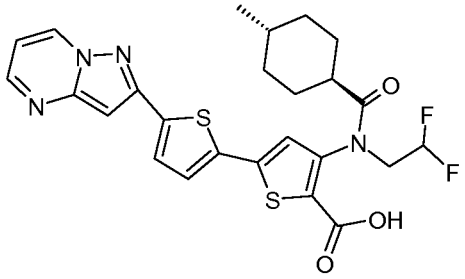
MS found (electrospray): $(M+H)^+$ = 549

^{1}H NMR (d_6-DMSO) δ 13.6-13.5 (1H, brs), 9.11 (1H, d), 8.56 (1H, d), 7.80 (1H, d), 7.69 (1H, s), 7.55 (1H, s), 7.24 (1H, d), 7.07 (1H, dd), 4.69 (1H, m), 4.22 (1H, m), 2.20 (1H, m), 1.74 (1H, m), 1.64-1.21 (6H, m), 0.81-0.61 (5H, m).

Example 3

4-{(2,2-Difluoroethyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-5'-pyrazolo[1,5-

a]pyrimidin-2-yl-2,2'-bithiophene-5-carboxylic acid



To a solution of methyl 4-{(2,2-difluoroethyl)[(trans-4-methylcyclohexyl)carbonyl]amino}-5'-pyrazolo[1,5-a]pyrimidin-2-yl-2,2'-bithiophene-5-carboxylate (Intermediate 18) (58 mg, 0.11 mmol) in THF (2 mL) and methanol (2 mL) was added 2N sodium hydroxide solution (0.5 mL) and the mixture stirred at room temperature for 3 days. The mixture was evaporated *in vacuo*, taken into water (15 mL), acidified with 2N hydrochloric acid and extracted with ethyl acetate (20 mL x 2). The organic layers were combined, dried using a hydrophobic frit, evaporated and purified by MDAP HPLC to give the title compound.

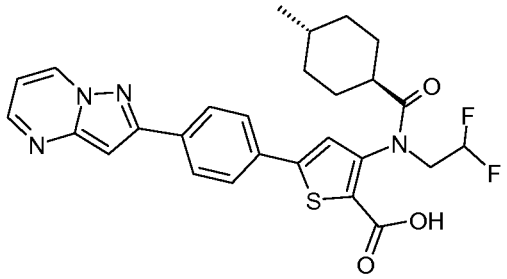
MS calcd for $(C_{25}H_{24}F_2N_4O_3S_2 + H)^+$: 531

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

^1H NMR (d_6-DMSO) δ 13.6-13.45 (1H, brs), 9.10 (1H, d), 8.56 (1H, d), 7.80 (1H, d), 7.65 (1H, s), 7.51 (1H, s), 7.24 (1H, d), 7.07 (1H, dd), 6.12 (1H, m), 4.14 (1H, m), 3.81 (1H, m), 2.18 (1H, m), 1.76-1.54 (4H, m), 1.49-1.20 (3H, m), 0.82-0.60 (5H, m).

Example 4

3-{(2,2-Difluoroethyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylic acid



To a solution of methyl 3-{(2,2-difluoroethyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylate (Intermediate 20) (46 mg, 0.085 mmol) in THF (2 mL) and methanol (2 mL) was added 2N sodium hydroxide solution (1 mL) and the mixture stirred at room temperature for 20 hours. The mixture was evaporated *in vacuo*, taken into water (10 mL), acidified with 2N hydrochloric acid and extracted with ethyl acetate (15 mL x 2). The organic layers were combined, dried using a hydrophobic frit, evaporated and purified by MDAP HPLC to give the title compound.

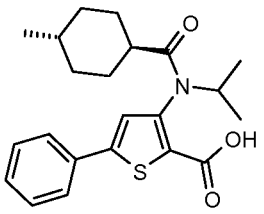
MS calcd for $(C_{27}H_{26}F_2N_4O_3S + H)^+$: 525

MS found (electrospray): $(M+H)^+ = 525$

^1H NMR (d_6-DMSO) δ 13.55-13.4 (1H, brs), 9.16 (1H, d), 8.57 (1H, d), 8.16 (2H, d), 7.92 (2H, d), 7.74 (1H, s), 7.34 (1H, s), 7.06 (1H, dd), 6.12 (1H, m), 4.17 (1H, m), 3.82 (1H, m), 2.20 (1H, m), 1.78-1.54 (3H, m), 1.49-1.2 (4H, m), 0.83-0.58 (5H, m).

Compound A

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



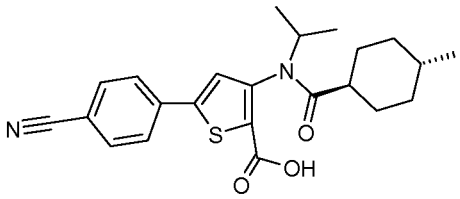
To a mixture of methyl 3-[[(trans-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-5-phenyl-2-thiophenecarboxylate (Intermediate 31) (390 mg) in THF/MeOH/water (3:2:1, vol/vol, 40 mL total) was added lithium hydroxide monohydrate (246 mg). The mixture was stirred at room temperature for 20 hours, the solvents removed in vacuo, and the residue partitioned between water (40 mL) and ethyl acetate (40 mL). The organic layer was dried (Na_2SO_4), evaporated and triturated with ether to give the title compound.

MS calcd for $(C_{22}H_{27}NO_3S+ H)^+$: 356

MS found (electrospray): $(M+H)^+$ =356

Compound B

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

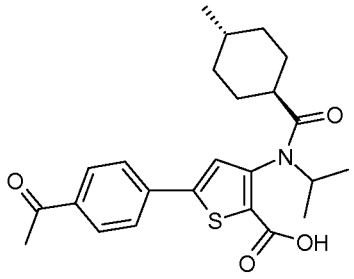


Methyl 5-(4-cyanophenyl)-3-[[(trans-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylate (Intermediate 29) (113 mg) was dissolved in THF (0.7 mL) and methanol (0.7 mL). 2N Sodium hydroxide solution (0.7 mL) was added and the mixture stirred at room temperature for 20 hours. The methanol and THF were evaporated under vacuum, and the residue was partitioned between DCM and 2N HCl solution. The DCM layer was separated using a hydrophobic frit and concentrated. The residue was purified by ISCO Companion chromatography over silica, eluting with a gradient of 0-30% EtOAc in

cyclohexane (containing 0.8 % of acetic acid) to give the title compound.
MS calcd for $(C_{23}H_{26}N_2O_3S+ H)^+$: 411
MS found (electrospray): $(M+H)^+$ = 411

Compound C

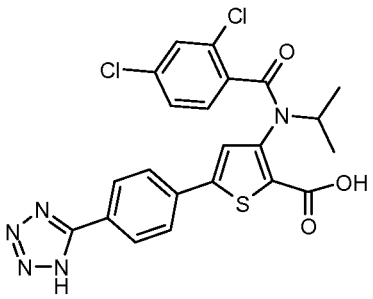
5-(4-Acetylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylic acid



Methyl 5-(4-acetylphenyl)-3-[[(trans-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylate (Intermediate 28) (129 mg) was dissolved in THF (0.7 mL) and methanol (0.7 mL). 2N Sodium hydroxide solution (0.7 mL) was added and the mixture stirred at room temperature for 20 hours . The methanol and THF were evaporated *in vacuo*, and the residue was partitioned between DCM and 2N HCl solution. The DCM layer was separated using a hydrophobic frit and concentrated to give the title compound.
MS calcd for $(C_{24}H_{29}NO_4S+ H)^+$: 428
MS found (electrospray): $(M+H)^+$ = 428
^{1}H NMR (DMSO-d_6) δ 8.09 (2H, d), 7.90 (2H, d), 7.52 (1H, s), 4.86 (1H, m, partially obscured by water peak), 2.63 (3H, s), 2.08 (1H, tt), 1.81-1.50 (5H, m), 1.44-1.19 (5H, m), 0.99 (3H, d), 0.80-0.54 (5H, m), carboxylic acid proton not seen.

Compound D

3-[[(2,4-Dichlorophenyl)carbonyl](1-methylethyl)amino]-5-[4-(1*H*-tetrazol-5-yl)phenyl]-2-thiophenecarboxylic acid



2N Sodium hydroxide (1 mL) was added to a solution of methyl 3-[[(2,4-dichlorophenyl)carbonyl](1-methylethyl)amino]-5-[4-(1H-tetrazol-5-yl)phenyl]-2-

thiophenecarboxylate (Intermediate 25) (50 mg) in THF (1 mL) and MeOH (2 mL). The solution was left to stir for 24 hours, then evaporated and the residue acidified to pH 1.0 with 2N HCl. The resulting suspension was applied to an OASIS HLB cartridge and eluted with water (3 x column volumes) then MeOH (3 x column volumes). The appropriate MeOH fractions were combined and evaporated *in vacuo*. The crude material was purified further by MDAP HPLC to give the title compound.

MS calcd for $(C_{22}H_{17}Cl_2N_5O_3S + H)^+$: 502/504/506

MS found (electrospray): $(M+H)^+$ = 502/504/506

^{1}H NMR (DMSO-d_6) δ 8.15-7.96 (dd 4H), 7.8 (s, 1H), 7.7-7.3 (m, 3H), 4.87 (1H, m), 1.4-0.9 (dd, 6H): the carboxylic acid and tetrazole protons are assumed to be exchanged with moisture in the solvent.

The compounds of Formula (I) 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 thereof in admixture with one or more pharmaceutically acceptable diluents or carriers.

The compounds of Formula (I) can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical, transdermal, or transmucosal administration. For systemic administration, oral administration is convenient. For oral administration, for example, the compounds of Formula (I) 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 compounds of Formula (I) are formulated in liquid solutions, for example, in pharmaceutically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds 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 Formula (I) can be formulated into ointments, salves, gels, or creams, as is generally known in the art.

The amounts of various compounds of Formula (I) 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 of Formula (I) with low oral bioavailability, relatively higher doses will have to be administered. Oral administration is a convenient method of administration of the compounds of Formula (I).

Suitably 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 3 times per day, suitably 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 of Formula (I) or a pharmaceutically acceptable salt thereof 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 compounds of Formula (I) 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.

Genotype 1b Full-Length Enzyme

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} values 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 potential for compounds of Formula (I) to inhibit HCV replication, genotype 1a and genotype 1b, may be demonstrated, for example, using the following cell based assay:

Replicon Luciferase cell based assay

Method

A 40mM stock solution in DMSO of each test compound was further diluted into 50μL of DMSO in the first row of a 96 well, V-bottom microplate, to give 100 times the top concentration of the required dilution series. Aliquots of 25μL of DMSO were added to each well of the remaining rows, and doubling dilutions of compound were prepared by the serial transfer of 25μL volumes from the first row onwards. A Plate-mate robot was used to transfer 1μL volumes from each dilution well into duplicate wells of a clear bottom, black walled, 96 well assay plate (COSTAR #3603). Control wells received 1μL of DMSO alone.

Suspensions were prepared from cultures of Huh-7 cells stably transfected with sub-genomic HCV NS3-NS5B replicons of either genotype 1b (the ET subline described by Pietschmann,T., Lohmann, V., Kaul, A., Krieger, N., Rinck, G., Rutter, G., Strand, D. &

Bartenschlager, R., *Journal of Virology*, 2002, **76**, 4008-4021) or genotype 1a (subline 1.19 constructed in-house) linked to a firefly luciferase reporter gene. Monolayers nearing confluency were stripped from growth flasks with versene-trypsin solution and the cells re-suspended in assay medium comprising DMEM (Invitrogen #41965-039) supplemented with 5% v/v foetal calf serum, 1% v/v non-essential amino acids solution, 100 units/ml penicillin, 100μg/ml streptomycin and 2mM L-glutamine. 100μL of suspension containing either 15,000 cells (genotype 1b luciferase replicon) or 20,000 cells (genotype 1a luciferase replicon) were added to all wells, except medium controls, of the assay plate and the plate incubated for 48 hours at 37°C in a 5% CO_2 atmosphere.

One tablet of Resazurin (Fisher #R/0040/79) was dissolved in 50mL of phosphate buffered saline and 100μL of solution added to all wells. The plate was re-incubated at 37°C for a further 2 to 4 hours, wrapped in aluminium foil, before reading in a FluoStar Optima at 595nm. All growth medium and Resazurin was removed by aspiration, and an opaque mask applied to the bottom of the plate. A solution of SteadyLite cytolytic buffer/luciferase substrate (Perkin-Elmer #6016987) was prepared according to the manufacturer's instructions, and 25μL added to each well. The plate was then read for luminescence on a TopCount NXT.

Data Analysis

Toxicity : The Resazurin absorbance values from duplicate wells were averaged and expressed as a percentage of the mean absorbance of compound free control wells to determine comparative cell viability. Compound cytotoxicity was expressed either as the lowest concentration at which a significant reduction in viability was observed or a 50% toxic concentration ($CCID_{50}$) was determined by plotting percentage cytotoxicity against compound concentration using Grafit software (Erithacus Software Ltd.).

Potency : The luminescence values from all compound-free wells containing cells were averaged to obtain a positive control value. The mean luminescence value from the compound-free wells that had received no cells was used to provide the negative (background) control value. The readings from the duplicate wells at each compound concentration were averaged and, after the subtraction of the mean background from all values, were expressed as a percentage of the positive control signal. The quantifiable and specific reduction of luciferase signal in the presence of a drug is a direct measure of replicon inhibition. GraFit software was used to plot the curve of percentage inhibition against compound concentration and derive the 50% inhibitory concentration (IC_{50}) for the compound.

Results

Compound	IC_{50} in 1a replicon cell-based assay (μM)	IC_{50} in 1b replicon cell-based assay (μM)
Example 1	+++++++	not measured
Example 2	++++++	++++++
Example 3	++++++	++++++
Example 4	++++++	++++++
Compound A	++++	+++++
Compound B	not measured	not measured
Compound C	++	+++
Compound D	+	+

Activity ranges

Genotype 1a		Genotype 1b	
+	>5.00 μM	+	>5.00 μM
++	1.000 - 4.999 μM	++	1.000 - 4.999 μM
+++	0.500 – 0.999 μM	+++	0.500 – 0.999 μM
++++	0.100 – 0.499 μM	++++	0.100 – 0.499 μM
+++++	0.050 – 0.099 μM	+++++	0.050 – 0.099 μM
++++++	0.010 – 0.049 μM	++++++	0.010 – 0.049 μM
+++++++	0.005 – 0.009 μM	+++++++	0.005 – 0.009 μM
++++++++	<0.005 μM	++++++++	<0.005 μM

Compound A corresponds to the compound disclosed as Example 317 in WO2002/100851, 5-Phenyl-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylic acid.

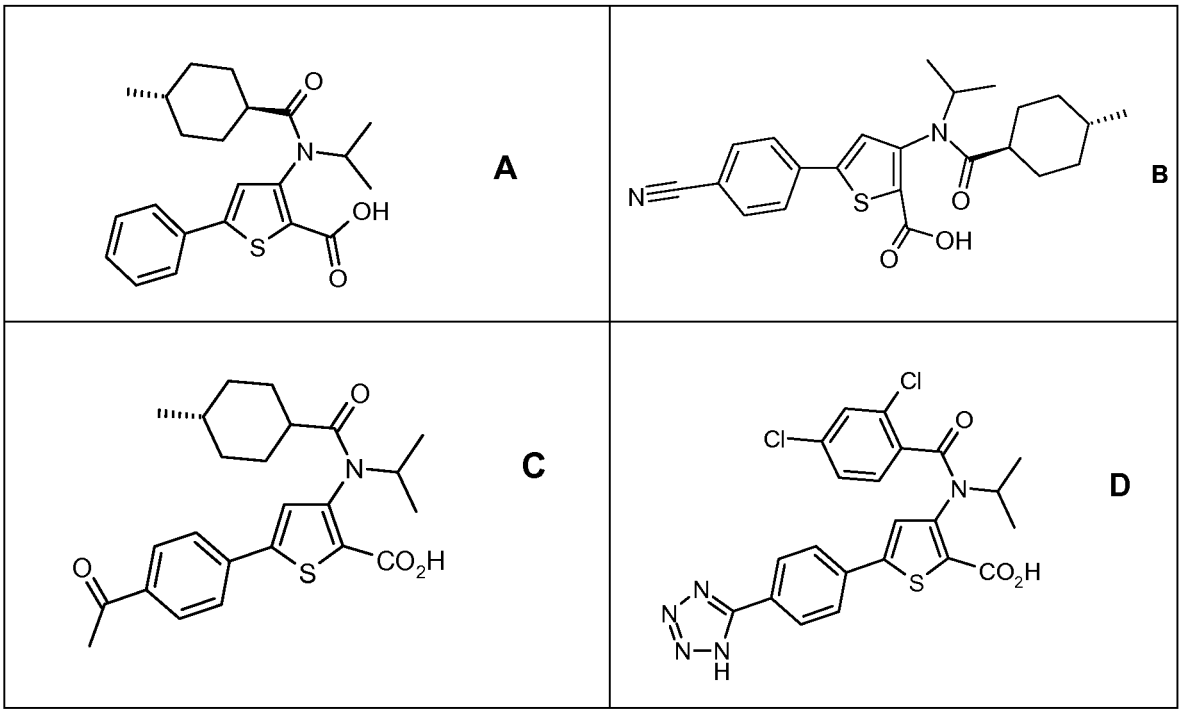
Compound B corresponds to the compound disclosed as Example 576 in WO2002/100851, 5-(4-Cyanophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylic acid.

Compound C corresponds to the compound disclosed as Example 460 in WO2002/100851, 5-(4-Acetylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-2-thiophenecarboxylic acid.

Compound D corresponds to the compound disclosed as Example 430 in WO2002/100851, 3-[[(2,4-Dichlorophenyl)carbonyl](1-methylethyl)amino]-5-[4-(1*H*-tetrazol-5-yl)phenyl]-2-thiophenecarboxylic acid.

Compounds A, B, C and D may be made according to the processes described in WO2002/100851 or as described hereinabove.

Structures of Compounds A, B, C and D are shown below for the avoidance of doubt.



The compounds of Formula (I) which have been tested demonstrate a surprisingly superior potency as HCV polymerase inhibitors, as shown by the IC_{50} values in the cell-based assays across both of the 1a and 1b genotypes of HCV, compared to Compounds A, B, C and D. Accordingly, the compounds of Formula (I) are of great potential therapeutic benefit in the treatment and prophylaxis of HCV.

The pharmaceutical compositions comprising compounds of Formula (I) may also be used in combination with other therapeutic agents, for example immune therapies (e.g. 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 (e.g. N-acetylcysteine), cytokine agonists, cytokine antagonists, lung surfactants and/or antimicrobial, anti-viral agents (e.g. ribavirin and amantidine), and anti-HCV agents, for example HCV NS3 protease inhibitors, e.g. VX950 (telapravir; Vertex) or SCH503034 (Schering Plough), or HCV NS5b polymerase inhibitors, for example HCV796 (Wyeth), R1626 (Roche) or NM208 (valopicitabine; Idenix). The compositions comprising compounds of Formula (I) may also be used in combination with gene replacement therapy.

The invention thus provides, in a further aspect, a combination comprising at least one compound of Formula (I) or pharmaceutically acceptable salt thereof 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.

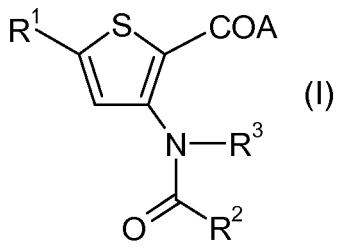
The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

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.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. A compound of Formula (I)



(I)

wherein:

A represents hydroxy;

R^1 represents $-R^xR^y$;

R^X represents phenyl (optionally substituted at one of the *meta*-positions to the thiophene by chloro, fluoro, methyl, ethyl, $-CF_3$, -OMe, $-NH_2$ or –OH); thienyl (optionally substituted by chloro, fluoro, methyl, ethyl, $-CF_3$ or –OMe) bonded through a ring carbon atom to the carbon atom of the thiophene; or pyridyl wherein the N atom is positioned at the *meta*-position to the thiophene (optionally substituted at the other *meta*-position to the thiophene by chloro, fluoro, methyl, ethyl, $-CF_3$, -OMe, $-NH_2$ or –OH);

R^Y represents optionally substituted 8-, 9- or 10-membered bicyclic heteroaryl, bonded such that when R^X is phenyl or pyridyl, the R^Y group is attached to R^x in the *para*-position to the thiophene;

R^2 represents $-C_{5-7}$cycloalkyl (optionally substituted by one or more substituents independently selected from $-C_{1-2}$alkyl (optionally substituted with one or more fluoro substituents), and –OH) or C_6cycloalkenyl;

R^3 represents linear or branched $–C_{2-6}$alkyl substituted by one or more fluoro substituents, or $–(CH_2)_mC_{3-6}$cycloalkyl substituted by one or more fluoro substituents;

m represents 0 or 1;

or a salt thereof.

2. A compound as claimed in claim 1, wherein R^X represents unsubstituted phenyl or unsubstituted thienyl.

3. A compound as claimed in claim 1 or claim 2, wherein R^Y represents optionally substituted 8- or 9-membered bicyclic heteroaryl.

4. A compound as claimed in any one of claims 1 to 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, 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, 5-amino-1,3-benzoxazol-2-yl, [1,3]oxazolo[5,4-b]pyridin-2-yl, furo[3,2-*c*]pyridin-2-yl, 4-amino-1,3-benzoxazol-2-yl, pyrazolo[1,5-*a*]pyrimidin-5-yl, 7-hydroxy-1-benzofuran-2-yl, 7-hydroxy-1,3-benzoxazol-2-yl, pyrazolo[1,5-*b*]pyridazin-2-yl, 6-aminoimidazo[1,2-*a*]pyridin-2-yl, 1*H*-benzimidazol-5-yl, 5-amino-1-benzofuran-2-yl, 6-amino-1-benzofuran-2-yl, 6-amino-1,3-benzoxazol-2-yl, 1,3-benzoxazol-2-yl, 1*H*-indol-5-yl or 1*H*-indol-6-yl, all of which may be optionally substituted.

5. A compound as claimed in any one of claims 1 to 4, 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 or 7-aminopyrazolo[1,5-*a*]pyrimidin-2-yl, all of which may be optionally substituted.

6. A compound as claimed in any one of claims 1 to 5, 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 or 7-aminopyrazolo[1,5-*a*]pyrimidin-2-yl, all of which may be optionally substituted.

7. A compound as claimed in any one of claims 1 to 6, wherein R^Y represents furo[3,2-*b*]pyridin-2-yl, pyrazolo[1,5-*a*]pyrimidin-2-yl or imidazo[1,2-*a*]pyridin-2-yl, all of which may be optionally substituted. In a further aspect, R^Y represents unsubstituted pyrazolo[1,5-a]pyrimidinyl.

8. A compound as claimed in any one of claims 1 to 7, wherein R^Y represents optionally substituted pyrazolo[1,5-a]pyrimidinyl.

9. A compound as claimed in any one of claims 1 to 8, wherein R^Y represents unsubstituted pyrazolo[1,5-a]pyrimidinyl.

10. A compound as claimed in any one of claims 1 to 9, wherein R^2 represents C_6cycloalkyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl optionally substituted with one or more fluoro groups) or cyclohex-3-en-1-yl.

11. A compound as claimed in any one of claims 1 to 10, wherein R^2 represents -C_6cycloalkyl (optionally substituted by methyl or trifluoromethyl).

12. A compound as claimed in any one of claims 1 to 11, wherein R^2 represents *trans*-4-methylcyclohexyl.

13. A compound as claimed in any one of claims 1 to 12, wherein R^3 represents $-CH_2CHF_2$ or $-CH_2CF_3$.

14. A compound as claimed in any one of claims 1 to 13, wherein R^X represents unsubstituted phenyl or unsubstituted thienyl; R^Y represents optionally substituted 8- or 9-membered bicyclic heteroaryl group; R^2 represents -C_6cycloalkyl (optionally substituted by one or more substituents selected from -C_{1-2}alkyl optionally substituted with one or more fluoro groups); and R^3 represents $-CH_2CHF_2$ or $-CH_2CF_3$.

15. A compound as claimed in any one of claims 1 to 14, wherein R^X represents unsubstituted phenyl or unsubstituted thienyl; R^Y represents unsubstituted pyrazolo[1,5-a]pyrimidinyl; R^2 represents *trans*-4-methylcyclohexyl; and R^3 represents $-CH_2CHF_2$ or $-CH_2CF_3$.

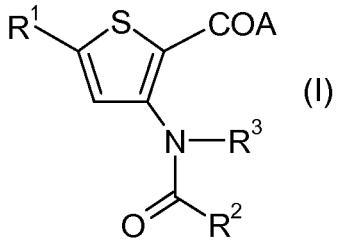
16. A compound of Formula (I) according to claim 1 selected from:
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylate;
4-[[(*trans*-4-Methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5'-pyrazolo[1,5-*a*]pyrimidin-2-yl-2,2'-bithiophene-5-carboxylic acid;
4-{(2,2-Difluoroethyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-5'-pyrazolo[1,5-*a*]pyrimidin-2-yl-2,2'-bithiophene-5-carboxylic acid; and
3-{(2,2-Difluoroethyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylic acid
or a salt thereof.

17. A compound as claimed in claim 16, wherein the compound is Ammonium 3-[[(*trans*-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylate or a salt thereof.

18. A compound of formula (I) or a salt thereof as claimed in any one of claims 1 to 17 wherein the salt is a pharmaceutically acceptable salt.

19. A compound as claimed in claim 17 wherein the compound is ammonium 3-[[(*trans*-4-methylcyclohexyl)carbonyl](2,2,2-trifluoroethyl)amino]-5-(4-pyrazolo[1,5-*a*]pyrimidin-2-ylphenyl)-2-thiophenecarboxylate.

20. 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 $-R^xR^y$;

R^X represents phenyl (optionally substituted at one of the *meta*-positions to the thiophene by chloro, fluoro, methyl, ethyl, $-CF_3$, -OMe, $-NH_2$ or –OH); thienyl (optionally substituted by chloro, fluoro, methyl, ethyl, $-CF_3$ or –OMe) bonded through a ring carbon atom to the carbon atom of the thiophene; or pyridyl wherein the N atom is positioned at the *meta*-position to the thiophene (optionally substituted at the other *meta*-position to the thiophene by chloro, fluoro, methyl, ethyl, $-CF_3$, -OMe, $-NH_2$ or –OH);

R^Y represents optionally substituted 8-, 9- or 10-membered bicyclic heteroaryl, bonded such that when R^X is phenyl or pyridyl, the R^Y group is attached to R^x in the *para*-position to the thiophene;

R^2 represents $-C_{5-7}$cycloalkyl (optionally substituted by one or more substituents independently selected from $-C_{1-2}$alkyl (optionally substituted with one or more fluoro substituents), and –OH) or C_6cycloalkenyl;

R^3 represents linear or branched $–C_{2-6}$alkyl substituted by one or more fluoro substituents, or $–(CH_2)_mC_{3-6}$cycloalkyl substituted by one or more fluoro substituents;

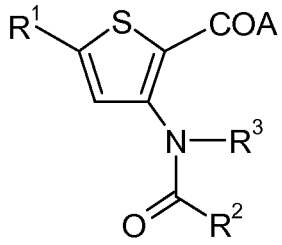
m represents 0 or 1;

or a pharmaceutically acceptable salt thereof.

21. A method as claimed in claim 20 which involves inhibiting HCV replication.

22. A method as claimed in claim 20 or 21 in which the chemical entity is administered in an oral dosage form.

23. A compound of Formula (I):



(I)

wherein:

A represents hydroxy;

R^1 represents $-R^xR^y$;

R^X represents phenyl (optionally substituted at one of the *meta*-positions to the thiophene by chloro, fluoro, methyl, ethyl, $-CF_3$, -OMe, $-NH_2$ or –OH); thienyl (optionally substituted by chloro, fluoro, methyl, ethyl, $-CF_3$ or –OMe) bonded through a ring carbon atom to the carbon atom of the thiophene; or pyridyl wherein the N atom is positioned at the *meta*-position to the thiophene (optionally substituted at the other *meta*-position to the thiophene by chloro, fluoro, methyl, ethyl, $-CF_3$, -OMe, $-NH_2$ or –OH);

R^Y represents optionally substituted 8-, 9- or 10-membered bicyclic heteroaryl, bonded such that when R^X is phenyl or pyridyl, the R^Y group is attached to R^x in the *para*-position to the thiophene;

R^2 represents $-C_{5-7}$cycloalkyl (optionally substituted by one or more substituents independently selected from $-C_{1-2}$alkyl (optionally substituted with one or more fluoro substituents), and –OH) or C_6cycloalkenyl;

R^3 represents linear or branched $–C_{2-6}$alkyl substituted by one or more fluoro substituents, or $–(CH_2)_mC_{3-6}$cycloalkyl substituted by one or more fluoro substituents;

m represents 0 or 1;

or a pharmaceutically acceptable salt thereof, for use in medical therapy.

24. A compound as claimed in claim 23 wherein the medical therapy is the treatment of viral infection.

25. A compound as claimed in claim 24 wherein the viral infection is HCV.

26. A pharmaceutical formulation comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof as defined in Claim 1 in conjunction with at least

one pharmaceutically acceptable diluent or carrier.

27. Use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1, in the manufacture of a medicament for the treatment and/or prophylaxis of viral infection.

28. Use of a compound as claimed in claim 27 wherein the viral infection is HCV.

29. A combination comprising a compound of Formula (I) or pharmaceutically acceptable salt thereof as defined in claim 1, together with at least one other therapeutically active agent.

30. A combination as claimed in claim 29, wherein the other therapeutically active agent is selected from Interferon, ribavirin and/or an additional anti-HCV agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/057984

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/381 A61K31/519 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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, 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 02/100851 A (SHIRE BIOCHEM INC.) 19 December 2002 (2002-12-19) cited in the application claims 1-118	1-30
P,Y	WO 2008/017688 A (SMITHKLINE BEECHAM CORP.) 14 February 2008 (2008-02-14) claims 1-20	1-30
Y	WO 2006/119646 A (VIROCHEM PHARMA INC.) 16 November 2006 (2006-11-16) claims 1-60	1-30
P,Y	WO 2008/059042 A (SMITHKLINE BEECHAM CORP.) 22 May 2008 (2008-05-22) claims 1-29	1-30

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[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
15 October 2008	30/10/2008

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/057984

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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P,Y	WO 2008/043791 A (SMITHKLINE BEECHAM INC.) 17 April 2008 (2008-04-17) claims 1-27	1-30

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Information on patent family members

International application No
PCT/EP2008/057984

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