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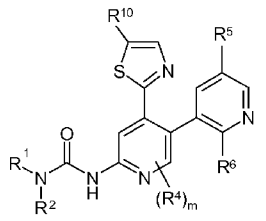
(54) Title: HETEROCYCLIC UREA DERIVATIVES USEFUL FOR TREATMENT OF BACTERIAL INFECTION



(I)

(57) Abstract: Compounds of formula (I) and their pharmaceutically acceptable salts are described. Processes for their preparation, pharmaceutical compositions containing them, their use as medicaments and their use in the treatment of bacterial infections are also described.

HETEROCYCLIC UREA DERIVATIVES USEFUL FOR TREATMENT OF BACTERIAL INFECTION

FIELD OF THE INVENTION

The present invention relates to compounds which demonstrate antibacterial activity, processes for their preparation, pharmaceutical compositions containing them as the active ingredient, to their use as medicaments and to their use in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans. In particular, this invention relates to compounds useful for the treatment of bacterial infections in warm-blooded animals such as humans, more particularly to the use of these compounds in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans.

BACKGROUND OF THE INVENTION

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded as effective against both Gram-positive and certain Gram-negative pathogens.

Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant *staphylococcus aureus* (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiple resistant *Enterococcus faecium*.

The preferred clinically effective antibiotic for treatment of last resort of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with various toxicities, including nephrotoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of

Gram-positive pathogens. There is also now increasing resistance appearing towards agents such as β-lactams, quinolones and macrolides used for the treatment of upper respiratory tract infections, also caused by certain Gram negative strains including *H.influenzae* and *M.catarrhalis*.

Consequently, in order to overcome the threat of widespread multi-drug resistant organisms, there is an on-going need to develop new antibiotics, particularly those with either a novel mechanism of action and/or containing new pharmacophoric groups.

Deoxyribonucleic acid (DNA) gyrase is a member of the type II family of topoisomerases that control the topological state of DNA in cells (Champoux, J. J.; 2001. Ann. Rev. Biochem. 70: 369-413). Type II topoisomerases use the free energy from adenosine triphosphate (ATP) hydrolysis to alter the topology of DNA by introducing transient double-stranded breaks in the DNA, catalyzing strand passage through the break and resealing the DNA. DNA gyrase is an essential and conserved enzyme in bacteria and is unique among topoisomerases in its ability to introduce negative supercoils into DNA. The enzyme consists of two subunits, encoded by *gyrA* and *gyrB*, forming an A_2B_2 tetrameric complex. The A subunit of gyrase (GyrA) is involved in DNA breakage and resealing and contains a conserved tyrosine residue that forms the transient covalent link to DNA during strand passage. The B subunit (GyrB) catalyzes the hydrolysis of ATP and interacts with the A subunit to translate the free energy from hydrolysis to the conformational change in the enzyme that enables strand-passage and DNA resealing.

Another conserved and essential type II topoisomerase in bacteria, called topoisomerase IV, is primarily responsible for separating the linked closed circular bacterial chromosomes produced in replication. This enzyme is closely related to DNA gyrase and has a similar tetrameric structure formed from subunits homologous to Gyr A and to Gyr B. The overall sequence identity between gyrase and topoisomerase IV in different bacterial species is high. Therefore, compounds that target bacterial type II topoisomerases have the potential to inhibit two targets in cells, DNA gyrase and topoisomerase IV; as is the case for existing quinolone antibacterials (Maxwell, A. 1997, Trends Microbiol. 5: 102-109).

DNA gyrase is a well-validated target of antibacterials, including the quinolones and the coumarins. The quinolones (*e.g.* ciprofloxacin) are broad-spectrum antibacterials that inhibit the DNA breakage and reunion activity of the enzyme and trap the GyrA subunit covalently complexed with DNA (Drlica, K., and X. Zhao, 1997, Microbiol. Molec. Biol. Rev. 61: 377-392). Members of this class of antibacterials also inhibit topoisomerase IV and

as a result, the primary target of these compounds varies among species. Although the quinolones are successful antibacterials, resistance generated primarily by mutations in the target (DNA gyrase and topoisomerase IV) is becoming an increasing problem in several organisms, including *S. aureus* and *Streptococcus pneumoniae* (Hooper, D. C., 2002, The Lancet Infectious Diseases 2: 530-538). In addition, quinolones, as a chemical class, suffer from toxic side effects, including arthropathy that prevents their use in children (Lipsky, B. A. and Baker, C. A., 1999, Clin. Infect. Dis. 28: 352-364). Furthermore, the potential for cardiotoxicity, as predicted by prolongation of the QT_c interval, has been cited as a toxicity concern for quinolones.

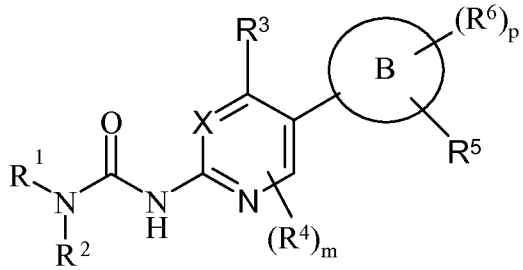
There are several known natural product inhibitors of DNA gyrase that compete with ATP for binding the GyrB subunit (Maxwell, A. and Lawson, D.M. 2003, Curr. Topics in Med. Chem. 3: 283-303). The coumarins are natural products isolated from *Streptomyces spp*., examples of which are novobiocin, chlorobiocin and coumermycin A1. Although these compounds are potent inhibitors of DNA gyrase, their therapeutic utility is limited due to toxicity in eukaryotes and poor penetration in Gram-negative bacteria (Maxwell, A. 1997, Trends Microbiol. 5: 102-109). Another natural product class of compounds that targets the GyrB subunit is the cyclothialidines, which are isolated from *Streptomyces filipensis* (Watanabe, J. et al 1994, J. *Antibiot*. 47: 32-36). Despite potent activity against DNA gyrase, cyclothialidine is a poor antibacterial agent showing activity only against some eubacterial species (Nakada, N, 1993, *Antimicrob. Agents Chemother*. 37: 2656-2661).

Synthetic inhibitors that target the B subunit of DNA gyrase and topoisomerase IV are known in the art. For example, coumarin-containing compounds are described in patent application number WO 99/35155, 5,6-bicyclic heteroaromatic compounds are described in patent application WO 02/060879, and pyrazole compounds are described in patent application WO 01/52845 (US patent US6,608,087). AstraZeneca has also published certain applications describing anti-bacterial compounds: WO2005/026149, WO2006/087544, WO2006/087548, WO2006/087543, WO2006/092599, WO2006/092608, WO2007/071965. WO2008/020227, WO2008/020222, WO2008/020229, WO2008/068470, WO2008/152418, WO2009/027732, and WO2009/027733.

SUMMARY OF THE INVENTION

We have discovered a new class of compounds which are useful for inhibiting DNA gyrase and / or topoisomerase IV. The compounds of the present invention are regarded as effective against both Gram-positive and certain Gram-negative pathogens.

Certain compounds described herein, *e.g.*, in the Example section, are compounds that fall within formula **(IA)**, and were previously described in PCT Application No. PCT/GB2009/050187. Such compounds depict the utility of certain substituents at particular positions in the compounds. The disclosure of these particular compounds, in addition to the general substituents illustrated in formula **(IA)**, are incorporated herein as support for the substituents of formula **(I)** provided in the present application. The compounds of formula **(IA)** fall within the following formula:



(IA)

or a pharmaceutically acceptable salt thereof, wherein:

X is N, CH or CR^4;

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more R^7;

R^2 is selected from hydrogen or C_{1-6}alkyl; wherein said C_{1-6}alkyl may be optionally substituted by one or more groups independently selected from halo, cyano, hydroxy, nitro and amino;

or **R^1 and R^2 together** with the nitrogen to which they are attached form a heterocyclyl; wherein said heterocyclyl may be optionally substituted on one or more carbon atoms with one or more R^8; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^3 is a C_{3-14}carbocyclyl or a heterocyclyl; wherein the carbocyclyl or heterocyclyl may be optionally substituted on one or more carbon atoms by one or more R^{10}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{11};

R^4, for each occurrence, is independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, and C_{1-6}alkylsulfanyl; wherein R^4, for each occurrence, is independently optionally substituted on one or more carbon atoms with one or more R^{12};

R^5 is hydrogen or a heterocyclyl; wherein the heterocyclyl may be optionally substituted on one or more carbon atoms with an =O, =S, or one or more R^{14}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15};

R^6, for each occurrence, is independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, mercapto, sulphamoyl, =O, =S, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$- wherein a is 0, 1 or 2, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, *N'*-hydroxycarbamimidoyl, carbamimidoyl, C_{3-14}carbocyclyl-L- and heterocyclyl-L-; wherein R^6, for each occurrence, is independently optionally substituted on one or more carbon atoms with one or more R^{16}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

m is 0 or 1;

p is 0, 1, 2, or 3;

Ring B is C_{3-14}carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{15}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally

substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups;

R^7, R^8, R^{10}, R^{12}, R^{14} and R^{16} are substituents on carbon which, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$- wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{3-6}carbocyclyl-L- or heterocyclyl-L-; wherein R^7, R^8, R^{10}, R^{12}, R^{14} and R^{16} independently of each other may be optionally substituted on one or more carbon by one or more R^{19}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{20}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups

R^9, R^{11}, R^{13}, R^{15}, and R^{20}, for each occurrence, are independently selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, imidazolylcarbonyl, amino, benzoyl and phenylsulphonyl; wherein R^9, R^{11}, R^{13}, R^{15}, and R^{20} independently of each other may be optionally substituted on carbon by one or more R^{23};

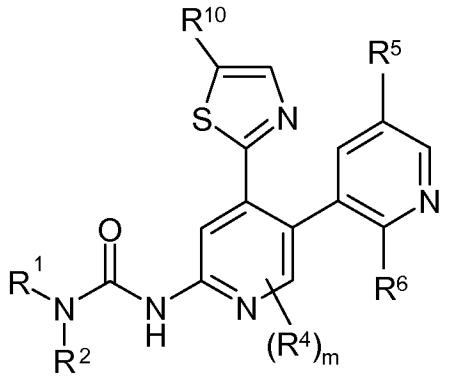
R^{19} and R^{23}, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, 2-methoxyethoxy, morpholinyl, piperazinyl, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, N-(2-morpholinoethyl)-amino, cyclohexylamino, cyclopentylamino, cyclohexyl, acetylamino, 2-methyoxyethylamino, tetrahydropyran-4-ylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, benzyloxy, 9*H*-fluoren-9-ylmethoxycarbonylamino, t-butoxycarbonylamino, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

L is a direct bond, -O-, -C(O)-, -C(O)NR^{25}-, -NR^{25}C(O)-, or –CH_2-; and

R^{25} is H or a C_{1-6}alkyl.

Accordingly, the present invention provides certain other novel compounds, which are advantageous for inhibiting DNA gyrase and / or topoisomerase IV, and are regarded as effective against both Gram-positive and certain Gram-negative pathogens.

In one embodiment, according to the present invention there is provided a compound of formula **(I)**:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more R^7;

R^2 is selected from hydrogen or C_{1-6}alkyl; wherein said C_{1-6}alkyl may be optionally substituted by one or more groups independently selected from halo, cyano, hydroxy, nitro and amino;

or **R^1 and R^2 together** with the nitrogen to which they are attached form a heterocyclyl; wherein said heterocyclyl may be optionally substituted on one or more carbon atoms with one or more R^8; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^4, for each occurrence, is independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, and C_{1-6}alkylsulfanyl; wherein R^4, for each occurrence, is independently optionally substituted on one or more carbon atoms with one or more R^{12};

R^5 is a nitrogen-containing heterocyclyl, wherein said nitrogen is substituted by a methyl dihydrogen phosphate group; wherein the heterocyclyl may be optionally substituted on one or more carbon atoms with an =O, =S, or one or more R^{14}; and wherein if said

heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups;

R^6, for each occurrence, is independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, mercapto, sulphamoyl, =O, =S, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$- wherein a is 0, 1 or 2, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, *N'*-hydroxycarbamimidoyl, carbamimidoyl, C_{3-14}carbocyclyl-L- and heterocyclyl-L-; wherein R^6, for each occurrence, is independently optionally substituted on one or more carbon atoms with one or more R^{16}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

m is 0 or 1;

R^7, R^8, R^{10}, R^{12}, R^{14} and R^{16} are substituents on carbon which, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$- wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{3-6}carbocyclyl-L- or heterocyclyl-L-; wherein R^7, R^8, R^{10}, R^{12}, R^{14} and R^{16} independently of each other may be optionally substituted on one or more carbon by one or more R^{19}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{20}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups

R^9, R^{13}, and R^{20}, for each occurrence, are independently selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, imidazolylcarbonyl, amino, benzoyl and phenylsulphonyl; wherein R^9, R^{13}, and R^{20} independently of each other may be optionally substituted on carbon by one or more R^{23};

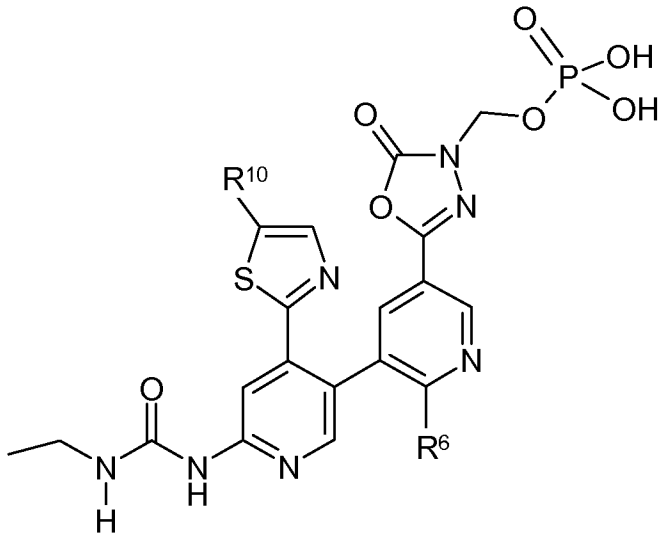
R^{19} and R^{23}, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto,

sulphamoyl, methyl, ethyl, methoxy, ethoxy, 2-methoxyethoxy, morpholinyl, piperazinyl, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, N-(2-morpholinoethyl)-amino, cyclohexylamino, cyclopentylamino, cyclohexyl, acetylamino, 2-methyoxyethylamino, tetrahydropyran-4-ylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, benzyloxy, 9*H*-fluoren-9-ylmethoxycarbonylamino, t-butoxycarbonylamino, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

L is a direct bond, -O-, -C(O)-, -C(O)NR^{25}-, -NR^{25}C(O)-, or –CH$_2$-; and

R^{25} is H or a C$_{1\text{-}6}$alkyl.

In a particular embodiment of formula (**I**), the invention provides a compound represented by the following formula:



or a pharmaceutically acceptable salt thereof, wherein:

R^6 is hydrogen or methoxy; and

R^{10} is trifluoromethyl or cyclopropyl. In specific embodiments, and as described herein for all other compounds of formula (**I**), the present invention provides pharmaceutical compositions, methods of use, and methods of preparation of compounds represented by this formula.

In another embodiment, the invention provides pharmaceutical compositions comprising a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

In another embodiment, the invention provides a method of inhibiting bacterial DNA gyrase and/or bacterial topoisomerase IV in a warm-blooded animal in need of such treatment, comprising administering to the animal an effective amount of a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides a method of producing an antibacterial effect in a warm-blooded animal in need of such treatment, comprising administering to the animal an effective amount of a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides a method of treating a bacterial infection in a warm-blooded animal in need thereof, comprising administering to the animal an effective amount of a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof. In a particular embodiment, the warm-blooded animal is a human. In one embodiment, the bacterial infection is selected from the group consisting of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides the use of a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the production of an antibacterial effect in a warm-blooded animal. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides the use of a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in inhibition of bacterial DNA gyrase and/or topoisomerase IV in a warm-blooded animal. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides the use of a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use the treatment of a bacterial infection in a warm-blooded animal. In one embodiment, the bacterial infection is selected from the group consisting of community-acquired

pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections, Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci. In a particular embodiment, the warm-blooded animal is a human.

In another embodiment, the invention provides a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in production of an anti-bacterial effect in a warm-blooded animal.

In another embodiment, the invention provides a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in inhibition of bacterial DNA gyrase and/or topoisomerase IV in a warm-blooded animal.

In another embodiment, the invention provides a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a bacterial infection in a warm-blooded animal.

In another embodiment, the invention provides a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections, Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis or Vancomycin-Resistant Enterococci.

DETAILED DESCRIPTION OF THE INVENTION

In this specification the term alkyl includes both straight chained and branched saturated hydrocarbon groups. For example, "C_{1-6}alkyl" refers to an alkyl that has from 1 to 6 carbon atom and includes, for example, methyl, ethyl, propyl, isopropyl and *t*-butyl. However references to individual alkyl groups such as propyl are specific for the straight chain version only unless otherwise indicated (e.g., isopropyl). An analogous convention applies to other generic terms.

As used herein, the term "C_{1-6}haloalkyl" refers to an alkyl group that has from 1 to 6 carbon atoms in which one or more of the carbon atoms are substituted with a halo group.

Representative haloalkyl groups include $-CF_3$, $-CHF_2$, $-CCl_3$, $-CH_2CH_2Br$, $-CH_2CH(CH_2CH_2Br)CH_3$, $-CHICH_3$, and the like.

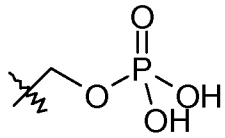
As used herein, the term "halo" refers to fluoro, chloro, bromo, and iodo.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-14 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and a ring sulphur atom may be optionally oxidised to form the S-oxide(s). In one embodiment of the invention a "heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, it may, unless otherwise specified, be carbon or nitrogen linked, a $-CH_2-$ group can optionally be replaced by a -C(O)-and a ring sulphur atom may be optionally oxidised to form the S-oxides. In a further aspect of the invention a "heterocyclyl" is an unsaturated, carbon-linked, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen. Examples and suitable values of the term "heterocyclyl" are morpholinyl, piperidyl, pyridinyl, pyranyl, pyrrolyl, pyrazolyl, isothiazolyl, indolyl, quinolinyl, thienyl, 1,3-benzodioxolyl, benzothiazolyl, thiadiazolyl, oxadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, tetrahydropyranyl, imidazolyl, 4,5-dihydro-oxazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, isoxazolyl, thiazolyl, 1*H*-tetrazolyl, 1*H*-triazolyl, *N*-methylpyrrolyl, 4-pyridone, quinolin-4(1*H*)-one, pyridin-2(1*H*)-one, imidazo[1,2-a]pyridinyl, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, quinoxalinyl, 5,6-dihydro[1,3]thiazolo[4,5-*d*]pyridazinyl, pyridine-*N*-oxide and quinoline-*N*-oxide. Suitable examples of "a nitrogen linked heterocyclyl" are morpholino, piperazin-1-yl, piperidin-1-yl and imidazol-1-yl. The term "heterocyclyl" encompasses the term "heteroaryl." A "heteroaryl" is an aromatic mono-, bi- or tricyclic heterocycle.

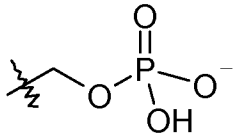
A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono-, bi- or tricyclic carbon ring that contains 3-14 atoms; wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. In one embodiment, "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Examples of carbocyclyls include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. The term carbocyclyl encompasses both cycloalkyl and aryl groups. The term cycloalkyl refers to a carbocyclyl which is completely saturated, for example cyclopropyl, cyclobutyl, cyclopentyl, and

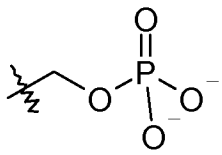
cyclohexyl. The term "aryl" refers to a carbocyclyl which is completely unsaturated and is aromatic. A C_{6-14}aryl is an aromatic, mono-, bi- or tricyclic carbon ring that contains 6-14 atoms, for example phenyl or naphthenyl.

A "methyl dihydrogen phosphate" is a group having the following structure:



A methyl dihydrogen phosphate group may lose one or two protons, for example when in solution depending on the pH of the solution, to form the following structures which are included in the definition of a methyl dihydrogen phosphate group:





As used herein, a "C_{1-6}alkoxy" refers to a group which has a C_{1-6}alkyl that is attached to another moiety via an oxygen atom. Examples of "C_{1-6}alkoxy" are methoxy, ethoxy and propoxy.

As used herein, a "*N*-(C_{1-6}alkyl)amino" refers to a group which has a C_{1-6}alkyl that is attached to another moiety via –NH-. Examples of "*N*-(C_{1-6}alkyl)amino" are methylamino and ethylamino.

As used herein, a "*N,N*-(C_{1-6}alkyl)$_2$amino" refers to a group which has two independently selected C_{1-6}alkyl that are attached to another moiety via a nitrogen atom. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" are *N,N*-dimethylamino, *N,N*-diethylamino and *N*-ethyl-*N*-methylamino.

As used herein, a "C_{1-6}alkanoyloxy" refers to a group which has the formula –OC(O)R, wherein R is a C_{1-6}alkyl. An example of "C_{1-6}alkanoyloxy" is acetoxy.

As used herein, a "C_{1-6}alkoxycarbonyl" refers to a group which has the formula -C(O)OR, wherein R is a C_{1-6}alkyl. Examples of "C_{1-6}alkoxycarbonyl" are methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl.

As used herein, a "C_{1-6}alkoxycarbonylamino" refers to a group which has the formula -NHC(O)OR, wherein R is a C_{1-6}alkyl. Examples of "C_{1-6}alkoxycarbonylamino" are methoxycarbonylamino, ethoxycarbonylamino, *n*- and *t*-butoxycarbonylamino.

As used herein, a "C_{1-6}alkanoylamino" refers to a group which has the formula -NHC(O)R, wherein R is a C_{1-6}alkyl. Examples of "C_{1-6}alkanoylamino" are formamido, acetamido and propionylamino.

As used herein, a "C_{1-6}alkanoyl" refers to a group which has the formula -C(O)R, wherein R is a C_{1-6}alkyl. Examples of "C_{1-6}alkanoyl" are propionyl and acetyl.

As used herein, a "*N*-(C_{1-6}alkyl)sulphamoyl" refers to a group which has the formula -$S(O)_2NHR$, wherein R is a C_{1-6}alkyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl.

As used herein, a "*N,N*-(C_{1-6}alkyl)$_2$sulphamoyl" refers to a group which has the formula -$S(O)_2NR_2$, wherein R, for each occurrence, is independently a C_{1-6}alkyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl.

As used herein, a "*N*-(C_{1-6}alkyl)carbamoyl" refers to a group which has the formula -C(O)NHR, wherein R is a C_{1-6}alkyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl.

As used herein, a "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" refers to a group which has the formula -$C(O)NR_2$, wherein R, for each occurrence, is independently a C_{1-6}alkyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl.

As used herein, a "C_{1-6}alkylsulphonylamino" refers to a group which has the formula -$S(O)_2NHR$, wherein R is a C_{1-6}alkyl. Examples of "C_{1-6}alkylsulphonylamino" are methylsulphonylamino, isopropylsulphonylamino and *t*-butylsulphonylamino.

As used herein, a "C_{1-6}alkylsulphonyl" refers to a group which has the formula -$S(O)_2R$, wherein R is a C_{1-6}alkyl. Examples of "C_{1-6}alkylsulphonyl" are methylsulphonyl, isopropylsulphonyl and *t*-butylsulphonyl.

Examples of "C_{1-6}alkyl$S(O)_a$ wherein a is 0, 1, or 2" are methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl.

An example of "C_{1-6}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" are methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxycarbonylamino" are methoxycarbonylamino, ethoxycarbonylamino, *n*- and *t*-butoxycarbonylamino. Examples of "C_{1-6}alkoxy" are methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkanoylamino" are formamido, acetamido and propionylamino. Examples of "C_{1-6}alkyl$S(O)_a$ wherein a is 0, 1, or 2" are methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" are propionyl and

acetyl. Examples of "*N*-(C_{1-6}alkyl)amino" are methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" are di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-4}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-4}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "*N*-(C_{1-6}alkoxy)carbamoyl" are methoxyaminocarbonyl and isopropoxyaminocarbonyl. Examples of "*N*-(C_{1-6}alkyl)-*N*-(C_{1-6}alkoxy)carbamoyl" are *N*-methyl-*N*-methoxyaminocarbonyl and *N*-methyl-*N*-ethoxyaminocarbonyl. Examples of "C_{3-6}cycloalkyl" are cyclopropyl, cyclobutyl, cyclopropyl and cyclohexyl. Examples of "C_{1-6}alkylsulphonylamino" are methylsulphonylamino, isopropylsulphonylamino and *t*-butylsulphonylamino. Examples of "C_{1-6}alkylsulphonylaminocarbonyl" are methylsulphonylaminocarbonyl, isopropylsulphonylaminocarbonyl and *t*-butylsulphonylaminocarbonyl. Examples of "C_{1-6}alkylsulphonyl" are methylsulphonyl, isopropylsulphonyl and *t*-butylsulphonyl.

A compound of formula **(I)** may form stable acid or basic salts, and in such cases administration of a compound as a salt may be appropriate, and pharmaceutically acceptable salts may be made by conventional methods such as those described below.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, tosylate, α-glycerophosphate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine, tris-(2-hydroxyethyl)amine, *N*-methyl d-glucamine and amino acids such as lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

Within the present invention it is to be understood that a compound of the formula **(I)**, or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits DNA gyrase and / or topoisomerase IV and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein. The same applies to compound names.

It will be appreciated by those skilled in the art that certain compounds of formula **(I)** contain an asymmetrically substituted carbon and/or sulphur atom, and accordingly may exist in, and be isolated in, optically-active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the inhibition of DNA gyrase and / or topoisomerase IV, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, by enzymatic resolution, by biotransformation, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the inhibition of DNA gyrase and / or topoisomerase IV by the standard tests described hereinafter.

By way of clarity, compounds of the invention included all isotopes of the atoms present in formula **(I)** and any of the examples or embodiments disclosed herein. For example, H (or hydrogen) represents any isotopic form of hydrogen including ^{1}H, ^{2}H (D), and ^{3}H (T); C represents any isotopic form of carbon including ^{12}C, ^{13}C, and ^{14}C; O represents any isotopic form of oxygen including ^{16}O, ^{17}O and ^{18}O; N represents any isotopic form of nitrogen including ^{13}N, ^{14}N and ^{15}N; P represents any isotopic form of phosphorous including ^{31}P and ^{32}P; S represents any isotopic form of sulfur including ^{32}S and ^{35}S; F represents any isotopic form of fluorine including ^{19}F and ^{18}F; Cl represents any isotopic form of chlorine including ^{35}Cl, ^{37}Cl and ^{36}Cl; and the like. In a preferred embodiment, compounds

represented by formula **(I)** comprises isomers of the atoms therein in their naturally occurring abundance. However, in certain instances, it is desirable to enrich one or more atom in a particular isotope which would normally be present in less abundance. For example, ^{1}H would normally be present in greater than 99.98% abundance; however, a compound of the invention can be enriched in ^{2}H or ^{3}H at one or more positions where H is present. In particular embodiments of the compounds of formula **(I)**, when, for example, hydrogen is enriched in the deuterium isotope, the symbol "D" may be used to represent the enrichment in deuterium. In one embodiment, when a compound of the invention is enriched in a radioactive isotope, for example ^{3}H and ^{14}C, they may be useful in drug and/or substrate tissue distribution assays. It is to be understood that the invention encompasses all such isotopic forms which inhibit DNA gyrase and / or topoisomerase IV.

It is also to be understood that certain compounds of the formula **(I)**, and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit DNA gyrase and / or topoisomerase IV.

Another embodiment of the invention provides a compound selected from the group consisting of any one or more of the compounds described in the Examples, or a salt, *e.g.*, a pharmaceutically acceptable salt, thereof, provided that at least one of the compounds is selected from Examples 289-292. Moreover, if such compound is represented as a salt, the present invention is intended to include free bases, free acids, or alternative salts of these particular compounds. Additional embodiments comprise compositions and medicaments containing the same (including the aforementioned free bases, free acids, or alternative salts), as well as processes for the preparation and use of such compounds, compositions and medicaments. Moreover, it should be noted that each of these compounds, and salts thereof, are also intended to be separate embodiments, and in this regard, each species listed in the Examples, and salt thereof, should be considered to be an individual embodiment.

Moreover, it should be understood that the present invention is intended to include any novel compound or pharmaceutical composition described herein, including any compound described as an intermediate.

There follow particular and suitable values for certain substituents and groups referred to in this specification. These values may be used where appropriate with any of the definitions and embodiments disclosed hereinbefore, or hereinafter. For the avoidance of doubt each stated species represents a particular and independent aspect of this invention.

In one embodiment the invention provides compounds represented by formula **(I)**, or pharmaceutically acceptable salts thereof, wherein R^1 is a C_{1-6}alkyl.

In another embodiment the invention provides compounds represented by formula **(I)**, or pharmaceutically acceptable salts thereof, wherein R^1 is ethyl.

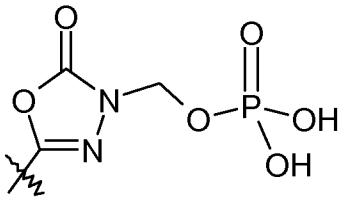
In yet another embodiment the invention provides compounds represented by formula **(I)**, or pharmaceutically acceptable salts thereof, wherein R^2 is hydrogen.

In an additional embodiment the invention provides compounds represented by formula **(I)**, or pharmaceutically acceptable salts thereof, wherein m is 0.

In another embodiment the invention provides compounds represented by formula **(I)**, or pharmaceutically acceptable salts thereof, wherein R^{10} is selected from the group consisting of methyl, cyclopropyl, phenyl, trifluoromethyl, and pyridinyl, *e.g.*, cyclopropyl and trifluoromethyl.

Another embodiment the invention provides compounds represented by formula **(I)**, or pharmaceutically acceptable salts thereof, wherein R^5 is a nitrogen-containing five membered aromatic heterocyclyl, wherein said nitrogen is substituted by a methyl dihydrogen phosphate group. In certain embodiments, the invention provides compounds represented by formula **(I)**, or pharmaceutically acceptable salts thereof, wherein R^{14} is selected from the group consisting of C_{1-4}alkyl or hydroxy. In particular embodiments, the invention provides compounds represented by formula **(I)**, or pharmaceutically acceptable salts thereof, wherein R^{15} is a C_{1-4}alkyl. In specific embodiments, the invention provides compounds represented by formula **(I)**, or pharmaceutically acceptable salts thereof, wherein R^5 is a nitrogen-containing heterocyclyl, wherein said nitrogen is substituted by a methyl dihydrogen phosphate group, and wherein the heterocyclyl is selected from the group consisting of 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1*H*-tetrazolyl, 1,2,4-oxadiazolyl, 1*H*-pyrazolyl, 3*H*-1,2,3,5-oxathiadiazolyl, 1*H*-imidazolyl, morpholinyl, 4,5-dihydro-oxazolyl, and 1*H*-1,2,4-triazolyl, wherein the 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1*H*-tetrazolyl, 1,2,4-oxadiazolyl, 1*H*-pyrazolyl, 3*H*-1,2,3,5-oxathiadiazolyl, 1*H*-imidazolyl, morpholinyl, 4,5-dihydro-oxazolyl, and 1*H*-1,2,4-triazolyl may be optionally substituted on one or more carbon atoms with one or more R^{14}; and wherein the =N- moiety of 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1*H*-tetrazolyl, 1,2,4-oxadiazolyl, 1*H*-pyrazolyl, 3*H*-1,2,3,5-oxathiadiazolyl, 1*H*-imidazolyl, 4,5-dihydro-oxazolyl, and 1*H*-1,2,4-triazolyl may be optionally substituted with one oxo group and the –S- moiety of 1,3,4-thiadiazolyl or the 3*H*-1,2,3,5-oxathiadiazolyl, may be optionally substituted by one or two oxo groups; and wherein the -NH- moiety of the 1*H*-tetrazolyl, 1*H*-pyrazolyl, 3*H*-1,2,3,5-oxathiadiazolyl, 1*H*-

imidazolyl, morpholinyl, or the 1*H*-1,2,4-triazolyl may be optionally substituted by a group selected from R^{15}. In one particular embodiment, the heterocyclyl is 5-oxo-4,5-dihydro-1,3,4-oxadiazo-2-yl, *e.g.*, wherein R^5 is



Another embodiment the invention provides compounds represented by formula **(I)**, or pharmaceutically acceptable salts thereof, wherein R^6 is hydrogen or or C_{1-6}alkoxy (*e.g.*, methoxy).

Particular compounds of the invention are the compounds of formula **(I)** selected from Examples 289-292, and pharmaceutically acceptable salts thereof, each of which provides a further independent aspect of the invention. In further aspects, the present invention also comprises any two or more compounds of the Examples, provided that at least one of the compounds is selected from Examples 289-292.

In another embodiment, the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable excipient or carrier and a compound represented by formula **(I)**, or a pharmaceutically acceptable salt thereof.

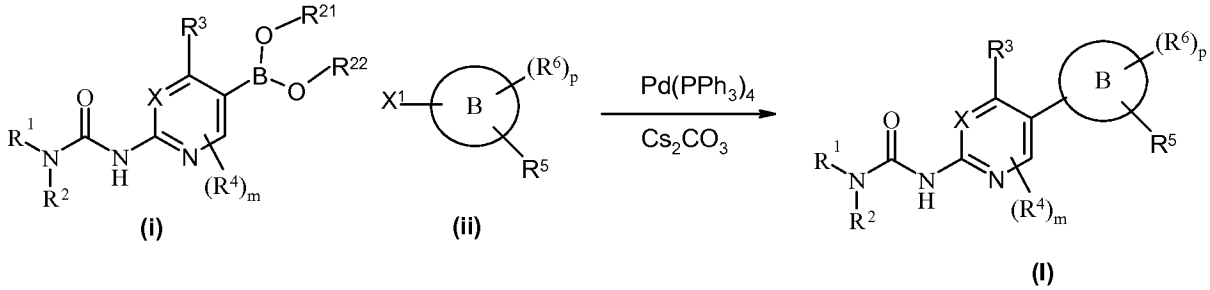
In a further aspect, the present invention provides a process for preparing a compound of formula **(I)**, or a pharmaceutically-acceptable salt thereof, which may be prepared using synthetic schemes identical to those used for the compounds described in PCT Application No. PCT/GB2009/050187, and generally described herein as formula **(IA)**. As such, Schemes I-XI are derived from PCT/GB2009/050187 (and were used to prepare Examples 1-288), wherein variable groups recited in the schemes below are as defined in formula **(IA)**, as described hereinabove, unless otherwise specified.

However, it would be understood by the skilled artisan, based on the present disclosure, and as exemplified in the instant Examples section (*e.g.*, Examples 289-292), such synthetic schemes are applicable to compounds of formula **(I)**, as described herein, *i.e.*, with the exception that the variable substituents (*e.g.*, p, m, ring B, X, R^3, R^5, and R^6) would be as defined in formula **(I)**, explicitly or by implication. For example, ring B would be a pyridinyl moiety, R^3 would be thiazolyl, X would be -CH-, and p is 1.

Accordingly, in general, the compounds of the invention can be prepared by a palladium catalyzed Suzuki coupling reaction of a boronic ester derivative **(i)** or **(iv)** and a

halo derivative **(ii)** or **(iii)**, as shown in Schemes I and II. Typically, the coupling reaction is heated and is carried out in the presence of a base such as Cs_2CO_3.

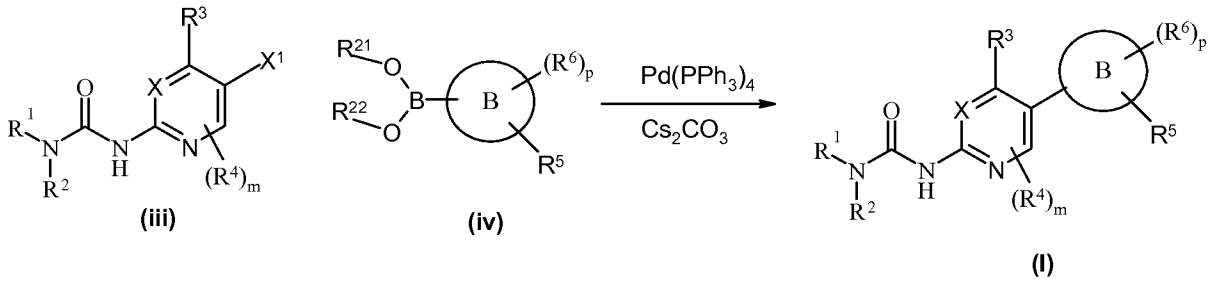
Scheme I



X^1 is a halo.

R^{21} and R^{22} are each independently an alkyl group or R^{21} and R^{22}, together with -O-B-O-, can form a cyclic boronic ester such as 4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl.

Scheme II



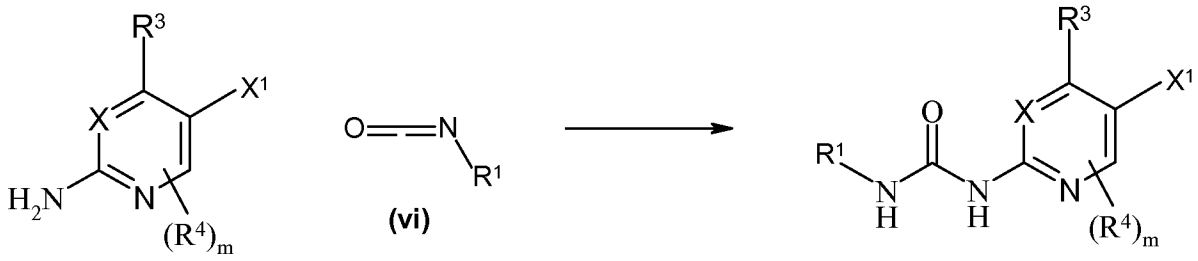
X^1 is a halo.

R^{21} and R^{22} are each independently an alkyl group or R^{21} and R^{22}, together with -O-B-O-, can form a cyclic boronic ester such as 4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl.

Boronic ester derivatives can be prepared by heating a halo derivative with a diboron compound such as 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) in the presence of 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride in an organic solvent.

The urea portion of the compounds of the invention can be prepared from an isocyanate derivative and an amine derivative either before or after the Suzuki coupling reaction (as shown in Schemes I and II). If the Suzuki coupling reaction is preformed before formation of the urea, the amine is protected with an amine protecting group. When forming the urea derivative, the isocyanate derivative **(vi)** is typically combined with the amine derivative **(v)** in an organic solvent and heated, as shown in Scheme III. The solvent can be aqueous, organic or a mixture of an aqueous miscible organic solvent and water.

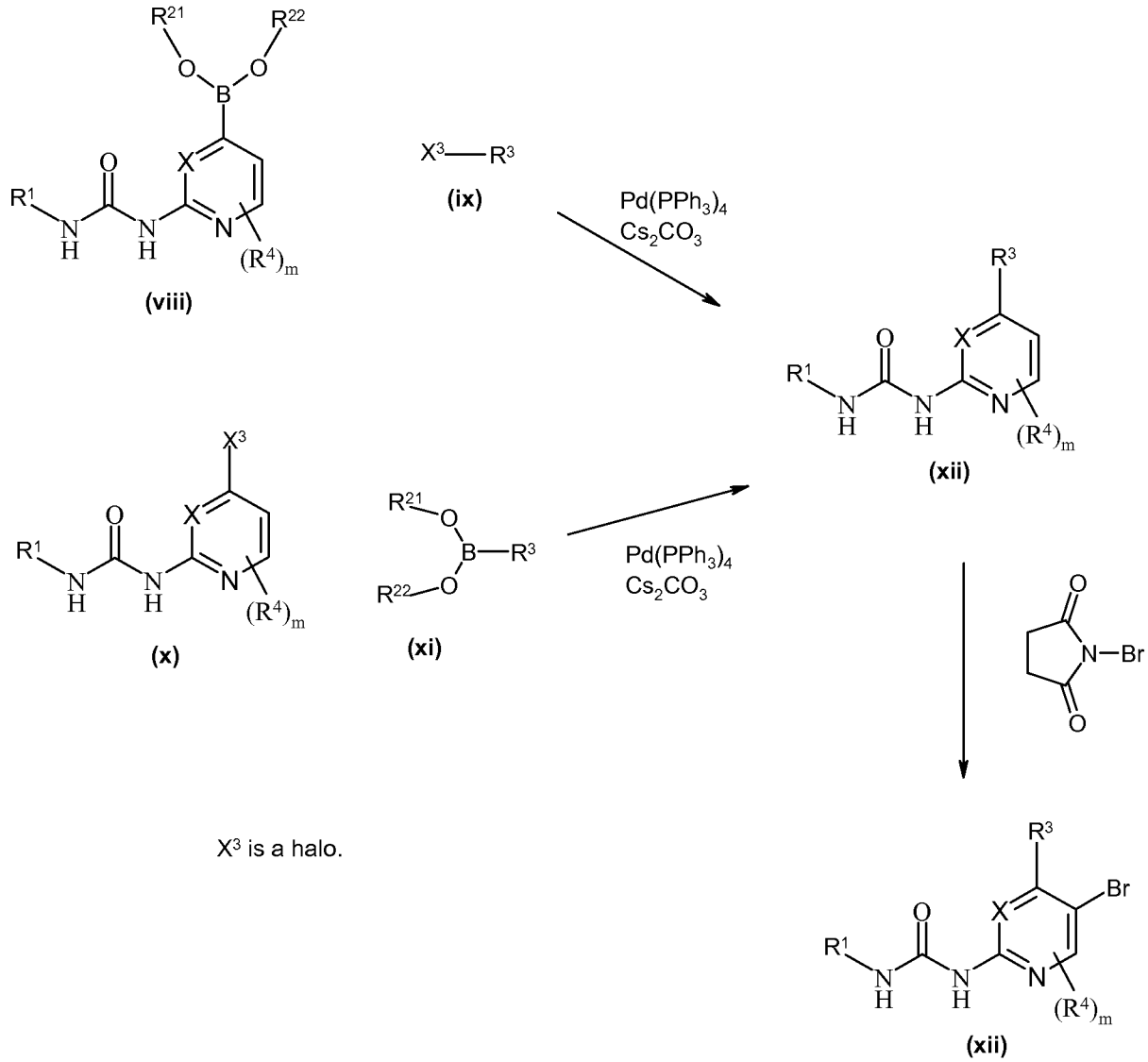
Scheme III



(v) **(vi)** **(vii)**

When R^3 is an aryl or a heteroaryl, *e.g.*, as in formula **(I)**, a Suzuki coupling reaction can be used to attach it to the pyridinyl or pyrimidinyl center ring as shown in Scheme IV. Although Scheme IV shows the coupling reaction of R^3 occurring before the coupling reaction to attach ring B, the reactions could be preformed in the alternative order. When the R^3 group is attached before the coupling reaction to attach ring B, the center ring can be brominated by heating it with 1-bromopyrrolidine-2,5-dione to form a substrate for the Suzuki coupling reaction shown in Scheme II.

Scheme IV

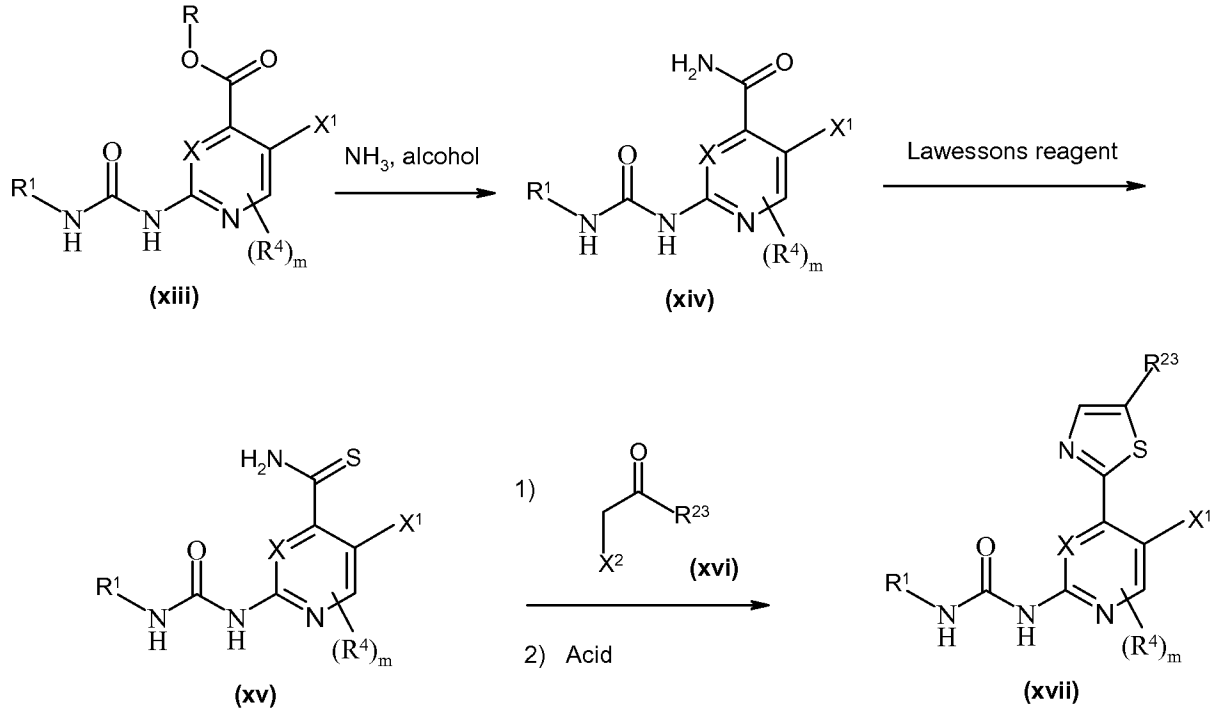


In general, when R^5 is a heteroaryl, it can be added by a Suzuki coupling reaction analogous to that shown for R^3. Likewise, R^5 can be coupled to ring B either before or after ring B is coupled to the pyridinyl or pyrimidinyl center ring.

Alternatively, when R^3 or R^5 is a heterocyclyl, it can be prepared from an ester derivative either before or after coupling of ring B to the pyridinyl or pyrimidinyl center ring. For example, when R^3 is a thiazolyl group, an ester derivative **(xiii)** can be converted to an amide **(xiv)** by treating it with a solution of ammonia in an alcohol. The amide derivative **(xiv)** can then be converted to a thioamide **(xv)** by treating the amide with Lawessons reagent. The thioamide **(xv)** is then heated with an α-halo-ketone or an α-halo-aldehyde **(xvi)** followed by treatment with an acid such as trifluoroacetic acid to form the thiazole **(xvii)** (see Scheme V). Although the thiazole ring is prepared before the Suzuki coupling reaction to attach ring

B in Scheme V, it could also be prepared after the coupling reaction from the ester derivative. When R^5 is a thiazolyl group, it can be prepared in an analogous manner either before or after coupling of ring B.

Scheme V



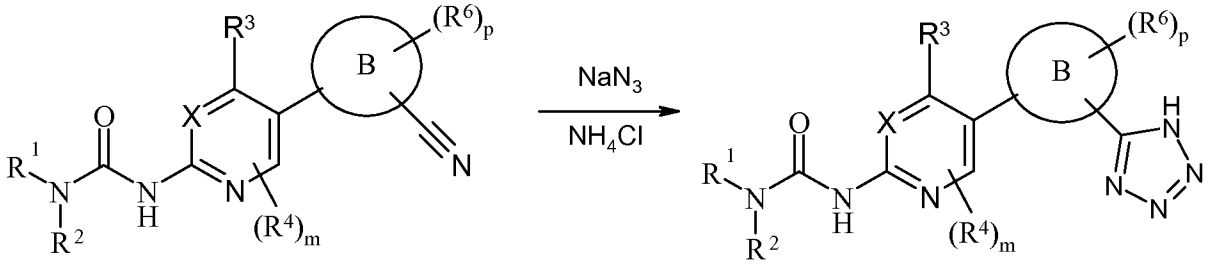
X^2 is a halo.

R is an alkyl.

R^{23} is hydrogen or an optionally substituted alkyl.

When R^3 or R^5 is tetrazolyl, it can be prepared by heating a cyano derivative with sodium azide and ammonium chloride in a solvent as shown in Scheme VI for an R^5 tetrazolyl group. When R^3 is a tetrazolyl group it can be prepared in an analogous manner to that shown in Scheme VI. In addition R^3 or R^5 tetrazolyl groups can be prepared by the reaction shown in Scheme VI either before or after coupling of ring B to the pyridinyl or pyrimidinyl center ring.

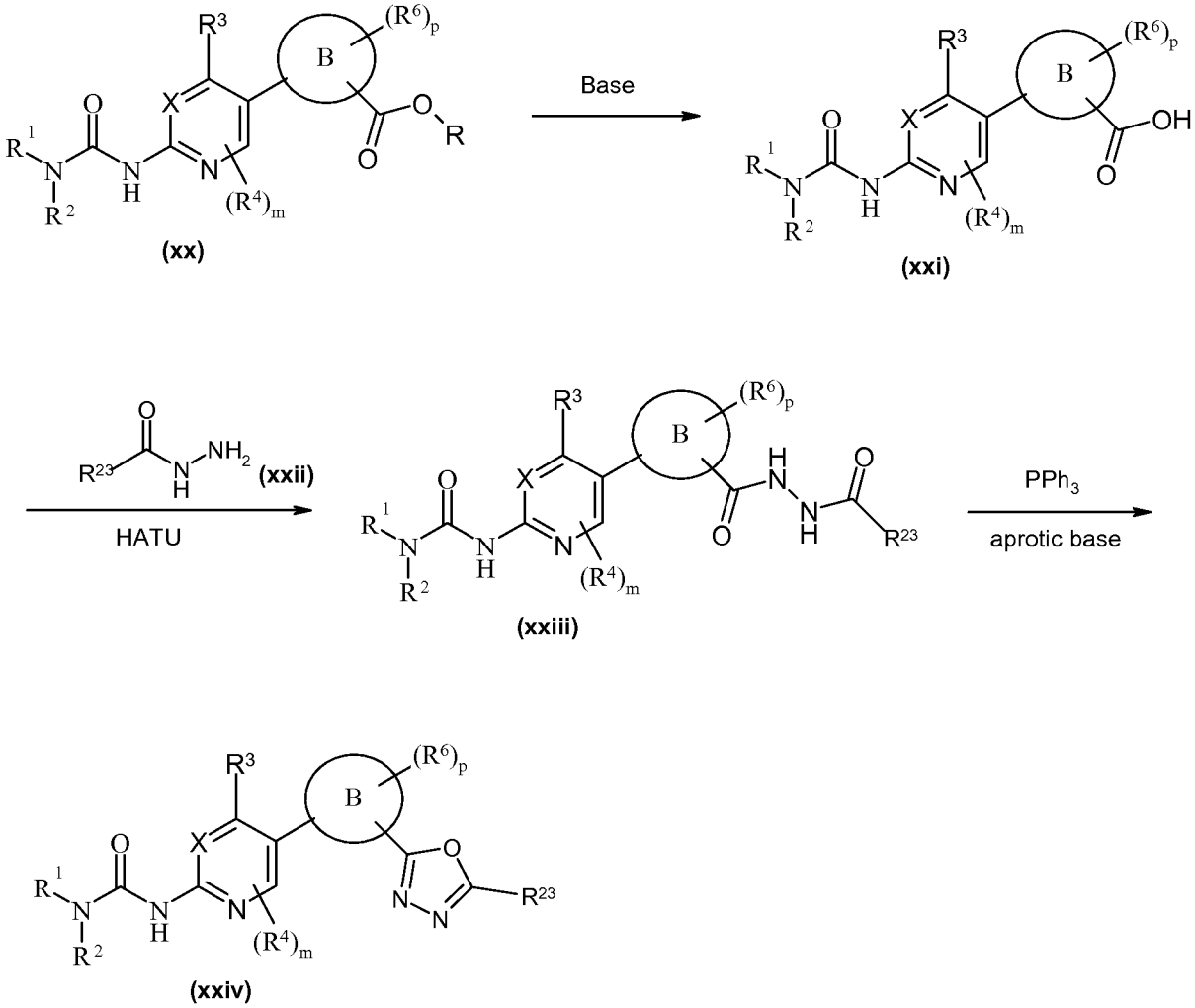
Scheme VI



(xviii) **(xix)**

When R^3 or R^5 is a 1,3,4-oxadiazolyl group, it can be prepared from an ester derivative **(xx)** by treating the ester with a base in to form a carboxylic acid **(xxi)**. The carboxylic acid **(xxi)** is then coupled to a hydrazide derivative **(xxii)** in the presence of the amide coupling reagent HATU to form a dihydrazide derivative **(xxiii)**. The dihydrazide **(xxiii)** is then treated with triphenyl phosphine in an aprotic organic solvent in the presence of an excess amount of an aprotic base to form a compound of the invention in which the R^5 group is 1,3,4-oxadiazolyl **(xxiv)** as shown in Scheme VII. When R^3 is a 1,3,4-oxadiazolyl group it can be prepared in an analogous manner to that shown in Scheme VII. In addition R^3 or R^5 1,3,4-oxadiazolyl groups can be prepared by the reaction shown in Scheme VII either before or after coupling of ring B to the pyridinyl or pyrimidinyl center ring.

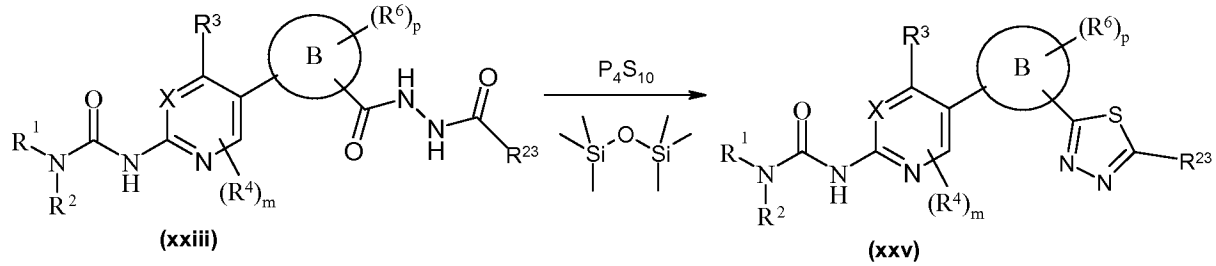
Scheme VII



(xx) (xxi) (xxii) (xxiii) (xxiv)

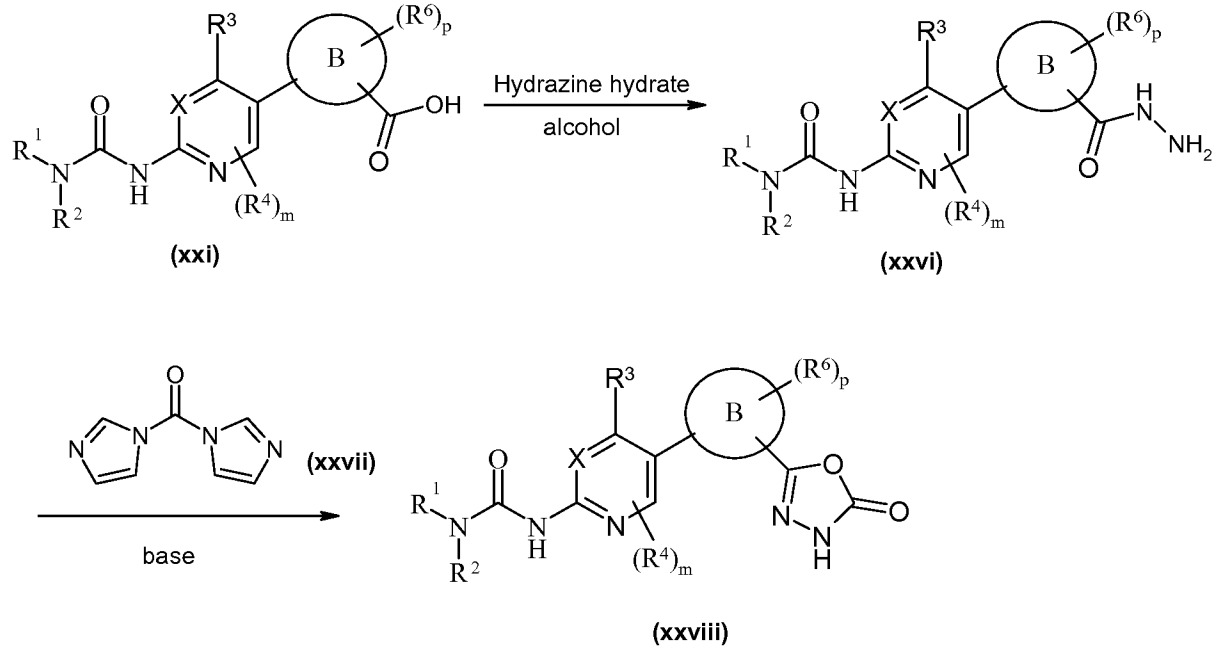
When R^3 or R^5 is a 1,3,4-thiadiazolyl group, it can be prepared from a dihydrazide derivative **(xxiii)** (see Scheme VII for preparation of dihydrazide derivatives). The dihydrazide derivative **(xxiii)** is heated with phosphorous pentasulfide and hexamethyldisiloxane in an organic solvent to form a compound of the invention having an R^5 1,3,4-thiadiazolyl group **(xxv)** as shown in Scheme VIII. When R^3 is a 1,3,4-thiadiazolyl group it can be prepared in an analogous manner to that shown in Scheme VIII. In addition R^3 or R^5 1,3,4-thiadiazolyl groups can be prepared by the reaction shown in Scheme VIII either before or after coupling of ring B to the pyridinyl or pyrimidinyl center ring.

Scheme VIII



When R^3 or R^5 is a 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl group, it can be prepared from a carboxylic acid **(xxi)** or an ester **(x)** (see Scheme VII for preparation of the carboxylic acid derivative). The carboxylic acid **(xxi)** or ester **(x)** derivative is heated with hydrazine hydrate in an alcohol to form a hydrazide derivative **(xxvi)**. The hydrazide derivative **(xxvi)** is then reacted with carbonyl diimidazole **(xxvii)** in the presence of an aprotic base in an aprotic solvent to form a compound of the invention which has an R^5 is 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl **(xxviii)** as shown in Scheme IX. When R^3 is a 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl group it can be prepared in an analogous manner to that shown in Scheme IX. In addition, R^3 or R^5 5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl groups can be prepared by the reaction shown in Scheme IX either before or after coupling of ring B to the pyridinyl or pyrimidinyl center ring.

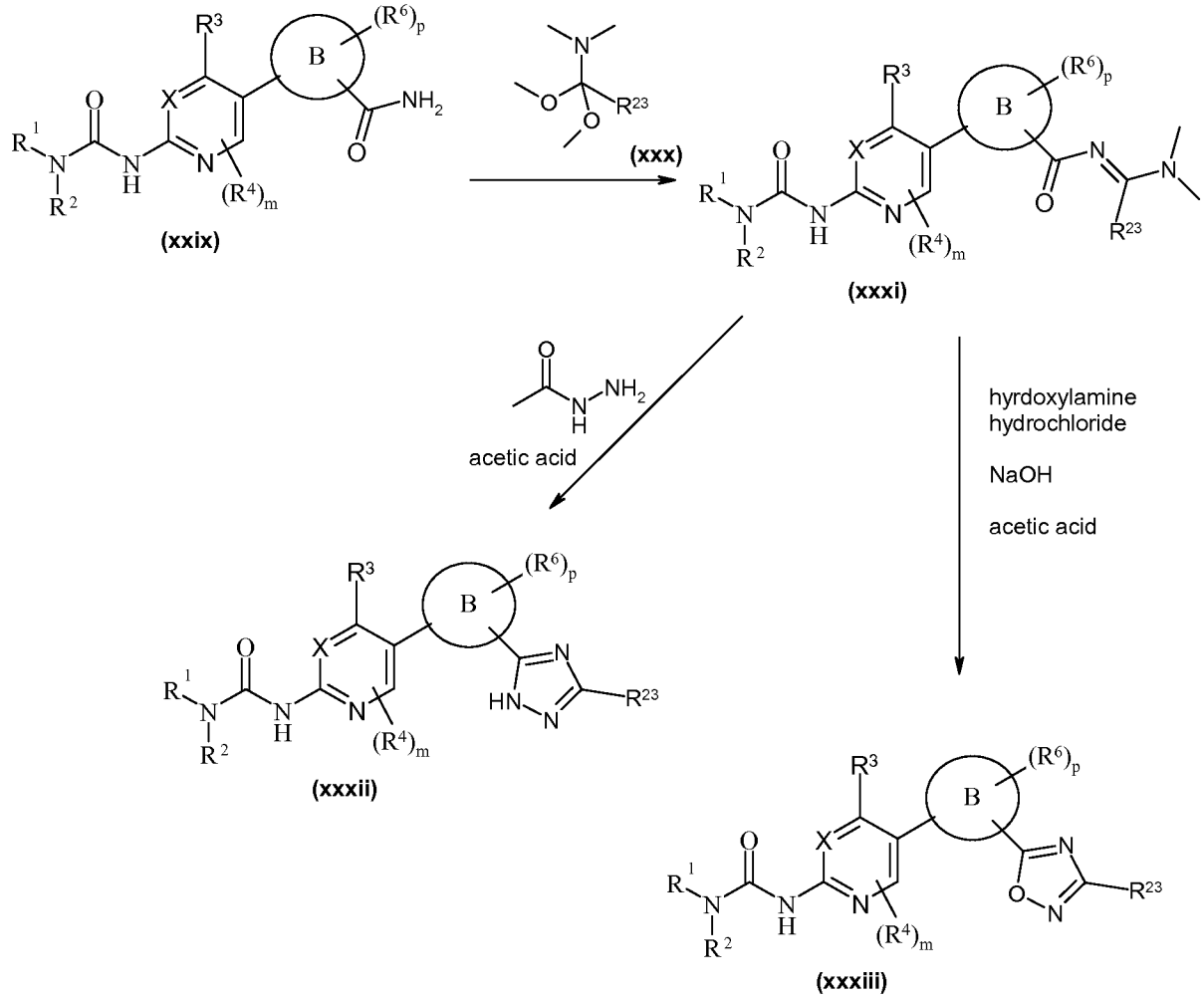
Scheme IX



When R^3 or R^5 is a 1,2,4-triazolyl group, it can be prepared from an amide derivative **(xxix)** by heating it in 1-(N,N-dimethylamino)-1,1-dimethoxy-ethane **(xxx)** to form **(xxxi)**. **(xxxi)** is then heated with acetohydrazide in acetic acid to form a compound of the invention that has an R^5 1,2,4-triazolyl group **(xxxii)** as shown in Scheme X. When R^3 is a 1,2,4-triazolyl group it can be prepared in an analogous manner to that shown in Scheme X. In addition, R^3 or R^5 1,2,4-triazolyl groups can be prepared by the reaction shown in Scheme X either before or after coupling of ring B to the pyridinyl or pyrimidinyl center ring.

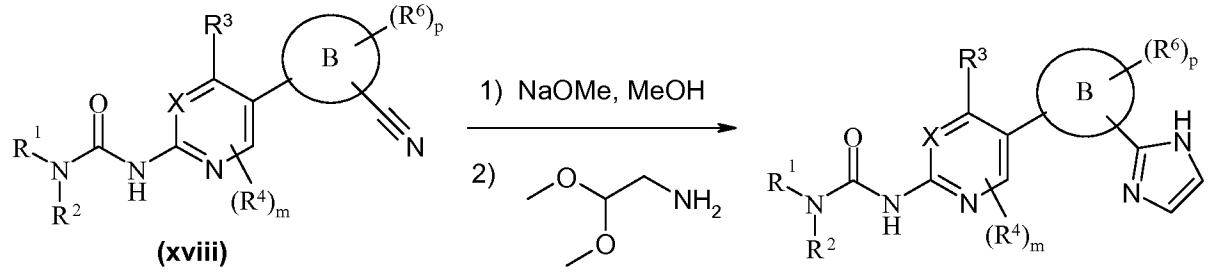
When R^3 or R^5 is a 1,2,4-oxadiazolyl group, it can be prepared from **(xxxi)** by heating **(xxxi)** with hydroxyl amine hydrochloride in a solution of sodium hydroxide in 70% acetic acid in dioxane to form a compound of the invention in which R^5 is a 1,2,4-oxadiazolyl group **(xxxiii)** as shown in Scheme X. When R^3 is a 1,2,4-oxadiazolyl group it can be prepared in an analogous manner to that shown in Scheme X. In addition, R^3 or R^5 1,2,4-oxadiazolyl groups can be prepared by the reaction shown in Scheme X either before or after coupling of ring B to the pyridinyl or pyrimidinyl center ring.

Scheme X



When R^3 or R^5 is an imidazolyl group, it can be prepared from a cyano derivative **(xvii)** by stirring the cyano derivative **(xvii)** at room temperature in a solution of sodium methoxide in methanol for several hours. 1,1-Dimethoxy-2-aminoethane **(xxxiv)** is then added to the solution and it is heated to give a compound of the invention in which R5 is an imidazolyl group **(xxxv)** as shown in Scheme XI. When R^3 is an imidazolyl group it can be prepared in an analogous manner to that shown in Scheme XI. In addition, R^3 or R^5 imidazolyl groups can be prepared by the reaction shown in Scheme XI either before or after coupling of ring B to the pyridinyl or pyrimidinyl center ring.

Scheme XI



The formation of a pharmaceutically-acceptable salt is within the skill of an ordinary organic chemist using standard techniques.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. The reagents used to introduce such ring substituents are either commercially available or are made by processes known in the art.

Introduction of substituents into a ring may convert one compound of the formula **(I)** into another compound of the formula **(I)**. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents, oxidation of substituents, esterification of substituents, amidation of substituents, formation of heteroaryl rings. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of alkoxides, diazotization reactions followed by introduction of thiol group, alcohol group, halogen group. Examples of modifications include; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples herein, to obtain necessary starting materials, and products. If not commercially available, the necessary starting materials for the procedures such as those described above may be made by procedures which are selected from standard organic chemical techniques,

techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the above described procedure or the procedures described in the examples. It is noted that many of the starting materials for synthetic methods as described above are commercially available and/or widely reported in the scientific literature, or could be made from commercially available compounds using adaptations of processes reported in the scientific literature. The reader is further referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in compounds. The instances where protection is necessary or desirable are known to those skilled in the art, as are suitable methods for such protection. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991).

Examples of a suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, a silyl group such as trimethylsilyl or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively a silyl group such as trimethylsilyl may be removed, for example, by fluoride or by aqueous acid; or an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon.

A suitable protecting group for an amino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid

as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine or 2-hydroxyethylamine, or with hydrazine.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or for example, an allyl group which may be removed, for example, by use of a palladium catalyst such as palladium acetate.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art, or they may be removed during a later reaction step or work-up.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

Enzyme Potency Testing Methods

Compounds were tested for inhibition of GyrB ATPase activity using an ammonium molybdate/malachite green-based phosphate detection assay (Lanzetta, P. A., L. J. Alvarez, P. S. Reinach, and O. A. Candia, 1979, 100: 95-97). Assays were performed in multiwell plates in 100µl reactions containing: 50 mM TRIS buffer pH 7.5, 75 mM ammonium acetate,

5.5 mM magnesium chloride, 0.5 mM ethylenediaminetetraacetic acid, 5% glycerol, 1 mM 1,4-Dithio-DL-threitol, 200 nM bovine serum albumin, 16 µg/ml sheared salmon sperm DNA, 4 nM *E. coli* GyrA, 4 nM *E. coli* GyrB, 250 µM ATP, and compound in dimethylsulfoxide. Reactions were quenched with 150 µl of ammonium molybdate/malachite green detection reagent containing 1.2 mM malachite green hydrochloride, 8.5 mM ammonium molybdate tetrahydrate, and 1 M hydrochloric acid. Plates were read in an absorbance plate reader at 625 nm and percent inhibition values were calculated using dimethylsulfoxide (2%)-containing reactions as 0% inhibition and novobiocin-containing (2 µM) reactions as 100% inhibition controls. Compound potency was based on IC_{50} measurements determined from reactions performed in the presence of 10 different compound concentrations.

Compounds were tested for inhibition of topoisomerase IV ATPase activity as described above for GyrB except the 100µl reactions contained the following: 20 mM TRIS buffer pH 8, 50 mM ammonium acetate, 8 mM magnesium chloride, 5% glycerol, 5 mM 1,4-Dithio-DL-threitol, 0.005% Brij-35, 5 µg/ml sheared salmon sperm DNA, 10 nM *E. coli* ParC, 10 nM *E. coli* ParE, 160 µM ATP, and compound in dimethylsulfoxide. Compound potency was based on IC_{50} measurements determined from reactions performed in the presence of 10 different compound concentrations.

Compounds of the invention generally have IC_{50} values of <200µg/ml in one or both assays described herein above.

Compounds were tested for inhibition of GyrB ATPase activity using an ammonium molybdate/malachite green-based phosphate detection assay (Lanzetta, P. A., L. J. Alvarez, P. S. Reinach, and O. A. Candia, 1979, 100: 95-97). Assays were performed in multiwell plates in 100µl reactions containing: 50 mM Hepes buffer pH 7.5, 75 mM ammonium acetate, 8.0 mM magnesium chloride, 1.0 mM ethylenediaminetetraacetic acid, 5% glycerol, 2 mM 1,4-Dithio-DL-threitol, 400 nM bovine serum albumin, 5 µg/ml sheared salmon sperm DNA, 1.25 nM *E. coli* GyrA, 1.25 nM *S. aureus* GyrB, 500 µM ATP, and compound in dimethylsulfoxide. Reactions were quenched with 150 µl of ammonium molybdate/malachite green detection reagent containing 1.2 mM malachite green hydrochloride, 8.5 mM ammonium molybdate tetrahydrate, and 1 M hydrochloric acid. Plates were read in an absorbance plate reader at 650 nm and percent inhibition values were calculated using dimethylsulfoxide (2%)-containing reactions as 0% inhibition and novobiocin-containing (2 µM) reactions as 100% inhibition controls. Compound potency was based on IC_{50}

measurements determined from reactions performed in the presence of 10 different compound concentrations.

Table 1 shows *S. aureus* (SAU) GyrB ATPase IC_{50} values for representative compounds described herein.

Table 1

Example Number	IC_{50} (μM)
14	0.010
17	0.010
25	0.003
32	0.062

Table 2 shows *S. aureus* (SAU) GyrB ATPase percent inhibition for compounds of the invention at a compound concentration of 1.0 μM unless otherwise noted. Where the assay was carried out more than one time for a particular compound of the invention, the percent inhibition shown in Table 2 is an average value.

Table 2

Example Number	% Inhibition (μM)	Example Number	% Inhibition (μM)
1	99	147	95
2	88	148	97
3	88	149	94
4	99	150	96
5	112	151	97
6	106	152	95
7	90	153	100
8	95	154	105
9	106	155	96
10	95	156	95
11	107	157	96
12	108	158	97
13	103	159	97

14	86	160	98
15	93	161	97
16	115	162	98
17	102.2	163	96
18	113.0	164	96
19	109.9	165	98
20	110.6	166	72
21	No data	167	96
22	114	168	69
23	110	169	96
24	109	170	No data
25	100	171	106
26	105	172	No data
27	109	173	95
28	70	174	No data
29	114	175	93
30	105	176	98
31	113	177	86
32	106	178	97
33	117	179	101
34	93	180	96
35	103	181	97
36	107	182	99
37	112	183	96
38	108	184	No data
39	102	185	99
40	117	186	110
41	109	187	100
42	106	188	97
43	No data	189	103
44	96	190	100
45	103	191	99

46	-1	192	101
47	72	193	89
48	95	194	101
49	99	195	98
50	105	196	118
51	98	197	106
52	108	198	104
53	109	199	94
54	97	200	93
55	96	201	107
56	96	202	43
57	96	203	104
58	97	204	101
59	98	205	100
60	92	206	99
61	95	207	101
62	86	208	100
63	96	209	95
64	98	210	65
65	94	211	109
66	93	212	97
67	93	213	95
68	96	214	109
69	91	215	96
70	96	216	96
71	93	217	95
72	95	218	99
73	97	219	97
74	94	220	91
75	99	221	99
76	100	222	97
77	97	223	95

78	99	224	94
79	95	225	117
80	96	226	109
81	94	227	100
82	86	228	93
83	94	229	99
84	No data	230	91
85	93	231	96
86	97	232	99
87	99	233	100
88	94	234	105
89	87	235	101
90	116	236	109
91	No data	237	110
92	104	238	96
93	No data	239	94
94	98	240	95
95	99	241	97
96	100	242	118
97	99	243	122
98	100	244	96
99	97	245	No data
100	98	246	No data
101	97	247	100
102	92	248	104
103	86	249	97
104	98	250	101
105	101	251	99
106	102	252	99
107	97	253	No data
108	103	254	97
109	98	255	98

110	95	256	103
111	106	257	102
112	95	258	96
113	45	259	95
114	97	260	96
115	96	261	96
116	90	262	97
117	105	263	100
118	118	264	98
119	96	265	101
120	118	266	98
121	No data	267	98
122	102	268	98
123	78	269	No data
124	No data	270	97
125	103	271	100
126	102	272	90
127	100	273	98
128	92	274	99
129	102	275	98
130	103	276	98
131	93	277	No data
132	92	278	68
133	104	279	No data
134	120	280	95
135	101	281	94
136	102	282	96
137	101	283	94
138	104	284	No data
139	103	285	No data
140	97	286	No data
141	97	287	80

142	96	288	91
143	98	289	105
144	90	290	107
145	100	291	94
146	97	292	96

Bacterial Susceptibility Testing Methods

Compounds were tested for antimicrobial activity by susceptibility testing in liquid media. Compounds were dissolved in dimethylsulfoxide and tested in 10 doubling dilutions in the susceptibility assays. The organisms used in the assay were grown overnight on suitable agar media and then suspended in a liquid medium appropriate for the growth of the organism. The suspension was a 0.5 McFarland and a further 1 in 10 dilution was made into the same liquid medium to prepare the final organism suspension in 100 μL. Plates were incubated under appropriate conditions at 37 °C for 24 hrs prior to reading. The Minimum Inhibitory Concentration was determined as the lowest drug concentration able to reduce growth by 80% or more.

Example 14 had an MIC of 0.39 uM against *Streptococcus pneumoniae*.

According to a further feature of the invention there is provided a compound of the formula **(I)**, or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

In one embodiment, the invention provides a method of treating a bacterial infection in an animal, such as a human, comprising administering to the animal or human an effective amount of a compound of any one of formulas **(I)**, or a pharmaceutically acceptable salt thereof.

We have found that compounds of the present invention inhibit bacterial DNA gyrase and / or topoisomerase IV and are therefore of interest for their antibacterial effects. In one aspect of the invention the compounds of the invention inhibit bacterial DNA gyrase and are therefore of interest for their antibacterial effects. In one aspect of the invention, the compounds of the invention inhibit topoisomerase IV and are therefore of interest for their antibacterial effects. In one aspect of the invention, the compounds of the invention inhibit both DNA gyrase and topoisomerase IV and are therefore of interest for their antibacterial

effects. Thus, the compounds of the invention are useful in treating or preventing bacterial infections.

In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter baumanii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter haemolyticus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter junii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter johnsonii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Acinetobacter lwoffi*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Bacteroides bivius*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Bacteroides fragilis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Burkholderia cepacia*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Campylobacter jejuni*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Chlamydia pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Chlamydia urealyticus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Chlamydophila pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Clostridium difficile*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Enterobacter aerogenes*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Enterobacter cloacae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Enterococcus faecalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Enterococcus faecium*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Escherichia coli*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Gardnerella vaginalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Haemophilus parainfluenzae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Haemophilus influenzae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Helicobacter pylori*. In one aspect of the invention an "infection" or "bacterial infection" refers to an

infection caused by *Klebsiella pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Legionella pneumophila*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Methicillin-resistant *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Methicillin-susceptible *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Moraxella catarrhalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Morganella morganii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Mycoplasma pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Neisseria gonorrhoeae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Penicillin-resistant *Streptococcus pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Penicillin-susceptible *Streptococcus pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus magnus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus micros*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus anaerobius*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus asaccharolyticus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus prevotii*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus tetradius*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Peptostreptococcus vaginalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Proteus mirabilis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Pseudomonas aeruginosa*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Quinolone-Resistant *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Quinolone-Resistant *Staphylococcus epidermis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Salmonella typhi*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Salmonella paratyphi*. In

one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Salmonella enteritidis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Salmonella typhimurium*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Serratia marcescens*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Staphylococcus epidermidis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Staphylococcus saprophyticus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Streptoccocus agalactiae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Streptococcus pneumoniae*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Streptococcus pyogenes*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Stenotrophomonas maltophilia*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by *Ureaplasma urealyticum*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Vancomycin-Resistant *Enterococcus faecium*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Vancomycin-Resistant *Enterococcus faecalis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Vancomycin-Resistant *Staphylococcus aureus*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Vancomycin-Resistant *Staphylococcus epidermis*. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Mycobacterium tuberculosis. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Clostridium perfringens. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Klebsiella oxytoca. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Neisseria miningitidis. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Fusobacterium spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Peptococcus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Proteus vulgaris. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Coagulase-negative Staphylococcus

(including Staphylococcus lugdunensis, Staphylococcus capitis, Staphylococcus hominis, and Staphylococcus saprophyticus).

In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Acinetobacter spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Bacteroides spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Burkholderia spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Campylobacter spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Chlamydia spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Chlamydophila spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Clostridium spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Enterobacter spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Enterococcus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Escherichia spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Gardnerella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Haemophilus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Helicobacter spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Klebsiella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Legionella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Moraxella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Morganella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Mycoplasma spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Neisseria spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Peptostreptococcus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Proteus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Pseudomonas spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Salmonella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Serratia spp.

In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Staphylococcus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Streptoccocus spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Stenotrophomonas spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Ureaplasma spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by aerobes. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by obligate anaerobes. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by facultative anaerobes. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by gram-positive bacteria. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by gram-negative bacteria. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by gram-variable bacteria. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by atypical respiratory pathogens. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Enterics. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Shigella spp. In one aspect of the invention an "infection" or "bacterial infection" refers to an infection caused by Citrobacter.

In one aspect of the invention "infection" or "bacterial infection" refers to a gynecological infection. In one aspect of the invention "infection" or "bacterial infection" refers to a respiratory tract infection (RTI). In one aspect of the invention "infection" or "bacterial infection" refers to a sexually transmitted disease. In one aspect of the invention "infection" or "bacterial infection" refers to a urinary tract infection. In one aspect of the invention "infection" or "bacterial infection" refers to acute exacerbation of chronic bronchitis (ACEB). In one aspect of the invention "infection" or "bacterial infection" refers to acute otitis media. In one aspect of the invention "infection" or "bacterial infection" refers to acute sinusitis. In one aspect of the invention "infection" or "bacterial infection" refers to an infection caused by drug resistant bacteria. In one aspect of the invention "infection" or "bacterial infection" refers to catheter-related sepsis. In one aspect of the invention "infection" or "bacterial infection" refers to chancroid. In one aspect of the invention "infection" or "bacterial infection" refers to chlamydia. In one aspect of the invention "infection" or "bacterial infection" refers to community-acquired pneumonia (CAP). In one

aspect of the invention "infection" or "bacterial infection" refers to complicated skin and skin structure infection. In one aspect of the invention "infection" or "bacterial infection" refers to uncomplicated skin and skin structure infection. In one aspect of the invention "infection" or "bacterial infection" refers to endocarditis. In one aspect of the invention "infection" or "bacterial infection" refers to febrile neutropenia. In one aspect of the invention "infection" or "bacterial infection" refers to gonococcal cervicitis. In one aspect of the invention "infection" or "bacterial infection" refers to gonococcal urethritis. In one aspect of the invention "infection" or "bacterial infection" refers to hospital-acquired pneumonia (HAP). In one aspect of the invention "infection" or "bacterial infection" refers to osteomyelitis. In one aspect of the invention "infection" or "bacterial infection" refers to sepsis. In one aspect of the invention "infection" or "bacterial infection" refers to syphilis. In one aspect of the invention "infection" or "bacterial infection" refers to ventilator-associated pneumonia. In one aspect of the invention "infection" or "bacterial infection" refers to intraabdominal infections. In one aspect of the invention "infection" or "bacterial infection" refers to gonorrhoeae. In one aspect of the invention "infection" or "bacterial infection" refers to meningitis. In one aspect of the invention "infection" or "bacterial infection" refers to tetanus. In one aspect of the invention "infection" or "bacterial infection" refers to tuberculosis.

In one embodiment, it is expected that the compounds of the present invention will be useful in treating bacterial infections including, but not limited to community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt thereof.

According to a further feature of the invention there is provided a method for inhibition of bacterial DNA gyrase and / or topoisomerase IV in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an

effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating a bacterial infection in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating a bacterial infection selected from community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococciin a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof as defined hereinbefore.

A further feature of the present invention is a compound of formula **(I)**, and pharmaceutically acceptable salts thereof for use as a medicament. Suitably the medicament is an antibacterial agent.

According to a further 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 use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

According to a further 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 use in inhibition of bacterial DNA gyrase and / or topoisomerase IV in a warm-blooded animal such as a human being.

Thus according to a further 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 use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

Thus according to a further 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 use in the treatment of a bacterial infection selected from community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in inhibition of bacterial DNA gyrase and / or topoisomerase IV in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, for use in the treatment of a bacterial infection selected from community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci in a warm-blooded animal such as a human being.

In order to use a compound of the formula **(I)**, or a pharmaceutically-acceptable salt thereof, (hereinafter in this section relating to pharmaceutical composition "a compound of this invention") for the therapeutic (including prophylactic) treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula **(I)**, or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(I)**, as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in producing an anti-bacterial effect in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(I)**, as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in inhibition of bacterial DNA gyrase and / or topoisomerase IV in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(I)**, as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in the treatment of a bacterial infection in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula **(I)**, as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in the treatment of a bacterial infection selected from community-acquired pneumoniae, hospital-acquired pneumoniae, skin & skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci in an warm-blooded animal, such as a human being.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile

fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The compounds of the invention described herein may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the beneficial effect of the combination. Suitable classes and substances may be selected from one or more of the following:

i) other antibacterial agents for example macrolides e.g. erythromycin, azithromycin or clarithromycin; quinolones e.g. ciprofloxacin or levofloxacin; ß-lactams e.g. penicillins e.g. amoxicillin or piperacillin; cephalosporins e.g. ceftriaxone or ceftazidime; carbapenems, e.g. meropenem or imipenem etc; aminoglycosides e.g. gentamicin or tobramycin; or oxazolidinones; and/or

ii) anti-infective agents for example, an antifungal triazole e.g. or amphotericin; and/or

iii) biological protein therapeutics for example antibodies, cytokines, bactericidal/permeability-increasing protein (BPI) products; and/or

iv) efflux pump inhibitors.

Therefore, in a further aspect of the invention there is provided a compound of the formula **(I)**, or a pharmaceutically acceptable salt thereof, and a chemotherapeutic agent selected from:

i) one or more additional antibacterial agents; and/or

ii) one or more anti-infective agents; and/or

iii) biological protein therapeutics for example antibodies, cytokines, bactericidal/permeability-increasing protein (BPI) products; and/or

iv) one or more efflux pump inhibitors.

In another embodiment, the invention relates to a method of treating a bacterial infection in an animal, such as a human, comprising administering to the animal an effective amount of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof, and a chemotherapeutic agent selected from:

i) one or more additional antibacterial agents; and/or

ii) one or more anti-infective agents; and/or

iii) biological protein therapeutics for example antibodies, cytokines, bactericidal/permeability-increasing protein (BPI) products; and/or

iv) one or more efflux pump inhibitors.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration, the severity of the illness being treated, and whether or not an additional chemotherapeutic agent is administered in combination with a compound of the invention. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, the severity of the illness being treated, and whether or not an additional chemotherapeutic agent is administered in combination with a compound of the invention. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

As noted above, one embodiment of the present invention is directed to treating or preventing diseases caused by bacterial infections, wherein the bacteria comprise a GyrB ATPase or topoisomerase IV ATPase enzyme. "Treating a subject with a disease caused by a

bacterial infection" includes achieving, partially or substantially, one or more of the following: the reducing or amelioration of the progression, severity and/or duration of the infection, arresting the spread of an infection, ameliorating or improving a clinical symptom or indicator associated with a the infection (such as tissue or serum components), and preventing the reoccurrence of the infection.

As used herein, the terms "preventing a bacterial infection" refer to the reduction in the risk of acquiring the infection, or the reduction or inhibition of the recurrence of the infection. In a preferred embodiment, a compound of the invention is administered as a preventative measure to a patient, preferably a human, before a surgical procedure is preformed on the patient to prevent infection.

As used herein, the term "effective amount" refers to an amount of a compound of this invention for treating or preventing a bacterial infection is an amount which is sufficient to prevent the onset of an infection, reduce or ameliorate the severity, duration, or progression, of an infection, prevent the advancement of an infection, cause the regression of an infection, prevent the recurrence, development, onset or progression of a symptom associated with an infection, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

In addition to its use in therapeutic medicine, compounds of formula **(I)**, and their pharmaceutically acceptable salts, are also useful as pharmacological tools in the development and standardization of *in-vitro* and *in-vivo* test systems for the evaluation of the effects of inhibitors of DNA gyrase and / or topoisomerase IV in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and particular embodiments of the compounds of the invention described herein also apply.

EXAMPLES

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :

(i) evaporations were carried out by rotary evaporation in-vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were generally carried out at ambient temperature, that is typically in the range 18-26 °C and without exclusion of air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable; the structure of the end-products of the invention were generally confirmed by NMR and mass spectral techniques; proton magnetic resonance spectra is quoted and was generally determined in DMSO-d_6 unless otherwise stated using a Bruker DRX-300 spectrometer operating at a field strength of 300 MHz. Chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet, m, multiplet; br, broad; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected or using Agilent 1100series LC/MSD equipped with Sedex 75ELSD, run in atmospheric pressure chemical ionisation mode and, where appropriate, either positive ion data or negative ion data were collected; mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported;

(vi) each intermediate was purified to the standard required for the subsequent stage and was characterised in sufficient detail to confirm that the assigned structure was correct; purity was assessed by high pressure liquid chromatography, thin layer chromatography, or NMR and identity was determined by infra-red spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate;

(vii) the following abbreviations may be used:

ACN is acetonitrile;

$CDCl_3$ is deuterated chloroform;

CDI is 1,1'-carbonyl diimidazole;

DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene;

DCM is dichloromethane;

DIEA is diisopropyl ethylamine;

DMAP is N,N-dimethylaminopyridine;

DMF is *N,N*-dimethylformamide;

DMSO is dimethylsulfoxide;

EDC is 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide;

EtOAc is ethyl acetate;

EtOH is ethanol;

HATU is N-[(dimethylamino)-1H,2,3-triazolo[4,5-b-]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide;

HOBT is 1-hydroxybenzotriazole;

MeOH is methanol;

MS is mass spectroscopy;

MTBE is methyl tert-butyl ether;

RT or rt is room temperature;

SM is starting material;

TBFA is tetra-*n*-butylammonium fluoride;

TFA is trifluoroacetic acid;

TFAA is trifluoroacetic anhydride;

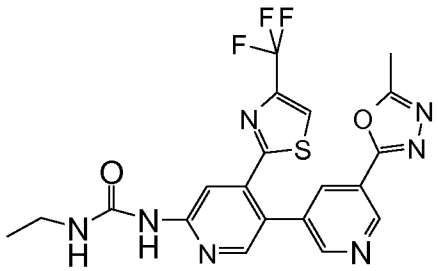
THF is tetrahydrofuran;

XPhos is dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine; and

(viii) temperatures are quoted as °C.

Example 1

1-Ethyl-3-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



Triethylamine (0.054 mL, 0.39 mmol) and acetohydrazide (14.40 mg, 0.19 mmol) were added to a solution of 6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 1, 85 mg, 0.19 mmol) in DMF (1.5 mL). The mixture was stirred

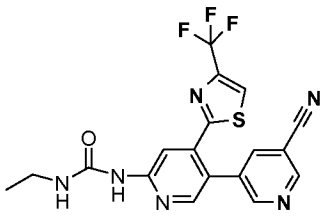
for 5 minutes and then HATU (89 mg, 0.23 mmol) was added. The resulting light yellow solution was stirred at room temperature for one hour. Then the reaction was diluted with water and the aqueous layer was lyophilized to remove water. The residue obtained was extracted with THF and concentrated to give thick oil. The oil was taken up in DCM (5 mL) and triphenyl phosphine (6 eq, 306 mg, 1.16 mmol,), carbon tetrachloride (3 eq, 180 mg, 113 uL, 0.58 mmol), and triethylamine (6 eq, 319 mg, 0.431 uL, 1.16 mmol) were added and allowed to stir overnight at room temperature. The reaction was concentrated and partitioned between water and dichloromethane. The organic layer was washed with water and brine, then dried over magnesium sulfate. The crude residue was purified by normal phase chromatography to give a white solid as the product (48 mg).

MS (ES) MH^+: 476 for $C_{20}H_{16}F_3N_7O_2S$

^{1}H-NMR (DMSO-d_6) δ: 1.09 (t, 3H); 2.58 (s, 3H); 3.16-3.24 (m, 2H); 7.54 (brs, 1H); 8.23 (s, 1H); 8.35 (s, 1H); 8.40 (s, 1H); 8.56 (s, 1H); 8.69 (s, 1H); 9.15 (d, 1H); 9.51 (s, 1H).

Example 2

1-(5'-Cyano-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



1-(5-Bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 3, 300 mg, 0.76 mmol), cesium carbonate (495 mg, 1.52 mmol), tetrakis(triphenylphosphine)palladium (0) (88 mg, 0.08 mmol), and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (349 mg, 1.52 mmol) were taken in a microwave vial and degassed with nitrogen. Then dioxane:water (4:1, 6 mL) was added to the vial and the mixture was microwaved at 100 °C for half an hour. The reaction mixture was partitioned between water and ethyl acetate and the layers were separated. The aqueous layer was back extracted with ethyl acetate (2-3 times). The combined organic layers were washed with saturated sodium bicarbonate solution, water, brine and dried over magnesium sulfate. The

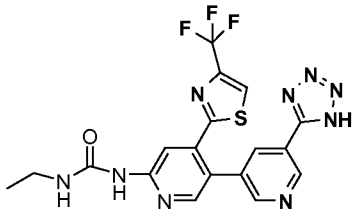
solvent was removed and the residue was washed with acetonitrile to give the title compound as a white solid (270 mg).

MS (ESP): 419 (M+1) for $C_{18}H_{13}FN_6OS$

^{1}H-NMR (DMSO-d_6) δ: 1.09 (t, 3H); 3.16-3.22 (m, 2H); 7.49 (t, 1 H); 8.22 (s, 1H); 8.36 (s, 1H); 8.38 (d, 1H); 8.60 (s, 1H); 8.76 (s, 1H); 9.04 (s, 1H); 9.52 (s, 1H).

Example 3

1-(5'-(2H-tetrazol-5-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



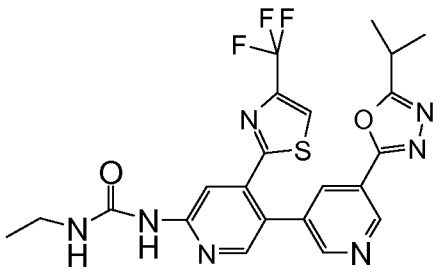
Sodium azide (18.65 mg, 0.29 mmol) and ammonium chloride (14.57 mg, 0.27 mmol) were added to a solution of 1-(5'-cyano-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Example 2, 60 mg, 0.14 mmol) in DMF (1.5 mL), and the mixture was heated at 100 ° C for 5-6 hours. The reaction was then concentrated and dissolved in water and methanol (3 mL, 1:1) and purified by reverse phase. Fractions were collected and lyophilized to give the product as a white solid (23 mg).

MS (ESP): 462 (M+1) for $C_{18}H_{14}FN_9OS$

^{1}H-NMR (DMSO-d_6) δ: 1.09 (t, 3H); 3.17-3.22 (m, 2H); 7.53 (t, 1 H); 8.25 (s, 1H); 8.35 (s, 1H); 8.40 (s, 1H); 8.55 (s, 1H); 8.77 (d, 1H); 9.22 (s, 1H); 9.53 (s, 1H).

Example 4

1-Ethyl-3-(5'-(5-isopropyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



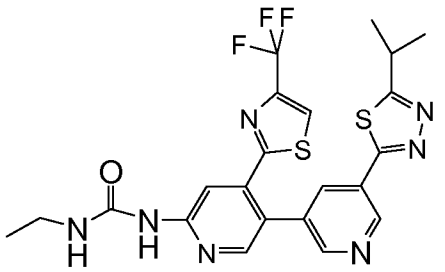
Triphenylphosphine (211 mg, 0.81 mmol), carbon tetrachloride (0.039 mL, 0.40 mmol) and triethylamine (0.112 mL, 0.81 mmol) were added to a mixture of 1-ethyl-3-(5'-(2-isobutyrylhydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 8, 70 mg, 0.13 mmol) in DCM (4 mL),. The resulting mixture was allowed to stir overnight at room temperature, then was partitioned between water and dichloromethane. The layers were separated and the aqueous was back extracted with dichloromethane. The combined extract was washed with water, dried over magnesium sulfate and concentrated. The residue obtained was purified by normal phase (1%MeOH to 5% MeOH in dichloromethane) to give the product as a white solid (23 mg).

MS (ESP): 504 (M+1) for $C_{22}H_{20}F_3N_7O_2S$

^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 1.35 (d, 6H); 3.10-3.25 (m, 2H); 3.23-3.30 (m, 1H); 7.55 (brs, 1H); 8.22 (s, 1H); 8.29 (s, 1H); 8.41(s, 1H); 8.57 (s, 1H); 8.70 (d, 1H); 9.18 (s, 1H); 9.51 (s, 1H).

Example 5

1-Ethyl-3-(5'-(5-isopropyl-1,3,4-thiadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



Phosphorus pentasulfide (79 mg, 0.35 mmol) and hexamethyldisiloxane (0.030 mL, 0.14 mmol) were added to a mixture of 1-ethyl-3-(5'-(2-isobutyrylhydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 8, 70 mg, 0.14 mmol) in toluene, and the mixture was refluxed overnight. The reaction was cooled to the room temperature and diluted with acetone (5 mL) and potassium carbonate (31.4 mg, 0.23 mmol) was added slowly. After the completion of the addition, the reaction was concentrated and the residue was partitioned between water and dichloromethane. The layers separated and the aqueous was back extracted with dichloromethane. The combined organic layers were washed

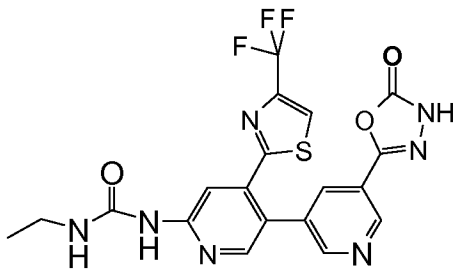
with water, dried over magnesium sulfate and concentrated. The crude residue was purified by normal phase chromatograpy (1% MeOH in dichloromethane to 5 % MeOH) to give the desired product (20 mg).

MS (ESP): 520 (M+1) for $C_{22}H_{20}F_3N_7OS$

^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 1.40 (d, 6H); 3.10-3.26 (m, 2H); 3.43-3.63 (m, 1H); 7.55 (brs, 1H); 8.23 (s, 1H); 8.28 (s, 1H); 8.41(s, 1H); 8.56 (s, 1H); 8.64 (d, 1H); 9.16 (d, 1H); 9.50 (s, 1H).

Example 6

1-Ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



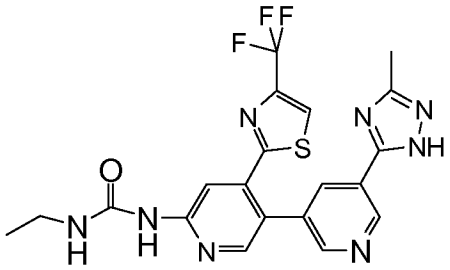
Diisopropylethylamine (0.061 mL, 0.35 mmol) and carbonyldiimidazole (56.6 mg, 0.35 mmol) were added to a solution of 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 9, 105 mg, 0.23 mmol) in DMF (1.5 mL), and the mixture was stirred at room temperature for 1.5 hours. The reaction was diluted with water and extracted with 5% methanol in dichloromethane. The combined extract was washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude residue obtained was purified by normal phase chromatography (2 % MeOH in dichloromethane to 8 % MeOH) to give the desired compound as a white solid (65 mg).

MS (ESP): 478 (M+1) for $C_{19}H_{14}F_3N_7O_3S$

^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 3.16-3.28 (m, 2H); 7.55 (brs, 1H); 8.09 (s, 1H); 8.22 (s, 1H); 8.37 (s, 1H); 8.57 (s, 1H); 8.62 (s, 1H); 8.97 (s, 1H); 9.50 (s, 1H); 12.80 (s, 1H).

Example 7

1-Ethyl-3-(5'-(3-methyl-1H-1,2,4-triazol-5-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



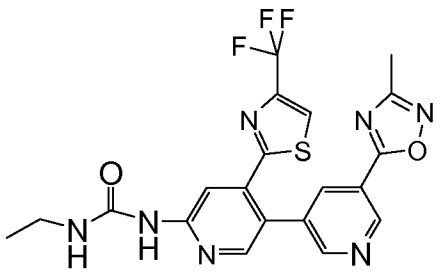
N-(1-(dimethylamino)ethylidene)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxamide (Intermediate 10, 80 mg, 0.16 mmol) was added to a solution of acetohydrazide (12.90 mg, 0.17 mmol) in acetic acid (2 mL), and the resulting solution was heated at 90 °C for one hour. Then the reaction was concentrated, diluted with water and extracted with dichloromethane. During the work up process, the product started to precipitate. The mixture was washed with a 1M potassium carbonate solution twice and the precipitate was collected by filtration and dried to give the product as a white solid (35 mg).

MS (ESP): 475 (M+1) for $C_{20}H_{17}F_3N_8OS$

^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 2.31 (s, 3H); 3.12-3.26 (m, 2H); 7.74 (brs, 1H); 8.18 (s, 1H); 8.27 (s, 1H); 8.34 (s, 1H); 8.38 (s, 1H); 8.51 (s, 1H); 9.14 (d, 1H); 9.61 (s, 1H).

Example 8

1-Ethyl-3-(5'-(3-methyl-1,2,4-oxadiazol-5-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



N-(1-(dimethylamino)ethylidene)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxamide (Intermediate 10, 80 mg, 0.16 mmol) was added to a solution of hydroxylamine hydrochloride (13.20 mg, 0.19 mmol) in a mixture of sodium hydroxide (0.038 mL, 0.19 mmol) and 70 % aq acetic acid (2 mL), and 3 ml of dioxane. The resulting mixture was slowly warmed to temperature 80 °C. Most of the solid went into solution at 35 °C and solid precipitated out of solution at 50°C. The mixture was allowed to stir for 30

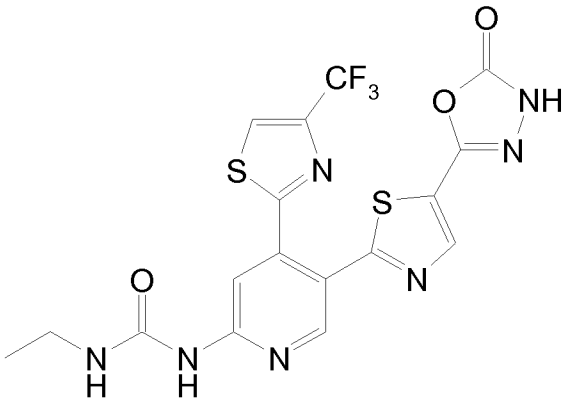
minutes then concentrated. The residue was partitioned between with water and dichloromethane, the layers separated and the aqueous layer was back extracted 2 -3 times. During the process, the product started to precipitate. The mixture was washed with saturated sodium bicarbonate solution and water. Then the precipitated product was filtered off and dried to give the title compound as a white solid (55 mg).

MS (ESP): 476 (M+1) for $C_{20}H_{16}F_3N_7O_2S$

^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 2.31 (s, 3H); 3.05-3.28 (m, 2H); 7.74 (brs, 1H); 8.24 (s, 1H); 8.40 (s, 2H); 8.56 (s, 1H); 8.77 (d, 1H); 9.25 (d, 1H); 9.60 (s, 1H).

Example 9

1-ethyl-3-(5-(5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea



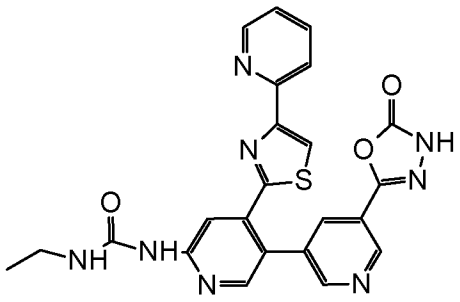
Methyl 2-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)thiazole-5-carboxylate (Intermediate 13; 128 mg, 0.28 mmol) was suspended hydrazine hydrate (0.2 mL, 6.43 mmol) and ethanol (5 mL). The slurry was heated until it became homogeneous. The reaction was monitored by LC/MS, and once it was determined to be complete, the reaction mixture concentrated to dryness. The solids were suspended in THF (5 mL) and diisopropylethylamine (0.073 mL, 0.42 mmol) and di(1H-imidazol-1-yl)methanone (45.4 mg, 0.28 mmol) were added. The mixture was heated to reflux, and the product precipitated out of solution. The solids were filtered and washed with methanol, then dried in vacuo. Isolation gave 24 mg of the title compound.

MS (ESP): 484 (M+1) for $C_{17}H_{12}F_3N_7O_3S_2$.

^{1}H NMR (300 MHz, d_6-DMSO): 1.03 (t, 3H), 3.14 (m, 2H), 7.42 (t, 1H), 8.03 (s, 1H), 8.30 (s, 1H), 8.66 (s, 1H), 8.68 (s, 1H), 9.63 (s, 1H), 12.73 (s, 1H).

Example 10

N-ethyl-N'-[5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-pyridin-2-yl-1,3-thiazol-2-yl)-3,3'-bipyridin-6-yl]urea



1,1'-Carbonylbis-1H-imidazole (0.050 g, 0.31 mmol) and DIEA (0.053 mL, 0.31 mmol) were added to a suspension of N-ethyl-N'-[5'-(hydrazinocarbonyl)-4-(4-pyridin-2-yl-1,3-thiazol-2-yl)-3,3'-bipyridin-6-yl]urea (Intermediate 22, 94 mg, 0.31 mmol) in DMF (2 mL), and the mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure, then purified by Gilson HPLC (5-95% ACN / 0.1% TFA in 14 min). Isolation gave 19 mg of the title compound.

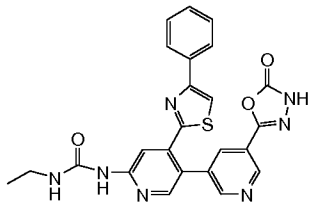
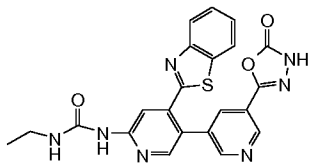
LC/MS (ES^+)[$(M+H)^+$]: 487 for $C_{23}H_{18}N_8O_3S$.

^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.22 (m, 2H), 7.36 (t, 1H), 7.62 (t, 1H), 7.67 (d, 1H), 7.84 (m, 1H), 8.21 (t, 1H), 8.28 (s, 1H), 8.34 (s, 1H), 8.37 (s, 1H), 8.6 (d, 1H), 8.70 (d, 1H), 8.98 (d, 1H), 9.39 (s, 1H), 12.79 (s, 1H).

Examples 11-12

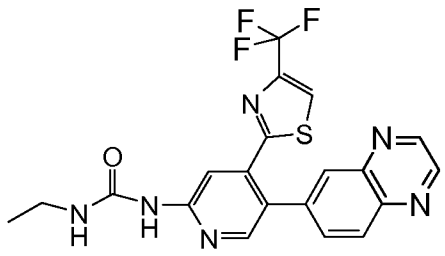
The following compounds have been synthesized as described for Example 10 from the starting materials indicated in the table below.

Ex	Compound	Data	SM

Ex	Compound	Data	SM
11	1-ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-phenylthiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 486 for $C_{24}H_{19}N_7O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.10 (t, 3H), 3.20 (m, 2H), 7.35 (m, 3H), 7.63 (t, 1H), 7.71 (d, 1H), 7.73 (d, 1H), 8.20 (t, 1H), 8.23 (s, 1H), 8.25 (s, 1H), 8.32 (s, 1H), 8.69 (d, 1H), 8.99 (d, 1H), 9.48 (s, 1H), 12.80 (s, 1H).	Intermediate 23 and CDI
12	1-(4-(benzo[d]thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 460 for $C_{22}H_{17}N_7O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.10 (t, 3H), 3.21 (m, 2H), 7.46-7.58 (m, 3H), 7.97 (d, 1H), 8.09 (d, 1H), 8.19 (t, 1H), 8.28 (s, 1H), 8.39 (s, 1H), 8.6 (d, 1H), 8.96 (d, 1H), 9.54 (s, 1H), 12.78 (s, 1H).	Intermediate 24 and CDI

Example 13

1-ethyl-3-(5-(quinoxalin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea



A reaction mixture of 1-ethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea (Intermediate 12, 100 mg, 0.23 mmol), 6-bromoquinoxaline (43.0 mg, 0.21 mmol),Tetrakis (23.75 mg, 0.02 mmol), and cesium carbonate (73.7 mg, 0.23 mmol) in dioxane and water was prepared. The reaction mixture

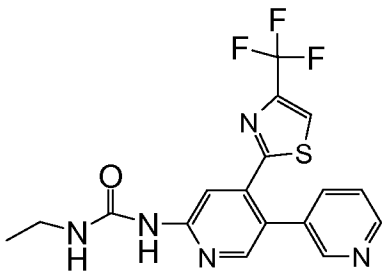
was degassed with nitrogen for 15 minutes and then heated to 100 °C for 1 h. The reaction mixture was partitioned between methylene chloride and water. The organic layer was washed with saturated sodium chloride, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatogrpahy (silica, 15:1 methylene chloride/methanol) gave 44 mg of desired product.

MS (ESP): 445 (M+1) for $C_{20}H_{15}F_3N_6OS$.

^{1}H NMR (300 MHz, DMSO-d_6): 1.12 (t, J = 7 Hz, 3H), 3.24 (m, 2H), 7.23 (m, 1H), 7.43 (m, 1H), 8.04 (m, 1H), 8.21 (m, 1H), 8.36 (m, 1H), 8.55 (m, 1H), 9.02 (br s, 2H), 9.36 (s, 1H), 9.52 (s, 1H).

Example 14

1-Ethyl-3-(4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



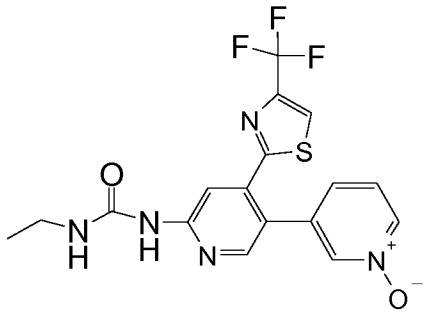
1-(5-Bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 3, 70 mg, 0.18 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, cesium carbonate (115 mg, 0.35 mmol), tetrakis(triphenylphosphine)palladium (0) (20.47 mg, 0.02 mmol) were taken in a microwave vial and degassed with nitrogen. Then dioxane:water (4:1, 5 mL) was added and the resulting mixture was heated in a microwave at 100 °C for 30 minutes. The palladium catalyst was filtered off and the filtrate was partitioned between water and ethyl acetate. The layers were separated and the aqueous layer was back extracted with ethyl acetate three times. The combined organic extract was washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude residue was washed with acetonitrile several times to give off-white solid (42mg).

MS (ESP): 394 (M+1) for $C_{17}H_{14}F_3N_5OS$

^{1}H-NMR (DMSO-d_6) δ: 1.09 (t, 3H); 3.17-3.22 (m, 2H); 7.44-7.50 (m, 1 H); 7.55 (t, 1H); 7.76 (d, 1H); 8.20 (s, 1H); 8.30 (s, 1H); 8.49 (s, 1H); 8.55 (s, 1H);8.64 (d, 1H); 9.45 (s, 1H).

Example 15

6'-(3-Ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine 1-oxide



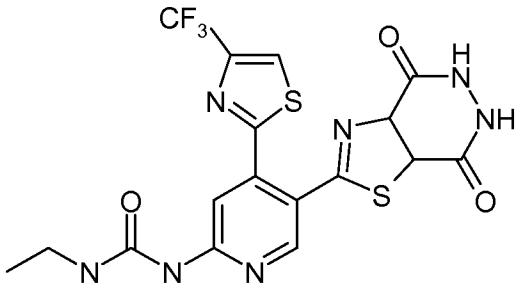
1-Ethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea (Intermediate 12, 150 mg, 0.34 mmol), 3-bromopyridine 1-oxide, tetrakis(triphenylphosphine)palladium (0) (39.2 mg, 0.03 mmol), cesium carbonate (221 mg, 0.68 mmol) were taken in a microwave vial and degassed with nitrogen. Then dioxane:water (4:1, 5 mL) was added and the resulting mixture was heated in a microwave at 100 °C for 30 minutes. The product precipitated from the reaction as a white solid and was collected by filtration and washed with water and 1% methanol in dichloromethane to provide the desired product (27 mg).

MS (ESP): 410 (M+1) for $C_{17}H_{14}F_3N_5O_2S$

^{1}H-NMR (DMSO-d_6) δ: 1.09 (t, 3H); 3.12-3.22 (m, 2H); 7.23 (d, 1 H); 7.40-7.45 (m, 1H); 7.45 (brs, 1H); 8.19 (s, 1H); 8.27 (d, 1H); 8.29 (s, 1H); 8.31 (s, 1H); 8.61 (s, 1H); 9.48 (s, 1H).

Example 16

1-{5-(4,7-dioxo-4,5,6,7-tetrahydro[1,3]thiazolo[4,5-d]pyridazin-2-yl)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}-3-ethylurea



A solution of diethyl 2-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)thiazole-4,5-dicarboxylate (Intermediate 25, 150 mg, 0.28mmol) and hydrazine hydrate (0.4mL, 1.0N in MeOH) in methanol (10mL) was refluxed for 5h. The mixture was cooled and additional 0.4mL of hydrazine hydrate-MeOH solution was added. The mixture was

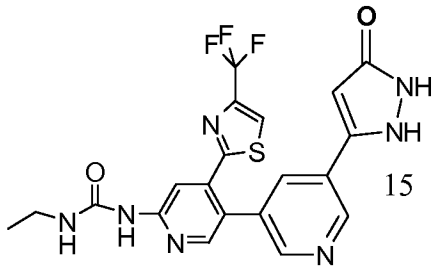
stirred for additional 5h. The reaction mixture was cooled and 1.0 N HCl (1mL) was added. The mixture was stirred at 45 °C for 1h, cooled to room temperature, neutralized with powdered $NaHCO_3$, then purified via a reverse phase C18 column (10%-75% MeOH-water) to afford 70 mg (53%) of desired product as off-white powder.

MS (ESP): 484.0 ($M+H^+$) for $C_{17}H_{12}F_3N_7O_3S_2$

^1H NMR (DMSO-d_6): δ ppm 1.11 (t, 3H), 3.21 (m, 2H), 7.46 (t, 1H), 8.16 (s, 1H), 8.72 (d, 1H), 8.78 (s, 1H), 9.78 (s, 1H)

Example 17

1-Ethyl-3-(5'-(5-oxo-2,5-dihydro-1H-pyrazol-3-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



]

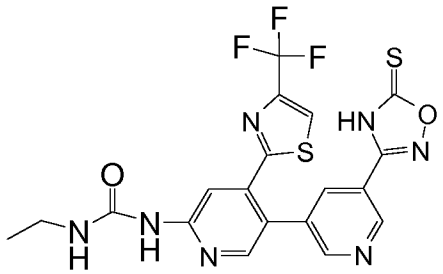
1-Ethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea (Intermediate 12, 140 mg, 0.32 mmol), 5-(5-bromopyridin-3-yl)-1H-pyrazol-3(2H)-one (Intermediate 26, 76 mg, 0.32 mmol), cesium carbonate (103 mg, 0.32 mmol), tetrakis(triphenylphosphine)palladium(0) (36.6 mg, 0.03 mmol) and water (1.500 mL) were taken in a microwave vial and degassed with nitrogen. Then dioxane:water (8 mL 4:1) was added and the reaction mixture was heated in a microwave at 100 °C for 2 h. The reaction mixture was diluted with water and extracted with 5% MeOH in dichloromethane. The combined extract was dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by reverse phase HPLC (25% to 70% ACN in water, 0.01 % TFA). The fractions containing the product were combined, concentrated under reduced pressure and lypholized to give a white solid (42 mg) that was triturated with acetonitrile and dried under high vacuum.

MS (ESP): 476 (M+1) for $C_{20}H_{16}F_3N_7O_2S$

^1H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.16-3.24 (m, 2H); 6.05 (s, 1H); 7.58 (brs, 1H); 8.18 (s, 1H); 8.28 (s, 1H); 8.38 (s, 1H); 8.45 (s, 1H); 8.56 (s, 1H); 9.01 (s, 1H); 9.51 (s, 1H).

Example 18

1-Ethyl-3-(5'-(5-thioxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



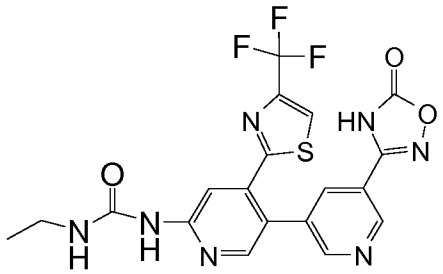
DBU (0.080 mL, 0.53 mmol) followed by di(1H-imidazol-2-yl)methanethione (35.5 mg, 0.20 mmol) were added to a mixture of 6'-(3-ethylureido)-N-hydroxy-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboximidamide (Intermediate 27, 60 mg, 0.13 mmol) in acetonitrile (3 mL), and the mixture was stirred at room temperature overnight. The reaction was concentrated and the residue was partitioned between water and ethyl acetate. The layers were separated and the organic layer was washed with water and brine, then dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by reverse phase chromatography and the fractions containing the product were combined and lypholyzed to give white solid (22 mg, low yield).

MS (ESP): 494 (M+1) for $C_{19}H_{14}F_3N_7O_2S_2$

^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 3.16-3.24 (m, 2H); 7.56 (brs, 1H); 8.23 (s, 1H); 8.24 (s, 1H); 8.37 (s, 1H); 8.58 (s, 1H); 8.70 (d, 1H); 9.06 (s, 1H); 9.52 (s, 1H).

Example 19

1-Ethyl-3-(5'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



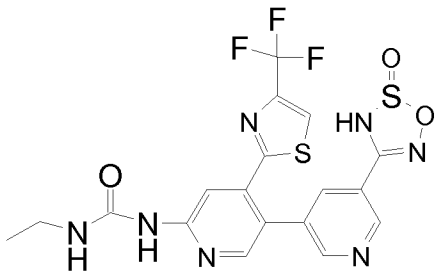
DBU (0.023 mL, 0.16 mmol) followed by carbonyl diimidazole (25.1 mg, 0.16 mmol) were added to a suspension of 6'-(3-ethylureido)-N'-hydroxy-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboximidamide (Intermediate 27, 70 mg, 0.16 mmol) in dioxane (3 mL). The resulting solution was stirred overnight at room temperature. The solvent was removed and the crude residue was partitioned between water and ethyl acetate. The layers were separated and the aqueous was back extracted with ethyl acetate three times. The aqueous layer was concentrated under reduced pressure and purified by reverse phase HPLC (5 %ACN in water to 70 % ACN) to give the title compound as a white solid (33 mg).

MS (ESP): 478 (M+1) for $C_{19}H_{14}F_3N_7O_3S$

^{1}H-NMR (DMSO-d_6) δ: 1.09 (t, 3H); 3.15-3.24 (m, 2H); 7.51 (br s, 1H); 8.15 (s, 1H); 8.24 (s, 1H); 8.37 (s, 1H); 8.59 (s, 1H); 8.70 (s, 1H); 8.99 (d, 1H); 9.52 (s, 1H); 13.14 (br s, 1H).

Example 20

N-Ethyl-N'-{5'-(2-Oxido-3H-1,2,3,5-oxathiadiazol-4-yl)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-6-yl}urea



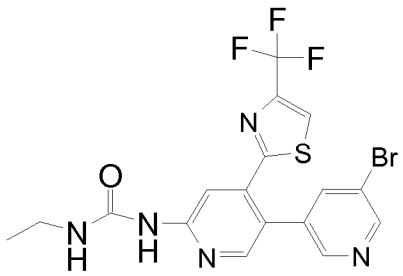
To a suspension of 6'-(3-ethylureido)-N-hydroxy-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboximidamide (Interemdiate 27, 70 mg, 0.16 mmol) in THF (1.5 mL) at 0 °C, pyridine (0.025 mL, 0.31 mmol) was added followed by a drop wise addition of a solution of sulfurous dichloride (0.023 mL, 0.31 mmol) in dichloromethane (1.5 mL). The resulting mixture was slowly warmed up to room temperature and allowed to stir for an hour. Then the reaction was quenched by adding water (1 mL). The layers were separated and the aqueous layer was back extracted with 1%MeOH in DCM twice and the combined organic layers were washed with water and brine, then dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by normal phase chromatography to give the title compound as a white solid (25 mg).

MS (ESP): 498 (M+1) for $C_{18}H_{14}F_3N_7O_3S_2$

^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 3.18-3.22 (m, 2H); 7.58 (br s, 1H); 8.17 (t, 1H); 8.25(s, 1H); 8.36 (s, 1H); 8.54 (d, 1H); 8.57(d, 1H); 9.04 (d, 1H); 9.50 (br s, 1H).

Example 21

1-(5'-Bromo-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



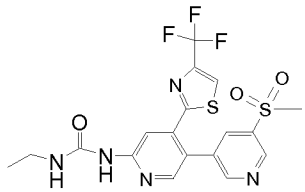
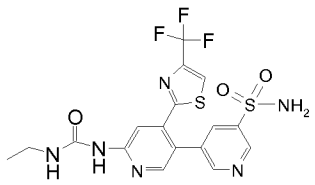
3-Bromo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (596 mg, 2.10 mmol), 1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 3, 830 mg, 2.10 mmol), tris(dibenzylideneacetone)dipalladium(0) (192 mg, 0.21 mmol), 2-dicyclohexylphosphino-2',4',6'-tri-iso-propyl-1,1'-biphenyl (300 mg, 0.63 mmol) and sodium carbonate (223 mg, 2.10 mmol) were taken in a round bottomed flask, and the flask was flushed with nitrogen. Solvent (5:1; acetonitrile, water, 10 mL) was added and degassed with nitrogen, and the mixture was heated at 100 °C for 3 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The resulting crude residue was partitioned between water and ethyl acetate. The layers were separated and the aqueous was back extracted with ethyl acetate three times. The combined organic layers were washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue obtained was purified by normal phase chromatography (gradient of MeOH in DCM) to give a white solid (483 mg).

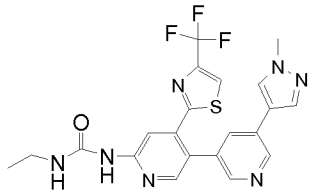
MS (ESP): 473 (M+1) for $C_{17}H_{13}BrF_3N_5OS$

Example 22-24

The following Examples were synthesized according to the procedure described for Intermediate 2 from the starting materials indicated.

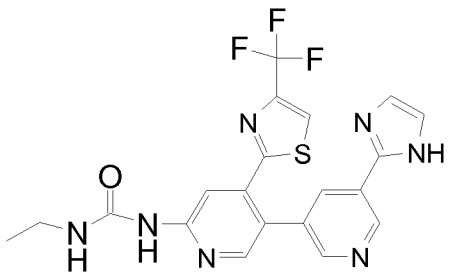
5

Ex	Compound	Data	SM
22	1-Ethyl-3-(5'-(methylsulfonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 472 (M+1) for $C_{18}H_{16}F_3N_5O_3S_2$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.16-3.28 (m, 2H); 3.31 (s, 3H); 7.53 (brs, 1H); 8.23 (s, 1H); 8.25 (t, 1H); 8.42 (s, 1H); 8.60 (d, 1H); 8.84 (d, 1H); 9.08 (d, 1H); 9.54 (brs, 1H).	Intermediate 3 and 5-(methylsulfonyl)pyridin-3-ylboronic acid
23	6'-(3-Ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-sulfonamide 	MS (ESP): 473 (M+1) for $C_{17}H_{15}F_3N_6O_3S_2$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.17-3.28 (m, 2H); 7.43 (brs, 1H); 7.63 (s, 2H); 8.10 (d, 1H); 8.25 (s, 1H); 8.36 (s, 1H); 8.60 (s, 1H); 8.72 (d, 1H); 8.98 (d, 1H); 9.53 (s, 1H).	Intermediate 12 and 5-bromopyridine-3-sulfonamide

Ex	Compound	Data	SM
24	1-Ethyl-3-(5'-(1-methyl-1H-pyrazol-4-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 474 (M+1) for $C_{21}H_{18}F_3N_7OS$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.14-3.25 (m, 2H); 3.87 (s, 3H); 7.59 (brs, 1H); 7.98 (s, 1H); 8.02 (s, 1H); 8.28 (d, 3H); 8.35 (s, 1H); 8.54 (s, 1H); 8.90 (d, 1H); 9.47 (s, 1H).	Example 21 and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

Example 25

1-(5'-(1H-Imidazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



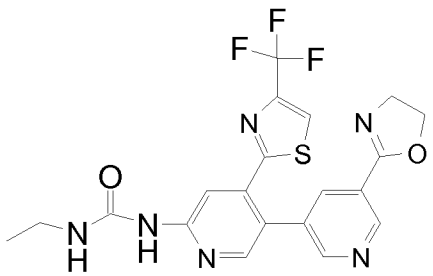
Sodium methoxide (10.291 µl, 0.06 mmol) was added to a suspension of 1-(5'-cyano-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Example 2, 120 mg, 0.29 mmol) in methanol (3 mL), and the resulting mixture was stirred overnight at room temperature. 2,2-Dimethoxyethanamine (30.9 µl, 0.29 mmol) followed by acetic acid (32.8 µl, 0.57 mmol) were added, and the mixture was heated to 50 °C for 1.5 hours. The reaction mixture was cooled to room temperature and isopropanol (3 mL) followed by HCl (500 µl, 6N) were added and the mixture was refluxed overnight. The solvent was removed and the residue was dissolved in water and neutralized by adding 2N NaOH. The aqueous layer was extracted with ethyl acetate, and the ethyl acetate layer was washed with water and brine, dried over magnesium sulfate, and concentrated under reduced pressure. The off-white solid obtained was triturated with acetonitrile and dried to give a white solid (43 mg).

MS (ESP): 460 (M+1) for $C_{20}H_{16}F_3N_7OS$

^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.14-3.25 (m, 2H); 7.09 (s, 1H); 7.35 (s, 1H); 7.58 (brs, 1H); 8.24 (s, 1H); 8.28 (s, 1H); 8.37 (s, 1H); 8.43 (s, 1H); 8.53 (s, 1H); 9.19 (s, 1H); 9.49 (s, 1H); 12.73 (s, 1H).

Example 26

1-(5'-(4,5-Dihydrooxazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



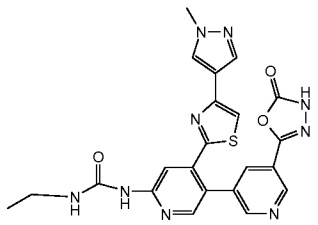
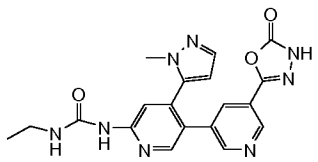
Bismuth(III) trifluoromethanesulfonate (10.98 mg, 0.02 mmol) was added to a suspension of 1-(5'-cyano-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Example 2, 100 mg, 0.24 mmol) and 2-aminoethanol (115 µl, 1.91 mmol), and the resulting reaction mixture was stirred at 70 °C for overnight. The reaction mixture was partitioned between water and 3% MeOH in ethyl acetate. The layers were separated and the aqueous layer was back extracted twice with 3% methanol in ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to give a white solid. The solid was triturated with acetonitrile and dried under high vacuum to give the product as a white solid (26 mg).

MS (ESP): 463 (M+1) for $C_{20}H_{17}F_3N_6O_2S$

^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.14-3.28 (m, 2H); 3.99 (t, 2H); 4.43 (t, 2H); 7.57 (t, 1H); 8.12 (t, 1H); 8.23 (s, 1H); 8.36 (s, 1H); 8.56 (s, 1H); 8.65 (d, 1H); 9.04 (s, 1H); 9.50 (s, 1H).

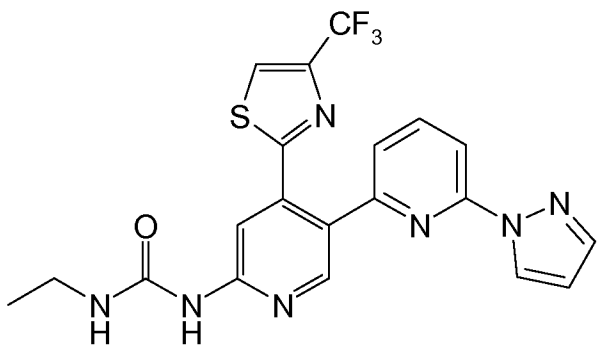
Examples 27-28

The following Examples were synthesized according to the procedure described for Example 10 from the starting materials indicated.

Ex	Compound	Data	SM
27	1-ethyl-3-(4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 490 for $C_{22}H_{19}N_9O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.22 (m, 2H), 3.84(s, 3H), 7.62 (s, 1H), 7.63 (m, 1H), 7.78 (s, 1H), 7.92 (s, 1H), 8.16 (m, 1H), 8.19 (s, 1H), 8.32 (s, 1H), 8.66 (d, 1H), 8.98 (d, 1H), 9.42 (s, 1H), 12.81 (s, 1H).	Intermediate 36 and 1,1'-carbonylbis-1H-imidazole, diispropylethyl amine
28	1-ethyl-3-(4-(1-methyl-1H-pyrazol-5-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 407 for $C_{19}H_{18}N_8O_3$. ^1H NMR (300 MHz, d_6-DMSO): 1.06 (t, 3H), 3.16 (m, 2H), 3.78(s, 3H), 7.03 (m, 1H), 7.40 (s, 1H), 7.86 (m, 1H), 7.92 (t, 1H), 8.07 (s, 1H), 8.32 (m, 1H), 8.53 (d, 1H), 8.77 (d, 1H), 9.44 (s, 1H), 12.76 (s, 1H).	Intermediate 35 and 1,1'-carbonylbis-1H-imidazole, diispropylethyl amine

Example 29

1-(6-(1H-pyrazol-1-yl)-4'-(4-(trifluoromethyl)thiazol-2-yl)-2,3'-bipyridin-6'-yl)-3-ethylurea:



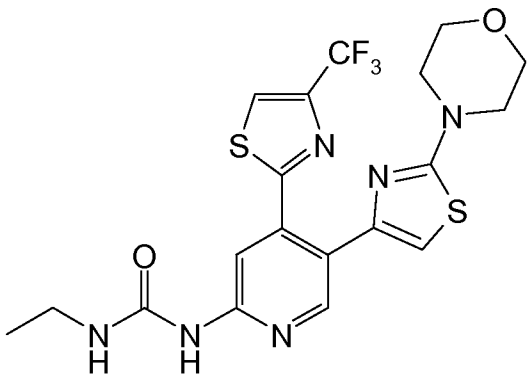
In a microwave reaction vessel, 1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 3, 200 mg, 0.51 mmol), 2-(1H-pyrazol-1-yl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (137 mg, 0.51 mmol) and cesium carbonate (64.4 mg, 0.61 mmol) were combined and suspended in a 4:1 mixture of dioxane and water. $Pd(PPh_3)_4$ (29.2 mg, 0.03 mmol) was added in a single portion. The vessel was sealed, degassed, purged with nitrogen and heated to 100°C in the microwave for 120 min. The crude reaction mixture was concentrated to dryness. The resulting residue was dissolved in DMSO, filtered and then purified by Gilson HPLC (5-95% ACN / 0.1% TFA water in 14 minutes). Isolation gave 56 mg of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 460 for $C_{20}H_{16}F_3N_7OS$.

^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.20 (m, 2H), 6.47 (m, 1H), 7.59 (d, 1H), 7.61 (m, 1H), 7.79 (m, 1H), 7.85 (d, 1H), 7.95 (d, 1H), 8.06 (m, 2H), 8.55 (m, 1H), 8.62 (s, 1H), 9.56 (s, 1H).

Example 30

1-ethyl-3-(5-(2-morpholinothiazol-4-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea



In a microwave reaction vessel, 1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 3, 100 mg, 0.25 mmol), 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazol-2-yl)morpholine (82 mg's, 0.28 mmol), sodium carbonate (40 mg, 0.38 mmol), $Pd_2(dba)_3$ (23.17 mg, 0.03 mmol) and X-Phos (2-(Dicyclohexylphosphino)-2',4',6'-tri-i-propyl-1.1'-biphenyl) (38.1 mg, 0.08 mmol) were combined and suspended in 4:1 mixture of acetonitrile (3 mL) and water (0.75 mL). The vessel was sealed and heated to 90 °C in an oil bath for 30 min. The reaction mixture was cooled to room temperature and concentrated to dryness. The crude residue was dissolved in minimal DMSO, filtered and

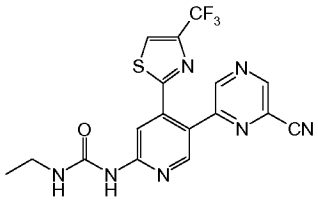
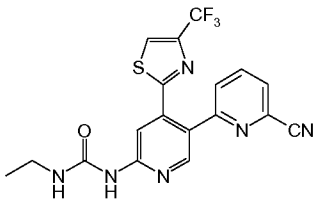
then purified by Gilson HPLC (5-95% ACN / 0.1% TFA water in 14 min.). Isolation gave 58 mg of the compound.

LC/MS (ES^+)[$(M+H)^+$]: 485 for $C_{19}H_{19}F_3N_6O_2S_2$.

^1H NMR (300 MHz, d_6-DMSO): 1.03 (t, 3H), 3.11 (m, 2H), 3.18 (m, 4H), 3.58 (m, 4H), 7.01 (s, 1H), 7.54 (t, 1H), 8.00 (s, 1H), 8.35 (s, 1H), 8.56 (s, 1H), 9.31 (s, 1H).

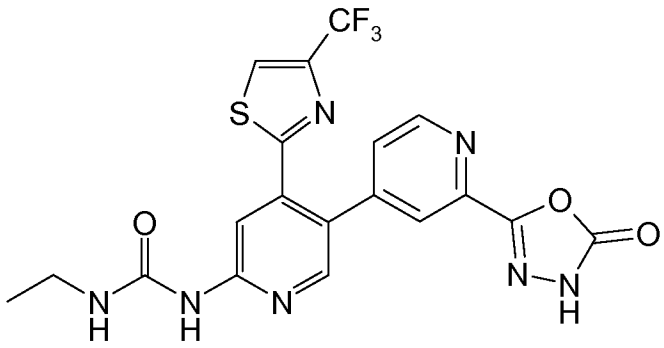
Examples 31-32

The following Examples were synthesized according to the procedure for Example 30 from the starting materials indicated below.

Ex	Compound	Data	SM
31	1-(5-(6-cyanopyrazin-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 420 for $C_{17}H_{12}F_3N_7OS$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.20 (m, 2H), 7.50 (m, 1H), 8.18 (s, 1H), 8.61 (s, 1H), 8.68 (s, 1H), 9.08 (s, 1H), 9.20 (s, 1H), 9.67 (s, 1H).	Intermediate 3 and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazine-2-carbonitrile
32	1-(6-cyano-4'-(4-(trifluoromethyl)thiazol-2-yl)-2,3'-bipyridin-6'-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 418 for $C_{18}H_{12}F_3N_6OS$. ^1H NMR (300 MHz, d_6-DMSO): 1.04 (t, 3H), 3.12 (m, 2H), 7.49 (m, 1H), 7.80 (m, 1H), 7.93 (m, 1H), 8.01 (m, 1H), 8.04 (s, 1H), 8.45 (s, 1H), 8.56 (s, 1H), 9.51 (s, 1H).	Intermediate 3 and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile

Example 33

1-ethyl-3-(2'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea:

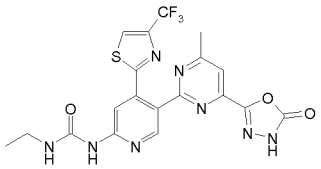
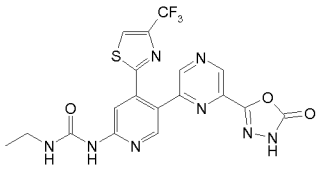
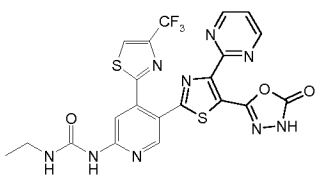


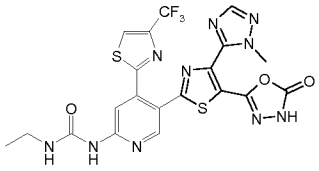
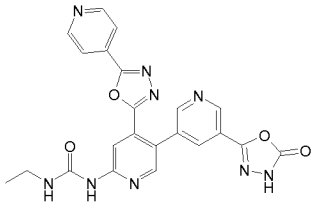
6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylic acid (Intermediate 50, 72.1 mg, 0.16 mmol) was dissolved in a DMF solution containing diisopropylethyl amine (0.057 mL, 0.33 mmol) and HATU (75 mg, 0.20 mmol). The solution was allowed to stir for 30 min., then hydrazine monohydrate (0.052 mL, 1.65 mmol) was added in a single in portion. The reaction mixture was diluted with EtOAc then washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure.

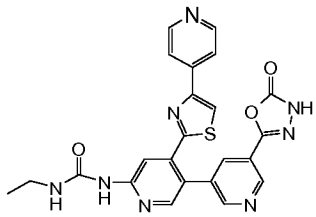
The crude reaction mixture was dissolved in THF (2 mL) and carbonyl diimidazole (66 mg, 0.41 mmol) was added in a single portion. The reaction mixture was heated to reflux in a sealed microwave vial. The crude reaction mixture was concentrated under reduced pressure. The resulting residue was treated with water and the solid that formed was collected by filtration, washed with water and dried *in vacuo*. Isolation gave 61 mg of the crude product. The crude product was dissolved in minimal DMSO and purified by Gilson HPLC (5-95% ACN / 0.1% TFA water in 14 min). Isolation gave 21 mg of the title compound.
LC/MS (ES^+)[$(M+H)^+$]: 478 for $C_{19}H_{14}F_3N_7O_3S$.
^1H NMR (300 MHz, d_6-DMSO): 1.04 (t, 3H), 3.12 (m, 2H), 7.43 (d, 1H), 7.46 (t, 1H), 7.73 (s, 1H), 8.10 (s, 1H), 8.32 (s, 1H), 8.55 (s, 1H), 8.62 (d, 1H), 9.49 (s, 1H), 12.74 (s, 1H).

Example 34-39

The following Examples were prepared according to the procedure described for Example 9 from the indicated starting materials.

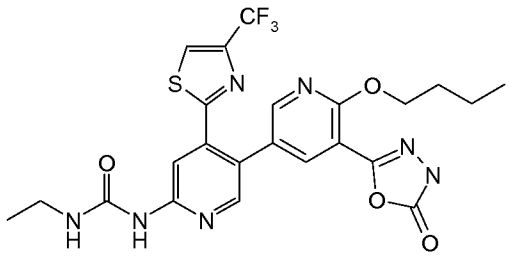
Ex	Compound	Data	SM
34	1-ethyl-3-(5-(4-methyl-6-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 493 for $C_{19}H_{15}F_3N_8O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.04 (t, 3H), 2.35 (s, 3H), 3.12 (m, 2H), 7.54 (t, 1H), 7.68 (s, 1H), 7.92 (s, 1H), 8.55 (s, 1H), 8.79 (s, 1H), 9.62 (s, 1H), 12.99 (s, 1H).	Intermediate 41 and CDI
35	1-ethyl-3-(5-(6-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 479 for $C_{18}H_{13}F_3N_8O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.10 (t, 3H), 3.19 (m, 2H), 7.53 (t, 1H), 8.15 (s, 1H), 8.60 (s, 1H), 8.61 (s, 1H), 8.88 (s, 1H), 9.06 (s, 1H), 9.63 (s, 1H), 12.97 (s, 1H).	Intermediate 42 and CDI
36	1-ethyl-3-(5-(5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(pyrimidin-2-yl)thiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 562 for $C_{21}H_{14}F_3N_9O_3S_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.09 (t, 3H), 3.18 (m, 2H), 7.47 (t, 1H), 7.57 (t, 1H), 8.15 (s, 1H), 8.72 (s, 1H), 8.79 (s, 1H), 8.91 (d, 2H), 9.72 (s, 1H), 12.08 (s, 1H).	Intermediate 39 and CDI

37	1-ethyl-3-(5-(4-(1-methyl-1H-1,2,4-triazol-5-yl)-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 565 for $C_{20}H_{15}F_3N_{10}O_3S_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.09 (t, 3H), 3.17 (m, 2H), 3.77 (s, 3H), 7.46 (t, 1H), 8.07 (s, 1H), 8.09 (s, 1H), 8.73 (s, 1H), 8.82 (s, 1H), 9.74 (s, 1H), 12.88 (s, 1H).	Intermediate 40 and CDI
38	1-ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea: 	LC/MS (ES^+)[$(M+H)^+$]: 472 for $C_{22}H_{17}N_9O_4$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.22 (m, 2H), 7.44 (t, 1H), 7.68 (d, 2H), 8.28 (d, 1H), 8.44 (s, 1H), 8.51 (s, 1H), 8.80 (s, 1H), 8.81 (d, 2H), 9.03 (d, 1H), 9.59 (s, 1H), 12.77 (s, 1H).	Intermediate 54 and CDI

39	N-ethyl-N'-[5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-pyridin-4-yl-1,3-thiazol-2-yl)-3,3'-bipyridin-6-yl]urea 	LC/MS (ES^+)[$(M+H)^+$]: 487 for $C_{23}H_{18}N_8O_3S$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.22 (m, 2H), 7.36 (t, 1H), 7.62 (t, 1H), 7.67 (d, 1H), 7.84 (m, 1H), 8.21 (t, 1H), 8.28 (s, 1H), 8.34 (s, 1H), 8.37 (s, 1H), 8.62 (d, 1H), 8.65 (d, 1H), 8.98 (d, 1H), 9.39 (s, 1H), 12.79 (s, 1H).	Intermediate 34 and CDI

Example 40

1-(6'-butoxy-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



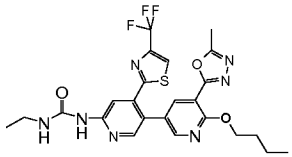
6-Butoxy-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 57, <100 mg) was stirred in anhydrous MeOH in the presence of catalytic amount of $SOCl_2$ overnight at rt. The mixture was concentrated and the residue was dissolved in EtOH, and treated with >10 eq. of hydrazine hydrate at 70-80 °C for 48 h. The mixture was concentrated and residue was purified via a reverse phase column (10-60% EtOH-water). The hydrazide product was dissolved in THF, treated with 1.5 eq. of carbonyl diimidazole and Et_3N at room temperature for 1h. The reaction mixture was concentrated and purified via a silica gel column chromatograph with heptane-EtOAc(1:1)+2% EtOH to give a 15% yield of 1-(6'-butoxy-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea.

MS (ESP): 550.2 ($M+H^+$) for $C_{23}H_{22}F_3N_7O_4S$.

^{1}H NMR (CD_3OD): δ ppm 0.99 (t, 3H), 1.22 (t, 3H), 1.43-1.59 (m, 2 H), 1.75-1.83 (m, 2H), 3.31 (q, 2 H), 4.49 (t, 2H), 7.87 (s, 1H), 7.99 (d, 1 H), 8.16 (d, 1H), 8.21 (d, 1H), 8.32 (d, 1H)

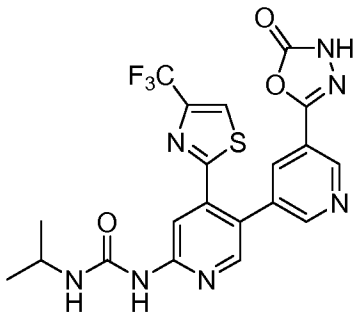
Example 41

The following Example was prepared according to the procedure for Example 1 from the starting materials indicated.

Ex	Compound	Data	SM
41	6-Butoxy-1-ethyl-3-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	^{1}H NMR (CD_3OD): δ ppm 0.99 (t, 3H), 1.22 (t, 3H), 1.43-1.59 (m, 2 H), 1.75-1.83 (m, 2H), 2.61 (s, 3H), 3.31 (q, 2 H), 4.49 (t, 2H), 7.87 (s, 1H), 7.99 (d, 1 H), 8.16 (d, 1H), 8.21 (d, 1H), 8.32 (d, 1H)	Intermediate 57 and acetohydrazide

Example 42

1-isopropyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



To a 100 mL of round bottom flask was charged methyl 6'-(3-isopropylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 79, 80 mg, 0.172 mmol) with ethanol (20 mL), then hydrazine monohydrate (3 mL) was added. The mixture was heated at reflux for 1.5 h. The mixture was concentrated under reduced pressure to give a white solid. To the crude material was charged anhydrous tetrahydrofuran (20 mL) with 1,1'-carbonyl diimidazole (1.43 g). The mixture was allowed to stir at room temperature overnight. The mixture was concentrated to dryness, water was added and the mixture was

allowed to stand for 1-2 hours. A white solid precipitated from the water and was collected then dried *in vacuo* overnight at 50°C to give a white solid (56 mg, 66.4%).

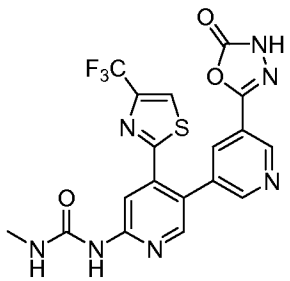
MS (ESP): 492.0 (MH^+) for $C_{20}H_{16}F_3N_7O_3S$

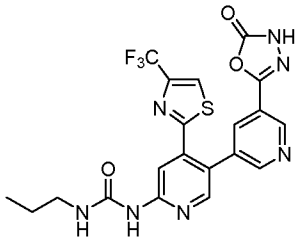
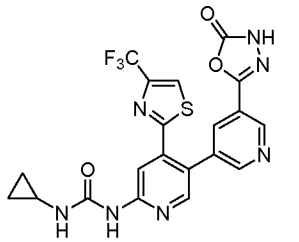
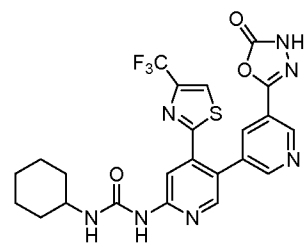
^{1}H NMR (300 MHz, CD_3OD): δ 1.25 (d, 6H), 3.99 (m, 1H), 7.90 (s, 1H), 8.17 (t, 1H), 8.25 (d, 1H), 8.37 (d, 1H), 8.57 (d, 1H), 9.00 (d, 1H)

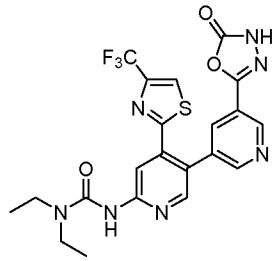
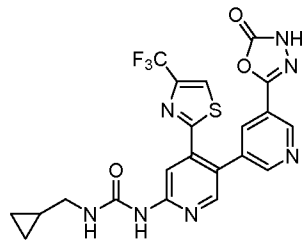
^{19}F NMR (CD_3OD) -66.00

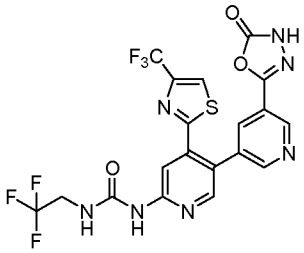
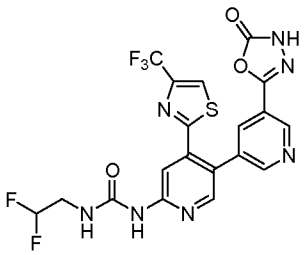
Example 43-50

The following Examples were prepared as described for Example 42 from the starting materials indicated in the Table.

Ex	Compound	Data	SM
43	1-methyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 464.1 (MH^+) for $C_{18}H_{12}F_3N_7O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 2.90 (s, 3H), 7.81 (s, 1H), 8.16 (t, 1H), 8.25 (d, 1H), 8.37 (d, 1H), 8.54 (d, 1H), 9.00 (d, 1H) ^{19}F NMR (300 MHz, CD_3OD) -65.99	Intermediate 70

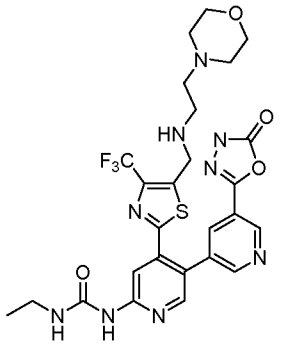
44	1-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-propylurea 	MS (ESP): 492.0 (MH^+) for $C_{20}H_{19}F_3N_7O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.59-1.66 (m, 2H), 3.29 (t, 2H), 7.86 (s, 1H), 8.17 (t, 1H), 8.25 (d, 1H), 8.38 (d, 1H), 8.58 (d, 1H), 9.00 (d, 1H) ^{19}F NMR (300 MHz, CD_3OD) -66.00	Intermediate 80
45	1-cyclopropyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 490.2 (MH^+) for $C_{20}H_{14}F_3N_7O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 0.56-0.61 (m, 2H), 0.76-0.82 (m, 2H), 2.67-2.72 (m, 1H), 7.96 (br, 1H), 8.14 (s, 1H), 8.24 (s, 1H), 8.36 (s, 1H), 8.50 (s, 1H), 8.99 (s, 1H) ^{19}F NMR (300 MHz, CD_3OD) -65.97	Intermediate 71
46	1-cyclohexyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 532.2 (MH^+) for $C_{23}H_{20}F_3N_7O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 1.28-1.46 (m, 5H), 1.60-1.99 (m, 5H), 3.70 (br, 1H), 7.89 (d, 1H), 8.17 (t, 1H), 8.26 (d, 1H), 8.38 (d, 1H), 8.58 (d, 1H), 9.00 (d, 1H) ^{19}F NMR (300 MHz, CD_3OD) -66.00	Intermediate 72

47	1,1-diethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 506.1 (MH^+) for $C_{21}H_{18}F_3N_7O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 1.26 (t, 6H), 3.53 (q, 4H), 8.30 (s, 1H), 8.34 (s, 1H), 8.41 (s, 1H), 8.52 (s, 1H), 8.69 (s, 1H), 9.10 (d, 1H) ^{19}F NMR (300 MHz, CD_3OD) -65.99	Intermediate 73
48	1-(cyclopropylmethyl)-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 504.0 (MH^+) for $C_{21}H_{16}F_3N_7O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 0.28-0.32 (m, 2H), 0.52-0.56 (m, 2H), 1.09-1.20 (m, 1H), 3.20 (d, 2H), 8.00 (s, 1H), 8.36 (s, 1H), 8.41 (d, 1H), 8.48 (s, 1H), 8.80 (s, 1H), 9.16 (s, 1H) ^{19}F NMR (300 MHz, CD_3OD) -66.01	Intermediate 74

49	1-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-(2,2,2-trifluoroethyl)urea 	MS (ESP): 531.9 (MH^+) for $C_{19}H_{11}F_6N_7O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 4.06 (q, 2H), 7.92 (s, 1H), 8.18 (t, 1H), 8.26 (d, 1H), 8.40 (d, 1H), 8.56 (d, 1H), 9.00 (d, 1H) ^{19}F NMR (300 MHz, CD_3OD) -65.99 (s, 3F), -74.94 (t, 3F)	Intermediate 75
50	1-(2,2-difluoroethyl)-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 514.2 (MH^+) for $C_{19}H_{12}F_5N_7O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 3.71 (td, 2H), 5.99 (tt, 1H), 7.89 (s, 1H), 8.17 (t, 1H), 8.26 (d, 1H), 8.39 (d, 1H), 8.56 (d, 1H), 9.00 (d, 1H) ^{19}F NMR (300 MHz, CD_3OD) -65.99 (s, 3F), -125.32 (t, 1F), -125.52 (t, 1F)	Intermediate 76

Example 51

1-ethyl-3-(5'-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(5-((2-morpholinoethylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea trihydrochloride



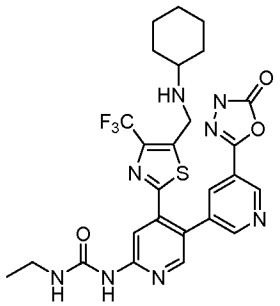
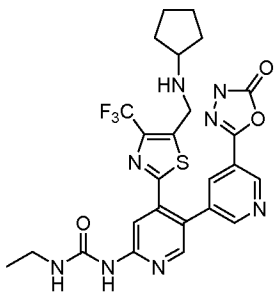
Methyl 6'-(3-ethylureido)-4'-(5-((2-morpholinoethylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 98, 0.35 mmol) was dissolved in tetrahydrofuran (5 mL) and saturated sodium bicarbonate solution (3 mL) was added followed by di-tert-butyl dicarbonate (0.7 mmol) and the reaction was stirred at room temperature for 96 hours at 35°C. Ethyl acetate (10 mL) was added, the layers separated and the solvent was removed *in vacuo*. The residue was dissolved in ethanol (20 mL), hydrazine monohydrate (1 mL) was added and the solution stirred at room temperature for 3 hours. The solvent was removed *in vacuo*, and the residue was twice suspended in 2:1 toluene:tetrahydrofuran (10 mL) and the solvent was removed *in vacuo*. This residue was then dissolved in anhydrous tetrahydrofuran (10 mL) and 1,1'-carbonyl diimidazole (500 mg) was added. The reaction was stirred at room temperature for 5 hours and the solvent was removed. The residue was chromatographed on an 8g Analogix silica gel column eluting with 0-10% methanol in dichloromethane. The product containing fractions were combined and subjected to further HPLC purification using water and acetonitrile. The product fractions were combined, and hydrochloric acid (1 mL) was added. As the solvent was removed from the product on a rotovap at 45°C, the Boc group was cleaved to give final product (18% yield)

MS (ESP): 620.1 ($M+H^+$) for $C_{26}H_{31}Cl_3F_3N_9O_4S$

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 3.19-3.22 (m, 2H), 3.42-3.52 (m, 4H), 3.80-3.99 (m, 4H), 4.58 (s, 2H), 7.52 (bt, 1H), 8.18 (t, 1H), 8.29 (s, 1H), 8.38 (s, 1H), 8.64 (d, 1H), 8.99 (d, 1H), 9.63 (s, 1H), 12.88 (s, 1H).

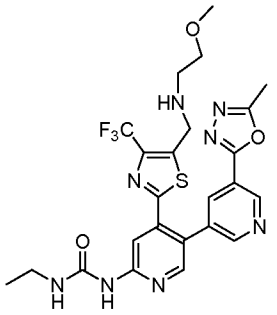
Examples 52-53

The following compounds were prepared according to the procedure described for Example 51 from the starting material as indicated in the Table.

Ex	Compound	Data	SM
52	1-(4-(5-((cyclohexylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-5'-(5-hydroxy-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea hydrochloride 	MS (ESP): 464.1 (MH^+) for $C_{18}H_{12}F_3N_7O_3S$ ^1H NMR (300 MHz, CD_3OD): δ 2.90 (s, 3H), 7.81 (s, 1H), 8.16 (t, 1H), 8.25 (d, 1H), 8.37 (d, 1H), 8.54 (d, 1H), 9.00 (d, 1H) ^{19}F NMR (300 MHz, CD_3OD) -65.99	Intermediate 101
53	1-(4-(5-((cyclopentylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-5'-(5-hydroxy-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea hydrochloride 	MS (ESP): 575.1 ($M+H^+$) for $C_{25}H_{26}ClF_3N_8O_3S$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 1.51 (m, 2H), 1.52-1.76 (m, 4H), 1.93 (m, 2H), 1.72-1.76 (m, 2H), 3.18-3.22 (m, 2H), 3.49 (m, 1H), 4.49 (m, 2H), 7.52 (m, 1H), 8.18 (t, 1H), 8.27 (s, 1H), 8.38 (s, 1H), 8.65 (d, 1H), 9.00 (d, 1H), 9.61 (m, 2H), 12.88 (bs, 1H).	Intermediate 102

Example 54

1-ethyl-3-(4-(5-((2-methoxyethylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea



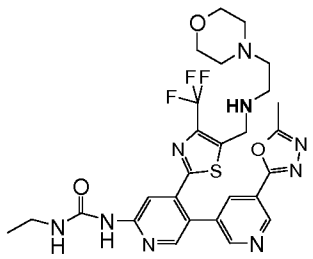
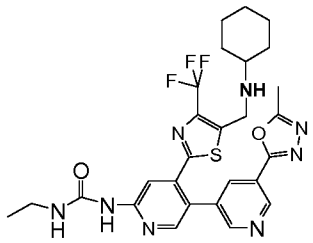
Methyl 6'-(3-ethylureido)-4'-(5-((2-methoxyethylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 97, 200 mg) was dissolved in tetrahydrofuran (3 mL) and methanol (3 mL). 1N Sodium hydroxide (3 mL) was added, and the reaction mixture was stirred at room temperature for 3 h. The organics were removed and the residual aqueous phase was acidified to pH ~2 with 1N hydrochloric acid. The water was then removed *in vacuo*. The residue was dissolved in phosphorous oxychloride (3 mL), acetic hydrazide (200 mg) was added and the solution heated at 60°C for 3 hours. Most of the phosphorous oxychloride was removed *in vacuo* and then saturated sodium bicarbonate was added to pH ~7. The solution was extracted with 2:1 ethyl acetate: tetrahydrofuran (3×, 3 mL each). The organic phases were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*. The crude product was chromatographed on a 4g Analogix silica gel column using 0-10% methanol in dichloromethane.

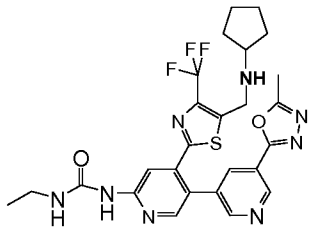
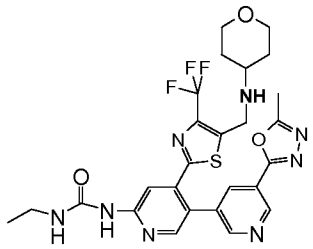
MS (ESP): 563.1 ($M+H^+$) for $C_{24}H_{25}F_3N_8O_3S$

^1H NMR (300 MHz, DMSO-d_6): δ 1.22 (t, 3H), 2.63 (s, 3H), 2.71 (t, 2H), 3.31 (s, 3H), 3.31-3.41 (m, 4H), 4.07 (d, 2H), 7.79 (s, 1H), 8.34-8.36 (m, 2H), 8.63 (d, 1H), 9.17 (d, 1H).

Examples 55-58

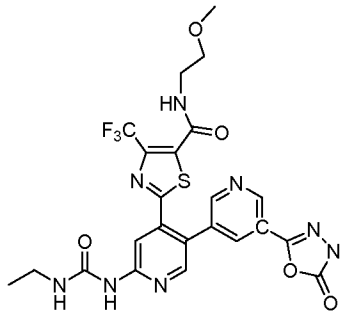
The following Examples were prepared according to the procedure described for Example 54 from the starting materials indicated in the Table.

Ex	Compound	Data	SM
55	1-ethyl-3-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(5-((2-morpholinoethylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 618.3 ($M+H^+$) for $C_{27}H_{30}F_3N_9O_3S$; ^1H NMR (300 MHz, $CDCl_3$): δ 1.27 (t, 3H), 2.66 (s, 3H), 2.66-2.72 (bs, 4H), 2.82-2.88 (m, 2H), 3.42-3.48 (m, 2H), 3.77-3.84 (m, 4H), 4.10 (d, 2H), 5.05 (bs, 1H), 7.62 (s, 1H), 8.23 (s, 1H), 8.30 (t, 1H), 8.59 (d, 1H), 8.98 (bs, 1H), 9.24 (d, 1H), 9.64 (s, 1H)	Intermediate 98
56	1-(4-(5-((cyclohexylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 587.1 ($M+H^+$) for $C_{27}H_{29}F_3N_8O_2S$; ^1H NMR (300 MHz, CD_3OD): δ 0.97-1.18 (m, 2H), 1.19-1.25 (m, 3H), 1.22 (t, 3H), 1.59-1.79 (m, 5H), 2.32-2.37 (m, 1H), 2.64 (s, 3H), 3.30-3.38 (m, 2H), 4.05 (m, 2H), 7.82 (s, 1H), 8.35-8.38 (m, 2H), 8.65 (d, 1H), 9.19 (d, 1H).	Intermediate 101

57	1-(4-(5-((cyclopentylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 573.3 ($M+H^+$) for $C_{26}H_{27}F_3N_8O_2S$; ^1H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 1.23-1.31 (m, 2H), 1.48-1.52 (m, 2H), 1.61-1.65 (m, 2H), 1.72-1.76 (m, 2H), 2.64 (s, 3H), 3.02-3.06 (m, 1H), 3.31-3.39 (m, 2H), 4.03 (m, 2H), 7.81 (m, 1H), 8.34-8.37 (m, 2H), 8.64 (d, 1H), 9.17 (d, 1H).	Intermediate 102
58	1-ethyl-3-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(5-((tetrahydro-2H-pyran-4-ylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 589.2 ($M+H^+$) for $C_{26}H_{27}F_3N_8O_3S$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.29 (t, 3H), 1.24-1.38 (m, 2H), 1.69-1.78 (m, 2H), 2.60-2.69 (m, 1H), 2.67 (s, 3H), 3.30-3.38 (m, 2H), 3.43-3.52 (m, 2H), 3.90-3.96 (m, 2H), 4.07 (d, 2H), 7.45 (s, 1H), 8.25 (s, 1H), 8.35 (t, 1H), 8.61 (d, 1H), 8.85 (bs, 1H), 9.01 (bs, 1H), 9.26 (d, 1H).	Intermediate 103

Example 59

2-(6-(3-ethylureido)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl)-*N*-(2-methoxyethyl)-4-(trifluoromethyl) thiazole-5-carboxamide



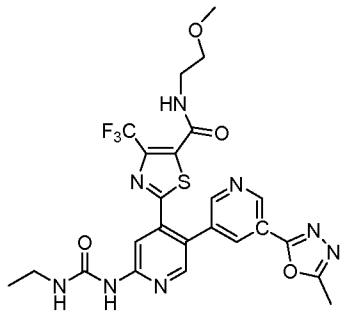
To a 50 mL round bottom flask was added methyl 6'-(3-ethylureido)-4'-(5-(2-methoxyethylcarbamoyl)-4-(trifluoromethyl) thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 104, 80 mg), ethanol (10 mL) and hydrazine (0.3 mL) and the solution heated to reflux for 3 h. The solvent was removed *in vacuo* and the residue evaporated from toluene (3×, 60mL) to remove excess hydrazine. The yellowish gum was then dried at 50 °C in a vacuum oven overnight. The crude solid was re-dissolved in tetrahydrofuran (10 mL), then triethylamine (1 mL) and 1,1'-carbonyl diimidazole (0.5 g) were added. The solution was then stirred at room temperature for 2hrs. The solvent was removed under reduced pressure, DIUF water (10mL) was added, and the mixture was stirred for 30min. A white solid precipitated out which was filtered and dried to give 40mg product as off-white solid.

MS (ESP): 579.0 ($M+H^+$) for $C_{23}H_{21}F_3N_8O_5S$

^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 3.21 (m, 2H), 3.24 (s, 3H), 3.36 (m, 4H), 7.01 and 7.64 (bs, tautomers, 1H), 7.49 (t, 1H), 8.20 (m,1H), 8.26 (s, 1H), 8.37 (s, 1H), 8.64 (d, 1H), 9.01 (m, 2H), 9.52 (bs, 1H).

Example 60

2-(6-(3-ethylureido)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl)-*N*-(2-methoxyethyl)-4-(trifluoromethyl) thiazole-5-carboxamide



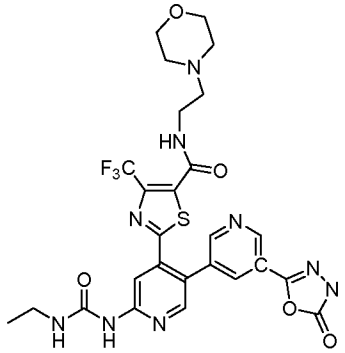
To a 50 mL round bottom flask was added crude 6'-(3-ethylureido)-4'-(5-(2-methoxyethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 105, 90 mg), phosphorus oxychloride (3 mL) and acetyl hydrazine (0.2 g). The solution was then heated to 65 °C for 3 h after which time no starting material remained by LC/MS (LC purity was ~40%). The solvent was removed under reduced pressure and toluene (3×, 60 mL) was added to remove excess phosphorus oxychloride. Saturated sodium bicarbonate was then added until pH~7. The solution was extracted with ethyl acetate (3×, 100 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated. The residue was dissolved in methanol and purified by prep HPLC to give 20mg light yellow solid.

MS (ESP): 577.2 ($M+H^+$) for $C_{24}H_{23}F_3N_8O_4S$

^{1}H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 2.35 and 2.64 (s, 3H), 3.30 (m, 6H), 3.47 (s, 3H), 7.91 (s, 1H), 8.39 (m, 2H), 8.67 (d, 1H), 9.21 (s, 1H).

Example 61

2-(6-(3-ethylureido)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl)-*N*-(2-morpholinoethyl)-4-(trifluoromethyl) thiazole-5-carboxamide



To a 50 mL round bottom flask was added methyl 6'-(3-ethylureido)-4'-(5-(2-morpholinoethylcarbamoyl)-4-(trifluoromethyl) thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 106, 200 mg), ethanol (10 mL) and hydrazine (0.5 mL) and the solution heated to reflux for 3 h. The solvent was removed *in vacuo* and the residue evaporated from toluene (3×, 60mL) to remove excess hydrazine. The crude intermediate was then dried at 50 °C in a vacuum oven overnight. The solid was re-dissolved in tetrahydrofuran (10 mL), then triethylamine (1 mL) and 1,1'-carbonyl diimidazole (0.5 g) were added. The solution was then allowed to stir at room temperature for 2hrs. The solvent was removed under reduced pressure and water (10mL) was added. The mixture was stirred at room temperature

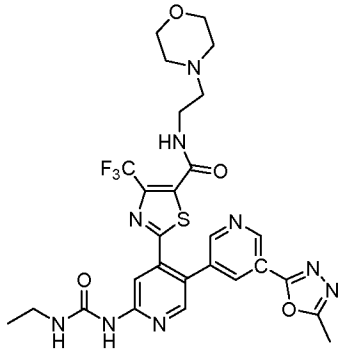
overnight however no product precipitated. The crude solution was then purified on a 30g Analogix C18 column (water/methanol: 40% MeOH/H_2O) to give 60mg light yellow solid.

MS (ESP): 634.2 ($M+H^+$) for $C_{26}H_{26}F_3N_9O_5S$

^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 2.36 (m, 8H), 3.21 (m, 2H), 3.52 (m, 4H), 7.02 and 7.63 (bs, tautomers, 1H), 7.51 (t, 1H), 8.17 (t,1H), 8.27 (s, 1H), 8.36 (s, 1H), 8.62 (d, 1H), 8.85 (t, 1H), 8.99 (d, 1H), 9.53 (s, 1H).

Example 62

2-(6-(3-ethylureido)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl)-*N*-(2-morpholinoethyl)-4-(trifluoromethyl) thiazole-5-carboxamide



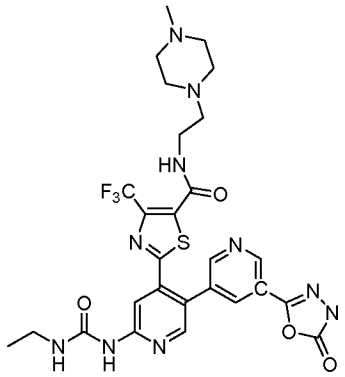
To a 50 mL round bottom flask was added crude 6'-(3-ethylureido)-4'-(5-(2-morpholinoethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 107, 200 mg), phosphorus oxychloride (3 mL) and acetyl hydrazine (0.2 g) and the solution heated to 65 °C for 3h. The solvent was removed under reduced pressure and toluene (3×, 60mL) was added to remove excess phosphorus oxychloride. Saturated sodium bicarbonate was added until pH~7 and the solution was extracted with ethyl acetate (3×, 100mL). The combined organics were dried over sodium sulfate, filtered, and concentrated. The residue was then dissolved in methanol and purified by prep HPLC to give 60 mg light yellow solid.

MS (ESP): 632.1 ($M+H^+$) for $C_{27}H_{28}F_3N_9O_4S$

^1H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 2.50 (m, 6H), 2.62 and 2.64 (s, 3H), 3.34 (m, 2H), 3.44 (t, 2H), 3.64 (t, 4H), 7.92 (s, 1H), 8.41 (m, 2H), 8.68 (d, 1H), 9.21 (s, 1H).

Example 63

2-(6-(3-ethylureido)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl)-*N*-(2-(4-methylpiperazin-1-yl)ethyl)-4-(trifluoromethyl)thiazole-5-carboxamide



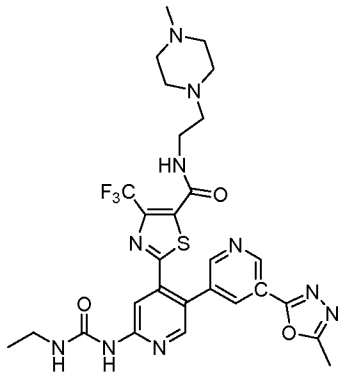
To a 50 mL round bottom flask was added methyl 6'-(3-ethylureido)-4'-(5-(2-(4-methylpiperazin-1-yl)ethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 108, 300 mg), ethanol (10 mL) and hydrazine (0.5 mL) and the solution heated to reflux for 3hrs. The solvent was removed *in vacuo* and the residue evaporated from toluene (3×, 60 mL) to remove excess hydrazine. The crude yellowish gum was then dried at 50 °C in a vacuum oven overnight. The crude solid was re-dissolved in tetrahydrofuran (10 mL), 1,1'-carbonyl diimidazole (0.5 g) was added and the solution stirred at room temperature for 2hrs. The solvent was then removed *in vacuo*. Water (10mL) was added and the mixture was then left to stir overnight however no product precipitated. The product was purified by prep HPLC (water/acetonitrile) to give 150mg off-white solid.

MS (ESP): 647.1 ($M+H^+$) for $C_{27}H_{29}F_3N_{10}O_4S$

^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 2.15 (s, 3H), 2.38 (m, 10H), 3.21 (m, 4H), 7.50 (t, 1H), 8.20 (t, 1H), 8.27 (s, 1H), 8.36 (s, 1H), 8.64 (d, 1H), 8.81 (t, 1H), 9.00 (d, 1H), 9.52 (bs, 1H).

Example 64

2-(6-(3-ethylureido)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl)-*N*-(2-(4-methylpiperazin-1-yl)ethyl)-4-(trifluoromethyl)thiazole-5-carboxamide



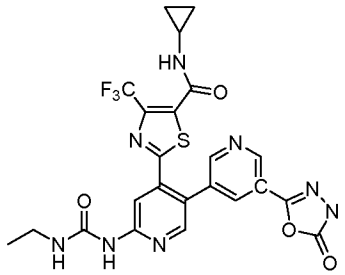
To a 50 mL round bottom flask was added crude 6'-(3-ethylureido)-4'-(5-(2-(4-methylpiperazin-1-yl)ethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 109, 200 mg), phosphorus oxychloride (3 mL) and acetyl hydrazine (0.2 g). The solution was then heated at 65 °C for 3h. The solvent was removed *in vacuo* and the residue evaporated from toluene (3×, 60 mL) to remove excess phosphorus oxychloride. Saturated sodium bicarbonate was added to pH~7 and the solution was extracted with ethyl acetate/tetrahydrofuran (1/1) (5×, 100 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated. The residue was then dissolved in methanol and purified by prep HPLC to give 30 mg pale yellow solid.

MS (ESP): 645.3 ($M+H^+$) for $C_{28}H_{31}F_3N_{10}O_3S$

^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 2.44 (s, 3H), 2.58 (m, 10H), 2.60 (s, 3H), 3.21 (m, 4H), 7.47 (t, 1H), 8.28 (s, 1H), 8.36 (s, 1H), 8.41 (s, 1H), 8.71 (s, 1H), 8.87 (t, 1H), 9.18 (s, 1H), 9.54 (bs, 1H).

Example 65

N-cyclopropyl-2-(6-(3-ethylureido)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl)-4-(trifluoromethyl)thiazole-5-carboxamide



To a 50 mL round bottom flask was added methyl 4'-(5-(cyclopropylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate (Intermediate 110, 300 mg), ethanol (10 mL) and hydrazine (0.5 mL) and the solution was heated to reflux for 3hrs. The solvent was removed *in vacuo* and the residue evaporated from toluene (3×, 60mL) to remove excess hydrazine. The crude dark yellowish gum was then dried at 50 °C in a vacuum oven overnight. The crude solid was re-dissolved in tetrahydrofuran (10 mL), 1,1'-carbonyl diimidazole (0.5 g) was added and the solution was stirred at room temperature for 2hrs. The solvent was removed under reduced pressure, water (10mL) was added and the mixture left to stir at room temperature overnight. The yellow solids were filtered and

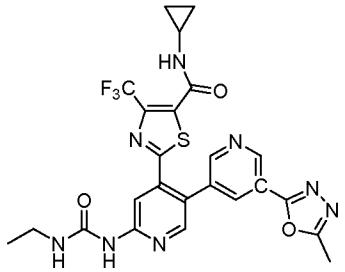
washed with water to give 80mg product at ~80% purity. The material was further purified by prep HPLC (water/acetonitrile) to give 30mg white solid.

MS (ESP): 561.3 ($M+H^+$) for $C_{23}H_{19}F_3N_8O_4S$

^1H NMR (300 MHz, DMSO-d_6): δ 0.48 (m, 2H), 0.69 (m, 2H), 1.11 (t, 3H), 2.76 (m, 1H), 3.22 (m, 2H), 7.78 (t, 1H), 8.19 (s, 1H), 8.24 (s, 1H), 8.37 (s, 1H), 8.63 (s, 1H), 9.00 (s, 2H), 9.52 (bs, 1H).

Example 66

N-cyclopropyl-2-(6-(3-ethylureido)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl)-4-(trifluoromethyl)thiazole-5-carboxamide



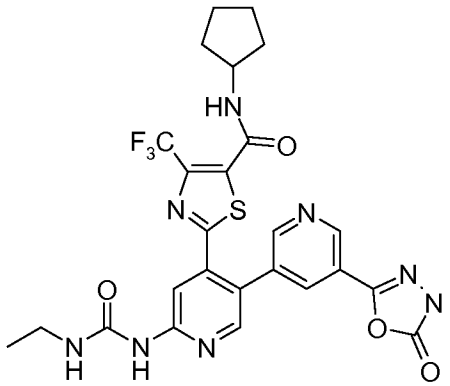
To a 50 mL round bottom flask was added crude 4'-(5-(cyclopropylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylic acid (Intermediate 111, 200 mg), phosphorus oxychloride (3 mL) and acetyl hydrazine (0.2 g). The solution was then heated at 65 °C for 3 h. The solvent was removed *in vacuo* and the residue evaporated from toluene (3×, 60mL) to remove excess phosphorus oxychloride. Saturated sodium bicarbonate was added to pH~7 and the solution was extracted with ethyl acetate (3×, 100mL). The combined organics were dried over sodium sulfate, filtered, and concentrated. The residue was then dissolved in methanol and purified by prep HPLC to give 40mg pale yellow solid.

MS (ESP): 559.2 ($M+H^+$) for $C_{24}H_{21}F_3N_8O_3S$

^1H NMR (300 MHz, DMSO-d_6): δ 0.47 (m, 2H), 0.69 (m, 2H), 1.11 (t, 3H), 2.60 (s, 3H), 2.74 (m, 1H), 3.22 (m, 2H), 7.47 (t, 1H), 8.24 (s, 1H), 8.34 (t, 1H), 8.41 (s, 1H), 8.69 (d, 1H), 8.99 (d, 1H), 9.17 (d, 1H), 9.53 (bs, 1H).

Example 67

N-cyclopentyl-2-(6-(3-ethylureido)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl)-4-(trifluoromethyl)thiazole-5-carboxamide



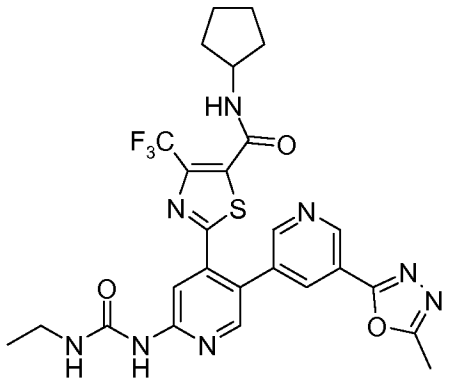
To a 50 mL round bottom flask was added methyl 4'-(5-(cyclopentylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate (Intermediate 112, 200 mg), ethanol (10 mL) and hydrazine (1.0 mL). The solution was heated to reflux for 3hrs. The solvent was removed *in vacuo* and the residue evaporated from toluene (3×, 60mL) to remove excess hydrazine. The crude dark yellowish gum was then dried at 50 °C in a vacuum oven overnight. The crude solid was re-dissolved in tetrahydrofuran (10 mL), and 1,1'-carbonyl diimidazole (0.5 g) was added. The solution was then allowed to stir at room temperature for 18hrs. The solvent was removed under reduced pressure, water (10mL) was added and the mixture was then stirred at room temperature for 3 hours. A yellow solid precipitated out and was filtered and triturated with acetonitrile to give 84 mg of pale yellow solid.

MS (ESP): 589.2 ($M+H^+$) for $C_{25}H_{23}F_3N_8O_4S$

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 1.35-1.64 (m, 6H), 1.80-1.99 (m, 2H), 3.16-3.23 (m, 2H), 4.06-4.12 (m, 1H), 7.48 (bt, 1H), 8.20 (t, 1H), 8.24 (s, 1H), 8.38 (s, 1H), 8.63 (d, 1H), 8.91 (d, 1H), 9.00 (d, 1H), 9.53 (bs, 1H)

Example 68

N-cyclopentyl-2-(6-(3-ethylureido)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl)-4-(trifluoromethyl)thiazole-5-carboxamide



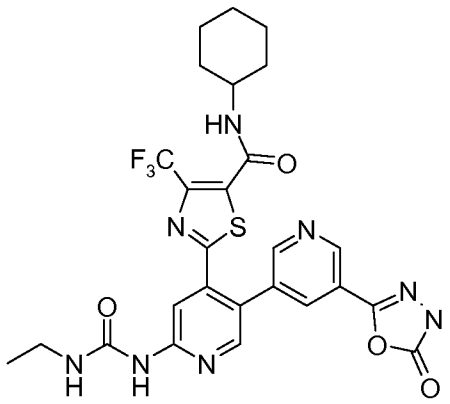
To a 20 mL vial was added crude 4'-(5-(cyclopentylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylic acid (Intermediate 113, 150 mg), phosphorus oxychloride (3 mL) and acetyl hydrazine (0.2 g). The solution was then heated at 60 °C for 3 h. The solvent was removed *in vacuo* and the residue evaporated from toluene (3×, 60mL) to remove excess phosphorus oxychloride. Saturated sodium bicarbonate was added to pH~7 and the solution extracted with ethyl acetate (3×, 10 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated. The residue was then chromatographed on a 4g Analogix silica gel column using 0-10% methanol in dichloromethane to give 42 mg of pale yellow solid.

MS (ESP): 587.1 ($M+H^+$) for $C_{26}H_{25}F_3N_8O_3S$

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 1.39-1.61 (m, 6H), 1.79-1.83 (m, 2H), 2.61 (s, 3H), 3.18-3.25 (m, 2H), 4.02-4.16 (m, 1H), 7.48 (bt, 1H), 8.24 (s, 1H), 8.35 (t, 1H), 8.41 (d, 1H), 8.69 (d, 1H), 8.90 (d, 1H), 9.17 (d, 1H), 9.55 (bs, 1H).

Example 69

N-cyclohexyl-2-(6-(3-ethylureido)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl)-4-(trifluoromethyl)thiazole-5-carboxamide



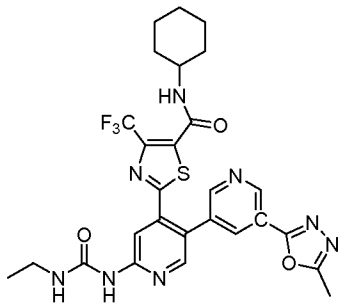
To a 50 mL round bottom flask was added methyl 4'-(5-(cyclohexylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate (Intermediate 114, 200 mg), ethanol (10 mL) and hydrazine (0.5 mL). The solution was then heated to reflux for 3hrs. The solvent was removed *in vacuo* and the residue evaporated from toluene (3×, 60mL) to remove excess hydrazine. The crude yellowish gum was then dried at 50 °C in a vacuum oven overnight. The crude solid was re-dissolved in tetrahydrofuran (10 mL), 1,1'-carbonyl diimidazole (0.5 g) was added and the solution allowed to stir at room temperature for 2hrs. The solvent was removed under reduced pressure, water (10mL) was added and the mixture stirred at room temperature for 2 h. The solids were removed by filtration, triturated with acetonitrile and dried in a vacuum oven at 50°C for 18 hours to give 73mg pale yellow solid.

MS (ESP): 603.3 ($M+H^+$) for $C_{26}H_{25}F_3N_8O_4S$

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 1.12-1.36 (m, 4H), 1.53-1.60 (m, 1H), 1.60-1.78 (m, 5H), 3.16-3.25 (m, 2H), 3.60-3.65 (m, 1H), 7.48 (bt, 1H), 8.21 (t, 1H), 8.24 (s, 1H), 8.37 (s, 1H), 8.63 (d, 1H), 8.84 (d, 1H), 9.00 (d, 1H), 9.53 (s, 1H).

Example 70

N-cyclohexyl-2-(6-(3-ethylureido)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl)-4-(trifluoromethyl)thiazole-5-carboxamide



To a 50 mL round bottom flask was added crude 4'-(5-(cyclohexylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylic acid (Intermediate 115, 200 mg), phosphorus oxychloride (3 mL) and acetyl hydrazine (0.2 g). The solution was then heated at 60 °C for 3 h. The solvent was removed *in vacuo* and the residue evaporated from toluene (3×, 60mL) to remove excess phosphorus oxychloride. Saturated sodium bicarbonate was added to pH~7 and the solution extracted with ethyl acetate (3×, 20mL). The combined organics were dried over sodium sulfate, filtered, and

concentrated. The residue was then chromatographed on a 4g Analogix silica gel column using 0-10% methanol in dichloromethane to give 53mg pale yellow solid.

MS (ESP): 601.2 ($M+H^+$) for $C_{27}H_{27}F_3N_8O_3S$

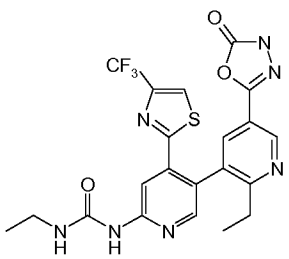
^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 1.12-1.29 (m, 6H), 1.50-1.60 (m, 1H), 1.60-1.78 (m, 3H), 2.60 (s, 3H), 3.16-3.26 (m, 2H), 3.60-3.65 (m, 1H), 7.49 (bt, 1H), 8.25 (s, 1H), 8.35 (t, 1H), 8.41 (s, 1H), 8.69 (d, 1H), 8.83 (d, 1H), 9.17 (d, 1H), 9.55 (bs, 1H).

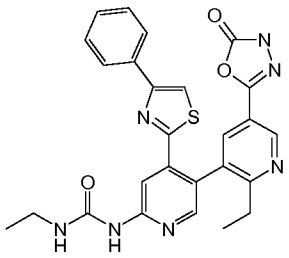
Examples 71-72

The following Examples were prepared according to the general procedures described below from the starting materials indicated in the Table.

General Procedure

A methyl ester (0.2 mmol) was suspended in ethanol (10 mL) and anhydrous hydrazine (0.1 mL) was added. The resulting suspension was heated at reflux for 3 h. The solvent was removed *in vacuo*. Toluene (5 mL) was added to the residue and removed *in vacuo* twice to remove traces of hydrazine. Anhydrous tetrahydrofuran (10 mL) and1,1'-carbonyl diimidazole (100 mg) were added, and the reaction was stirred at room temperature for 16 h. The solvent was removed *in vacuo* and the residue subjected to reverse phase chromatography using 10-99% acetonitrile in water to isolate the product.

Ex	Compound	Data	SM
71	1-ethyl-3-(2'-ethyl-5'-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 506.1 (MH^+) for $C_{21}H_{18}F_3N_7O_3S$ ^1H NMR (300 MHz, DMSO-d_6): 1.05 (t, 3H), 1.22 (t, 1H), 2.51-2.57 (m, 2H), 3.280-3.39 (m, 2H), 8.02 (s, 1H), 8.05 (d, 1H), 8.18 (d, 1H), 8.26 (d, 1H), 9.00 (d, 1H)	Intermediate 120

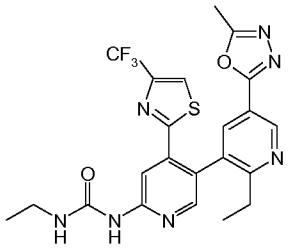
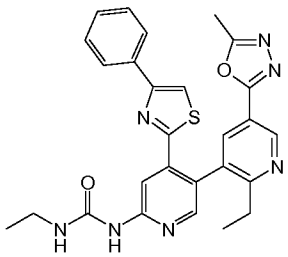
72	1-ethyl-3-(2'-ethyl-5'-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-phenylthiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 514.2(MH^+) for $C_{26}H_{23}N_7O_3S$ ^1H NMR (300 MHz, DMSO-d_6): 1.06 (t, 3H), 1.24 (t, 1H), 2.58-2.62 (m, 2H), 3.30-3.40 (m, 2H), 7.31-7.34 (m, 3H), 7.60-7.69 (m, 2H), 7.86 (s, 1H), 8.01 (s, 1H), 8.08 (d, 1H), 8.24 (d, 1H), 9.00 (d, 1H)	Intermediate 121

Examples 73-74

The following Examples were prepared according to the general procedures described below from the starting materials indicated in the Table.

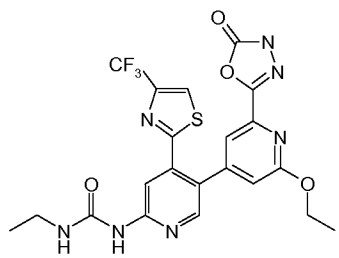
General Procedure

The appropriate carboxylic acid (0.1 mmol) and acetic hydrazide (0.15 mmol) were suspended in phosphorous oxychloride (3 mL). The reaction was heated at 65°C for 3 h. The phosphorous oxychloride was removed *in vacuo* and toluene (5 mL) was added and also removed *in vacuo*. Saturated sodium bicarbonate solution (10 mL) was added and the suspension was extracted with 2:1 ethyl acetate:tetrahydrofuran (3×, 5 mL). The organic phases were combined and the solvent was removed *in vacuo*. The residue was dissolved twice in methyl *tert*-butyl ether (5 mL each) and the solvent removed *in vacuo* to remove trace solvents. The residue was given a final trituration with methyl *tert*-butyl ether (5 mL) and filtered to give the appropriate methyl oxadiazole.

Ex	Compound	Data	SM
73	1-ethyl-3-(2'-ethyl-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 504.0 (MH^+) $C_{22}H_{20}F_3N_7O_2S$ ^1H NMR (300 MHz, DMSO-d_6): 1.01 (t, 3H), 1.12 (t, 1H), 2.42-2.53 (m, 2H), 2.58 (s, 3H), 3.20-3.26 (m, 2H), 7.61 (bt, 1H), 8.19 (d, 1H), 8.30 (s, 1H), 8.37 (s, 1H), 9.20 (d, 1H), 9.48 (bs, 1H)	Intermediate 122
74	1-ethyl-3-(2'-ethyl-5'-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-phenylthiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 512.1 (MH^+) for $C_{27}H_{25}N_7O_2S$ ^1H NMR (300 MHz, DMSO-d_6): 1.02 (t, 3H), 1.12 (t, 1H), 2.41-2.56 (m, 2H), 2.58 (s, 3H), 3.20-3.31 (m, 2H), 7.34-7.38 (m, 3H), 7.68-7.72 (m, 3H), 8.17 (d, 1H), 8.19 (s, 1H), 8.27 (s, 1H), 8.39 (s, 1H), 9.19 (d, 1H), 9.48 (bs, 1H)	Intermediate 123

Example 75

1-(2'-ethoxy-6'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)-3-ethylurea



To a 100 mL round bottom flask was charged methyl 6'-ethoxy-6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 145, 160 mg, 0.323

mmol) with ethanol (20 mL). Hydrazine monohydrate (4 mL) was added and the mixture was heated to reflux for 1 h. After concentrating under reduced pressure, the crude product was further dried in vacuum oven at 50 °C for overnight.

To the crude product was charged tetrahydrofuran (30 mL) with 1,1'-carbonyl diimidazole (160 mg, 0.97 mmol) and the mixture was stirred at room temperature for 0.5 h. Starting material remained so another portion of 1,1'-carbonyl diimidazole (110 mg) was added and the mixture stirred for another 1 h. After concentration under reduced pressure, the crude product was triturated with water. The precipitate was collected by filtration and dried in oven at 60 °C to give a beige solid (140 mg, 83.3% over two steps).

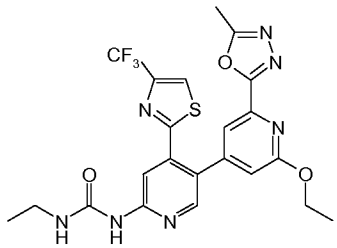
MS (ESP): 522.0 (MH^+) for $C_{21}H_{18}F_3N_7O_4S$

^{1}H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 1.39 (t, 3H), 3.31 (q, 2H), 4.45 (q, 2H), 6.86 (d, 1H), 7.32 (d, 1H), 7.79 (s, 1H), 8.26 (s, 1H), 8.35 (s, 1H)

^{19}F NMR (300 MHz, CD_3OD): -66.04

Example 76

1-(2'-ethoxy-6'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)-3-ethylurea



To a vial was charged methyl 6'-ethoxy-6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 145, 200 mg, 0.404 mmol) with tetrahydrofuran (2 mL) and water (2 mL). Lithium hydroxide (100 mg) was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and methyl tert-butyl ether was added. Solid was observed between the layers and was collected and dried in a vacuum oven at 50°C overnight.

The carboxylic salt (140 mg) was treated with acetic hydrazide (28 mg, 0.342 mmol) and phosphorus oxychloride (3 mL) then heated at 65°C for 2 h. The excess phosphorus oxychloride was removed *in vacuo* and the residue was quenched by saturated sodium bicarbonate (30 mL). The product was extracted with ethyl acetate and tetrahydrofuran (3× each). The organic layers was combined and dried over sodium sulfate. After concentration,

the crude mixture was triturated with ethanol (5 mL), and washed with methyl *tert*-butyl ether (3mL) to give a white solid (45 mg, 30.4%).

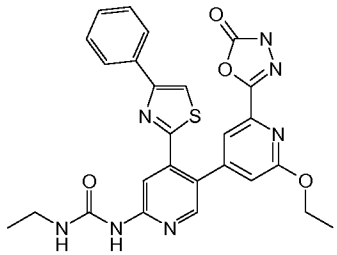
MS (ESP): 520.2 (MH^+) for $C_{22}H_{20}F_3N_7O_3S$

^1H NMR (300 MHz, CD_3OD): δ 1.22 (t, 3H), 1.39 (t, 3H), 3.31 (q, 2H), 4.45 (q, 2H), 6.86 (d, 1H), 7.32 (d, 1H), 7.79 (s, 1H), 8.26 (s, 1H), 8.35 (s, 1H)

^{19}F NMR (300 MHz, CD_3OD): -66.04

Example 77

1-(2'-ethoxy-6'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridin-6-yl)-3-ethylurea



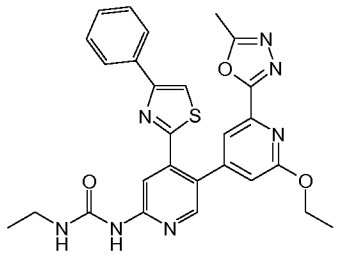
To a 100 mL round bottom flask was charged impure methyl 6'-ethoxy-6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 146, 400 mg) with ethanol (40 mL). Hydrazine monohydrate (6 mL) was added and the reaction mixture was heated to reflux for 2 h. After concentrating to dryness, the crude product was triturated with ethanol to remove Pd residue from previous step. The filtrate was concentrated under reduced pressure and dissolved in tetrahydrofuran (30 mL) with 1,1'-carbonyl diimidazole (230 mg, 1.42 mmol), and the mixture was stirred at room temperature overnight. After concentration under reduced pressure, the crude product was purified by Analogix (dichloromethane/methanol) to give an off-white solid (60 mg).

MS (ESP): 530.1 (MH^+) for $C_{26}H_{23}N_7O_4S$

^1H NMR (300 MHz, CD_3OD): δ 1.23 (t, 3H), 1.38 (t, 3H), 3.35 (q, 2H), 4.46 (q, 2H), 6.90 (d, 1H), 7.32 (m, 3H), 7.42 (d, 1H), 7.70 (d, 1H), 7.73 (d, 1H), 7.81 (s, 1H), 7.91 (s, 1H), 8.31 (d, 1H)

Example 78

1-(2'-ethoxy-6'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridin-6-yl)-3-ethylurea



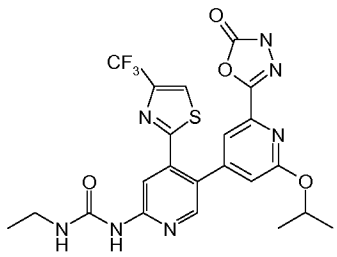
To a vial was charged methyl 6'-ethoxy-6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 146, 250 mg), tetrahydrofuran (30 mL) and water (30 mL). Lithium hydroxide (500 mg) was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and a cloudy mixture resulted. Filtration was applied to remove the solid. Methyl *tert*-butyl ether was added to the filtrate and a white solid precipitated which was collected as clean carboxylate salt (220 mg). The carboxylic salt (130 mg) was treated with acetic hydrazide (35 mg, 0.405 mmol) and phosphorus oxychloride (5 mL) then heated at 60°C for 3 h. The solution was poured into cold saturated sodium bicarbonate (30 mL) in an ice bath and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate and after concentration under reduced pressure, the crude material was purified by Analogix (dichloromethane/methanol) to give an off- white solid (60 mg, 43.3%).

MS (ESP): 528.0 (MH^+) for $C_{27}H_{25}N_7O_3S$

^1H NMR (300 MHz, CD_3OD): δ 1.23 (t, 3H), 1.40 (d, 6H), 2.57 (s, 3H), 3.35 (q, 2H), 4.50 (q, 2H), 6.97 (d, 1H), 7.31 (m, 3H), 7.63 (d, 1H), 7.68 (d, 1H), 7.70 (d, 1H), 7.83 (s, 1H), 7.91 (s, 1H), 8.33 (d, 1H)

Example 79

1-ethyl-3-(2'-isopropoxy-6'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea



To a 100 mL round bottom flask was charged methyl 6-(3-ethylureido)-6'-isopropoxy-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 147, 450 mg) with ethanol (20 mL). Hydrazine monohydrate (6 mL) was added and the mixture heated to reflux

for 1 h. After concentration under reduced pressure, the crude product was dried in a vacuum oven at 50°C for 2 h. The residue was dissolved in tetrahydrofuran (30 mL), 1,1'-carbonyl diimidazole (0.53 g) was added and the mixture was stirred at room temperature for 3 h. Since starting material remained, another portion of 1,1'-carbonyl diimidazole (1 g) was added and the mixture was stirred for another 10 min. After concentration, the crude product was purified by prep. HPLC to give an off-white solid (130 mg)

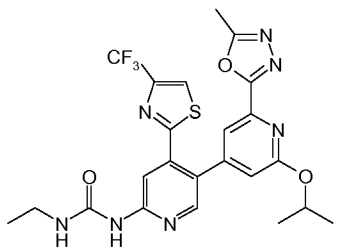
MS (ESP): 536.1 (MH^+) for $C_{22}H_{20}F_3N_7O_4S$

^{1}H NMR (300 MHz, CD_3OD): 1.22 (t, 3H), 1.36 (d, 6H), 3.35 (q, 2H), 5.46 (m, 1H), 6.89 (s, 1H), 7.41 (s, 1H), 7.92 (s, 1H), 8.33 (s, 1H), 8.36 (s, 1H)

^{19}F NMR (300 MHz, CD_3OD): -65.92

Example 80

1-ethyl-3-(2'-isopropoxy-6'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea



To a vial was charged methyl 6-(3-ethylureido)-6'-isopropoxy-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 147, 450 mg), tetrahydrofuran (30 mL) and water (30 mL). Lithium hydroxide (0.8 g) was added and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was filtered, the solid was washed with methyl *tert*-butyl ether and determined to be by-products. The aqueous layer was diluted with water and extracted with methyl *tert*-butyl ether twice. The aqueous was acidified with 6 N HCl to pH 2-3, and extracted with ethyl acetate (3×). The combined ethyl acetate layers were dried over sodium sulfate and dried in a vacuum oven at 50°C for overnight to give a yellow solid (190 mg) as clean carboxylic acid.

The carboxylic acid (180 mg, 0.364 mmol) was treated with acetic hydrazide (48 mg, 0.581 mmol) and phosphorus oxychloride (3 mL) then heated at 65°C for 2 h. The excess phosphorus oxychloride was removed *in vacuo* and the residue quenched by saturated sodium bicarbonate (30 mL). The resulting mixture was extracted with ethyl acetate (3×). The organic layers were combined and dried over sodium sulfate. After concentration under

reduced pressure, the crude mixture was purified by Analogix (dichloromethane/methanol) to give a yellow solid (52 mg, 26.8%)

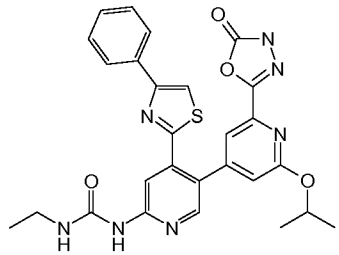
MS (ESP): 534.3 (MH^+) for $C_{23}H_{22}F_3N_7O_3S$

^1H NMR (300 MHz, CD_3OD): 1.22 (t, 3H), 1.36 (d, 6H), 2.62 (s, 3H), 3.35 (q, 2H), 5.48 (m, 1H), 6.85 (d, 1H), 7.53 (d, 1H), 7.80 (s, 1H), 8.26 (d, 1H), 8.37 (d, 1H)

^{19}F NMR (300 MHz, CD_3OD): -65.94

Example 81

1-ethyl-3-(2'-isopropoxy-6'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridin-6-yl)urea



To a 100 mL round bottom flask was charged methyl 6-(3-ethylureido)-6'-isopropoxy-4-(4-phenylthiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 148, 500 mg) with anhydrous ethanol (20 mL). Hydrazine monohydrate (6 mL) was added and the mixture was heated to reflux for 2 h. After concentration the crude product was dried in a vacuum oven at 60°C overnight.

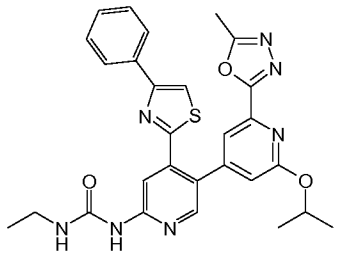
The crude hydrazide was dissolved in tetrahydrofuran (30 mL), 1,1'-carbonyl diimidazole (660 mg) added, and the mixture was stirred at room temperature for 1 h. After concentration under reduced pressure, the crude product was purified by prep. HPLC to give a yellow solid (100 mg).

MS (ESP): 544.2 (MH^+) for $C_{27}H_{25}N_7O_4S$

^1H NMR (300 MHz, CD_3OD): δ 1.23 (t, 3H), 1.35 (d, 6H), 3.35 (q, 2H), 5.46 (m, 1H), 6.92 (d, 1H), 7.34 (m, 2H), 7.46 (d, 1H), 7.58 (d, 1H), 7.72 (d, 1H), 7.75 (d, 1H), 7.93 (s, 1H), 8.02 (s, 1H), 8.29 (s, 1H)

Example 82

1-ethyl-3-(2'-isopropoxy-6'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridin-6-yl)urea



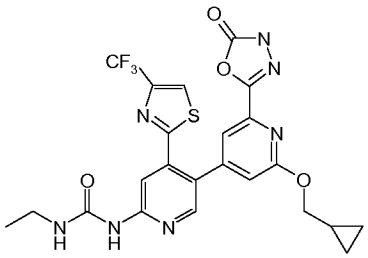
To a vial was charged methyl 6-(3-ethylureido)-6'-isopropoxy-4-(4-phenylthiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 148, 0.66 g), tetrahydrofuran (30 mL) and water (30 mL). Lithium hydroxide (1 g) was added and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with water and a cloudy mixture resulted. Filtration was applied to remove the solid and the filtrate was extracted with methyl *tert*-butyl ether (3×). The aqueous layer was acidified by 6 N HCl to pH 2-3, and extracted with ethyl acetate (3×). The combined ethyl acetate layers were dried over sodium sulfate, to give solid carboxylic acid (100 mg). The carboxylic acid (100 mg, 0.199 mmol) was treated with acetic hydrazide (25 mg, 0.298mmol) and phosphorus oxychloride (5 mL) then heated at 60°C for 3 h. The solution was poured into cold saturated sodium bicarbonate (30 mL) in an ice bath and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate. After concentration, the crude mixture was purified by Analogix (dichloromethane/methanol) to give a white solid (50 mg, 46.5%).

MS (ESP): 542.1 (MH^+) for $C_{28}H_{27}N_7O_3S$

^{1}H NMR (300 MHz, CD_3OD): δ 1.23 (t, 3H), 1.35 (d, 6H), 2.57 (s, 3H), 3.35 (q, 2H), 5.48 (m, 1H), 6.91 (d, 1H), 7.29 (m, 3H), 7.60 (d, 1H), 7.66 (s, 1H), 7.67 (s, 1H), 7.82 (s, 1H), 7.91 (s, 1H), 8.33 (d, 1H).

Example 83

1-(2'-(cyclopropylmethoxy)-6'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)-3-ethylurea



To a 100 mL round bottom flask was charged methyl 6'-(cyclopropylmethoxy)-6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate

149, 100 mg) with ethanol (20 mL). Hydrazine monohydrate (1.2 mL) was added and the mixture heated to reflux for 1 h. After concentrating the crude product was dried in a vacuum oven at 50°C for 2 h.

The crude product was dissolved in anhydrous 1,4-dioxane (30 mL), 1,1'-carbonyl diimidazole (0.53 g) added and the mixture was stirred at room temperature for 3 h, starting material remained. Another portion of 1,1'-carbonyl diimidazole (0.4 g) was added, and the mixture was stirred for another 10 min. After concentration, the crude product was purified by Analogix (dichloromethane/methanol) to give an off-white solid (35 mg)

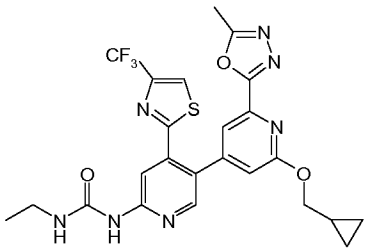
MS (ESP): 548.1 (MH^+) for $C_{23}H_{20}F_3N_7O_4S$

^1H NMR (300 MHz, CD_3OD): 0.37-0.41 (m, 2H), 0.58-0.61 (m, 2H), 1.23 (t, 3H), 1.20-1.30 (m, 1H), 3.35 (q, 2H), 4.24 (d, 2H), 6.88 (d, 1H), 7.32 (d, 1H), 7.80 (s, 1H), 8.26 (s, 1H), 8.36 (s, 1H)

^{19}F NMR (300 MHz, CD_3OD): -66.01

Example 84

1-(2'-(cyclopropylmethoxy)-6'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)-3-ethylurea



To a vial was charged methyl 6'-(cyclopropylmethoxy)-6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 149), tetrahydrofuran (30 mL) and water (30 mL). Lithium hydroxide (0.5 g) was added and the resulting mixture was stirred at room temperature for 2 h. The mixture was extracted with ethyl acetate once then the aqueous layer acidified by 6 N HCl to pH 2-3. The resulting acidic solution was extracted with ethyl acetate (3×), the combined organic layers dried over sodium sulfate and concentrated. The crude carboxylic acid (450 mg) was treated with acetic hydrazide (70 mg, 0.945 mmol) and phosphorus oxychloride (4 mL). The mixture was heated at 65°C for 3 hours, to give very impure product. The solution was poured into cold saturated sodium bicarbonate (30 mL) in an ice bath and extracted with ethyl acetate (3×). The organic layers was combined and dried over sodium sulfate. After concentration under reduced

pressure, the crude mixture was purified by Analogix (dichloromethane/methanol) to give a light yellow solid (24mg)

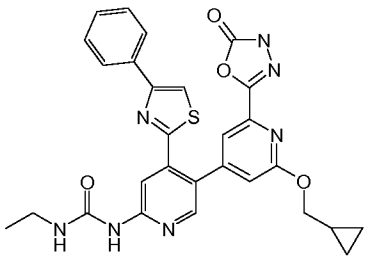
MS (ESP): 546.0 (MH^+) for $C_{24}H_{22}F_3N_7O_3S$

^1H NMR (300 MHz, CD_3OD): 0.37-0.41 (m, 2H), 0.58-0.61 (m, 2H), 1.23 (t, 3H), 1.20-1.30 (m, 1H), 3.35 (q, 2H), 4.24 (d, 2H), 6.88 (d, 1H), 7.55 (d, 1H), 7.81 (s, 1H), 8.26 (d, 1H), 8.38 (d, 1H).

^{19}F NMR (300 MHz, CD_3OD): -67.56

Example 85

1-(2'-(cyclopropylmethoxy)-6'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridin-6-yl)-3-ethylurea



To a 100 mL round bottom flask was charged methyl 6'-(cyclopropylmethoxy)-6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 150, 600 mg) with anhydrous ethanol (20 mL). Hydrazine monohydrate (2.5 mL) was added and the mixture was heated to reflux for 2 h. After concentration under reduced pressure, the crude product was dried in a vacuum oven at 60˚C overnight.

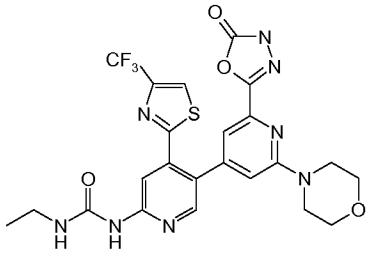
The residue was dissolved in anhydrous 1,4-dioxane (30 mL), and 1,1'-carbonyl diimidazole (600 mg) was added, and the mixture was stirred at room temperature for 1 h. Another portion of 1,1'-carbonyl diimidazole (0.7 g) was added, and the reaction went to completion. After concentration under reduced pressure, the crude product was purified by prep. HPLC to give a white solid (15 mg).

MS (ESP): 556.2 (MH^+) for $C_{28}H_{25}N_7O_4S$

^1H NMR (300 MHz, DMSO-d_6): δ 0.3-0.4 (m, 2H), 0.5-0.6 (m, 2H), 1.11 (t, 3H), 1.2-1.3 (m, 1H), 3.35 (q, 2H), 4.17 (d, 2H), 6.98 (s, 1H), 7.36-7.40 (m, 3H), 7.62 (s, 1H), 7.74-7.77 (m, 2H), 8.21 (s, 1H), 8.23 (d, 1H), 8.30 (s, 1H), 9.47 (s, 1H).

Example 86

1-ethyl-3-(2'-morpholino-6'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea



To a 100 mL round bottom flask was charged methyl 6-(3-ethylureido)-6'-morpholino-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 151, 150 mg, 0.28 mmol) with ethanol (20 mL). Hydrazine monohydrate (3 mL) was added and the mixture was heated to reflux for 0.5 h. While hot, the reaction mixture was filtered through a Celite pad to remove residual Pd catalyst from previous step. The filtrate was concentrated and dried in a vacuum oven at 50°C for 2 h.

The crude was dissolved in tetrahydrofuran (30 mL), 1,1'-carbonyl diimidazole (0.2 g) added, and the mixture was stirred at room temperature for 2 h. Since starting material remained, another portion of 1,1'-carbonyl diimidazole (0.3 g) was added, and the mixture was stirred for another 1 h. After concentration under reduced pressure, the crude product was purified by Analogix, but the product still contained imidazole. The material was triturated by water to give an off-white solid (60 mg, 38.2%)

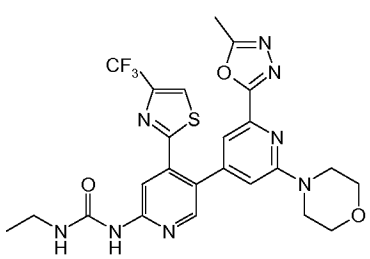
MS (ESP): 563.1 (MH^+) for $C_{23}H_{21}F_3N_8O_4S$

^{1}H NMR (300 MHz, DMSO-d_6): 1.10 (t, 3H), 3.35 (q, 2H), 3.52-3.56 (m, 4H), 3.64-3.70 (m, 4H), 7.01 (d, 2H), 7.56 (m, 1H), 8.18 (s, 1H), 8.36 (s, 1H), 8.58 (d, 1H), 9.51 (s, 1H), 12.7 (m, 1H)

^{19}F NMR (300 MHz, DMSO-d_6): -65.76

Example 87

1-ethyl-3-(2'-morpholino-6'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea



To a vial was charged methyl 6-(3-ethylureido)-6'-morpholino-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 151, 200 mg, 0.373 mmol), tetrahydrofuran (30 mL) and water (10 mL). Lithium hydroxide (0.5 g) was added, and the resulting mixture was stirred at room temperature for 1 h. The mixture was diluted with water and extracted with ethyl acetate once. The aqueous layer was acidified by 6 N HCl to pH 2-3, and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate and after concentration dried in a vacuum oven at 50°C overnight to give a yellow solid (120 mg, 61.5%).

The carboxylic acid (110 mg, 0.21 mmol) was treated with acetic hydrazide (26 mg, 0.32 mmol) and phosphorus oxychloride (3 mL) then heated at 60°C for 2 h. The solution was poured into cold saturated sodium bicarbonate in an ice bath. The resulting mixture was extracted with ethyl acetate (3×). The organic layers were combined and dried over sodium sulfate. After concentration under reduced pressure, the crude mixture was purified by Analogix (dichloromethane/methanol) to give a yellow solid (41 mg, 34.9%)

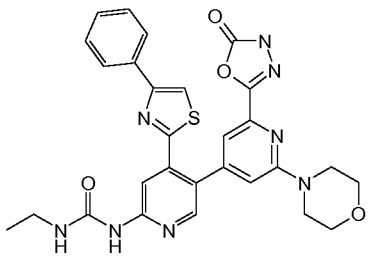
MS (ESP): 561.3 (MH^+) for $C_{24}H_{23}F_3N_8O_3S$

^{1}H NMR (300 MHz, CD_3OD): 1.22 (t, 3H), 2.61 (s, 3H), 3.34 (q, 2H), 3.60 (t, 4H), 3.77 (t, 4H), 6.92 (d, 1H), 7.30 (d, 1H), 7.82 (s, 1H), 8.25 (d, 1H), 8.36 (d, 1H)

^{19}F NMR (300 MHz, CD_3OD): -65.79

Example 88

1-ethyl-3-(2'-isopropoxy-6'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridin-6-yl)urea



To a 100 mL round bottom flask was charged methyl 6-(3-ethylureido)-6'-morpholino-4-(4-phenylthiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 152, 350 mg) with anhydrous ethanol (50 mL). Hydrazine monohydrate (2 mL) was added and the mixture was heated to reflux for 1 hour. After concentration under reduced pressure, the crude product was dried in a vacuum oven at 60°C overnight.

The crude residue was dissolved in tetrahydrofuran (30 mL), 1,1'-carbonyl diimidazole (600 mg) added, and the mixture was stirred at room temperature for 1 h. After

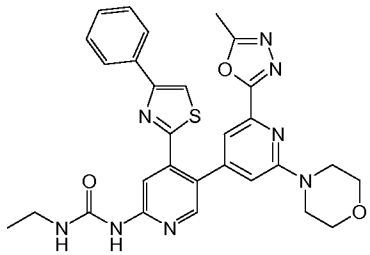
concentration under reduced pressure, the crude product was purified by Analogix (dichloromethane/methanol) to give a white solid (62 mg).

MS (ESP): 571.2 (MH^+) for $C_{28}H_{26}N_8O_4S$

^1H NMR (300 MHz, CD_3OD): δ 1.11 (t, 3H), 3.22 (q, 2H), 3.50 (t, 4H), 3.65 (t, 4H), 6.97 (s, 1H), 7.10 (d, 2H), 7.36-7.45 (m, 3H), 7.67 (br, 1H), 7.83 (d, 1H), 7.85 (d, 1H), 8.22 (s, 1H), 8.24 (s, 1H), 8.29 (d, 1H), 9.48 (s, 1H)

Example 89

1-ethyl-3-(2'-(5-methyl-1,3,4-oxadiazol-2-yl)-6'-morpholino-4-(4-phenylthiazol-2-yl)-3,4'-bipyridin-6-yl)urea



To a vial was charged methyl 6-(3-ethylureido)-6'-morpholino-4-(4-phenylthiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 152, 0.34 g), tetrahydrofuran (30 mL) and water (30 mL). Lithium hydroxide (300 mg) was added, and the resulting mixture was stirred at room temperature overnight. The mixture was diluted with water and extracted with ethyl acetate once. The aqueous layer was then acidified to pH 2-3, and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate, and after concentration, the resulting solid (acid) was used without further purification (100 mg).

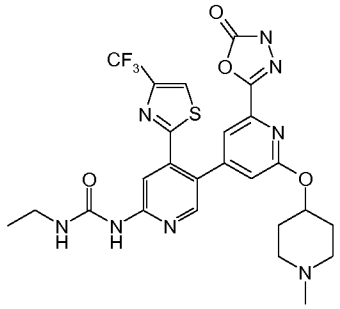
The carboxylic acid (80 mg, 0.151 mmol) was treated with acetic hydrazide (25 mg, 0.305mmol) and phosphorus oxychloride (3 mL) then heated at 60°C for 4 h. The solution was poured into cold saturated sodium bicarbonate (30 mL) in an ice bath and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate. After concentration, the crude mixture was purified by Analogix (dichloromethane/methanol) to give an off-white solid (25 mg).

MS (ESP): 569.1 (MH^+) for $C_{29}H_{28}N_8O_3S$

^1H NMR (300 MHz, CD_3OD): δ ppm 1.23 (t, 3H), 2.57 (s, 3H), 3.35 (q, 2H), 3.57 (t, 4H), 3.71 (t, 4H), 6.94 (s, 1H), 7.33-7.39 (m, 4H), 7.75 (d, 1H), 7.78 (d, 1H), 7.82 (s, 1H), 7.90 (s, 1H), 8.35 (d, 1H)

Example 90

1-ethyl-3-(2'-(1-methylpiperidin-4-yloxy)-6'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea



To a 100 mL round bottom flask was charged methyl 6-(3-ethylureido)-6'-(1-methylpiperidin-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 153, 100 mg, 0.213 mmol) with ethanol (20 mL). Hydrazine monohydrate (0.2 mL) was added and the mixture heated to reflux for overnight. The reaction was concentrated and dried in a vacuum oven at 40°C for 2 h.

The crude product was dissolved in anhydrous tetrahydrofuran (10 mL), 1,1'-carbonyl diimidazole (80 mg) added, and the mixture was stirred at room temperature for 1 h. After concentration, the crude product was triturated with water to give an off-white solid (56 mg, 53.8% in two steps)

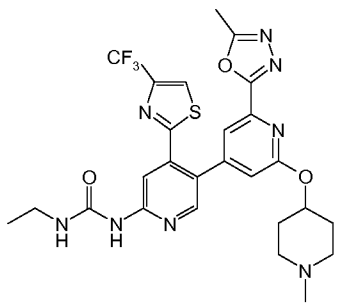
MS (ESP): 563.1 (MH^+) for $C_{25}H_{25}F_3N_8O_4S$

^{1}H NMR (300 MHz, DMSO-d_6): 1.10 (t, 3H), 1.67-1.80 (m, 2H), 1.98-2.05 (m, 2H), 2.20 (s, 3H), 2.15-2.30 (m, 2H), 2.60-2.70 (m, 2H), 3.16-3.25 (m, 2H), 4.03 (br, 1H), 5.06 (m, 1H), 6.93 (d, 1H), 7.30 (d, 1H), 7.52 (s, 1H), 8.15 (d, 1H), 8.36 (s, 1H), 8.60 (d, 1H), 9.51 (s, 1H)

^{19}F NMR (300 MHz, DMSO-d_6): -62.91

Example 91

1-ethyl-3-(2'-(5-methyl-1,3,4-oxadiazol-2-yl)-6'-(1-methylpiperidin-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea



To a vial was charged methyl 6-(3-ethylureido)-6'-(1-methylpiperidin-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 153, 150 mg, 0.266 mmol), tetrahydrofuran (30 mL), sodium hydroxide (24wt% in water, 0.5 mL) and the resulting mixture was stirred at room temperature for overnight. The mixture was concentrated to dryness and the crude salt used for the cyclization.

The carboxylic salt was treated with acetic hydrazide (37 mg, 0.449 mmol) and phosphorus oxychloride (4 mL) then heated at 65°C for 1 h. The reaction went to completion based on LC, and the solution was poured into cold saturated sodium bicarbonate in an ice bath and extracted with ethanol/tetrahydrofuran (1:1) three times. The organic layers were combined and dried over sodium sulfate. After concentration, the crude mixture was purified by Analogix (dichloromethane/methanol) to give a light yellow solid (35 mg, 22.4%)

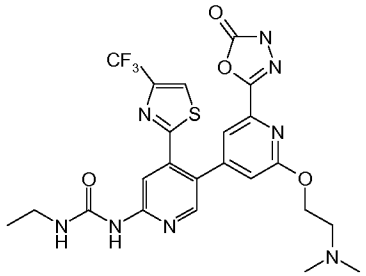
MS (ESP): 589.2 (MH^+) for $C_{26}H_{27}F_3N_8O_3S$

^{1}H NMR (300 MHz, DMSO-d_6): 1.18 (t, 3H), 1.9-2.1 (br, 2H), 2.2-2.3 (br, 2H), 2.59 (s, 3H), 2.6-2.8 (br, 2H), 3.05 (q, 2H), 3.6-3.8 (br, 2H), 5.2-5.3 (br, 1H), 7.06 (s, 1H), 7.56 (br, 2H), 8.20 (s, 1H), 8.40 (s, 1H), 8.62 (s, 1H), 9.57 (s, 1H)

^{19}F NMR (300 MHz, DMSO-d_6): -62.97

Example 92

1-(2'-(2-(dimethylamino)ethoxy)-6'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)-3-ethylurea



To a 100 mL round bottom flask was charged methyl 6'-(2-(dimethylamino)ethoxy)-6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 154, 100 mg, 0.185 mmol) with of ethanol (20 mL). Hydrazine monohydrate (0.4 mL) was added and the mixture was heated to reflux for overnight. While hot, the reaction was filtered through a Celite pad to remove residual Pd catalyst and the filtrate was concentrated to dryness.

The crude product was dissolved in anhydrous tetrahydrofuran (10 mL), 1,1'-carbonyl diimidazole (110 mg) was added, and the mixture was stirred at room temperature for

overnight. After concentration, the brown oily solid was triturated with water to give a light brown solid (50 mg, 47.6% in two steps)

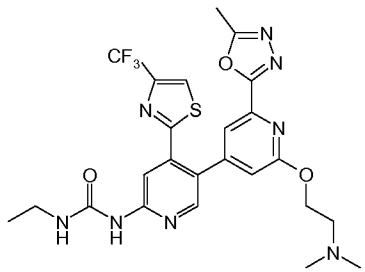
MS (ESP): 565.2 (MH^+) for $C_{23}H_{23}F_3N_8O_4S$

^1H NMR (300 MHz, DMSO-d_6): 1.10 (t, 3H), 2.22 (s, 6H), 2.65 (t, 2H), 3.20 (m, 2H), 4.42 (t, 2H), 6.99 (d, 1H), 7.32 (d, 1H), 7.54 (t, br, 1H), 7.62-7.70 (m, 1H), 8.15 (d, 1H), 8.36 (s, 1H), 8.60 (d, 1H), 9.53 (s, 1H)

^{19}F NMR (DMSO-d_6): -62.90

Example 93

1-(2'-(2-(dimethylamino)ethoxy)-6'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)-3-ethylurea

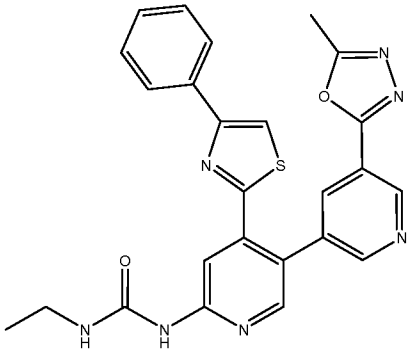


Methyl 6'-(2-(dimethylamino)ethoxy)-6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 154, 500 mg) was treated with acetic hydrazide (100 mg, 1.21 mmol) and phosphorus oxychloride (5 mL) then heated at 65°C for 1 h. After cooling the solution was poured into cold saturated sodium bicarbonate in an ice bath. The resulting mixture was extracted with ethanol/tetrahydrofuran (1:1) three times. The organic layers was combined and dried over sodium sulfate. After concentration, the crude mixture was purified by prep. HPLC

MS (ESP): 563.1 (MH^+) for $C_{24}H_{25}F_3N_8O_3S$

Example 94

1-ethyl-3-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)--4-(4-phenylthiazol-2-yl)-3,3'-bipyridin-6-yl)urea



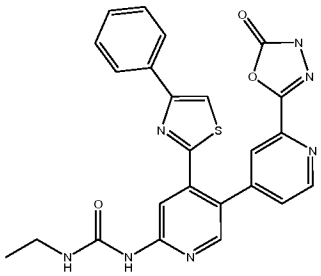
6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-ylboronic acid (0.100 g, 0.27 mmol, Intermediate 16), 2-(5-bromopyridin-3-yl)-5-methyl-1,3,4-oxadiazole (0.111 g, 0.46 mmol, Intermediate 418), cesium carbonate (0.150 g, 0.46 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (XPhos) (0.039 g, 0.08 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.025 g, 0.03 mmol) were combined in dioxane (2.00 mL)/water (0.50 mL) and heated to 100 °C. The solution was cooled to room temperature and the reaction mixture was diluted with ethyl acetate and washed twice with water, once with saturated sodium bicarbonate and brine. The combined organic extracts were dried over magnesium sulfate, filtered and evaporated to a yellow solid. Isco column (0%-100% ethyl acetate/dichloromethane) afforded the desired compound as a white solid 0.106 g, 81% yield.

MS (ESP): 484 ($M+H^+$) for $C_{23}H_{22}F_3N_7O_4S$.

^{1}H NMR (DMSO-d_6): δ 1.12 (t, 3H), 2.57 (s, 3H), 3.22 (q, 2 H), 7.33 (q, 3H), 7.63 (m, 1H), 7.70 (d, 1 H), 8.23 (s, 1H), 8.28 (s, 1H), 8.36 (s, 2H), 8.74 (s, 1H), 9.17 (s, 1H), 9.50 (s, 1H)

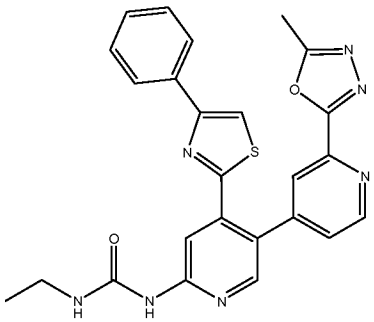
Examples 95

The following compounds have been synthesized as described for Example 10 from the starting materials indicated in the table below.

Ex	Compound	Data	SM
95	1-ethyl-3-(2'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 486 for $C_{24}H_{19}N_7O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.1 (t, 3H), 3.2 (q, 2H), 7.54 (m, 2H), 7.68 (t, 1H), 7.9 (s, 1H), 8.20 (d, 2H), 8.33 (s, 1H), 8.7 (d, 1H), 9.52 (s, 1H), 12.78 (s, 1H).	Intermediate 155

Example 96

1-ethyl-3-(2'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridin-6-yl)urea



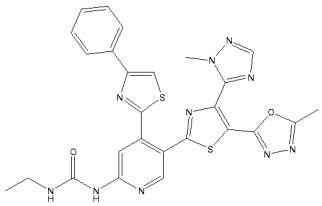
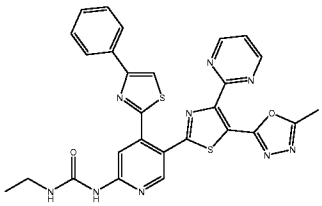
To a solution of 1-ethyl-3-(2'-(hydrazinecarbonyl)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridin-6-yl)urea (0.036 g, 0.08 mmol, Intermediate 155) in THF (2.5 mL) and 1,1,1-trimethoxyethane (5 mL, 0.08 mmol) was added HCl (2.380 µL, 0.08 mmol) and the reaction was stirred at 120 °C. DBU (0.118 mL, 0.78 mmol) was added and heating was continued. The reaction mixture was cooled to room temperature and concentrated to a red oil. Isco column (0%-10% methanol/dichloromethane) yielded pure product as a white solid 0.031 g, 82% yield.

MS (ESP): 484 ($M+H^+$) for $C_{25}H_{21}N_7O_2S$.

^1H NMR (DMSO-d6): δ 1.11 (t, 3H), 2.59 (s, 3H), 3.22 (q, 2 H), 7.33 (q, 3H), 7.63 (dd, 4H), 8.11 (s, 1 H), 8.22 (d, 1H), 8.36 (s, 1H), 8.75 (d, 1H), 9.53 (s, 1H).

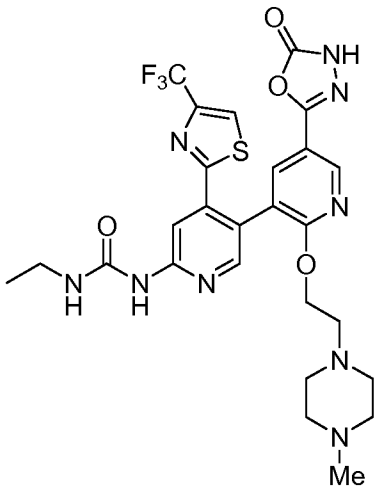
Example 97-98

The following compounds have been synthesized as described for **Example 96** from the starting materials indicated in the table below.

Ex	Compound	Data	SM
97	1-ethyl-3-(5-(5-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazol-2-yl)-4-(4-phenylthiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 571 for $C_{26}H_{22}N_{10}O_2S_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.1 (t, 3H), 3.2 (q, 2H), 3.33 (s, 3H), 3.77 (s, 3H), 7.37 (m, 3H), 7.53 (m, 1H), 7.83 (d, 2H), 8.04 (s, 1H), 8.17 (s, 1H), 8.38 (s, 1H), 8.82 (s, 1H), 9.71 (s, 1H)	Intermediate 156
98	1-ethyl-3-(5-(5-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(pyrimidin-2-yl)thiazol-2-yl)-4-(4-phenylthiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 568 for $C_{27}H_{21}N_9O_2S_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.1 (t, 3H), 2.47 (s, 3H), 3.2 (q, 2H), 7.39 (m, 4H), 7.57 (m, 2H), 7.85 (d, 2H), 8.23 (s, 1H), 8.38 (s, 1H), 8.78 (s, 1H), 8.88 (d, 1H), 9.69 (s, 1H)	Intermediate 157

Example 99

1-Ethyl-3-(2'-(2-(4-methylpiperazin-1-yl)ethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



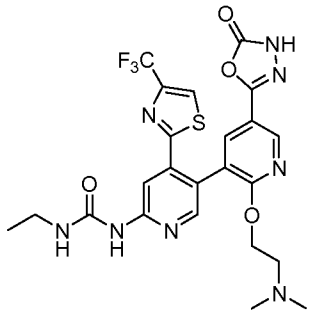
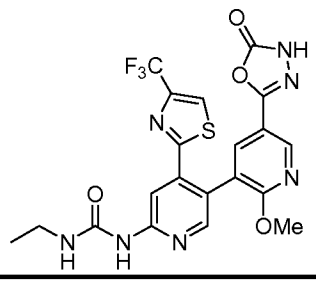
The 1-ethyl-3-(5'-(hydrazinecarbonyl)-2'-(2-(4-methylpiperazin-1-yl)ethoxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 165, 142 mg, 0.24 mmol) was dissolved in THF (2.4 mL) and cooled to 0 °C. Diisopropylethylamine (46.0 µl, 0.26 mmol) was added dropwise, followed by the addition of 1,1'-carbonyldiimidazole (42.8 mg, 0.26 mmol). The ice bath was then removed and the mixture was stirred at RT for 3 h. The mixture was conc *in vacuo* and purified by silica gel chromatography (5-10% MeOH/CH_2Cl_2 + 1% NH_4OH) to give 16.6 mg (11%) of the title compound.

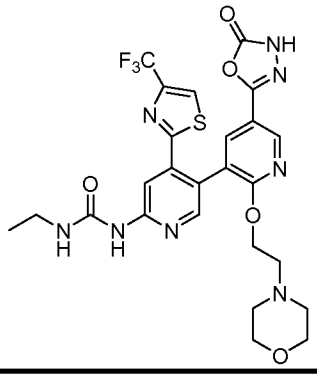
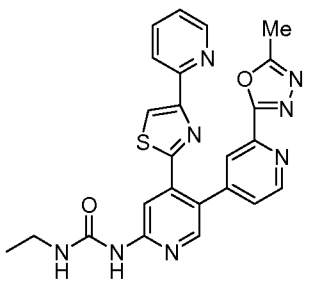
LC/MS (ES^+)[$(M+H)^+$]: 620 for $C_{26}H_{28}F_3N_9O_4S$

^1H NMR (DMSO-d_6): δ 9.47 (s, 1H); 8.65 (m, 1H); 8.54 (m, 1H); 8.25 (d, 2H); 8.14 (m, 1H); 7.61 (m, 1H); 4.15 (t, 2H); 3.21 (m, 2H); 2.18 (m, 10H); 2.07 (s, 3H); 1.10 (t, 3H).

Example 100-103

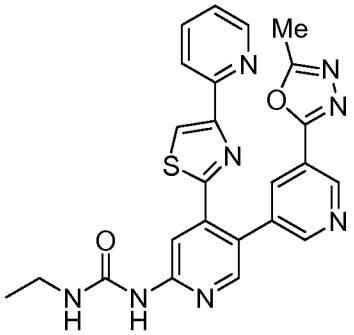
The following compounds have been synthesized as described for **Example 99** from the starting materials indicated in the table below.

Ex	Compound	Data	SM
100	1-(2'-(2-(Dimethylamino)ethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 565 for $C_{23}H_{23}F_3N_8O_4S$ ^1H NMR (DMSO-d_6): δ 9.47 (s, 1H); 8.65 (m, 1H); 8.54 (s, 1H); 8.27 (s, 1H); 8.23 (s, 1H); 8.15 (m, 1H); 7.58 (m, 1H); 4.10 (t, 2H); 3.21 (m, 2H); 2.13 (t, 2H); 1.95 (s, 6H); 1.10 (t, 3H).	Intermediate 168
101	1-Ethyl-3-(2'-methoxy-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 508 for $C_{20}H_{16}F_3N_7O_4S$ ^1H NMR (DMSO-d_6): δ 12.65 (br s, 1H); 9.47 (s, 1H); 8.66 (m, 1H); 8.55 (s, 1H); 8.29 (s, 1H); 8.20 (s, 1H); 8.13 (m, 1H); 7.58 (m, 1H); 3.59 (s, 3H); 3.21 (m, 2H); 1.10 (t, 3H).	Intermediate 170

Ex	Compound	Data	SM
102	1-Ethyl-3-(2'-(2-morpholinoethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 607 for $C_{25}H_{25}F_3N_8O_5S$ ^1H NMR (DMSO-d_6): δ 12.67 (br s, 1H); 9.47 (s, 1H); 8.66 (m, 1H); 8.55 (s, 1H); 8.27 (s, 1H); 8.25 (s, 1H); 8.15 (m, 1H); 7.59 (m, 1H); 4.18 (m, 2H); 3.41 (m, 4H); 3.20 (m, 2H); 2.24 (m, 6H); 1.10 (t, 3H).	Intermediate 173
103	1-Ethyl-3-(2'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(pyridin-2-yl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 485 for $C_{24}H_{20}N_8O_2S$ ^1H NMR (DMSO-d_6): δ 9.54 (s, 1H); 8.76 (d, 1H); 8.59 (m, 1H); 8.38 (s, 2H); 8.23 (s, 1H); 8.13 (s, 1H); 7.77 (m, 1H); 7.60 (m, 3H); 7.34 (m, 1H); 3.22 (m, 2H); 2.58 (s, 3H); 1.12 (t, 3H).	Intermediate 174 and Intermediate 176

Example 104

1-Ethyl-3-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(pyridin-2-yl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



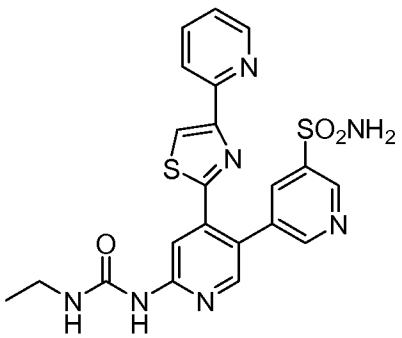
The 6-(3-ethylureido)-4-(4-(pyridin-2-yl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 174, 0.076 g, 0.21 mmol), 2-(5-bromopyridin-3-yl)-5-methyl-1,3,4-oxadiazole (Intermediate 418, 0.059 g, 0.25 mmol), tetrakis (triphenylphosphine)palladium (0) (0.024 g, 0.02 mmol) and cesium carbonate (0.101 g, 0.31 mmol) were placed in a microwave vessel. The vessel was degassed and purged with N_2 several times. Acetonitrile (2.5 ml) and water (0.625 ml) were added and the vessel was degassed and purged with N_2 again. The vessel was heated in the microwave at 100 °C for 2 h. The mixture was then conc *in vacuo*. Acetonitrile was added and the resultant precipitate was collected and washed with acetonitrile and water. Purification by silica gel chromatography (0-10% MeOH/CH_2Cl_2) gave 0.017 g (17%) of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 485 for $C_{24}H_{20}N_8O_2S$

^{1}H NMR (DMSO-d_6): δ 9.51 (s, 1H); 9.18 (d, 1H); 8.76 (d, 1H); 8.59 (m, 1H); 8.38 (m, 3H); 8.30 (s, 1H); 7.81 (m, 1H); 7.65 (m, 2H); 7.35 (m, 1H); 3.23 (m, 2H); 2.57 (s, 3H); 1.12 (t, 3H).

Example 105

6'-(3-Ethylureido)-4'-(4-(pyridin-2-yl)thiazol-2-yl)-3,3'-bipyridine-5-sulfonamide

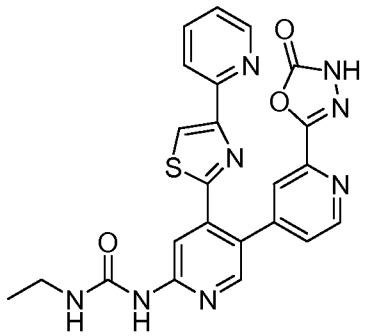


Following the procedure for Example 104, 6-(3-ethylureido)-4-(4-(pyridin-2-yl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 174, 0.076 g, 0.21 mmol) and 5-bromopyridine-3-

sulfonamide (0.073 g, 0.31 mmol) were reacted in the microwave at 100 °C for 1 h. The mixture was then conc *in vacuo*. Acetonitrile was added and the resultant precipitate was collected and washed with acetonitrile and water to give 0.016 g (16%) of the title compound.
LC/MS (ES^+)[$(M+H)^+$]: 482 for $C_{21}H_{19}N_7O_3S_2$
^1H NMR (DMSO-d_6): δ 9.51 (s, 1H); 8.99 (m, 1H); 8.74 (m, 1H); 8.60 (m, 1H); 8.37 (s, 1H); 8.31 (m, 2H); 8.20 (m, 1H); 7.84 (m, 1H); 7.63 (m, 4H); 7.36 (m, 1H); 3.22 (m, 2H); 1.12 (t, 3H).

Example 106

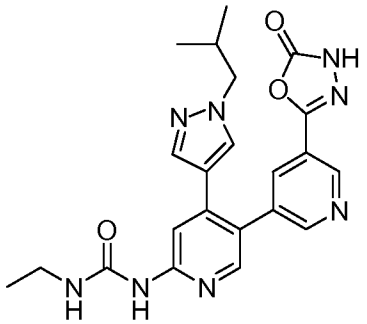
1-Ethyl-3-(2'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(pyridin-2-yl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea



A solution of 1-ethyl-3-(2'-(hydrazinecarbonyl)-4-(4-(pyridin-2-yl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea (Intermediate 178, 56.4 mg, 0.12 mmol) in DMF (1 mL) was treated with diisopropylethylamine (0.03 mL, 0.18 mmol) and 1,1'-carbonyldiimidazole (29.8 mg, 0.18 mmol). The mixture was stirred at RT for 2 h. Methanol was added and the mixture was conc *in vacuo*. Purification by silica gel chromatography (0-10% MeOH/CH_2Cl_2) gave 15 mg (25%) of the title compound.
LC/MS (ES^+)[$(M+H)^+$]: 487 for $C_{23}H_{18}N_8O_3S$
^1H NMR (500 MHz, $CDCl_3$): δ 12.77 (br s, 1H); 9.52 (s, 1H); 8.73 (d, 1H); 8.61 (m, 1H); 8.39 (s, 1H); 8.36 (s, 1H); 8.24 (s, 1H); 7.92 (s, 1H); 7.82 (m, 1H); 7.59 (m, 3H); 7.36 (m, 1H); 3.23 (m, 2H); 1.13 (t, 3H).

Example 107

1-Ethyl-3-(4-(1-isobutyl-1*H*-pyrazol-4-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea



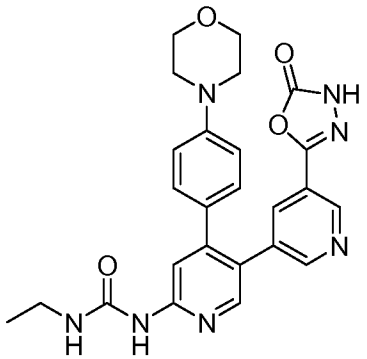
The 1-(4-chloro-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Intermediate 183, 0.065 g, 0.18 mmol) and cesium carbonate (0.117 g, 0.36 mmol) were placed in a microwave vessel. The vessel was degassed and purged with N_2. Tetrakis (triphenylphosphine)palladium (0) (0.021 g, 0.02 mmol) was added and the vessel was degassed and purged with N_2. The 1-isobutyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.10 mL, 0.40 mmol) was added, followed by dioxane (1.6 mL) and water (0.4 mL). The vessel was degassed and purged with N_2 twice. The vessel was placed in the microwave for 2 h at 100 °C. Purification by silica gel chromatography (0-10% MeOH/CH_2Cl_2) gave 0.017 g (21%) of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 449 for $C_{22}H_{24}N_8O_3$

^{1}H NMR (DMSO-d_6): δ 12.79 (s, 1H); 9.28 (s, 1H); 8.94 (m, 1H); 8.61 (m, 1H); 8.19 (s, 1H); 7.90 (m, 2H); 7.60 (s, 1H); 7.43 (s, 1H); 7.27 (s, 1H); 3.82 (d, 2H); 3.20 (m, 2H); 1.96 (m, 1H); 1.10 (t, 3H); 0.71 (s, 3H); 0.69 (s, 3H).

Example 108

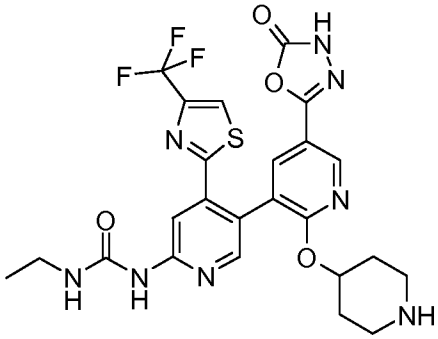
1-Ethyl-3-(4-(4-morpholinophenyl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea



Diisopropylethylamine (0.058 mL, 0.33 mmol) was added to a solution of 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-morpholinophenyl)-3,3'-bipyridin-6-yl)urea (Intermediate 185, 0.102 g, 0.22 mmol) in DMF (2 mL). 1,1'-Carbonyldiimidazole (0.054 g, 0.33 mmol) was added in one portion and the resultant mixture was stirred at RT overnight. Purification by silica gel chromatography (0-10% MeOH/CH_2Cl_2) gave 0.066 g (62%) of the title compound.
LC/MS (ES^+)[$(M+H)^+$]: 488 for $C_{25}H_{25}N_7O_4$
^{1}H NMR (DMSO-d_6): δ 12.77 (s, 1H); 9.36 (s, 1H); 8.82 (m, 1H); 8.39 (m, 1H); 8.26 (s, 1H); 7.95 (m, 2H); 7.49 (s, 1H); 7.01 (m, 2H); 6.89 (m, 2H); 3.70 (m, 4H); 3.21 (m, 2H); 3.11 (m, 4H); 1.10 (t, 3H).

Example 109

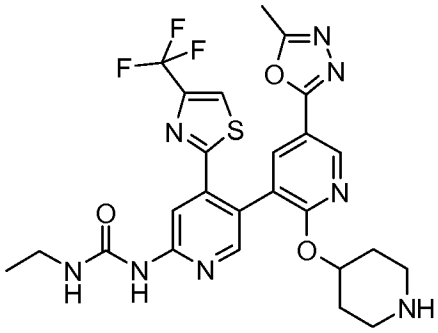
1-Ethyl-3-{5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2'-(piperidin-4-yloxy)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-6-yl}urea



To a solution of *tert*-butyl 4-({6'-[(ethylcarbamoyl)amino]-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)piperidine-1-carboxylate (Intermediate 191, 170 mg, 0.25 mmol) in dichloromethane (10 mL), trifluoroacetic acid (0.1 mL, 1.25 mmol) was added and stirred for 3 h at room temperature. Dichloromethane was evaporated from the reaction mixture, pH was adjusted to 8 with saturated sodium bicarbonate solution to obtain solid compound which was filtered and dried to afford 45 mg (31%) of 1-Ethyl-3-{5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2'-(piperidin-4-yloxy)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-6-yl}urea.
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (m, 5H), 1.56 (br, 2H), 2.50 (m, 4H), 4.99 (m, 1H), 7.59 (m, 1H), 8.10 (m, 1H), 8.22 – 8.26 (m, 2H), 8.51 -8.56 (m., 2H), 9.44 (s, 1H).
LC-MS: m/z 575.3 (M+H).

Example 110

1-Ethyl-3-{5'-(5-methyl-1,3,4-oxadiazol-2-yl)-2'-(piperidin-4-yloxy)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-6-yl}urea



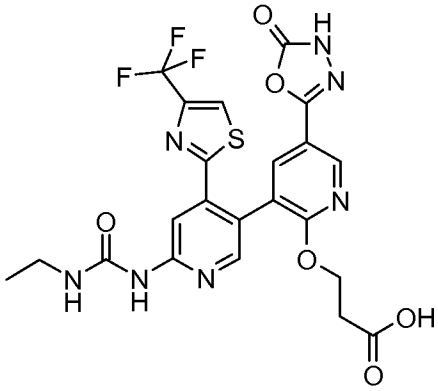
Tert-butyl 4-({6'-[(ethylcarbamoyl)amino]-5-(5-methyl-1,3,4-oxadiazol-2-yl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)piperidine-1-carboxylate (Intermediate 192, 150 mg, 0.22 mmol) was dissolved in dichloromethane (10 mL), trifluoroacetic acid (0.3 mL, 1.1 mM) was added and stirred for 3 h at room temperature. Dichloromethane was evaporated from the reaction mixture, pH was adjusted to 8 with saturated sodium bicarbonate solution to yield solid compound which was filtered and dried to afford 60 mg (47%) of 1-Ethyl-3-{5'-(5-methyl-1,3,4-oxadiazol-2-yl)-2'-(piperidin-4-yloxy)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-6-yl}urea.

^{1}H NMR (400 MHz, CD_3OD): δ 1.34 (m, 5H), 1.76 (m, 3H), 2.62 (t, 3H), 2.72 (m, 5H), 4.28 (q, 2H), 5.21 (m, 1H), 8.21 (m, 1H), 8.29 (m, 2H), 8.58 (s, 1H), 8.85 (d, 1H)

LC-MS: m/z 576.2 (M+H)

Example 111

3-({6'-[(ethylcarbamoyl)amino]-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)propanoic acid



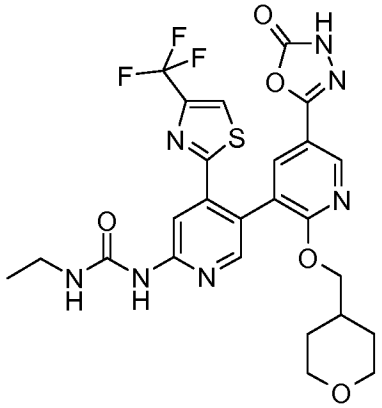
To a stirred solution of 3-({6'-[(ethylcarbamoyl)amino]-5-(hydrazinylcarbonyl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)propanoic acid (Intermediate 196, 240 mg, 0.44 mmol) in tetrahydrofuran (15 mL) which was cooled to 0 °C, phosgene (66 mg, 0.66 mmol) (slowly added to the reaction mixture at 0 °C. The reaction mixture was maintained at room temperature for 3 h. The solvent was distilled completely under reduced pressure to give crude product which was washed with diethyl ether and pentane and purified by reverse phase preparative HPLC to afford 45 mg (18%) of 3-({6'-[(ethylcarbamoyl)amino]-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)propanoic acid.

^{1}H NMR (400 MHz, CD_3OD): δ 1.2.0 – 1.24 (t, 3H), 2.69 (br , 4H), 3.36 (m, 3H), 4.17 (br s, 2H), 7.789 (d, 1H), 7.98 (d, 1H), 8.19 (d, 1H), 8.26 (s, 1H), 8.39 (s, 2H).

LC-MS: m/z 566.3 (M+H).

Example 112

1-Ethyl-3-{5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-ylmethoxy)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-6-yl}urea



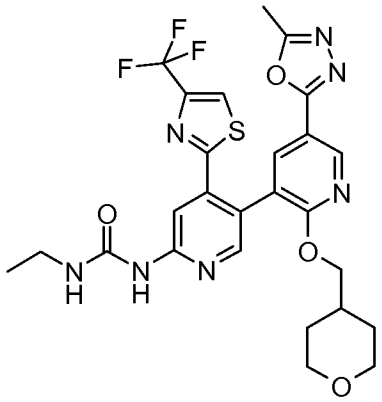
To a stirred solution of 1-Ethyl-3-{5'-(hydrazinylcarbonyl)-2'-(tetrahydro-2H-pyran-4-ylmethoxy)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-6-yl}urea (Intermediate 199, 0.4 g, 0.70 mmol) in tetrahydrofuran (10 mL) which was cooled to 0 °C, phosgene (0.1 g, 1.06 mmol) was slowly added to the reaction mixture at 0 °C. The reaction mixture was maintained at room temperature for 3 h. The solvent was distilled off completely under reduced pressure to get crude compound which was washed with diethyl ether and pentane to afford 200 mg (48%) of 1-ethyl-3-{5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-ylmethoxy)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-6-yl}urea.

^{1}H NMR (400 MHz, DMSO-d_6): δ 0.91 – 1.23 (m, 4H), 1.55 (br, 1H), 1.76 (s, 1H), 1.90 – 1.92 (d, 1H), 2.08 (s, 1H), 3.08 – 3.14 (m, 2H), 3.19 – 3.22 (m, 2H), 3.67 – 3.69 (dd, 2H), 3.91 – 3.93 (d, 2H), 7.61 (br, 1H), 8.15 (d, 1H), 8.26 – 8.32 (m, 2H), 8.66 – 8.67 (d, 1H), 9.47 – 9.48 (d, 1H)

LC-MS: m/z 592.3 (M+2).

Example 113

1-Ethyl-3-{5'-(5-methyl-1,3,4-oxadiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-ylmethoxy)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-6-yl}urea



1-Ethyl-3-{5'-(hydrazinylcarbonyl)-2'-(tetrahydro-2H-pyran-4-ylmethoxy)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-6-yl}urea (Intermediate 199, 400 mg, 1.7 mmol) was taken in triethylorthoacetate (5 mL) and the reaction mixture was heated to 120 °C for 12 h. The reaction mixture was cooled to room temperature, the solvent was distilled completely under reduced pressure to give crude product which was washed with diethyl ether and pentane to afford 150 mg 36.5% **1**-ethyl-3-{5'-(5-methyl-1,3,4-oxadiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-ylmethoxy)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-6-yl}urea as solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 – 1.13 (m, 2H), 1.31 (br, 2H), 1.37 – 1.56 (t, 3H), 1.69 (br , 1H), 2.63 (s, 3H), 3.23 – 3.29 (t, 2H), 3.84 – 3.87 (dd, 2H), 3.98 – 4.00 (d, 2H), 4.29 – 4.34 (q, 2H), 7.71 (s, 2H), 8.20 (d, 1H), 8.26 (s, 1H), 8.64 (s, 1H), 8.85 (d, 1H)

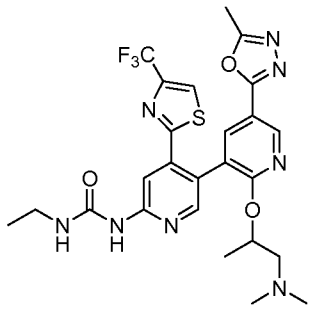
LC-MS: m/z 591 (M+2).

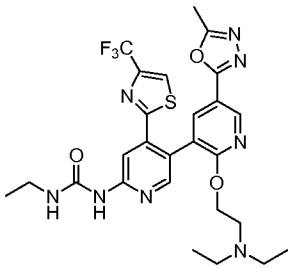
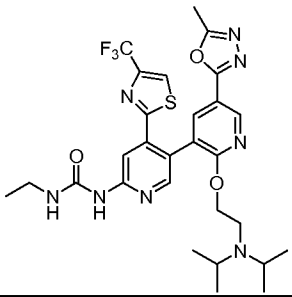
Example 114-117

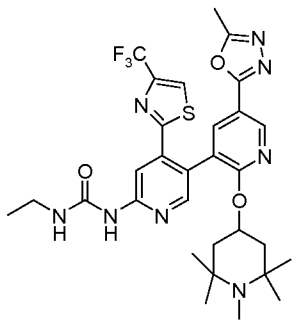
The following Examples were prepared according to the general procedure described below from the starting material indicated in the Table.

General Procedure

A suspension of corresponding carboxylic acid (0.3 mmol), hydrazine acetate (0.9 mmol) in phosphorus oxychloride (2.5 mL) was heated at 70°C for 2 h. The solution was then cooled and concentrated to dryness. A solution of saturated potassium carbonate was added to the crude and extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under vacuum and the crude product was purified by Analogix using dichloromethane-methanol.

Ex	Compound	Data	SM
114	1-(2'-(1-(Dimethylamino)propan-2-yloxy)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 577.2 (MH^+) for $C_{25}H_{27}F_3N_8O_3S$ ^1H NMR (300 MHz, CD_3OD): δ 0.88-0.91 (m, 3H), 1.24-1.28 (m, 3H), 1.57-1.59 (m, 6H), 2.63 (s, 3H), 2.72-2.87 (m, 2H), 3.44-.347 (m, 2H), 4.84-4.87 (m, 2H), 5.65 (m, 1H), 7.91 (s, 1H), 8.26 (m, 1H) 8.32 (m, 1H), 8.36-8.37 (m, 1H), 8.90-8.91 (m, 1H). ^{19}F NMR (300 MHz, CD_3OD): δ -65.81	Intermediate 201

Ex	Compound	Data	SM
115	1-(2'-(2-(diethylamino)ethoxy)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 591.2 (MH^+) for $C_{26}H_{29}F_3N_8O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 0.91-0.94 (m, 6H), 1.21-1.22 (m, 3H), 2.47-2.50 (m, 4H), 2.52-2.55 (m, 2H) 2.62 (s, 3H), 3.34-3.36 (m, 2H), 4.25 (m, 2H), 7.91 (s, 1H), 8.22-8.26 (m, 1H), 8.30-8.31 (m, 2H), 8.86-8.86 (m, 1H). ^{19}F NMR (300 MHz, CD_3OD) -65.83	Intermediate 202
116	1-(2'-(2-(diisopropylamino)ethoxy)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 619.2 (MH^+) for $C_{28}H_{33}F_3N_8O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 1.15-1.19 (m, 3H), 1.33-1.39 (m, 12H), 2.62, (s, 3H), 3.24-3.28 (m, 4H), 3.77 (m, 2H), 3.82 (m, 2H), 7.94 (s, 1H), 8.26 (s, 1H), 8.32-8-34 (m, 2H), 8.89-8.90 (m, 1H) ^{19}F NMR (300 MHz, CD_3OD): δ -65.798	Intermediate 200

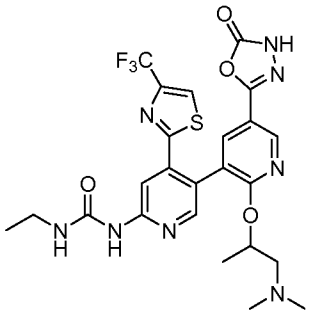
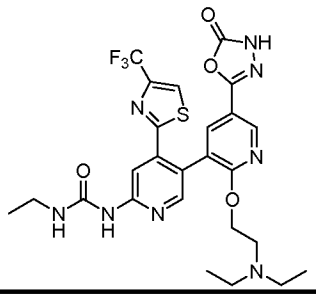
Ex	Compound	Data	SM
117	1-Ethyl-3-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-2'-(1,2,2,6,6-pentamethylpiperidin-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 645.3 (MH^+) for $C_{30}H_{35}F_3N_8O_3S$ ^1H NMR (300 MHz, CD_3OD): δ 0.85-0.87 (m, 2H), 1.24-1.28 (m, 3H), 1.39 (s, 6H), 1.63 (s, 6H), 1.93 (m, 2H), 2.64 (s, 3H), 2.69 (m, 3H), 3.41-3.43 (m, 2H), 3.45-3.79 (m, 1H), 7.80 (m, 1H), 8.14-8.15 (m, 2H), 8.25 (m, 1H), 8.80-8.81 (m, 1H), 11.10 (m, 1H) ^{19}F NMR (300 MHz, $CDCl_3$): δ -64.30	Intermediate 203

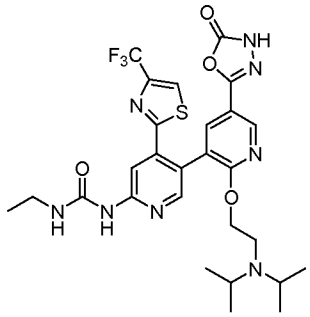
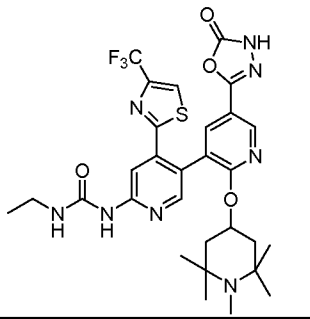
Examples 118-121

The following Examples were prepared as described in the general procedure from the starting materials indicated in the Table.

General Procedure

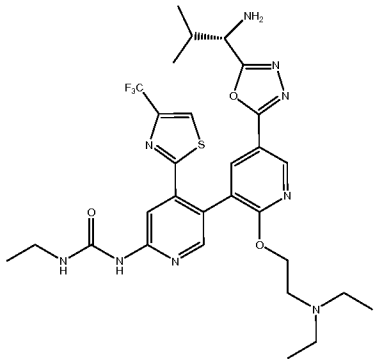
A suspension of the corresponding hydrazide (0.3 mmol) in anhydrous tetrahydrofuran (2 mL) was treated with triethyl amine (0.6 mmol) and 1,1'-carbonyl diimidazole (0.12 mmol). The reaction was stirred at room temperature for 12 h, concentrated to dryness and purified directly by Analogix using dichloromethane-methanol to give (~50%) product as an off-white solid.

Ex	Compound	Data	SM
118	1-(2'-(1-(Dimethylamino)propan-2-yloxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 579.3 (MH^+) for $C_{24}H_{25}F_3N_8O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.81-0.87 (m, 3H), 1.08-1.13 (m, 3H), 1.97 (s. 6H), 3.18-3.25 (m, 4H), 5.10-5.16 (m, 1H), 7,02 (s, 1H), 7.57-7.60 (m, 1H), 8.15-8.19 (m, 2H), 8.26 (s, 1H), 8.54 (s, 1H), 8.62 (s, 1H), 9.45 (s, 1H). ^{19}F NMR (300 MHz, DMSO-d_6): δ -63.007	Intermediate 207
119	1-(2'-(2-(diethylamino)ethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 593.1 (MH^+) for $C_{25}H_{27}F_3N_8O_4S$ H NMR (300 MHz, DMSO-d_6): δ 0.74-0.79 (m, 6H), 1.10-1.13 (m, 3H), 2.27-2.34 (m, 6H), 3.19-3.24 (m, 2H), 4.04-4.08 (m, 2H), 8.12-8.14 (m, 1H), 8.23-8.26 (m, 2H), 8.54 (m, 1H), 8.63-8.64 (m, 1H), 9.44 (m, 1H) ^{19}F NMR (300 MHz, DMSO-d_6): δ -102.2	Intermediate 208

Ex	Compound	Data	SM
120	1-(2'-(2-(diisopropylamino)ethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 621.3 (MH^+) for $C_{27}H_{31}F_3N_8O_4S$ ^{1}H NMR (300 MHz, CD_3OD): δ 0.80-0.85 (m, 12H), 0.93-0.95 (m, 3H), 2.19-2.27 (m, 1H), 2.31-2.33 (m, 1H), 2.73-2.81 (m, 2H), 3.21-3.23 (m, 2H), 3.87-3.90 (m, 2H), 7.57 (m, 1H), 8.14-8.15 (m, 1H), 8.22-8.30 (m, 2H), 8.54-8.56 (m, 1H), 8.62-8.64 (m, 1H), 9.45 (m, 1H). ^{19}F NMR (300 MHz, CD_3OD): δ -63.07	Intermediate 206
121	1-Ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2'-(1,2,2,6,6-pentamethylpiperidin-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 647.1 (MH^+) for $C_{29}H_{33}F_3N_8O_4S$ ^{1}H NMR (300 MHz, CD_3OD): δ 0.87-0.89 (m, 3H), 1.19-1.22 (m, 6H), 1.24-1.28 (m, 12H), 1.30-1.41 (m, 4H), 2.74 (s, 3H), 3.31 (m, 3H), 7.91 (m, 1H), 8.18-8.19 (m, 1H), 8.25-8.26 (m, 2H), 8.69-8.70 (m, 1H). ^{19}F NMR (300 MHz, CD_3OD): δ -65.53	Intermediate 209

Example 122

1-(5'-(5-(1-amino-2-methylpropyl)-1,3,4-oxadiazol-2-yl)-2'-(2-(diethylamino)ethoxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea hydrochloride



A suspension of (S)-*tert*-butyl 1-(5-(2-(2-(diethylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)-2-methylpropylcarbamate (Intermediate 212, 0.2 mmol) in methanol (1 mL) was treated with HCl in 1,4-dioxane (4N, 2 mL) at room temperature for 6 h. The solution was then concentrated to dryness to give an off-white solid (80%).

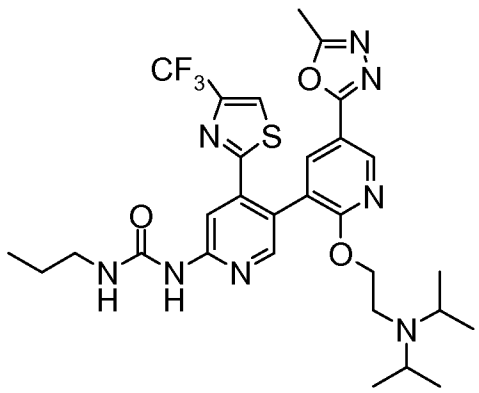
MS (ESP): 648 (MH^+) for $C_{29}H_{37}ClF_3N_9O_3S$

^{1}H NMR (300 MHz, CD_3OD): δ 1.06-1.28 (m, 15H), 2.48 (m, 2H), 2.65 (m, 1H), 3.10-3.11 (m, 4H), 3.31-3.32 (m, 2H), 3.73 (m, 1H), 4.76 (m, 2H), 8.01 (m, 1H), 8.35 (m, 1H), 8.40 (m, 1H), 8.44-8.45 (m, 1H), 9.01 (m, 1H)

^{19}F NMR (300 MHz, CD_3OD): δ -65.81

Example 123

1-(2'-(2-(Diisopropylamino)ethoxy)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-propylurea



A suspension of 2-(2-(diisopropylamino)ethoxy)-6'-(3-propylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 220, 0.3 mmol),

and hydrazine acetate (0.9 mmol) in phosphorus oxychloride (2.5 mL) was heated at 70°C for 2 h. The solution was then cooled and concentrated to dryness. A solution of saturated potassium carbonate was added to the crude and product was extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate. All solvents were removed under vacuum and the crude was purified by Analogix using dichloromethane-methanol.

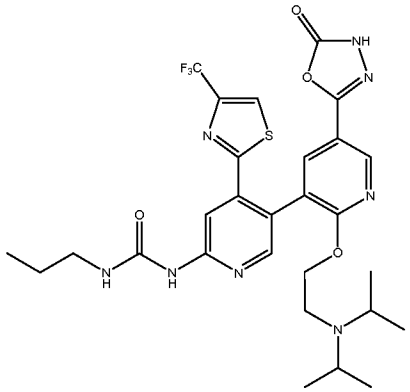
MS (ESP): 633.3 ($M+H^+$) for $C_{29}H_{35}F_3N_8O_3S$

^{1}H NMR (300 MHz, CD_3OD): δ 0.95 (m, 12H), 0.99 (m, 3H), 1.64-1.66 (m, 2H), 2.35-2.40 (m, 2H)2.62 9(s, 3H), 2.88-2.92 (m, 2H), 3.27 (m, 2H), 4.02-4.06 (m, 2H), 7.84 (s, 1H), 8.27(s, 1H), 8.29-8.30 (m, 2H), 8.83-8.84 (m, 1H).

^{19}F NMR (300 MHz, CD_3OD): δ 65.92

Example 124

1-(2'-(2-(Diisopropylamino)ethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-propylurea



A suspension of 1-(2'-(2-(diisopropylamino)ethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-propylurea (Intermediate 221, 0.3 mmol) in anhydrous tetrahydrofuran (2 mL) was treated with triethyl amine (0.6 mmol) and 1,1'-carbonyl diimidazole (0.12 mmol). The reaction was stirred at room temperature for 12 h, concentrated to dryness and purified by Analogix chromatography using dichloromethane-methanol to give (50%) of an off-white solid.

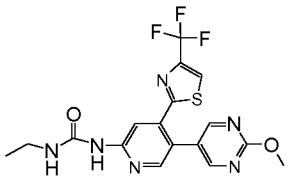
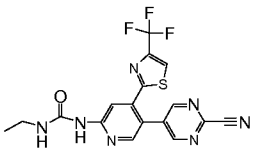
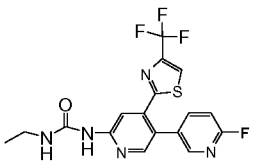
MS (ESP): 635.1 (MH^+) for $C_{28}H_{33}F_3N_8O_4S$

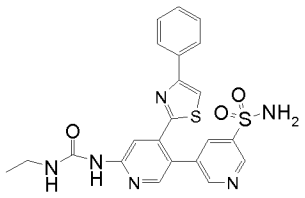
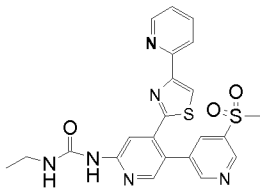
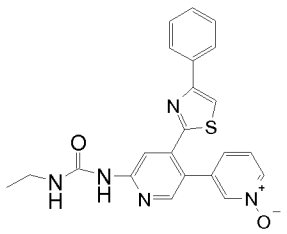
^{1}H NMR (300 MHz, DMSO-d_6): δ 0.81-0.88 (m, 12H), 0.90-0.93 (m, 3H), 1.51 (m, 2H), 2.16-2.18 (m, 2H), 2.82-2.84 (m, 2H), 3.14-3.18 (m, 2H), 3.84-3.86 (m, 2H), 7.01 (m, 1H), 7.63 (m, 1H), 8.02-8.02 (m, 1H) 8.21-8.25 (m, 2H), 8.48-8.51 (m, 2H), 9.43 (m, 1H)

^{19}F NMR (300 MHz, DMSO-d_6): δ -62.97

Examples 125-130

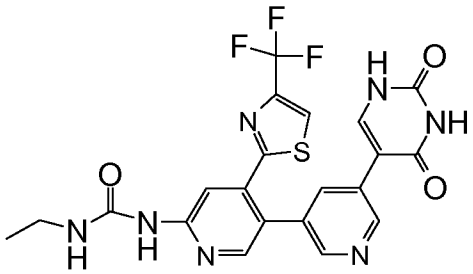
The following compounds have been synthesized as described for Example 21 from the starting materials indicated in the table below.

Ex	Compound	Data	SM
125	1-Ethyl-3-(5-(2-methoxypyrimidin-5-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	MS (ESP): 425 (M+1) for $C_{17}H_{15}F_3N_6O_2S$ ^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 3.16-3.22 (m, 2H); 3.96 (s, 3H); 7.57 (brs, 1H); 8.24 (s, 1H); 8.32 (s, 1H); 8.58 (s, 3H); 9.47 (s, 1H).	2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine and Intermediate 3
126	1-(5-(2-Cyanopyrimidin-5-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 420 (M+1) for $C_{17}H_{12}F_3N_7OS$ ^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 3.16-3.25 (m, 2H); 7.46 (brs, 1H); 8.25 (s, 1H); 8.44 (s, 1H); 8.65 (s, 1H); 9.00 (s, 2H); 9.60 (s, 1H).	5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine-2-carbonitrile and Intermediate 3
127	1-Ethyl-3-(6'-fluoro-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 412 (M+1) for $C_{17}H_{13}F_4N_5OS$ ^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 3.08-3.28 (m, 2H); 7.27 (dd, 1H); 7.57 (brs, 1H); 7.95 (td, 1H); 8.22 (s, 2H); 8.31 (s, 1H); 8.56 (s, 1H); 9.47 (s, 1H).	6-fluoropyridin-3-ylboronic acid and Intermediate 3

Ex	Compound	Data	SM
128	6'-(3-Ethylureido)-4'-(4-phenylthiazol-2-yl)-3,3'-bipyridine-5-sulfonamide 	MS (ESP): 481 (M+1) for $C_{22}H_{20}N_6O_3S_2$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.14-3.29 (m, 2H); 7.27-7.50 (m, 3H); 7.57 (brs, 1H); 7.66 (s, 2 H); 7.73 (d, 2H); 8.18 (d, 1H); 8.25 (s, 1H); 8.31 (d, 2H); 8.73 (d, 1H); 9.00 (d, 1H); 9.50 (s, 1H).	Intermediate 161 and 5-bromopyridine-3-sulfonamide
129	1-Ethyl-3-(5'-(methylsulfonyl)-4-(4-(pyridin-2-yl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 481 (M+1) for $C_{22}H_{20}N_6O_3S_2$ ^{1}H-NMR (DMSO-d_6) δ: 1.12 (t, 3H); 3.13-3.26 (m, 2H); 3.28 (s, 3H); 7.35 (dd, 1H); 7.51 (d, 1 H); 7.59 (brs, 1H); 7.82 (t, 1H); 8.28 (s, 1H); 8.33 (s, 1H); 8.38 (d, 2H); 8.59 (d, 1H); 8.87 (s, 1H); 9.09 (d, 1H); 9.52 (s, 1H).	Intermediate 15 and 5-(methylsulfonyl)pyridin-3-ylboronic acid
130	6'-(3-Ethylureido)-4'-(4-phenylthiazol-2-yl)-3,3'-bipyridine 1-oxide 	MS (ESP): 418 (M+1) for $C_{22}H_{19}N_5O_2S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.17-3.29 (m, 2H); 7.21-7.53 (m, 5H); 7.62 (brs, 1H); 7.81 (d, 2 H); 8.13-8.42 (m, 5H); 9.47 (s, 1H).	Intermediate 161 and 3-bromopyridine 1-oxide

Example 131

1-(5'-(2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



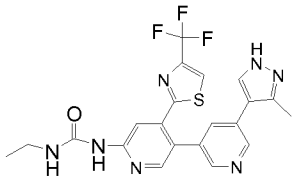
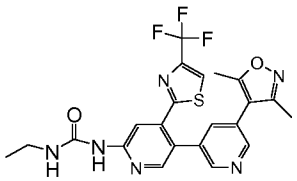
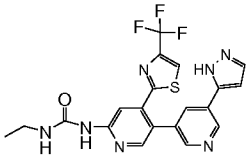
1-(5'-Bromo-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Example 21, 100 mg, 0.21 mmol), 2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-ylboronic acid (49.5 mg, 0.32 mmol), tris(dibenzylideneacetone)dipalladium(0) (19.39 mg, 0.02 mmol), 2-dicyclohexylphosphino-2',4',6'-tri-iso-propyl-1,1'-biphenyl (30.3 mg, 0.06 mmol) and sodium carbonate were taken in a round bottomed flask. It was degassed with nitrogen and 5 mL of dioxane:water (4:1) was added and degassed again. The resulting mixture was heated at 100 °C for 40 min, then the reaction mixture was filtered. The filtrate was concentrated under reduced pressure and the resulting residue was partitioned between water and 3% MeOH in dichloromethane. The layers were separated and the aqueous was back extracted with the solvent three times. The extracts were combined, washed with water and brine and dried over magnesium sulfate, then concentrated under reduced pressure and purified by reverse phase HPLC to give a white solid (62 mg).

MS (ESP): 504 (M+1) for $C_{21}H_{16}F_3N_7O_3S$

^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 3.01-3.48 (m, 2H); 7.57 (br s, 1H); 7.92 (d, 1H); 8.12 (s, 1H); 8.25 (s, 1H); 8.36 (s, 1H); 8.45 (d, 1H); 8.57 (s, 1H); 8.92 (d, 1H); 9.49 (s, 1H): 11.42 (brs, 2H).

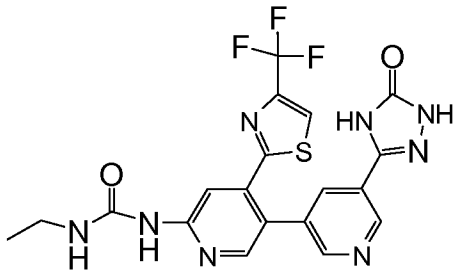
Examples 132-134

The following compounds have been synthesized as described for Example 131 from the starting materials indicated in the table below.

Ex	Compound	Data	SM
132	1-Ethyl-3-(5'-(3-methyl-1H-pyrazol-4-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 474 (M+1) for $C_{21}H_{18}F_3N_7OS$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 2.28 (s, 3H); 3.05-3.26 (m, 2H); 7.62 (br s, 1H); 7.79 (brs, 2H); 8.21 (s, 1H); 8.37 (d, 2H); 8.56 (s, 1H); 8.76 (d, 1H); 9.47 (s, 1H); 12.82 (brs, 1H).	Example 21 and 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole
133	1-(5'-(3,5-dimethylisoxazol-4-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 489 (M+1) for $C_{22}H_{19}F_3N_6O_2S$ ^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 2.15 (s, 3H); 2.36 (s, 3H); 3.08-3.29 (m, 2H); 7.58 (br s, 1H); 7.80 (s, 1H); 8.21 (s, 1H); 8.37 (s, 1H); 8.55 (d, 1H); 8.57 (s, 1H); 8.67 (d, 1H); 9.48 (s, 1H).	Example 21 and 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole
134	1-(5'-(1H-Pyrazol-5-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 460 (M+1) for $C_{20}H_{16}F_3N_7OS$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.15-3.25 (m, 2H); 6.89 (d, 1H); 7.58 (br s, 1H); 7.83 (d, 1H); 8.27 (s, 1H); 8.30 (s, 1H); 8.39 (s, 1H); 8.50 (s, 1H); 8.55 (s, 1H); 9.14 (s, 1H); 9.51 (s, 1H).	Intermediate 12 and Intermediate 222

Example 135

1-Ethyl-3-(5'-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



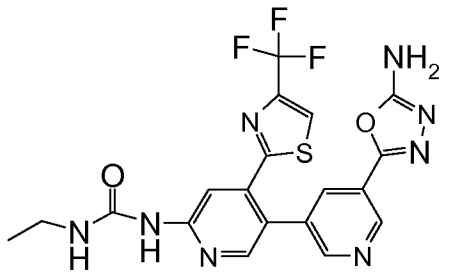
To a mixture of 1-(5'-(5-amino-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Example 136, 70 mg, 0.15 mmol) in methanol (4 mL), potassium hydroxide (16.49 mg, 0.29 mmol) was added and heated at 70 °C for 20 h. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the resulting residue was taken in conc. hydrochloric acid (3 mL) and heated at 80 °C for another 1 h. The reactiom mixture was cooled to room temperature and neutralized with 10 N sodium hydroxide solution. The solid that precipitated was collected by filtration, dried, and purified by reverse phase HPLC.

MS (ESP): 477 (M+1) for $C_{19}H_{15}F_3N_8O_2S$

^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 3.14-3.28 (m, 2H); 7.55 (brs, 1H); 8.10 (t, 1 H); 8.25 (s, 1H); 8.36 (s, 1H); 8.56 (s, 2H); 9.00 (s, 1H); 9.51 (s, 1H); 11.89 (s, 1H); 12.17 (s, 1H)

Example 136

1-(5'-(5-Amino-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



To a mixture of 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 9, 138 mg, 0.31 mmol) in 1,4-dioxane (3 mL), sodium bicarbonate (25.7 mg, 0.31 mmol) in water (1 mL) was added and the mixture was stirred for 5 min at room temperature. Cyanic bromide (0.122 mL, 0.37 mmol) (3M sol. in DCM) was

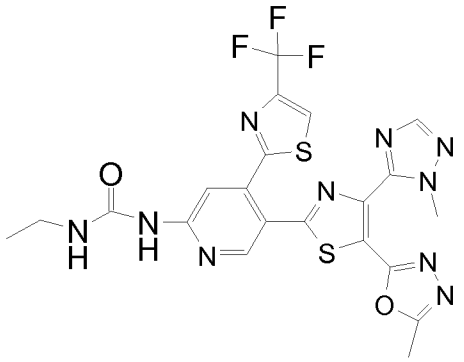
added to the reactiom mixture and stirred at room temperature for 1 h. The product was precipitated with water, collected by filtration and dried to give a light yellow solid (101 mg).

MS (ESP): 477 (M+1) for $C_{19}H_{15}F_3N_8O_2S$

^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.14-3.28 (m, 2H); 7.43 (brs, 2H); 7.56 (brs, 1H); 8.08 (t, 1 H); 8.24 (s, 1H); 8.38 (s, 1H); 8.56 (s, 1H); 8.61 (d, 1H); 9.00 (d, 1H); 9.51 (s, 1H).

Example 137

1-Ethyl-3-(5-(5-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea



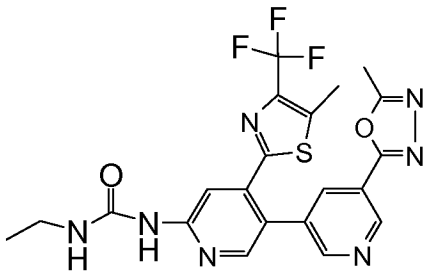
1-Ethyl-3-(5-(5-(hydrazinecarbonyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea (Intermediate 234, 70 mg, 0.13 mmol) was taken in 1,1,1-trimethoxyethane (2 mL, 0.13 mmol) and a drop of HCl was added to it. The mixture was refluxed at 120 °C for 25 min, then DMF (2 mL) and DBU (4-8 drops) were added and the mixture was refluxed for 20 h at 100 °C. The reaction mixture was cooled to room temperature and water was added to precipitate the product. The product was collected via filtration and washed with 1:1 water and acetonitrile. The filtrate was extracted with ethyl acetate three times. The combined extracts were washed with water and brine, dried over magnesium sulfate and concentrated. The crude was combined with the precipitated product and purified by normal phase chromatography (2%MeOH in DCM to 6 % MeOH in DCM). The fractions containing the product were combined and concentrated to give off-white solid (20 mg).

MS (ESP): 563 (M+1) for $C_{21}H_{17}F_3N_{10}O_2S_2$

^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 2.50 (s, 3H); 3.13-3.27 (m, 2H); 3.80 (s, 3H); 7.48 (brs, 1H); 8.05 (s, 1H); 8.11 (s, 1 H); 8.74 (s, 1H); 8.85 (s, 1H); 9.76 (s, 1H).

Example 138

1-Ethyl-3-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



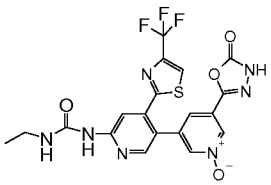
The title compound was synthesized by a method analogous to the synthesis of Example 137 starting with 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea Intermediate 237 and 1,1,1-trimethoxyethane.

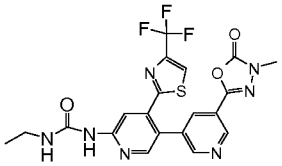
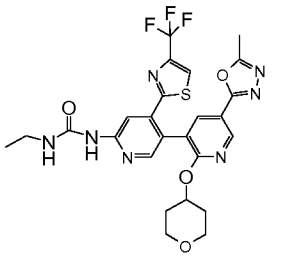
MS (ESP): 490 (M+1) for $C_{21}H_{18}F_3N_7O_2S$

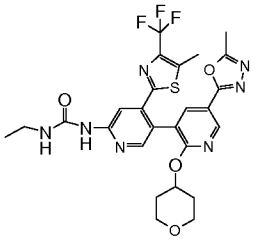
^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 2.52 (s, 3H); 2.60 (s, 3H); 3.09-3.29 (m, 2H); 7.58 (br s, 1H); 8.18 (s, 1H); 8.31 (s, 1 H); 8.36 (s, 1H); 8.70 (d, 1H); 9.17 (d, 1H); 9.51 (s, 1H).

Examples 139-142

The following compounds have been synthesized as described for Example 21 from the starting materials indicated in the table below.

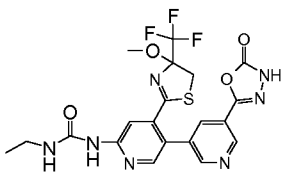
Ex	Compound	Data	SM
139	6'-(3-Ethylureido)-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine 1-oxide 	MS (ESP): 494 (M+1) for $C_{19}H_{14}F_3N_7O_4S$ ^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 3.15-3.24 (m, 2H); 7.53 (brs, 1H); 7.61 (s, 1H); 8.22 (s, 1H); 8.38 (s, 1H); 8.49 (s, 1H); 8.53 (s, 1H); 8.64 (s, 1H); 9.54 (s, 1H); 12.95 (s, 1H)	3-bromo-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyridine 1-oxide (Intermediate 465) and Intermediate 12

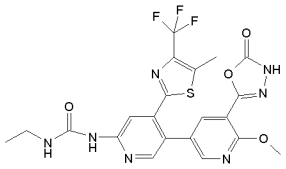
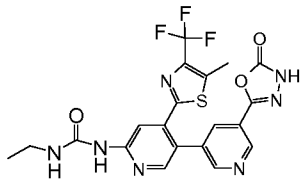
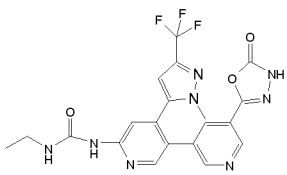
Ex	Compound	Data	SM
140	1-Ethyl-3-(5'-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 492 (M+1) for $C_{20}H_{16}F_3N_7O_3S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.12-3.29 (m, 2H); 3.42 (s, 3H); 7.56 (brs, 1H); 8.13 (d, 1H); 8.23 (s, 1H); 8.38 (s, 1H); 8.59 (s, 1H); 8.66 (d, 1H); 8.99 (d, 1H); 9.52 (s, 1H)	Intermediate 12 and Intermediate 246
141	1-Ethyl-3-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 576 (M+1) for $C_{25}H_{24}F_3N_7O_4S$ ^{1}H-NMR (DMSO-d_6) δ: 1.05-1.15 (m, 2H); 1.11 (t, 3H); 1.64 (br s, 2H); 2.59 (s, 3H); 3.09-3.27 (m, 2H); 3.30-3.36 (m, 2H); 3.38-3.71 (m, 2H); 4.81-5.28 (m, 1H); 7.59 (brs, 1H); 8.22 (s, 1H); 8.31 (s, 1 H); 8.33 (d, 1H); 8.54 (s, 1H); 8.82 (d, 1H); 9.50 (s, 1H).	Intermediate 12 and Intermediate 484

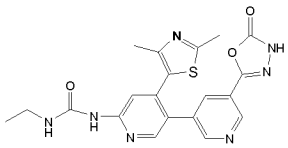
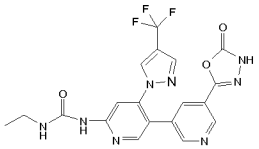
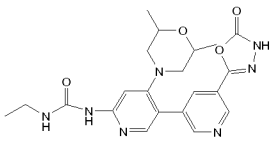
Ex	Compound	Data	SM
142	1-Ethyl-3-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-yloxy)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 590 (M+1) for $C_{26}H_{26}F_3N_7O_4S$ ^{1}H-NMR (DMSO-d_6) δ: 1.05-1.16 (m ,2 H); 1.11 (t, 3H); 1.65 (brs, 2H); 2.52 (s, 3H); 2.59 (s, 3H); 3.09-3.27 (m, 2H); 3.32-3.36 (m, 2H); 3.38-3.67 (m, 2H); 4.82-5.38 (m, 1H); 7.61 (brs, 1H); 8.16 (s, 1H); 8.27 (s, 1 H); 8.29 (d, 1H); 8.81(d, 1H); 9.48 (s, 1H).	Intermediate 245 and Intermediate 484

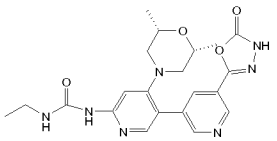
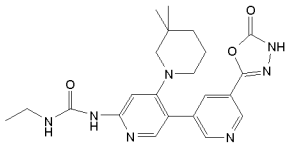
Examples 143-151

The following compounds have been synthesized as described for Example 6 from the starting materials indicated in the table below.

Ex	Compound	Data	SM
143	1-Ethyl-3-(4-(4-methoxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 510 (M+1) for $C_{20}H_{18}F_3N_7O_4S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.11 (s, 3H); 3.10-3.29 (m, 2H); 3.76 (s, 2H); 7.42 (brs, 1H); 8.05 (s, 1H); 8.09 (s, 1H); 8.41 (s, 1H); 8.71 (s, 1 H); 8.96 (s, 1H); 9.53 (s, 1H); 12.82 (s, 1H).	Intermediate 235

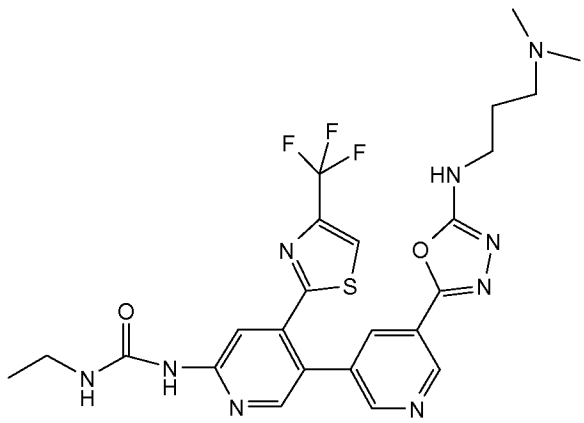
Ex	Compound	Data	SM
144	1-Ethyl-3-(6'-methoxy-4-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 522 (M+1) for $C_{21}H_{18}F_3N_7O_4S$ ^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 2.53 (s, 3H); 3.15-3.24 (m, 2H); 4.03 (s, 3H); 7.62 (brs, 1H); 8.03 (d, 1H); 8.18 (s, 1H); 8.29 (s, 1 H); 8.32 (d, 1H); 9.45 (s, 1H); 12.68 (s, 1H)	Intermediate 236
145	1-Ethyl-3-(4-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 492 (M+1) for $C_{20}H_{16}F_3N_7O_3S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 2.51 (s, 3H); 3.15-3.24 (m, 2H); 7.58 (brs, 1H); 8.16 (s, 1H); 8.18 (s, 1H); 8.34 (s, 1H); 8.65 (s, 1H); 9.00 (s, 1H); 9.49 (s, 1H); 12.78 (s, 1H)	Intermediate 237
146	1-Ethyl-3-(4-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 475 (M+1) for $C_{20}H_{17}F_3N_8O_3$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.11-3.28 (m, 2H); 3.44 (s, 3H); 6.88 (s, 1H); 7.63 (brs, 1H); 7.70 (s, 1H); 7.93 (t, 1H); 8.52 (s, 1H); 8.53 (s, 1H); 8.89 (d, 1H); 9.55 (s, 1H); 12.80 (s, 1H)	Intermediate 238

Ex	Compound	Data	SM
147	1-(4-(2,4-Dimethylthiazol-5-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 438 (M+1) for $C_{20}H_{19}N_7O_3S$ ^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 1.89 (s, 3H); 2.57 (s, 3H); 3.11-3.28 (m, 2H); 7.62 (s, 1H); 7.73 (brs, 1H); 7.97 (t, 1H); 8.39 (s, 1H); 8.51 (s, 1H); 8.88 (d, 1H); 9.45 (s, 1H); 12.79 (s, 1H)	Intermediate 239
148	1-Ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 461 (M+1) for $C_{19}H_{15}F_3N_8O_3$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.11-3.28 (m, 2H); 6.94 (d, 1H); 7.41 (t, 1H); 7.76 (t, 1H); 7.95 (s, 1H); 8.09 (s, 1H); 8.43 (d, 1H); 8.53 (s, 1H); 8.90 (d, 1H); 9.58 (s, 1H); 12.78 (s, 1H)	Intermediate 240
149	1-(4-(2,6-dimethylmorpholino)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 440 (M+1) for $C_{21}H_{25}N_7O_4$ ^{1}H-NMR (DMSO-d_6) δ: 0.96 (d, 6H); 1.09 (t, 3H); 2.28 (t, 2H); 2.95 (d, 2H); 3.11-3.26 (m, 2H); 3.51 (brs, 2H); 7.13 (s, 1H); 8.01 (s, 2H); 8.38 (t, 1H); 8.91 (t, 2 H); 9.11 (s, 1H); 12.72 (s, 1H)	Intermediate 241

Ex	Compound	Data	SM
150	1-(4-((2R,6S)-2,6-dimethylmorpholino)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 440 (M+1) for $C_{21}H_{25}N_7O_4$ ^{1}H-NMR (DMSO-d_6) δ: 0.96 (d, 6H); 1.09 (t, 3H); 2.27 (t, 2H); 2.95 (d, 2H); 3.11-3.26 (m, 2H); 3.51 (brs 2H); 7.13 (s, 1H); 8.01 (s, 2H); 8.38 (s, 1H); 8.91 (s, 2 H); 9.13 (s, 1H); 12.80 (s, 1H)	Intermediate 242
151	1-(4-(3,3-dimethylpiperidin-1-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 438 (M+1) for $C_{22}H_{27}N_7O_3$ ^{1}H-NMR (DMSO-d_6) δ: 0.89 (s, 6H); 1.09 (t, 3H); 1.15-1.51 (m, 4 H); 2.54-2.79 (m, 4H); 3.09-3.26 (m, 2H); 7.13 (s, 1H); 7.95 (s, 1H); 8.09 (brs, 1H); 8.33 (s, 1H); 8.86 (d, 1 H); 8.92 (d, 1H); 9.11 (s, 1H); 12.80 (s, 1H)	Intermediate 243

Example 152

1-(5'-(5-(3-(Dimethylamino)propylamino)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



To a solution 1-ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Example 6, 130 mg, 0.27 mmol) in

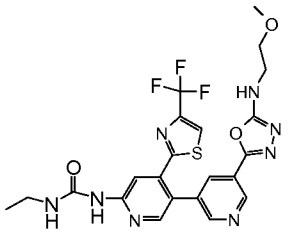
ethanol (5 mL), N,N-dimethylpropane-1,3-diamine (41.7 mg, 0.41 mmol) was added and microwaved at 100 ° for 2 h. The reaction was concentrated and the crude resulted was taken in acetonitrile (5 mL), and 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (0.081 mL, 0.54 mmol) (DBU) was added to it. Then triphenyl phosphine (143 mg, 0.54 mmol) followed by perchloromethane (0.053 mL, 0.54 mmol) (carbon tetrachloride) were added to the resulting solution and stirred over the weekend at room temperature. The solvent was removed and the crude was partitioned between water and ethyl acetate. The layers were separated. The aqueous layer was saturated with sodium chloride and extracted with ethyl acetate. The combined layers were washed with brine and dried over magnesium sulfate, concentrated and purified by normal phase (2 % MeOH in DCM to 15% MeOH in DCM with 1% ammonium hydroxide). The fractions containing the products were combined and concentrated to give a white solid (34 mg).

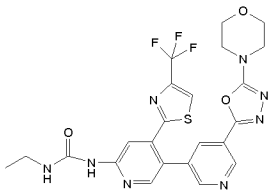
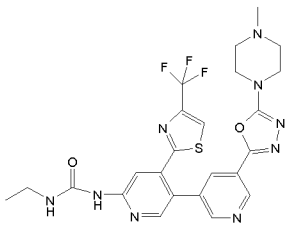
MS (ESP): 562 (M+1) for $C_{24}H_{26}F_3N_9O_2S$

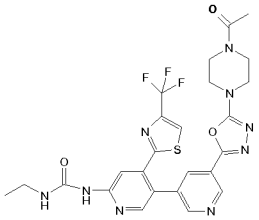
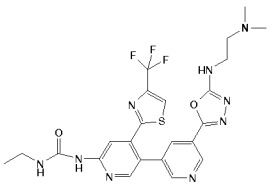
^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 1.52-1.78 (m, 2H); 2.15 (s, 6H); 2.25-2.35 (m, 2H); 3.10-3.32 (m, 4H); 7.56 (brs, 1H); 7.93 (t, 1H); 8.09 (s, 1H); 8.24 (s, 1H); 8.39 (s, 1H); 8.57 (s, 1H); 8.61 (d, 1H); 9.01 (d, 1H); 9.51 (s, 1H)

Examples 153-157

The following compounds have been synthesized as described for Example 152 from the starting materials indicated in the table below.

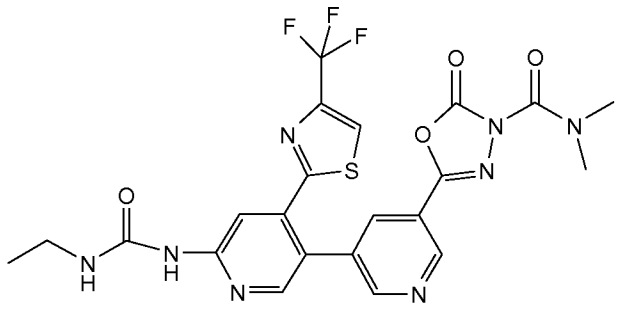
Ex	Compound	Data	SM
153	1-Ethyl-3-(5'-(5-(2-methoxyethylamino)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 535 (M+1) for $C_{22}H_{21}F_3N_8O_3S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.12-3.24 (m, 2H); 3.27 (s, 3H); 3.36-3.45 (m, 2H); 3.46-3.52 (m, 2H); 7.57 (brs, 1H); 7.95 (t, 1H); 8.10 (t, 1H); 8.24 (s, 1H); 8.39 (s, 1H); 8.56 (s, 1H); 8.61 (s, 1H); 9.02 (s, 1H); 9.51 (s, 1H)	Example 6 and methoxyethylamine

Ex	Compound	Data	SM
154	1-Ethyl-3-(5'-(5-morpholino-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 547 (M+1) for $C_{23}H_{21}F_3N_8O_3S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.10-3.26 (m, 2H); 3.45-3.61 (m, 4H); 3.58-3.84 (m, 4 H); 7.56 (brs, 1H); 8.23 (s, 1H); 8.24 (s, 1H); 8.40 (s, 1H); 8.58 (s, 1H); 8.62 (s, 1H); 9.12 (s, 1H); 9.51 (s, 1H)	Example 6 and morpholine
155	1-Ethyl-3-(5'-(5-(4-methylpiperazin-1-yl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 560 (M+1) for $C_{24}H_{24}F_3N_9O_2S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 2.32 (s, 3H); 2.30-2.45 (m, 4H); 3.09-3.29 (m, 2H); 3.39-3.73 (m, 4H); 7.57 (brs, 1H); 8.22 (t, 1H); 8.24 (s, 1H); 8.40 (s, 1H); 8.57 (s, 1H); 8.62 (d, 1H); 9.11 (d, 1H); 9.52 (s, 1H)	Example 6 and 1-methylpiperazine

Ex	Compound	Data	SM
156	1-(5'-(5-(4-Acetylpiperazin-1-yl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 588 (M+1) for $C_{25}H_{24}F_3N_9O_3S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 2.05 (s, 3H); 3.08-3.27 (m, 2H); 3.50 (brs, 2H); 3.57 (brs, 6H); 7.56 (brs, 1H); 8.24 (s, 2H); 8.39 (s, 1H); 8.58 (s, 1H); 8.62 (d, 1H); 9.12 (d, 1H); 9.51 (s, 1H)	Example 6 and 1-acetylpiperazine
157	1-(5'-(5-(2-(Dimethylamino)ethylamino)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 548 (M+1) for $C_{23}H_{24}F_3N_9O_2S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 2.17 (s, 6H); 2.35-2.48 (m, 2H); 3.10-3.40 (m, 4H); 7.55 (brs, 1H); 7.82 (t, 1H); 8.09 (d, 1H); 8.25 (s, 1H); 8.39 (s, 1H); 8.56 (s, 1H); 8.61 (d, 1H); 9.02 (d, 1H); 9.48 (s, 1H)	Example 6 and N1,N1-dimethylethane-1,2-diamine

Example 158

5-(6'-(3-Ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-N,N-dimethyl-2-oxo-1,3,4-oxadiazole-3(2H)-carboxamide



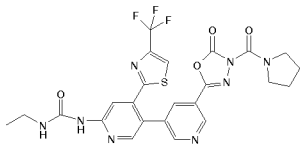
To a solution of 1-ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (example 6) (150 mg, 0.31 mmol) in THF (3 mL), potassium t-butoxide (0.377 mL, 0.38 mmol) was added at room temperature. It resulted a mixture that was stirred for 15 minutes and then dimethylcarbamic chloride (0.058 mL, 0.63 mmol) was added. Then the resulting mixture was stirred for one hour at room temperature and at 60 ºC over night. The solvent was removed and the crude was diluted with water and extracted with ethyl acetate. The organic layer was washed with water several times followed by brine and dried over magesium sulfate, filtered then concentrated and purified by normal phase chromatography to isolate the desired product as a white solid (53 mg).

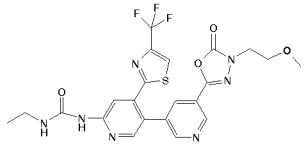
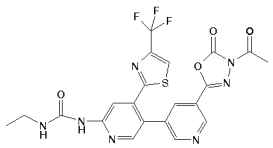
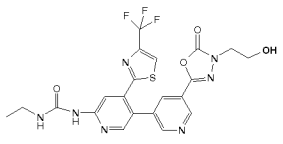
MS (ESP): 549 (M+1) for $C_{22}H_{19}F_3N_8O_4S$

^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.05 (brs, 6H); 3.15-3.28 (m, 2H); 7.55 (brs, 1H); 8.22 (d, 1H); 8.24 (s, 1H); 8.39 (s, 1H); 8.60 (s, 1H); 8.71 (d, 1H); 9.04 (d, 1H); 9.52 (s, 1H)

Examples 159-162

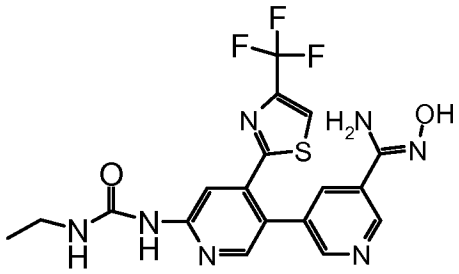
The following compounds have been synthesized as described for Example 158 from the starting materials indicated in the table below.

Ex	Compound	Data	SM
159	1-Ethyl-3-(5'-(5-oxo-4-(pyrrolidine-1-carbonyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 575 (M+1) for $C_{24}H_{21}F_3N_8O_4S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 1.87 (br s, 4 H); 3.15-3.28 (m, 2H); 3.46 (brs, 2H); 3.66 (brs, 2H); 7.56 (brs, 1H); 8.23 (s, 2H); 8.39 (s, 1H); 8.60 (s, 1H); 8.71 (s, 1H); 9.04 (s, 1H); 9.52 (s, 1H)	Example 6 and pyrrolidine-1-carbonyl chloride

Ex	Compound	Data	SM
160	1-Ethyl-3-(5'-(4-(2-methoxyethyl)-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 536 (M+1) for $C_{22}H_{20}F_3N_7O_4S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.15-3.30 (m, 2H); 3.26 (s, 3H); 3.65 (t, 2H); 3.92 (t, 2H); 7.56 (brs, 1H); 8.14 (s, 1H); 8.22 (s, 1H); 8.39 (s, 1H); 8.58 (s, 1H); 8.71 (s, 1H); 9.00 (d, 1H); 9.52 (s, 1H)	Example 6 and 1-bromo-2-methoxyethane
161	1-(5'-(4-Acetyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 520 (M+1) for $C_{21}H_{16}F_3N_7O_4S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.15-3.30 (m, 2H); 7.56 (brs, 1H); 8.23 (s, 1H); 8.24 (s, 1H); 8.39 (s, 1H); 8.60 (s, 1H); 8.71 (s, 1H); 9.08 (d, 1H); 9.53 (s, 1H) ^{1}H-NMR ($MeOD_3$) δ: 1.11 (t, 3H); 2.59 (s, 3H); 3.32-3.43 (m, 2H); 7.87 (s, 1H); 8.29 (d, 2H); 8.39 (s, 1H); 8.66 (d, 1H); 9.10 (d, 1H)	Example 6 and acetyl chloride
162	1-Ethyl-3-(5'-(4-(2-hydroxyethyl)-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 522 (M+1) for $C_{21}H_{18}F_3N_7O_4S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.11-3.28 (m, 2H); 3.78 (t, 2H); 4.45 (t, 2H); 7.54 (brs, 1H); 8.23 (s, 1H); 8.25 (s, 1H); 8.37 (s, 1H); 8.57 (s, 1H); 8.68 (d, 1H); 9.05 (d, 1H); 9.51 (s, 1H); 11.06 (s, 1H)	Example 6 and (2-bromoethoxy)(*tert*-butyl)dimethylsilane followed by deprotection with TBAF in THF.

Example 163

6'-(3-Ethylureido)-N'-hydroxy-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboximidamide



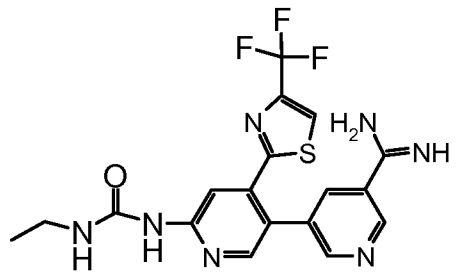
To a suspension of 1-(5'-cyano-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Example 2, 70 mg, 0.17 mmol)in ethanol (3 mL), hydroxylamine (0.015 mL, 0.25 mmol) (50% by weight, aq.) was added and microwaved at 80 °C for 1 h. The reaction was concentrated to give a white solid. It was slurried in acetonitrile, filtered and dried to give a white solid (52 mg).

MS (ESP): 452 (M+1) for $C_{18}H_{16}F_3N_7O_2S$

^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.10-3.27 (m, 2H); 6.02 (s, 2H); 7.57 (brs, 1H); 8.03 (s, 1H); 8.26 (s, 1H); 8.35 (s, 1H); 8.46 (d, 1H); 8.56 (s, 1H); 8.93 (d, 1H); 9.48 (s, 1H); 9.91 (s, 1H)

Example 164

6'-(3-Ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboximidamide



To a solution of sodium methoxide (50 µl, 0.22 mmol) (25 % by wt solution in MeOH) in MeOH (3 mL), 1-(5'-cyano-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Example 2, 85 mg, 0.20 mmol) was added and the resulting mixture was stirred at room temperature for 4 hours. Then ammonium chloride (13.04 mg, 0.24 mmol) was added and the mixture was stirred overnight at room temperature. As there was no reaction the reaction mixture was transferred to a microwave vial and microwaved at 80 ° for 20 minutes.

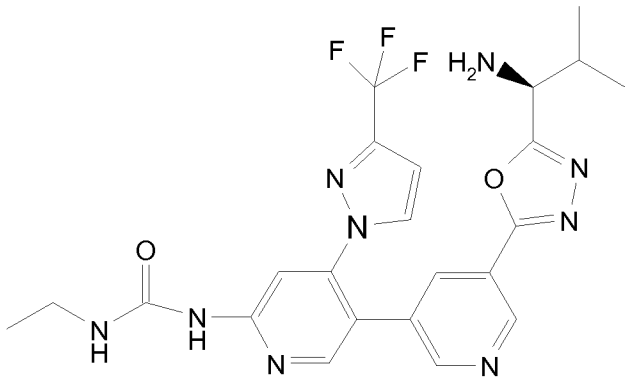
The reaction was complete. The solid formed was filtered off and the washed with acetonitrile and dichloromethane. Then the solid was taken in water and sodium bicarbonate was added to it. The mixture was extracted with ethyl acetate. The extract was washed with water and dried over magnesium sulfate and concentrated to give a white solid which was slurried in acetonitrile, filtered and dried to give a white solid as the product (35 mg).

MS (ESP): 436 (M+1) for $C_{18}H_{16}F_3N_7OS$

^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.10-3.27 (m, 2H); 6.44 (brs, 2H); 6.55 (brs, 1H); 7.59 (brs, 1H); 8.17 (brs, 1H); 8.26 (s, 1H); 8.35 (s, 1H); 8.52 (s, 1H); 8.56 (s, 1H); 9.06 (brs, 1H); 9.48 (s, 1H)

Example 165

S)-1-(5'-(5-(1-Amino-2-methylpropyl)-1,3,4-oxadiazol-2-yl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



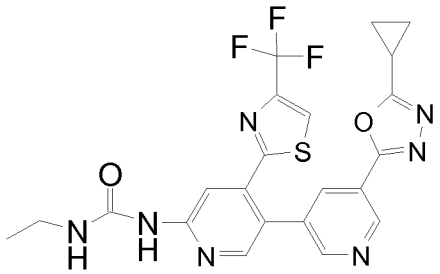
To a solution of (S)-tert-butyl 1-(5-(6'-(3-ethylureido)-4'-(3-(trifluoromethyl)-1H-pyrazol-1-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)-2-methylpropylcarbamate (Intermediate 257, 65 mg, 0.11 mmol), in dioxane (3 mL), 4M HCl in dioxane (3 mL, 86.39 mmol) was added and the mixture was allowed to stir overnight. The reaction was concentrated and the solid obtained was taken in water, basified with 1N NaOH to precipitate the product.

MS (ESP): 516 (M+1) for $C_{23}H_{24}F_3N_9O_2$

^{1}H-NMR (DMSO-d_6) δ: 0.87 (d, 3H); 0.96 (d, 3H); 1.11 (t, 3H); 1.88-208 (m, 1H); 3.10-3.27 (m, 2H); 3.88 (d, 1H); 6.94 (d, 2H); 7.42 (brs, 1H); 7.93 (s, 1H); 7.94 (s, 1H); 7.97 (s, 1H); 8.14 (d, 1H); 8.50 (d, 1H); 8.57 (s, 1H); 9.12 (d, 1H); 9.62 (s, 1H).

Example 166

1-(5'-(5-Cyclopropyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



To a suspension of 1-(5'-(2-(cyclopropanecarbonyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Intermediate 258, 80 mg, 0.15 mmol), triethylamine (0.021 mL, 0.15 mmol) and triphenylphosphine (81 mg, 0.31 mmol) were added followed by carbon tetrachloride (0.015 mL, 0.15 mmol). The resulting mixture was stirred at 40°C for 1h, then concentrated and the crude was partitioned between water and ethyl acetate. The layers separated and the organic layer was washed with water and brine, dried over magnesium sulfate and concentrated. The crude was purified by normal phase chromatography (1%MeOH in DCM to 5 %). The fractions containing the product were combined, concentrated and lyophilized to give a white solid (42 mg).

MS (ESP): 502 (M+1) for $C_{22}H_{18}F_3N_7O_2S$

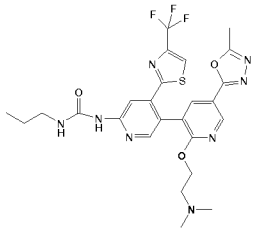
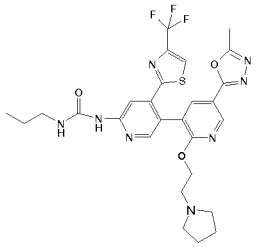
^{1}H-NMR (DMSO-d_6) δ: 0.72-155 (m, 4 H); 1.10 (t, 3H); 2.19-2.46 (m, 1H); 3.08-3.29 (m, 2H); 7.56 (brs, 1H); 8.23 (s, 1H); 8.28 (t, 1 H); 8.40 (s, 1H); 8.57 (s, 1H); 8.68 (s, 1H); 9.15 (s, 1H); 9.52 (s, 1H).

Examples 167-168

The following Examples were synthesized from the general procedure described below from the starting materials in the Table.

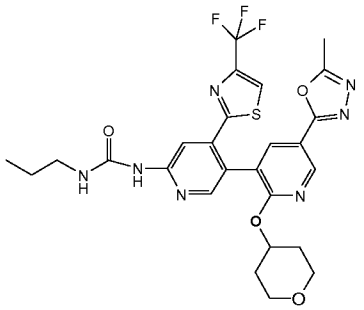
General Procedures

A suspension of corresponding carboxylic acid (0.3 mmol), hydrazine acetate (0.9 mmol) in phosphorus oxychloride (2.5 mL) was heated at 70°C for 2 h. The solution was then cooled and concentrated to dryness. A solution of saturated potassium carbonate was added to the crude and extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under vacuum and the crude was purified by Analogix using dichloromethane-methanol.

Ex	Compound	Data	SM
167	1-(2'-(2-(Dimethylamino)ethoxy)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-propylurea 	MS (ESP): 577.2 (MH^+) for $C_{25}H_{27}F_3N_8O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 0.97-1.02 (m, 3H), 1.58-1.65 (m, 2H), 2.62, (s, 3H), 2.67 (s, 6H), 3.23-3.28 (m, 4H), 4.50 (m, 2H), 7.94 (s, 1H), 8.24 (s, 1H), 8.32-8-34 (m, 2H), 8.89-8.90 (m, 1H) ^{19}F NMR (300 MHz, CD_3OD): δ -65.94	Intermediate 259
168	1-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-2'-(2-(pyrrolidin-1-yl)ethoxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-propylurea 	MS (ESP): 606.3 (MH^+) for $C_{27}H_{29}F_3N_8O_3S$ ^{1}H NMR (300 MHz, CD_3OD): δ 0.92-0.95 (m, 3H), 1.09-1.10 (m, 2H), 1.21-1.28 (m, 4H), 1.58-1.65 (m, 2H), 1.99 (m, 2H), 2.11 (m, 4H), 2.62 (s, 3H), 3.63 (m, 2H), 3.93-3.96 (m, 2H), 7.98 (s, 1H), 8.25 (m, 1H), 8.33-8.35 (m, 2H), 8.91 (m, 1H) ^{19}F NMR (300 MHz, CD_3OD): δ -65.94	Intermediate 260

Examples 169

1-(5'-(5-Methyl-1,3,4-oxadiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-propylurea



A suspension of 6'-(3-propylureido)-2-(tetrahydro-2H-pyran-4-yloxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 262, ~0.3 mmol) and hydrazine acetate (0.9 mmol) in phosphorus oxychloride (2.5 mL) was heated at 70°C for 2 h. The solution was then cooled and concentrated to dryness. A solution of saturated potassium carbonate was added to the crude and extracted with ethyl acetate (3×). The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under vacuum and the crude was purified by Analogix using dichloromethane-methanol.

MS (ESP): 590.1 (MH^+) for $C_{26}H_{26}F_3N_7O_4S$

^1H NMR (300 MHz, $CDCl_3$): δ 1.002-1.05 (m, 3H), 1.25-1.28 (m, 2H), 1.65-1.75 (m, 4H), 2.62 (s, 3H), 3.39-3.47 (m, 4H), 3.64-3.68 (m, 2H), 5.10-5.18 (m, 1H), 7.61 (s, 1H), 7.73 (s, 1H), 8.20 (s, 1H), 8.24-8.26 (m, 1H), 8.83 (m, 1H), 9.12 (bs, 1H), 9.48 (bs, 1H)

^{19}F NMR (300 MHz, $CDCl_3$): δ -64.51

Examples 170-172

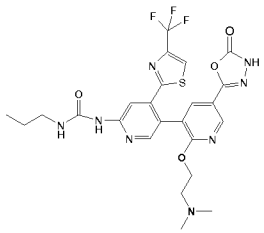
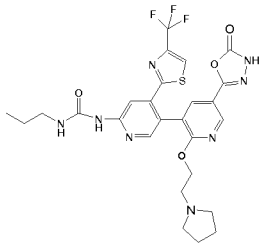
The following Examples were prepared by the general procedure described below from the starting materials indicated in the Table.

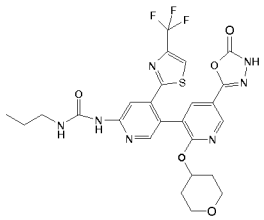
General Procedure

A suspension of corresponding carboxylic acid (0.3 mmol) in thionyl chloride (2 mL) was heated at 50°C for 1 h. The solution was then cooled and concentrated to dryness. The crude suspended in tetrahydrofuran (2 mL) was added slowly to a solution of hydrazine/ tetrahydrofuran (1/2 vol., 3 mL) and stirred at room temperature for 12 h. After this period of time, the crude was concentrated to dryness and purified by reverse phase on Analogix C18-column (water-methanol) to give (~60%) hydrazides as off-white solids.

A suspension of corresponding hydrazide (0.3 mmol) in anhydrous tetrahydrofuran (2 mL) was treated with triethyl amine (0.6 mmol) and 1,1'-carbonyl diimidazole (0.12 mmol). The reaction was stirred at room temperature for 12 h, concentrated to dryness and purified

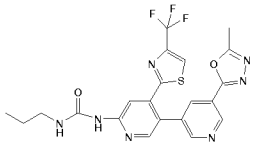
directly by Analogix using dichloromethane-methanol to give (~50%) product as an off-white solid.

Ex	Compound	Data	SM
170	1-(2'-(2-(Dimethylamino)ethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-propylurea 	MS (ESP): 579.3 (MH^+) for $C_{24}H_{25}F_3N_8O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88-0.93 (m, 3H), 1.51-1.53 (m, 2H), 2.20 (s, 6H), 2.50-2.54 (m, 2H), 3.11-3.18 (m, 4H), 4.23 (m, 2H), 7.62 (m, 1H), 8.15 (m, 1H), 8.25-8.29 (m, 2H), 8.55 (m, 1H), 8.66-8.67 9 (m, 1H), 9.47 (s, 1H). ^{19}F NMR (300 MHz, DMSO-d_6): δ -62.86	Intermediate 259
171	1-(5'-(5-Oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2'-(2-(pyrrolidin-1-yl)ethoxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-propylurea 	MS (ESP): 605.1 (MH^+) for $C_{26}H_{27}F_3N_8O_4S$ ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88-0.93 (m, 3H), 1.46-1.48 (m, 2H), 1.53-1.62 (m, 4H), 2.49 (m, 4H), 2.51 (m, 2H), 3.11-3.18 (m, 2H), 4.22 (m, 2H), 7.62-7.65 (m, 1H), 8.16 (s, 1H), 8.26-8.29 (m, 2H), 8.52-8.55 (m, 1H), 8.66-8.67 (m, 1H), 9.47 (s, 1H). ^{19}F NMR (300 MHz, dmso-d_6): δ -62.85	Intermediate 260

Ex	Compound	Data	SM
172	1-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-propylurea 	MS (ESP): 592.2 (MH^+) for $C_{25}H_{24}F_3N_7O_5S$ ^1H NMR (300 MHz, CD_3OD): δ 0.97-1.02 (m, 3H), 1.28 (m, 2H), 1.59-1.64 (m, 2H), 1.66-1.70 (m, 2H), 3.26-3.30 (m, 2H), 3.38-3.41 (m, 2H), 3.44-3.59 (m, 2H), 5.14-5.16 (m, 1H), 7.87 (s, 1H), 8.14-8.15 (m, 1H), 8.20 (s, 1H), 8.24 (s, 1H), 8.56-8.65 (m, 1H) ^{19}F NMR (300 MHz, CD_3OD): δ-64.82	Intermediate 261

Example 173

1-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-propylurea



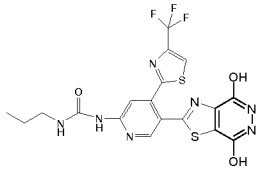
Methyl 6'-(3-propylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 263, 140 mg) was dissolved in tetrahydrofuran (3 mL) and methanol (3 mL). 1N Sodium hydroxide (3 mL) was added, and the reaction was stirred at room temperature for 3 h. The organics were removed and the residual aqueous phase was acidified to pH ~2 with 1N hydrochloric acid. The mixture was filtered and the solid dried in a vacuum oven at 50°C for 18 h. The solid was then dissolved in phosphorous oxychloride (3 mL), acetic hydrazide (25 mg) was added and the solution heated at 60°C for 3 h. Most of the phosphorous oxychloride was removed *in vacuo* and then saturated sodium bicarbonate was added to the mixture to obtain a pH ~7. The solution was extracted with 2:1 ethyl acetate: tetrahydrofuran (3×, 3 mL each). The organic phases were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*.

MS (ESP): 490.2 ($M+H^+$) for $C_{21}H_{18}F_3N_7O_2S$

^{1}H NMR (300 MHz, DMSO-d_6): δ 0.91 (t, 3H), 1.46-1.54 (m, 2H), 2.60 (s, 3H), 3.12-3.18 (m, 2H), 7.64 (bt, 1H), 8.24 (s, 1H), 8.30 (dd, 1H), 8.41 (d, 1H), 8.58 (d, 1H), 8.70 (d, 1H), 9.17 (d, 1H), 9.54 (bs, 1H)

Example 174

1-(5-(4,7-dihydroxythiazolo[5,4-d]pyridazin-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea



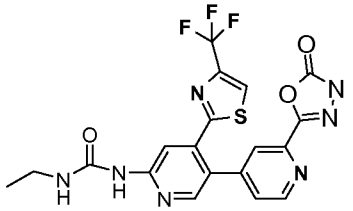
Diethyl 2-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)thiazole-4,5-dicarboxylate (Intermediate 264, 73 mg, 0.13 mmol), was dissolved in methanol (10 mL) and hydrazine (0.4 mL) was added. The reaction was heated at reflux for 3 h. 12 M Hydrochloric acid (1 mL) was then added and the reaction heated for a further 2 h. The solvents were removed *in vacuo*. The residue was chromatographed on the preparative HPLC to give 18 mg (26% yield) of 1-(5-(4,7-dihydroxythiazolo[5,4-d]pyridazin-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea as a tan solid.

MS (ESP): 498.0 ($M+H^+$) for $C_{18}H_{14}F_3N_7O_3S_2$

^{1}H NMR (300 MHz, DMSO-d_6): δ 0.93 (t, 3H), 1.46-1.53 (m, 2H), 2.60 (s, 3H), 3.11-3.15 (m, 2H), 7.52 (bt, 1H), 8.17 (s, 1H), 8.71 (d, 1H), 8.78 (s, 1H), 9.76 (bs, 1H).

Example 175

1-(2'-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)-3-propylurea



Methyl 6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 265, 65 mg, 0.14 mmol) was dissolved in ethanol (10 mL) and hydrazine monohydrate (1 mL) was added. The reaction was heated at reflux for 6 h. The solvent was removed *in vacuo*, and the residue was placed in a vacuum oven at 60°C for 1 h. The residue

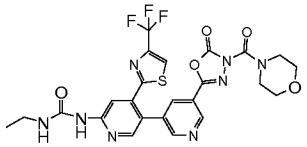
was then dissolved in anhydrous tetrahydrofuran (10 mL). 1,1'-Carbonyl diimidazole (100 mg) was added and the reaction was stirred at 25°C for 18 h. The solvent was removed *in vacuo* and the residue was subjected to preparative HPLC. This gave 19 mg (27% yield) of 1-(2'-(5-hydroxy-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)-3-propylurea as a white powder.

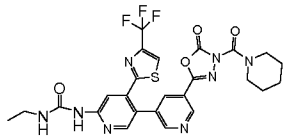
MS (ESP): 492.0 ($M+H^+$) for $C_{20}H_{17}F_3N_6O_3S$

^{1}H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.61-1.63 (m, 2H), 3.11-3.15 (m, 2H), 7.44 (dd, 1H), 7.80 (s, 1H), 7.84 (dd, 1H), 8.28 (d, 1H), 8.39 (d, 1H) 8.62 (dd, 1H)

Examples 176-177

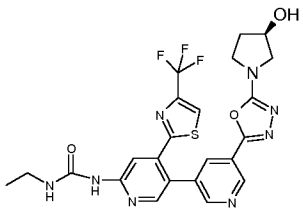
The following Examples were synthesized according to the procedure for Example 158 from the starting materials indicated in the Table.

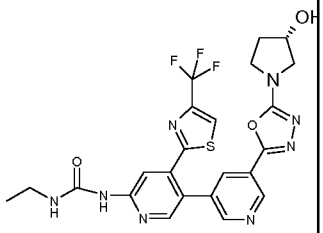
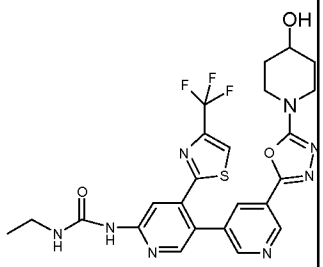
Ex	Compound	Data	SM
176	1-Ethyl-3-(5'-(4-(morpholine-4-carbonyl)-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 590.99 (M^+) for $C_{24}H_{21}F_3N_8O_5S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ 1.11 (t, *J*=7.20 Hz, 3H); 3.14 - 3.28 (m, 2H); 3.51 - 3.63 (m, 4H); 3.62 - 3.72 (m, 4H); 7.54 (br. s., 1H); 8.21 (t, *J*=2.15 Hz, 1H); 8.23 (s, 1H); 8.38 (s, 1H); 8.60 (s, 1H); 8.71 (d, *J*=2.27 Hz, 1H); 9.04 (d, *J*=2.02 Hz, 1H); 9.50 (s, 1H).	Example 6 and morpholine-4-carbonyl chloride

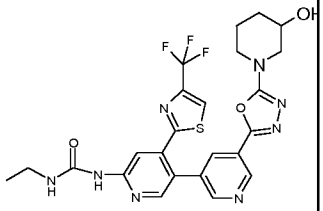
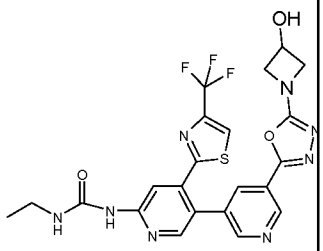
Ex	Compound	Data	SM
177	1-Ethyl-3-(5'-(5-oxo-4-(piperidine -1-carbonyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoro methyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 588.98 (M+) for $C_{25}H_{23}F_3N_8O_4S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.10 (t, *J*=7.07 Hz, 3H); 1.50 - 1.70 (m, 6H); 3.14 - 3.27 (m, 2H); 3.48 - 3.59 (m, 4H); 7.46 - 7.63 (m, 1H); 8.12 - 8.28 (m, 2H); 8.38 (s, 1H); 8.60 (s, 1H); 8.70 (d, *J*=2.02 Hz, 1H); 9.02 (d, *J*=2.02 Hz, 1H); 9.51 (s, 1H)	Example 6 and piperidine-1-carbonyl chloride

Examples 178-182

The following Examples were synthesized according to the procedure for Example 166 from the starting materials indicated in the Table.

Ex	Compound	Data	SM
178	(R)-1-Ethyl-3-(5'-(5-(3-hydroxypyrrolidin-1-yl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol -2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 547.11 (M+1) for $C_{23}H_{21}F_3N_8O_3S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.11 (t, *J*=7.07 Hz, 3H); 1.77 - 2.14 (m, 2H); 3.11 - 3.28 (m, 2H); 3.35 - 3.43 (m, 1H); 3.51 - 3.66 (m, 3H); 4.41 (br. s., 1H); 5.10 (d, *J*=3.79 Hz, 1H); 7.47 - 7.63 (m, 1H); 8.15 (br. s., 1H); 8.23 (s, 1H); 8.40 (s, 1H); 8.56 (s, 1H); 8.61 (d, *J*=2.02 Hz, 1H); 9.07 (d, *J*=2.02 Hz, 1H); 9.50 (s, 1H).	Intermediate 267

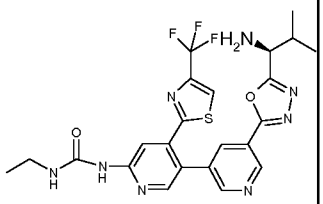
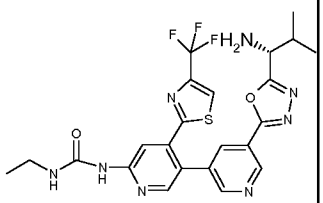
Ex	Compound	Data	SM
179	(S)-1-Ethyl-3-(5'-(5-(3-hydroxy pyrrolidin-1-yl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 546.99 (M+) for $C_{23}H_{21}F_3N_8O_3S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.11 (t, J=7.20Hz, 3H); 1.82 - 2.12 (m, 2H); 3.13 - 3.27 (m, 2 H); 3.39 (d, J=10.86 Hz, 1 H); 3.58 (dd, J=9.85, 4.55 Hz, 3H); 4.41 (br. s., 1H); 5.11 (d, J=3.54 Hz, 1H); 7.57 (br. s., 1H); 8.09 - 8.18 (m, 1H); 8.23 (s, 1H); 8.40 (s, 1H); 8.56 (s, 1H); 8.61 (d, J=2.02 Hz, 1H); 9.07 (d, J=2.02 Hz, 1H); 9.50 (s, 1H)	Intermediate 268
180	1-Ethyl-3-(5'-(5-(4-hydroxy piperidin-1-yl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 561.16 (M+1) for $C_{24}H_{23}F_3N_8O_3S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.11 (t, *J*=7.20 Hz, 3H); 1.34 - 1.57 (m, 2H); 1.70 - 1.93 (m, 2H); 3.07 - 3.40 (m, 4H); 3.59 - 3.97 (m, 3H); 4.82 (d, *J*=4.04 Hz, 1H); 7.56 (br. s., 1H); 8.18 - 8.22 (m, 1H); 8.23 (s, 1H); 8.40 (s, 1H); 8.56 (s, 1H); 8.61 (d, 1H); 9.10 (d, *J*=2.02 Hz, 1H); 9.49 (s, 1H)	Intermediate 269

Ex	Compound	Data	SM
181	1-Ethyl-3-(5'-(5-(3-hydroxy piperidin-1-yl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol -2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 561.16 (M+1) for $C_{24}H_{23}F_3N_8O_3S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.11 (t, J=7.20 Hz, 3H); 1.35 - 1.62 (m, 2H); 1.69 - 1.94 (m, 2H); 3.00 - 3.30 (m, 4H); 3.52 - 3.72 (m, 2H); 3.70 - 3.86 (m, 1H); 4.95 (d, J=4.04 Hz, 1H); 7.56 (br. s., 1H); 8.21 (t, J=2.02 Hz, 1H); 8.24 (s, 1H); 8.39 (s, 1H); 8.56 (s, 1H); 8.60 (d, J=2.02 Hz, 1H); 9.09 (d, J=2.02 Hz, 1H); 9.49 (s, 1H)	Intermediate 270
182	1-Ethyl-3-(5'-(5-(3-hydroxy azetidin-1-yl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol -2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 533.01 (M+1) for $C_{22}H_{19}F_3N_8O_3S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.11 (t, *J*=7.07 Hz, 3H); 3.13 - 3.27 (m, *J*=7.07, 6.76, 6.60, 6.60 Hz, 2H); 3.94 (dd, *J*=8.59, 4.80 Hz, 2H); 4.35 (t, *J*=7.58 Hz, 2H); 4.54 - 4.73 (m, 1H); 5.87 (d, *J*=6.57 Hz, 1H); 7.45 - 7.64 (m, 1H); 8.13 (t, *J*=2.15 Hz, 1H); 8.23 (s, 1H); 8.39 (s, 1H); 8.57 (s, 1H); 8.62 (d, *J*=2.02 Hz, 1H); 9.05 (d, *J*=2.02 Hz, 1H); 9.49 (s, 1H)	Intermediate 266

Examples 183-184

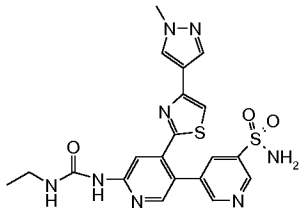
The following Examples were synthesized according to the procedure for Example 165 from the starting materials indicated in the Table.

Ex	Compound	Data	SM

Ex	Compound	Data	SM
183	(S)-1-(5'-(5-(1-Amino-2-methyl propyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoro methyl) thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 533.02 (M+1) for $C_{23}H_{23}F_3N_8O_2S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.87 (d, *J*=6.82 Hz, 3H); 0.95 (d, *J*=6.82 Hz, 3H); 1.11 (t, *J*=7.20 Hz, 3H); 1.90 - 2.19 (m, 3H); 3.14 - 3.27 (m, 2H); 3.89 (br. s., 1H); 7.55 (br. s., 1H); 8.23 (s, 1H); 8.30 (d, *J*=1.01 Hz, 1H); 8.42 (s, 1H); 8.57 (s, 1H); 8.72 (d, *J*=1.26 Hz, 1H); 9.20 (d, *J*=1.26 Hz, 1H); 9.51 (s, 1H)	Intermediate 271 followed by HCl
184	(R)-1-(5'-(5-(1-Amino-2-methylpropyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol -2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 533.01 (M+1) for $C_{23}H_{23}F_3N_8O_2S$ ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.87 (d, *J*=6.57 Hz, 2H); 0.95 (d, *J*=6.82 Hz, 2H); 1.11 (t, *J*=7.07Hz, 3H); 1.95 - 2.08 (m, 1H); 2.06 - 2.21 (m, 1H); 3.21 (dq, *J*=6.95, 6.69 Hz, 1H); 3.88 (d, *J*=6.32 Hz, 1H); 7.55 (br. s., 1H); 8.23 (s, 1H); 8.30 (t, *J*=1.77 Hz, 1H); 8.42 (s, 1H); 8.57 (s, 1H) 8.72 (d, *J*=1.77 Hz, 1H); 9.20 (d, *J*=1.26 Hz, 1H); 9.51 (s, 1H)	Intermediate 272 followed by HCl

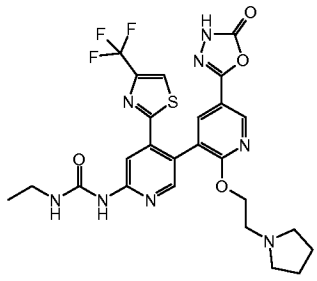
Example 185

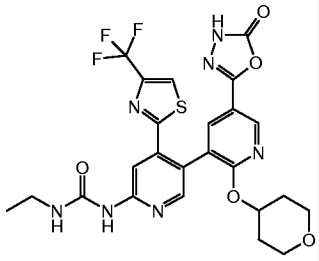
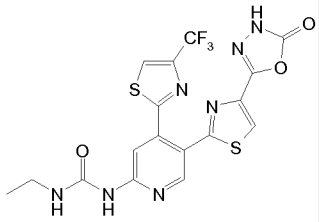
The following Example was prepared according to the procedure described for Intermediate 2 using the starting materials indicated in the table.

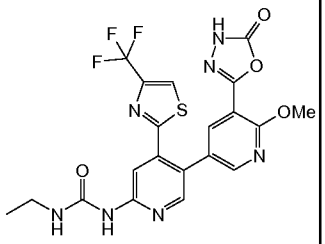
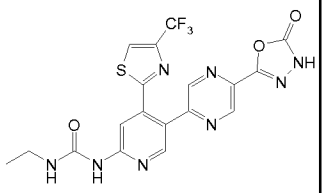
Ex	Compound	Data	SM
185	6'-(3-ethylureido)-4'-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-3,3'-bipyridine-5-sulfonamide 	LC/MS (ES^+)[$(M+H)^+$]: 485 for $C_{20}H_{20}N_8O_3S_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.21 (m, 2H), 3.84(s, 3H), 6.96 (s, 2H), 7.64 (t, 1H), 7.68 (s, 1H), 7.78 (s, 1H), 7.92 (s, 1H), 8.13 (t, 1H), 8.21 (s, 1H), 8.27 (s, 1H), 8.60 (d, 1H), 8.94 (d, 1H), 9.49 (s, 1H).	Intermediate 302 and 5-bromopyridine-3-sulfonamide

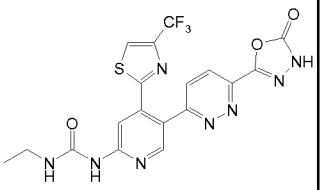
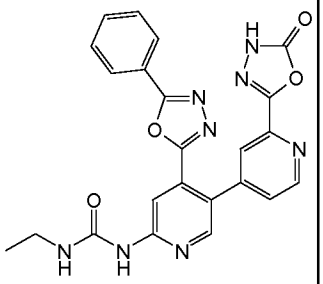
Examples 186-227

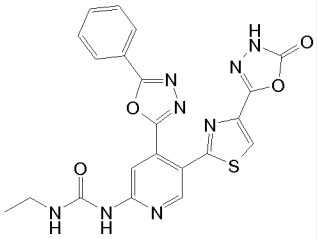
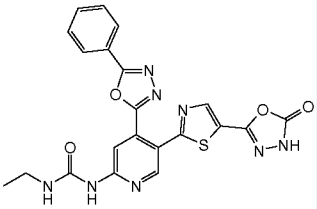
The following Examples were prepared according to the procedure described for Example 33 using the starting materials indicated in the table.

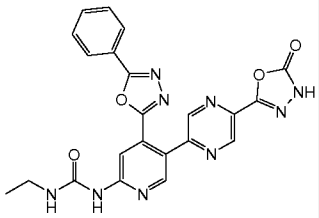
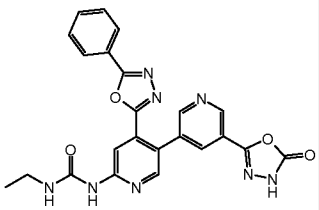
Ex	Compound	Data	SM
186	1-ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2'-(2-(pyrrolidin-1-yl)ethoxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 591 for $C_{25}H_{25}F_3N_8O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.04 (t, 3H), 1.48 (m, 4H), 2.21 (m, 4H), 2.30 (t, 1H), 3.14 (m, 2H), 4.07 (t, 2H), 7.50 (t, 1H), 8.80 (d, 1H), 8.17 (s, 1H), 8.21 (s, 1H), 8.48 (s, 1H), 8.58 (d, 1H), 9.40 (s, 1H), 12.30 (s, 1H).	Intermediate 387

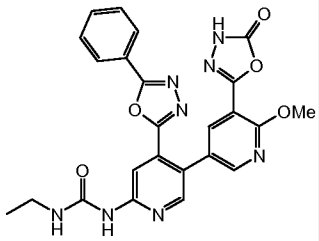
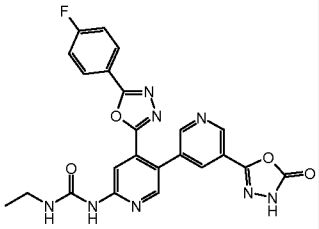
Ex	Compound	Data	SM
187	1-ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 578 for $C_{24}H_{22}F_3N_7O_5S$. ^1H NMR (300 MHz, d_6-DMSO): 1.09 (m, 2H), 1.11 (t, 3H), 1.62 (m, 2H), 3.21 (m, 2H), 3.34 (m, 2H), 3.45 (m, 2H), 5.06 (m, 1H), 7.60 (t, 1H), 8.18 (m, 1H), 8.21 (s, 1H), 8.28 (s, 1H), 8.55 (s, 1H), 8.63 (s, 1H), 9.49 (s, 1H), 12.67 (s, 1H).	Intermediate 287
188	1-ethyl-3-(5-(4-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 484 for $C_{17}H_{12}F_3N_7O_3S_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.20 (m, 2H), 7.48 (t, 1H), 8.15 (s, 1H), 8.48 (s, 1H), 8.69 (s, 1H), 9.68 (s, 1H), 12.67 (s, 1H).	Intermediate 351

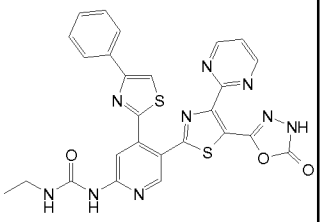
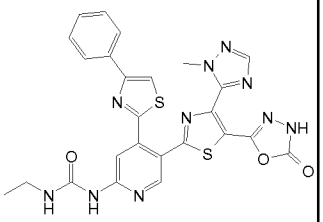
Ex	Compound	Data	SM
189	1-ethyl-3-(6'-methoxy-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 508 for $C_{20}H_{16}F_3N_7O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.21 (m, 2H), 4.02 (s, 3H), 7.61 (m, 1H), 8.03 (s, 1H), 8.25 (s, 1H), 8.33 (s, 2H), 8.58 (s, 1H), 9.46 (s, 1H), 12.67 (s, 1H).	Intermediate 352
190	1-ethyl-3-(5-(5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 479 for $C_{18}H_{13}F_3N_8O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.04 (t, 3H), 3.15 (m, 2H), 6.96 (s, 1H), 7.47 (m, 1H), 8.09 (s, 1H), 8.54 (s, 1H), 8.55 (s, 1H), 8.81 (s, 1H), 8.98 (s, 1H), 9.57 (s, 1H).	Intermediate 353

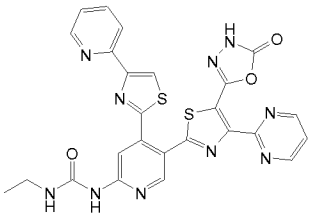
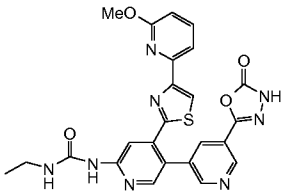
Ex	Compound	Data	SM
191	1-ethyl-3-(5-(6-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyridazin-3-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 479 for $C_{18}H_{13}F_3N_8O_3S$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.12 (t, 3H), 3.23 (m, 2H), 7.54 (m, 1H), 7.97 (d, 1H), 8.19 (m, 2H), 8.58 (s, 1H), 8.63 (s, 1H), 8.83 (s, 1H), 9.63 (s, 1H).	Intermediate 388
192	1-ethyl-3-(2'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,4'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 471 for $C_{23}H_{18}N_8O_4$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.05 (t, 3H), 3.16 (m, 2H), 7.21 (dd, 1H), 7.46 (m, 3H), 7.52 (m, 1H), 7.62 (m, 2H), 7.71 (s, 1H), 8.34 (d, 2H), 8.47 (d, 1H), 9.53 (s,1H).	Intermediate 354

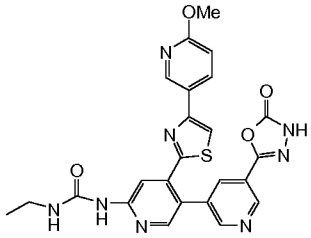
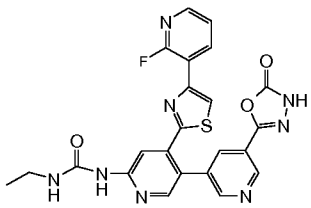
Ex	Compound	Data	SM
193	1-ethyl-3-(5-(4-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 476 for $C_{21}H_{16}N_8O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.05 (t, 3H), 3.15 (m, 2H), 7.39 (t, 1H), 7.49 (m, 3H), 7.74 (m, 2H), 8.27 (s, 1H), 8.42 (s, 1H), 8.70 (s, 1H), 9.72 (s, 1H), 12.50 (s, 1H).	Intermediate 355
194	1-ethyl-3-(5-(5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 477 for $C_{21}H_{16}N_8O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.04 (t, 3H), 3.15 (m, 2H), 7.39 (t, 1H), 7.55 (m, 3H), 7.78 (m, 2H), 8.23 (s, 1H), 8.26 (s, 1H), 8.74 (s, 1H), 9.74 (s, 1H), 12.74 (s, 1H).	Intermediate 356

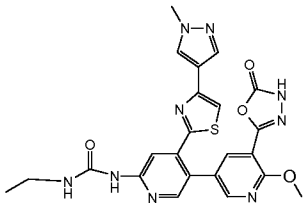
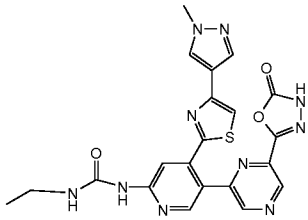
Ex	Compound	Data	SM
195	1-ethyl-3-(5-(5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 472 for $C_{22}H_{17}N_9O_4$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.12 (t, 3H), 3.23 (m, 2H), 7.48 (t, 1H), 7.60 (m, 3H), 7.79 (m, 2H), 8.39 (s, 1H), 8.73 (s, 1H), 9.06 (d, 1H), 9.17 (d, 1H), 9.73 (s, 1H), 12.82 (s, 1H).	Intermediate 357
196	1-ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 471 for $C_{23}H_{18}N_8O_4$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.12 (m, 2H), 7.01 (s, 1H), 7.51 (t, 1H), 7.56 (m, 3H), 7.74 (d, 2H), 8.28 (d, 1H), 8.41 (s, 1H), 8.47 (s, 1H), 8.79 (d, 1H), 9.02 (d, 1H), 9.57 (s, 1H).	Intermediate 358

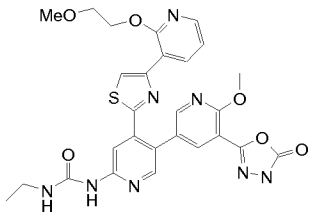
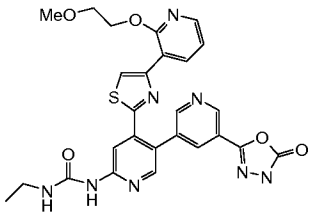
Ex	Compound	Data	SM
197	1-ethyl-3-(6'-methoxy-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 501 for $C_{24}H_{20}N_8O_5$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.12 (t, 3H), 3.25 (m, 2H), 4.05 (s, 3H), 7.52 (t, 1H), 7.60 (m, 3H), 7.78 (m, 2H), 8.21 (d, 1H), 8.40 (s, 1H), 8.44 (d, 1H), 8.45 (s, 1H), 9.54 (s, 1H), 12.67 (s, 1H).	Intermediate 359
198	1-ethyl-3-(4-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 489 for $C_{23}H_{17}FN_8O_4$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.12 (t, 3H), 3.23 (m, 2H), 7.45 (m, 3H), 7.82 (m, 2H), 8.28 (s, 1H), 8.42 (s, 1H), 8.47 (s, 1H), 8.81 (s, 1H), 9.02 (s, 1H), 9.57 (s, 1H), 12.82 (s, 1H).	Intermediate 360

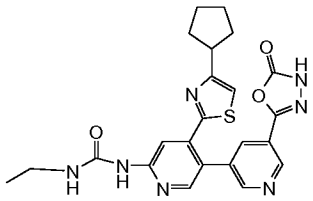
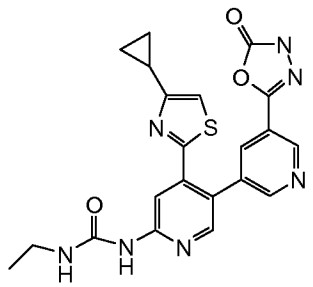
Ex	Compound	Data	SM
199	1-ethyl-3-(5-(5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(pyrimidin-2-yl)thiazol-2-yl)-4-(4-phenylthiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 570 for $C_{26}H_{19}N_9O_3S_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.05 (t, 3H), 3.15 (m, 2H), 7.33 (m, 2H), 7.50 (m, 1H), 7.51 (m, 1H), 7.77 (d, 2H), 8.16 (s, 1H), 8.31 (s, 1H), 8.68 (s, 1H), 8.86 (d, 2H), 9.62 (s, 1H), 12.71 (s, 1H).	Intermediate 361
200	1-ethyl-3-(5-(4-(1-methyl-1H-1,2,4-triazol-5-yl)-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-4-(4-phenylthiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 573 for $C_{25}H_{20}N_{10}O_3S_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.04 (t, 3H), 3.13 (m, 2H), 3.69 (s, 3H), 7.32 (m, 3H), 7.47 (m, 1H), 7.76 (d, 2H), 8.01 (s, 1H), 8.10 (s, 1H), 8.32 (s, 1H), 8.73 (s, 1H), 9.65 (s, 1H), 12.80 (s, 1H).	Intermediate 362

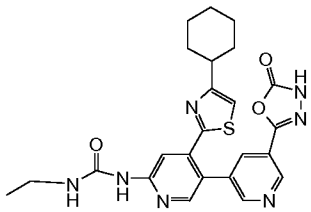
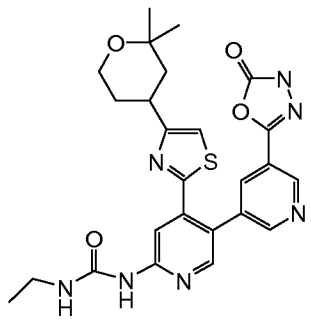
Ex	Compound	Data	SM
201	1-ethyl-3-(5-(5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(pyrimidin-2-yl)thiazol-2-yl)-4-(4-(pyridin-2-yl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 571 for $C_{25}H_{18}N_{10}O_3S_2$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.12 (t, 3H), 3.21 (m, 2H), 7.37 (m, 1H), 7.57 (m, 2H), 7.83 (m, 2H), 8.24 (m, 1H), 8.50 (m, 1H), 8.63 (m, 1H), 8.77 (m, 1H), 8.93 (m, 2H), 9.70 (s, 1H), 12.77 (s, 1H).	Intermediate 363
202	1-ethyl-3-(4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 517 for $C_{24}H_{20}N_8O_4S$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.22 (m, 2H),3.91 (s, 3H), 6.78(d, 1H), 7.25 (d, 1H), 7.61 (m, 1H), 7.72 (t, 1H), 8.20 (m, 1H), 8.27 (s, 1H), 8.34 (d, 2H), 8.69 (d, 1H), 8.99 (d, 1H), 9.50 (s, 1H), 12.80 (s, 1H).	Intermediate 364

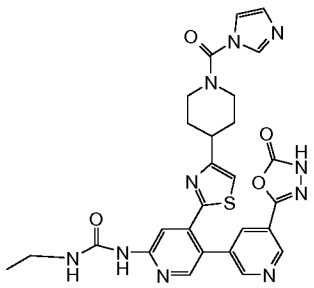
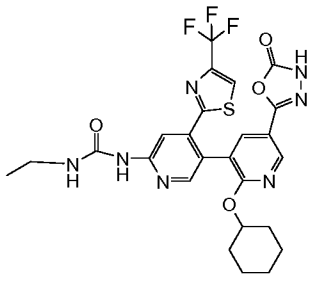
Ex	Compound	Data	SM
203	1-ethyl-3-(4-(4-(6-methoxypyridin-3-yl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 517 for $C_{24}H_{20}N_8O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.22 (m, 2H),3.88 (s, 3H), 6.84(d, 1H), 7.62 (m, 1H), 8.01 (m, 1H), 8.20 (m, 1H), 8.21 (s, 1H), 8.26 (s, 1H), 8.34 (s, 1H), 8.52 (d, 1H), 8.69 (d, 1H), 8.99 (d, 1H), 9.49 (s, 1H), 12.80 (s, 1H).	Intermediate 369
204	1-ethyl-3-(4-(4-(2-fluoropyridin-3-yl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 505 for $C_{23}H_{17}FN_8O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.21 (m, 2H), 7.43(m, 1H), 7.60 (m, 1H), 8.15 (m, 1H), 8.19 (m, 1H), 8.20 (s, 1H), 8.22 (m, 1H), 8.27 (s, 1H), 8.36 (s, 1H), 8.70 (d, 1H), 8.99 (d, 1H), 9.50 (s, 1H), 12.80 (s, 1H).	Intermediate 389

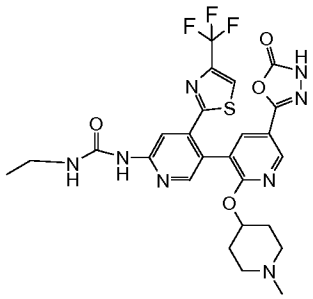
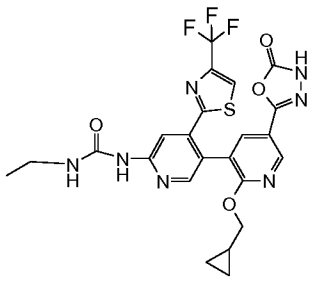
Ex	Compound	Data	SM
205	1-ethyl-3-(6'-methoxy-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 520 for $C_{23}H_{21}N_9O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.21 (m, 2H), 3.85(s, 3H), 4.02 (s, 3H), 7.68 (m, 1H), 7.70 (s, 1H), 7.77 (s, 1H), 7.99 (s, 1H), 8.06 (d, 1H), 8.20 (s, 1H), 8.27 (s, 1H), 8.31 (d, 1H), 9.42 (s, 1H), 12.52 (s, 1H).	Intermediate 368
206	1-ethyl-3-(4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-5-(6-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 491 for $C_{21}H_{18}N_{10}O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.21 (m, 2H), 3.80(s, 3H), 7.54 (s, 1H), 7.57 (m, 1H), 7.79 (s, 1H), 7.82 (s, 1H), 8.15 (s, 1H), 8.52 (s, 1H), 8.79 (d, 1H), 9.10 (d, 1H), 9.57 (s, 1H), 12.98 (s, 1H).	Intermediate 365

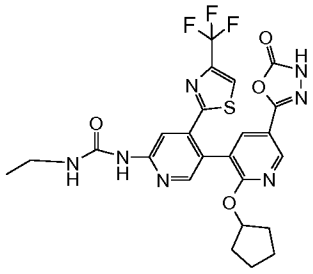
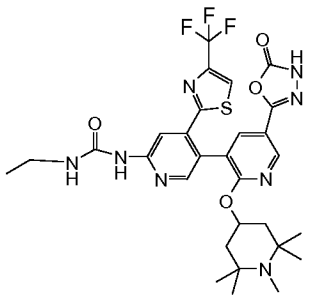
Ex	Compound	Data	SM
207	1-ethyl-3-(6'-methoxy-4-(4-(2-(2-methoxyethoxy)pyridin-3-yl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 591 for $C_{27}H_{26}N_8O_6S$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.22 (m, 2H), 3.31(s, 3H), 3.76 (m, 2H), 4.01 (s, 3H), 4.53 (m, 2H), 7.06 (m, 1H), 7.70 (m, 1H), 8.09 (d, 1H), 8.15 (m, 1H), 8.20 (m, 1H), 8.26 (s, 1H), 8.28 (m, 1H), 8.29 (s, 1H), 8.33 (d, 1H), 9.44(s, 1H), 12.66 (s, 1H).	Intermediate 370
208	1-ethyl-3-(4-(4-(2-(2-methoxyethoxy)pyridin-3-yl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 561 for $C_{26}H_{24}N_8O_5S$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.22 (m, 2H), 3.31(s, 3H), 3.76 (t, 2H), 4.52 (t, 2H), 7.02 (m, 1H), 7.64 (m, 1H), 8.01 (d, 1H), 8.13 (d, 1H), 8.20 (s, 1H), 8.26 (s, 2H), 8.34 (s, 1H), 8.68 (s, 1H), 8.98 (s, 1H), 9.49(s, 1H), 12.63 (s, 1H).	Intermediate 371

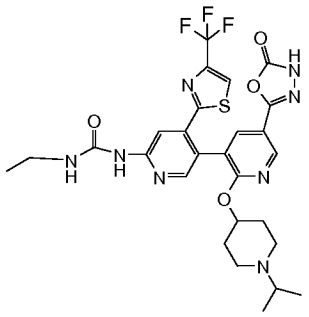
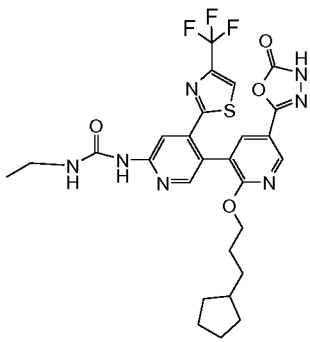
Ex	Compound	Data	SM
209	1-(4-(4-cyclopentylthiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 478 for $C_{23}H_{23}N_7O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.37 (m, 2H), 1.50 (m, 4H), 1.79 (m, 2H), 3.05(m, 1H), 3.21 (m, 2H), 7.41 (s, 1H), 7.66 (m, 1H), 8.01 (m, 1H), 8.09 (s, 1H), 8.30 (s, 1H), 8.60 (d, 1H), 8.93 (d, 1H), 9.45 (s, 1H), 12.77 (s, 1H).	Intermediate 375
210	1-(4-(4-cyclopropylthiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 450 for $C_{21}H_{19}N_7O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 0.45 (m, 2H), 0.76 (m, 2H), 1.10 (t, 3H), 1.97 (m, 1H), 3.21 (m, 2H), 7.40 (s, 1H), 7.63 (m, 1H), 8.02 (m, 1H), 8.08 (s, 1H), 8.27 (s, 1H), 8.55 (d, 1H), 8.95 (d, 1H), 9.41 (s, 1H), 12.74 (s, 1H).	Intermediate 376

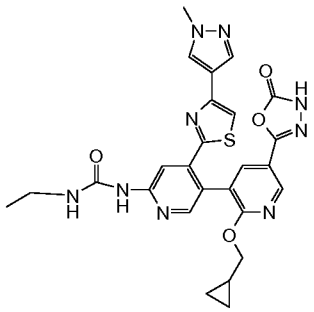
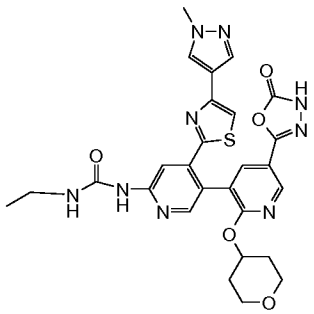
Ex	Compound	Data	SM
211	1-(4-(4-cyclohexylthiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 492 for $C_{24}H_{25}N_7O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.14 (m, 2H), 1.23 (m, 3H), 1.61 (m, 3H), 1.71 (m, 2H), 2.57 (m, 1H), 3.21(m, 2H), 7.37 (s, 1H), 7.65 (m, 1H), 8.04 (m, 1H), 8.11 (s, 1H), 8.30 (s, 1H), 8.61 (d, 1H), 8.94 (d, 1H), 9.44 (s, 1H), 12.74 (s, 1H).	Intermediate 374
212	1-(4-(4-(2,2-dimethyltetrahydro-2H-pyran-4-yl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 522 for $C_{25}H_{27}N_7O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.05 (s, 3H), 1.11 (t, 3H), 1.13 (s, 3H), 1.14 (m, 1H), 1.33 (m, 1H), 1.45 (m, 1H), 1.61 (m, 1H), 2.98 (m, 1H), 3.21 (m, 2H), 3.59 (m, 2H), 7.43 (s, 1H), 7.63 (m, 1H), 7.99 (m, 1H), 8.10 (s, 1H), 8.31 (s, 1H), 8.61 (d, 1H), 8.93 (d, 1H), 9.43 (s, 1H), 12.78 (s, 1H).	Intermediate 373

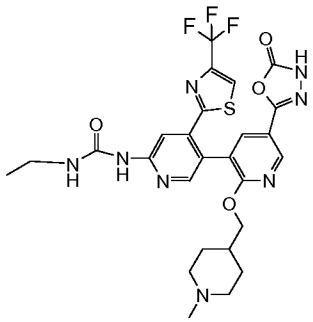
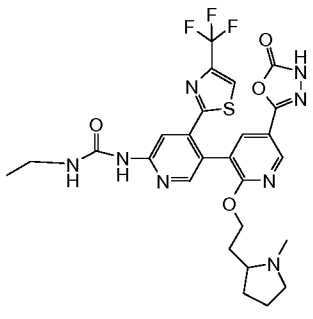
Ex	Compound	Data	SM
213	1-(4-(4-(1-(1H-imidazole-1-carbonyl)piperidin-4-yl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 587 for $C_{27}H_{26}N_{10}O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.52 (m, 2H), 1.83 (m, 2H), 2.79 (m, 1H), 3.11(m, 1H), 3.21 (m, 2H), 3.83 (m, 2H), 7.12 (s, 1H), 7.49 (m, 1H), 7.50 (s, 1H), 7.60 (m, 1H), 7.70 (m, 1H) 8.04 (m, 1H), 8.14 (s, 1H), 8.16 (s, 1H), 8.32 (s, 1H), 8.61 (d, 1H), 8.92 (d, 1H), 9.43 (s, 1H), 12.77 (s, 1H).	Intermediate 377
214	1-(2'-(cyclohexyloxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 576 for $C_{25}H_{24}F_3N_7O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.07 (m, 2H), 1.11 (t, 3H), 1.17 (m, 2H), 1.35 (m, 4H), 1.52 (m, 2H), 3.21 (m, 2H), 4.87(m, 1H), 7.60 (m, 1H), 8.16 (d, 1H), 8.19 (s, 1H), 8.26 (s, 1H), 8.53 (s, 1H), 8.62 (d, 1H), 9.47 (s, 1H), 12.65 (s, 1H).	Intermediate 378

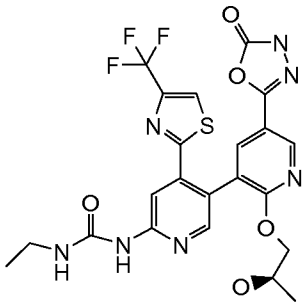
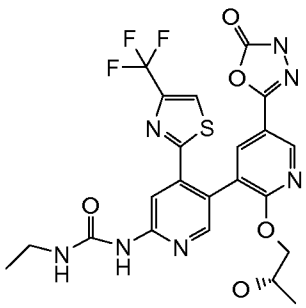
Ex	Compound	Data	SM
215	1-ethyl-3-(2'-(1-methylpiperidin-4-yloxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 591 for $C_{25}H_{25}F_3N_8O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.17 (m, 2H), 1.57 (m, 2H), 2.0 (m, 2H), 2.02 (s, 3H), 2.12 (m, 2H), 3.21 (m, 2H), 4.87(m, 1H), 7.61 (m, 1H), 8.15 (d, 1H), 8.23 (s, 1H), 8.26 (s, 1H), 8.54 (s, 1H), 8.62 (d, 1H), 9.48 (s, 1H), 12.61 (s, 1H).	Intermediate 380
216	1-(2'-(cyclopropylmethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 548 for $C_{23}H_{20}F_3N_7O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 0.04 (m, 2H), 0.26 (m, 2H), 0.81 (m, 1H), 1.11 (t, 3H), 3.21 (m, 2H), 3.88(m, 2H), 7.58 (m, 1H), 8.15 (m, 1H), 8.24 (s, 1H), 8.28 (s, 1H), 8.54 (s, 1H), 8.63 (d, 1H), 9.47 (s, 1H), 12.68 (s, 1H).	Intermediate 383

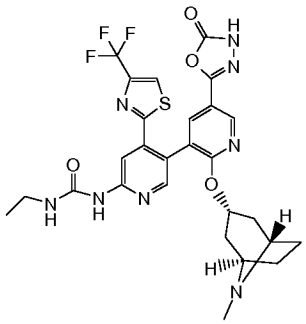
Ex	Compound	Data	SM
217	1-(2'-(cyclopentyloxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 562 for $C_{24}H_{22}F_3N_7O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.20 (m, 2H), 1.23 (m, 2H), 1.34 (m, 2H), 1.66 (m, 2H), 3.21(m, 2H), 5.18 (m, 1H), 7.61 (m, 1H), 8.12 (d, 1H), 8.20 (s, 1H), 8.25 (s, 1H), 8.53 (s, 1H), 8.60 (d, 1H), 9.47 (s, 1H), 12.66 (s, 1H).	Interemediate 379
218	1-ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2'-(1,2,2,6,6-pentamethylpiperidin-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 647 for $C_{29}H_{33}F_3N_8O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.23 (s, 2H), 1.25 (m, 2H), 1.30 (s, 12H), 1.42 (m, 2H), 2.65 (s, 3H), 5.27 (m, 1H), 7.52 (m, 1H), 8.18(m, 1H), 8.28 (s, 1H), 8.59 (s, 1H), 8.61 (s, 1H), 8.9 (s, 1H), 9.5 (s, 1H), 12.7 (s, 1H).	Intermediate 382

Ex	Compound	Data	SM
219	1-ethyl-3-(2'-(1-isopropylpiperidin-4-yloxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 619 for $C_{27}H_{29}F_3N_8O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 0.85 (d, 6H), 1.10 (t, 3H), 1.14 (m, 2H), 1.60 (m, 2H), 2.27 (m, 4H), 2.64 (m, 1H), 3.22 (m, 2H), 4.94(m, 1H), 7.63 (m, 1H), 8.15 (d, 1H), 8.23 (s, 1H), 8.26 (s, 1H), 8.53 (s, 1H), 8.63 (d, 1H), 9.47 (s, 1H), 12.33 (s, 1H).	Intermediate 381
220	1-(2'-(3-cyclopentylpropoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 604 for $C_{27}H_{28}F_3N_7O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 0.86 (m, 2H), 1.00 (m, 2H), 1.11 (t, 3H), 1.27 (m, 2H), 1.41 (m, 2H), 1.45(m, 2H), 1.54 (m, 3H), 3.21 (m, 2H), 4.03(m, 2H), 7.61 (m, 1H), 8.12 (d, 1H), 8.26 (s, 2H), 8.53 (s, 1H), 8.64 (d, 1H), 9.45 (s, 1H), 12.63 (s, 1H).	Intermediate 384

Ex	Compound	Data	SM
221	1-(2'-(cyclopropylmethoxy)-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 560 for $C_{26}H_{25}N_9O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 0.08 (m, 2H), 0.23 (m, 2H), .79 (m, 1H), 1.11 (t, 3H), 3.22 (m, 2H), 3.82 (m, 2H), 3.84 (s, 3H), 7.56 (s, 1H), 7.66 (m, 1H), 7.73 (s, 1H), 7.88 (s, 1H), 8.08 (m, 1H), 8.21 (s, 1H), 8.23 (s, 1H), 8.62 (d, 1H), 9.43 (s, 1H), 12.61 (s, 1H).	Intermediate 367
222	1-ethyl-3-(4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-yloxy)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 590 for $C_{27}H_{27}N_9O_5S$. ^1H NMR (300 MHz, d_6-DMSO): 0.9 (m, 2H), 1.11 (t, 3H), 1.14 (m, 2H), 1.6 (m, 2H), 3.22 (m, 2H), 3.25 (m, 2H), 3.83(s, 3H), 5.05 (m, 1H), 7.53 (s, 1H), 7.68 (m, 1H), 7.73 (s, 1H), 7.87 (s, 1H), 8.11 (m, 1H), 8.19 (s, 1H), 8.23 (s, 1H), 8.63 (d, 1H), 9.44 (s, 1H), 12.60 (s, 1H).	Intermediate 366

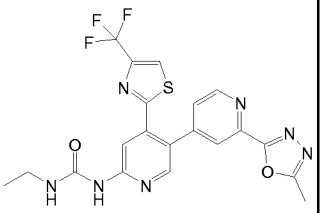
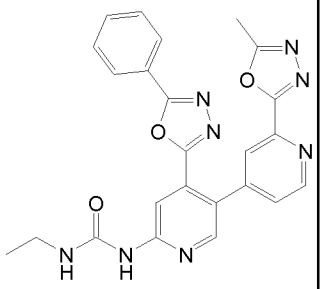
Ex	Compound	Data	SM
223	1-ethyl-3-(2'-((1-methylpiperidin-4-yl)methoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 605 for $C_{26}H_{27}F_3N_8O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 0.94 (m, 2H), 1.11 (t, 3H), 1.23 (m, 3H), 1.70 (m, 2H), 2.07 (s, 3H), 2.58 (m, 2H), 3.21 (m, 2H), 3.92(m, 2H), 7.58 (m, 1H), 8.13 (d, 1H), 8.26 (s, 1H), 8.28 (s, 1H), 8.52 (s, 1H), 8.65 (d, 1H), 9.44(s, 1H), 12.41 (s, 1H).	Intermediate 386
224	1-ethyl-3-(2'-(2-(1-methylpyrrolidin-2-yl)ethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 605 for $C_{26}H_{27}F_3N_8O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.17 (m, 2H), 1.48 (m, 4H), 1.78 (m, 1H), 1.92 (m, 1H), 2.04 (s, 3H), 2.84 (m, 1H), 3.21 (m, 2H), 4.06(m, 2H), 7.59 (m, 1H), 8.13 (d, 1H), 8.25 (s, 1H), 8.26 (s, 1H), 8.54 (s, 1H), 8.64 (d, 1H), 9.44 (s, 1H), 12.54 (s, 1H).	Intermediate 385

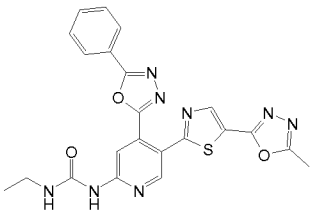
Ex	Compound	Data	SM
225	1-ethyl-3-(2'-((R)-2-hydroxypropoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 552 for $C_{22}H_{20}F_3N_7O_5S$. ^1H NMR (300 MHz, d_6-DMSO): 0.75 (d, 3H), 1.11 (t, 3H), 3.21 (m, 2H), 3.53 (m, 1H), 3.70 (m, 1H), 4.02 (m, 1H), 4.61 (d, 1H), 7.58 (m, 1H), 8.12 (s, 1H), 8.25 (s, 1H), 8.28 (s, 1H), 8.52 (s, 1H), 8.64 (s, 1H), 9.45 (s, 1H), 12.63 (s, 1H).	Intermediate 390
226	1-ethyl-3-(2'-((S)-2-hydroxypropoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 552 for $C_{22}H_{20}F_3N_7O_5S$. ^1H NMR (300 MHz, d_6-DMSO): 0.76 (d, 3H), 1.11 (t, 3H), 3.21 (m, 2H), 3.53 (m, 1H), 3.71 (m, 1H), 4.02 (m, 1H), 4.60 (d, 1H), 7.58 (t, 1H), 8.11 (s, 1H), 8.25 (s, 1H), 8.28 (s, 1H), 8.51(s, 1H), 8.64 (s, 1H), 9.44 (s, 1H), 12.63 (s, 1H).	Intermediate 391

Ex	Compound	Data	SM
227	1-ethyl-3-(2'-((1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yloxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 617 for $C_{27}H_{27}F_3N_8O_4S$. ^1H NMR (400 MHz, d_6-DMSO): 1.11 (t, 3H), 1.17 (m, 2H), 1.24 (s, 3H), 1.35 (m, 2H), 1.81 (m,2H), 2.25 (m, 2H), 3.06 (m, 2H), 3.21 (m, 1H), 3.61 (m, 1H), 5.17 (m, 1H), 7.50 (m, 1H), 8.19 (m, 1H), 8.29 (s, 1H), 8.34 (s, 1H), 8.54 (s, 1H), 8.66 (s, 1H), 9.46 (s, 1H), 12.63 (s, 1H).	Intermediate 414

Examples 228-230

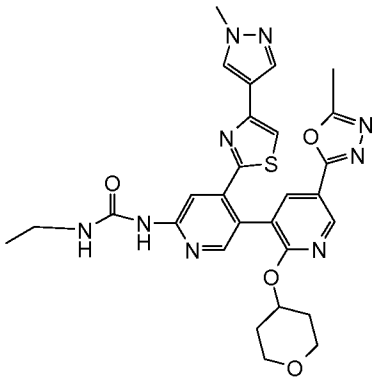
The following Examples were prepared as described for Example 1 using the starting materials as indicated in the table.

Ex	Compound	Data	SM
228	1-ethyl-3-(2'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 476 for $C_{20}H_{16}F_3N_7O_2S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 2.61 (s, 3H), 3.19 (m, 2H), 7.55 (m, 2H), 8.01 (s, 1H), 8.18 (s, 1H), 8.42 (s, 1H), 8.61 (s, 1H), 8.74 (m, 1H), 9.57 (s, 1H).	Intermediate 399
229	1-ethyl-3-(2'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,4'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 469 for $C_{24}H_{20}N_8O_3$. ^1H NMR (300 MHz, d_6-DMSO): 1.05 (t, 3H), 2.54 (s, 3H), 3.16 (m, 2H), 7.41 (t, 1H), 7.50 (m, 3H), 7.65 (m, 3H), 8.16 (s, 1H), 8.39 (s, 2H), 8.73 (d, 1H), 9.56 (s, 1H).	Intermediate 400

Ex	Compound	Data	SM
230	1-ethyl-3-(5-(5-(5-methyl-1,3,4-oxadiazol-2-yl)thiazol-2-yl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 475 for $C_{22}H_{18}N_8O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.05 (t, 3H), 2.51 (s, 3H), 3.15 (m, 2H), 7.39 (t, 1H), 7.53 (m, 3H), 7.78 (m, 2H), 8.24 (s, 1H), 8.40 (s, 1H), 8.77 (s, 1H), 9.75 (s, 1H).	Intermediate 401

Example 231

1-ethyl-3-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-yloxy)-3,3'-bipyridin-6-yl)urea



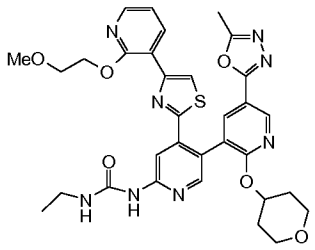
In a 25 mL pear flask, 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-yloxy)-3,3'-bipyridin-6-yl)urea (Intermediate 366, 68.1 mg, 0.12 mmol) and 1,1,1-trimethoxyethane (461 µl, 3.62 mmol) were suspended in solvent. The reaction slurry was heated to reflux for 30min. 2,3,4,6,7,8,9,10-octahydropyrimido[1,2-a]azepine (18.07 µl, 0.12 mmol) was added in a single portion. The reaction was heated for an additional for 2h. The reaction mixture was cooled to room temperature, diluted with EtOAc and washed with water then brine. The organic phase was dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The crude was purified by silica gel flash column chromatography (95:5 CH_2Cl_2 / MeOH). Isolation gave 40mg of the desired product.

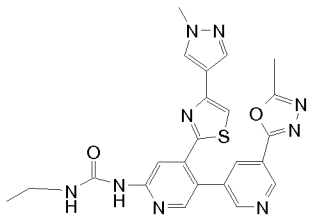
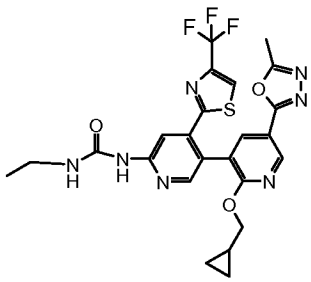
LC/MS (ES^+)[$(M+H)^+$]: 588 for $C_{28}H_{29}N_9O_4S$.

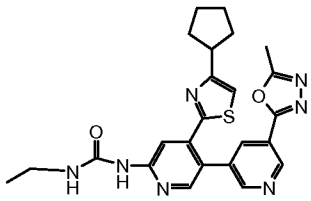
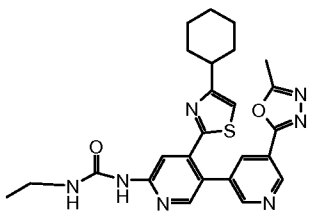
^{1}H NMR (300 MHz, d_6-DMSO): 1.12 (t, 3H), 1.16 (m, 2H), 1.60 (m, 2H), 2.59 (s, 3H), 3.22 (m, 2H), 3.25 (m, 2H), 3.37 (m, 2H), 3.83 (s, 3H), 5.08 (m, 1H), 7.50 (s, 1H), 7.67 (m, 1H), 7.72 (s, 1H), 7.88 (s, 1H), 8.21 (s, 1H), 8.26 (s, 1H), 8.27 (m, 1H), 8.81 (m, 1H), 9.45 (s, 1H).

Examples 232-236

The following Examples were prepared according to the procedure as described by Example 231 using the starting materials as indicated.

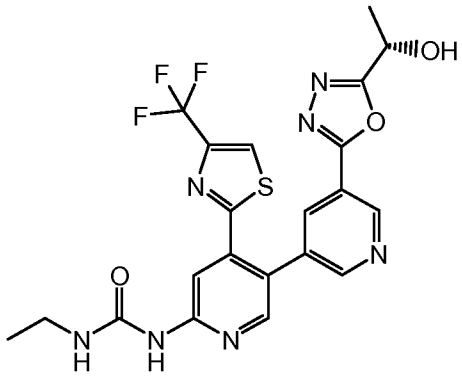
Ex	Compound	Data	SM
232	1-ethyl-3-(4-(4-(2-(2-methoxyethoxy)pyridin-3-yl)thiazol-2-yl)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-yloxy)-3,3'-bipyridin-6-yl)urea 	MS (ES^+)[$(M+H)^+$]: 658 for $C_{32}H_{34}N_8O_6S$. ^{1}H NMR (300 MHz, d_6-DMSO): 0.87 (m, 2H), 1.12 (t, 3H), 1.28 (m, 2H), 1.76 (m, 2H), 2.60 (s, 3H), 2.64 (m, 2H), 3.24 (m, 2H), 3.31 (s, 3H), 3.75 (t, 2H), 4.52 (t, 2H), 5.06 (m, 1H), 6.99 (m, 1H), 7.69 (m, 1H), 7.83 (m, 1H), 8.11 (m, 1H), 8.22 (s, 1H), 8.27 (s, 1H), 8.29 (s, 1H), 8.30 (d, 1H), 8.81 (m, 1H), 9.47 (s, 1H).	Intermediate 372

Ex	Compound	Data	SM
233	1-ethyl-3-(5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 488 for $C_{23}H_{21}N_9O_2S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 2.58 (s, 3H), 3.20 (m, 2H), 3.82 (s, 3H), 7.61 (s, 1H), 7.62 (m, 1H), 7.77 (s, 1H), 7.92 (s, 1H), 8.20 (s, 1H), 8.33 (s, 1H), 8.34 (s, 1H), 8.70 (m, 1H), 9.15 (m, 1H), 9.48 (s, 1H).	Intermediate 36
234	1-(2'-(cyclopropylmethoxy)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 546 for $C_{24}H_{22}F_3N_7O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 0.04 (m, 2H), 0.28 (m, 2H), 0.82 (m, 1H), 1.11 (t, 3H), 2.59 (s, 3H), 3.21 (m, 2H), 3.88 (d, 2H), 7.57 (m, 1H), 8.25 (s, 1H), 8.30 (m, 1H), 8.31 (s, 1H), 8.54 (s, 1H), 8.81 (d, 1H), 9.48 (s, 1H).	Intermediate 383

Ex	Compound	Data	SM
235	1-(4-(4-cyclopentylthiazol-2-yl)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 476 for $C_{24}H_{25}N_7O_2S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.36 (m, 2H), 1.46 (m, 4H), 1.74 (m, 2H), 2.59 (s, 3H), 3.03 (m, 1H), 3.21 (m, 2H), 7.40 (s, 1H), 7.66 (m, 1H), 8.11 (s, 1H), 8.19 (m, 1H), 8.33 (s, 1H), 8.64 (d, 1H), 9.11 (d, 1H), 9.49 (s, 1H).	Intermediate 375
236	1-(4-(4-cyclohexylthiazol-2-yl)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 490 for $C_{25}H_{27}N_7O_2S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.16 (m, 5H), 1.58 (m, 3H), 1.72 (m, 2H), 2.57 (m, 1H), 2.59 (s, 3H), 3.21 (m, 2H), 7.38 (s, 1H), 7.67 (m, 1H), 8.14 (s, 1H), 8.22 (m, 1H), 8.32 (s, 1H), 8.65 (d, 1H), 9.12 (d, 1H), 9.47 (s, 1H).	Intermediate 374

Example 237

(S)-1-ethyl-3-(5'-(5-(1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea

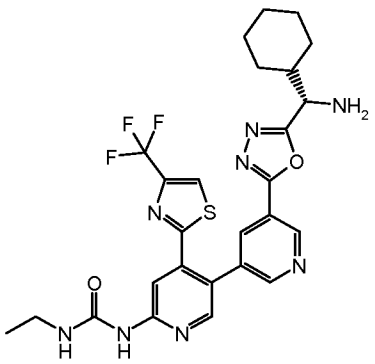


In a glass vial, (S)-1-ethyl-3-(5'-(2-(2-(triethylsilyloxy)propanoyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 403, 200 mg, 0.31 mmol) was suspended in a acetonitrile solution containing carbon tetrachloride (0.091 mL, 0.94 mmol) and diisopropylethyl amine (0.168 mL, 0.94 mmol). Triphenylphosphine (247 mg, 0.94 mmol) was added in a single portion. The reaction mixture was gently warmed to form a homogenous solution and was then allowed to stir at room temperature overnight. Once cyclized, the reaction mixture was acidified to pH=1 with 6N HCl. The reaction mixture was diluted with EtOAc, washed with $NaHCO_3$ (sat.) then brine. Dried the organic phase over Na_2SO_4, filtered and concentrated to dryness by rotary evaporation. Purified by silica gel flash column chromatography (95:5 CH_2Cl_2 / MeOH). Isolated 72 mg of the title compound. LC/MS (ES^+)[$(M+H)^+$]: 506 for $C_{21}H_{18}F_3N_7O_3S$.

^1H NMR (300 MHz, d_6-DMSO): 1.12 (t, 3H), 1.53 (d, 3H), 3.22 (m, 2H), 5.02 (m, 1H), 6.03 (d, 1H), 7.55 (t, 1H), 8.25 (s, 1H), 8.33 (t, 1H), 8.42 (s, 1H), 8.57 (s, 1H), 8.72 (d, 1H), 9.20 (d, 1H), 9.50 (s, 1H).

Example 238

(S)-1-(5'-(5-(amino(cyclohexyl)methyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea

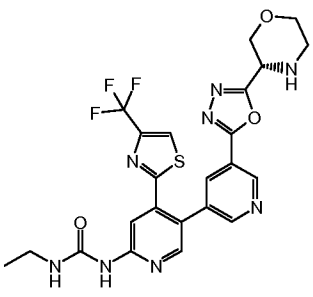


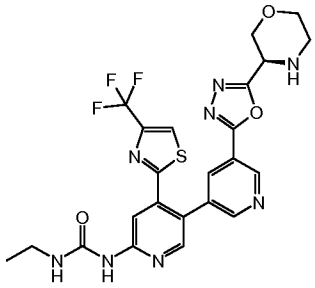
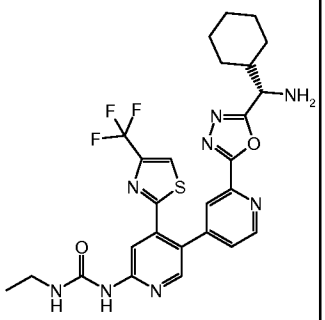
(S)-tert-butyl cyclohexyl(5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)methylcarbamate (Intermediate 404, 100 mg, 0.15 mmol) was dissolved in 1,4 dioxane. 4N HCl in dioxane (4 mL, 16.00 mmol) was added in a single portion. The solution was stirred at room temperature for 12 h. Concentrate the reaction mixture to dryness by rotary evaporation. Dissolve the crude in EtOAc, washed with 10% $NaHCO_3$, dried over Na_2SO_4, filtered, concentrated and purified by silica gel flash column chromatography (95:5 CH_2Cl_2 / MeOH). Isolation gave 63 mg of the title compound. LC/MS (ES^+)[$(M+H)^+$]: 573 for $C_{26}H_{27}F_3N_8O_2S$.

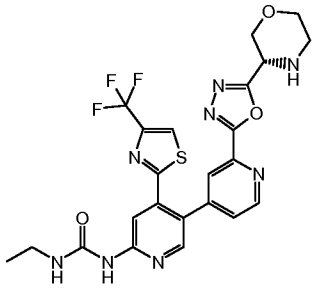
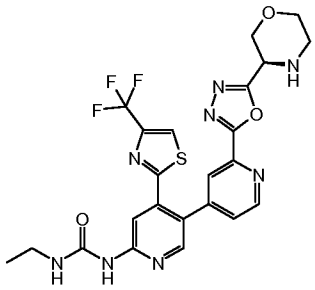
^1H NMR (300 MHz, d_6-DMSO): 1.01 - 1.21 (m, 5H), 1.12 (t, 3H), 1.44 (m, 1H), 1.69 (m, 4H), 1.85 (m, 1H), 2.16 (s, 2H), 3.22 (m, 2H), 3.88 (d, 1H), 7.55 (t, 1H), 8.24 (s, 1H), 8.30 (t, 1H), 8.42 (s, 1H), 8.57 (s, 1H), 8.72 (d, 1H), 9.20 (d, 1H), 9.51 (s, 1H).

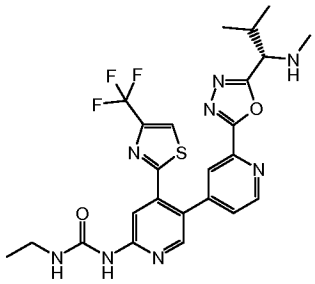
Examples 239-244

The following Examples were prepared according to the procedures described for Example 238 using the starting materials indicated in the table.

Ex	Compound	Data	SM
239	(S)-1-ethyl-3-(5'-(5-(morpholin-3-yl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 547 for $C_{23}H_{21}F_3N_8O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 2.82 (m, 1H), 2.94 (m, 1H), 3.14 (m, 2H), 3.23 (s, 1H), 3.54 (m, 1H), 3.65 (m, 1H), 3.78 (m, 1H), 3.96 (dd, 1H), 4.34 (dd, 1H), 7.48 (t, 1H), 8.19 (s, 1H), 8.29 (t, 1H), 8.34 (s, 1H), 8.50 (s, 1H), 8.65 (d, 1H), 9.15 (d, 1H), 9.44 (s, 1H).	Intermediate 405

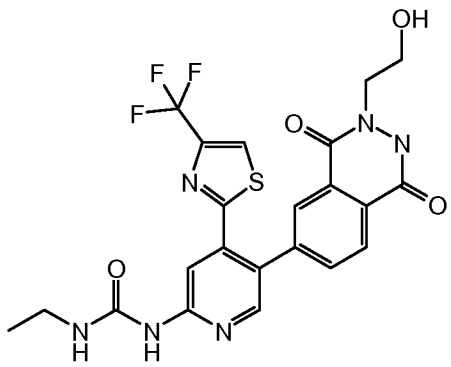
Ex	Compound	Data	SM
240	(R)-1-ethyl-3-(5'-(5-(morpholin-3-yl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 547 for $C_{23}H_{21}F_3N_8O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 2.82 (m, 1H), 2.94 (m, 1H), 3.14 (m, 2H), 3.23 (s, 1H), 3.54 (m, 1H), 3.65 (m, 1H), 3.78 (m, 1H), 3.96 (dd, 1H), 4.34 (dd, 1H), 7.48 (t, 1H), 8.19 (s, 1H), 8.29 (t, 1H), 8.34 (s, 1H), 8.50 (s, 1H), 8.65 (d, 1H), 9.15 (d, 1H), 9.44 (s, 1H).	Intermediate 406
241	(S)-1-(2'-(5-(amino(cyclohexyl)methyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 573 for $C_{26}H_{27}F_3N_8O_2S$. ^1H NMR (300 MHz, d_6-DMSO): 1.02 - 1.21 (m, 5H), 1.11 (t, 3H), 1.43 (m, 1H), 1.69 (m, 4H), 1.85 (m, 1H), 2.15 (m, 2H), 3.22 (m, 2H), 3.90 (d, 1H), 7.53 (t, 1H), 7.56 (dd, 1H), 8.01 (d, 1H), 8.18 (s, 1H), 8.43 (s, 1H), 8.60 (d, 1H), 8.76 (d, 1H), 9.54 (s, 1H).	Intermediate 407

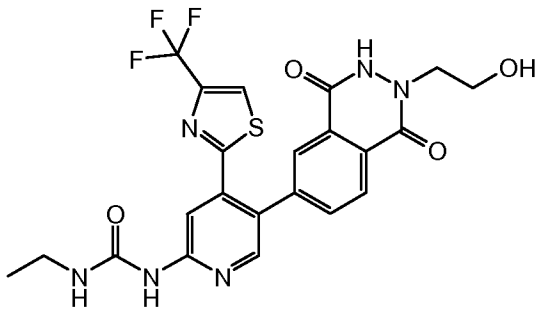
Ex	Compound	Data	SM
242	(S)-1-ethyl-3-(2'-(5-(morpholin-3-yl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 547 for $C_{23}H_{21}F_3N_8O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 2.80 (m, 1H), 2.92 (m, 1H), 3.21 (m, 3H), 3.56 (m, 1H), 3.66 (m, 1H), 3.79 (m, 1H), 3.94 (m, 1H), 4.25 (m, 1H), 7.53 (t, 1H), 7.56 (dd, 1H), 8.06 (d, 1H), 8.19 (s, 1H), 8.42 (s, 1H), 8.60 (s, 1H), 8.76 (d, 1H), 9.54 (s, 1H).	Intermediate 408
243	(R)-1-ethyl-3-(2'-(5-(morpholin-3-yl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 547 for $C_{23}H_{21}F_3N_8O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 2.80 (m, 1H), 2.92 (m, 1H), 3.21 (m, 3H), 3.56 (m, 1H), 3.66 (m, 1H), 3.79 (m, 1H), 3.94 (m, 1H), 4.25 (m, 1H), 7.53 (t, 1H), 7.56 (dd, 1H), 8.06 (d, 1H), 8.19 (s, 1H), 8.42 (s, 1H), 8.60 (s, 1H), 8.76 (d, 1H), 9.54 (s, 1H).	Intermediate 409

Ex	Compound	Data	SM
244	(S)-1-ethyl-3-(2'-(5-(2-methyl-1-(methylamino)propyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 547 for $C_{24}H_{25}F_3N_8O_2S$. ^1H NMR (300 MHz, d_6-DMSO): 0.83 (d, 3H), 0.99 (d, 3H), 1.11 (t, 3H), 2.09 (m, 1H), 2.21 (s, 3H), 2.31 (m, 1H), 3.22 (m, 2H), 3.63 (d, 1H), 7.54 (t, 1H), 7.58 (dd, 1H), 8.00 (s, 1H), 8.18 (s, 1H), 8.43 (s, 1H), 8.60 (s, 1H), 8.76 (d, 1H), 9.55 (s, 1H).	Intermediate 410

Example 245 and Example 246

1-ethyl-3-(5-(3-(2-hydroxyethyl)-1,4-dioxo-1,2,3,4-tetrahydrophthalazin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea and 1-ethyl-3-(5-(2-(2-hydroxyethyl)-1,4-dioxo-1,2,3,4-tetrahydrophthalazin-6-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea





6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 12, 400 mg, 1.11 mmol), a 1:1 mixture of 6-bromo-2-(2-hydroxyethyl)-2,3-dihydrophthalazine-1,4-dione and 7-bromo-2-(2-hydroxyethyl)-2,3-dihydrophthalazine-1,4-dione (Intermediates 411 and 412, 348 mg, 1.22 mmol), $Pd(PPh_3)_4$ (64.2 mg, 0.06 mmol) and

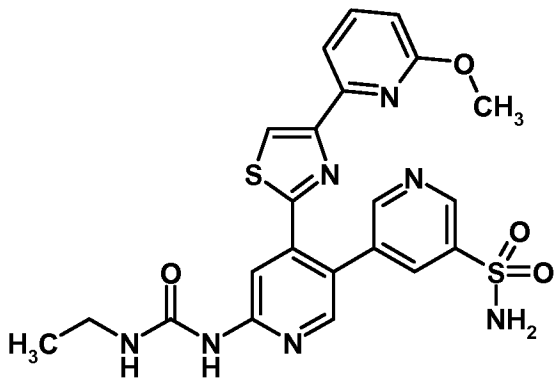
cesium carbonate (543 mg, 1.67 mmol) were combined in a microwave vessel and suspended in a 4:1 mixture of dioxane and water. The reaction slurry was degassed and purged with nitrogen. The reaction mixture was heated in the microwave at 100°C for 2 hours. The reaction mixture was concentrated to dryness by rotary evaporation. The residue was dissolved in minimal DMSO and water to help solubilize the inorganic salts. The two regioisomers were separated by reverse phase (C30 column) Gilson HPLC (10-50% MeOH / 0.1% formic acid).

Example 245: Isolated 38 mg. LC/MS (ES^+)[$(M+H)^+$]: 521 for $C_{22}H_{19}F_3N_6O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.04 (t, 3H), 3.14 (m, 2H), 3.66 (t, 2H), 3.98 (t, 2H), 7.57 (t, 1H), 7.65 (d, 1H), 7.83 (s, 1H), 8.12 (d, 1H), 8.17 (s, 1H), 8.27 (s, 1H), 8.41 (s, 1H), 9.48 (s, 1H).

Example 246: Isolated 37 mg. LC/MS (ES^+)[$(M+H)^+$]: 521 for $C_{22}H_{19}F_3N_6O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.04 (t, 3H), 3.14 (m, 2H), 3.66 (t, 2H), 3.97 (t, 2H), 7.56 (t, 1H), 7.69 (dd, 1H), 7.92 (d, 1H), 8.06 (d, 1H), 8.17 (s, 1H), 8.28 (s, 1H), 8.42 (s, 1H), 9.45 (s, 1H).

Example 247

6'-(3-ethylureido)-4'-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-3,3'-bipyridine-5-sulfonamide

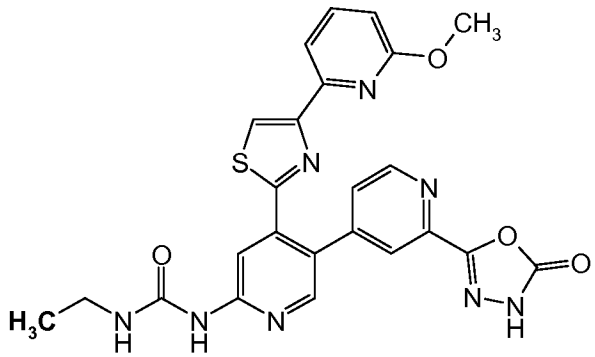


To a mixture of 6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 415, 270 mg, 0.68 mmol), 5-bromopyridine-3-sulfonamide (192 mg, 0.81 mmol), Pd_2dba_3 (31.0 mg, 0.03 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (97 mg, 0.20 mmol), and cesium carbonate (264 mg, 0.81 mmol) under vacuum, was added 1,4-dioxane (20 mL), water (5 mL), the reaction was then heated to 80 °C in an oil bath, purged with nitrogen, then stirred at that temperature under nitrogen pressure for 45 minutes. The reaction was then diluted with ethyl acetate (100 ml) and water (100ml), then

the layers were separated. The aqueous phase was extracted with ethyl acetate (3x100 ml), then the organics were combined, washed with brine, dried over sodium sulfate, filtered, concentrated under reduced pressure. The residue was suspended in methylene chloride with 5% methanol, loaded onto a silica gel column, eluted with a gradient of methanol in methylene chloride to give the desired product as a tan gum, which was suspended in dichloromethane and filtered to give the title compound as a pale tan solid (30mg, 8.6%).
MS (EI) $(M+H)^+$ 512 for $C_{22}H_{22}N_7O_4S_2$ $(M-H)^-$ 510 for $C_2 2H_{20}N_7O_4S_2$
^{1}H NMR (DMSO-*d*6) δ: 9.51 (s, 1 H), 8.98 (d, *J*=2.07 Hz, 1 H), 8.73 (d, *J*=1.88 Hz, 1 H), 8.34 (s, 1 H), 8.32 (s, 1 H), 8.29 (s, 1 H),8.18 (s, 1 H), 7.73 (t, *J*=7.82 Hz, 1 H), 7.66 (s, 1 H), 7.58 (t, *J*=4.71 Hz, 1 H), 7.22 (d, *J*=7.35 Hz, 1 H), 6.78 (d, *J*=8.29 Hz, 1 H), 3.92 (s, 3 H), 3.22 (dq, *J*=6.88, 6.56 Hz, 2 H), 1.11 (t, *J*=7.16 Hz, 3 H)

Example 248

1-ethyl-3-(4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-2'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,4'-bipyridin-6-yl)urea

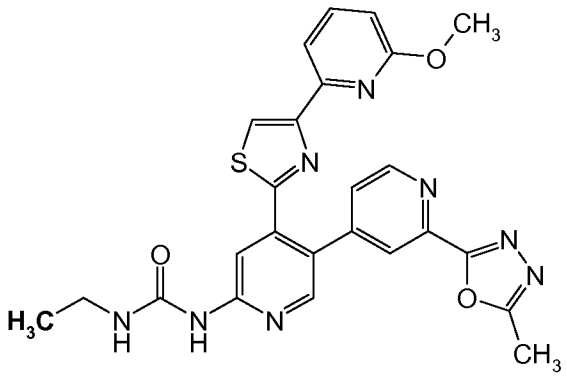


A solution of 1-ethyl-3-(2'-(hydrazinecarbonyl)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea (Intermediate 416, 91 mg, 0.19 mmol) in DMF (2 mL) was treated with di(1H-imidazol-1-yl)methanone (60 mg, 0.37 mmol), warmed to 50 °C in an oil bath for 20 min, and cooled to room temperature. The reaction was held at room temperature for 1 hour, diluted with ethyl acetate (50 ml), washed with water (2X50 ml) and brine (30ml). The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford a tan mass. This material was suspended into acetonitrile (20 ml), warmed to reflux and cooled to give the title compound as a tan powder (70 mg, 73.1 %).
MS (EI) $(M+H)^+$ 517 for $C_{24}H_{21}N_8O_4S$ $(M-H)^-$ 515 for $C_{24}H_{19}N_8O_4S$

^{1}H NMR (DMSO-*d6*) δ: 12.77 (br. s., 1 H), 9.52 (s, 1 H), 8.70 (d, J=4.90 Hz, 1 H), 8.35 (s, 1 H), 8.35 (s, 1 H), 8.22 (s, 1 H), 7.90 (s,1 H), 7.70 (t, J=7.82 Hz, 1 H), 7.58 (br. s., 1 H), 7.54 (d, J=5.09 Hz, 1 H), 7.20 (d, J=7.35 Hz, 1 H), 6.78 (d, J=8.29 Hz, 1 H), 3.91 (s, 3 H), 3.22 (quin, J=6.69 Hz, 2 H), 1.11 (t, J=7.16 Hz, 3 H);

Example 249

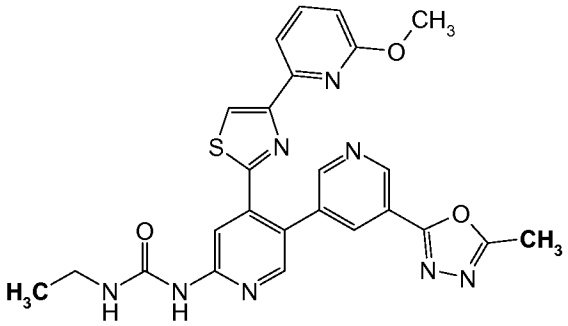
1-ethyl-3-(4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-2'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,4'-bipyridin-6-yl)urea



A suspension of 1-ethyl-3-(2'-(hydrazinecarbonyl)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea (Intermediate 416, 80 mg, 0.16 mmol) in 1,1,1-trimethoxyethane (5 mL, 41.62 mmol) was treated with concentrated aqueous HCl (drop), and the resulting solution was heated to reflux for 5 minutes, the resulting pink solution was treated with DBU (0.1 mL, 0.66 mmol) and refluxed for an additional 30 minutes at which point solvent was removed and the residue purified by flash chromatography eluting with a gradient of methanol in methylene chloride to give the desired product as a tan solid (9 mg, 10.72 %).
MS (EI) $(M+H)^+$ 515 for $C_{25}H_{23}N_8O_3S$) $(M-H)^-$ 513 for $C_{25}H_{21}N_8O_3S$
^{1}H NMR (DMSO-*d6*) δ: 9.48 - 9.64 (m, 1 H), 8.75 (d, *J*=5.09 Hz, 1 H), 8.38 (s, 1 H), 8.35 (s, 1 H), 8.23 (s, 1 H), 8.11 (s, 1 H), 7.66(t, *J*=7.82 Hz, 1 H), 7.54 - 7.63 (m, 2 H), 7.18 (d, *J*=7.35 Hz, 1 H), 6.76 (d, *J*=8.29 Hz, 1 H), 3.90 (s, 3 H), 3.12 - 3.25 (m, 2 H), 2.59 (s, 3 H), 1.11(t, *J*=7.16 Hz, 3 H);

Example 250

1-ethyl-3-(4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea



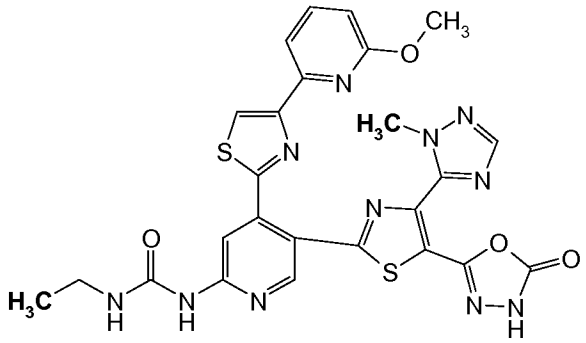
To a mixture of 6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 415, 510 mg, 0.15 mmol), 2-(5-bromopyridin-3-yl)-5-methyl-1,3,4-oxadiazole (Intermediate 418, 36.8 mg, 0.15 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (21.92 mg, 0.05 mmol), Pd_2dba_3 (7.02 mg, 7.66 μmol), and Cs_2CO_3 (59.9 mg, 0.18 mmol), under vacuum was added 1,4-dioxane (20 mL), water (5 mL), and the resulting suspension was heated in an oil bath at 80 °C, placed under nitrogen, and held at that temperature for 1 hour. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (100ml) and washed with water. The aqueous phase was extracted with ethyl acetate (2x50ml), and the combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes to give the title compound as a cream colored solid (20 mg, 25.4 %).

MS (EI) $(M+H)^+$ 515 for $C_{25}H_{23}N_8O_3S$ $(M-H)^-$ 513 for $C_{25}H_{21}N_8O_3S$

^{1}H NMR (DMSO-*d6*) δ: 9.50 (s, 1 H), 9.16 (d, *J*=2.07 Hz, 1 H), 8.75 (d, *J*=1.88 Hz, 1 H), 8.37 (s, 1 H), 8.36 (t, *J*=2.07 Hz, 1 H),8.33 (s, 1 H), 8.28 (s, 1 H), 7.69 (t, *J*=7.82 Hz, 1 H), 7.60 (t, *J*=5.75 Hz, 1 H), 7.23 (d, *J*=7.35 Hz, 1 H), 6.77 (d, *J*=8.10 Hz, 1 H), 3.90 (s, 3 H), 3.17- 3.28 (m, 2 H), 2.57 (s, 3 H), 1.12 (t, *J*=7.16 Hz, 3 H);

Example 251

1-ethyl-3-(4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-5-(4-(1-methyl-1H-1,2,4-triazol-5-yl)-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)thiazol-2-yl)pyridin-2-yl)urea



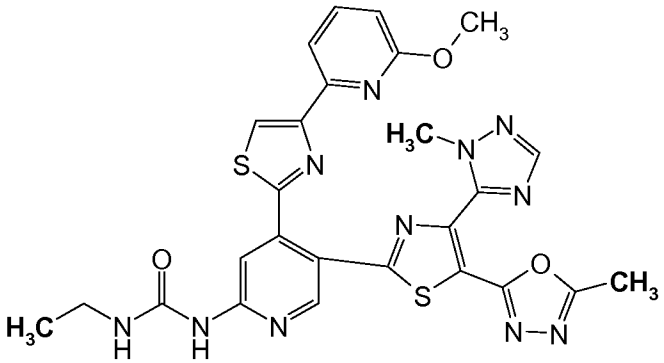
A mixture of 1-ethyl-3-(5-(5-(hydrazinecarbonyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazol-2-yl)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-2-yl)urea (Intermediate 419, 115 mg, 0.20 mmol) and 1,1'-carbonyl diimidazole (120 mg, 0.74 mmol) was suspended in DMF (3 mL) and heated to 110 °C for 20 min. The grey suspension was filtered hot, the filtrate was then treated with water (9ml) and allowed to cool slowly, the resulting yellow precipitate was collected by filtration, washed with methanol to give the title compound as a pale yellow solid (30 mg, 24.96 %).

MS (EI) $(M+H)^+$ 604 for $C_{25}H_{22}N_{11}O_4S_2$ $(M-H)^-$ 602 for $C_{25}H_{20}N_{11}O_4S_2$

^{1}H NMR (DMSO-*d*6) δ: 12.58 - 12.96 (m, 1 H), 9.71 (s, 1 H), 8.82 (s, 1 H), 8.49 (s, 1 H), 8.17 (s, 1 H), 8.07 (s, 1 H), 7.73 (t, *J*=7.82 Hz, 1 H), 7.51 (t, *J*=5.84 Hz, 1 H), 7.41 (d, *J*=7.35 Hz, 1 H), 6.81 (d, *J*=8.10 Hz, 1 H), 3.95 (s, 3 H), 3.79 (s, 3 H), 3.13 - 3.28 (m, 2 H), 1.11 (t, *J*=7.16 Hz, 3 H);

Example 252

1-ethyl-3-(4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-5-(5-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazol-2-yl)pyridin-2-yl)urea



A suspension of 1-ethyl-3-(5-(5-(hydrazinecarbonyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazol-2-yl)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-2-yl)urea (Intermediate 419, 50 mg, 0.08 mmol) in DMF (2ml) and 1,1,1-trimethoxyethane (5 ml, 41.62 mmol) was

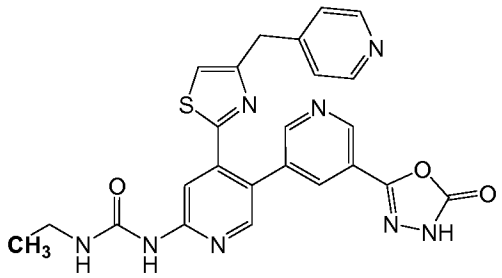
treated with aqueous HCl (1 drop), heated to 100 °C for 15 minutes, then treated with DBU (1ml) and refluxed for 5 minutes. The reaction mixture was then cooled, diluted with water (25ml) and ethyl acetate (100ml), and the layers were separated. The organic phase was washed sequentially with saturated sodium hydrogen carbonate, brine, then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by chromatography on silica gel eluting with a gradient of methanol in methylene chloride. The appropriate fractions were pooled and the crude product was precipitated from ethyl acetate with hexanes to give product as a pale yellow solid (15 mg, 15%).

MS (EI) $(M+H)^+$ 602 for $C_{26}H_{24}N_{11}O_3S_2$ $(M-H)^-$ 600 for $C_{26}H_{22}N_{11}O_3S_2$

^{1}H NMR (DMSO-*d*6) δ: 9.72 (s, 1 H), 8.85 (s, 1 H), 8.49 (s, 1 H), 8.17 (s, 1 H), 8.04 (s, 1 H), 7.71 (t, *J*=7.82 Hz, 1 H), 7.51 (t, *J*=4.99 Hz, 1 H), 7.41 (d, *J*=7.35 Hz, 1 H), 6.80 (d, *J*=8.29 Hz, 1 H), 3.94 (s, 3 H), 3.81 (s, 3 H), 3.10 - 3.28 (m, 2 H), 2.50 (br. s., 3 H), 1.11 (t, *J*=7.06 Hz, 3 H);

Example 253

1-ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(pyridin-4-ylmethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



To a mixture of 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(pyridin-4-ylmethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 421, 55 mg, 0.12 mmol) in THF (10 ml) was added di(1H-imidazol-1-yl)methanone (75 mg, 0.46 mmol) and the resulting suspension was warmed slightly to afford a solution which was stirred at room temperatere for one hour at which point the solvents were removed under reduced pressure and the resulting solid was dissolved in ethyl acetate (50 ml), methanol (5 ml), and water (50 ml). The layers were separated, and the organic phase was washed sequentially with saturated aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate, filtered, concentrated, and purified by normal phase

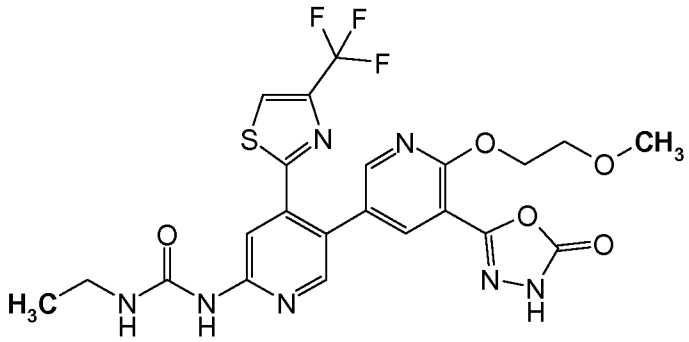
chromatography eluting on silica gel with a gradient of methanol in dichloromethane to afford 40 mg (61%)of the title compound as an off white powder.

MS (EI) $(M+H)^+$ 501 for $C_{24}H_{21}N_8O_3S$ $(M-H)^-$ 499 for $C_{24}H_{19}N_8O_3S$;

^{1}H NMR (DMSO-*d6*) δ: 12.59 (br. s., 1 H), 9.47 (s, 1 H), 8.89 (d, *J*=1.70 Hz, 1 H), 8.59 (d, *J*=1.70 Hz, 1 H), 8.36 (d, *J*=5.65 Hz, 2H), 8.29 (s, 1 H), 8.06 (s, 1 H), 7.93 (s, 1 H), 7.67 (br. s., 1 H), 7.58 (s, 1 H), 7.03 (d, *J*=5.27 Hz, 2 H), 3.99 (s, 2 H), 3.20 (dq, *J*=6.97, 6.59 Hz, 2H), 1.10 (t, *J*=7.06 Hz, 3 H);

Example 254

1-ethyl-3-(6'-(2-methoxyethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



To a solution of ethyl 6'-(3-ethylureido)-6-(2-methoxyethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 425, 90 mg, 0.05 mmol) in ethanol (10 mL) was added hydrazine (200 µL, 6.24 mmol). The solution was heated to reflux for 1 hour, solvents were removed, and the resulting gum was taken up into THF (10 ml) and treated with 1,1'-carbonyl di-imidazole (2X50 mg). The resulting solution was stirred at RT for 8 hours. The solvents were removed and the residue was purified by normal phase chromatography eluting with a gradient of methanol in dichloromethane, to afford crude product, which was purified by normal phase chromatography eluting with a gradient of ethyl acetate in hexanes to give the title compound as an off white solid.

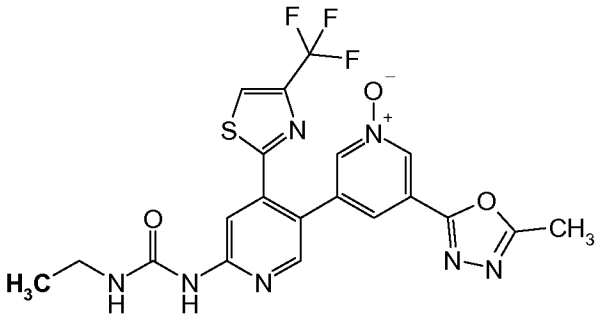
MS (EI) $(M+H)^+$ 551 for $C_{22}H_{21}F_3N_7O_5S$ $(M-H)^-$ 549 for $C_{22}H_{19}F_3N_7O_5S$;

^{1}H NMR (DMSO-*d6*) δ: 12.65 (s, 1 H), 9.44 (s, 1 H), 8.49 (s, 1 H), 8.28 (s, 1 H), 8.23 (d, *J*=1.70 Hz, 2 H), 7.67 (t, *J*=4.71 Hz, 1 H),7.15 (s, 1 H), 4.49 (dd, *J*=5.37, 3.11 Hz, 2 H), 3.71 (t, *J*=4.33 Hz, 2 H), 3.31 (br. s., 3 H), 3.14 - 3.27 (m, 2 H), 1.11 (t, *J*=7.25 Hz, 3 H);

^{19}F-NMR (DMSO-*d6*) δ -62.51 (br. s., 3 F);

Example 255

6'-(3-ethylureido)-5-(5-methyl-1,3,4-oxadiazol-2-yl)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine 1-oxide



A mixture of 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 12, 300 mg, 0.83 mmol), potassium carbonate (142 mg, 1.03 mmol), palladium diphenylphosphinoferocene dichloride (50.0 mg, 0.07 mmol) and 3-bromo-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine 1-oxide (Intermediate 428, 175 mg, 0.68 mmol) was treated with acetonitrile (10 mL) under vacuum. Water (10.00 mL) was added and after degassing for 1 minute the suspension was heated to 80 °C for 30 minutes. The reaction was then cooled to RT, diluted with ethyl acetate (100 ml) and methanol (10 ml). The organic layer were washed with water, saturated bicarbonate, and brine, and the aqueous phase was back extracted with ethyl acetate (2x100 ml). The combined organics were washed with brine, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The residue was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in dichloromethane. The major peak was concentrated down to a pale amber solid which was suspended in dichloromethane and filtered to give 170 mg of the title compound as a white solid.

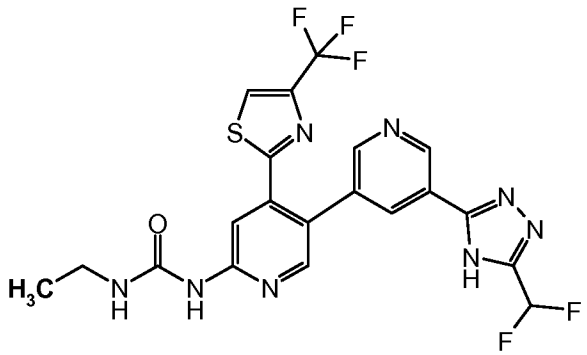
MS (EI) $(M+H)^+$ 492 for $C_{20}H_{17}F_3N_7O_3S$ $(M-H)^-$ 490 for $C_{20}H_{15}F_3N_7O_3S$;

^{1}H NMR (DMSO-*d6*) δ: 9.54 (s, 1 H), 8.71 (s, 1 H), 8.63 (s, 1 H), 8.53 (s, 1 H), 8.40 (s, 1 H), 8.23 (s, 1 H), 7.77 (s, 1 H), 7.52 (t,*J*=4.99 Hz, 1 H), 3.14 - 3.28 (m, *J*=7.16, 7.16, 6.22, 6.22 Hz, 2 H), 2.58 (s, 3 H), 1.10 (t, *J*=7.16 Hz, 3 H);

^{19}F-NMR (DMSO-*d6*) δ: -62.57 (s, 3 F);

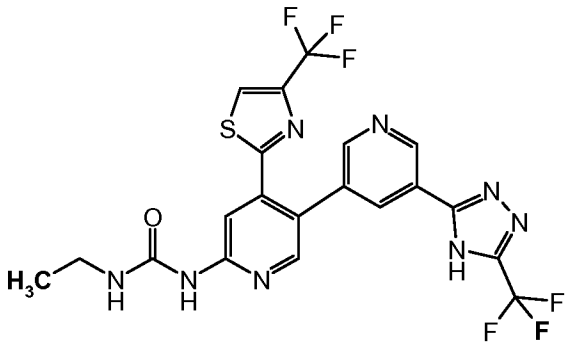
Example 256

1-(5'-(5-(difluoromethyl)-4H-1,2,4-triazol-3-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



A mixture of 3-bromo-5-(5-(difluoromethyl)-4H-1,2,4-triazol-3-yl)pyridine (Intermediate 429, 76 mg, 0.28 mmol), 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 12, 100 mg, 0.28 mmol), cesium carbonate (181 mg, 0.56 mmol), DicyclohexylTriisopropylBiphenylphosphine (39.7 mg, 0.08 mmol), and dipalladium(0)trisdibenzilidineacetone (12.71 mg, 0.01 mmol) in 1,4-dioxane (12 mL) was degassed, treated with water (3 mL) and heated to 80 °C for 30 minutes. The reaction was diluted with ethyl acetate (100 ml) and water (100 ml) and the layers were separated. The aqueous phase was extracted with ethyl acetate (3X50 ml), and the combined organics were washed with brine, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure, and the residue was purified by normal phase chromatography on silica gel, first eluting with a gradient of ethyl acetate in hexanes to provide crude product which was further purified by normal phase chromatography on silica gel eluting with a gradient of methanol in dichloromethane to afford a tan solid which was triturated from dichloromethane with hexanes to afford 50 mg of the title compound as a beige solid.
MS (EI) $(M+H)^+$ 511 for $C_{20}H_{16}F_5N_8OS$ $(M-H)^-$ 509 for $C_{20}H_{14}F_5N_8OS$;
^{1}H NMR (DMSO-*d6*) δ: 15.19 (br. s., 1 H), 9.52 (s, 1 H), 9.22 (d, *J*=0.94 Hz, 1 H), 8.64 (s, 1 H), 8.55 (s, 1 H), 8.40 (s, 1 H), 8.34 (br. s., 1 H), 8.27 (s, 1 H), 7.55 (t, *J*=5.09 Hz, 1 H), 7.19 (t, *J*=53.50 Hz, 1 H), 3.21 (quin, *J*=6.73 Hz, 2 H), 1.11 (t, *J*=7.06 Hz, 3 H);
^{19}F-NMR (DMSO-*d6*) δ: -62.49 (s, 3 F), -116.16 (br. s., 2 F);

Example 257
1-ethyl-3-(5'-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



Example 257 was synthesized as described for Example 256 from Intermediate 431 and Intermediate 12 as a tan solid.

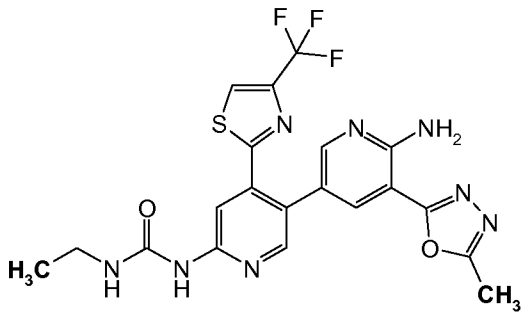
MS (EI) $(M+H)^+$ 529 for $C_{20}H_{15}F_6N_8OS$ $(M-H)^-$ 527 for $C_{20}H_{13}F_6N_8OS$

^{1}H NMR (DMSO-*d6*) δ: 15.56 (br. s., 1 H), 9.52 (s, 1 H), 9.22 (s, 1 H), 8.66 (s, 1 H), 8.52 - 8.61 (m, 1 H), 8.41 (s, 1 H), 8.36 (s, 1H), 8.26 (s, 1 H), 7.54 (t, *J*=5.09 Hz, 1 H), 3.21 (dq, *J*=6.97, 6.66 Hz, 2 H), 1.11 (t, *J*=7.16 Hz, 3 H);

^{19}F-NMR (DMSO-*d6*) δ: -62.52 (s, 3 F), -63.75 (br. s., 3 F);

Example 258

1-(6'-amino-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



Example 258 was synthesized according to the procedure for Example 255 from Intermediate 12 and Intermediate 434 as an off white solid.

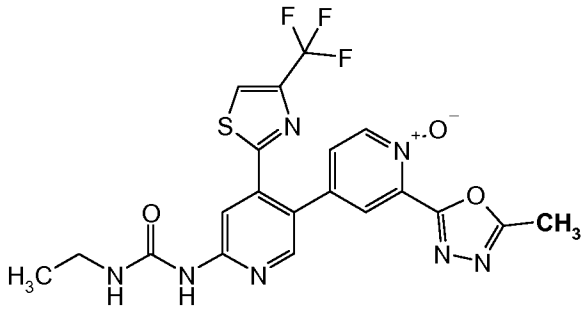
MS (EI) $(M+H)^+$ 491 for $C_{20}H_{18}F_3N_8O_2S$ $(M-H)^-$ 489 for $C_{20}H_{16}F_3N_8O_2S$;

^{1}H NMR (DMSO-*d6*) δ: 9.41 (s, 1 H), 8.52 (s, 1 H), 8.30 (s, 1 H), 8.25 (s, 1 H), 8.13 (d, *J*=2.26 Hz, 1 H), 7.96 (d, *J*=2.45 Hz, 1 H),7.63 (t, *J*=4.52 Hz, 1 H), 7.53 (br. s., 2 H), 3.20 (quin, *J*=6.59 Hz, 2 H), 2.54 (s, 3 H), 1.10 (t, *J*=7.16 Hz, 3 H);

^{19}F-NMR (DMSO-*d6*) δ: -62.33 (s, 3 F);

Example 259

6-(3-ethylureido)-2'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine 1'-oxide



Example 259 was synthesized according to the procedure for Example 255 from Intermediate 12 and Intermediate 436 as a white solid.

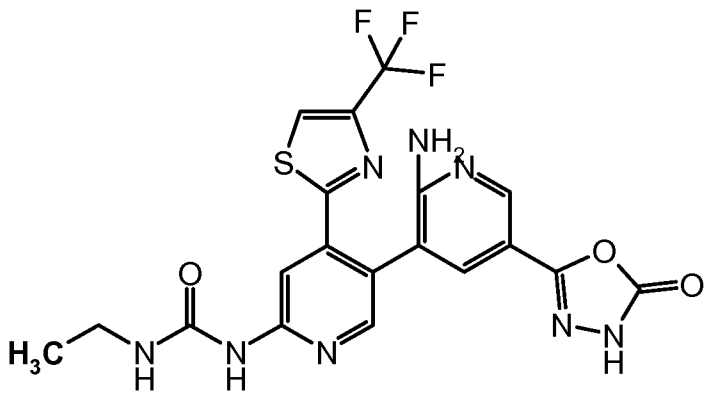
MS (EI) $(M+H)^+$ 492 for $C_{20}H_{17}F_3N_7O_3S$ $(M-H)^-$ 490 for $C_{20}H_{15}F_3N_7O_3S$;

^{1}H NMR (DMSO-*d6*) δ : 9.53 (s, 1 H), 8.64 (s, 1 H), 8.47 (d, *J*=6.97 Hz, 1 H), 8.40 (s, 1 H), 8.18 (s, 1 H), 7.91 (d, *J*=2.45 Hz, 1 H),7.56 (dd, *J*=6.78, 2.26 Hz, 1 H), 7.49 (t, *J*=4.71 Hz, 1 H), 3.11 - 3.25 (m, 2 H), 2.61 (s, 3 H), 1.10 (t, *J*=7.16 Hz, 3 H);

^{19}F-NMR (DMSO-*d6*) δ: -62.47 (s, 3 F);

Example 260

1-(2'-amino-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



Example 260 was synthesized according to the procedure for Example 255 from Intermediate 12 and Intermediate 437 as a pale yellow solid.

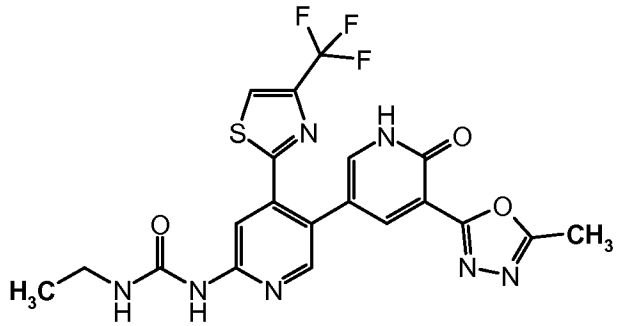
MS (EI) $(M+H)^+$ 493 for $C_{19}H_{16}F_3N_8O_3S$ $(M-H)^-$ 491 for $C_{19}H_{14}F_3N_8O_3S$;

^{1}H NMR (DMSO-*d6*) δ: 12.40 (br. s., 1 H), 9.43 (s, 1 H), 8.50 (s, 1 H), 8.48 (d, *J*=2.26 Hz, 1 H), 8.34 (s, 1 H), 8.17 (s, 1 H), 7.82 (t,*J*=5.56 Hz, 1 H), 7.69 (d, *J*=2.26 Hz, 1 H), 6.51 (br. s., 2 H), 3.15 - 3.27 (m, 2 H), 1.10 (t, *J*=7.16 Hz, 3 H)

^{19}F-NMR (DMSO-*d6*) δ: -62.29 (s, 3 F)

Example 261

1-ethyl-3-(5-(5-(5-methyl-1,3,4-oxadiazol-2-yl)-6-oxo-1,6-dihydropyridin-3-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea



Perchloromethane (19.32 mg, 0.13 mmol) was added to a solution of crude 1-(5-(5-(2-acetylhydrazinecarbonyl)-6-oxo-1,6-dihydropyridin-3-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 441, 16 mg, 0.03 mmol), triphenylphosphine (16.47 mg, 0.06 mmol), and DBU (9.47 μL, 0.06 mmol) in acetonitrile (5 mL) and the mixture was stirred for 80 hours at RT. The reaction was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in dichloromethane to afford 10mg of the title compound as an off white solid.

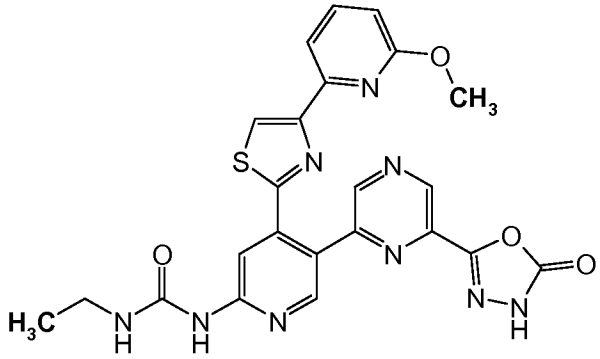
MS (EI) $(M+H)^+$ 492 for $C_{20}H_{17}F_3N_7O_3S$ $(M-H)^-$ 490 for $C_{20}H_{15}F_3N_7O_3S$;

^{1}H NMR (DMSO-*d6*) δ: 12.64 (br. s., 1 H), 9.42 (s, 1 H), 8.60 (s, 1 H), 8.32 (s, 1 H), 8.24 (s, 1 H), 7.97 (d, *J*=2.64 Hz, 1 H), 7.82 (s,1 H), 7.59 (t, *J*=5.09 Hz, 1 H), 3.20 (dq, *J*=6.97, 6.59 Hz, 2 H), 2.52 (br. s., 3 H), 1.10 (t, *J*=7.16 Hz, 3 H)

^{19}F-NMR (DMSO-*d6*) δ: -62.39 (s, 3 F)

Example 262

1-ethyl-3-(4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-5-(6-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyrazin-2-yl)pyridin-2-yl)urea



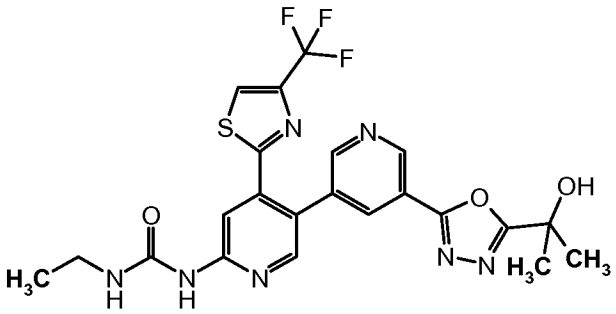
1,1'-Carbonyl di-imidazole (CDI, 50 mg, 0.31 mmol) was added to a solution of crude 1-ethyl-3-(5-(6-(hydrazinecarbonyl)pyrazin-2-yl)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-2-yl)urea (Intermediate 446, 30 mg, 0.06 mmol) in tetrahydrofuran (10 mL) and DIEA (100 µL, 0.57 mmol). The amber solution was treated with CDI (3x20 mg), solvent was removed under reduced pressure, purified by normal phase chromatography on silica gel eluting with a gradient of methanol in dichloromethane, the crude product was dissolved in ethyl acetate (50 ml), washed with water (50 ml). The aqueous layer was back extracted with ethyl acetate (2x50 ml), combined organics were washed with brine, dried over magnesium sulfate, filtered, and concentrated to give 23 mg of the title compound as a pale off white solid.

MS (EI) $(M+H)^+$ 518 for $C_{23}H_{20}N_9O_4S$ $(M-H)^-$ 516 for $C_{23}H_{18}N_9O_4S$;

^{1}H NMR (DMSO-*d*6) δ: 9.64 (s, 1 H), 9.06 (s, 1 H), 8.77 (s, 1 H), 8.49 (s, 1 H), 8.36 (s, 1 H), 8.28 (s, 1 H), 7.71 (d, *J*=7.91 Hz, 1H), 7.59 - 7.67 (m, 1 H), 6.86 - 7.10 (m, 2 H), 6.76 (d, *J*=8.29 Hz, 1 H), 3.91 (s, 3 H), 3.22 (quin, *J*=6.69 Hz, 2 H), 1.12 (t, *J*=7.25 Hz, 3 H)

Example 263

1-ethyl-3-(5'-(5-(2-hydroxypropan-2-yl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



Potassium carbonate (1 ml, 1N in water) was added to a solution of 2-(5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)propan-2-yl

acetate (Example 264, 50 mg, 0.09 mmol) in methanol (5 mL) and stirred at RT for 1 hour, at which time solvents were removed and the residue was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in methylene chloride to afford 15 mg of the title compound as a white solid.

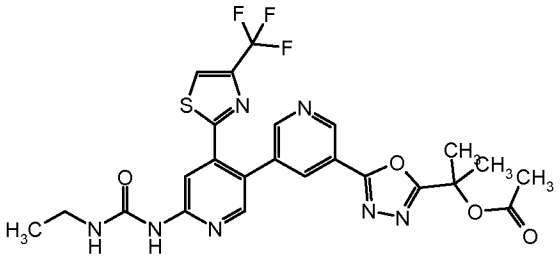
MS (EI) $(M+H)^+$ 520 for $C_{22}H_{21}F_3N_7O_3S$ $(M-H)^-$ 518 for $C_{22}H_{19}F_3N_7O_3S$;

^{1}H NMR (DMSO-*d6*) δ: 9.53 (s, 1 H), 9.21 (d, *J*=1.88 Hz, 1 H), 8.72 (d, *J*=1.88 Hz, 1 H), 8.57 (s, 1 H), 8.42 (s, 1 H), 8.33 (t, *J*=1.98Hz, 1 H), 8.24 (s, 1 H), 7.57 (t, *J*=5.18 Hz, 1 H), 5.96 (s, 1 H), 3.21 (qd, *J*=7.16, 6.03 Hz, 2 H), 1.60 (s, 6 H), 1.11 (t, *J*=7.16 Hz, 3 H);

^{19}F-NMR (DMSO-*d6*) δ: -62.57 (s, 3 F);

Example 264

2-(5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)propan-2-yl acetate



A solution of triphenyl phosphine (55 mg, 0.2 mmol) and DIEA (0.15 ml) in acetonitrile (2 ml) was added to 1-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-2-methyl-1-oxopropan-2-yl acetate (Intermediate 448, 50 mg, 0.1 mmol). The resulting solution was treated with carbontetrachloride (0.1 ml) and let stir at RT for 2 hours. Volatiles were removed under reduced pressure and the residue was purified by normal phase chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes to afford 30 mg of the title compound as an off white solid.

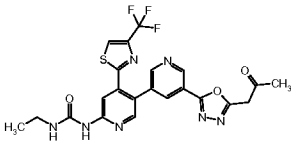
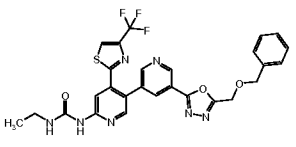
MS (EI) $(M+H)^+$ 562 for $C_{24}H_{23}F_3N_7O_4S$ $(M-H)^-$ 560 for $C_{24}H_{21}F_3N_7O_4S$;

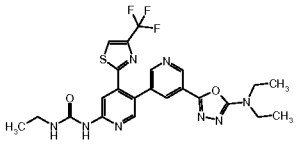
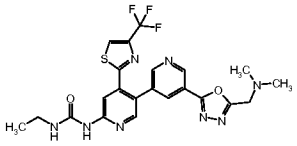
^{1}H NMR (DMSO-*d6*) δ: 9.53 (s, 1 H), 9.20 (br. s., 1 H), 8.73 (br. s., 1 H), 8.57 (s, 1 H), 8.42 (s, 1 H), 8.32 (br. s., 1 H), 8.22 (s, 1H), 7.45 - 7.70 (m, 1 H), 3.14 - 3.28 (m, 2 H), 2.04 (s, 3 H), 1.79 (s, 6 H), 1.11 (t, J=7.06 Hz, 3 H);

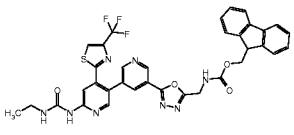
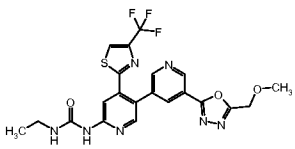
^{19}F-NMR (DMSO-*d6*) δ: -62.61 (s, 3 F);

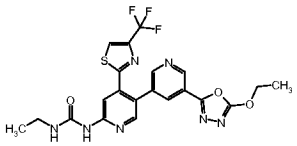
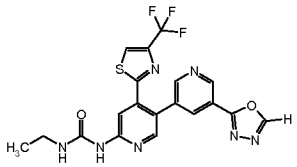
Examples 265-279

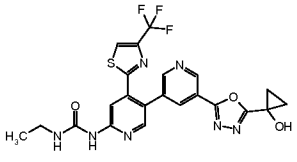
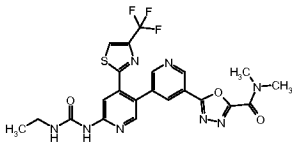
The following Examples were prepared according to the procedure for Example 264 using the starting materials indicated in the table.

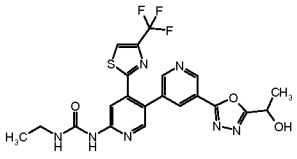
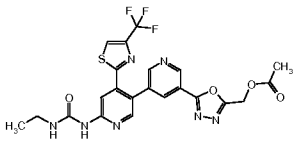
Ex	Compound	Data	SM
265	1-ethyl-3-(5'-(5-(2-oxopropyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (EI) $(M+H)^+$ 518 for $C_{22}H_{19}F_3N_7O_5S$ $(M-H)^-$ 516 for $C_{22}H_{17}F_3N_7O_5S$; ^{1}H NMR (DMSO-d6) δ: 9.52 (s, 1 H), 9.17 (d, J=2.07 Hz, 1 H), 8.72 (d, J=2.07 Hz, 1 H), 8.56 (s, 1 H), 8.41 (s, 1 H), 8.30 (t, J=2.07Hz, 1 H), 8.24 (s, 1 H), 7.48 - 7.65 (m, 1 H), 4.40 (s, 2 H), 3.15 - 3.25 (m, 2 H), 2.28 (s, 3 H), 1.11 (t, J=7.16 Hz, 3 H); ^{19}F-NMR (DMSO-d6) δ: -62.56 (s, 3 F)	Intermediate 449
266	1-(5'-(5-(benzyloxymethyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (EI) $(M+H)^+$ 582 for $C_{27}H_{23}F_3N_7O_3S$ $(M-H)^-$ 580 for $C_{27}H_{21}F_3N_7O_3S$; ^{1}H NMR (DMSO-d6) δ: 9.53 (br. s., 1 H), 9.19 (br. s., 1 H), 8.72 (br. s., 1 H), 8.56 (br. s., 1 H), 8.40 (br. s., 1 H), 8.33 (br. s., 1 H),8.24 (br. s., 1 H), 7.59 (br. s., 3 H), 7.22 - 7.43 (m, 3 H), 4.85 (br. s., 2 H), 4.65 (br. s., 2 H), 3.21 (br. s., 2 H), 1.11 (br. s., 3 H); ^{19}F-NMR (DMSO-d6) δ: -62.59 (s, 3 F)	Intermediate 450

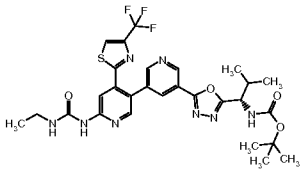
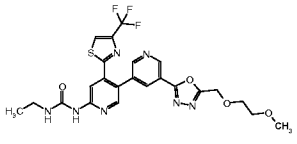
Ex	Compound	Data	SM
267	1-(5'-(5-(diethylamino)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (EI) $(M+H)^+$ 533 for $C_{23}H_{24}F_3N_8O_2S$ $(M-H)^-$ 531 for $C_{23}H_{22}F_3N_8O_2S$; ^{1}H NMR (DMSO-d6) δ: 9.51 (s, 1 H), 9.08 (d, J=2.07 Hz, 1 H), 8.62 (d, J=2.07 Hz, 1 H), 8.57 (s, 1 H), 8.40 (s, 1 H), 8.23 (s, 1 H),8.14 (t, J=1.98 Hz, 1 H), 7.58 (t, J=5.75 Hz, 1 H), 3.48 (q, J=7.28 Hz, 4 H), 3.13 - 3.27 (m, J=7.54, 6.97, 6.97, 5.84 Hz, 2 H), 1.17 (t, J=7.06 Hz, 6H), 1.11 (t, J=7.25 Hz, 3 H); ^{19}F-NMR (DMSO-d_6) δ: -62.52 (s, 3 F);	Intermediate 451
268	1-(5'-(5-((dimethylamino)methyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (EI) $(M+H)^+$ 519 for $C_{22}H_{22}F_3N_8O_2S$ $(M-H)^-$ 517 for $C_{22}H_{20}F_3N_8O_2S$; ^{1}H NMR (DMSO-d6) δ: 9.52 (s, 1 H), 9.19 (d, J=1.88 Hz, 1 H), 8.73 (d, J=1.88 Hz, 1 H), 8.57 (s, 1 H), 8.41 (s, 1 H), 8.30 (t, J=1.98 Hz, 1 H), 8.23 (s, 1 H), 7.46 - 7.70 (m, 1 H), 3.83 (s, 2 H), 3.21 (quin, J=6.31 Hz, 2 H), 2.26 (s, 6 H), 1.11 (t, J=7.16 Hz, 3 H); ^{19}F-NMR (DMSO-d_6) δ: -62.59 (s, 3 F);	Intermediate 452

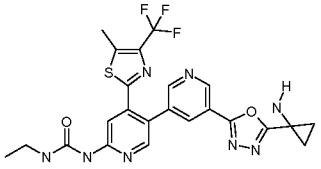
Ex	Compound	Data	SM
269	(9H-fluoren-9-yl)methyl (5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)methylcarbamate 	MS (EI) $(M+H)^+$ 713 for $C_{35}H_{28}F_3N_8O_4S$ $(M-H)^-$ 711 for $C_{35}H_{26}F_3N_8O_4S$; ^{1}H NMR (DMSO-d6) δ: 9.52 (s, 1 H), 9.15 (d, J=2.07 Hz, 1 H), 8.71 (d, J=2.26 Hz, 1 H), 8.54 (s, 1 H), 8.38 (s, 1 H), 8.25 - 8.29 (m,1 H), 8.23 (s, 1 H), 8.13 - 8.20 (m, 1 H), 7.86 (d, J=7.91 Hz, 2 H), 7.69 (d, J=7.16 Hz, 2 H), 7.56 (br. s., 1 H), 7.33 - 7.42 (m, 2 H), 7.24 - 7.33 (m, 2H), 4.54 (d, J=5.46 Hz, 2 H), 4.37 (d, J=6.97 Hz, 2 H), 4.15 - 4.29 (m, 1 H), 3.13 - 3.27 (m, 2 H), 1.11 (t, J=7.16 Hz, 3 H); ^{19}F-NMR (DMSO-d6) δ: -62.56 (s, 3 F);	Intermediate 453
270	1-ethyl-3-(5'-(5-(methoxymethyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (EI) $(M+H)^+$ 506 for $C_{21}H_{19}F_3N_7O_3S$ $(M-H)^-$ 504 for $C_{21}H_{17}F_3N_7O_3S$; ^{1}H NMR (DMSO-d6) δ: 9.53 (s, 1 H), 9.20 (d, J=1.70 Hz, 1 H), 8.73 (d, J=1.88 Hz, 1 H), 8.57 (s, 1 H), 8.41 (s, 1 H), 8.34 (t, J=1.88Hz, 1 H), 8.23 (s, 1 H), 7.56 (br. s., 1 H), 4.74 (s, 2 H), 3.35 (s, 3 H), 3.15 - 3.28 (m, 2 H), 1.11 (t, J=7.16 Hz, 3 H); ^{19}F-NMR (DMSO-d6) δ: -62.59 (s, 3 F);	Intermediate 454

Ex	Compound	Data	SM
271	1-(5'-(5-ethoxy-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (EI) $(M+H)^+$ 506 for $C_{21}H_{19}F_3N_7O_3S$ $(M-H)^-$ 504 for $C_{21}H_{17}F_3N_7O_3S$; ^{1}H NMR (DMSO-d6) δ: 9.52 (s, 1 H), 9.08 (d, J=2.07 Hz, 1 H), 8.68 (d, J=1.88 Hz, 1 H), 8.58 (s, 1 H), 8.39 (s, 1 H), 8.23 (s, 1 H), 8.21 (t, J=2.07 Hz, 1 H), 7.60 - 7.67 (m, 1 H), 4.58 (q, J=6.97 Hz, 2 H), 3.14 - 3.27 (m, 2 H), 1.42 (t, J=7.06 Hz, 3 H), 1.11 (t, J=7.16 Hz, 3 H); ^{19}F-NMR (DMSO-d6) δ: -62.53 (s, 3 F)	Intermediate 455
272	1-(5'-(1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (EI) $(M+H)^+$ 462 for $C_{19}H_{15}F_3N_7O_2S$ $(M-H)^-$ 460 for $C_{19}H_{13}F_3N_7O_2S$; ^{1}H NMR (MEO-D) δ: 9.25 (d, J=2.07 Hz, 1 H), 9.10 (s, 1 H), 8.67 (d, J=2.07 Hz, 1 H), 8.43 (t, J=2.07 Hz, 1 H), 8.42 (s, 1 H), 8.26(s, 1 H), 7.88 (s, 1 H), 3.32 - 3.41 (m, 2 H), 1.23 (t, J=7.25 Hz, 3 H); ^{19}F-NMR (MEOD) δ: -65.63 (s, 3 F);	Intermediate 456

Ex	Compound	Data	SM
273	1-ethyl-3-(5'-(5-(1-hydroxycyclopropyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (EI) $(M+H)^+$ 518 for $C_{22}H_{19}F_3N_7O_3S$ $(M-H)^-$ 516 for $C_{22}H_{17}F_3N_7O_3S$; ^{1}H NMR (CHLOROFORM-d) δ: 9.16 (d, J=1.70 Hz, 1 H), 8.75 (br. s., 1 H), 8.53 (d, J=1.88 Hz, 1 H), 8.25 (t, J=1.98 Hz, 1 H), 8.21 (s, 1 H), 7.78 (s, 1 H), 7.65 (s, 1 H), 3.65 (s, 1 H), 3.15 - 3.44 (m, 2 H), 1.37 (d, J=2.45 Hz, 4 H), 1.20 (t, J=7.25 Hz, 3 H); ^{19}F-NMR (CHLOROFORM-d) δ: -64.30 (s, 3 F);	Intermediate 457
274	5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-N,N-dimethyl-1,3,4-oxadiazole-2-carboxamide 	MS (EI) $(M+H)^+$ 533 for $C_{22}H_{20}F_3N_8O_3S$ $(M-H)^-$ 531 for $C_{22}H_{18}F_3N_8O_3S$; ^{1}H NMR (DMSO-d6) δ: 9.53 (s, 1 H), 9.24 (d, J=2.26 Hz, 1 H), 8.76 (d, J=2.07 Hz, 1 H), 8.59 (s, 1 H), 8.42 (s, 1 H), 8.40 (t, J=2.07Hz, 1 H), 8.25 (s, 1 H), 7.48 - 7.62 (m, 0 H), 3.33 (s, 3 H), 3.22 (dd, J=7.72, 6.03 Hz, 2 H), 3.08 (s, 3 H), 1.11 (t, J=7.16 Hz, 3 H); ^{19}F-NMR (DMSO-d$_6$) δ: -62.54 (s, 3 F);	Intermediate 458

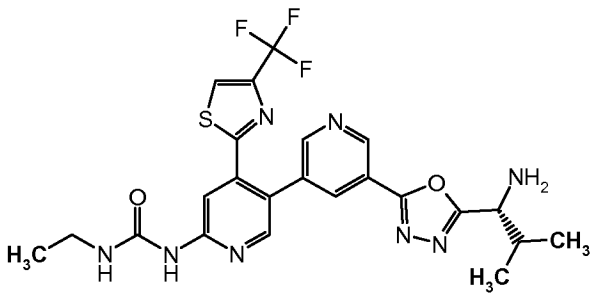
Ex	Compound	Data	SM
275	1-ethyl-3-(5'-(5-(1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (EI) $(M+H)^+$ 506 for $C_{21}H_{19}F_3N_7O_3S$ $(M-H)^-$ 504 for $C_{21}H_{17}F_3N_7O_3S$; ^{1}H NMR (DMSO-d6) δ: 9.53 (s, 1 H), 9.20 (d, J=2.07 Hz, 1 H), 8.72 (d, J=2.07 Hz, 1 H), 8.57 (s, 1 H), 8.42 (s, 1 H), 8.33 (t, J=2.07Hz, 1 H), 8.25 (s, 1 H), 7.57 (t, J=5.09 Hz, 1 H), 6.07 (d, J=5.65 Hz, 1 H), 5.02 (dq, J=6.59, 6.28 Hz, 1 H), 3.18 - 3.27 (m, 2 H), 1.53 (d, J=6.59 Hz,3 H), 1.11 (t, J=7.16 Hz, 3 H); ^{19}F-NMR (DMSO-d6) δ: -62.56 (s, 3 F);	Intermediate 459
276	(5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)methyl acetate 	MS (EI) $(M+H)^+$ 534 for $C_{22}H_{19}F_3N_7O_4S$ $(M-H)^-$ 532 for $C_{22}H_{17}F_3N_7O_4S$; ^{1}H NMR (DMSO-d6) δ: 9.52 (br. s., 1 H), 9.19 (br. s., 1 H), 8.73 (br. s., 1 H), 8.57 (br. s., 1 H), 8.41 (br. s., 1 H), 8.33 (br. s., 1 H),8.23 (br. s., 1 H), 7.57 (br. s., 1 H), 5.40 (br. s., 2 H), 3.21 (br. s., 2 H), 2.13 (br. s., 3 H), 1.11 (br. s., 3 H); ^{19}F-NMR (DMSO-d6) δ: -62.60 (s, 3 F)	Intermediate 460

Ex	Compound	Data	SM
277	(S)-tert-butyl 1-(5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)-2-methylpropylcarbamate 	MS (EI) $(M+H)^+$ 633 for $C_{28}H_{32}F_3N_8O_4S$; ^{1}H NMR (DMSO-d6) δ: 9.53 (s, 1 H), 9.18 (d, J=1.88 Hz, 1 H), 8.73 (d, J=1.88 Hz, 1 H), 8.57 (s, 1 H), 8.42 (s, 1 H), 8.27 (s, 1 H),8.24 (s, 1 H), 7.42 - 7.77 (m, 2 H), 4.68 (t, J=7.82 Hz, 1 H), 3.12 - 3.27 (m, J=7.16, 7.16, 7.16, 6.03 Hz, 2 H), 2.08 - 2.24 (m, 1 H), 1.38 (s, 9 H),1.11 (t, J=7.16 Hz, 3 H), 0.92 - 1.01 (m, 3 H), 0.85 (dd, J=7.06, 2.92 Hz, 3 H); ^{19}F-NMR (DMSO-d6) δ: -62.62 (s, 3 F);	Intermediate 461
278	1-ethyl-3-(5'-(5-((2-methoxyethoxy)methyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (EI) $(M+H)^+$ 550 for $C_{23}H_{23}F_3N_7O_4S$ $(M-H)^-$ 548 for $C_{23}H_{21}F_3N_7O_4S$; ^{1}H NMR (DMSO-d6) δ: 9.52 (s, 1 H), 9.21 (d, J=1.88 Hz, 1 H), 8.73 (d, J=2.07 Hz, 1 H), 8.57 (s, 1 H), 8.41 (s, 1 H), 8.34 (t, J=2.07Hz, 1 H), 8.24 (s, 1 H), 7.56 (br. s., 1 H), 4.82 (s, 2 H), 3.69 (dd, J=5.46, 3.58 Hz, 2 H), 3.48 (dd, J=5.37, 3.67 Hz, 2 H), 3.15 - 3.27 (m, 5 H), 1.11(t, J=7.16 Hz, 3 H); ^{19}F-NMR (DMSO-d6) δ: -62.57 (s, 3 F)	Intermediate 462

Ex	Compound	Data	SM
279	1-(5'-(5-(1-aminocyclopropyl)-1,3,4-oxadiazol-2-yl)-4-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (EI) $(M+H)^+$ 531 for $C_{23}H_{22}F_3N_8O_2S$ $(M-H)^-$ 529 for $C_{23}H_{22}F_3N_8O_2S$; ^{1}H NMR (DMSO-d6) δ: 9.49 (s, 1 H), 9.19 (d, J=2.07 Hz, 1 H), 8.68 (d, J=2.26 Hz, 1 H), 8.36 (s, 1 H), 8.33 (t, J=2.17 Hz, 1 H),8.19 (s, 1 H), 7.56 (t, J=5.27 Hz, 1 H), 3.10 - 3.27 (m, 2 H), 2.66 - 2.84 (m, 2 H), 2.51 - 2.55 (m, 3 H), 1.26 - 1.35 (m, 2 H), 1.06 - 1.16 (m, 5 H); ^{19}F-NMR (DMSO-d6) δ: -59.69 (s, 3 F)	Intermediate 463

Example 280

(R)-1-(5'-(5-(1-amino-2-methylpropyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



Hydrochloric acid (3 ml, 1M in 1,4-dioxane) was added to a solution of (R)-tert-butyl 1-(5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)-2-methylpropylcarbamate (Intermediate 468, 75 mg, 0.12 mmol) in 1,4-dioxane (10 mL) and methanol (5 ml), warmed to 50 °C for 1 hour, solvent was removed and the residue was precipitated from methanol with ethyl acetate to afford 50 mg of the HCl salt of the title compound as a white solid.

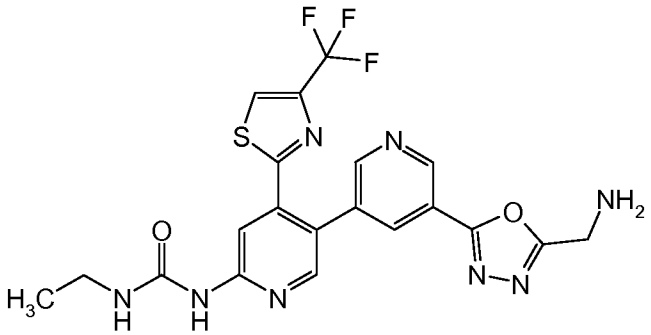
MS (EI) $(M+H)^+$ 533 for $C_{23}H_{26}F_3N_8O_3S$ $(M-H)^-$ 531 for $C_{23}H_{24}F_3N_8O_3S$;

^{1}H NMR (DMSO-*d6*) δ: 9.57 (s, 1 H), 9.23 (d, *J*=2.07 Hz, 1 H), 9.00 (d, *J*=1.51 Hz, 3 H), 8.77 (d, *J*=2.07 Hz, 0 H), 8.60 (s, 0 H),8.42 (s, 0 H), 8.34 (t, *J*=1.88 Hz, 0 H), 8.26 (s, 1 H), 7.52 - 7.61 (m, 0 H), 4.74 (d, *J*=4.52 Hz, 1 H), 3.17 - 3.27 (m, 2 H), 2.33 - 2.43 (m, 1 H), 1.11(t, *J*=7.25 Hz, 3 H), 1.06 (d, *J*=6.78 Hz, 3 H), 0.94 (d, *J*=6.78 Hz, 3 H);

^{19}F-NMR (DMSO-*d6*) δ: -62.60 (s, 3 F);

Example 281

1-(5'-(5-(aminomethyl)-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



A solution of (9H-fluoren-9-yl)methyl (5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)methylcarbamate (Example 269, 40 mg, 0.06 mmol) in 1,4-dioxane (10 mL) was treated with piperidine (2 mL, 0.06 mmol), and stirred for 1 hour at room temperature, solvents were removed under reduced pressure. The residue was dissolved in methanol (5 ml) and treated with HCl (4 M in dioxane, 0.4 ml), the solution was diluted with ethyl acetate and the resulting solid was isolated by filtration to afford the HCl salt of the title compound as a white solid.

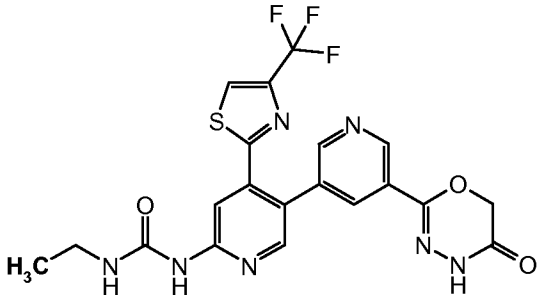
MS (EI) $(M+H)^+$ 491 for $C_{20}H_{18}F_3N_8O_2S$ $(M-H)^-$ 489 for $C_{20}H_{16}F_3N_8O_2S$;

^{1}H NMR (DMSO-*d6*) δ: 9.66 (br. s., 1 H), 9.22 (s, 1 H), 8.97 (br. s., 3 H), 8.75 (d, *J*=1.88 Hz, 1 H), 8.60 (s, 1 H), 8.41 (s, 1 H), 8.38(d, *J*=1.70 Hz, 1 H), 8.29 (s, 1 H), 7.63 (br. s., 1 H), 4.51 (d, *J*=5.09 Hz, 2 H), 3.17 - 3.29 (m, 2 H), 1.17 (t, *J*=6.97 Hz, 3 H);

^{19}F-NMR (DMSO-*d6*) δ: -62.56 (s, 3 F)

Example 282

1-ethyl-3-(5'-(5-oxo-5,6-dihydro-4H-1,3,4-oxadiazin-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



Potassium carbonate (200 mg, 1.45 mmol) was added to a solution of 1-(5'-(2-(2-chloroacetyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Intermediate 464, 130 mg, 0.25 mmol) in DMF (3 ml) and the resulting solution was heated to 60 °C for 210 minutes. The reaction was then diluted with ethyl acetate (50 ml), water (20 ml), and saturated ammonium chloride (40 ml). The layers separated and the aqueous phase extracted with ethyl acetate (2x50 ml). The combined organics were washed with brine, dried over magnesium sulfate, filtered, and the solvents removed under reduced pressure. The resulting residue was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in methylene chloride to give 26 mg of the title compound as a white powder.

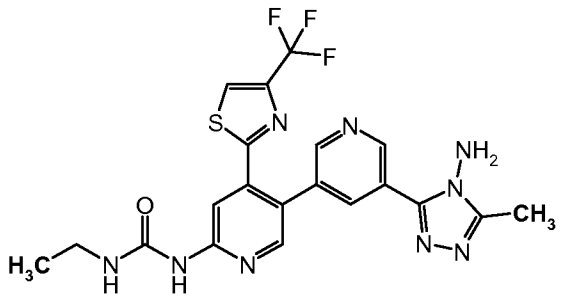
MS (EI) $(M+H)^+$ 492 for $C_{20}H_{17}F_3N_7O_3S$ $(M-H)^-$ 490 for $C_{20}H_{15}F_3N_7O_3S$;

^{1}H NMR (DMSO-*d*6) δ : 11.19 (s, 1 H), 9.49 (s, 1 H), 8.95 (br. s., 1 H), 8.56 (br. s., 2 H), 8.34 (s, 1 H), 8.22 (s, 1 H), 8.03 (br. s., 1H), 7.57 (br. s., 1 H), 4.80 (s, 2 H), 3.12 - 3.27 (m, 2 H), 1.10 (t, J=6.97 Hz, 3 H);

^{19}F-NMR (DMSO-*d*6) δ: -62.45 (s, 3 F)

Example 283

1-(5'-(4-amino-5-methyl-4H-1,2,4-triazol-3-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



A solution of 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 9, 250 mg, 0.55 mmol), 1,1-dimethoxy-N,N-

dimethylethanamine (0.5 mL, 0.55 mmol) in methanol (5 mL), was stirred at RT for 17 hours, hydrazine (0.2 mL, 0.55 mmol) was added and the suspension was stirred at RT for 10 hours, a small amount of insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in dichloromethane to give 60 mg of the title compound as a tan solid.

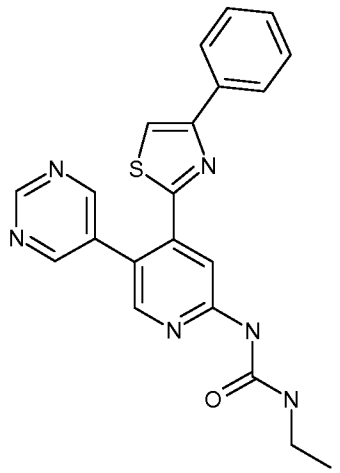
MS (EI) $(M+H)^+$ 490 for $C_{20}H_{19}F_3N_9OS$ $(M-H)^-$ 488 for $C_{20}H_{17}F_3N_9OS$;

^{1}H NMR (DMSO-*d*6) δ: 9.51 (s, 1 H), 9.23 (d, *J*=1.88 Hz, 1 H), 8.59 (d, *J*=2.07 Hz, 1 H), 8.56 (s, 1 H), 8.34 - 8.41 (m, 2 H), 8.26 (s,1 H), 7.60 (t, *J*=5.18 Hz, 1 H), 6.06 (s, 2 H), 3.14 - 3.27 (m, 2 H), 2.38 (s, 3 H), 1.11 (t, *J*=7.16 Hz, 3 H);

^{19}F-NMR (DMSO-*d*6) δ: -62.35 (s, 3 F)

Example 284

1-Ethyl-3-(4-(4-phenylthiazol-2-yl)-5-(pyrimidin-5-yl)pyridin-2-yl)urea



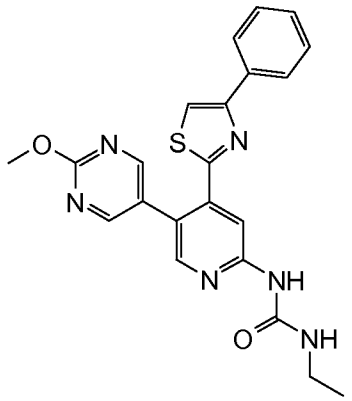
To a nitrogen-purged mixture of 1-(5-bromo-4-(4-phenylthiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 16, 125 mg, 0.31 mmol) in DME (3 mL) were added pyrimidin-5-ylboronic acid (46.1 mg, 0.37 mmol), sodium bicarbonate (52.1 mg, 0.62 mmol) and water (1 mL), followed by tetrakis(triphenylphosphine)palladium(0) (71.6 mg, 0.06 mmol). The mixture was microwaved for 60 min at 110°C. The solvent was evaporated from the reaction mixture. The crude mass was washed with ethyl acetate and purified on reverse phase preparative HPLC to yield pure 1-ethyl-3-(4-(4-phenylthiazol-2-yl)-5-(pyrimidin-5-yl)pyridin-2-yl)urea (28.0 mg, 22.45 %) as white solid powder.

MS (ES$^+$): 402.9 for $C_{21}H_{18}N_6OS$

^{1}H NMR δ(DMSO D6): 1.1(t, 3H), 3.2(qn, 2H), 7.29-7.43 (m, 3H), 7.58 (t, 1H), 7.70 (d, 2H), 8.23 (s, 2H), 8.35 (s, 1H), 8.80 (s, 2H), 9.20 (s, 1H), 9.48 (s, 1H)

Example 285

1-Ethyl-3-(5-(2-methoxypyrimidin-5-yl)-4-(4-phenylthiazol-2-yl)pyridin-2-yl)urea



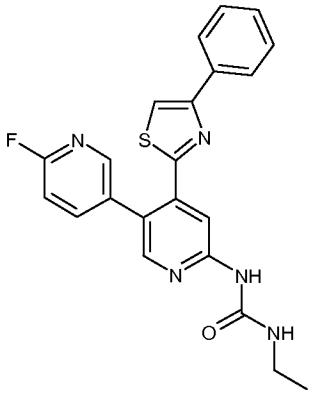
To a nitrogen-purged mixture of 1-(5-bromo-4-(4-phenylthiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 16, 125 mg, 0.31 mmol) in DME (3 mL) were added 2-methoxypyrimidin-5-ylboronic acid (57.3 mg, 0.37 mmol), sodium bicarbonate (52.1 mg, 0.62 mmol) and water (1 mL), followed by tetrakis(triphenylphosphine)palladium(0) (71.6 mg, 0.06 mmol). The resulting mixture was microwaved for 60 min at 110°C. The solvent was evaporated from the reaction mixture, and the crude mass was washed with ethyl acetate and purified on reverse phase preparative HPLC to yield pure 1-ethyl-3-(5-(2-methoxypyrimidin-5-yl)-4-(4-phenylthiazol-2-yl)pyridin-2-yl)urea (40.0 mg, 29.8 %) as white solid powder.

MS (ES$^+$): 432.8 for $C_{22}H_{20}N_6O_2S$

^{1}H NMR δ(DMSO D6): 1.1(t, 3H), 3.2(qn, 2H), 4.0 (s, 3H), 7.32-7.45 (m, 3H), 7.61 (t, 1H), 7.78 (d, 2H), 8.24 (s, 1H), 8.27 (s, 1H), 8.30 (s, 1H), 8.61 (s, 2H), 9.40 (s, 1H)

Example 286

1-Ethyl-3-(6'-fluoro-4-(4-phenylthiazol-2-yl)-3,3'-bipyridin-6-yl)urea



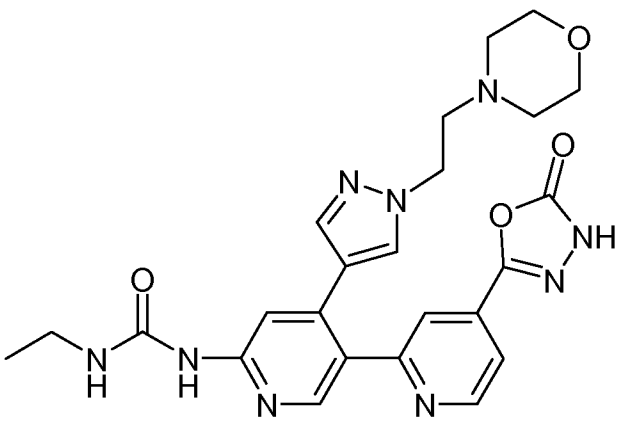
To a nitrogen-purged mixture of 1-(5-bromo-4-(4-phenylthiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 16, 125 mg, 0.31 mmol) in DME (3 mL) were added 6-fluoropyridin-3-ylboronic acid (65.5 mg, 0.46 mmol), sodium bicarbonate (52.1 mg, 0.62 mmol) and water (1 mL), followed by tetrakis(triphenylphosphine)palladium(0) (71.6 mg, 0.06 mmol). The resulting mixture was microwaved for 60 min at 110°C. When LCMS indicated that the required product had formed and absence of starting material, the solvent was evaporated from the reaction mixture. The crude mass was washed with ethyl acetate and purified on reverse phase preparative HPLC to yield pure 1-ethyl-3-(6'-fluoro-4-(4-phenylthiazol-2-yl)-3,3'-bipyridin-6-yl)urea (45.0 mg, 34.6 %).

MS (ES^+): 419.8 for $C_{22}H_{18}FN_5OS$

^{1}H NMR δ(DMSO D6): 1.1(t, 3H), 3.2(qn, 2H), 7.24-7.28 (m, 1H), 7.33-7.45 (m, 3H), 7.64 (t, 1H), 7.77-7.80 (m, 2H), 7.93-8.0 (m, 1H), 8.22-8.25 (m, 2H), 8.27 (d, 2H), 9.42 (b, 1H)

Example 287

1-ethyl-3- (4-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-5'-(5-oxo-4, 5-dihydro-1, 3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl) urea



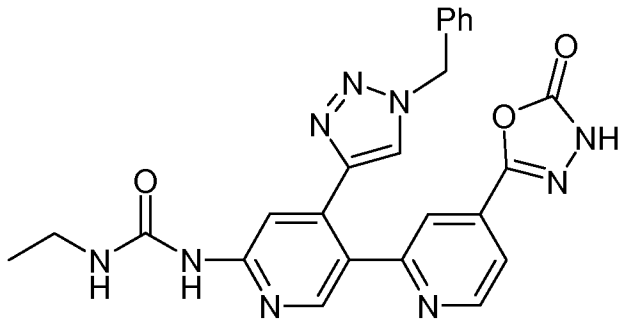
A mixture of (1-(4-bromo-5'- (5-oxo-4, 5-dihydro-1, 3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Intermediate 470, 54mg, 0.13 mmol), 4-(2-(4-(4,4,5,5-tetramethyl-1, 3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl) ethyl) morpholine (43.0 mg, 0.14 mmol), K_2CO_3 (27.6 mg, 0.20 mmol) and tetrkis(triphenylphosphine) palladium (0) (15.40 mg, 0.01 mmol) was suspended in DMF (3.5ml)/water (0.1ml) in a microwave reaction vassel, purged with N_2 and heated under microwave at 95°C for 2 hours. The crude sample was filtered through celite and the filtrate was concentrated and purified by column chromatography on silica gel, eluted with 10% methanol in dichloromethane to give the desired product (25 mg).

MS (ESP) 428.2 (MH^+) for $C_{24}H_{27}N_9O_4$.

^{1}H-NMR (DMSO-d_6): 1.10(t, 3H); 2.32(m, 2H); 2.38(m, 2H); 2.59(m, 1H); 2.68(t, 1H); 3.21(t, 1H); 3.45~3.55 (m, 4H); 4.13~4.24(m, 3H); 7.03 (s, 1H); 7.18 (s, 1H); 7.63 (t, 1H); 7.72 (t, 1H); 7.97 (s, 1H); 8.17 (s, 1H); 8.58 (d, 1H); 8.95 (s, 1H); 9.31 (s, 1H); 12.80 (br, 1H).

Example 288

1-ethyl-3- (4-(1-(2-morpholinoethyl)-1H-pyrazol-4-yl)-5'-(5-oxo-4, 5-dihydro-1, 3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl) urea



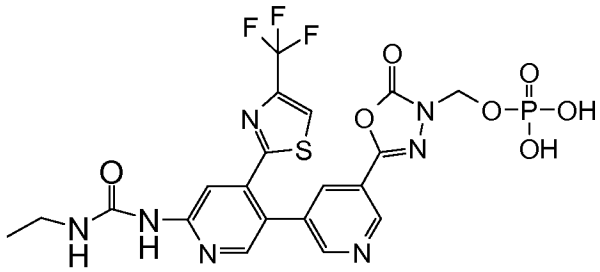
1-Ethyl-3- (4-ethynyl-5'- (5-oxo-4, 5-dihydro-1, 3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl) urea (Intermediate 475, 45mg, 0.13 mmol), 2,6-lutidine (0.022 ml, 0.19 mmol), copper (I) iodide (2.446 mg, 0.01 mmol) and (azidomethyl) benzene (18.19 mg, 0.13 mmol) were mixed in acetonitrile (10 ml) and NMP (1 ml) and stirred at 65 °C overnight. The reaction mixture was diluted with DCM and filtered through membrane. The filtrate was concentrated and purified by ISCO column (silica gel) eluted with MeOH/DCM (10:1), and then purified again with Gilson (C-18 column,10%~85%MeCN in H2O, 0.1% TFA) to give the desired product as a white solid(10mg).

MS (ESP) 484 (MH^+) for $C_{24}H_{21}N_9O_3$

^{1}H-NMR (DMSO-d_6): 1.10 (t, 3H); 3.20 (m, 2H); 5.51 (s, 2H); 7.15 (m, 2H); 7.27 (m, 3H); 7.72 (m, 1H); 7.87 (m, 2H); 7.98 (s, 1H); 8.24 (s, 1H); 8.62 (d, 1H); 8.94 (d, 1H); 9.42 (s, 1H); 12.82 (br, 1H).

Example 289

(5-(6'-(3-Ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-yl)methyl dihydrogen phosphate



To a solution of di-tert-butyl (5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-yl)methyl phosphate (Intermediate 487, 980 mg, 1.40 mmol) in dichloromethane (15 mL), TFA (5 mL, 64.90 mmol) was added and stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure to give a thick clear oil. The product was precipitated with 1:1 hexanes:ethyl acetate (50 mL) and the resulting mixture was stirred for 1 h. The precipitated product was collected by filtration and washed with ethyl acetate and acetonitrile. It was then dried under vacuum to give a white solid (740 mg).

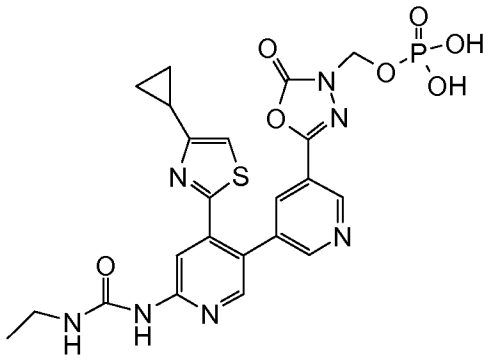
MS (ESP): 588 (M+1) for $C_{20}H_{17}F_3N_7O_7PS$.

^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.16-3.24 (m, 2H); 5.47 (d, 2H); 7.55 (b rs, 1H); 8.20 (d, 1H); 8.24 (s, 1H); 8.38 (s, 1H); 8.57 (s, 1H); 8.69 (d, 1H); 9.04 (d, 1H); 9.51 (s, 1H).

^{13}P-NMR (DMSO-d_6) δ: -3.08

Example 290

5-(4'-(4-cyclopropylthiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-yl)methyl dihydrogen phosphate



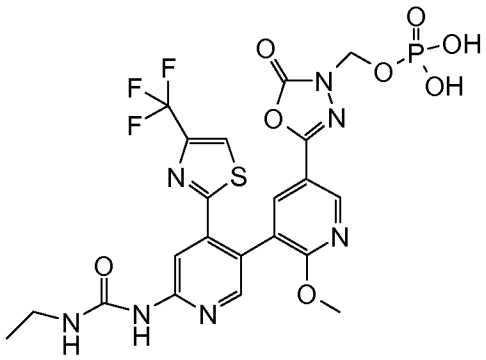
Di-tert-butyl (5-(4'-(4-cyclopropylthiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-yl)methyl phosphate Intermediate 21, 3.51 g, 5.23 mmol) was dissolved in DCM (15 mL). TFA (2.416 mL, 31.35 mmol) was added drop-wise. The reaction was stirred at 40°C for 1 h. The reaction mixture was cooled to room temperature, and concentrated under reduced pressure. The crude product was purified by reverse phase chromatography (0-35% MeOH in 0.1% NH_4OH/water). Collected fractions and concentrated under reduced pressure. The solid product was triturated from ACN/MeOH (1:4). The solid was filtered off, washed with ACN, dried. Isolation gave 707mg of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 560 for $C_{22}H_{22}N_7O_7PS$.

^1H NMR (300 MHz, d_6-DMSO): 0.45 (m, 2H), 0.77 (m, 2H), 1.11 (t, 3H), 1.97 (m, 1H), 3.21 (m, 2H), 5.46 (d, 2H), 7.41 (s, 1H), 7.62 (m, 1H), 8.10 (m, 2H), 8.28 (s, 1H), 8.60 (d, 1H), 8.99 (d, 1H), 9.49 (s, 1H).

Example 291

The following example was prepared in accordance to the procedure described for Example 290 using the starting materials indicated in the table.

Ex	Compound	Data	SM
291	(5-(6'-(3-ethylureido)-2-methoxy-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-yl)methyl dihydrogen phosphate 	LC/MS (ES^+)[$(M+H)^+$]: 618 for $C_{21}H_{19}F_3N_7O_8PS$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.21 (m, 2H), 3.60 (s, 3H), 5.48 (d, 2H), 7.55 (t, 1H), 8.16 (s, 1H), 8.21 (s, 1H), 8.31 (s, 1H), 8.54 (s, 1H), 8.71 (d, 1H), 9.46 (s, 1H). .	Intermediate 508

Example 292

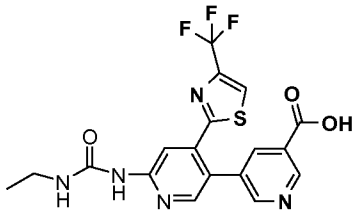
(5-(4'-(4-cyclopropylthiazol-2-yl)-6'-(3-ethylureido)-2-(1-methylpiperidin-4-yloxy)-3,3'-bipyridin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-yl)methyl dihydrogen phosphate

A solution of di-tert-butyl (5-(4'-(4-cyclopropylthiazol-2-yl)-6'-(3-ethylureido)-2-(1-methylpiperidin-4-yloxy)-3,3'-bipyridin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-yl)methyl phosphate (147 mg) in acetic acid/water (4:1, 4 mL) was allowed to stir at room temperature. The reaction mixture was then concentrated under vacuum, cool bath and then diluted with DIUF and concentrated (2-3×) until no odor of acetic acid remained. The product was then suspended in a small amount of water and lyophilized to give product.

MS (ESP): 673.2 ($M+H^+$) for $C_{28}H_{33}N_8O_8PS$.

Intermediate 1

6'-{[(Ethylamino)carbonyl]amino}-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylic acid



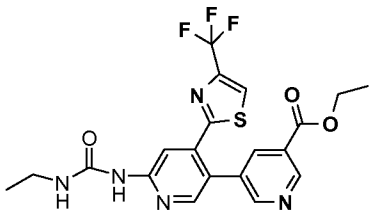
2N LiOH (1 mL) was added to a mixture of ethyl 6'-{[(ethylamino)carbonyl]amino}-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylate (Intermediate 2, 0.385 g, 0.83 mmol) in MeOH (3mL) and THF (3 mL). The resulting solution was stirred at room temperature for two hours. The solvent was removed and the residue was diluted with water and acidified with 1N HCl. The precipitated product was collected by filtration and washed with water and dried (0.297 g).

MS (ES) MH^+: 437 for $C_{18}H_{14}F_3N_5O_3S$;

^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 3.18- 3.24 (m, 2H); 7.57 (brs, 1H); 8.15-8.18 (m, 1H); 8.22 (s, 1H); 8.37 (s, 1H); 8.57 (s, 1H); 8.72 (s, 1H); 9.08 (s, 1H); 9.51 (s, 1H); 13.53 (s, 1H)

Intermediate 2

Ethyl 6'-{[(ethylamino)carbonyl]amino}-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylate



1-(5-Bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 3, 500 mg, 1.27 mmol), cesium carbonate (618 mg, 1.90 mmol), tetrakis(triphenylphosphine)palladium(0) (146 mg, 0.13 mmol), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (526 mg, 1.52 mmol) were taken in a microwave vial and

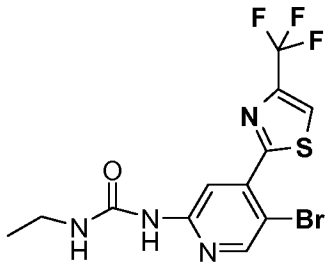
degassed with Argon. Then dioxane:water (4:1, 8 mL) was added to it and microwaved at 100 °C for half an hour. The reaction mixture was partitioned between water and ethyl acetate and layers separated. The organic layer was washed with saturated sodium bicarbonate solution, water, brine and dried over magnesium sulfate. The solvent was removed and the residue was purified by flash chromatography eluting with 2% MeOH in dichloromethane to 3 % MeOH in dichloromethane to give 330 mg of the title compound.

MS (ES) MH^+: 466 for $C_{20}H_{18}F_3N_5O_3S$;

^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 1.31(t , 3H); 3.18- 3.24 (m, 2H); 4.34 (q, 2H); 7.57 (brs, 1H); 8.16-8.18 (m, 1H); 8.21 (s, 1H); 8.39 (s, 1H); 8.58 (s, 1H); 8.75 (d, 1H); 9.10 (s, 1H); 9.52 (s, 1H).

Intermediate 3

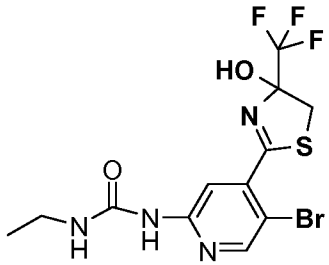
N-{5-Bromo-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}-*N'*-ethylurea



TFAA (1.128 mL, 7.99 mmol) followed by TEA (1.113 mL, 7.99 mmol) were added to a mixture of 1-(5-bromo-4-(4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 4, 2.2 g, 5.32 mmol) in DCM (30 mL). The reaction mixture was allowed to stir overnight at room temperature. Another 150 uL of TEA and TFAA were added and the reaction mixture was stirred for additional 3 h. Then the reaction was concentrated under reduced pressure and the residue was partitioned between water and ethyl acetate. The layers were separated and the organic layer was washed with sodium bicarbonate solution, water and brine. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The light yellow solid obtained was purified by normal phase chromatography (1% MeOH in dichloromethane to 3% MeOH in dichloromethane) to give the desired product (617 mg). MS (ESP): 396 (M+1) for $C_{12}H_{10}BrN_3O$; NMR: 1.07 (t, 3H); 3.11-3.17 (m, 2H); 7.24 (t, 1H); 8.35 (s, 1H); 8.50 (s, 1H); 8.77 (s, 1H); 9.34 (s, 1H).

Intermediate 4

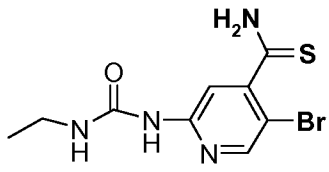
1-(5-Bromo-4-(4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-yl)-3-ethylurea



To a mixture of 5-bromo-2-(3-ethylureido)pyridine-4-carbothioamide (Intermediate 5, 1.1 g, 3.63 mmol) in acetonitrile (25 mL), was added 3-bromo-1,1,1-trifluoropropan-2-one (2.260 mL, 21.77 mmol) and the reaction mixture was heated at 80 °C for 4 h. A clear solution resulted within an hour. The solution was then concentrated under reduced pressure and the resulting residue was partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure to give light yellow solid, which, was purified by normal phase column chromatogrpahy (silica, 2% MeOH in dichloromethane to 5 % MeOH in dichloromethane) to give white solid (470 mg). MS (ESP): 414 (M+1) for $C_{12}H_{12}BrF_3N_4O_2S$; NMR: 1.06 (t, 3H); 3.12-3.18 (m, 2H); 3.60 (dd, 1H); 3.90 (dd, 1H); 7.13 (brs, 1H); 7.98 (s, 1H); 8.47 (s, 1H); 9.41 (s, 1H).

Intermediate 5

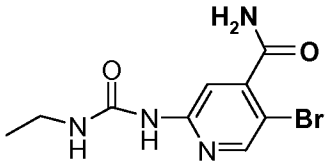
5-Bromo-2-(3-ethylureido)pyridine-4-carbothioamide



To a mixture of 5-bromo-2-(3-ethylureido)isonicotinamide (Intermediate 6, 1.25 g, 4.35 mmol) in THF (20 mL), was added Lawessons reagent (1.761 g, 4.35 mmol). The reaction mixture was then heated to 70 °C overnight. The solid that formed was collected by filtration and washed with THF to provide 1 g of desired product. MS (ESP): 304 (M+1) for $C_{19}H_{11}BrN_4OS$

Intermediate 6

5-Bromo-2-(3-ethylureido)isonicotinamide

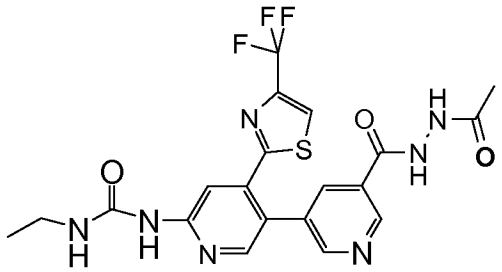


To a mixture of methyl 2-amino-5-bromoisonicotinate (3 g, 12.98 mmol) and chloroform (12 mL) in a microwave vial, isocyanatoethane (1.122 mL, 14.28 mmol) was added and the reaction mixture was heated at 110 °C for 3 h. The reaction mixture was concentrated under reduced pressure and 50 mL of 7N ammonia in MeOH was added. The resulting mixture was stirred at room temperature overnight, concentrated under reduced pressure and the resulting solid obtained was washed with acetonitrile to give a white solid (3.5 g).

MS (ESP): 287 (M+1) for $C_{19}H_{11}BrN_4O_2$

Intermediate 7

1-(5'-(2-Acetylhydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea

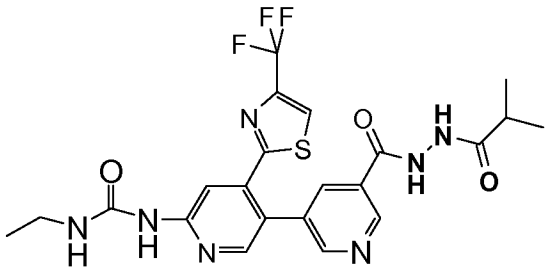


Triethylamine (0.054 mL, 0.39 mmol) and acetohydrazide (14.40 mg, 0.19 mmol) were added to a solution of 6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 1, 85 mg, 0.19 mmol) in DMF (1.5 mL). The mixture was stirred for 5 minutes and then HATU (89 mg, 0.23 mmol) was added. The resulting light yellow solution was stirred at room temperature for one hour then it was diluted with water. The aqueous layer was freeze dried and the solid obtained was extracted with THF and concentrated to give 184 mg of the crude product.

. MS (ESP): 494 (M+1) for $C_{20}H_{18}F_3N_7O_3S$

Intermediate 8

1-Ethyl-3-(5'-(2-isobutyrylhydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



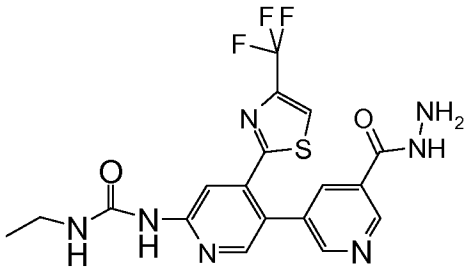
Intermediate 9 was synthesized according to the procedure described for Intermediate 7 using 6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid and isobutylhydrazide as the starting material.

MS (ESP): 522 (M+1) for $C_{22}H_{22}F_3N_7O_3S$

^{1}H-NMR (DMSO-d_6) δ: 1.06 (d, 6 H); 1.10 (t, 3H); 3.12-3.27 (m, 3H); 7.54 (brs, 1H); 8.19 (s, 1H); 8.24 (s, 1H); 8.36 (s, 1H); 8.56 (s, 1H); 8.64 (d, 1H); 9.04 (d, 1H); 9.49 (s, 1H); 9.94 (s, 1H); 10.54 (s, 1H).

Intermediate 9

1-Ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



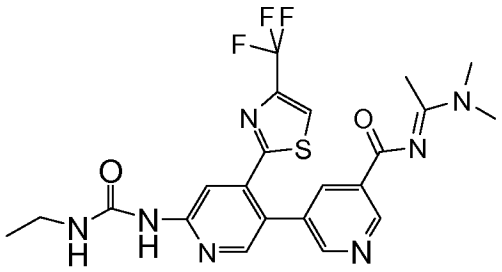
Ethyl 6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 2, 150 mg, 0.32 mmol) and hydrazine hydrate (31 mg, 0.97 mmol) were taken in ethanol (6 ml) and heated at 80 °C for 5 h. The reaction was cooled down and concentrated to give tan colored solid that was washed with 10% MeOH in dichloromethane and dried to give the title compound (101 mg).

MS (ESP): 452 (M+1) for $C_{18}H_{16}F_3N_7O_3S$

^{1}H-NMR (DMSO-d_6) δ: 1.09 (t, 3H); 3.10-3.25 (m, 2H); 4.57 (brs, 2H); 7.55 (brs, 1H); 8.13 (s, 1H); 8.23 (s, 1H); 8.34 (s, 1H); 8.55 (s, 1H); 8.59 (s, 1H); 8.99 (s, 1H); 9.48 (s, 1H); 9.97 (s, 1H).

Intermediate 10

N-(1-(Dimethylamino)ethylidene)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxamide



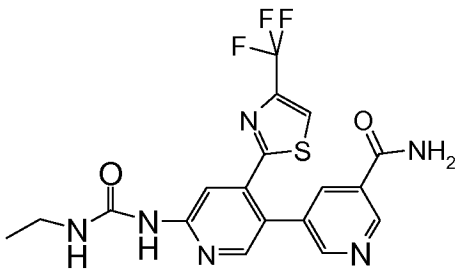
A mixture of 6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxamide (Intermediate 11, 270 mg, 0.62 mmol) in 1,1-dimethoxy-N,N-dimethylethanamine (10 mL, 68.40 mmol) was heated to 120 °C for one hour and cooled down. The solid was filtered off and washed with acetonitrile and dried to give product as off-white solid (178 mg).

MS (ESP): 506 (M+1) for $C_{22}H_{22}F_3N_7O_2S$

^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 2.29 (s, 3H); 3.11 (s, 3H); 3.14 (s, 3 H); 3.15-3.28 (m, 2H); 7.60 (brs, 1H); 8.14 (s, 1H); 8.20 (s, 1H); 8.37 (s, 1H); 8.55 (s, 1H); 8.63 (d, 1H); 9.16 (d, 1H); 9.48 (s, 1H).

Intermediate 11

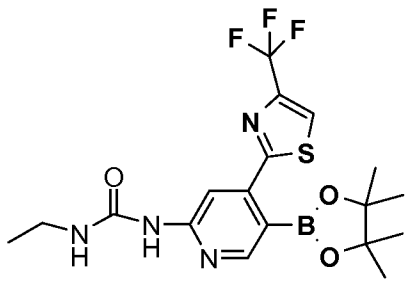
6'-(3-Ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxamide



Triethylamine (0.040 mL, 0.29 mmol) and 2-phenylpropan-2-amine (19.47 mg, 0.14 mmol) were added to a solution of 6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 1, 63 mg, 0.14 mmol) in DMF (1.5 mL). The reaction solution was stirred for 5 minutes and then 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (54.8 mg, 0.14 mmol) were added. The resulting light yellow solution was stirred at room temperature for 30 min. The desired product was precipitated with water and collected via filtration and dried to give an off-white solid (62 mg). The precipitate was taken in TFA (2 mL) and stirred overnight at room temperature and at 40 °C for another 3 h. The reaction was concentrated under reduced pressure and the residue was taken up in ethyl acetate and washed with sodium bicarbonate solution, water and brine. It was then dried over magnesium sulfate and concentrated to give white solid that was triturated with acetonitrile and dried to give the product (33 mg).
MS (ESP): 437 (M+1) for $C_{18}H_{15}F_3N_6O_2S$
^{1}H-NMR (DMSO-d_6): δ: 1.09 (t, 3H); 3.18- 3.24 (m, 2H); 7.45 (br s, 1H); 7.65 (s, 1H); 8.16 (s, 1H); 8.18 (s, 1H); 8.24 (s, 1H); 8.35 (s, 1H); 8.55 (d, 1H); 8.60 (d, 1H); 9.05 (s, 1H); 9.49 (s, 1H).

Intermediate 12

1-Ethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea

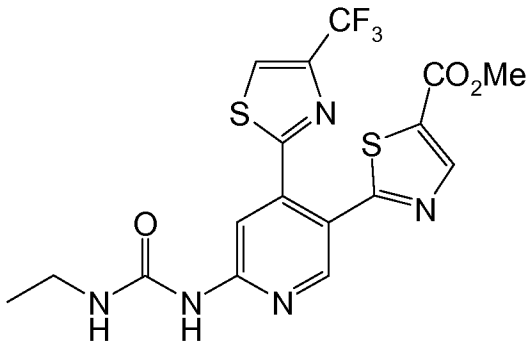


1-(5-Bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 3, 200 mg, 0.51 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (386 mg, 1.52 mmol), potassium acetate (149 mg, 1.52 mmol), and 1,1'-bis(diphenylphosphino)ferrocene-palladium dichloride (20.72 mg, 0.03 mmol) were taken in a microwave vial and degassed with argon. DMSO (4 mL) was added to the vial and the solution was heated at 90 °C for 5 h. The reaction mixture was partitioned between water and ethyl acetate. The layers were separated and the organic layer was back extracted three times with ethyl acetate. The organic layers were combined and washed with water and brine, then dried over magnesium sulfate

and concentrated under reduced pressure to give a light brown solid that was a mixture of the title compound (35%), {6-{[(ethylamino)carbonyl]amino}-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}boronic acid (25 %) and *N*-ethyl-*N*'-{4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}urea (25 %). The crude mixture was taken to the next step without further purification.

Intermediate 13

Methyl 2-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)thiazole-5-carboxylate

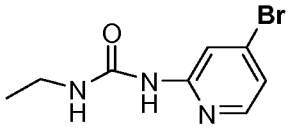


In a microwave reaction vessel, 1-ethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea (Intermediate 12, 415 mg, 0.94 mmol), methyl 2-bromothiazole-5-carboxylate (208 mg, 0.94 mmol) and cesium carbonate (119 mg, 1.13 mmol) were combined and suspended in dioxane / water. $Pd(PPh_3)_4$ (54.2 mg, 0.05 mmol) was added in a single portion. The vessel was sealed and heated to 100°C in the microwave for 60 minutes, then diluted with water and EtOAc. The aqueous and organic layers were separated, and the organic was dried over Na_2SO_4, filter and concentrate. Solids precipitated from solution upon concentrating and were collected and washed with minimal CH_2Cl_2. Analysis showed the solids to the desired reaction product. The mother liquor was concentrated further and the crude product was purified by flash column chromatography (0-100% EtOAc / hexanes). Isolation gave 128 mg of the title compound.

MS (ESP): 458 (M+1) for $C_{17}H_{14}F_3N_5O_3S_2$.

Intermediate 14

N-(4-Bromopyridin-2-yl)-*N*'-ethylurea



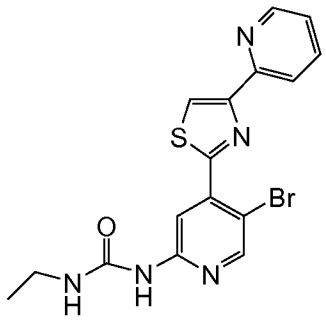
Isocyanatoethane (0.913 mL, 11.56 mmol) was added to a mixture of 4-bromopyridin-2-amine (2 g, 11.56 mmol) in chloroform (10 mL), and the mixture was heated at 110 °C for 2 h. The reaction mixture was concentrated under reduced pressure and triturated with acetonitrile to give a white solid (2.15 g).

MS (ESP): 243 (M+1) for $C_8H_{10}BrN_3O$

^{1}H-NMR (DMSO-d_6) δ: 1.08 (t, 3H); 3.12-3.18 (m, 2H); 7.16 (dd, 1H); 7.65 (brs, 1H); 7.74 (s, 1H); 8.07 (d, 1H); 9.29 (s, 1H)

Intermediate 15

N-[5-bromo-4-(4- pyridin -2-yl-1,3-thiazol-2-yl)pyridin-2-yl]-N'-ethylurea



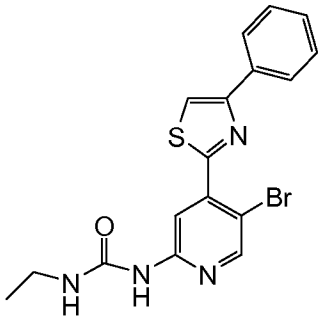
2-Bromo-1-pyridin-2-ylethanone (0.463 g, 1.65 mmol) was added to a mixture of 5-bromo-2-(3-ethylureido)pyridine-4-carbothioamide (Intermediate 5, 0.5 g, 1.65 mmol) in acetonitrile (3 mL), and the reaction mixture was heated to 80 ° for six hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (Silica gel, 10% MeOH in CH_2Cl_2). Isolation gave 670 mg of the title compound as an off-white solid.

LC/MS (ES^+)[$(M+H)^+$]: 404, 406 for $C_{16}H_{14}BrN_5OS$.

^{1}H NMR (300 MHz, d_6-DMSO): 1.08 (t, 3H), 3.18 (m, 2H), 7.33 (t, 1H), 7.42 (m, 1H), 7.98 (m, 1H), 8.16 (m, 1H), 8.51 (s, 1H), 8.55 (s, 1H), 8.59 (s, 1H), 8.67 (s, 1H), 9.39 (s, 1H).

Intermediate 16

N-[5-bromo-4-(4-phenyl-1,3-thiazol-2-yl)pyridin-2-yl]-N'-ethylurea



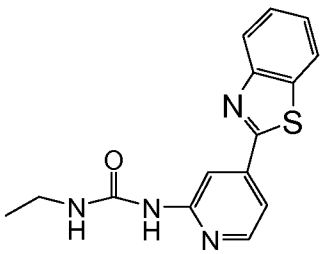
2-Bromo-1-phenylethanone (0.105 g, 0.53 mmol) was added to a mixture of 5-bromo-2-(3-ethylureido)pyridine-4-carbothioamide (Intermediate 5, 0.146 g, 0.48 mmol) in acetonitrile (3 mL), and the reaction mixture was heated to 80 ° for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting solids were filtered and washed with acetonitrile. Isolation gave 164 mg of the title compound as an off-white solid.

LC/MS (ES^+)[$(M+H)^+$]: 403, 405 for $C_{17}H_{15}BrN_4OS$.

^1H NMR (300 MHz, d_6-DMSO): 1.08 (t, 3H); 3.04-3.28 (m, 2H); 7.36 (m, 1H); 7.45 (m, 1H); 7.50 (t, 2H); 8.02-8.10 (m, 2H); 8.47 (s, 1H); 8.50 (s, 1H); 8.53 (s, 1H); 9.39 (s, 1H).

Intermediate 17

1-(4-(benzo[d]thiazol-2-yl)pyridin-2-yl)-3-ethylurea



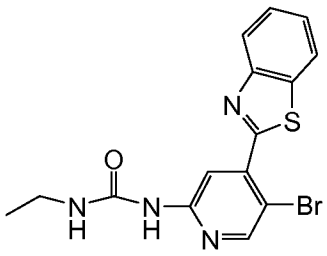
1-(4-bromopyridin-2-yl)-3-ethylurea (Intermediate 14, 0.50 g, 2.05 mmol), copper(I) iodide (0.039 g, 0.20 mmol), and $Pd(PPh_3)_4$ (0.118 g, 0.10 mmol) were combined in a microwave vial and degassed with nitrogen. DMF (4mL) was added to the vial followed by slow addition of 2-(tributylstannyl)benzo[d]thiazole (1.130 g, 2.66 mmol), and the reaction mixture was heated to 100 °C for 60 minutes. The reaction mixture was partitioned between water and ethyl acetate and layers separated. The organic layer was washed with saturated $NaHCO_3$, water, brine and dried over magnesium sulfate, and concentrated. The resulting solids were filtered and then washed with acetonitrile followed by chloroform to yield 140 mg of the title compound as an off-white solid.

LC/MS (ES^+)[$(M+H)^+$]: 299 for $C_{15}H_{14}N_4OS$.

^{1}H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.21 (m, 2H), 7.54 (t, 1H), 7.56 (d, 1H), 7.61 (m, 1H), 7.76 (t, 1H), 8.15 (d, 1H), 8.21 (d, 1H), 8.23 (s, 1H), 8.35 (d, 1H), 9.39 (s, 1H).

Intermediate 18

1-(4-(benzo[d]thiazol-2-yl)-5-bromopyridin-2-yl)-3-ethylurea



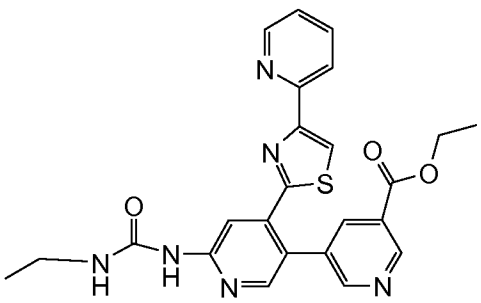
In a 25 mL pear-shaped flask 1-(4-(benzo[d]thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 17, 144 mg, 0.48 mmol) and 1-bromopyrrolidine-2,5-dione (96 mg, 0.54 mmol) were suspended in DMF (2 mL). The reaction mixture was heated to 80° C for 4 hrs. The reaction was partitioned between water and ethyl acetate. The layers were separated and the organic layer was washed with a 5 % sodium thiosulfate solution, followed by water and brine, then dried over magnesium sulfate and concentrated. The solids were tichurated with acetonitrile, filtered, washed and dried in vacuo. Isolation gave 160 mg of the title compound as an off-white solid.

LC/MS (ES^+)[$(M+H)^+$]: 377, 379 for $C_{15}H_{13}BrN_4OS$.

^{1}H NMR (300 MHz, d_6-DMSO): 1.09 (t, 3H), 3.17 (m, 2H), 7.27 (t, 1H), 7.58 (t, 1H), 7.65 (t, 1H), 8.19 (d, 1H), 8.27 (d, 1H), 8.42 (s, 1H), 8.58 (s, 1H), 9.44 (s, 1H).

Intermediate 19

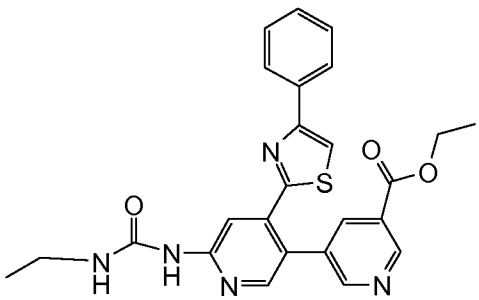
Ethyl 6'-{[(ethylamino)carbonyl]amino}-4'-(4-pyridin-2-yl-1,3-thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



In a microwave vessel, N-[5-bromo-4-(4-pyridin-2-yl -1,3-thiazol-2-yl)pyridin-2-yl]-N'-ethylurea (Intermediate 15, 0.1 g, 0.25 mmol), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (0.103 g, 0.37 mmol) and cesium carbonate (0.121 g, 0.37 mmol) were combined and suspended in a mixture of dioxane and water (4:1; 2.5 mL/0.5mL). The suspension was degassed and purged with nitrogen. $Pd(PPh_3)_4$ (0.014 g, 0.01 mmol) was added and the mixture was degassed and purged a second time. The reaction mixture was heated in the microwave at 100 °C for 60 minutes. The reaction was partitioned between water and ethyl acetate. The layers were separated, and the organic phase was washed with saturated $NaHCO_3$, water and brine, then dried over magnesium sulfate and concentrated. The resulting solids were filtered, then washed with acetonitrile followed by chloroform. Isolation gave 80 mg of the title compound as an off-white solid.
LC/MS $(ES^+)[(M+H)^+]$: 475 for $C_{24}H_{22}N_6O_3S$.
^1H NMR (300 MHz, $CHCl_3$): 1.11 (t, 3 H), 1.25 (t, 3 H), 3.21 (m, 2 H), 4.29 (m, 2 H), 7.35 (m, 1 H), 7.60 (s, 1H), 7.63 (s, 1H), 7.82 (m, 1 H), 8.26 (m, 2 H), 8.34 (s, 1 H), 8.36 (s, 1H), 8.60 (m, 1 H), 8.80 (d, 1 H), 9.10 (d, 1 H), 9.49 (s, 1 H).

Intermediate 20

Ethyl 6'-{[(ethylamino)carbonyl]amino}-4'-(4-phenyl-1,3-thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



In a microwave vessel, N-[5-bromo-4-(4-phenyl-1,3-thiazol-2-yl)pyridin-2-yl]-N'-ethylurea (Intermediate 16, 0.17 g, 0.42 mmol), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (0.14 g, 0.51 mmol) and cesium carbonate (0.165 g, 0.51 mmol) were combined and suspended in a mixture of dioxane and water (4:1; 2.5 mL/0.5mL). The suspension was degassed and purged with nitrogen. $Pd(PPh_3)_4$ (0.024 g, 0.02 mmol) was added and the mixture was degassed and purged a second time. The reaction mixture was heated in the

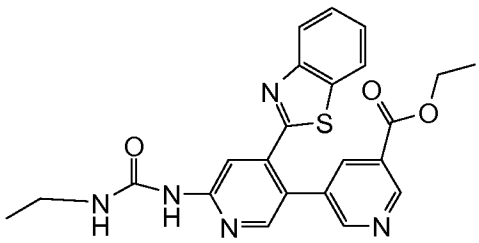
microwave at 100 °C for 60 minutes. The reaction was partitioned between water and ethyl acetate, the layers were separated, and the organic phase was washed with saturated $NaHCO_3$, water and brine, then dried over magnesium sulfate, and concentrated. The resulting solids were filtered, washed with acetonitrile followed by chloroform. Isolation gave 200 mg of the title compound as an off-white solid.

LC/MS (ES^+)[$(M+H)^+$]: 474 for $C_{25}H_{23}N_5O_3S$;

^1H NMR (300 MHz, $CHCl_3$): 1.10 (t, 3 H), 1.26 (t, 3 H), 3.21 (m, 2 H), 4.30 (q, 2 H), 7.25 (t, 1H), 7.63 (t, 1H), 7.35 (s, 1 H), 7.38 (s, 1H), 7.68 (d, 1H), 7.71 (d, 1H), 8.22 (s, 1 H), 8.24 (s, 1 H), 8.26 (t, 1H), 8.32 (t, 1 H), 8.77 (d, 1 H); 9.10 (d, 1 H), 9.48 (s, 1 H).

Intermediate 21

ethyl 4'-(benzo[d]thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate



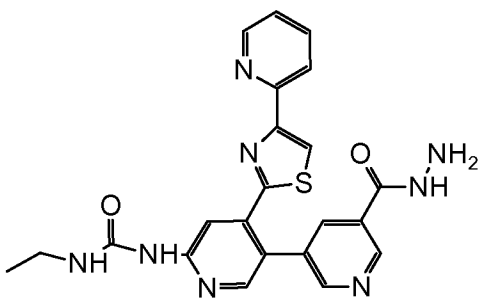
Intermediate 21 was synthesized as described for Intermediate 20 from Intermediate 18 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate.

LC/MS (ES^+)[$(M+H)^+$]: 448 for $C_{23}H_{21}N_5O_3S$.

^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.25 (t, 3H), 3.21 (m, 2H), 4.29 (q, 2H), 7.47 (m, 1H), 7.54 (m, 1H), 7.60 (t, 1H), 7.98 (m, 1H), 8.09 (m, 1H), 8.24 (t, 1H), 8.27 (s, 1H), 8.41 (s, 1H), 8.74 (d, 1H), 9.07 (d, 1H), 9.54 (s, 1H).

Intermediate 22

N-ethyl-N'-[5'-(hydrazinocarbonyl)-4-(4-pyridin-2-yl-1,3-thiazol-2-yl)-3,3'-bipyridin-6-yl]urea



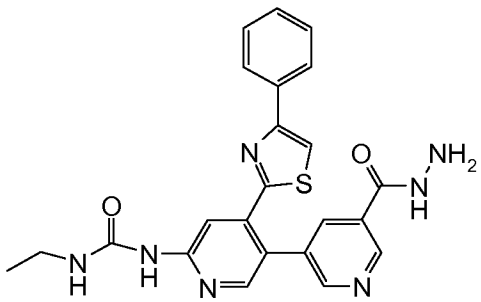
In a 25 mL round-bottom flask, ethyl 6'-{[(ethylamino)carbonyl]amino}-4'-(4-pyridin-2-yl-1,3-thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 19, 0.26 g, 0.55 mmol) and hydrazine hydrate (0.165 g, 3.29 mmol) were mixed in ethanol (6 mL), and stirred at 80°C overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was tichurated with 10% MeOH in DCM. The resulting solid was filtered, washed and dried in vacuo. Isolation gave 250 mg of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 461 for $C_{22}H_{20}N_8O_2S$.

^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.22 (m, 2H), 4.58 (s, 2H), 7.36 (m, 1H), 7.68 (s, 1H), 7.70 (s, 1 H), 7.86 (m, 1H), 8.21 (t, 1H), 8.32 (s, 1H), 8.33 (s, 1H), 8.36 (s, 1H), 8.60 (m, 1H), 8.64 (d, 1H), 9.0 (d, 1H), 9.52 (s, 1H), 10.02 (s, 1H).

Intermediate 23

1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-phenylthiazol-2-yl)-3,3'-bipyridin-6-yl)urea



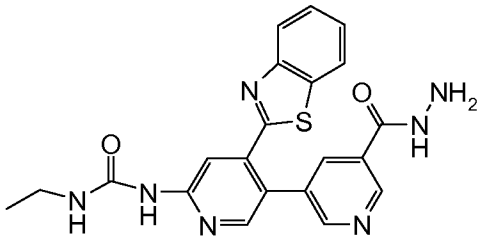
Intermediates 23 was synthesized according to the procedure described for Intermediate 22 from Intermediate 20 and hydrazine.

LC/MS (ES^+)[$(M+H)^+$]: 460 for $C_{23}H_{21}N_7O_2S$.

^1H NMR (300 MHz, d_6-DMSO): 1.12 (t, 3H), 3.22 (m, 2H), 4.58 (s, 2H), 7.34- 7.43 (m, 3H), 7.64 (t, 1H), 7.74 (d, 1H), 7.76 (d, 1H), 8.20 (t, 1H), 8.23 (s,1H), 8.28 (s, 1H), 8.32 (s, 1H), 8.63 (d, 1H), 9.01 (d, 1H), 9.48 (s, 1H), 10.01 (s, 1H).

Intermediate 24

1-(4-(benzo[d]thiazol-2-yl)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea



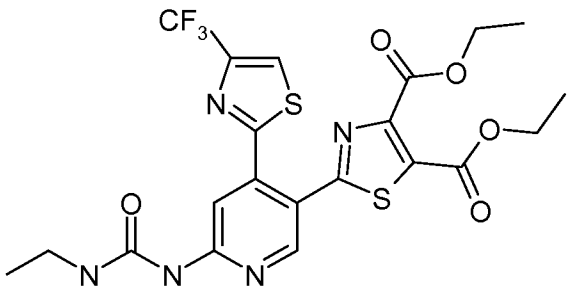
Intermediates 24 was synthesized according to the procedure described for Intermediate 22 from Intermediate 21 and hydrazine

LC/MS (ES^+)[$(M+H)^+$]: 434 for $C_{21}H_{19}N_7O_2S$.

^1H NMR (300 MHz, $CHCl_3$): 1.10 (t, 3 H), 3.16 (m, 2 H), 4.55 (s, 2 H), 7.48 (m, 1 H), 7.54 (m, 1H), 7.57 (m, 1H), 7.98 (d, 1 H), 8.09 (d, 1 H), 8.18 (t, 1 H), 8.28 (s, 1H), 8.38 (s, 1 H), 8.58 (d, 1 H), 8.97 (d, 1 H), 9.52 (s, 1 H), 9.98 (s, 1H).

Intermediate 25

diethyl 2-{6-[(ethylcarbamoyl)amino]-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-3-yl}-1,3-thiazole-4,5-dicarboxylate

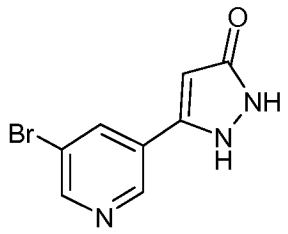


A slurry of crude 1-ethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea (Intermediate 12, 110 mg, 0.25 mmol), diethyl 2-chlorothiazole-4,5-dicarboxylate (WO2006087543, 66 mg, 0.25 mmol) and K_2CO_3 (86 mg, 0.625 mmol) in 1,4-dioxane-water (8+3 ml) was purged with nitrogen for 30 min at room temperature. Bis(triphenylphosphine)palladium dichloride (18mg, 0.025mmol) was added and the resulting mixture was stirred at 80-90 °C for 1.2 h. The reaction mixture was cooled, diluted with water (10mL), and extracted with EtOAc (2×80mL). The combined extracts were dried over sodium sulfate and concentrated to a residue under reduced pressure. The residue was purified via flash chromatography (50% EtOAc-heptane+10% EtOH) to afford 90 mg (67%) of desired product as light brown gum.

MS (ESP): 544 ($M+H^+$) for $C_{21}H_{20}F_3N_5O_5S_2$

Intermediate 26

5-(5-Bromopyridin-3-yl)-1H-pyrazol-3(2H)-one



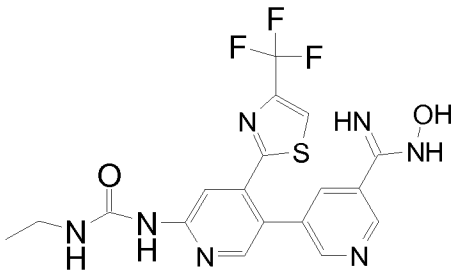
Hydrazine hydrate (0.110 mL, 3.49 mmol) was added to a mixture of methyl 3-(5-bromopyridin-3-yl)-3-oxopropanoate (300 mg, 1.16 mmol) in methanol (5 mL). The resulting mixture was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and the solid that formed was collected by filtration. The solid was washed with methanol and dried under vacuum to give the title compound as an off-white solid.

MS (ESP): 239 (M-1) for $C_8H_6BrN_3$

^{1}H-NMR (DMSO-d_6) δ: 6.12 (brs, 1H); 8.32 (s, 1H); 8.60 (s, 1H); 8.90 (s, 1H); 9.88 (br s, 1H); 12.33 (br s, 1H).

Intermediate 27

6'-(3-Ethylureido)-N'-hydroxy-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboximidamide

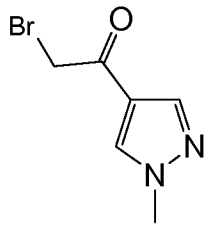


Hydroxylamine (0.040 mL, 0.65 mmol) (50% in water) was added to a suspension of 1-(5'-cyano-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Example 2, 180 mg, 0.43 mmol) in ethanol (10 mL), and the mixture was heated to 80 °C for 1.5 hours. The reaction mixture was concentrated under reduced pressure and the resulting residue was triturated with acetonitrile to give the title compound as a tan colored solid (180 mg).

MS (ESP): 452 (M+1) for $C_{19}H_{14}F_3N_7O_3S$

Intermediate 28

2-Bromo-1-(1-methyl-1H-pyrazol-4-yl)ethanone



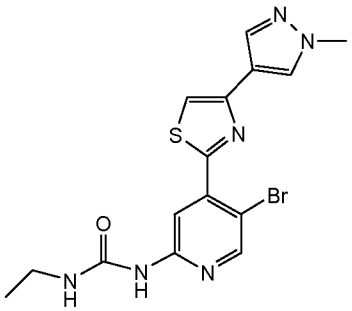
In a 25 mL flask, 1-(1-methyl-1H-pyrazol-4-yl)ethanone (0.602 g, 4.85 mmol) was dissolved in chloroform (20 mL). The colorless solution was made acidic with the addition of a few drops of HBr in acetic acid (3.92 mg, 0.05 mmol). A chloroform solution containing Br_2 (0.262 mL, 5.09 mmol) was added dropwise via an addition funnel. The reaction mixture was stirred at room temperature for 1 h, and then concentrated under reduced pressure. The crude solid was triturated in ethyl acetate, filtered, and dried *in vacuo*. The free base was obtained by triturating the product in 5% $NaHCO_3$ for 2 h. The solid was collected by filtration, washed with water, isopropyl alcohol and then dried *in vacuo*. Isolation gave 874 mg of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 204 for $C_6H_7BrN_2O$.

^1H NMR (300 MHz, d_6-DMSO): 3.88 (s, 3H), 4.56 (s, 2H), 7.99 (s, 1H), 8.47 (s, 1H).

Intermediate 29

1-(5-bromo-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea



In a 25 mL flask 5-bromo-2-(3-ethylureido)pyridine-4-carbothioamide (Intermediate 5, 478 mg, 1.58 mmol) and 2-bromo-1-(1-methyl-1H-pyrazol-4-yl)ethanone (Intermediate 28, 352 mg, 1.73 mmol) were suspended in EtOH (10 mL). The reaction mixture was heated at 80 °C

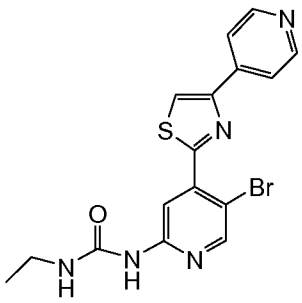
for 12 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting solid was collected by filtration and washed with acetonitrile. Isolation gave 640 mg of the title compound as an off-white solid.

LC/MS (ES^+)[$(M+H)^+$]: 407, 409 for $C_{15}H_{15}BrN_6OS$.

^1H NMR (300 MHz, d_6-DMSO): 1.08 (t, 3H), 3.18 (m, 2H), 3.9(s, 3H), 7.34 (m, 1H), 7.91 (s, 1H), 8.03 (s, 1H), 8.17 (s, 1H), 8.41 (s, 1H), 8.52 (s, 1H), 9.37 (s, 1H).

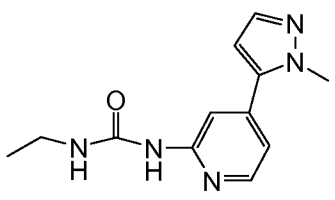
Intermediate 30

The following Intermediate was prepared according to the procedure described for Intermediate 29 using the starting materials indicated.

Int	Compound	Structure	Data	SM
30	1-(5-Bromo-4-(4-(pyridin-4-yl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea		LC/MS (ES^+)[$(M+H)^+$]: 404, 406 for $C_{16}H_{14}BrN_5OS$. ^1H NMR (300 MHz, d_6-DMSO): 1.09 (t, 3H), 3.16 (m, 2H), 7.21 (m, 1H), 8.53 (m, 1H), 8.55 (s, 2H) 8.59 (s, 1H), 9.0 (s, 1H), 9.02 (s, 1H), 9.23 (s, 1H), 9.42 (s, 1H).	Intermediate 5 and 2-bromo-1-pyridin-4-ylethanone

Intermediate 31

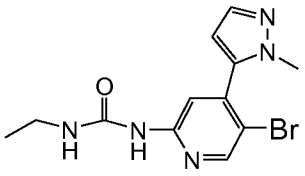
1-ethyl-3-(4-(1-methyl-1H-pyrazol-5-yl)pyridin-2-yl)urea



In a pear-shaped flask, 1-(4-bromopyridin-2-yl)-3-ethylurea (Intermediate 14, 0.3 g, 1.23 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.281g, 1.35 mmol), $Pd_2(dba)_3$ (0.113g, 0.12 mmol), 2-dicyclohexylphosphino-2',4',6'-tri-iso-propyl-1,1'-biphenyl (0.176g, 0.37 mmol), Na_2CO_3 (0.156g, 1.47 mmol) were combined and suspended in a mixture of acetonitrile and water (5:1; 7 mL/1.4 mL). The suspension was degassed and purged with nitrogen. The reaction mixture was heated at 90 °C for 60 min., then concentrated under reduced pressure, and partitioned between water and ethyl acetate. The organic phase was washed with water and brine, and then dried over magnesium sulfate. The mother liquor was concentrated under reduced pressure. The resulting solid was filtered and washed with acetonitrile. Isolation gave 146 mg of the title compound as an off-white solid.
LC/MS (ES^+)[$(M+H)^+$]: 246 for $C_{12}H_{15}N_5O$.
^1H NMR (300 MHz, d_6-DMSO): 1.08 (t, 3H), 3.19 (m, 2H), 3.9(s, 3H), 6.53 (d, 1H), 7.11 (m, 1H), 7.51 (d, 1H), 7.56 (s, 1H), 7.97 (m, 1H), 8.26 (d, 1H), 9.26 (s, 1H).

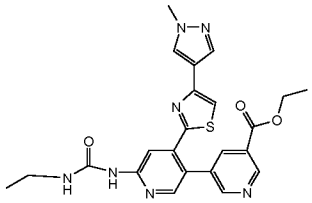
Intermediate 32

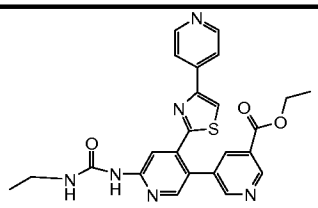
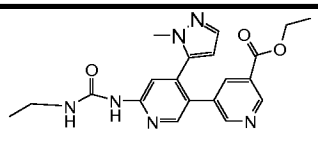
The following intermediate was prepared in accordance to the procedure described for Intermediate 18 using the starting materials indicated in the table.

Int	Compound	Structure	Data	SM
33	1-(5-bromo-4-(1-methyl-1H-pyrazol-5-yl)pyridin-2-yl)-3-ethylurea		LC/MS (ES^+)[$(M+H)^+$]: 324, 326 for $C_{12}H_{14}BrN_5O$. ^1H NMR (300 MHz, d_6-DMSO): 1.08 (t, 3H), 3.18 (m, 2H), 3.80 (s, 3H), 7.07 (m, 1H), 7.55 (s, 1H), 7.70 (s, 1H), 7.85 (m, 1H), 8.34 (d, 1H), 9.34 (s, 1H).	Intermediate 31 and 1-bromopyrrolidine-2,5-dione

Intermediate 33-35

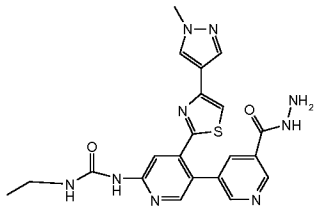
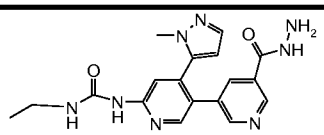
The following intermediates were prepared in accordance to the procedure described for Intermediate 20 using the starting materials indicated in the table.

Int	Compound	Structure	Data	SM
33	Ethyl 6'-(3-ethylureido)-4'-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate		LC/MS (ES^+)[$(M+H)^+$]: 478 for $C_{23}H_{23}N_7O3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.10 (t, 3H), 1.29 (t, 3H), 3.21 (m, 2H), 3.83 (s, 3H), 4.32 (m, 2H), 7.60 (s, 1H), 7.61 (m, 1H), 7.76 (s, 1H), 7.92 (s, 1H), 8.17 (s, 1H), 8.24 (m, 1H), 8.31 (s, 1H), 8.74 (m, 1H), 9.09 (m, 1H), 9.47 (s, 1H).	Intermediate 29 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate, cesium carbonate, $Pd(PPh_3)_4$

Int	Compound	Structure	Data	SM
34	Ethyl 6'-(3-ethylureido)-4'-(4-(pyridin-4-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate		LC/MS (ES^+)[$(M+H)^+$]: 475 for $C_{24}H_{22}N_6O3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.27 (t, 3H), 3.22 (m, 2H), 4.32 (m, 2H), 7.61 (m, 1H), 7.66 (m, 2H), 8.27 (m, 2H), 8.36 (s, 1H), 8.57 (s, 1H), 8.59 (m, 2H), 8.79 (d, 1H), 9.11 (d, 1H), 9.50 (s, 1H).	Intermediate 30 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate, cesium carbonate, $Pd(PPh_3)_4$
35	ethyl 6'-(3-ethylureido)-4'-(1-methyl-1H-pyrazol-5-yl)-3,3'-bipyridine-5-carboxylate		LC/MS (ES^+)[$(M+H)^+$]: 395 for $C_{20}H_{22}N_6O3$. ^1H NMR (300 MHz, d_6-DMSO): 1.07 (t, 3H), 1.26 (t, 3H), 3.17 (m, 2H), 3.77 (s, 3H), 4.27 (m, 2H), 7.0 (m, 1H), 7.39 (s, 1H), 7.94 (m, 1H), 7.96 (m, 1H), 8.08 (s, 1H), 8.34 (m, 1H), 8.71 (m, 1H), 8.80 (m, 1H), 9.31 (s, 1H).	Intermediate 32 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate, cesium carbonate, $Pd(PPh_3)_4$

Intermediates 36-37

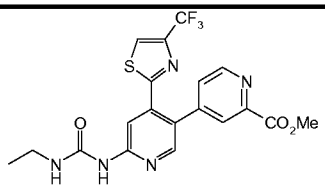
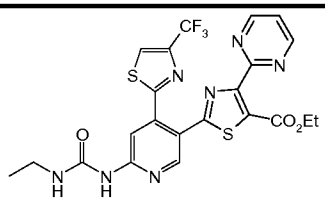
The following intermediates were prepared in accordance to the procedure described for Intermediate 22 using the starting materials indicated in the table.

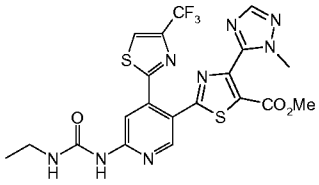
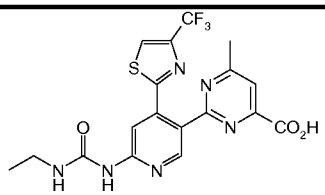
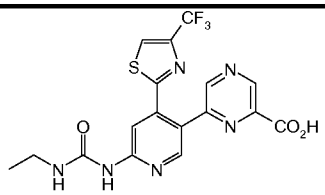
Int	Compound	Structure	Data	SM
36	1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea		LC/MS (ES^+)[$(M+H)^+$]: 464 for $C_{21}H_{21}N_9O_2S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.22 (m, 2H), 3.85 (s, 3H), 4.56 (m, 2H), 7.63 (m, 1H), 7.65 (s, 1H), 7.76 (s, 1H), 7.94 (s, 1H), 8.17 (m, 1H), 8.20 (m, 1H), 8.30 (s, 1H), 8.59 (d, 1H), 8.98 (d, 1H), 9.46 (s, 1H), 9.98 (s, 1H).	Intermediate 34 and hydrazine hydrate
37	1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(1-methyl-1H-pyrazol-5-yl)-3,3'-bipyridin-6-yl)urea		LC/MS (ES^+)[$(M+H)^+$]: 381 for $C_{18}H_{20}N_8O_2$.	Intermediate 35 and hydrazine hydrate

Intermediate 38-42

The following intermediates were prepared in accordance to the procedure described for Intermediate 20 using the starting materials indicated in the table.

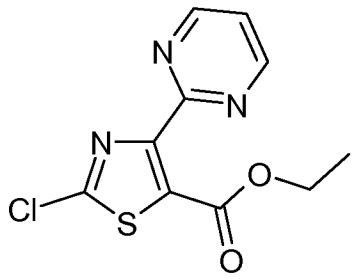
Int	Compound	Structure	Data	SM

Int	Compound	Structure	Data	SM
38	methyl 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate		LC/MS $(ES^+)[(M+H)^+]$: 452 for $C_{19}H_{16}F_3N_5O_3S$. ^1H NMR (300 MHz, CDCl3): 1.22 (t, 3H), 3.41 (m, 2H), 3.95 (s, 3H), 7.32 (d, 1H), 7.53 (s, 1H), 7.73 (s, 1H), 8.01 (s, 1H), 8.18 (s, 1H), 8.67 (d, 1H), 8.94 (broad s, 1H), 9.81 (broad s, 1H).	Intermediate 12 and methyl 4-bromopicolinate
39	Ethyl 2-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-(pyrimidin-2-yl)thiazole-5-carboxylate		LC/MS $(ES^+)[(M+H)^+]$: 550 for $C_{22}H_{18}F_3N_7O_3S_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.01 (q, 6H), 3.14 (m, 2H), 4.08 (q, 2H), 7.39 (m, 1H), 7.52 (t, 1H), 8.08 (s, 1H), 8.68 (s, 1H), 8.72 (s, 1H), 8.84 (d, 2H), 9.66 (s, 1H).	Intermediate 12 and Intermediate 45

Int	Compound	Structure	Data	SM
40	methyl 2-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazole-5-carboxylate		LC/MS (ES^+)[$(M+H)^+$]: 539 for $C_{20}H_{17}F_3N_8O_3S_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.03 (t, 3H), 3.11 (m, 2H), 3.62 (s, 3H), 3.70 (s, 3H), 7.52 (m, 1H), 8.00 (s, 1H), 8.05 (s, 1H), 8.67 (s, 1H), 8.72 (s, 1H), 9.67 (s, 1H).	Intermediate 12 and Intermediate 44
41	methyl 2-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-6-methylpyrimidine-4-carboxylate		LC/MS (ES^+)[$(M+H)^+$]: 453 for $C_{18}H_{15}F_3N_6O_3S$	Intermediate 12 and methyl 2-chloro-6-methylpyrimidine-4-carboxylate
42	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)pyrazine-2-carboxylic acid		LC/MS (ES^+)[$(M+H)^+$]: 439 for $C_{17}H_{13}F_3N_6O_3S$.	Intermediate 12 and 6-chloropyrazine-2-carboxylic acid

Intermediate 43

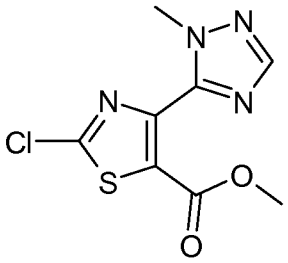
Ethyl 2-chloro-4-pyrimidin-2-yl-1,3-thiazole-5-carboxylate



Ethyl 2-amino-4-pyrimidin-2-yl-1,3-thiazole-5-carboxylate (Intermediate 47; 0.55 g, 2.2 mmol) was suspended in glacial acetic acid (20 ml) and concentrated HCl (30 ml). The solution was cooled to 0 °C and a solution of sodium nitrite in water (15 ml) was added dropwise. After stirring at 0 °C for 10 mins, the reaction was slowly warmed to room temperature and stirred for 1 hour. The reaction was monitored by LCMS and once complete, a solution of urea (0.25 g) in water (10 ml) was added dropwise. After stirring at room temperature for 30 mins, solvent was removed under reduced pressure. The residue was partitioned with sat. $NaHCO_3$ (aq) and EtOAc. The layers were separated and the water layer was back extracted with EtOAc (x3). The combined organic layers were drying with $MgSO_4$ and concentrating yielded an orange oil which was used without purification (0.20 g).
MS (ES) $(M+H)^+$: 270 for $C_{10}H_8ClN_3O_2S$.

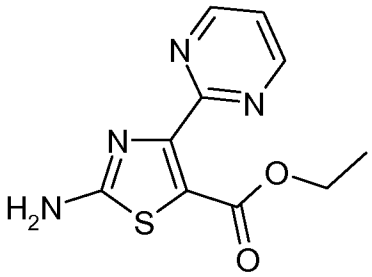
Intermediate 44

The following Intermediate was prepared according to the procedure described for Intermediate 43 from the starting materials indicated.

Int	Compound	Data	SM
44	Methyl 2-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-1,3-thiazole-5-carboxylate 	MS (ES) $(M+H)^+$: 259 for $C_8H_7ClN_4O_2S$ NMR: 3.92 (s, 6H), 8.04 (s, 1H).	Intermediate 46

Intermediate 45

Ethyl 2-amino-4-pyrimidin-2-yl-1,3-thiazole-5-carboxylate



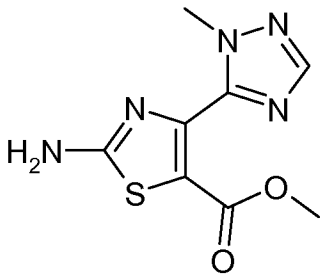
A suspension of ethyl 2-iodo-3-oxo-3-pyrimidin-2-ylpropanoate (Intermediate 47; 1.73 g, 5.4 mmol) and thiourea (0.62 g, 8.1 mmol) in EtOH was heated at reflux for 1 hour. After cooling to room temperature, the reaction was concentrated. The residue was suspended in water and basified with saturated aqueous Na_2CO_3. The resulting precipitate was filtered off and the filtrate was extracted with EtOAc (x3). The organic extracts were combined and dried with $MgSO_4$, then concentrated to an orange oil (0.55 g, 41%).

MS (ES) $(M+H)^+$: 251 for $C_{10}H_{10}N_4O_2S$

NMR: 0.97 (t, 3H), 3.95 (q, 2H), 7.55 (t, 1H), 7.94 (s, 1H), 8.85 (d, 1H), 9.05 (d, 1H).

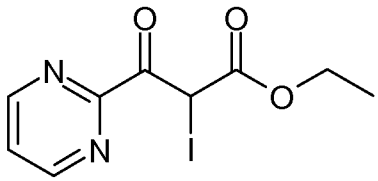
Intermediate 46

The following Intermediate was synthesized according to the procedure described for Intermediate 45 from the starting materials indicated.

Int	Compound	Data	SM
46	Methyl 2-amino-4-(1-methyl-1H-1,2,4-triazol-5-yl)-1,3-thiazole-5-carboxylate 	MS (ES) $(M+H)^+$: 240 for $C_8H_9N_5O_2S$ NMR: 3.61 (s, 3H), 3.71 (s, 3H), 7.96 (s, 1H), 8.10 (s, 2H).	Intermediate 48

Intermediate 47

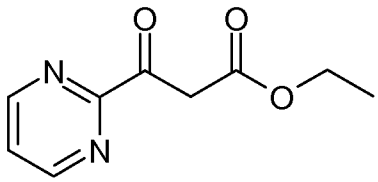
Ethyl 2-iodo-3-oxo-3-pyrimidin-2-ylpropanoate



To a suspension of ethyl 3-oxo-3-pyrimidin-2-ylpropanoate (Intermediate 48; 1.19 g, 6.1 mmol) in EtOAc was added *N*-iodosuccinamide (1.38 g, 6.1 mmol) and Amberlyst-15 resin (1.19 g). After stirring at room temperature for 30 mins, LCMS shows a mixture of desired product and bis-iodinated product. The reaction mixture was filtered to remove the Amberlyst-15 resin, and the filtrate was concentrated to an orange oil which was then suspended in diethyl ether. The resulting precipitate was filtered and washed with ether. The filtrate was concentrated to an orange oil to provide the desired product (1.73 g, 89%).
MS (ES) $(M+H)^+$: 321 for $C_9H_9IN_2O_3$

Intermediate 48

Ethyl 3-oxo-3-pyrimidin-2-ylpropanoate



To a solution of pyrimidine-2-carboxylic acid (0.99 g, 7.98 mmol) in anhydrous THF (20 ml) was added carbonyl diimidazole (1.55 g, 9.57 mmol) and the suspension was heated at reflux for 2 hours. The mixture was then cooled to room temperature and used without workup or

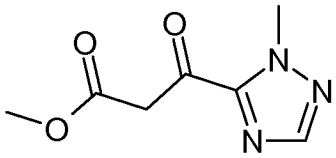
purification. In a separate flask, mono-ethyl malonate (0.94 ml, 7.98 mmol) was suspended in anhydrous THF (20 ml) and cooled to 0 °C. Methyl magnesium bromide (5.32 ml, 15.96 mmol, 3.0 M in diethyl ether) was added dropwise. After stirring at 0 °C for 20 mins, the crude imidazolide solution prepared earlier was added slowly. The reaction was then heated at reflux overnight. After cooling to room temperature, the reaction mixture was diluted with water and acidified with concentrated HCl to pH 5. The solution was extracted with EtOAc (x3), dried with $MgSO_4$ and concentrated to a yellow oil (1.19 g, 77%). NMR showed a 2:1 mixture of the keto:enol forms.

MS (ES) $(M+H)^+$: 195 for $C_9H_{10}N_2O_3$

NMR: 1.13-1.29 (t, 3H), 4.05-4.28 (q, 2H), 4.18 (s, 2H), 7.62-7.76 (t, 1H), 8.95-9.06 (d, 2H), 11.79 (s, 4H).

Intermediate 49

Methyl 3-(1-methyl-1*H*-1,2,4-triazol-5-yl)-3-oxopropanoate

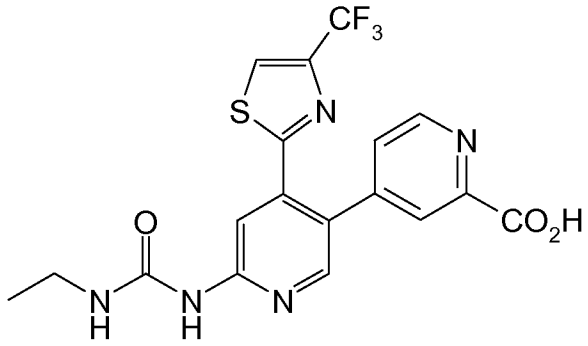


NaH (7.84 g, 196 mmol of a 60% dispersion in oil) was added portionwise to a solution of 6.18 g (34.5 mmol) of 1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethanone (Ohta, S.; Kawasaki, I.; Fukuno, A.; Yamashita, M.; Tada, T.; Kawabata, T. *Chem. Pharm. Bull.* (1993), 41(7), 1226-31) in 100 ml dimethylcarbonate. The mixture was heated to 90 °C for 2 hour forming a thick slurry. After cooling to room temperature, the mixture was slowly transferred to 1N HCl over ice. The pH of the mixture was brought to about 7 with $NaHCO_3$ before being saturated with NaCl and extracted 4 times with EtOAc. The EtOAc was dried ($MgSO_4$) and concentrated to give an oil that was chromatographed on silica gel (100% DCM followed by gradient elution to 50% EtOAc in DCM). The product (5.3 g) was obtained as an oil.

NMR: 3.78 (s, 3H), 4.11 (s, 2H), 4.22 (s, 3H), 7.94 (s, 1H).

Intermediate 50

6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylic acid:



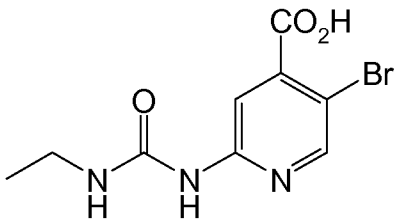
Methyl 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 38, 90 mg, 0.20 mmol) was dissolved in THF (2 mL) and methanol (2 mL). 1N LiOH (0.219 mL, 0.22 mmol) was added in a single portion, and the reaction mixture was heated to reflux for 15 min. The reaction mixture was cooled to room temperature and acidified with 2N HCl. The solid that precipitated was collected by filtration, washed with water and then dried *in vacuo*. Isolation gave 60 mg of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 438 for $C_{18}H_{14}F_3N_5O_3S$.

^1H NMR (300 MHz, d_6-DMSO): 1.09 (t, 3H), 3.19 (m, 2H), 7.53 (t, 1H), 7.56 (d, 1H), 7.86 (s, 1H), 8.14 (s, 1H), 8.37 (s, 1H), 8.59 (s, 1H), 8.68 (d, 1H), 9.53 (s, 1H).

Intermediate 51

5-bromo-2-(3-ethylureido)isonicotinic acid:



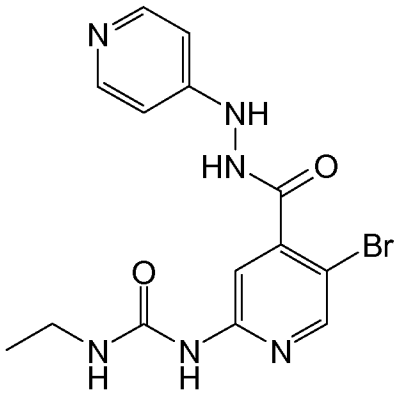
Methyl 5-bromo-2-(3-ethylureido)isonicotinate (Intermediate 6, 1 g, 3.31 mmol) was suspended in THF (5 mL) and methanol (5 mL). 1N LiOH (5 mL, 5.00 mmol) was added in a single portion, and the reaction was heated to reflux. The reaction mixture was cooled to room temperature and acidified with 2N HCl. The product precipitated from solution with the addition of water. The solid was collected by filtration and washed with water and dried *in vacuo* to give 843 mg of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 288, 290 for $C_9H_{10}BrN_3O_3$.

^{1}H NMR (300 MHz, d_6-DMSO): 1.07 (t, 3H), 3.16 (m, 2H), 7.28 (t, 1H), 7.92 (s, 1H), 8.42 (s, 1H), 9.38 (s, 1H), 14.02 (broad s, 1H).

Intermediate 52

1-(5-bromo-4-(2-isonicotinoylhydrazinecarbonyl)pyridin-2-yl)-3-ethylurea:



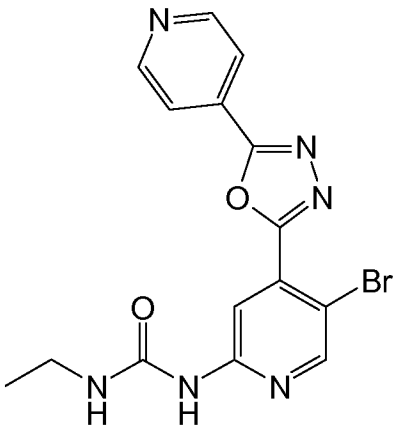
5-Bromo-2-(3-ethylureido)isonicotinic acid (Intermediate 51, 500 mg, 1.74 mmol) and HATU (792 mg, 2.08 mmol) were dissolved in DMF (5 mL) and DIEA (0.905 mL, 5.21 mmol). The solution was stirred for 5 min. Isonicotinohydrazide (238 mg, 1.74 mmol) was added in a single portion. The reaction mixture was diluted with water and acidified to pH 2 with 2N HCl. The solid that formed was collected by filtration, washed with water and dried *in vacuo*. Isolation gave 538 mg of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 407, 409 for $C_{15}H_{15}BrN_6O_3$.

^{1}H NMR (300 MHz, d_6-DMSO): 1.09 (t, 3H), 3.15 (m, 2H), 3.32 (d, 1H), 7.32 (m, 1H), 7.82 (m, 2H), 7.85 (s, 1H), 8.42 (s, 1H), 8.79 (m, 2H), 9.43 (s, 1H), 10.75-11.01 (d, 1H).

Intermediate 53

1-(5-bromo-4-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)-3-ethylurea:

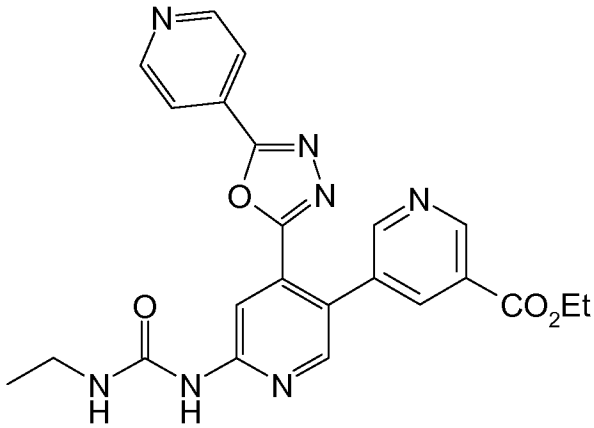


1-(5-Bromo-4-(2-isonicotinoylhydrazinecarbonyl)pyridin-2-yl)-3-ethylurea (Intermediate 52, 538 mg, 1.32 mmol) and triphenyl phosphine (693 mg, 2.64 mmol) were dissolved in methylene chloride (6 mL). Triethylamine (0.369 mL, 2.64 mmol) and carbon tetrabromide (876 mg, 2.64 mmol) were added sequentially. The solution was stirred at room temperature for 12 h, then diluted with water and stirred vigorously for 30 min. The organic and aqueous layers were separated and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The concentrate was dissolved in minimal DMSO and purified by Gilson HPLC. Isolation gave 105 mg of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 389, 390 for $C_{15}H_{13}BrN_6O_2$.

Intermediate 54

ethyl 6'-(3-ethylureido)-4'-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)-3,3'-bipyridine-5-carboxylate:



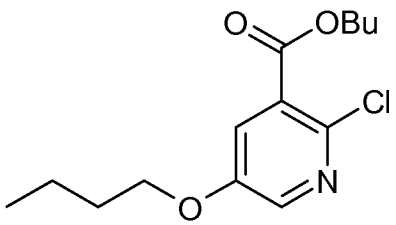
In a microwave reaction vessel, 1-(5-bromo-4-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 53, 105 mg, 0.27 mmol), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (82 mg, 0.30 mmol) and cesium carbonate (34.3 mg, 0.32 mmol) were combined and suspended in a 4:1 mixture of dioxane and water. $Pd(PPh_3)_4$ (15.59 mg, 0.01 mmol) was added in a single portion. The vessel was sealed, degassed, purged with nitrogen and heated to 100°C in the microwave for 60 min. The crude reaction mixture was concentrated to dryness. The resulting residue was dissolved in DMSO, filtered and then purified by Gilson HPLC (15-55% ACN / 0.1% TFA water in 14 minutes). Isolation gave 58 mg of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 460 for $C_{23}H_{21}N_7O_4$.

^1H NMR (300 MHz, d_6-DMSO): 1.05 (t, 3H), 1.23 (t, 3H), 3.16 (m, 2H), 4.29 (q, 2H), 7.38 (m, 1H), 7.63 (d, 2H), 8.30 (t, 1H), 8.37 (s, 1H), 8.45 (s, 1H), 8.76 (d, 2H), 8.83 (d, 1H), 9.08 (d, 1H), 9.53 (s, 1H).

Intermediate 55

Butyl 2-butoxy-5-iodonicotinate

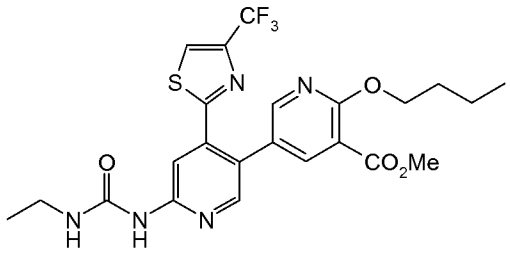


To a solution of methyl-2-chloro-5-iodonicotinate (1.0g, 3.37mmol) and butanol (0.74g, 10mmol) in THF (80mL) at 0 °C was added potassium hexamethyldisilizane (20mL, 0.5N in toluene) drop wise. Slight exotherm was observed. The mixture was stirred at -2-0 °C for 1h before quenching with acetic acid (0.5mL) and 6N HCl (0.3ml). The mixture was diluted with water (80 mL), and extracted with EtOAc (2×150mL). Combined organic extracts were dried and concentrated. The residue was purified via flash chromatography (10% EtOAc-heptane) to afford 1.2g (~90%) of oil as a mixture (~1:2) of methyl and butyl esters.

MS (ESP): 244.1 ($M+H^+$) for $C_{11}H_{14}ClNO_3$, methyl ester, 286.0 ($M+H^+$) for $C_{14}H_{20}ClNO_3$

Intermediate 56

Butoxy-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



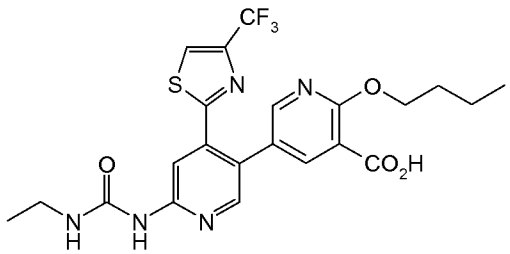
A slurry of 1-ethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea (Intermediate 12, 1.4g, 3.18mmol), 2-butoxy-5-iodonicotinate ester mix (Intermediate 57, 1.2g, 3.18mmol) and K_2CO_3 (1.32g, 9.6mmol) in 1,4-dioxane-H_2O (25+9mL) was bubbled with N_2 for 30 min at rt. Bis(triphenylphosphine)palladium dichloride (0.23g, 0.32mmol) was added and the resulting mixture was stirred at 70-80 °C for 1h. The mixture was cooled to room temperature, diluted with water (50mL), and the layers were separated. The organic layer was extracted with EtOAc (2×150mL). Combined organic layers were dried and concentrated. The residue was purified via flash chromatography (10-70% EtOAc-heptane+1% EtOH) to afford 1.6g (~70%) of a mixed ester of 6-butoxy-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate as light brown gum.

MS (ESP): 524.1 (MH^+) for $C_{23}H_{24}F_3N_5O_4S$

^1H NMR (d_6-DMSO):δ 0.91 (t, 3H), 1.10 (t, 3H), 1.39-1.48 (m, 2 H), 1.65-1.76 (m, 2H), 3.18 (q, 2 H), 3.75 (s, 3H), 4.36 (t, 2H), 7.57 (bt, 1H), 8.02 (d, 1 H), 8.20 (s, 1H), 8.29 (m, 2H), 8.53 (s, 1H), 9.44 (s, 1H).

Intermediate 57

6-butoxy-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid



The mixed ester of 6-butoxy-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 56, ~100 mg) was stirred in 1 N NaOH (~0.5 mL) in THF (~ 3 mL) at 50 °C until no starting materials remained by LCMS. The solvent was evaporated and the sodium salt of product was purified via a reverse-phase column with

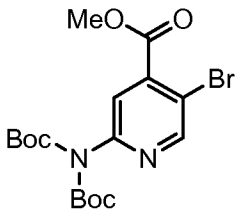
5-70% MeOH-water. The product fractions were concentrated and neutralized with HCl (1.0N) to give 6-butoxy-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid.

MS (ESP): 510.0 ($M+H^+$) for $C_{22}H_{22}F_3N_5O_4S$

^1H NMR (d_6-DMSO): δ 0.93 (t, 3H), 1.10 (t, 3H), 1.39-1.48 (m, 2 H), 1.65-1.76 (m, 2H), 3.19 (q, 2 H), 4.27 (t, 2H), 7.63 (d, 1H), 7.84 (t, 1 H), 7.93 (d, 1H), 8.17 (s, 1H), 8.30 (s, 1H), 8.55 (d, 1H), 9.62 (s, 1H).

Intermediate 58

Methyl 2-(bis(tert-butoxycarbonyl)amino)-5-bromoisonicotinate



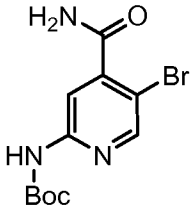
To a 1 L round bottom flask was charged methyl 2-amino-5-bromoisonicotinate (43.7 g, 189 mmol) and *tert*-butanol (360 mL). The mixture was kept at 30°C, then DMAP (1.40 g, 11.48 mmol, 6%) and di-*tert*-butyl dicarbonate (105 g, 481 mmol, 2.54 eq) were added. The resulting mixture was heated to 80°C for 30 minutes, then the reaction mixture was allowed to cool to room temperature and ethanol was added. The precipitated that formed was collected by filtration and washed with ethanol. After drying under vacuum overnight (~16 hour) at 25°C, the first crop was obtained as 67.8 g of light brown solid (90.2%).

MS (ESP): 277.1 (MH^+-Boc-tBu) for $C_{17}H_{23}BrN_2O_6$

^1H NMR (300 MHz, $CDCl_3$): δ 1.5 (s, 18H), 4.0 (s, 32H), 7.7 (s, 1H), 8.7 (s, 1H).

Intermediate 59

tert-butyl 5-bromo-4-carbamoylpyridin-2-ylcarbamate



A solution of methyl 2-(bis(tert-butoxycarbonyl)amino)-5-bromoisonicotinate (Intermediate 58, 67.8 g, 157.3 mmol) in 7 N ammonia in methanol (600 mL) was allowed to stir at 40-

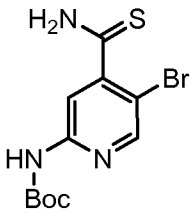
50°C in a sealed flask for overnight. The resulting mixture was evaporated to dryness and the crude product was directly used for the next step without further purification.

MS (ESP): 339.9 ($M+Na^+$) for $C_{11}H_{14}BrN_3O_3$

^1H NMR (300 MHz, DMSO-d_6): δ 1.47 (s, 9H), 7.82 (d, 2H), 8.07 (s, 1H), 8.41 (d, 1H), 10.2 (s, 1H).

Intermediate 60

tert-butyl 5-bromo-4-carbamothioylpyridin-2-ylcarbamate



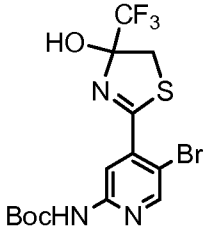
The crude tert-butyl 5-bromo-4-carbamoylpyridin-2-ylcarbamate (Intermediate 59, 157.3 mol) was treated with Lawesson's Reagent (65 g, 157.5 mmol) and tetrahydrofuran (500 mL). The resulting mixture was heated at reflux for 1 h, then it was allowed to stir at room temperature over the weekend. The mixture was concentrated to dryness *in vacuo* and toluene (~200 mL) was added. After initiating, a bright yellow solid precipitated, which was collected and washed with toluene, then dried in the vacuum oven at 50°C for 4 hours, yielding 49 g of a bright yellow solid (94%).

MS (ESP): 354.2 ($M+Na^+$) for $C_{11}H_{14}BrN_3O_2S$

^1H NMR (300 MHz, $CDCl_3$): δ 1.53 (s, 9H), 7.03 (br, 1H), 7.61 (br, 1H), 7.74 (br, 1H), 8.2 (s, 1H), 8.35 (s, 1H).

Intermediate 61

tert-butyl 5-bromo-4-(4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-ylcarbamate



To a 2 L round bottom flask was charged tert-butyl 5-bromo-4-carbamothioylpyridin-2-ylcarbamate (Intermediate 60, 48 g, 145 mmol) in tetrahydrofuran (800 mL), then solid sodium bicarbonate (24.4 g, 290 mmol) was added followed by 1,1,1-trifluoro-3-bromoacetone (31 mL, 290 mmol). The resulting mixture (yellow suspension) was allowed to stir at room temperature overnight. The

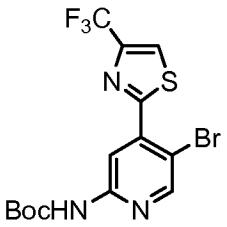
white suspension was filtered and the solid was washed with water (2.2~2.5 L). The white solid was dried under vacuum as the 1st crop (54.4, 85% yield). The mother liquor was concentrated to remove the tetrahydrofuran, filtered and washed to give after drying, 3.5 g white solid.

MS (ESP): 386.0 (M-Boc) for $C_{14}H_{15}BrF_3N_3O_3S$

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.6 (s, 9 H), 3.3 (br, 2H), 3.6 (d, 1H), 3.9 (d, 1H), 8.2 (s, 1H), 8.5 (s, 1H).

Intermediate 62

tert-butyl 5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-ylcarbamate



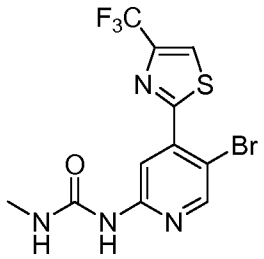
To a 2L round bottom flask was charged tert-butyl 5-bromo-4-(4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-ylcarbamate (Intermediate 61, 54.4 g, 123 mmol) and dimethoxyethane (800 mL). The mixture was chilled in an ice-water bath, then trifluoroacetic anhydride (68 mL, 502 mmol) and 2,6-lutidine (128 mL, 1.10 mol) were added simultaneously over 30 min. The temperature of the exothermic reaction was controlled below 6°C. The orange/yellow solution which resulted was allowed to stir in the ice-water bath for half an hour, then was warmed to room temperature for 2 h. The solution was concentrated to dryness, and the residue was triturated with methanol. The precipitated solid was collected and washed with more methanol, and dried under vacuum overnight, yielding 48.3 g of white solid as the 1st crop. The mother liquor was concentrated and triturated with methanol again, the 2nd crop was obtained as a light yellow solid (1.5 g). Totally 49.8 g of product was obtained in 95.4% yield.

MS (ESP): 368.0 (M-Boc) for $C_{14}H_{13}BrF_3N_3O_2S$

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.6 (s, 9H), 8.0 (s, 1H), 8.2 (br, 1H), 8.55 (s, 1H), 8.65 (s, 1H).

Intermediate 63

1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-methylurea

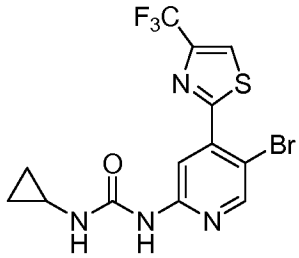
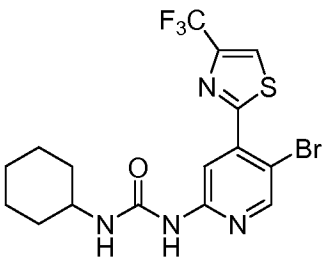


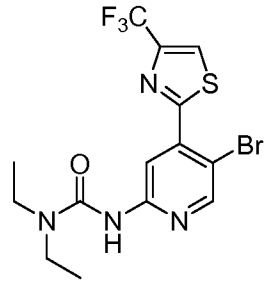
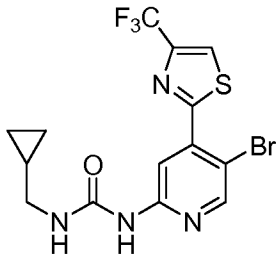
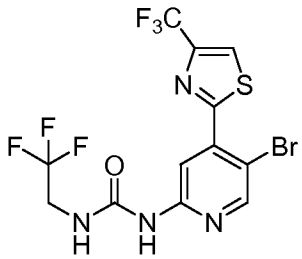
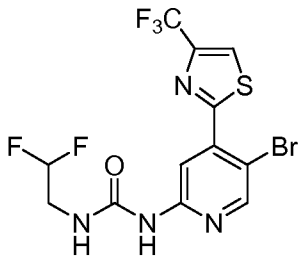
To a sealed tube was charged tert-butyl 5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-ylcarbamate (Intermediate 62, 1.2 g) with methylamine (15 mL, 2 M in methanol). The reaction mixture was heated at 145°C for 2h in a microwave. The mixture was concentrated to dryness to give desired product as a white solid (quantitative yield). The crude product was used directly for Suzuki couplings without further purification

MS (ESP): 381.0 (MH^+) for $C_{11}H_8BrF_3N_4OS$.

Intermediates 64-69

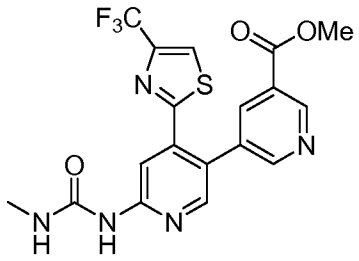
The following Intermediates were synthesized according to the procedure described for Intermediate 63 from the starting materials listed in the Table.

Int	Compound	Data	SM
64	1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-cyclopropylurea 	MS (ESP): 408.9 (MH^+) $C_{13}H_{10}BrF_3N_4OS$ ^1H NMR (300 MHz, CD_3OD): δ 0.56-0.65 (m, 2H), 0.80-0.85 (m, 2H), 2.65-2.75 (m, 1H), 7.55 (s, 1H), 8.21 (s, 1H), 8.55 (s, 1H)	Intermediate 62 and cyclopropyl amine
65	1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-cyclohexylurea 	MS (ESP): 450.9 (MH^+) for $C_{16}H_{16}BrF_3N_4OS$	Intermediate 62 and cyclohexyl amine

66	3-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-1,1-diethylurea 	MS (ESP): 424.9 (MH^+) for $C_{14}H_{14}BrF_3N_4OS$	Intermediate 62 and diethylamine
67	1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-(cyclopropylmethyl)urea 	MS (ESP): 423.0 (MH^+) for $C_{14}H_{12}BrF_3N_4OS$ ^{1}H NMR (300 MHz, CD_3OD): δ 0.25-0.30 (m, 2H), 0.55-0.65 (m, 2H), 1.01-1.10 (m, 1H), 3.20 (d, 2H), 7.80 (s, 1H), 8.10 (s, 1H), 8.57 (s, 1H)	Intermediate 62 and cyclopyanemethylamine
68	1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-(2,2,2-trifluoroethyl)urea 	MS (ESP): 450.9 (MH^+) for $C_{12}H_7BrF_6N_4OS$	Intermediate 62 and 1,1,1,-trifluroethylamine
69	1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-(2,2-difluoroethyl)urea 	MS (ESP): 432.9 (MH^+) for $C_{12}H_8BrF_5N_4OS$; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.80 (td, 2H), 5.99 (tt, 1H), 7.70 (s, 1H), 8.05 (s, 1H), 8.10 (s, br, 1H), 8.50(s, 1H), 9.30 (br, 1H)	Intermediate 62 and 1,1-difluroethylamine

Intermediate 70

Methyl 6'-(3-methylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



To a sealed tube was charged 1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-methylurea (Intermediate 63, 0.41 g, 1.07 mmol), trans dichlorobis(triphenylphosphine)palladium (II) (75 mg, 10mmol%), 1,4-dioxane (10 mL), sodium bicarbonate (180 mg, 2.14 mmol) in water (10 mL), and then methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (0.42 g, 1.61 mmol) was added. The resulting mixture was purged by nitrogen for 5 min then heated at 50°C for 2h (in a microwave). Based on LC, the reaction was incomplete and the mixture was further heated at 60 °C 1h (in a microwave). The resulting mixture was diluted with water, extracted ethyl acetate (3×), and the combined organic layers were dried over sodium sulfate. After concentration, the crude product was purified by Analogix to give the desired product as a white solid (200 mg, 42.7%).

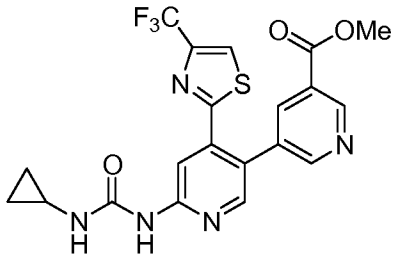
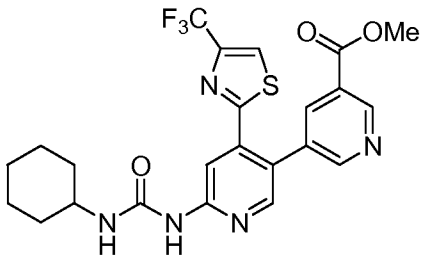
MS (ESP): 438.0 (MH^+) for $C_{18}H_{14}F_3N_5O_3S$

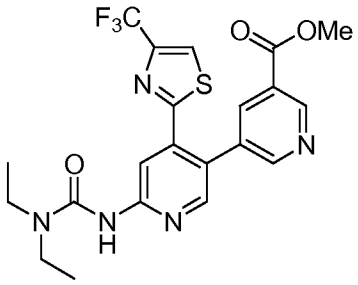
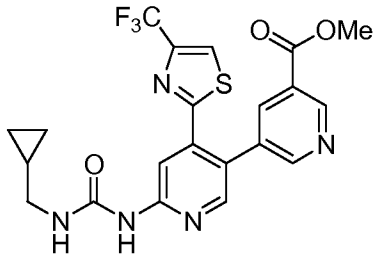
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.90 (s, 3H), 3.94 (s, 3H), 7.80 (s, 1H), 8.26 (t, 1H), 8.31 (t, 1H), 8.36 (t, , 1H), 8.65 (d, 1H), 9.12 (d, 1H)

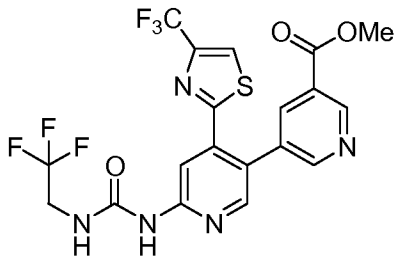
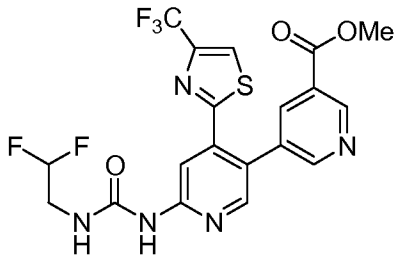
^{19}F NMR Spectrum (300 MHz, CD_3OD) -66.05

Intermediates 71-76

The following Intermediates were prepared according to the procedure described for Intermediate 70 from the starting materials indicated in the Table.

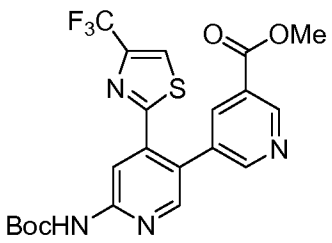
Int	Compound	Data	SM
71	methyl 6'-(3-cyclopropylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 464.1 (MH^+) for $C_{20}H_{16}F_3N_5O_3S$ ^1H NMR (300 MHz, CD_3OD): δ 0.57-0.60 (m, 2H), 0.77-0.80 (m, 2H), 2.65-2.75 (m, 1H), 3.94 (s, 3H), 7.97 (br, 1H), 8.25 (d, 1H), 8.30 (t, 1H), 8.35 (s, 1H), 8.65 (d, 1H), 9.12 (d, 1H) ^{19}F NMR (300 MHz, CD_3OD) -66.05	Intermediate 64 and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate
72	methyl 6'-(3-cyclohexylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 506.1 (MH^+) for $C_{23}H_{22}F_3N_5O_3S$ ^1H NMR (300 MHz, CD_3OD): δ 1.19-1.46 (m, 5H), 1.2-2.1 (m, 5H), 3.7 (br, 1H), 3.94 (s, 3H), 7.88 (s, 1H), 8.25 (d, 1H), 8.30 (t, 1H), 8.36 (d, 1H), 8.60 (d, 1H), 9.11 (d, 1H) ^{19}F NMR (300 MHz, CD_3OD) -66.04	Intermediate 65 and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

73	methyl 6'-(3,3-diethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 480.0 (MH^+) for $C_{21}H_{20}F_3N_5O_3S$ ^1H NMR (300 MHz, CD_3OD): δ 1.25 (t, 6H), 3.49 (q, 4H), 3.94 (s, 3H), 8.25 (d, 1H), 8.31 (t, 1H), 8.39 (d, 1H), 8.53 (d, 2H), 8.65 (d, 1H), 9.11 (d, 1H) ^{19}F NMR (300 MHz, CD_3OD) -66.04	Intermediate 66 and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate
74	methyl 6'-(3-(cyclopropylmethyl)ureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 478.2 (MH^+) for $C_{21}H_{18}F_3N_5O_3S$; ^1H NMR (300 MHz, CD_3OD): δ 0.27-0.31 (m, 2H), 0.51-0.58 (m, 2H), 1.07-1.20 (m, 1H), 3.20 (d, 2H), 3.95 (s, 3H), 7.88 (s, 1H), 8.25 (d, 1H), 8.31 (t, 1H), 8.37 (s, 1H), 8.66 (d, 1H), 9.12 (d, 1H); ^{19}F NMR (300 MHz, CD_3OD) -66.16	Intermediate 67 and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

75	methyl 6'-(3-(2,2,2-trifluoroethyl)ureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 506.1 (MH^+) for $C_{19}H_{13}F_6N_5O_3S$; ^{1}H NMR (300 MHz, CD_3OD): δ 3.95 (s, 3H), 4.06 (q, 2H), 7.91 (s, 1H), 8.26 (d, 1H), 8.32 (t, 1H), 8.39 (d, 1H), 8.66 (d, 1H), 9.13 (d, 1H); ^{19}F NMR (300 MHz, CD_3OD) -66.04 (s, 3F), -74.95 (t, 3F)	Intermediate 68 and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate
76	methyl 6'-(3-(2,2-difluoroethyl)ureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 488.1 (MH^+) for $C_{19}H_{14}F_5N_5O_3S$; ^{1}H NMR (300 MHz, CD_3OD): δ 3.71 (td, 2H), 3.94 (s, 3H), 5.99 (tt, 1H), 7.88 (s, 1H), 8.25 (d, 1H), 8.31 (t, 1H), 8.37 (d, 1H), 8.66 (d, 1H), 9.12 (d, 1H); ^{19}F NMR (300 MHz, CD_3OD) -66.04 (s, 3F), -125.33 (t, 1F), -125.53 (t, 1F)	Intermediate 69 and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

Intermediate 77

Methyl 6'-(tert-butoxycarbonylamino)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate

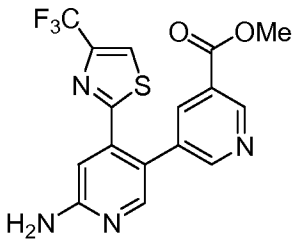


5

A solution of potassium carbonate (4 g, 28.9 mmol) in water (250 mL) was prepared and purged by N_2 for a few minutes. To a 1 L round bottom flask was charged tert-butyl 5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-ylcarbamate (Intermediate 62, 6 g, 14.2 mmol), trans dichlorobis(triphenylphosphine)palladium (II) (997 mg, 10mol%) and 1,4-dioxane (300 mL). The prepared potassium carbonate solution was added followed by methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (5.58 g, 21.2 mmol) and the mixture further diluted with 1,4-dioxane (200 mL). The resulting brown solution was purged by N_2 for a further ~10-15 min then heated to 55°C (reflux) for ~10-15 min. The brown solution became black. After 1h the reaction went to completion based on LCMS. The mixture was allowed to cool and was diluted by ethyl acetate (200 mL), then washed with brine twice. The combined aqueous layers were backwashed with ethyl acetate (400 mL), and the combined organic layers dried over sodium sulfate. After concentration, a gray solid was obtained. The crude solid was purified by a silica gel plug eluted with ethyl acetate/heptane (3:4 or 3:5). After concentration, the resulting solid was further triturated with ethanol to give 5.6 g white fluffy solid. The mother liquor was concentrated and triturated with ethanol to give a 2nd crop as a white solid (0.33 g). Totally 5.93 g of product was obtained (87.2%).
MS (ESP): 481.2 (MH^+) for $C_{21}H_{19}F_3N_4O_4S$
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (s, 9H), 3.9 (s, 3H), 7.6 (s, 1H), 7.8 (d, 1H), 8.30 (t, 1H), 8.35 (s, 1H), 8.5 (s, 1H), 8.6 (d, 1H), 9.2 (d, 1H).

Intermediate 78

methyl 6'-amino-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



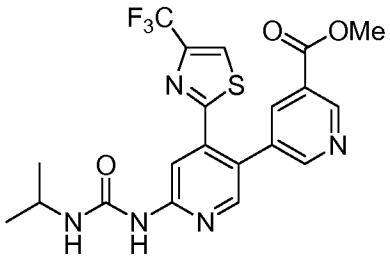
To a 250 mL round bottom flask was charged methyl 6'-(tert-butoxycarbonylamino)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 77, 1.6 g, 3.33 mmol) with 4 M HCl in 1,4-dioxane (110 mL), and the resulting clear solution was stirred at room temperature over the weekend (two days). Saturated sodium bicarbonate was added to the suspension was to neutralize the acid. The resulting clear solution was extracted with ethyl acetate (3×), and the combined organic layers were dried over sodium sulfate. After

concentration and drying, a yellow fluffy solid was obtained in quantitative yield which was used without purification.

MS (ESP): 381.0 (MH^+ average) for $C_{11}H_8BrF_3N_4OS$

Intermediate 79

methyl 6'-(3-isopropylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



To a sealed tube was charged methyl 6'-amino-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 78, 330 mg, 0.87 mmol) with chloroform (5 mL), then isopropyl isocyanate (0.5 mL) was added. The resulting mixture was heated at 50°C (oil bath) for 24 hours. The reaction was incomplete. More isopropyl isocyanate (1 mL) was added and the mixture heated at 50°C (oil bath) for another 3 days. The resulting suspension was concentrated to dryness and triturated by ethanol. After filtration and drying, a white solid was obtained (300 mg, 74.3%).

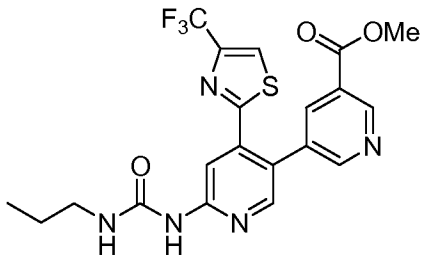
MS (ESP): 466.2 (MH^+) for $C_{20}H_{18}F_3N_5O_3S$

^{1}H NMR (300 MHz, CD_3OD): δ 1.24 (d, 6H), 3.93-4.02 (m, 1H), 3.93 (s, 3H), 7.88 (s, 1H), 8.24 (s, 1H), 8.30 (t, 1H), 8.35 (s, 1H), 8.64 (d, 1H), 9.11 (d, 1H)

^{19}F NMR (300 MHz, CD_3OD) -66.00

Intermediate 80

methyl 6'-(3-propylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



To a sealed tube was charged methyl 6'-amino-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 78, 350 mg, 0.921 mmol) with chloroform (5 mL), then propyl isocyanate (1.75 mL) was added. The resulting mixture was heated at 50°C (oil bath) for 4 days. The resulting suspension was concentrated to dryness and triturated by methanol. After filtration and drying, a white solid was obtained (257 mg, 60%).

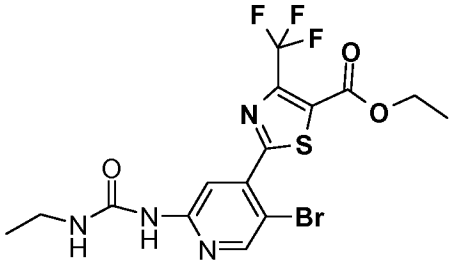
MS (ESP): 466.2 (MH^+) for $C_{20}H_{18}F_3N_5O_3S$

^{1}H NMR (300 MHz, CD_3OD): δ 0.99 (t, 3H), 1.58-1.66 (m, 2H), 3.29 (t, 2H), 3.94 (s, 3H), 7.84 (s, 1H), 8.24 (s, 1H), 8.30 (t, 1H), 8.35 (s, 1H), 8.64 (d, 1H), 9.11 (d, 1H)

^{19}F NMR (300 MHz, CD_3OD) -66.00

Intermediate 81

ethyl 2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-4-(trifluoromethyl)thiazole-5-carboxylate



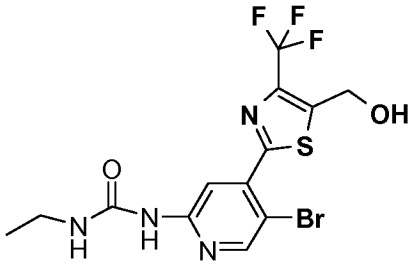
A suspension of 5-bromo-2-(3-ethylureido)pyridine-4-carbothioamide (Intermediate5, 5.0 g, 16.5 mmol), ethyl 2-chloro-3-keto-4,4,4-trifluorobutyrate (25 g, 114 mmol) in acetonitrile (250 mL) was heated at 60°C for 6 days. The solution was cooled triethylamine (12 mL, 87 mmol) was added followed by the dropwise addition of methane sulfonyl chloride (3.0 mL, 39 mmol). This mixture was then stirred at room temperature overnight. The solid was filtered, washed with water (500 mL) and dried in the vacuum oven at 50°C for 12 hours to give 3.2g (41%) of ethyl 2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-4-(trifluoromethyl)thiazole-5-carboxylate as a pale yellow solid.

MS (ESP): 467.1 and 468.9 ($M+H^+$) for $C_{15}H_{14}BrF_3N_4O_3S$

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08 (t, 3H), 1.34 (t, 3H), 3.17 (m, 2H), 4.40 (q, 2H), 7.20 (t, 1H), 8.54 (s, 1H), 8.59 (s, 1H), 9.43 (bs, 1H)

Intermediate 82

1-(5-bromo-4-(5-(hydroxymethyl)-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea



To a suspension of ethyl 2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-4-(trifluoromethyl)thiazole-5-carboxylate (Intermediate 81, 4.7 g, 10 mmol) in tetrahydrofuran (85 mL), was added lithium borohydride powder (653 mg, 30 mmol). The reaction was stirred for 3 hours at room temperature during which time the solution turned yellow and homogeneous. Water (50 mL) was then carefully added to the reaction and the organics were removed *in vacuo*. The remaining aqueous phase was extracted with ethyl acetate (3×, 50 mL). The organic extracts were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*. This gave 4.2g (92%) of 1-(5-bromo-4-(5-(hydroxymethyl)-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea as a pale yellow solid.

MS (ESP): 424.8 and 426.9 ($M+H^+$) for $C_{13}H_{12}BrF_3N_4O_2S$

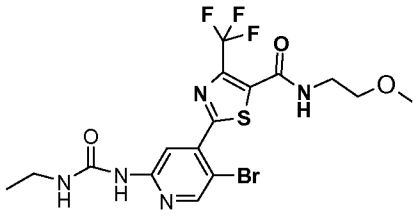
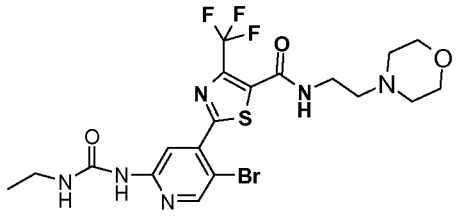
^1H NMR (300 MHz, DMSO-d_6): δ 1.08 (t, 3H), 3.17 (m, 2H), 4.93 (m, 2H), 6.37 (bt, 1H), 7.26 (bt, 1H), 8.38 (s, 1H), 8.54 (s, 1H), 9.38 (bs, 1H).

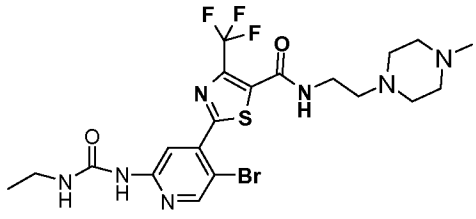
Intermediates 83-85

The following Intermediates were synthesized by the general procedure described below from the starting material indicated in the Table.

General Procedure

Ethyl 2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-4-(trifluoromethyl)thiazole-5-carboxylate (Intermediate 81, 0.5 g) and excess amine (neat or 4-6eq in ethanol solution) was heated to 80-90 °C in microwave for 3h. The solid that formed were collected by filtration and washed by methyl tert-butyl ether to give the desired product as pale yellow or off-white solid.

Int	Compound	Data	SM
83	2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-*N*-(2-methoxyethyl)-4-(trifluoromethyl)thiazole-5-carboxamide 	MS (ESP): 495.9 and 498.0 ($M+H^+$) for $C_{16}H_{17}BrF_3N_5O_3S$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08 (t, 3H), 3.17 (m, 2H), 3.28 (s, 3H), 3.45 (m, 4H), 7.22 (t, 1H), 8.46 (s, 1H), 8.59 (s, 1H), 9.18 (t, 1H), .43 (bs, 1H)	Intermediate 81 and methoxyethylamine
84	2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-*N*-(2-morpholinoethyl)-4-(trifluoromethyl)thiazole-5-carboxamide 	MS (ESP): 551.0 and 552.9 ($M+H^+$) for $C_{19}H_{22}BrF_3N_6O_3S$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08 (t, 3H), 2.41 (m, 6H), 3.18 (m, 2H), 3.38 (m, 2H), 3.57 (m, 4H), 7.21 (t, 1H), 8.45 (s, 1H), 8.58 (s, 1H), 9.02 (t, 1H), .42 (bs, 1H)	Intermediate 81 and 2-morpholinoethanamine

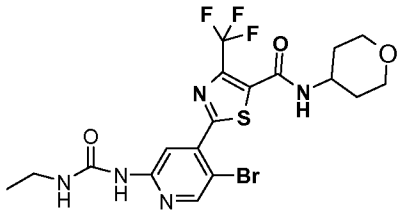
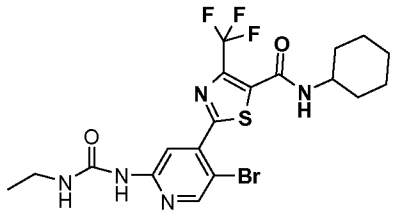
85	2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-*N*-(2-(4-methylpiperazin-1-yl)ethyl)-4-(trifluoromethyl)thiazole-5-carboxamide 	MS (ESP): 564.0 and 566.1 ($M+H^+$) for $C_{20}H_{25}BrF_3N_7O_2S$ ^1H NMR (300 MHz, DMSO-d_6): δ 1.08 (t, 3H), 2.14 (s, 3H), 2.44 (m, 10H), 3.18 (m, 2H), 3.36 (m, 2H), 7.21 (t, 1H), 8.45 (s, 1H), 8.58 (s, 1H), 8.98 (t, 1H), .43 (bs, 1H)	Intermediate 81 and 2-(4-methylpiperazin-1-yl)ethanamine

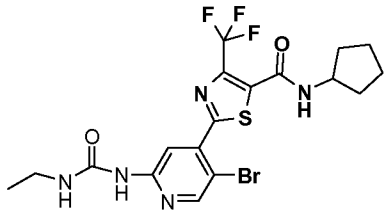
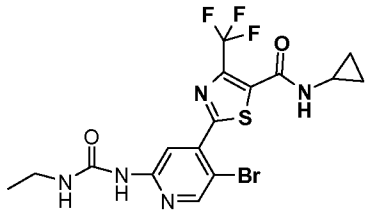
Intermediates 86-89

The following Intermediates were synthesized by the general procedure described below from the starting material indicated in the Table.

General Procedure

Ethyl 2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-4-(trifluoromethyl)thiazole-5-carboxylate (Intermediate 81, 0.5 g), magnesium chloride (1eq) and excess amine (4-6eq in ethanol solution) was heated to 90 °C in microwave for 3h. The solid was filtered, washed by water and methyl tert-butyl ether, then dried in vacuum oven at 50 °C for 12 hrs to give desired product as pale yellow or off-white solid.

Int	Compound	Data	SM
86	2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-*N*-(tetrahydro-2*H*-pyran-4-yl)-4-(trifluoromethyl)thiazole-5-carboxamide 	MS (ESP): 522.0 and 524.1 ($M+H^+$) for $C_{18}H_{19}BrF_3N_5O_3S$ ^1H NMR (300 MHz, DMSO-d_6): δ 1.08 (t, 3H), 1.48 (m, 2H), 1.80 (m, 2H), 3.17 (m, 2H), 3.40 (m, 2H), 3.87 (m, 2H), 3.98 (m, 1H), 7.21 (t, 1H), 8.45 (s, 1H), 8.58 (s, 1H), 9.10 (d, 1H), .42 (bs, 1H)	Intermediate 81 and tetrahydro-2H-pyran-4-amine
87	2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-*N*-cyclohexyl-4-(trifluoromethyl)thiazole-5-carboxamide 	MS (ESP): 520.2 and 522.0 ($M+H^+$) for $C_{19}H_{21}BrF_3N_5O_2S$ ^1H NMR (300 MHz, DMSO-d_6): δ 1.08 (t, 3H), 1.26 (m, 5H), 1.69 (m, 5H), 3.17 (m, 2H), 3.72 (m, 1H), 7.21 (t, 1H), 8.44 (s, 1H), 8.58 (s, 1H), 8.97 (d, 1H), .41 (bs, 1H)	Intermediate 81 and cyclohexanamine

88	2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-*N*-cyclopentyl-4-(trifluoromethyl)thiazole-5-carboxamide 	MS (ESP): 506.1 and 507.9 ($M+H^+$) for $C_{18}H_{19}BrF_3N_5O_2S$ ^1H NMR (300 MHz, DMSO-d_6): δ 1.08 (t, 3H), 1.66 (m, 6H), 1.89 (m, 2H), 3.18 (m, 2H), 4.18 (m, 1H), 7.22 (t, 1H), 8.44 (s, 1H), 8.58 (s, 1H), 9.04 (d, 1H), .42 (bs, 1H)	Intermediate 81 and cyclopentanamine
89	2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-*N*-cyclopropyl-4-(trifluoromethyl)thiazole-5-carboxamide 	MS (ESP): 477.9 and 480.0 ($M+H^+$) for $C_{16}H_{15}BrF_3N_5O_2S$ ^1H NMR (300 MHz, DMSO-d_6): δ 0.55 (m, 2H), 0.74 (m, 2H), 1.08 (t, 3H), 2.84 (m, 1H), 3.17 (m, 2H), 7.24 (t, 1H), 8.45 (s, 1H), 8.58 (s, 1H), 9.14 (d, 1H), .44 (bs, 1H)	Intermediate 81 and cyclopropanamine

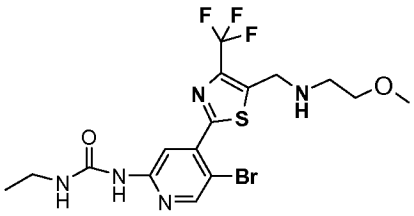
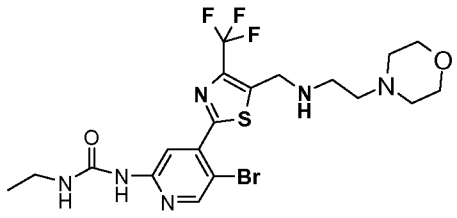
Intermediates 90-96

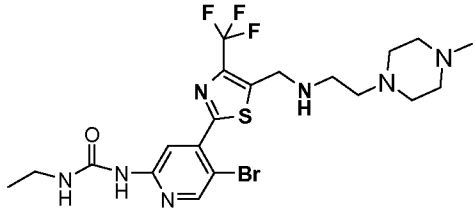
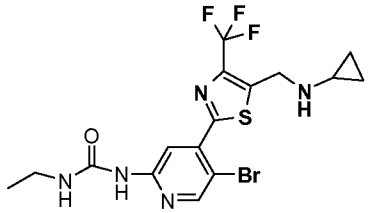
The following Intermediates were synthesized by the general procedure described below from the starting material indicated in the Table.

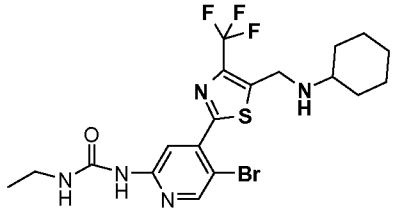
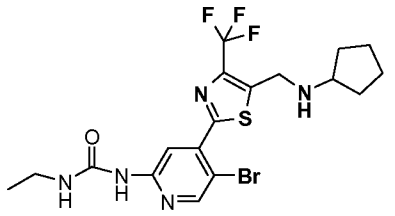
General Procedure

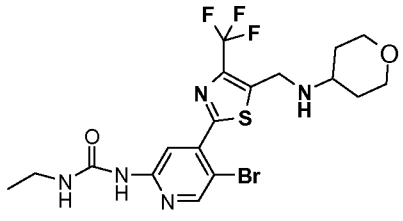
1-(5-Bromo-4-(5-(hydroxymethyl)-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 82, 0.5 g, 1.17 mmol) was dissolved in tetrahydrofuran (15 mL). Triethylamine (448 µl, 3.5 mmol) and methane sulfonyl chloride (137 µl, 1.77 mmol) were added sequentially and the reaction was stirred for 2 hours. The appropriate amine (5.9 mmol) was added, and the reaction stirred for an additional 18 hours at room temperature. The solvent

was then removed *in vacuo* and saturated sodium bicarbonate (3 mL) was added. The suspension was extracted with ethyl acetate (3×, 3 mL) and the organic phases were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*. The products were used without further purification.

Int	Compound	Data	SM
90	1-(5-bromo-4-(5-((2-methoxyethylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 482.1, 484.1 ($M+H^+$) for $C_{16}H_{19}BrF_3N_5O_2S$ ^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 2.78 (t, 2H), 3.19 (m, 2H), 3.36 (s, 3H), 3.41 (t, 2H), 4.16 (s, 2H), 7.26 (t, 1H), 8.31 (s, 1H), 8.56 (s, 1H), 9.38 (bs, 1H).	Intermediate 82 and methoxyethylamine
91	1-(5-bromo-4-(5-((2-morpholinoethylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 537.0, 539.1 ($M+H^+$) for $C_{19}H_{24}BrF_3N_6O_2S$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 2.28-2.44 (m, 6H), 2.79 (t, 2H), 3.58 (m, 4H), 4.14 (s, 2H), 7.21 (t, 1H), 8.31 (s, 1H), 8.52 (s, 1H), 9.36 (bs, 1H).	Intermediate 82 and 2-morpholinoethanamine

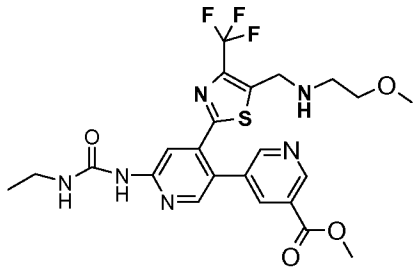
92	1-(5-bromo-4-(5-((2-(4-methylpiperazin-1-yl)ethylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 550.2, 552.2 ($M+H^+$) for $C_{20}H_{27}BrF_3N_7OS$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 2.16 (s, 3H), 2.21-2.44 (m, 10H), 2.76 (t, 2H), 3.18 (m, 2H), 4.14 (s, 2H), 7.22 (t, 1H), 8.33 (s, 1H), 8.57 (s, 1H), 9.39 (bs, 1H).	Intermediate 82 and 2-(4-methylpiperazin-1-yl)ethanamine
93	1-(5-bromo-4-(5-((cyclopropylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 464.1, 465.9 ($M+H^+$) for $C_{16}H_{17}BrF_3N_5OS$; ^1H NMR (300 MHz, DMSO-d_6): δ 0.24 (m, 2H), 0.41 (m, 2H), 1.11 (t, 3H), 2.21 (m, 1H), 3.17 (m, 2H), 4.18 (s, 2H), 7.22 (t, 1H), 8.33 (s, 1H), 8.54 (s, 1H), 9.37 (bs, 1H).	Intermediate 82 and cyclopropanamine

94	1-(5-bromo-4-(5-((cyclohexylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 506.1, 507.9 ($M+H^+$) for $C_{19}H_{23}BrF_3N_5OS$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.03-1.38 (m, 6H), 1.11 (t, 3H), 1.65 (m, 2H), 1.82 (m, 2H), 2.86 (m, 1H), 3.18 (m, 2H), 4.13 (s, 2H), 7.23 (t, 1H), 8.32 (s, 1H), 8.56 (s, 1H), 9.40 (bs, 1H).	Intermediate 82 and cyclohexanamine
95	1-(5-bromo-4-(5-((cyclopentylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 553.2 ($M+H^+$) for $C_{18}H_{21}BrF_3N_5OS$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 1.36 (m, 2H), 1.44 (m, 2H), 1.63 (m, 2H), 1.71 (m, 2H), 2.93 (m, 1H), 3.19 (m, 2H), 4.08 (s, 2H), 7.21 (t, 1H), 8.33 (s, 1H), 8.54 (s, 1H), 9.38 (bs, 1H).	Intermediate 82 and cyclopentanamine

96	1-(5-bromo-4-(5-((tetrahydro-2H-pyran-4-ylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 507.9, 510.0 ($M+H^+$) for $C_{18}H_{21}BrF_3N_5O_2S$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 1.29 (m, 2H), 1.80 (m, 2H), 3.01 (m, 1H), 3.19 (m, 2H), 3.28 (m, 2H), 3.81 (m, 2H), 4.16 (s, 2H), 7.22 (t, 1H), 8.36 (s, 1H), 8.52 (s, 1H), 9.38 (bs, 1H).	Intermediate 82 and tetrahydro-2H-pyran-4-amine

Intermediate 97

Methyl 6'-(3-ethylureido)-4'-(5-((2-methoxyethylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



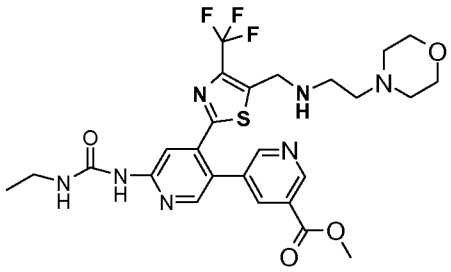
1-(5-bromo-4-(5-((2-methoxyethylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 90, ~500 mg, 1 mmol), methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (0.40 g, 1.5 mmol), and trans dichlorobis(triphenylphosphine)palladium (II) (70 mg, 0.1 mmol) were dissolved in 1,4-dioxane (10 mL). Sodium bicarbonate (252 mg, 3 mmol) was dissolved in water (3 mL) and added to the above mixture. The reaction was heated at 110°C in a microwave for 30 minutes. Ethyl acetate (10 mL) was then added to the reaction and the layers were separated. The solvent was removed *in vacuo* and the residue was chromatographed on a 12g Analogix column using 0-10% methanol in dichloromethane. The product containing fractions were combined to give the product ester (65% yield).

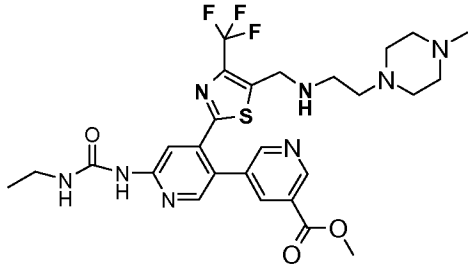
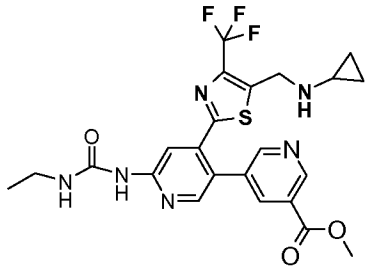
MS (ESP): 539.1 ($M+H^+$) for $C_{23}H_{25}F_3N_6O_4S$

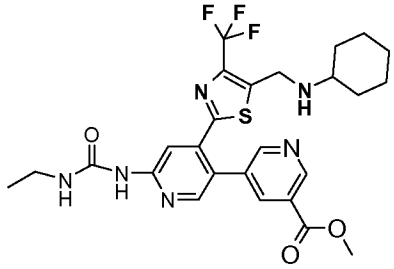
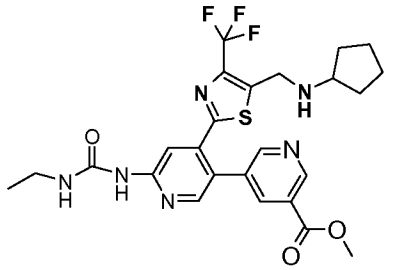
^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 3.21 (m, 2H), 3.23 (s, 3H), 3.37 (m, 4H), 3.89 (s, 3H), 7.49 (t, 1H), 8.24 (1H), 8.28 (t, 1H), 8.37 (s, 1H), 8.74 (d, 1H), 9.02 (t, 1H), 9.11 (d, 1H), 9.52 (bs, 1H).

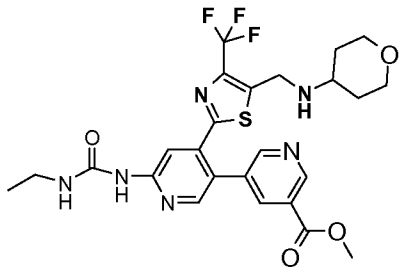
Intermediates 98-103

The following Intermediates were prepared as described for Intermediate 97 from the starting materials indicated in the Table.

Int	Compound	Data	SM
98	Methyl 6'-(3-ethylureido)-4'-(5-((2 morpholinoethylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 594.0 ($M+H^+$) for $C_{26}H_{30}F_3N_7O_4S$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 3.21 (m, 2H), 3.23 (s, 3H), 3.37 (m, 4H), 3.89 (s, 3H), 7.49 (t, 1H), 8.24 (1H), 8.28 (t, 1H), 8.37 (s, 1H), 8.74 (d, 1H), 9.02 (t, 1H), 9.11 (d, 1H), 9.52 (bs, 1H).	Intermediate 91 and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

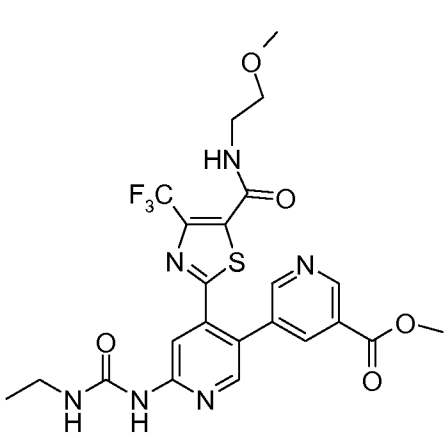
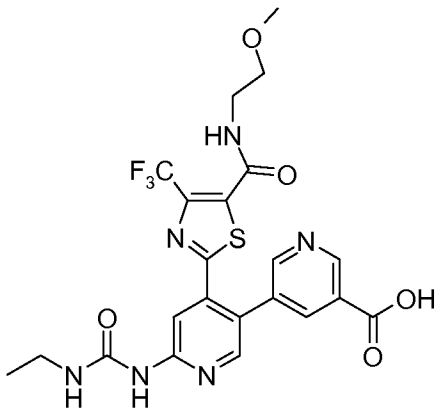
99	Methyl 6'-(3-ethylureido)-4'-(5-((2-(4-methylpiperazin-1-yl)ethylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP):521.2 ($M+H^+$) for $C_{23}H_{23}F_3N_6O_3S$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 3.21 (m, 2H), 3.23 (s, 3H), 3.37 (m, 4H), 3.89 (s, 3H), 7.49 (t, 1H), 8.24 (1H), 8.28 (t, 1H), 8.37 (s, 1H), 8.74 (d, 1H), 9.02 (t, 1H), 9.11 (d, 1H), 9.52 (bs, 1H).	Intermediate 92 and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate
100	Methyl 6'-(3-ethylureido)-4'-(5-((cyclopropylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP):521.2 ($M+H^+$) for $C_{23}H_{23}F_3N_6O_3S$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 3.21 (m, 2H), 3.23 (s, 3H), 3.37 (m, 4H), 3.89 (s, 3H), 7.49 (t, 1H), 8.24 (1H), 8.28 (t, 1H), 8.37 (s, 1H), 8.74 (d, 1H), 9.02 (t, 1H), 9.11 (d, 1H), 9.52 (bs, 1H).	Intermediate 93 and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

101	Methyl 6'-(3-ethylureido)-4'-(5-((cyclohexylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 563.1 ($M+H^+$) for $C_{26}H_{29}F_3N_6O_3S$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 3.21 (m, 2H), 3.23 (s, 3H), 3.37 (m, 4H), 3.89 (s, 3H), 7.49 (t, 1H), 8.24 (1H), 8.28 (t, 1H), 8.37 (s, 1H), 8.74 (d, 1H), 9.02 (t, 1H), 9.11 (d, 1H), 9.52 (bs, 1H).	Intermediate 94 and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate
102	Methyl 6'-(3-ethylureido)-4'-(5-((cyclopentylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 549.0 ($M+H^+$) for $C_{25}H_{27}F_3N_6O_3S$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 3.21 (m, 2H), 3.23 (s, 3H), 3.37 (m, 4H), 3.89 (s, 3H), 7.49 (t, 1H), 8.24 (1H), 8.28 (t, 1H), 8.37 (s, 1H), 8.74 (d, 1H), 9.02 (t, 1H), 9.11 (d, 1H), 9.52 (bs, 1H).	Intermediate 95 and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

103	Methyl 6'-(3-ethylureido)-4'-(5-((tetrahydro-2H-pyran-4-ylamino)methyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 565.2 ($M+H^+$) for $C_{25}H_{27}F_3N_6O_4S$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 3.21 (m, 2H), 3.23 (s, 3H), 3.37 (m, 4H), 3.89 (s, 3H), 7.49 (t, 1H), 8.24 (1H), 8.28 (t, 1H), 8.37 (s, 1H), 8.74 (d, 1H), 9.02 (t, 1H), 9.11 (d, 1H), 9.52 (bs, 1H).	Intermediate 96 and methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

Intermediate 104 and Intermediate 105

methyl 6'-(3-ethylureido)-4'-(5-(2-methoxyethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate and 6'-(3-ethylureido)-4'-(5-(2-methoxyethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid


+


To a 35 mL microwave vial was added sequentially 2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-N-(2-methoxyethyl)-4-(trifluoromethyl)thiazole-5-carboxamide (Intermediate 83, 0.5 g, 1.0 mmol), methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (0.40 g, 1.5 mmol), saturated sodium bicarbonate aqueous solution (3 mL), 1,4-dioxane (10 mL), and dichloro-bis(triphenylphosphino) palladium (II) (70 mg, 0.10 mmol). The mixture was then heated at 110 °C in a microwave for 30min. Ethyl acetate (40 mL) and water (40 mL) were added. The aqueous layer was then further extracted with ethyl acetate (2×, 50mL). The

combined organics were dried over sodium sulfate, filtered and concentrated. The residue was loaded on 24g Analogix silica gel column [Heptanes: (9/1) ethyl acetate/methanol] to give ester (Intemediate 105) as off-white powder. The aqueous layer was adjusted to pH ~4 with dilute HCl and extracted with ethyl acetate /tetrahydrofuran (1/1) (3×, 100mL). The combined organics were dried over sodium sulfate, filtered, and concentrated to give crude acid Intermediate 106 as yellow solid which was used without further purification.

Interemdiate 104: Methyl 6'-(3-ethylureido)-4'-(5-(2-methoxyethylcarbamoyl)-4-(trifluoromethyl) thiazol-2-yl)-3,3'-bipyridine-5-carboxylate

MS (ESP): 553.2 ($M+H^+$) for $C_{23}H_{23}F_3N_6O_5S$

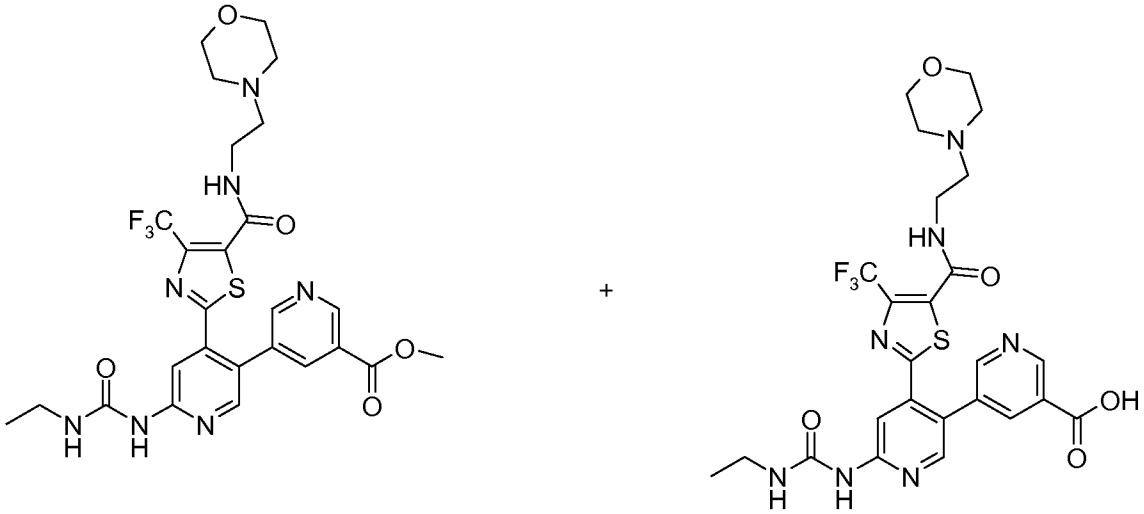
^1H NMR (300 MHz, DMSO-d_6): δ 1.11 (t, 3H), 3.21 (m, 2H), 3.23 (s, 3H), 3.37 (m, 4H), 3.89 (s, 3H), 7.49 (t, 1H), 8.24 (1H), 8.28 (t, 1H), 8.37 (s, 1H), 8.74 (d, 1H), 9.02 (t, 1H), 9.11 (d, 1H), 9.52 (bs, 1H).

Intermediate 105: 6'-(3-ethylureido)-4'-(5-(2-methoxyethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid

MS (ESP): 539.1 ($M+H^+$) for $C_{22}H_{21}F_3N_6O_5S$

Intermediate 106 and Intermediate 107

methyl 6'-(3-ethylureido)-4'-(5-(2-morpholinoethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate and 6'-(3-ethylureido)-4'-(5-(2-morpholinoethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid



To a 35 mL microwave vial was added sequentially 2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-N-(2-morpholinoethyl)-4-(trifluoromethyl)thiazole-5-carboxamide (Intermediate 84, 0.5 g,

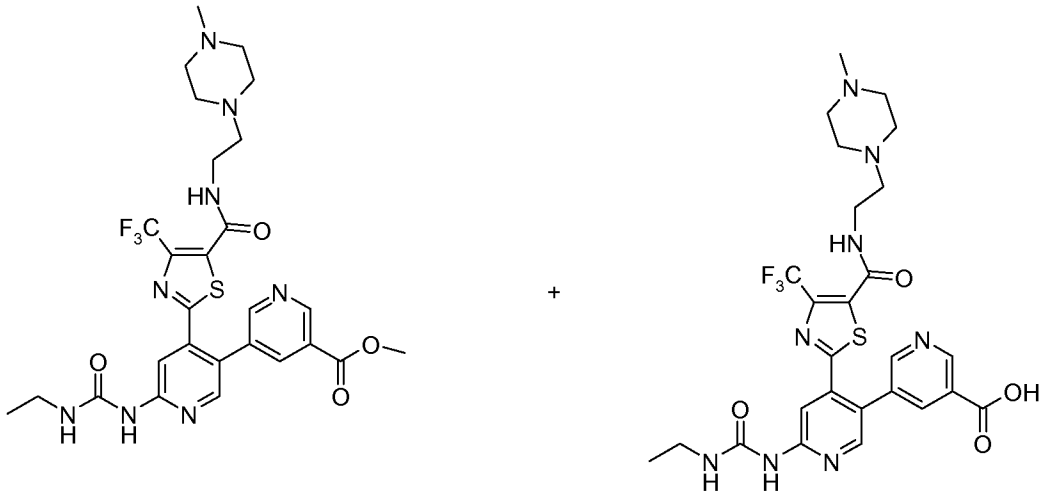
0.9 mmol), methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (0.36 g, 1.4 mmol), saturated sodium bicarbonate aqueous solution (3 mL), 1,4-dioxane (10 mL), and dichloro-bis(triphenylphosphino) palladium (II) (65 mg, 0.09 mmol). The mixture was then heated to 110 °C in a microwave for 30min. Ethyl acetate (40 mL) and water (40 mL) were added. The aqueous layer was then further extracted with ethyl acetate (2×, 50mL). The combined organics were dried over sodium sulfate, filtered, and concentrated to give the crude ester (Intermediate 106) which was used without further purification. The aqueous layer was adjusted to pH ~4 with dilute HCl and extracted with ethyl acetate /tetrahydrofuran (1/1) (3×, 100mL). The combined organics were dried over sodium sulfate, filtered, and concentrated to give crude acid Intermediate 107 as yellow solid which was also used without further purification.

Intermediate 106: Methyl 6'-(3-ethylureido)-4'-(5-(2-morpholinoethylcarbamoyl)-4-(trifluoromethyl) thiazol-2-yl)-3,3'-bipyridine-5-carboxylate
MS (ESP): 608.1 ($M+H^+$) for $C_{26}H_{28}F_3N_7O_5S$

Intermediate 107: 6'-(3-ethylureido)-4'-(5-(2-morpholinoethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid
MS (ESP): 594.0 ($M+H^+$) for $C_{25}H_{26}F_3N_7O_5S$

Intermediate 108 and Intermediate 109

methyl 6'-(3-ethylureido)-4'-(5-(2-(4-methylpiperazin-1-yl)ethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate and 6'-(3-ethylureido)-4'-(5-(2-(4-methylpiperazin-1-yl)ethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid



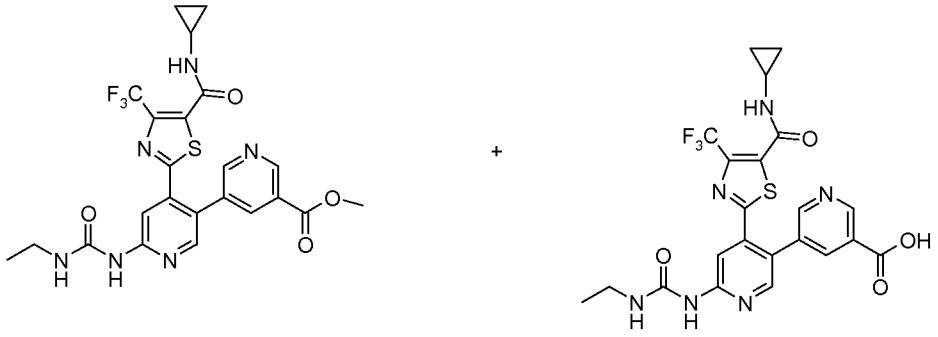
To a 35 mL microwave vial was added sequentially 2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-N-(2-(4-methylpiperazin-1-yl)ethyl)-4-(trifluoromethyl)thiazole-5-carboxamide (Intermediate 85, 0.5 g, 0.9 mmol), methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (0.36 g, 1.4 mmol), saturated sodium bicarbonate aqueous solution (3 mL), 1,4-dioxane (10 mL), and dichloro-bis(triphenylphosphino) palladium (II) (65 mg, 0.09 mmol). The mixture was then heated to 110 °C in a microwave for 30min. Ethyl acetate (40 mL) and water (40 mL) were added. The aqueous layer was then further extracted with ethyl acetate (2×, 50mL). The combined organics were dried over sodium sulfate, filtered, and concentrated to give the crude ester (Intermediate 108) which was used for the next step without further purification. The aqueous layer was then adjusted to pH ~6, 4, and 2 with dilute HCl, and extracted with ethyl acetate /tetrahydrofuran (1/1) however the product remained in the aqueous layer. The aqueous layer was then passed through a 30g Analogix C18 column (acetonitrile/water) to remove most of the salts and give acid Intermediate 109 as yellow solid which was used without further purification.

Intermediate 108: Methyl 6'-(3-ethylureido)-4'-(5-(2-(4-methylpiperazin-1-yl)ethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate
MS (ESP): 621.3 ($M+H^+$) for $C_{27}H_{31}F_3N_8O_4S$

Intermediate 109: 6'-(3-ethylureido)-4'-(5-(2-(4-methylpiperazin-1-yl)ethylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid
MS (ESP): 607.2 ($M+H^+$) for $C_{26}H_{29}F_3N_8O_4S$

Intermediate 110 and Intermediate 111

methyl 4'-(5-(cyclopropylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate and 4'-(5-(cyclopropylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylic acid



To a 35 mL microwave vial was added sequentially 2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-N-cyclopropyl-4-(trifluoromethyl)thiazole-5-carboxamide (Intermediate 89, 0.5 g, 1.0 mmol), methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (0.4 g, 1.5 mmol), saturated sodium bicarbonate aqueous solution (3 mL), 1,4-dioxane (10 mL), and dichloro-bis(triphenylphosphino) palladium (II) (70 mg, 0.1 mmol). The mixture was then heated to 110 °C in a microwave for 30min. Ethyl acetate (40 mL) and water (40 mL) were added. The aqueous layer was then further extracted with ethyl acetate (2×, 50mL). The combined organics were dried over sodium sulfate, filtered, and concentrated to give the crude ester (Intermediate 110) which was used without further purification. The aqueous layer was adjusted to pH ~4 with dilute HCl and extracted with ethyl acetate /tetrahydrofuran (1/1) (3×, 100mL). The combined organics were dried over sodium sulfate, filtered, and concentrated to give acid Intermediate 111 as yellow solid which was also used without further purification.

Intermediate 110: Methyl 4'-(5-(cyclopropylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate

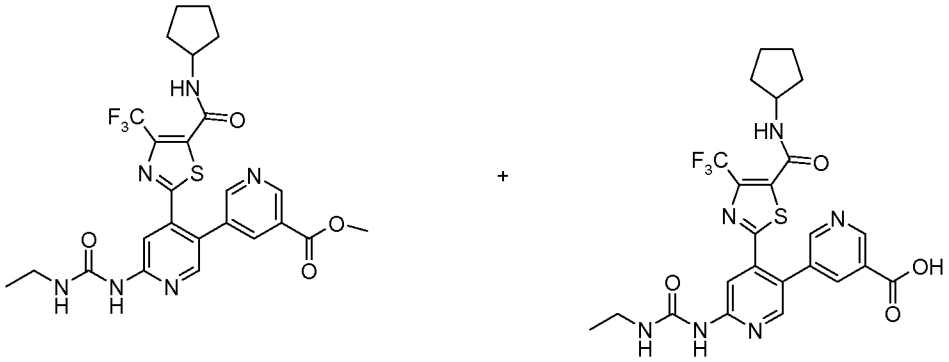
MS (ESP): 535.2($M+H^+$) for $C_{23}H_{21}F_3N_6O_4S$

Intermediate 111: 4'-(5-(cyclopropylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylic acid

MS (ESP): 521.1 ($M+H^+$) for $C_{22}H_{19}F_3N_6O_4S$

Intermediate 112 and Intermediate 113

methyl 4'-(5-(cyclopentylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate and 4'-(5-(cyclopentylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylic acid



To a 35 mL microwave vial was added sequentially 2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-N-cyclopentyl-4-(trifluoromethyl)thiazole-5-carboxamide (Intermediate 88, 0.5 g, 1.0 mmol), methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (0.4 g, 1.5 mmol), saturated sodium bicarbonate aqueous solution (3 mL), 1,4-dioxane (10 mL), and dichloro-bis(triphenylphosphino) palladium (II) (70 mg, 0.1 mmol). The mixture was then heated to 110 °C in a microwave for 30min. Ethyl acetate (40 mL) and water (40 mL) were added. The aqueous layer was then further extracted with ethyl acetate (2×, 50mL). The combined organics were dried over sodium sulfate, filtered, and concentrated to give the crude ester (Intermediate 112) which was used without further purification. The aqueous layer was adjusted to pH ~4 with dilute HCl and extracted with ethyl acetate /tetrahydrofuran (1/1) (3×, 100mL). The combined organics were dried over sodium sulfate, filtered, and concentrated to give crude acid Intermediate 113 as yellow solid which was also used without further purification.

Intermediate 112: Methyl 4'-(5-(cyclopentylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate

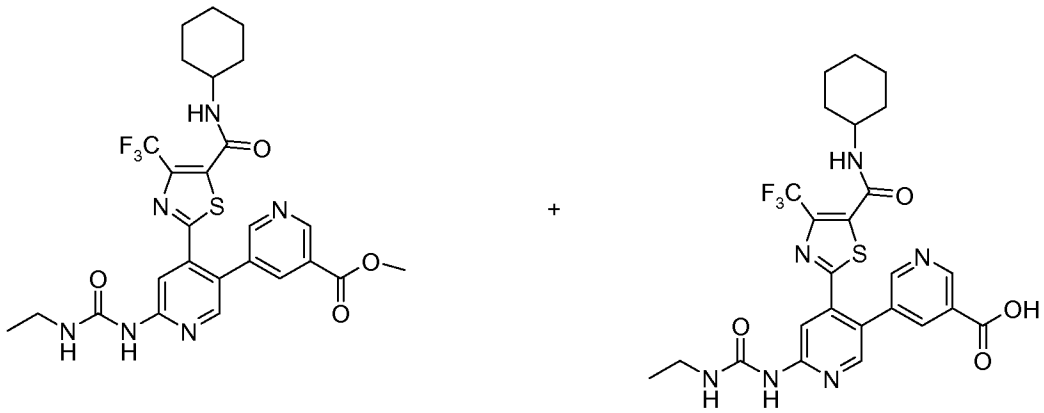
MS (ESP): 563.1($M+H^+$) for $C_{25}H_{25}F_3N_6O_4S$

Intermediate 113: 4'-(5-(cyclopentylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylic acid

MS (ESP): 549.0 ($M+H^+$) for $C_{24}H_{23}F_3N_6O_4S$

Intermediate 114 and Intermediate 115

methyl 4'-(5-(cyclohexylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate and 4'-(5-(cyclohexylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylic acid



To a 35 mL microwave vial was added sequentially 2-(5-bromo-2-(3-ethylureido)pyridin-4-yl)-N-cyclohexyl-4-(trifluoromethyl)thiazole-5-carboxamide (Intermediate 87, 0.5 g, 1.0 mmol), methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (0.4 g, 1.5 mmol), saturated sodium bicarbonate aqueous solution (3 mL) 1,4-dioxane (10 mL), and dichloro-bis(triphenylphosphino) palladium (II) (70 mg, 0.1 mmol). The mixture was then heated to 110 °C in a microwave for 30min. Ethyl acetate (40 mL) and water (40 mL) were added. The aqueous layer was then further extracted with ethyl acetate (2×, 50mL). The combined organics were dried over sodium sulfate, filtered, and concentrated to give the crude ester (Intermediate 114) which was used without any further purification. The aqueous layer was adjusted to pH ~4 with dilute HCl and extracted with ethyl acetate /tetrahydrofuran (1/1) (3×, 100mL). The combined organics were dried over sodium sulfate, filtered, and concentrated to give crude acid Intermediate 115 as yellow solid which was also used without further purification.

Intermediate 114: Methyl 4'-(5-(cyclohexylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate

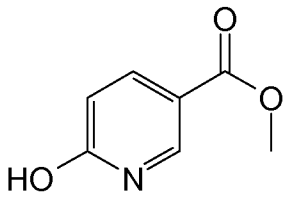
MS (ESP): 577.1($M+H^+$) for $C_{26}H_{27}F_3N_6O_4S$

Intermediate 115: 4'-(5-(cyclohexylcarbamoyl)-4-(trifluoromethyl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylic acid

MS (ESP): 563.1 ($M+H^+$) for $C_{25}H_{25}F_3N_6O_4S$

Intermediate 116

Methyl 6-hydroxynicotininate



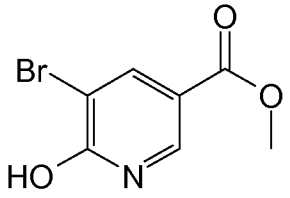
6-Hydroxy-nicotinic acid (100 g, 719 mmol) was suspended in methanol (1 L). 18M Sulfuric acid (50 mL) was added and the reaction was heated at reflux for 16 h. The reaction mixture was then cooled, and sodium bicarbonate powder (45 g) was added slowly to neutralize some of the acid. Most of the methanol was then removed *in vacuo*. Water (1L) was added, and the pH adjusted to 7 with the careful addition of bicarbonate solution. The suspension was extracted with dichloromethane (4×, 200 mL), and the organic phases were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*. The solid was dried in a vacuum oven at 50˚C for 1.5 h to give 83g (75%) of methyl 6-hydroxynicotinate as a white solid.

MS (ESP): 154.2 (MH^+) for $C_7H_7NO_3$

^1H NMR (300 MHz, $CDCl_3$): 3.88 (s, 3H), 6.59 (dd, 1H), 8.02 (dd, 1 H), 8.21 (m, 1H), 13.19 (bs, 1H).

Intermediate 117

Methyl 5-bromo-6-hydroxynicotininate



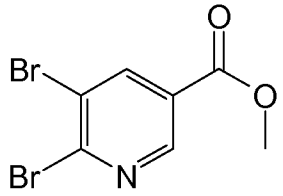
Methyl 6-hydroxynicotininate (Intermediate 116, 50 g, 327 mmol) was suspended in acetic acid (250 mL) and bromine (26.2 mL, 490.5 mmol) was added dropwise to the reaction. The reaction was then heated at 60˚C for 18 h. The reaction mixture was cooled to room temperature, and saturated sodium thiosulfate solution was added to remove remaining bromine. Saturated sodium bicarbonate solution (500 mL) was added slowly, then 1N sodium hydroxide was added carefully until the pH was ~7. The solid that precipitated were collected by filtration and dried in a vacuum oven at 50˚C for 18 h. This gave 76g (100%) of methyl 5-bromo-6-hydroxynicotininate as an off white solid.

MS (ESP): 231.9(MH^+) for $C_7H_6BrNO_3$

^{1}H NMR (300 MHz, DMSO-d_6): 3.80 (s, 3H), 8.12 (s, 1 H), 8.19 (s, 1H), 12.77 (bs, 1H).

Intermediate 118

Methyl 5,6-dibromonicotinate



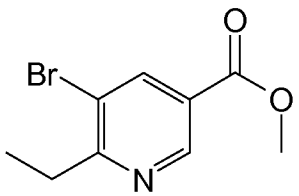
Methyl 5-bromo-6-hydroxynicotininate (Intermediate 117, 10 g, 43 mmol) was suspended in toluene (100 mL) and phosphorous pentoxide (12 g, 43 mmol) was added. Tetrabutyl ammonium bromide (20 g, 62.1 mmol) was added and the reaction was stirred at reflux for 5 h. The reaction mixture was cooled to ~50°C and toluene was decanted from the solution. Toluene (50 mL) was added to the viscous oil and heated to reflux for 30 min. The reaction mixture was cooled to ~50°C and toluene was decanted from the solution. This process was repeated twice more, and the toluene extracts were combined. The toluene was washed with saturated bicarbonate (2×, 30 mL), and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel using 10-50% ethyl acetate in heptane to give 6.3g (50%) of methyl 5,6-dibromonicotinate as an off white solid.

MS (ESP): 295.8 (MH^+) for $C_7H_5Br_2NO_2$

^{1}H NMR (300 MHz, DMSO-d_6): 3.91 (s, 3H), 8.51 (s, 1H), 8.86 (s, 1 H).

Intermediate 119

Methyl 5-bromo-6-ethyl nicotinate



Methyl 5,6-dibromonicotinate (Intermediate 118, 1 g, 3.3 mmol) was dissolved in anhydrous tetrahydrofuran (15 mL) and the reaction was cooled to 0°C. [1,3-Bis(diphenylphosphino)propane]dichloronickel (II) (368 mg, 0.67 mmol) was added, and the solution was stirred for 5 min. Ethyl magnesium bromide (2.0M in tetrahydrofuran, 2.7 mL, 5.4 mmol) was then added dropwise over 30 min keeping the reaction at 0 °C. When the addition was complete, the reaction was stirred at 0°C for 1 h, then water (15 mL) and ethyl

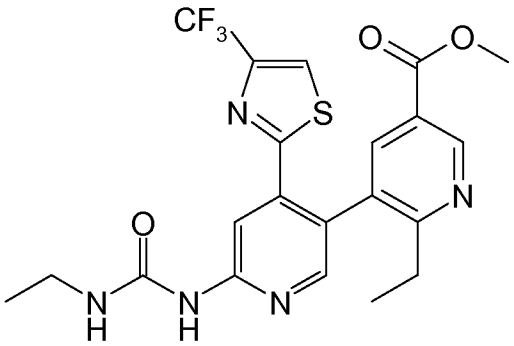
acetate (15 mL) were added. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3×, 5 mL). The organic phases were dried over sodium sulfate, filtered and the solvent was removed *in vacuo*. The residue was chromatographed on a 24g Analogix column using 0-15% ethyl acetate in heptane. This gave 408 mg (49%) of methyl 5-bromo-6-ethylnicotinate as a white semisolid.

MS (ESP): 243.9(MH^+) for $C_7H_5Br_2NO_2$

^1H NMR (300 MHz, $CDCl_3$): 1.33 (t, 1H), 3.08 (q, 2H), 3.92 (s, 3H), 8.35 (d, 1H), 9.01 (d, 1H).

Intermediate 120

methyl 2-ethyl-6'-(3-ethylureido)-4'-(4- (trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



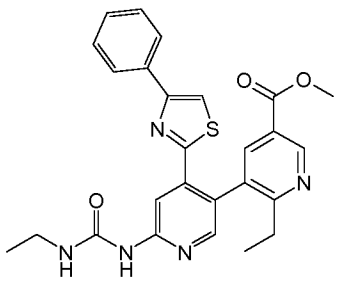
To a slurry of 6-(3-ethylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 12, 410 mg, 1.1 mmol), methyl 5-bromo-6-ethylnicotinate (Intermediate 119, 140 mg, 0.57 mmol) and trans dichlorobis(triphenylphosphine)palladium (II) (40 mg, 0.06 mmol) in 1,2-dimethoxyethane (12 mL) was added a solution of sodium bicarbonate (143 mg, 1.7 mmol) in water (3 mL). The reaction was stirred for 45 min at 125 °C in the microwave. The reaction mixture was cooled to room temperature, and ethyl acetate (20 mL) and water (10 mL) were added to help separate the layers. The water was removed, and the organic phase was washed with water (3 mL). The reaction was then concentrated and subjected to silica gel chromatography on a 12g Analogix column using 0-100% ethyl acetate in heptane. This gave 60 mg (21%) of methyl 2-ethyl-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate as an of white solid.

MS (ESP): 480.0 (MH^+) for $C_{21}H_{20}F_3N_5O_3S$

^{1}H NMR (300 MHz, DMSO-d_6): 0.98 (t, 3H), 1.11 (t, 3H), 2.39-2.51 (m, 2H), 3.18-3.28 (m, 2H), 3.92 (s, 3H), 7.61 (bt, 1H), 8.07 (d, 1H), 8.24 (s, 1H), 8.37 (s, 1H), 8.45 (s, 1H), 9.09 (d, 1H), 9.42 (bs, 1H).

Intermediate 121

The following compound was prepared according to the procedure for Intermediate 120 from the starting materials indicated in the Table.

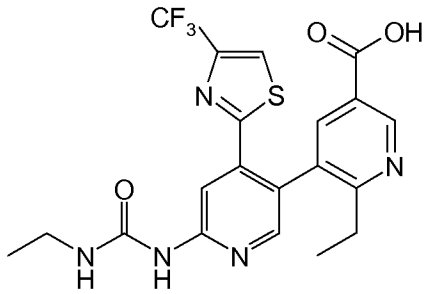
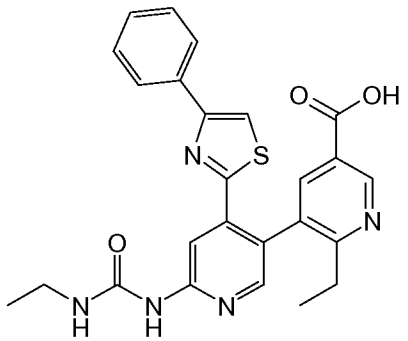
Int	Compound	Data	SM
121	methyl 2-ethyl-6'-(3-ethylureido)-4'-(4-phenylthiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 488.1(MH^+) for $C_{26}H_{25}N_5O_3S$	Intermediate 161 and Intermediate 119

Intermediates 122-123

The following Intermediates were prepared by the general procedure as described below from the starting materials indicated in the Table.

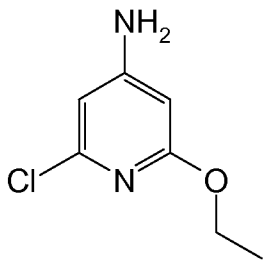
General Procedure

An ethyl ester (0.1 mmol) was suspended in 1:1 methanol:tetrahydrofuran (6 mL) and 1N sodium hydroxide (3 mL) was added. The reaction was stirred at room temperature for 16 h then concentrated under reduced pressure to remove the organic solvents to get a thin slurry. This slurry was acidified to pH~3 with 1N hydrochloric acid. This suspension was filtered and washed with water (3 mL) and dichloromethane (3 mL). The solid (or paste) was dried in a vacuum oven to give the product acid.

Int	Compound	Data	SM
122	2-ethyl-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid 	MS (ESP): 465.9 (MH^+) for $C_{20}H_{18}F_3N_5O_3S$ ^1H NMR (300 MHz, DMSO-d_6): 0.97 (t, 3H), 1.13 (t, 3H), 2.39-2.54 (m, 2H), 3.16-3.27 (m, 2H), 7.43 (bt, 1H), 8.06 (d, 1H), 8.29 (s, 1H), 8.36 (s, 1H), 8.49 (s, 1H), 9.11 (d, 1H), 9.44 (bs, 1H)	Intermediate 120
123	2-ethyl-6'-(3-ethylureido)-4'-(4-phenylthiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid 	MS (ESP): 474.0(MH^+) for $C_{25}H_{23}N_5O_3S$	Intermediate 121

Intermediate 124

2-chloro-6-ethoxypyridin-4-amine



To a sealed tube was charge 2,6-dichloro-4-aminopyridine (5 g, 30.7 mmol), and sodium ethoxide (21wt%, 9.92 g) with anhydrous ethanol (3 mL). The mixture was heated at 145 °C for 2 h in a microwave. Water was added, the crude product was extracted with ethyl acetate

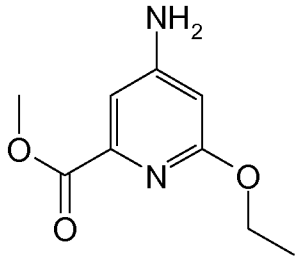
(3×), and the combined organic layers were dried over sodium sulfate, filtered and concentrated. During concentration, a crystalline solid precipitated from the crude to give clean product (2.4 g, 45.4%). The filtrate was purified (chromatography heptane/ ethyl acetate) and more product (1.5 g, 25.6%) was obtained.

MS (ESP): 173.1 (MH^+) for $C_7H_9ClN_2O$

^1H NMR (300 MHz, CD_3OD): δ 1.3 (t, 3H), 4.6 (q, 2H), 5.8 (d, 1H), 6.2 (d, 1H).

Intermediate 125

methyl 4-amino-6-ethoxypicolinate



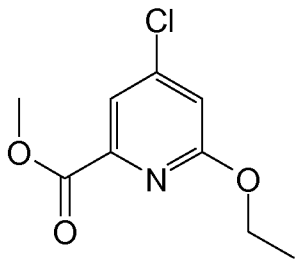
To a 2 L Parr Bomb was charged 2-chloro-6-ethoxypyridin-4-amine (Intermediate 124, 3.7 g, 21.4 mmol) and methanol (300 mL). [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (870 mg, 5mol%) was added followed by triethylamine (6 mL) and the resulting mixture was heated at 100 °C under 100 psi CO atmosphere for 2 d. The reaction mixture was cooled to room temperature and the mixture was concentrated to dryness and directly purified by Analogix in hexane/ ethyl acetate to give a light brown solid (3.7 g, 88.7%).

MS (ESP): 197.1 (MH^+) for $C_9H_{12}N_2O_3$

^1H NMR (300 MHz, CD_3OD): δ 1.36 (t, 3H), 3.85 (s, 3H), 4.22 (q, 2H), 6.05 (d, 1H), 7.0 (d, 1H).

Intermediate 126

methyl 4-chloro-6-ethoxypicolinate



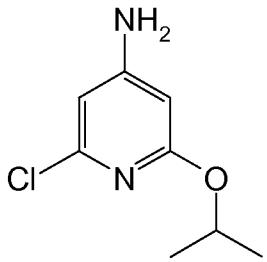
To a 1 L round bottom flask was charged t-butyl nitrite (1.55 mL, 11.48 mmol) with acetonitrile (200 mL), then copper (II) chloride (640 mg, 4.58 mmol) was added, and the mixture was allowed to heat at 70 °C to give a dark green solution. Methyl 4-amino-6-ethoxypicolinate (Intermediate 125, 1.51 g, 7.64 mmol) was added and gas evolution was observed. The mixture was heated at 70 °C for 1 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, ammonium chloride solution, and dried over sodium sulfate. After concentration, the crude product was purified by Analogix (heptane / ethyl acetate 0-30%) to give a white solid (1.45 g, 88.4%).

MS (ESP): 216.0 (MH^+) for $C_9H_{10}ClNO_3$

^1H NMR (300 MHz, CD_3OD): δ 1.38 (t, 3H), 4.0 (s, 3H), 4.42 (q, 2H), 7.05 (d, 1H), 7.65 (d, 1H).

Intermediate 127

2-chloro-6-isopropoxypyridin-4-amine

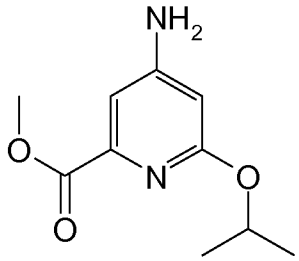


To a 500 mL sealed tube was charge 2,6-dichloro-4-aminopyridine (10.9 g, 66.9 mmol) with isopropanol (300 mL) and sodium hydride (95%, 9 g, 335 mmol). The mixture was heated at 150 °C for 2 d. Water was added, the crude product was extracted with ethyl acetate (3×), and the combined organic layers were dried over sodium sulfate. After concentration under reduced pressure, the crude mixture was directly used for the carbonylation without further purification.

MS (ESP): 186.9 (MH^+) for $C_8H_{11}ClN_2O$.

Intermediate 128

methyl 4-amino-6-isopropoxypicolinate



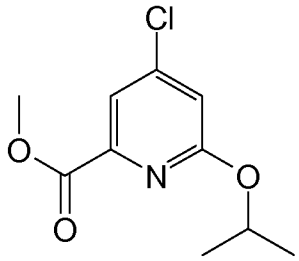
To a 2 L Parr Bomb was charged 2-chloro-6-isopropoxypyridin-4-amine (Intermediate 127, 12.5 g, 66.9 mmol) with methanol (300 mL). [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (2.80 g, 5mol%) was added followed by triethylamine (18.8 mL). The resulting mixture was heated at 100 °C under 100 psi CO atmosphere for overnight. The mixture was concentrated to dryness and directly purified by Analogix in hexane/ ethyl acetate to give a light yellow solid (10.3 g, 74%).

MS (ESP): 211.2 (MH^+) for $C_{10}H_{14}N_2O_3$

^1H NMR (300 MHz, CD_3OD): δ 1.27 (d, 6H), 3.94 (s, 3H), 5.12-5.20 (m, 1H), 6.03 (d, 1H), 7.00 (d, 1H).

Intermediate 129

methyl 4-chloro-6-isopropoxypicolinate



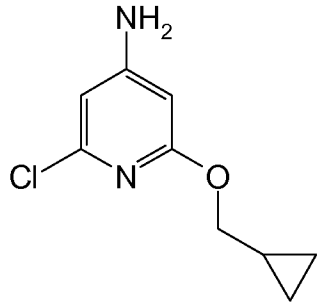
To a 1 L round bottom flask was charged t-butyl nitrite (6 mL, 44 mmol) with acetonitrile (200 mL), then copper (II) chloride (2.44 g, 17.2 mmol) was added, and the mixture was allowed to heat at 70 °C for 30 min to give a dark green solution. Methyl 4-amino-6-isopropoxypicolinate (Intermediate 128, 6 g, 28.6 mmol) was added and gas evolution was observed. The mixture was heated at 70 °C for 1 h. After cooling to room temperature, water was added and the mixture extracted with ethyl acetate (3×). The combined organic layers were washed with brine, ammonium chloride solution, and dried over sodium sulfate. After concentration, the crude product was purified by Analogix (heptane / ethyl acetate 0-50%) to give a light yellow liquid (4.33 g, 66%).

MS (ESP): 230.1 (MH^+) for $C_{10}H_{12}ClNO_3$

^1H NMR (300 MHz, CD_3OD): δ 1.25 (d, 6H), 3.9 (s, 3H), 5.4 (heptat, 1H), 7.00 (d, 1H), 7.60 (d, 1H).

Intermediate 130

2-chloro-6-(cyclopropylmethoxy)pyridin-4-amine



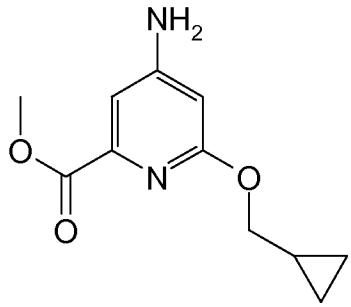
To a 500 mL sealed tube was charge 2,6-dichloro-4-aminopyridine (10 g, 61.3 mmol) with cyclopropylmethanol (200 mL) and sodium hydride (95%, 3.2 g, 122.9 mmol). The reaction mixture was heated at 150 °C for overnight. After cooling to room temperature, water was added, the crude product was extracted with ethyl acetate (3×), and the combined org. layers were dried over sodium sulfate. After concentration, the crude mixture was purified by Analogix (heptane / ethyl acetate 0-40%) to give a white solid (12 g, 98.4%).

MS (ESP): 199.2 (MH^+) for $C_9H_{11}ClN_2O$

^1H NMR (300 MHz, CD_3OD): δ ppm 0.30-0.34 (m, 2H), 0.54-0.60 (m, 2H), 1.16-1.25 (m, 1H), 3.94 (d, 2H), 5.83 (d, 1H), 6.22 (d, 1H).

Intermediate 131

methyl 4-amino-6-(cyclopropylmethoxy)picolinate



To a 2 L Parr Bomb was charged 2-chloro-6-(cyclopropylmethoxy)pyridin-4-amine (Intermediate 130, 9 g, 45.3 mmoL) with methanol (300 mL). [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (1.5

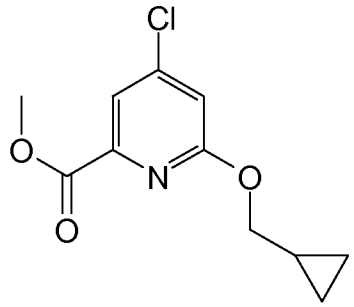
g, 6mol%) was added followed by triethylamine (13 mL). The resulting mixture was heated at 100 °C under 100 psi CO atmosphere for 2 d. The mixture was concentrated to dryness and directly purified by Analogix in hexane/ ethyl acetate system to give a light yellow solid (8.7 g, 61.4%).

MS (ESP): 223.2 (MH^+) for $C_{11}H_{14}N_2O_3$

^1H NMR (300 MHz, CD_3OD): δ 0.30-0.33 (m, 2H), 0.54-0.57 (m, 2H), 1.21-1.25 (m, 1H), 3.87 (s, 3H), 4.03 (d, 2H), 4.88 (s, 2H), 6.06 (d, 2H), 7.02 (d, 2H).

Intermediate 132

methyl 4-chloro-6-(cyclopropylmethoxy)picolinate



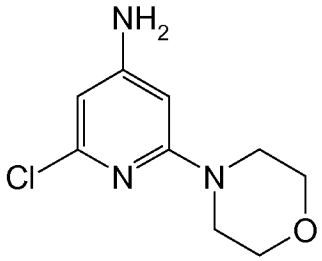
To a 1 L round bottom flask wash charged t-butyl nitrite (5.5 mL, 40.5 mmol) with acetonitrile (200 mL), then copper (II) chloride (2.26 g, 16.2 mmol) was added. The mixture was allowed to heat at 70 °C for 30 min to give a dark greenish solution. Methyl 4-amino-6-(cyclopropylmethoxy)picolinate (Intermediate 131, 6 g, 27 mmol) was added and gas evolution was observed. The mixture was heated at 70 °C for 1.5 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, ammonium chloride solution, and dried over sodium sulfate. After concentration, the crude product was purified by Analogix (heptane / ethyl acetate 0-30%) to give a light yellow liquid (4.46 g, 68.5%).

MS (ESP): 242.1 (MH^+) for $C_{11}H_{12}ClNO_3$

^1H NMR (300 MHz, CD_3OD): δ 0.34-0.39 (m, 2H), 0.54-0.62 (m, 2H), 1.22-1.33 (m, 1H), 4.21 (d, 2H), 7.04 (d, 1H), 7.65 (d, 1H).

Intermediate 133

2-chloro-6-morpholinopyridin-4-amine



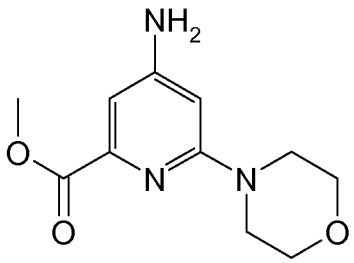
To a 500 mL sealed tube was charge 2,6-dichloro-4-aminopyridine (10 g, 61.3 mmol) with morpholine (11 mL) and 1,4-dioxane (50 mL). After heating at 150 °C for overnight the reaction was incomplete. More morpholine (11 mL) was added and the reaction again heated at 150°C for overnight. After cooling to room temperature, water was added and the crude product was extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate. After concentration, the crude mixture was purified by Analogix (heptane / ethyl acetate 0-40%) to give a white solid (11.5 g, 87.8%).

MS (ESP): 214.2 (MH^+) for $C_9H_{12}ClN_3O$

^1H NMR (300 MHz, CD_3OD): δ 3.30 (t, 4H), 3.68 (t, 4H), 5.8 (d, 1H), 6.0 (d, 1H).

Intermediate 134

methyl 4-amino-6-morpholinopicolinate



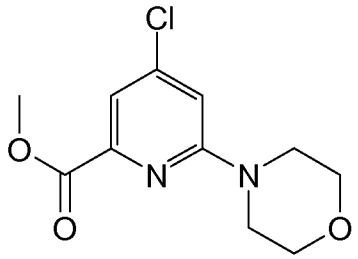
To a 2 L Parr Bomb was charged 2-chloro-6-morpholinopyridin-4-amine (Intermediate 133, 11 g, 51.4 mmoL) with methanol (300 mL). [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (2.11 g, 5mol%) was added followed by triethylamine (15 mL). The resulting mixture was heated at 100 °C under 100 psi CO atmosphere for 2 d. The mixture was filtered through a Celite pad and the filtrate was washed with water and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate. After concentration, the crude mixture was purified by Analogix (tetrahydrofuran/ ethyl acetate 0-40%) to give an off-white solid (8.4 g, 68.7%).

MS (ESP): 238.2 (MH^+) for $C_{11}H_{15}N_3O_3$

^{1}H NMR (300 MHz, CD_3OD): δ 3.42 (t, 4H), 3.74 (t, 4H), 3.86 (s, 3H), 6.09 (d, 1H), 6.84 (d, 1H).

Intermediate 135

methyl 4-chloro-6-morpholinopicolinate



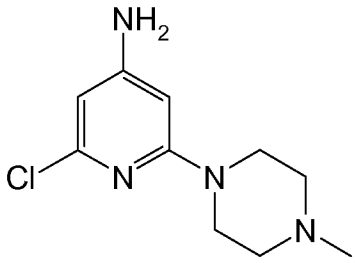
To a 1 L round bottom flask wash charged t-butyl nitrite (3.6 mL, 27 mmol) with acetonitrile (200 mL), then copper (II) chloride (1.4 g, 10.08 mmol) was added, and the reaction mixture was allowed to heat at 70 °C for 30 min to give a dark greenish solution. Methyl 4-amino-6-morpholinopicolinate (Intermediate 134, 4 g, 16.8 mmol) was added and gas evolution was observed. The mixture was heated at 70 °C for 0.5 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate (3×). The combined organic layers were washed with brine, ammonium chloride solution, and dried over sodium sulfate. After concentration, the crude product was purified by Analogix (heptane / ethyl acetate 0-30%) to give a yellow liquid (2.6 g, 60.2%).

MS (ESP): 257.1 (MH^+) for $C_{11}H_{13}ClN_2O_3$

^{1}H NMR (300 MHz, CD_3OD): δ 3.6 (t, 4H), 3.8 (t, 4H), 3.9 (s, 3H), 7.05 (d, 1H), 7.4 (d, 1H).

Intermediate 136

2-chloro-6-(4-methylpiperazin-1-yl)pyridin-4-amine



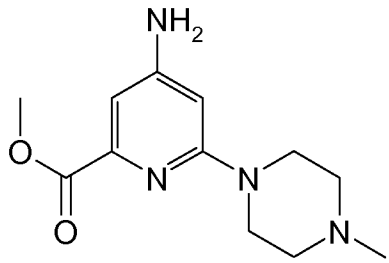
To a 500 mL sealed tube was charge 2,6-dichloro-4-aminopyridine (10 g, 61.3 mmol) with 1-methylpiperazine (8.4 mL) and 1,4-dioxane (50 mL). After heating at 170 °C for overnight the reaction was incomplete. More 1-methylpiperazine (12.6 mL) was added and the reaction heated at 170 °C for 2 d. After cooling to room temperature, water was added and the crude

product was extracted with ethyl acetate (3×). Most of the bis-(1-methylpiperazine) by-product stayed in the aqueous layer. The combined organic layers were dried over sodium sulfate and after concentration the crude was used for the carbonylation.

MS (ESP): 227.1 (MH^+) for $C_{10}H_{15}ClN$.

Intermediate 137

methyl 4-amino-6-(4-methylpiperazin-1-yl)picolinate



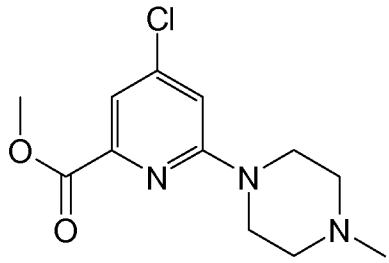
To a 2 L Parr Bomb was charged 2-chloro-6-(4-methylpiperazin-1-yl)pyridin-4-amine (Intermediate 136, 61.3 mmol) with methanol (300 mL). [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (2.5 g, 5mol%) was added followed by triethylamine (17 mL). The mixture was heated at 100 °C under 100 psi CO atmosphere overnight. The reaction mixture was triturated by dichloromethane to give a product as grey solid at 90% purity (6.5 g, 42.5% in two steps).

MS (ESP): 251.1 (MH^+) for $C_{12}H_{18}N_4O_2$

^{1}H NMR (300 MHz, CD_3OD): δ 2.9 (s, 3H), 3.3 (t, 4H), 3.9 (s, 3H), 4.9 (t, 4H), 6.2 (d, 1H), 6.9 (d, 1H).

Intermediate 138

methyl 4-chloro-6-(4-methylpiperazin-1-yl)picolinate



To a 1 L round bottom flask was charged t-butyl nitrite (2 mL, 15.3 mmol) with acetonitrile (200 mL), then copper (II) chloride (850 mg, 6.12 mmol) was added, and the mixture was allowed to heat at 70 °C for 30 min to give a dark greenish solution. Methyl 4-amino-6-(4-

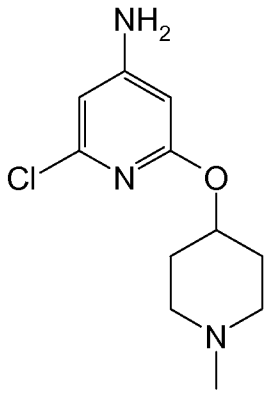
methylpiperazin-1-yl)picolinate (Intermediate 137, 2.55 g, 10.2 mmol) was added and gas evolution was observed. The mixture was heated at 70 °C for a further 2 h. After cooling to room temperature, the mixture was filtered through a Celite pad and the filtrate was concentrated. The crude product was purified by Analogix (heptane / ethyl acetate 0-30%) to give a white solid.

MS (ESP): 270.0 (MH^+) for $C_{12}H_{16}ClN_3O_2$

^1H NMR (300 MHz, CD_3OD): δ 2.95 (s, 3H), 3.55-3.65 (m, 4H), 3.90 (s, 3H), 4.6-4.7 (m, 4H), 7.22 (d, 1H), 7.45 (d, 1H).

Intermediate 139

2-chloro-6-(1-methylpiperidin-4-yloxy)pyridin-4-amine

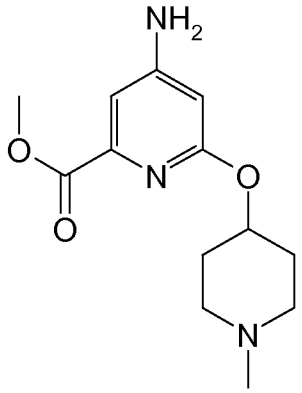


To a 500 mL sealed tube was charge 2,6-dichloro-4-aminopyridine (10 g, 61.3 mmol), sodium hydride (60% in mineral oil, 6.1 g, 153.37 mmol) with 1-methyl-4-hydroxypiperidine (25 g, 217 mmol). Toluene (50 mL, anhydrous) was added to aid transferring 1-methyl-4-hydroxypiperidine. Bubbling in the reaction mixture was observed on addition of the piperidine. When the gas evolution ceased, the reaction mixture was heated at 120°C for 2 h. More sodium hydride (1.4 g, 35 mmol) was added and heating continued at 120°C for another 1.5 h. After cooling to room temperature, water was added and the crude product was extracted with dichloromethane/isopropanol (2:1) three times. The combined organic layers were dried over sodium sulfate. After concentration, the crude was used for the carbonylation.

MS (ESP): 227.1 (MH^+) for $C_{11}H_{16}ClN_3O$.

Intermediate 140

methyl 4-amino-6-(1-methylpiperidin-4-yloxy)picolinate



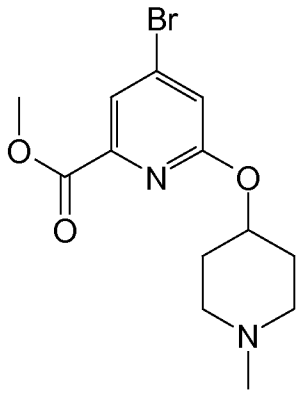
To a 2 L Parr Bomb was charged 2-chloro-6-(4-methylpiperazin-1-yl)pyridin-4-amine (Intermediate 139, 61.3 mmol) with methanol (300 mL). [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (2.5 g, 5mol%) was added followed by triethylamine (17 mL). The mixture was heated at 100 °C under 100 psi CO atmosphere overnight. The crude reaction was filtered through Celite and the filtrate was concentrated to dryness. The crude product was directly purified by chromatography (~2% (2M ammonia in methanol) in dichloromethane) to give a brown solid (4.75 g, 29.2%)

MS (ESP): 266.1 (MH^+) for $C_{13}H_{19}N_3O_3$

^{1}H NMR (300 MHz, CD_3OD): δ 1.7-1.9 (m, 2H), 2.35 (s, 3H), 2.7-2.8 (m, 2H), 3.95 (s, 3H), 5.0-5.1 (m, 1H), 6.1 (s, 1H), 7.0 (s, 1H).

Intermediate 141

methyl 4-bromo-6-(1-methylpiperidin-4-yloxy)picolinate



To a 1 L round bottom flask was charged methyl 4-amino-6-(1-methylpiperidin-4-yloxy)picolinate (Intermediate 140, 2.75 g, 10.4 mmol) with acetonitrile (200 mL). Then t-butyl nitrite (2.1 mL, 15.6 mmol) was added at 45 °C followed by copper (II) bromide (1.16 g, 5.19 mmol), and the dark greenish mixture heated at 45°C for 2 h. After cooling to room

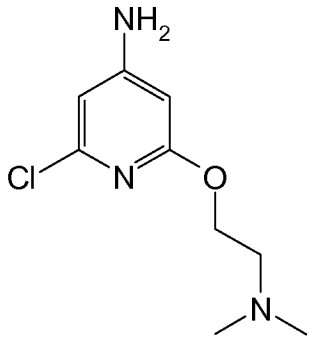
temperature, the mixture was filtered through a Celite pad and the filtrate concentrated under reduced pressure. The crude product was directly purified by Analogix (dichloromethane/ methanol) to give a light yellow solid (1 g, 29.4%).

MS (ESP): 329.1 (MH^+) for $C_{13}H_{17}BrN_2O_3$

^1H NMR (300 MHz, CD_3OD): δ 2.05-2.15 (br, 4H), 2.9 (s, 3H), 3.25-3.45 (br, 4H), 3.96 (s, 3H), 5.4-5.5 (m, 1H), 7.3 (s, 1H), 7.9 (s, 1H).

Intermediate 142

2-chloro-6-(2-(dimethylamino)ethoxy)pyridin-4-amine

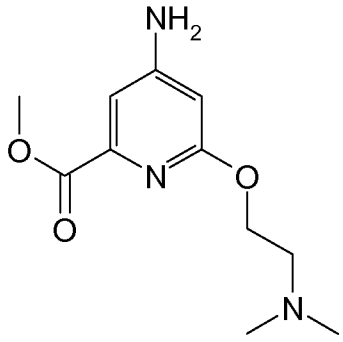


To a 500 mL sealed tube was charge 2,6-dichloro-4-aminopyridine (10.1 g, 62 mmol), sodium hydride (95%, 3.2 g, 126.8 mmol) and N, N-dimethylethanolamine (50 mL). After heating at 170°C for overnight the reaction was incomplete. More sodium hydride (0.5 g, 19.8 mmol) was added and heating continued at 170°C for another 1.5 h. After cooling to room temperature, water was added and the crude product was extracted with dichloromethane /isopropanol (2:1) three times. The combined organic layers were dried over sodium sulfate, filtered, concentrated under reduced pressure and the crude directly used for carbonylation.

MS (ESP): 216.0 (MH^+) for $C_9H_{14}ClN_3O$.

Intermediate 143

methyl 4-amino-6-(2-(dimethylamino)ethoxy)picolinate



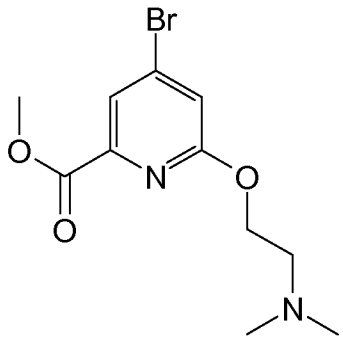
To a 2 L Parr Bomb was charged 2-chloro-6-(2-(dimethylamino)ethoxy)pyridin-4-amine (Intermediate 142, 62 mmol) with methanol (300 mL). [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (2.53 g, 5mol%) was added followed by triethylamine (17.3 mL). The resulting mixture was heated at 100°C under 100 psi CO atmosphere overnight. The mixture was concentrated to dryness and washed with water and brine, the mixture was extracted with dichloromethane /isopropanol (2:1) and ethanol /tetrahydorfuran (1:1). The organic layers were combined and dried over sodium sulfate. After concentration, the crude product was purified by chromatography (~2% (2M ammonia in methanol) in dichloromethane) to give a brown sticky solid. (8.5 g, 57%)

MS (ESP): 240.3 (MH^+) for $C_{11}H_{17}N_3O_3$

^1H NMR (300 MHz, CD_3OD): δ 2.4 (s, 6H), 2.8 (t, 2H), 3.9 (s, 3H), 4.4 (t, 2H), 6.1 (s, 1H), 7.1 (s, 1H).

Intermediate 144

methyl 4-bromo-6-(2-(dimethylamino)ethoxy)picolinate

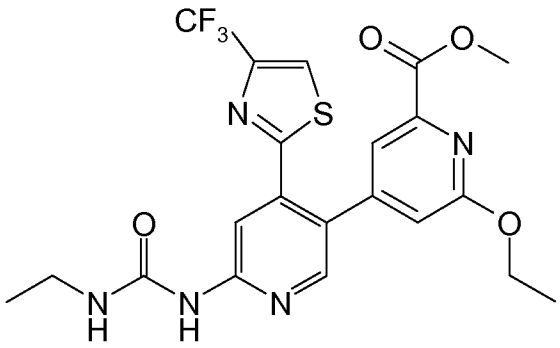


To a 1 L round bottom flask was charged methyl 4-amino-6-(2-(dimethylamino)ethoxy)picolinate (Intermediate 143, 1.35 g, 5.6 mmol) with acetonitrile (100 mL), then t-butyl nitrite (1.2 mL, 8.5 mmol) was added. The mixture was heated at 50 °C for ~10 min, then copper (II) bromide (1.16 g, 5.19 mmol) was added and the mixture heated at 50 °C for a further 2 h. After cooling to room temperature, the mixture was filtered through a Celite pad and the filtrate was concentrated. The crude product was purified by Analogix (dichloromethane/methanol) to give a light yellow solid (350 mg, 20.6%).

MS (ESP): 305.1 (MH^+) for $C_{11}H_{15}BrN_2O_3$

Intermediate 145

methyl 6'-ethoxy-6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate

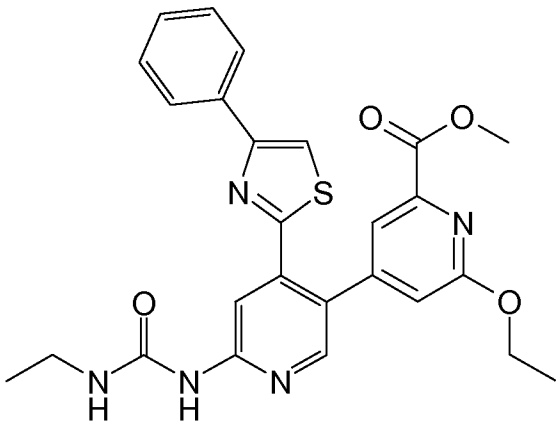


To a microwave sealed tube was charged methyl 4-chloro-6-ethoxypicolinate (Intermediate 126, 500 mg, 2.33 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (96 mg, 0.116 mmol) with dioxane (10 mL). Sodium bicarbonate (390 mg, 4.65 mmol), water (2 mL) were added, then 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 12, 920 mg, 5.12 mmol) weas added, and the mixture was purged with N_2 for ~5 min. The resulting mixture was heated to 80˚C for 0.5 h. The mixture was cooled to room temperature, diluted with water, extracted with ethyl acetate (3×) and the combined organic layers were dried over sodium sulfate. After concentration, the crude mixture was purified by Analogix (heptane/ethyl acetate 0-50%) to give a white solid (300 mg, 26%).

MS (ESP): 496.2 (MH^+) for $C_{21}H_{20}F_3N_5O_4S$.

Intermediate 146

methyl 6'-ethoxy-6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridine-2'-carboxylate



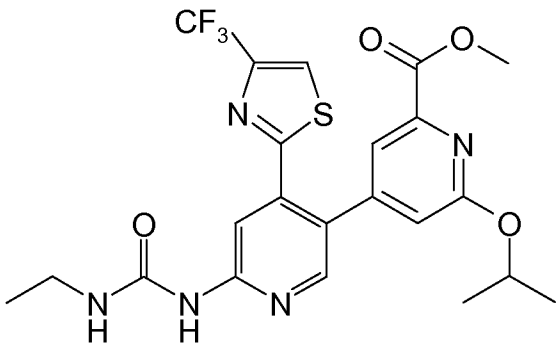
To a microwave sealed tube was charged methyl 4-chloro-6-ethoxypicolinate (Intermediate 126, 470 mg, 2.19 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II)

complex with dichloromethane (53 mg, 0.0649 mmol) and 1,4-dioxane (8 mL). Then sodium bicarbonate (374 mg, 4.45 mmol), water (2 mL) and 6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 161, 820 g, 2.23 mmol) were added and the reaction mixture purged with N_2 for 10 min. The resulting mixture was heated to 80 °C for 0.5 h. The reaction mixture was cooled to room temperature, diluted with water, extracted with ethyl acetate (3×) and the combined organic layers dried over sodium sulfate. After concentration under reduced pressure, the crude mixture was purified by Analogix (heptane/ethyl acetate 0-60%) to give an off-white solid (650 mg).

MS (ESP): 504.0 (MH^+) for $C_{26}H_{25}N_5O_4S$

Intermediate 147

methyl 6-(3-ethylureido)-6'-isopropoxy-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate

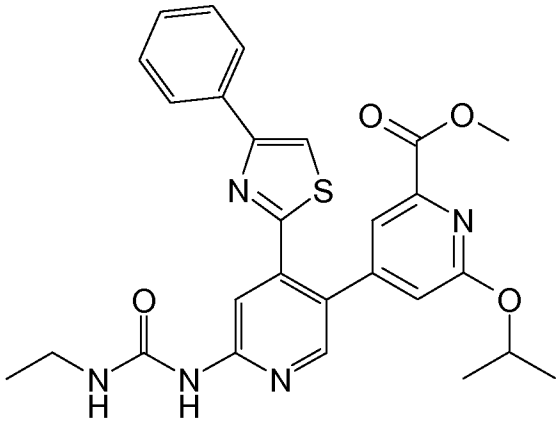


To a microwave sealed tube was charged methyl 4-chloro-6-isopropoxypicolinate (Intermediate 129, 510 mg, 2.23 mmol) and tetrakis(triphenylphosphine)palladium (0) (129 mg, 0.111 mmol) with 1,4-dioxane (12 mL). Then sodium bicarbonate (390 mg, 4.65 mmol), water (3 mL) and 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 12, 821 mg, 2.28 mmol) was added and the mixture purged with N_2 for 5 min. The resulting mixture was heated to 80°C for 0.5 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate then purified by Analogix (heptane/ethyl acetate 0-100%) to give a light brown solid (900 mg).

MS (ESP): 510.0 (MH^+) for $C_{22}H_{22}F_3N_5O_4S$

Intermediate 148

methyl 6-(3-ethylureido)-6'-isopropoxy-4-(4-phenylthiazol-2-yl)-3,4'-bipyridine-2'-carboxylate

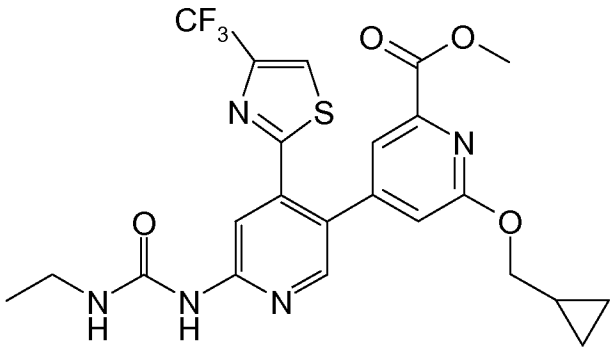


To a microwave sealed tube was charged methyl 4-chloro-6-isopropoxypicolinate (Intermediate 129, 1 g, 4.36 mmol) and tetrakis(triphenylphosphine)palladium (0) (252 mg, 0.21mmol) with 1,4-dioxane (24 mL). Sodium bicarbonate (540 mg, 8.8 mmol), water (6 mL), and 6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 161, 1.62 g, 4.38 mmol) were added. The mixture was purged with N_2 for ~5 min then heated to 80°C for 0.5 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate. After concentration, the crude mixture was triturated with ethanol to give a bright yellow solid which was a mixture of the desired methyl ester and de-boronated compound (1.1 g).

MS (ESP): 518.1 (MH^+) for $C_{27}H_{27}N_5O_4S$

Intermediate 149

methyl 6'-(cyclopropylmethoxy)-6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate



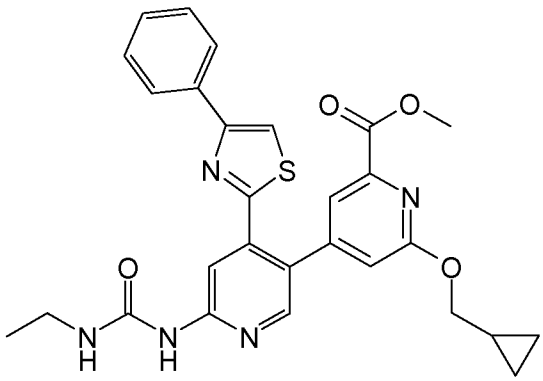
To a microwave sealed tube was charged methyl 4-chloro-6-(cyclopropylmethoxy)picolinate (Intermediate 132, 435 mg, 1.81 mmol), 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 12, 650 mg, 1.81 mmol) and 1,4-dioxane (12 mL).

Then sodium bicarbonate (305 mg, 2.64 mmol) and water (3 mL) were added and the mixture was purged by N_2 for 5 min. Tetrakis(triphenylphosphine)palladium (0) (104 mg, 0.095 mmol) was added, and the resulting mixture was heated to 80˚C for 1 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate. After concentration under reduced pressure, the crude mixture was triturated by ethanol to give a light brown solid (100 mg).

MS (ESP): 522.1 (MH^+) for $C_{23}H_{22}F_3N_5O_4S$

Intermediate 150

methyl 6'-(cyclopropylmethoxy)-6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridine-2'-carboxylate

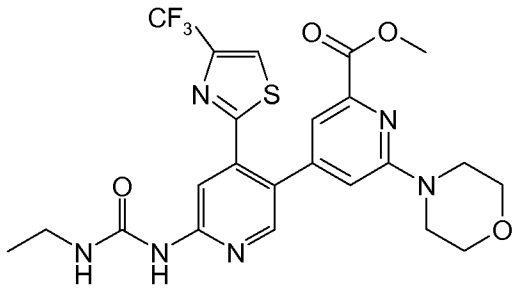


To a microwave sealed tube was charged methyl 4-chloro-6-(cyclopropylmethoxy)picolinate (Intermediate 132, 328 mg, 1.36 mmol), 6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 161, 510 mg, 1.38 mmol) and 1,4-dioxane (12 mL). Sodium bicarbonate (305 mg, 2.64 mmol) was added with water (3 mL) and the mixture was purged by N_2 for ~5 min. Tetrakis(triphenylphosphine)palladium (0) (82 mg, 0.071 mmol) was added and the resulting mixture was heated to 80˚C for 1 h. The mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate. After concentration under reduced pressure, the crude mixture was used without purification.

MS (ESP): 530.1 (MH^+) for $C_{28}H_{27}N_5O_4S$

Intermediate 151

methyl 6-(3-ethylureido)-6'-morpholino-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate

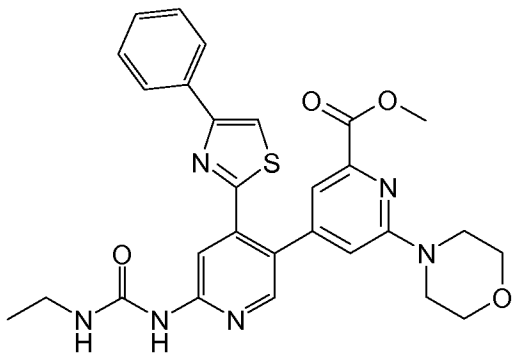


To a microwave sealed tube was charged methyl 4-chloro-6-morpholinopicolinate (Intermediate 135, 357 mg, 1.39 mmol), 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 12, 500 mg, 1.39 mmol) and 1,4-dioxane (15 mL). Sodium bicarbonate (240 mg, 2.86 mmol) was added with water (3 mL), the mixture was purged by N_2 for 10 min, then tetrakis(triphenylphosphine)palladium (0) (90 mg, 0.078 mmol) was added. The resulting mixture was heated to 80°C for 1 h. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate. After concentration under reduced pressure, a brown solid was obtained and triturated with ethanol (cold) to give an off-white solid (350 mg, 54%).

MS (ESP): 537.0 (MH^+) for $C_{23}H_{23}F_3N_6O_4S$

Intermediate 152

6-(3-ethylureido)-6'-morpholino-4-(4-phenylthiazol-2-yl)-3,4'-bipyridine-2'-carboxylate



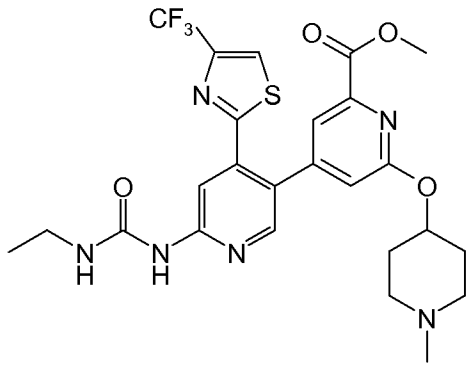
To a microwave sealed tube was charged methyl 4-chloro-6-morpholinopicolinate (Intermediate 135, 492 g, 1.91 mmol), 6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 161, 700 mg, 1.91 mmol) with 1,4-dioxane (12 mL). Sodium bicarbonate (320 mg, 3.81 mmol) was added with water (3 mL), the mixture was purged by N_2 for 10 min, then tetrakis(triphenylphosphine)palladium (0) (80 mg, 0.069 mmol) was added. The resulting mixture was heated to 85°C for 1 h. The reaction was incomplete so more 6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-ylboronic acid (230 mg) was added

with more tetrakis(triphenylphosphine)palladium (0) (84 mg, 0.073 mmol) and the resulting mixture was heated at 85˚C for two more hours. The mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate (3×). The combined organic layers were dried over sodium sulfate. After concentration, a yellow solid (700 mg) was obtained which is the mixture of the desired methyl ester, de-boronated compound and homocoupling product

MS (ESP): 545.1 (MH^+) for $C_{28}H_{28}N_6O_4S$

Intermediate 153

methyl 6-(3-ethylureido)-6'-(1-methylpiperidin-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate

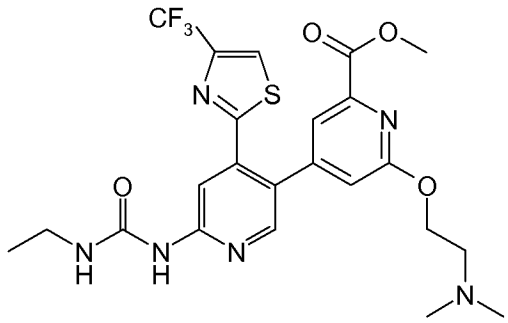


To a microwave sealed tube was charged methyl 4-bromo-6-(1-methylpiperidin-4-yloxy)picolinate (Intermediate 141, 400 mg, 1.22 mmol), 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 12, 800 mg, 2.22 mmol) and 1,4-dioxane (12 mL). Then K_3PO_4 solution (2 N in water, 1.4 mL), and tetrakis(triphenylphosphine)palladium (0) (140 mg, 0.121 mmol) were added and the mixture was purged by N_2 for ~10 min. The resulting mixture was heated to 90˚C for 1 h. LC showed starting bromide remained so more 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (200 mg) was added and the mixture was heated at 90˚C for a further 1 h. The mixture was concentrated to dryness and triturated with methyl tert-butyl ether. The filtrate was concentrated and triturated by methyl tert-butyl ether again. The second filtrate was concentrated and purified by Analogix (dichloromethane/methanol) to give a light yellow solid (250 mg, 36.3%)

MS (ESP): 565.2 (MH^+) for $C_{25}H_{27}F_3N_6O_4S$

Intermediate 154

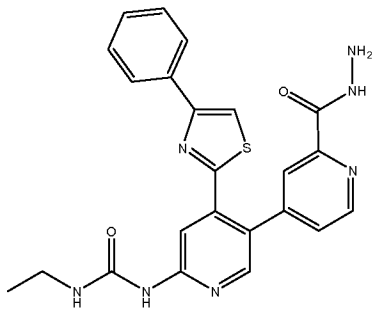
methyl 6'-(2-(dimethylamino)ethoxy)-6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate



To a microwave sealed tube was charged methyl 4-bromo-6-(2-(dimethylamino)ethoxy)picolinate (Intermediate 144, 300 mg, 0.987 mmol), 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 12, 426mg, 1.18 mmol) with 1,4-dioxane (12 mL). Then K_3PO_4 solution (2 N in water, 1.2 mL) was added with tetrakis(triphenylphosphine)palladium (0) (115 mg, 0.099 mmol),and the mixture purged by N_2 for 10 min. The resulting mixture was heated to 90˚C for 1 h. The reaction mixture was cooled to room temperature and some solid precipitated and was filtered to give de-boronated by-product. The filtrate was diluted with water and extracted with ethyl acetate (3×). The organic layers were combined and dried over sodium sulfate, after concentration, the crude product was triturated by dichloromethane twice to remove most of the less soluble de-boronated product. The resulting filtrate was concentrated and purified by Analogix (dichloromethane/methanol) to give a light yellow sticky solid (120 mg).
MS (ESP): 539.1 (MH^+) for $C_{23}H_{25}F_3N_6O_4S$

Intermediate 155

1-ethyl-3-(2'-(hydrazinecarbonyl)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridin-6-yl)urea



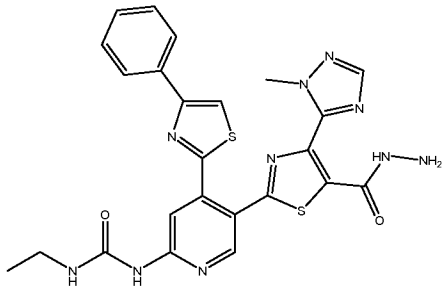
Intermediate 155 was synthesized according to the procedure described for Intermediate 22 from Intermediate 158 and hydrazine.

LC/MS (ES^+)[$(M+H)^+$]: 460 for $C_{23}H_{21}N_7O_2S$.

^1H NMR (300 MHz, d_6-DMSO): 1.12 (t, 3H), 3.22 (m, 2H), 4.58 (s, 2H), 7.34- 7.43 (m, 3H), 7.54 (d, 1H), 7.74 (d, 3H), 7.91 (s, 1H), 8.2 (d, 2H), 8.3 (s,1H), 8.6 (d, 1H), 9.5 (s, 1H), 10.0 (s, 1H).

Intermediate 156

1-ethyl-3-(5-(5-(hydrazinecarbonyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazol-2-yl)-4-(4-phenylthiazol-2-yl)pyridin-2-yl)urea



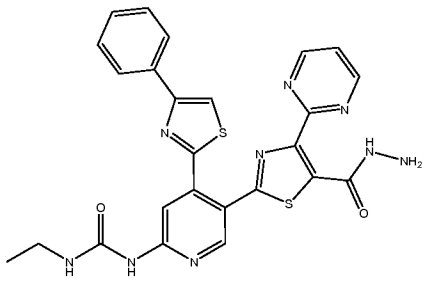
Intermediate 156 was synthesized according to the procedure described for Intermediate 22 from Intermediate 159 and hydrazine.

LC/MS (ES^+)[$(M+H)^+$]: 547 for $C_{24}H_{22}N_{10}O_2S_2$.

^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.21 (m, 2H), 3.93 (s, 3H), 4.75 (d, 2H), 7.37 (m, 3H), 7.56 (m, 1H), 7.83 (d, 2H), 8.11 (s, 1H), 8.24 (s, 1H), 8.36 (s,1H), 8.79 (s, 1H), 9.67 (s, 1H), 11.84 (s, 1H).

Intermediate 157

1-ethyl-3-(5-(5-(hydrazinecarbonyl)-4-(pyrimidin-2-yl)thiazol-2-yl)-4-(4-phenylthiazol-2-yl)pyridin-2-yl)urea

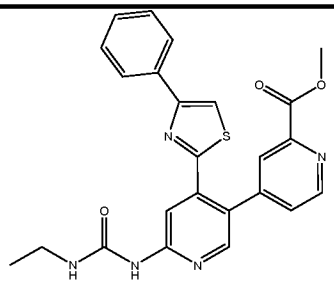
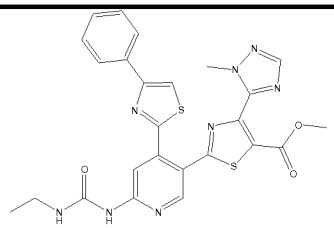


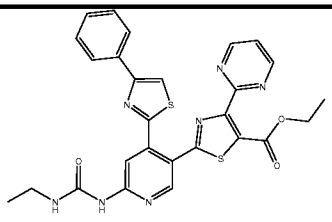
Intermediate 157 was synthesized according to the procedure described for Intermediate 22 from Intermediate 160 and hydrazine.

LC/MS (ES^+)[$(M+H)^+$]: 544 for $C_{25}H_{21}N_9O_2S_2$.

Intermediate 158-160

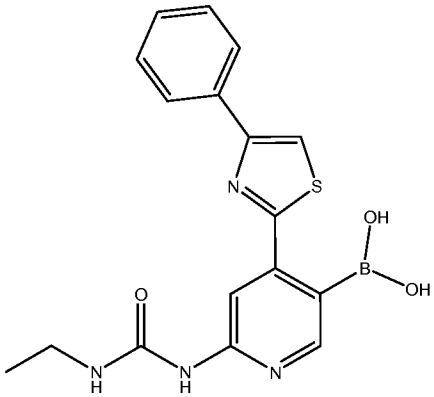
The following intermediates were prepared in accordance to the procedure described for Intermediate 20 using the starting materials indicated in the table.

Int	Compound	Structure	Data	SM
158	methyl 6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)-3,4'-bipyridine-2'-carboxylate		LC/MS (ES^+)[$(M+H)^+$]: 460 for $C_{24}H_{21}N_5O_3S$. ^1H NMR (300 MHz, DMSO-d6): 1.11 (t, 3H), 3.21 (q, 2H), 3.84 (s, 3H), 7.35 (m, 3H), 7.63 (m, 4H), 8.01 (s, 1H), 8.20 (d, 2H), 8.30 (s, 1H), 8.7 (d, 1H), 9.5 (s, 1H)	Intermediate 161 and methyl 4-bromopicolinate
159	methyl 2-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazole-5-carboxylate		LC/MS (ES^+)[$(M+H)^+$]: 547 for $C_{25}H_{22}N_8O_3S_2$. ^1H NMR (300 MHz, CDCl3): 1.11 (t, 3H), 3.21 (q, 2H), 3.6 (s, 3H), 3.75 (s, 3H), 7.4 (m, 5H), 7.84 (d, 2H), 8.05 (s, 1H), 8.17 (s, 1H), 8.38 (s, 1H), 8.76 (s, 1H), 9.70 (s, 1H)	Intermediate 161 and Intermediate 44

Int	Compound	Structure	Data	SM
160	ethyl 2-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-4-(pyrimidin-2-yl)thiazole-5-carboxylate		LC/MS (ES^+)[$(M+H)^+$]: 558 for $C_{27}H_{23}N_7O_3S_2$.	Intermediate 161 and Intermediate 43

Intermediate 161

6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-ylboronic acid



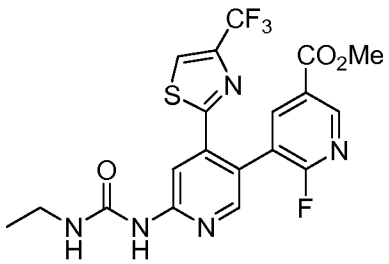
A solution of 1-(5-bromo-4-(4-phenylthiazol-2-yl)pyridin-2-yl)-3-ethylurea (2.97 g, 7.36 mmol, Intermediate 16) in THF (25 mL) was cooled to -78 °C. Isopropylmagnesium chloride, 2.0M in THF (8.84 mL, 17.67 mmol) was added slowly and the reaction was slowly warmed to -15 °C before being cooled back down to -78 °C. N-Butyllithium, 2.5M in hexanes (14.73 mL, 36.82 mmol) was then added and the reaction was stirred at -78 °C for 1 h. Trimethyl borate (8.21 mL, 73.64 mmol) was added all at once and an exotherm was observed. Following the exotherm, the reaction mixture was allowed to warm to room temperature and stir for 3 h. The reaction mixture was then cooled to 0 °C and 20 mL of water was added slowly followed by 10 mL of 6N HCl. The reaction mixture was allowed to warm to room temperature and stir for 30 min. The reaction mixture was concentrated under reduced pressure to remove THF. The aqueous portion was diluted with 1N NaOH and diethylether. The aqueous layer was acidified with HCl and the resulting precipitate was the title compound.

MS (ESP): 369 ($M+H^+$) for $C_{17}H_{17}BN_4O_3S$.

^1H NMR (DMSO-d6): δ 1.1 (t, 3H), 3.2 (q, 2 H), 7.4-7.5 (m, 3H), 7.8 (s, 1H), 7.9 (s, 1 H), 8.1 (d, 2H), 9.3 (s, 1H).

Intermediate 162

Methyl 6'-(3-ethylureido)-2-fluoro-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



The 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 12, 1.20 g, 3.33 mmol), methyl 5-bromo-6-fluoronicotinate (WO200224681, 0.819 g, 3.50 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.305 g, 0.33 mmol), and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (0.477 g, 1.00 mmol) were combined and then degassed and purged with N_2 twice. A solution of sodium carbonate (0.353 g, 3.33 mmol) in water (4.5 mL) was added, followed by the addition of acetonitrile (18 mL). The flask was degassed and purged with N_2 again. The mixture was heated at 80 °C for 1.5 h and then stirred at RT overnight. The mixture was conc *in vacuo*, diluted with EtOAc and water and filtered through a fritted funnel fitted with filter paper. The layers of the filtrate were separated. The organic layer was washed three times with sat NH_4Cl, once with brine, dried over Na_2SO_4, and conc *in vacuo*. Purification via silica gel chromatography (50% acetone/hexanes; then 5-10% MeOH/CH_2Cl_2) gave 0.351 g (22%) of the title compound.

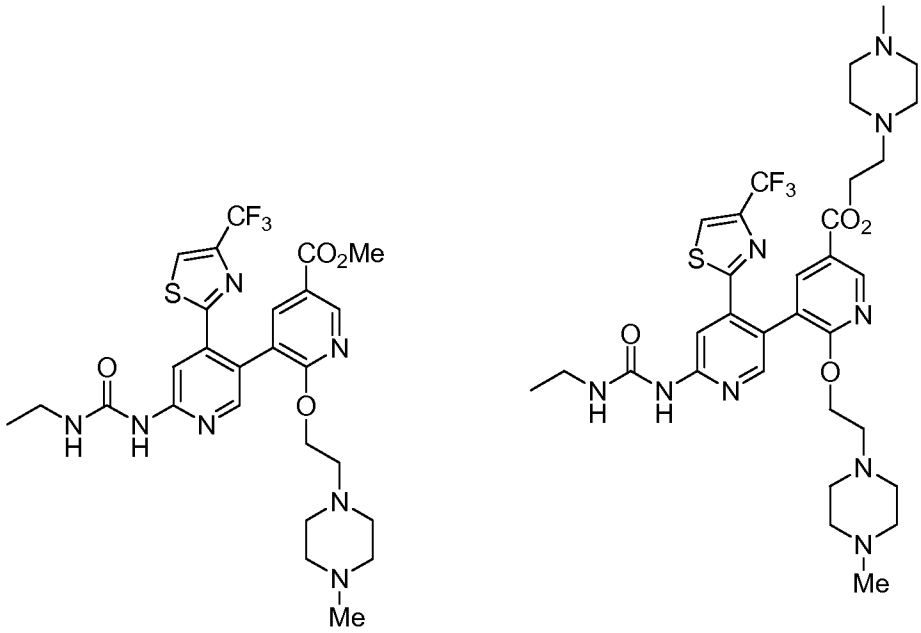
LC/MS (ES^+)[$(M+H)^+$]: 470 for $C_{19}H_{15}F_4N_5O_3S$

^1H NMR (DMSO-d_6): δ 9.56 (s, 1H); 8.82 (m, 1H); 8.61 (s, 1H); 8.49 (m, 1H); 8.40 (s, 1H); 8.25 (s, 1H); 7.50 (m, 1H); 3.90 (s, 3H); 3.21 (m, 2H); 1.11 (t, 3H).

Intermediate 163 and Intermediate 164

Methyl 6'-(3-ethylureido)-2-(2-(4-methylpiperazin-1-yl)ethoxy)-4'-(4 (trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate and 2-(4-Methylpiperazin-1-yl)ethyl 6'-(3-ethylureido)-2-

(2-(4-methylpiperazin-1-yl)ethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



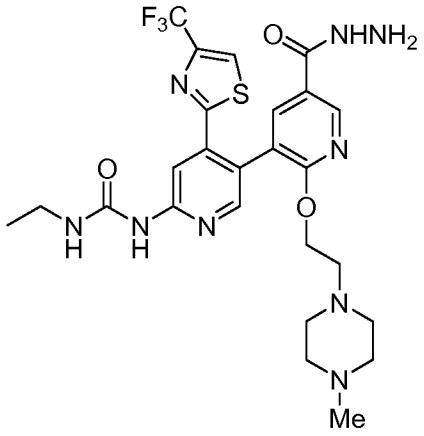
The 2-(4-methylpiperazin-1-yl)ethanol (0.154 g, 1.07 mmol) in THF (0.5 mL) was cooled to 0 °C. A 1.0 M solution of lithium bis(trimethylsilyl)amide in THF (1.066 mL, 1.07 mmol) was added dropwise. The mixture was stirred at 0 °C for 10 min and then stirred at RT for 15 min. This mixture was then added dropwise to a 0 °C solution of methyl 6'-(3-ethylureido)-2-fluoro-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 162, 0.115 g, 0.24 mmol) in THF (1 mL). Additional THF (0.5 mL) was added. The resultant mixture was stirred at 0 °C for 10 min and then stirred at RT for 30 min. The mixture was cooled to 0 °C, quenched with satd NH_4Cl and conc *in vacuo*. The residue was diluted with EtOAc and water and the layers were separated. The organic layer was washed with satd NH_4Cl, water, brine, dried over Na_2SO_4 and conc *in vacuo*. LC/MS indicated a mixture of methyl 6'-(3-ethylureido)-2-(2-(4-methylpiperazin-1-yl)ethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 163) and 2-(4-methylpiperazin-1-yl)ethyl 6'-(3-ethylureido)-2-(2-(4-methylpiperazin-1-yl)ethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 164) which was used without further purification.

Intemediate 163: LC/MS (ES^+)[$(M+H)^+$]: 594 for $C_{26}H_{30}F_3N_7O_4S$

Intermediate 164: LC/MS (ES^+)[$(M+H)^+$]: 706 for $C_{32}H_{42}F_3N_9O_4S$

Intermediate 165

1-Ethyl-3-(5'-(hydrazinecarbonyl)-2'-(2-(4-methylpiperazin-1-yl)ethoxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea

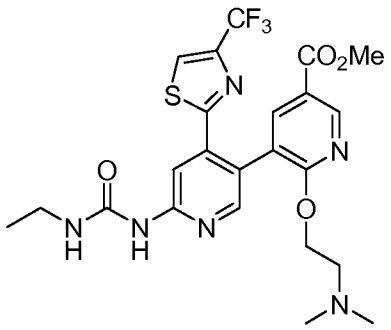


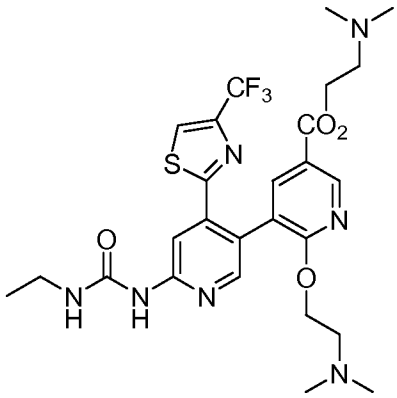
Hydrazine hydrate (0.117 mL, 2.40 mmol) was added to 142 mg of a mixture of methyl 6'-(3-ethylureido)-2-(2-(4-methylpiperazin-1-yl)ethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 163) and 2-(4-methylpiperazin-1-yl)ethyl 6'-(3-ethylureido)-2-(2-(4-methylpiperazin-1-yl)ethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 164). The reaction mixture was heated at 82 °C overnight. After conc *in vacuo*, the residue was diluted with EtOAc and water and the layers were separated. The organic layer was washed three times with satd NH_4Cl, once with brine, dried over Na_2SO_4 and conc *in vacuo* to give the title compound which was used without further purification.

LC/MS (ES^+)[$(M+H)^+$]: 594 for $C_{25}H_{30}F_3N_9O_3S$.

Intermediate 166 and Intermediate 167

Methyl 2-(2-(dimethylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate and 2-(Dimethylamino)ethyl 2-(2-(dimethylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate





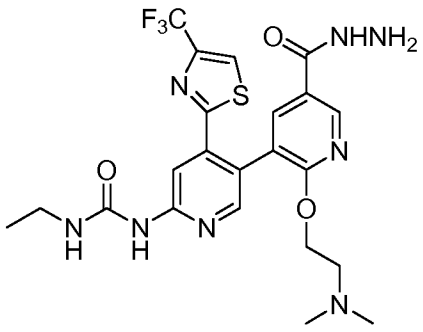
Following the procedure for Intermediates 163 and Intermediate 164, 2-(dimethylamino)ethanol (0.1 mL, 1.04 mmol) and methyl 6'-(3-ethylureido)-2-fluoro-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 162, 0.112 g, 0.24 mmol) were reacted to give a mixture of methyl 2-(2-(dimethylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 166) and 2-(dimethylamino)ethyl 2-(2-(dimethylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 167) which was used without further purifcation.

Intermediate 166: LC/MS (ES^+)[$(M+H)^+$]: 539 for $C_{23}H_{25}F_3N_6O_4S$

Intermediate 167: LC/MS (ES^+)[$(M+H)^+$]: 596 for $C_{26}H_{32}F_3N_7O_4S$

Intermediate 168

1-(2'-(2-(Dimethylamino)ethoxy)-5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea

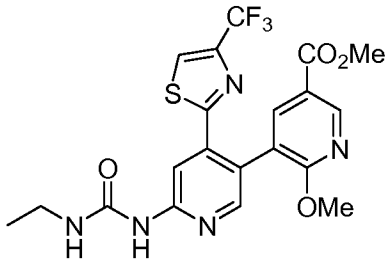


Following the procedure for Intermediate 165, 0.129 g of the mixture of methyl 2-(2-(dimethylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 166) and 2-(dimethylamino)ethyl 2-(2-(dimethylamino)ethoxy)-6'-

(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 167) was reacted to give the title compound which was used without further purification.
LC/MS (ES^+)[$(M+H)^+$]: 539 for $C_{22}H_{25}F_3N_8O_3S$.

Intermediate 169

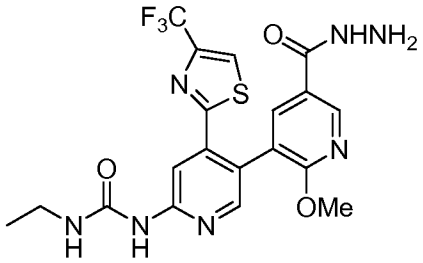
Methyl 6'-(3-ethylureido)-2-methoxy-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



The methyl 6'-(3-ethylureido)-2-fluoro-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 162, 0.121 g, 0.26 mmol) was suspended in THF (4 mL) and cooled to 0 °C. A 0.5 M solution of sodium methoxide in MeOH (2.243 mL, 1.12 mmol) was added dropwise. The mixture was stirred at 0 °C for 20 min and then warmed to RT. After quenching with satd NH_4Cl, the mixture was conc *in vacuo*. The residue was diluted with EtOAc and water and the layers were separated. The organic layer was washed with water, brine, dried over Na_2SO_4 and conc *in vacuo* to give the title compound which was used without further purification.
LC/MS (ES^+)[$(M+H)^+$]: 482 for $C_{20}H_{18}F_3N_5O_4S$.

Intermediate 170

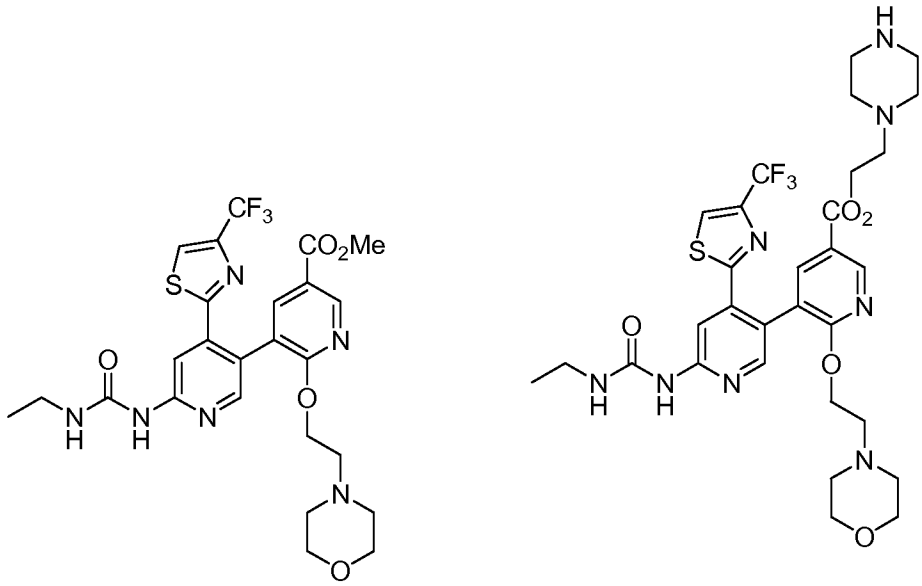
1-Ethyl-3-(5'-(hydrazinecarbonyl)-2'-methoxy-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



Following the procedure for Intermediate 165, methyl 6'-(3-ethylureido)-2-methoxy-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 169, 0.197 g, 0.41 mmol) was reacted to give the title compound which was used without further purification. LC/MS (ES^+)[$(M+H)^+$]: 482 for $C_{19}H_{18}F_3N_7O_3S$.

Intermediate 171 and Intermediate 172

Methyl 6'-(3-ethylureido)-2-(2-morpholinoethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate and 2-Morpholinoethyl 6'-(3-ethylureido)-2-(2-morpholinoethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



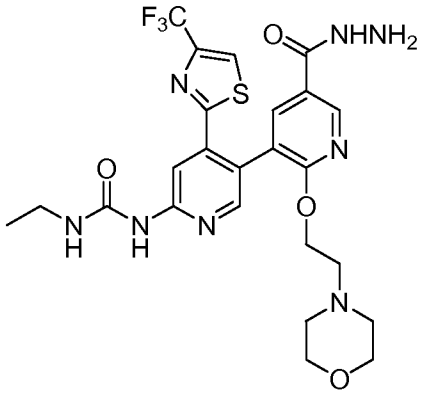
Following the procedure for Intermediates 163 and Intermediate 164, 2-morpholinoethanol (0.08 mL, 0.66 mmol) and methyl 6'-(3-ethylureido)-2-fluoro-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 162, 0.071 g, 0.15 mmol) were reacted to give a mixture of methyl 6'-(3-ethylureido)-2-(2-morpholinoethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 171) and 2-morpholinoethyl 6'-(3-ethylureido)-2-(2-morpholinoethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 172) which was used without further purification.

Intermediate 171: LC/MS (ES^+)[$(M+H)^+$]: 581 for $C_{25}H_{27}F_3N_6O_5S$

Intermediate 172: LC/MS (ES^+)[$(M+H)^+$]: 680 for $C_{30}H_{36}F_3N_7O_6S$

Intermediate 173

1-Ethyl-3-(5'-(hydrazinecarbonyl)-2'-(2-morpholinoethoxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea

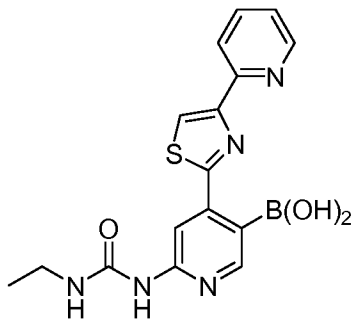


Following the procedure for Intermediate 165, 0.087 g of the mixture of methyl 6'-(3-ethylureido)-2-(2-morpholinoethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 171) and 2-morpholinoethyl 6'-(3-ethylureido)-2-(2-morpholinoethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 172) was reacted to give the title compound which was used without further purification.

LC/MS (ES^+)[$(M+H)^+$]: 581 for $C_{24}H_{27}F_3N_8O_4S$.

Intermediate 174

6-(3-Ethylureido)-4-(4-(pyridin-2-yl)thiazol-2-yl)pyridin-3-ylboronic acid



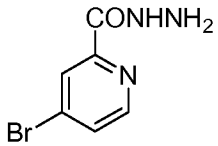
The N-[5-bromo-4-(4-(pyridin-2-yl)thiazol-2-yl)pyridin-2-yl]-N'-ethylurea (Intermediate 15, 0.965 g, 2.39 mmol) was suspended in THF (20 mL) and then cooled to -78 °C. A 1.8 M solution of phenyllithium in di-n-butylether (3.18 mL, 5.73 mmol) was added dropwise. After complete addition, the reaction mixture was stirred at -78 °C for 2 h. Next, a 2.5 M solution of n-BuLi in hexanes (4.77 mL, 11.93 mmol) was added dropwise. After complete addition, the reaction mixture was stirred at -78 °C for 1 h. Trimethyl borate (2.67 mL, 23.87 mmol) was then added all at once. The cold bath was removed and the thick mixture was

stirred at RT for 2 h. The mixture was re-cooled to 0 °C and water (6 mL) was added carefully, followed by 6 N HCl (6 mL, 36.00 mmol). The ice bath was then removed and the mixture was stirred at RT for 1 h and then placed in the refrigerator overnight. The aq and THF layers were separated and the THF layer was discarded. The aq layer was cooled to 0 °C and aq NaOH was added until the pH was approx. 5-6. The aq layer was extracted with several portions of EtOAc. The EtOAc extracts were conc *in vacuo* to give a solid. The solid was then treated with aq NaOH until the pH was >9. After diluting with MTBE, the aq and MTBE layers were separated. The aq layer was washed with several additional portions of MTBE. The MTBE layers were discarded. The aq layer was then cooled to 0 °C and treated with aq HCl until the pH was approx. 5-6. The aq layer was extracted with several portions of EtOAc. The EtOAc extracts were combined and conc *in vacuo* to give 0.331 g (38%) of the title compound which was used without further purification.

LC/MS (ES^+)[$(M+H)^+$]: 370 for $C_{16}H_{16}BN_5O_3S$.

Intermediate 175

4-Bromopicolinohydrazide

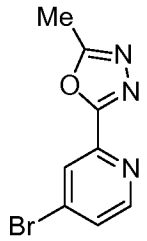


Methyl 4-bromopicolinate (1.080 g, 5.00 mmol) was dissolved in EtOH (25.00 ml). Hydrazine hydrate (2.432 ml, 50.00 mmol) was added and the mixture was heated at 85 °C for 1 h. After cooling to RT, the mixture was conc *in vacuo* to give the title compound which was used without further purification.

LC/MS (ES^+)[$(M+H)^+$]: 217 for $C_6H_6BrN_3O$

^1H NMR (DMSO-d_6): δ 10.03 (s, 1H); 8.50 (d, 1H); 8.12 (d, 1H); 7.87 (dd, 1H); 4.61 (br s, 2H).

Intermediate 176



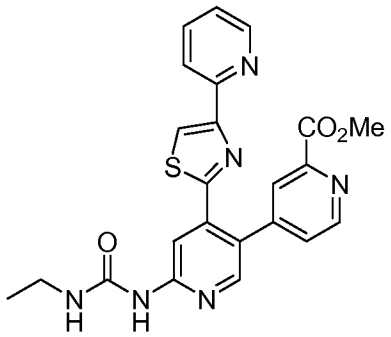
The 4-bromopicolinohydrazide (Intermediate 175 1.080 g, 5 mmol) was suspended in trimethyl orthoacetate (10 ml, 79.57 mmol). Using a pipet, 2 drops of conc HCl were added. The mixture was heated to 115 °C for 1 h and then cooled to RT. After conc *in vacuo*, the resultant solid was treated with additional trimethyl orthoacetate (10 ml, 79.57 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.6 mL) and heated at 110 °C for 48 h. After cooling to RT and conc *in vacuo*, the residue was diluted with EtOAc and washed with several portions of satd NH_4Cl until the washes were colorless. The organic layer was then washed with water, brine, dried over Na_2SO_4 and conc *in vacuo*. Purification by silica gel chromatography (0-10% MeOH/CH2Cl2) gave 0.524 g (39%) of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 241 for $C_8H_6BrN_3O$

^1H NMR (DMSO-d_6): δ 8.65 (d, 1H); 8.33 (d, 1H); 7.93 (dd, 1H); 2.62 (s, 3H).

Intermediate 177

Methyl 6-(3-ethylureido)-4-(4-(pyridin-2-yl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate



The 6-(3-ethylureido)-4-(4-(pyridin-2-yl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 174, 0.166 g, 0.45 mmol), methyl 4-bromopicolinate (0.117 g, 0.54 mmol), tetrakis (triphenylphosphine)palladium (0) (0.052 g, 0.05 mmol) and potassium carbonate (0.187 g,

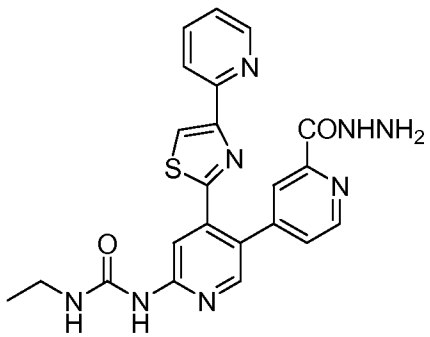
1.35 mmol) were placed in a microwave vessel. The vessel was degassed and purged with N_2 several times. DMF (3 mL) was added and the vessel was degassed and purged with N_2 again. The vessel was heated in the microwave at 95 °C for 2 h. The mixture was filtered through a fritted funnel fitted with filter paper and rinsed with several portions of CH_2Cl_2 and once with EtOAc. The filtrate was then conc *in vacuo*. Purification by silica gel chromatography (0-10% MeOH/CH_2Cl_2) gave 0.037 g (18%) of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 461 for $C_{23}H_{20}N_6O_3S$

^1H NMR (DMSO-d_6): δ 9.52 (s, 1H); 8.73 (d, 1H); 8.60 (m, 1H); 8.38 (s, 1H); 8.34 (s, 1H); 8.22 (s, 1H); 8.02 (s, 1H); 7.82 (m, 1H); 7.60 (m, 3H); 7.35 (m, 1H); 3.84 (s, 3H); 3.22 (m, 2H); 1.11 (t, 3H).

Intermediate 178

1-Ethyl-3-(2'-(hydrazinecarbonyl)-4-(4-(pyridin-2-yl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea

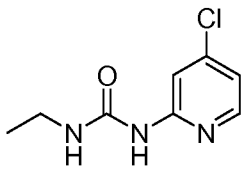


The methyl 6-(3-ethylureido)-4-(4-(pyridin-2-yl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate (Intermediate 177, 56.4 mg, 0.12 mmol), EtOH (1.75 mL), and hydrazine hydrate (0.060 mL, 1.22 mmol) were combined and heated at 85 °C for 1 h. After cooling to RT, the mixture was conc *in vacuo* to give the title compound which was used without further purificaiton.

LC/MS (ES^+)[$(M+H)^+$]: 461 for $C_{22}H_{20}N_8O_2S$

Intermediate 179

1-(4-Chloropyridin-2-yl)-3-ethylurea



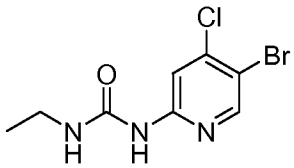
A suspension of 4-chloropyridin-2-amine (2.186 g, 17 mmol), ethyl isocyanate (2.69 mL, 34.00 mmol) and chloroform (8 mL) was heated in the microwave at 100 °C for 1 h. The resultant solution was then concentrated *in vacuo* to give the title compound in quantitative yield. No further purification was performed.

LC/MS (ES^+): 200, 202 for $C_8H_{10}ClN_3O$

^1H NMR (DMSO-d_6): δ 9.31 (s, 1H); 8.16 (d, 1H); 7.63 (m, 1H); 7.59 (m, 1H); 7.03 (m, 1H); 3.16 (m, 2H); 1.07 (t, 3H).

Intermediate 180

1-(5-Bromo-4-chloropyridin-2-yl)-3-ethylurea



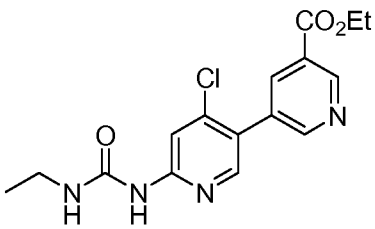
A solution of 1-(4-chloropyridin-2-yl)-3-ethylurea (Intermediate 179, 3.39 g, 16.98 mmol), *N*-bromosuccinimide (3.02 g, 16.98 mmol), acetonitrile (32 mL), and DMF (10 mL) were combined and heated at 80 °C for 2 h. Upon cooling to RT, a precipitate formed. Water was added and the solid was collected and washed with water to give 2.78 g (59%) of the title compound which was used without further purification.

LC/MS (ES^+): 278, 280 for $C_8H_9BrClN_3O$

^1H NMR (DMSO-d_6): δ 9.37 (s, 1H); 8.44 (s, 1H); 7.92 (s, 1H); 7.17 (m, 1H); 3.15 (m, 2H); 1.06 (t, 3H).

Intermediate 181

Ethyl 4'-chloro-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate



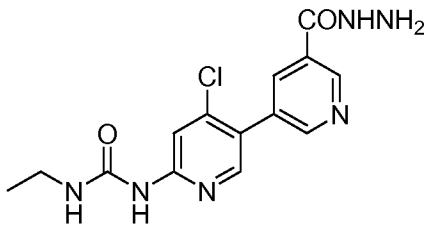
The 1-(5-bromo-4-chloropyridin-2-yl)-3-ethylurea (Intermediate 180, 0.404 g, 1.45 mmol), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (0.482 g, 1.74 mmol) and cesium carbonate (0.945 g, 2.90 mmol) were added to a microwave vessel. The vessel was degassed and purged with N_2. Tetrakis (triphenylphosphine)palladium (0) (0.168 g, 0.15 mmol) was added and the vessel was degassed and purged with N_2. Dioxane (10 mL) and water (2.5 mL) were added and the vessel was degassed and purged with N_2 three more times. The vessel was placed in the microwave and heated at 100 °C for 2 h. The organic layer was separated and conc *in vacuo*. After purification by silica gel chromatography (0-10% MeOH/CH_2Cl_2), the resultant solid was triturated with hot acetonitrile to give 0.339 g (67%) of the title compound.

LC/MS (ES^+): 349, 351 for $C_{16}H_{17}ClN_4O_3$

^1H NMR (DMSO-d_6): δ 9.47 (s, 1H); 9.12 (m, 1H); 8.92 (m, 1H); 8.37 (m, 1H); 8.33 (s, 1H); 7.85 (s, 1H); 7.46 (m, 1H); 4.38 (q, 2H); 3.18 (m, 2H); 1.35 (t, 3H); 1.09 (t, 3H).

Intermediate 182

1-(4-Chloro-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea



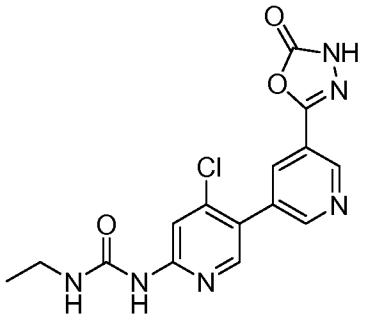
The ethyl 4'-chloro-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate (Intermediate 181, 0.234 g, 0.67 mmol), anhydrous hydrazine (0.211 ml, 6.71 mmol) and EtOH (10 ml) were heated at 80 °C overnight. Hydrazine hydrate (0.326 ml, 6.71 mmol) was then added and the mixture was heated at 80 °C for an additional 3 h. After cooling to RT, the mixture was diluted with MeOH and concentrated *in vacuo* to give the title compound which was used without further purification.

LC/MS (ES^+)[$(M+H)^+$]: 335 for $C_{14}H_{15}ClN_6O_2$

^1H NMR (DMSO-d_6): δ 10.03 (s, 1H); 9.46 (s, 1H); 9.00 (m, 1H); 8.80 (m, 1H); 8.33 (s, 1H); 8.26 (s, 1H); 7.85 (s, 1H); 7.45 (m, 1H); 4.60 (br s, 2H); 3.18 (m, 2H); 1.09 (t, 3H).

Intermediate 183

1-(4-Chloro-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



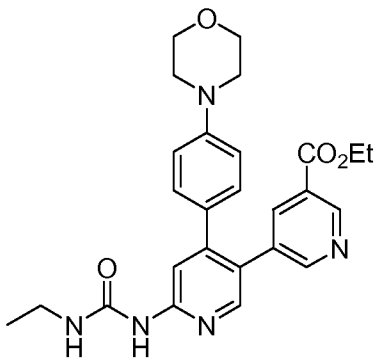
Diisopropylethylamine (0.176 ml, 1.01 mmol) was added to a solution of 1-(4-chloro-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea (Intermediate 182, 0.225 g, 0.67 mmol) in DMF (6 ml). 1,1'-Carbonyldiimidazole (0.163 g, 1.01 mmol) was added in one portion and the resultant mixture was stirred at RT overnight. Water was added and the mixture was concentrated *in vacuo*. Purification by silica gel chromatography (0-10% MeOH/CH_2Cl_2) gave the title compound.

LC/MS (ES^+): 361, 363 for $C_{15}H_{13}ClN_6O_3$

^1H NMR (DMSO-d_6): δ 12.83 (br s, 1H); 9.48 (s, 1H); 9.01 (m, 1H); 8.85 (m, 1H); 8.34 (s, 1H); 8.25 (m,1H); 7.86 (s, 1H); 7.46 (m, 1H); 3.21 (m, 2H); 1.09 (t, 3H).

Intermediate 184

Ethyl 6'-(3-ethylureido)-4'-(4-morpholinophenyl)-3,3'-bipyridine-5-carboxylate



Following the procedure for Example 107, ethyl 4'-chloro-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate (Intermediate 181, 0.315 g, 0.90 mmol) and 4-morpholinophenylboronic acid (0.251 g, 1.21 mmol) were heated in the microwave for 1 h at 100 °C. After conc *in vacuo*,

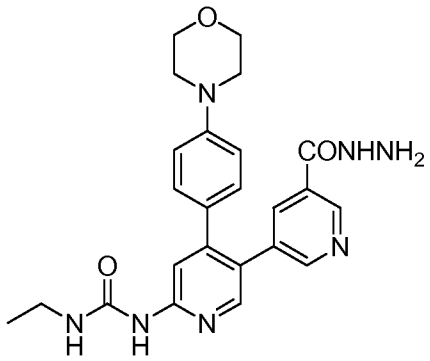
CH_2Cl_2 and water were added and the layers were separated. The organic layer was concentrated *in vacuo* and then purified by silica gel chromatography (0-100% EtOAc/hexanes) to give 0.268 g (62%) of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 476 for $C_{26}H_{29}N_5O_4$

^1H NMR (DMSO-d_6): δ 9.36 (s, 1H); 8.94 (m, 1H); 8.50 (m, 1H); 8.26 (s, 1H); 8.00 (m, 2H); 7.48 (s, 1H); 6.98 (m, 2H); 6.88 (m, 2H); 4.31 (q, 2H); 3.71 (m, 4H); 3.21 (m, 2H); 3.11 (m, 4H); 1.29 (t, 3H); 1.10 (t, 3H).

Intermediate 185

1-Ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-morpholinophenyl)-3,3'-bipyridin-6-yl)urea



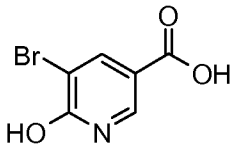
Hydrazine hydrate (0.215 mL, 4.42 mmol) was added to a suspension of ethyl 6'-(3-ethylureido)-4'-(4-morpholinophenyl)-3,3'-bipyridine-5-carboxylate (Intermediate 184, 0.105 g, 0.22 mmol) in EtOH (3 mL). The mixture was heated at 80 °C overnight. After cooling to RT, the mixture was diluted with MeOH and concentrated *in vacuo* to give the title compound which was used without further purification.

LC/MS (ES^+)[$(M+H)^+$]: 462 for $C_{24}H_{27}N_7O_3$

^1H NMR (DMSO-d_6): δ 9.93 (br s, 1H); 9.34 (s, 1H); 8.81 (m, 1H); 8.29 (m, 1H); 8.23 (s, 1H); 8.03 (m, 1H); 7.96 (m, 1H); 7.48 (s, 1H); 6.98 (m, 2H); 6.88 (m, 2H); 4.55 (br s, 2H); 3.70 (m, 4H); 3.20 (m, 2H); 3.11 (m, 4H); 1.10 (t, 3H).

Intermediate 186

5-bromo-6-hydroxypyridine-3-carboxylic acid



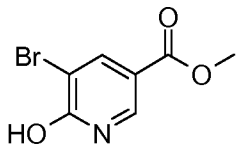
To a stirred suspension of 6-hydroxypyridine-3-carboxylic acid (13.0 g, 215 mmol) in water (150 mL) was added bromine (16 mL, 310 mmol) dropwise slowly at 0 °C over a period of 30 min. The reaction mixture was stirred at 0 °C for 30 min and slowly the temperature was allowed to rise to room temperature. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was treated with saturated sodium metabisulphite solution and stirred for another 30 min at room temperature. The precipitated product was collected by filtration and washed with excess water and dried to afford 35 g (70%) of 5-bromo-6-hydroxypyridine-3-carboxylic acid as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.03 (s, 1H), 8.16 (s, 1H), 12.58 (br s, 1H).

Mass: m/z 218, 220 (M, M+2)

Intermediate 187

Methyl 5-bromo-6-hydroxypyridine-3-carboxylate



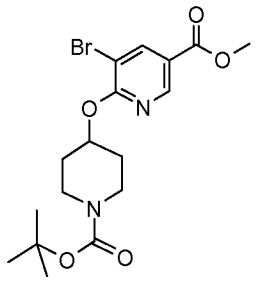
To a stirred solution of 5-bromo-6-hydroxypyridine-3-carboxylic acid (Intermediate 186, 10 g, 45.87 mmol) in methanol (100 mL) was added sulphuric acid (1 mL) and the reaction mixture was heated to reflux overnight. The solvent was concentrated under reduced pressure to get crude compound which was poured into saturated sodium bicarbonate solution. The solid that formed was collected by filtration and dried to afford 8.5 g (80%) of methyl 5-bromo-6-hydroxypyridine-3-carboxylate.

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.78 (s, 3H), 8.10 (s, 1H), 8.18 (s, 1H), 12.71 (br s, 1H).

MASS (ES): m/z 234 (M+H).

Intermediate 188

Methyl 5-bromo-6-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}pyridine-3-carboxylate



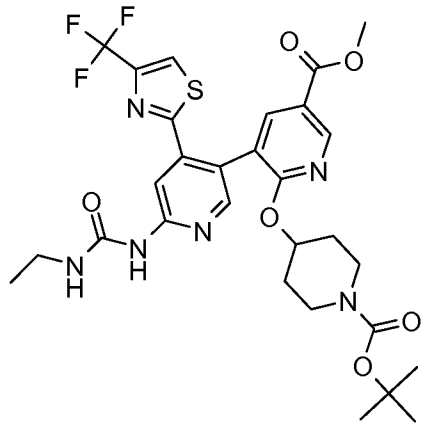
To a stirred solution of methyl 5-bromo-6-hydroxypyridine-3-carboxylate (Intermediate 187, 4.0 g, 17.24 mmol) in dry tetrahydrofuran (50 mL), was added tert-butyl 4-hydroxypiperidine-1-carboxylate (3.46 g, 17.24 mmol), and triphenylphosphine (13.42 g, 51.22 mmol) at 0 °C. The reaction mixture was stirred for 10 min followed by addition of diethyl azodicarboxylate (4.0 g, 22.9 mmol). The reaction mixture was maintained at room temperature and stirred for 3 h. The solvent was concentrated under reduced pressure, then water was added and the product was extracted into ethyl acetate (2 x 50 mL, 1 x 25 mL). The combined organic layers were dried over anhydrous sodium sulphate, filtered then concentrated under reduce pressure to obtain crude compound which was purified by flash column chromatography (25-30% ethyl acetate / pet ether) to afford 5.0 g (70%) of methyl 5-bromo-6-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}pyridine-3-carboxylate

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.45 (s, 9H), 1.85 (m, 2H), 1.95 (m, 2H), 3.48 (m, 2H), 3.65 (m, 2H), 3.91 (s, 3H), 5.39 (m, 1H), 8.39 (s, 1H), 8.70 (s, 1H).

MASS (APCI): m/z 417 (M+2).

Intermediate 189

Methyl 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}-6'-[(ethylcarbamoyl)amino]-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylate



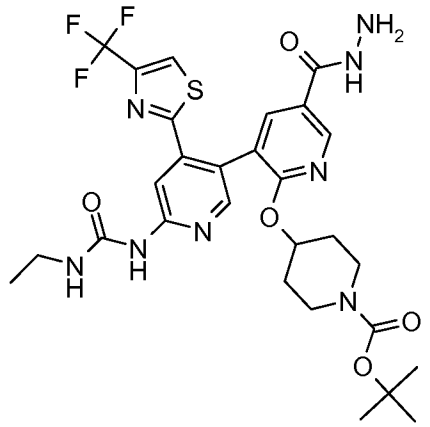
In a round bottomed flask methyl 5-bromo-6-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}pyridine-3-carboxylate (Intermediate 188, 300 mg, 0.72 mmol), 1-ethyl-3-{5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}urea (Intermediate 12, 351 mg, 8.31 mmol) and cesium carbonate (470 mg, 1.44 mmol) were suspended in 1,4 dioxane: water (8:2) (25 mL). This reaction mixture was purged with Argon gas for 30 min. Tetrakis (triphenylphosphine) palladium (167 mg, 0.14 mmol) was added under argon atmosphere and the reaction mixture was heated to 80-90 °C for 3 h. The reaction mixture was cooled to room temperature, filtered through celite, the filtrate was concentrated under reduced pressure to obtain a residue which was purified by flash column chromatography (20-25% ethyl acetate / pet ether) to afford 0.25 g (56.8%) of methyl 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}-6'-[(ethylcarbamoyl)amino]-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylate.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (t, 3H), 1.35 (s, 9H), 1.55 (d, 2H), 3.05 (m, 3H), 3.20 (m, 6H), 3.87 (s, 3H), 5.09 (m, 1H), 7.60 (br s, 1H), 8.20 (s, 1H), 8.25 (s, 1H), 8.50 (s, 1H), 8.79 (s, 1H), 9.46 (br s, 1H).

MASS (APCI): m/z 651.1 (M+H).

Intermediate 190

Tert-butyl 4-({6'-[(ethylcarbamoyl)amino]-5-(hydrazinylcarbonyl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)piperidine-1-carboxylate

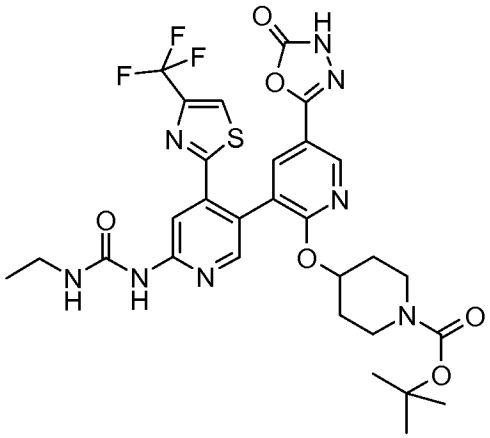


To a stirred solution of methyl 2-{[1-(tert-butoxycarbonyl)piperidin-4-yl]oxy}-6'-[(ethylcarbamoyl)amino]-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylate (Intermediate 189, 0.5 g, 0.76 mmol) in ethanol (20 mL) was added hydrazine hydrate (2.0 mL, 40 mmol) and the resulting mixture was heated to reflux temperature for 4 h. The reaction mixture was cooled, the solvent was concentrated under reduced pressure. Diethyl ether (10 mL) was added, and the mixture was stirred for 10 min. The resulting solid was collected by filtration and dried to afford 0.4 g (80%) of tert-butyl 4-({6'-[(ethylcarbamoyl)amino]-5-(hydrazinylcarbonyl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)piperidine-1-carboxylate as solid.

MASS (APCI): m/z 651.1 (M+H).

Intermediate 191

Tert-butyl 4-({6'-[(ethylcarbamoyl)amino]-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)piperidine-1-carboxylate



To a stirred solution of tert-butyl 4-({6'-[(ethylcarbamoyl)amino]-5-(hydrazinylcarbonyl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)piperidine-1-carboxylate (Intermediate 190, 300 mg, 0.46 mmol) in tetrahydrofuran (15 mL), phosgene (0.34 mL in

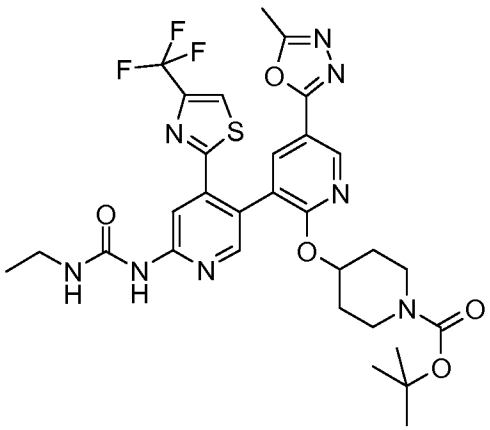
toluene, 0.67 mmol) was slowly added at 0 °C. The reaction mixture was stirred at room temperature which for 3 h. The solvent was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography (5-10% ethyl acetate / pet ether) to afford 0.2 g (64.9%) of tert-butyl 4-({6'-[(ethylcarbamoyl)amino]-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)piperidine-1-carboxylate.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (m, 6H), 1.40 (s, 9H), 3.11 (m, 2H), 3.42 (br s, 2H), 3.51 (m 2H), 3.94 (s, 3H), 5.13 (m, 1H), 7.53 (s, 1H), 7.70 (s, 1H), 8.13 (s, 1H), 8.21 (d, 1H), 8.81 (br s, 1H), 9.04 (m, 1H).

LC-MS: m/z 677.0 (M+2) .

Intermediate 192

Tert-butyl 4-({6'-[(ethylcarbamoyl)amino]-5-(5-methyl-1,3,4-oxadiazol-2-yl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)piperidine-1-carboxylate



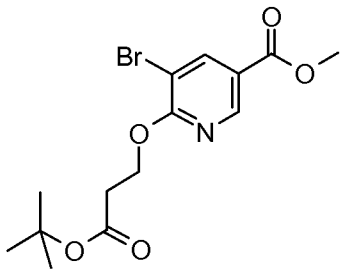
tert-Butyl 4-({6'-[(ethylcarbamoyl)amino]-5-(hydrazinylcarbonyl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)piperidine-1-carboxylate (Intermediate 190, 200 mg, 0.30 mmol) was dissolved in triethylorthoacetate (5 mL) and the reaction mixture was heated to 120 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and the organics were extracted into ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous sodium sulphate and evaporated under reduced pressure to obtain crude compound which was purified by flash column chromatography (25-35% ethyl acetate / pet ether) to afford 100 mg 48.3% tert-butyl 4-({6'-[(ethylcarbamoyl)amino]-5-(5-methyl-1,3,4-oxadiazol-2-yl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)piperidine-1-carboxylate as solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H), 1.48 (S, 9H), 2.52 (s, 3H), 3.18 (m, 2H), 3.38 – 3.46 (m, 4H), 5.18 (m, 1H), 7.42 – 7.56 (m, 7H), 8.18 – 8.24 (m, 2H), 8.82 (s, 1H), 9.02 (br s, 1H)

MASS (APCI): m/z 674.2 (M-H).

Intermediate 193

Methyl 5-bromo-6-(3-tert-butoxy-3-oxopropoxy)pyridine-3-carboxylate



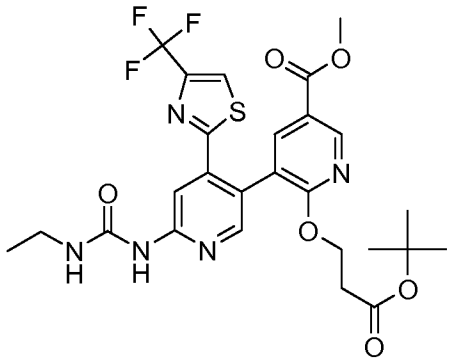
To a stirred solution of methyl 5-bromo-6-hydroxypyridine-3-carboxylate (Intermediate 187, 1.0 g, 4.31 mmol) in dry tetrahydrofuran (50 mL), tert-butyl 3-hydroxypropanoate (1.26 g, 8.62 mmol) and triphenylphosphine (2.25 g, 8.62 mmol) were added and stirred for 10 min. Then the reaction mixture was cooled to 0 °C, diethyl azodicarboxylate (1.5 g, 8.62 mmol) was added slowly. The reaction mixture was maintained at room temperature for 4 h. After the completion of the reaction, the solvent was concentrated under reduced pressure; water was added and the product was extracted into ethyl acetate (2 x 50 mL, 1 x 25 mL). The combined organic layers were dried over anhydrous sodium sulphate and evaporated under reduced pressure to yield the crude product which was purified by flash column chromatography (5-10% ethyl acetate / pet ether) to afford 700 mg (46%) of methyl 5-bromo-6-(3-tert-butoxy-3-oxopropoxy)pyridine-3-carboxylate.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.78 (t, 2H), 3.87 (s, 3H), 4.27 (t, 2H), 8.26 (s, 1H), 8.31 (s, 1H).

LC_MS: m/z 360.1 (M+H).

Intermediate 194

Methyl 2-(3-tert-butoxy-3-oxopropoxy)-6'-[(ethylcarbamoyl)amino]-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylate

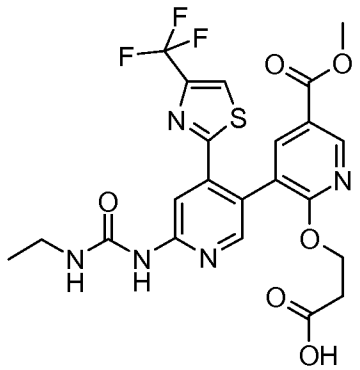


In a round bottomed flask methyl 5-bromo-6-(3-tert-butoxy-3-oxopropoxy)pyridine-3-carboxylate (Intermediate 193, 10.7 g, 1.94 mmol), 1-ethyl-3-{5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}urea (Intermediate 12, 0.94 g, 2.13 mmol) and cesium carbonate (1.26 g, 3.88 mmol), were suspended in 1,4 dioxane: water (10 mL) (1:4) The above mixture was purged with Argon gas for 30 min. Tetrakis (triphenylphosphine) palladium (0.44 g, 0.38 mM) was added under argon atmosphere and the reaction mixture was heated to 100 °C for 4 h. After the completion of the reaction, the reaction mixture was cooled to room temperature, filtered through celite, the organic solvent was concentrated under reduced pressure to get aresidue which was purified by flash column chromatography (gradient up to 40% ethyl acetate in pet ether) to afford 350 mg (30%) of methyl 2-(3-tert-butoxy-3-oxopropoxy)-6'-[(ethylcarbamoyl)amino]-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylate.

LC-MS: m/z 595 (M+H).

Intermediate 195

3-({6'-[(ethylcarbamoyl)amino]-5-(methoxycarbonyl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)propanoic acid



To a solution methyl 2-(3-tert-butoxy-3-oxopropoxy)-6'-[(ethylcarbamoyl)amino]-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylate (Intermediate 194, 350 mg,

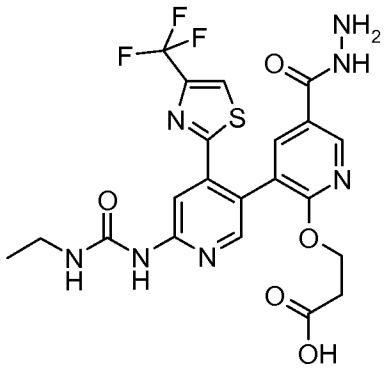
0.58 mmol) in dichloromethane (20 mL), trifluoroacetic acid (335 mg, 2.94 mmol) was added and the mixture was stirred for 6 h at room temperature. Volatiles were evaporated under reduced pressure to afford the crude product, which was purified by flash column chromatography (gradient up to 5% methanol in chloroform) to afford 300 mg (96%) 3-({6'-[(ethylcarbamoyl)amino]-5-(methoxycarbonyl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)propanoic acid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.21 (t, 1H), 1.25 (m, 2H), 1.85 (s, 2H), 2.35 (s, 2H), 3.30 (m, 2H), 3.89 (s, 3H), 4.00 (t, 2H), 7.90 (s, 1H), 8.15 (d, 2H), 8.50 (s, 1H), 8.63 (s, 1H), 9.39 (s, 1H).

LC-MS: m/z 540.3 (M+H).

Intermediate 196

3-({6'-[(ethylcarbamoyl)amino]-5-(hydrazinylcarbonyl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)propanoic acid

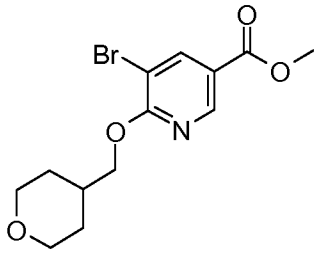


To a stirred solution of 3-({6'-[(ethylcarbamoyl)amino]-5-(methoxycarbonyl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)propanoic acid (Intermediate 195, 300 mg, 0.55 mmol) in ethanol (20 mL), hydrazine hydrate (1.28 g, 25.6 mmol) was added at room temperature and the resulting reaction mixture was heated to reflux for 3 h. The reaction mixture was cooled, and the solvent was concentrated under reduced pressure. Diethyl ether (10 mL) was added and the mixture was stirred for 10 min. The obtained solid was filtered and dried to afford 240 mg (80%) of 3-({6'-[(ethylcarbamoyl)amino]-5-(hydrazinylcarbonyl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-2-yl}oxy)propanoic acid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.12 (t, 3H), 2.35 (br s, 2H), 3.22 (t, 2H), 4.01 (m, 2H), 7.65 (br s, 1H), 8.10 (s, 1H), 8.20 (d, 2H), 8.50 (d, 2H), 9.40 (s, 1H), 9.50 (br s, 1H).

Intermediate 197

Methyl 5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridine-3-carboxylate



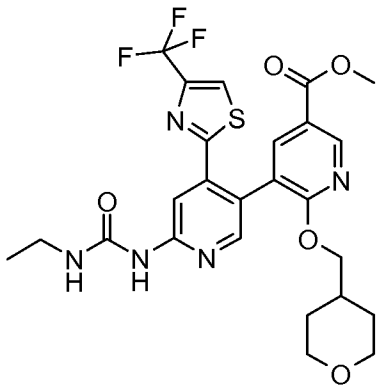
To a stirred solution of methyl 5-bromo-6-hydroxypyridine-3-carboxylate (Intermediate 187, 2.0 g, 8.62 mmol) in tetrahydrofuran (50 mL), was added tetrahydro-2H-pyran-4-ylmethanol (2.0 g, 17.24 mmol), triphenylphosphine (4.51 g, 17.24 mmol) stirred for 10 min. Then the reaction mixture was cooled to 0 °C. Diethyl azodicarboxylate (3.0 g, 17.24 mmol) was added slowly, and the reaction mixture was maintained at room temperature for 3 h. The solvent was concentrated under reduced pressure. Water was added and the product was extracted into ethyl acetate (2 x 50 mL, 1 x 25 mL). The combined organic layers were dried over anhydrous sodium sulphate and evaporated under reduced pressure to yield the crude product which was purified by flash column chromatography (product eluted with 5-10% ethyl acetate / pet ether) to afford 2.0 g (71%) of methyl 5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridine-3-carboxylate.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (m, 2H), 1.78 (d, 2H), 2.10 (m, 1H), 3.45 (t, 2H), 3.91 (s, 3H), 4.28 (d, 2H), 8.39 (s, 1H), 8.71 (s, 1H).

MASS: m/z 329.8 (M+H).

Intermediate 198

Methyl 6'-[(ethylcarbamoyl)amino]-2-(tetrahydro-2H-pyran-4-ylmethoxy)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylate



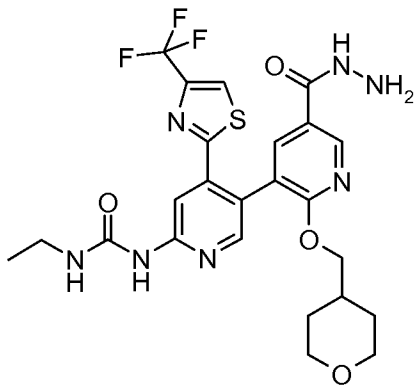
In a round bottomed flask methyl 5-bromo-6-(tetrahydro-2H-pyran-4-ylmethoxy)pyridine-3-carboxylate (Intermediate 197, 1.5 g, 4.54 mmol), 1-ethyl-3-{5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]pyridin-2-yl}urea (Intermediate 12, 2.22 g, 5.02 mmol) and sodium bicarbonate (0.76 g, 9.04 mmol) which was dissolved in minimum amount of water (10 mL), were combined and suspended in toluene: water (1:4). The reaction mixture was purged with argon gas for 30 min. Tetrakis (triphenylphosphine) palladium (3.31 g, 0.268 mmol) was added under argon atmosphere and the reaction mixture was heated to 80-90 °C for 5 h. The reaction mixture was cooled to room temperature, filtered through celite bed; the organic solvent was concentrated under reduced pressure to yield a residue. To this residue acetonitrile was added to obtain solid which was filtered and dried to afford 1.2 g (46%) of methyl 6'-[(ethylcarbamoyl)amino]-2-(tetrahydro-2H-pyran-4-ylmethoxy)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylate.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (m, 3H), 1.29 (t, 5H), 1.65 (m, 1H), 3.25 (t, 2H), 3.50 (m, 2H), 3.91 (dd, 2H), 3.95 (s, 3H), 7.51 (m, 2H), 7.71 (s, 2H), 7.95 (br s, 1H), 8.15 (s, 1H), 8.25 (d, 1H), 8.95 (d 1H)

LC-MS: m/z 566.5 (M+H).

Intermediate 199

1-Ethyl-3-{5'-(hydrazinylcarbonyl)-2'-(tetrahydro-2H-pyran-4-ylmethoxy)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-6-yl}urea



To a stirred solution of methyl 6'-[(ethylcarbamoyl)amino]-2-(tetrahydro-2H-pyran-4-ylmethoxy)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylate (Intermediate 198, 1.2 g, 2.12 mmol) in ethanol (20 mL), hydrazine hydrate (4.88 g, 97.69 mmol) was added at room temperature and the resulting reaction mixture was maintained at reflux temperature for 4 h. The reaction mixture was cooled, and the solvent was concentrated under reduced pressure to yield a residue. To this residue diethyl ether (10 mL) was added

and the mixture was stirred for 10 min to obtain solid which was filtered and dried to afford 0.8 g (66%) of 1-ethyl-3-{5'-(hydrazinylcarbonyl)-2'-(tetrahydro-2H-pyran-4-ylmethoxy)-4-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridin-6-yl}urea.

^{1}H NMR (400 MHz, DMSO-d_6): δ 0.91 (m, 2H), 1.15 (t, 4H), 1.55 (m, 1H), 3.20 (m, 4H), 3.75 (d, 2H), 3.95 (d, 2H), 4.50 (br s, 1H), 7.60 (br s, 1H), 8.35 (d, 1H), 7.37 (d, 1H), 8.45 (s, 1H), 8.65 (s, 1H), 9.45 (s, 1H), 9.85 (br s, 1H)

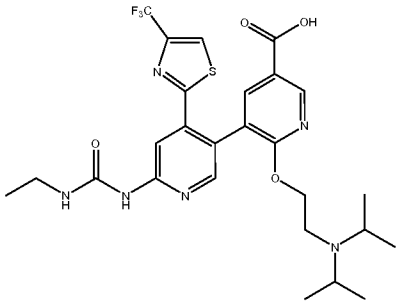
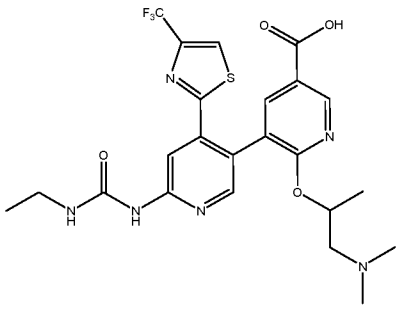
MASS (APCI): m/z 564.7 (M-H).

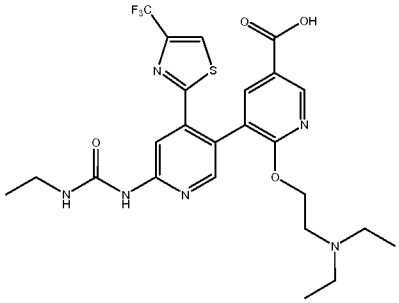
Intermediates 200-202

The following Intermediates were prepared according to the general procedure described below from the starting materials indicated in the Table.

General Procedure

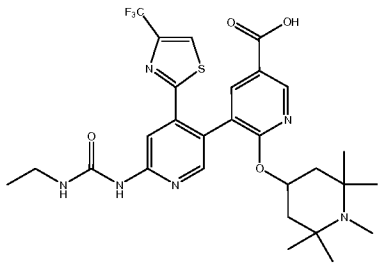
A suspension of methyl 6'-(3-ethylureido)-2-fluoro-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 162, 0.3 g, 6 mmol, 1 eq) in the appropriate alcohol (2-3 mL, ~50 equiv) in small vial was stirred for 2 min at room temperature. Sodium hydride (0.150 g, 60 mmol) was added over 5 min and the reaction mixture was stirred for a further 5 h at room temperature. The reaction mixture was cooled with an ice bath and slowly quenched with HCl (0.1N) solution until ~pH 7. The aqueous layer was extracted twice with ether to remove excess alcohol. The aqueous layer was concentrated *in vacuo* to almost dryness than loaded on Analogix C18-column for reverse phase purification (water-methanol) to remove excess of salt.

Int	Compound	Data	SM
200	2-(2-(diisopropylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid 	MS (ESP): 581.21 (MH^+) for $C_{26}H_{31}F_3N_6O_4S$	2-(2-(diisopropylamino)ethanol
201	2-(1-(dimethylamino)propan-2-yloxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid 	MS (ESP): 539.16 (MH^+) for $C_{23}H_{25}F_3N_6O_4S$	2-(1-(dimethylamino)propan-2-ylanol

Int	Compound	Data	SM
202	2-(2-(Diethylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid 	MS (ESP): 553.18 (MH^+) for $C_{24}H_{27}F_3N_6O_4S$	2-(2-(Diethylamino)ethanol

Intermediate 203

6'-(3-ethylureido)-2-(1,2,2,6,6-pentamethylpiperidin-4-yloxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid

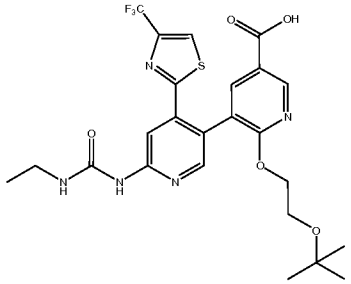


A suspension of methyl 6'-(3-ethylureido)-2-fluoro-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 162, 0.3 g, 6 mmol) in dimethyl formamide (3 mL) was treated with 1,2,2,6,6-pentamethylpiperidin-4-ol (5 eq) and potassium hexamethyl disilylazide (5 equivalents) in a small vial. The reaction was stirred for 48 h at room temperature. The dimethyl formamide was removed under vacuum, and the residue cooled with an ice bath and slowly quenched with HCl (0.1N) solution until pH 7. The aqueous layer was concentrated *in vacuo* to almost dryness than loaded on Analogix C18-column for reverse phase purification (water-methanol) to remove remaining starting materials and give an off-white solid.

MS (ESP): 606.22 (MH^+) for $C_{28}H_{33}F_3N_6O_4S$

Intermediate 204

2-(2-tert-butoxyethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid

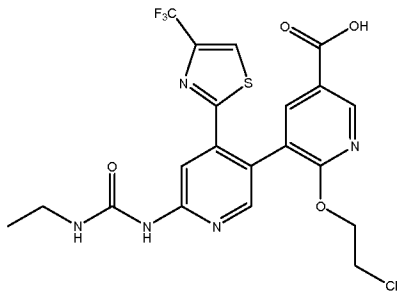


A suspension of methyl 6'-(3-ethylureido)-2-fluoro-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 162, 0.3 g, 6 mmol, 1 eq) in 2-tert-butoxyethanol (2-3 mL) in a small vial was stirred for 2 min at room temperature. Sodium hydride (0.150 g, 60 mmol) was added over 5 min and the reaction mixture was stirred for a further 5 h at room temperature. The reaction was cooled with an ice bath and slowly quenched with HCl (0.1N) solution to pH 7. The aqueous layer was extracted twice with ether to remove excess of alcohol. The aqueous layer was concentrated *in vacuo* to almost dryness than loaded on Analogix C18-column for reverse phase purification (water-methanol) to remove excess salt and give an off-white solid.

MS (ESP): 553.16 (MH^+) for $C_{24}H_{26}F_3N_5O_5S$.

Intermediate 205

1-(2'-(2-chloroethoxy)-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



A suspension of 2-(2-tert-butoxyethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 204, 0.3 mmol), and hydrazine acetate (0.9 mmol) in phosphorus oxychloride (2.5 mL) was heated at 70°C for 2 h. The solution was then cooled and concentrated to dryness. A solution of saturated potassium carbonate was added to the crude and product was extracted with ethyl acetate (3×). The combined organic layers

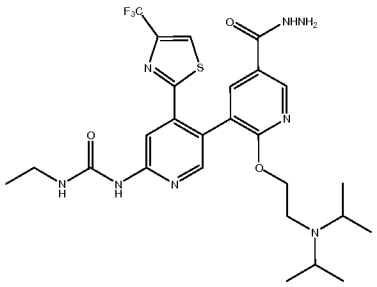
were washed with brine and dried over sodium sulfate. All solvents were removed under vacuum and the crude was purified by Analogix using dichloromethane-methanol.
MS (ESP): 553.09 (MH^+) for $C_{22}H_{19}ClF_3N_7O_3S$.

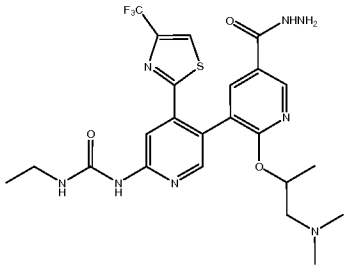
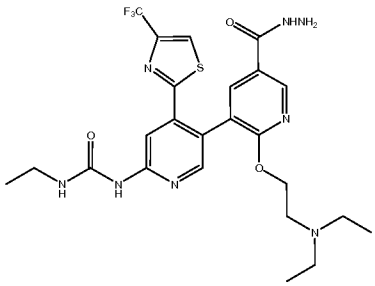
Intermediates 206-209

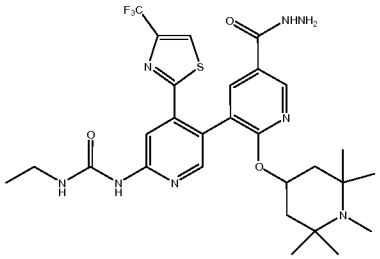
The following Intermediates were synthesized according to the general procedure described below from the starting materials indicated in the Table.

General Procedure

A suspension of corresponding carboxylic acid (0.3 mmol) in thionyl chloride (2 mL) was heated at 50°C for 1 h. The solution was then cooled and concentrated under reduced pressure to dryness. The crude suspended in tetrahydrofuran (2 mL) was added slowly to a solution of hydrazine/ tetrahydrofuran (1/2 vol., 3 mL) and stirred at room temperature for 12 h. The crude reaction mixture was concentrated to dryness and purified by reverse phase on Analogix C18-column (water-methanol) to give a (~60%) hydrazide as an off-white solid.

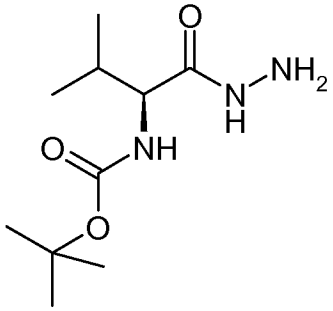
Int	Compound	Data	SM
206	1-(2'-(2-(diisopropylamino)ethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 594.23 (MH^+) for $C_{26}H_{33}F_3N_8O_3S$	Intermediate 162 and 2-(2-(diisopropylamino)ethanol

Int	Compound	Data	SM
207	1-(2'-(1-(dimethylamino)propan-2-yloxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 552.19 (MH^+) for $C_{23}H_{27}F_3N_8O_3S$	Intermediate 162 and 1-(2'-(1-(dimethylamino)propan-2-ol
208	1-(2'-(2-(diethylamino)ethoxy)-5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 566.20 (MH^+) for $C_{24}H_{29}F_3N_8O_3S$	Intermediate 162 and 1-(2'-(2-(diethylamino)ethanol

Int	Compound	Data	SM
209	1-ethyl-3-(5'-(hydrazinecarbonyl)-2'-(1,2,2,6,6-pentamethylpiperidin-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 620.25 (MH^+) for $C_{28}H_{35}F_3N_8O_3S$	Intermediate 162 and 1,2,2,6,6-pentamethylpiperidin-4-ol

Intermediate 210

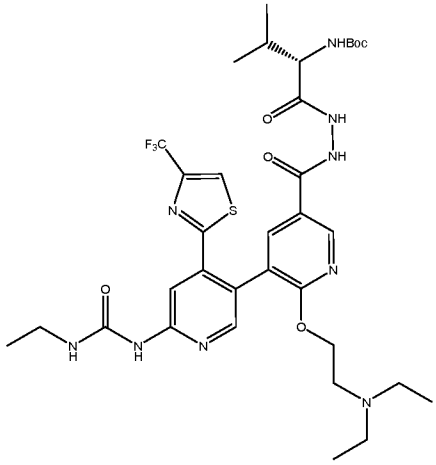
(S)-tert-butyl 1-hydrazinyl-3-methyl-1-oxobutan-2-ylcarbamate



To (S)-methyl 2-(tert-butoxycarbonylamino)-3-methylbutanoate (5 g, 0.0215 mol) in ethanol (50 mL) was added hydrazine hydrate (16 mL, 0.323 mol) and the solution heated at 70°C overnight. The solvent was evaporated and the residue dissolved in ethyl acetate, washed with water, dried over sodium sulfate and the solvent evaporated to give ~3 g of product.

Intermediate 211

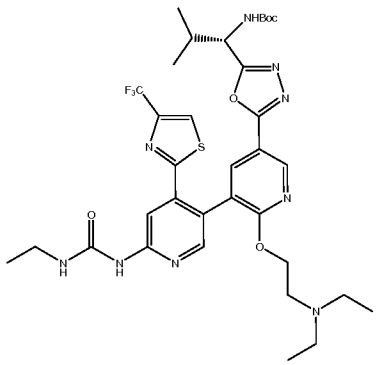
(S)-tert-butyl 1-(2-(2-(2-(diethylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-3-methyl-1-oxobutan-2-ylcarbamate



A suspension of 2-(2-(diethylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 202, 0.3 mmol) in tetrahydrofuran (2 mL) was treated with (S)-tert-butyl 1-hydrazinyl-3-methyl-1-oxobutan-2-ylcarbamate (Intermediate 210, 0.6 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 0.4 mmol) and triethyl amine (0.6 mmol) at room temperature for 12 h. The solution was then concentrated to dryness and purified by Analogix silica gel chromatography (dichloromethane-methanol) to give (60%) of (S)-tert-butyl 1-(2-(2-(2-(diethylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-3-methyl-1-oxobutan-2-ylcarbamate as an off-white solid.
MS (ESP): 766 (MH^+) for $C_{34}H_{46}F_3N_9O_6S$.

Intermediate 212

(S)-tert-butyl 1-(5-(2-(2-(diethylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)-2-methylpropylcarbamate



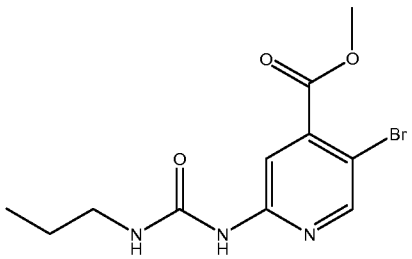
A suspension of (S)-tert-butyl 1-(2-(2-(2-(diethylamino)ethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-3-methyl-1-oxobutan-2-ylcarbamate (Intermediate 211, 0.3 mmol) in tetrahydrofuran (2 mL) was treated with

triphenylphosphine (0.6 mmol), and carbon tetrachloride (0.6 mmol) at room temperature for 12 h. The solution was then concentrated to dryness and purified by Analogix silica gel chromatography (dichloromethane-methanol) to give an off-white solid (80%).

MS (ESP): 748.3 (MH^+) for $C_{34}H_{44}F_3N_9O_5S$.

Intermediate 213

methyl 5-bromo-2-(3-propylureido)isonicotinate



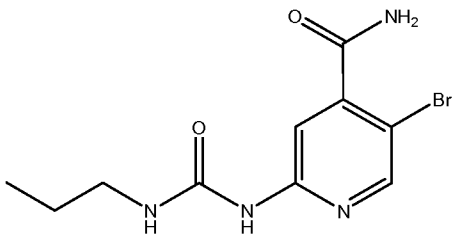
Methyl 2-amino-5-bromoisonicotinate (100 g, 433 mmol) was dissolved in chloroform (600 mL) and placed into a 1 L sealed tube. Propyl isocyanate (122.5 mL, 1.29 mol) was then added. The reaction was heated at 55°C for 72 h at which time the reaction was determined to be complete. The mixture was then cooled to room temperature, concentrated under reduced pressure, and the solid was dissolved in 2:1 ethyl acetate: tetrahydrofuran (3 L). This solution was washed with water (2×, 200 mL), and the water was back extracted with ethyl acetate (300 mL). The organic layers were then dried with sodium sulfate, filtered, and concentrated yielding 129g (95%) of methyl 5-bromo-2-(3-propylureido)isonicotinate as a dark yellow solid.

MS (ESP): 316.1 (MH^+) for $C_{11}H_{14}BrN_3O_3$

^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H), 1.45 (m, 2H), 3.11 (m, 2H), 3.90 (s, 3H), 7.21 (bt, 1H), 8.02 (s, 1H), 8.46 (s, 1H), 9.40 (s, 1H)

Intermediate 214

5-bromo-2-(3-propylureido)isonicotinamide



A solution of methyl 5-bromo-2-(3-propylureido)isonicotinate(Intermediate 213, 128 g, 405 mmol) and 7N ammonia in methanol (1 L) was allowed to stir at room temperature for 3 d,

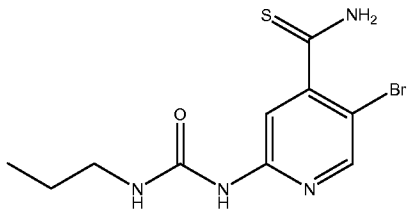
then the solids were allowed to settle. The precipitated was vacuum filtered, rinsed with methanol (2×, 500 mL), and dried on the high vacuum pump overnight, yielding 123 g (quant) of 5-bromo-2-(3-propylureido)isonicotinamide as a white solid.

MS (ESP): 301.1 (MH^+) for $C_{10}H_{13}BrN_4OS$

^1H NMR (300 MHz, DMSO-d_6): δ 0.88 (t, 3H), 1.46 (m, 2H), 3.18 (q, 2H), 7.41 (bs, 1H), 7.58 (s, 1H), 7.78 (bs, 1H), 8.08 (bs, 1H), 8.33 (s, 1H), 9.31 (s, 1H)

Intermediate 215

5-bromo-2-(3-propylureido)pyridine-4-carbothioamide



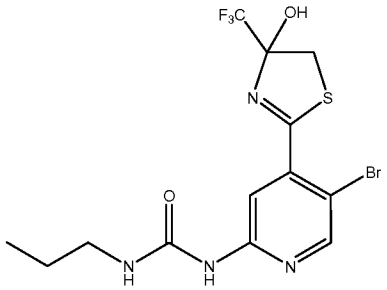
A suspended mixture of 5-bromo-2-(3-propylureido)isonicotinamide (Intermediate 214, 123 g, 407 mmol), Lawesson's Reagent (131.6 g, 326 mmol), and tetrahydrofuran (1.55 L) was stirred at 70°C for 18 h. Stirring was stopped and a bright yellow precipitate was allowed to settle. The precipitate was vacuum filtered and washed with methyl tert-butyl ether (2×, 500 L). This solid was then dried in the vacuum oven at 50°C for 12 hours to give 50g of product solid. The mother liquor was concentrated and the residue was suspended in toluene (300 mL). The solid thus obtained was filtered and combined with the previous solid. The combined totaled 110g (85%) of 5-bromo-2-(3-propylureido)pyridine-4-carbothioamide as an off white solid

MS (ESP): 317.2 (MH^+) for $C_{10}H_{13}BrN_4OS$

^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H), 1.42 (m, 2H), 3.13 (m, 2H), 7.38 (s, 1H), 7.50 (s, 1H), 8.28 (s, 1H), 9.25 (s, 1H), 9.80 (s, 1H), 10.28 (s, 1H)

Intermediate 216

1-(5-bromo-4-(4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-yl)-3-propylurea



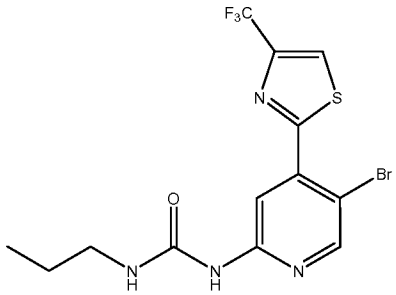
A suspension of 5-bromo-2-(3-propylureido)pyridine-4-carbothioamide (Intermediate 215, 100 g, 315 mmol), 3-bromo-1,1,1-trifluoroacetone (64 mL, 630 mmol) in acetonitrile (1.5 L) was heated at 80°C for 20 hours. The solution was then cooled down and was concentrated under reduced pressure to give an orange oil that was carried on without further purification.

MS (ESP): 426.9 (MH^+) for $C_{13}H_{14}BrF_3N_4O_2S$

^1H NMR (300 MHz, DMSO-d_6): δ 0.88(t, 3H), 1.48 (m, 2H), 3.11 (m, 2H), 3.62 (d, 1H), 3.92 (d, 1H), 7.30 (bs, 1H), 7.98 (s, 1H), 8.46 (s, 1H), 9.42 (s, 1H).

Intermediate 217

1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea



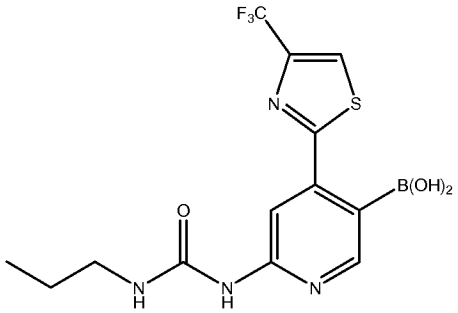
A solution of 1-(5-bromo-4-(4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-yl)-3-propylurea (Intermediate 216, 315 mmol) and triethylamine (217 mL, 1.57 mol) in tetrahydrofuran (1.3 L) was prepared and stirred at room temperature. Methane sulfonyl chloride (61 mL, 787 mmol) was added dropwise over the course of 1 h. This mixture was stirred at 26°C for 4 h. Stirring was then stopped and the solids were filtered, washed with tetrahydrofuran (3×, 200 mL), and discarded. The combined tetrahydrofuran layers were concentrated to a viscous, yellow semi-solid which was then triturated with methanol (1L). The solid was filtered and washed with methanol (2×, 300 mL), then dried in the vacuum oven at 50°C for 12 h to give 99.4g (76%) of 1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea as an off-white solid.

MS (ESP): 409.1 (MH^+) for $C_{13}H_{12}BrF_3N_4OS$

^{1}H NMR (300 MHz, DMSO-d_6): δ 0.89 (t, 3H), 1.47 (m, 2H), 3.16 (m, 2H), 7.25 (s, 1H), 8.41 (s, 1H), 8.57 (s, 1H), 8.82 (s, 1H), 9.39 (s, 1H).

Intermediate 218

6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid



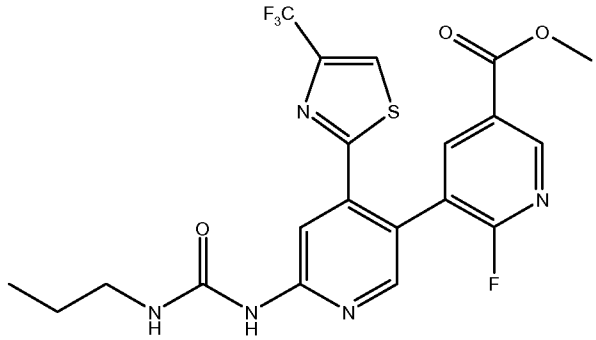
A suspension of 1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea (Intermediate 217, 50 g, 123 mmol) in tetrahydrofuran (1.25 L) was prepared and stirred at -50°C. 2.0 M isopropyl magnesium chloride in tetrahydrofuran (183 mL, 368 mmol) was added dropwise over 45 min so that the temperature never rose above -35°C. The reaction mixture was stirred for a further hour at -40°C then was cooled to -78°C. A solution of 2.5 M n-butyl lithium in hexanes (295 mL, 735 mmol) was then added dropwise to the reaction solution over the course of 1 h so that the temperature never rose above -65°C. This mixture was then allowed to react at -78°C for 1.5 h. Boron methoxide (164 mL, 1.47 mol) was added in 1 portion and the cold bath was removed. The reaction was allowed to warm to room temperature and stir for 1 h. 3N Hydrochloric acid (500 mL) was then added slowly to minimize foaming and the reaction was stirred at room temperature for 30 min so that all of the solids dissolved. The reaction was concentrated to remove the tetrahydrofuran and water (1L) was added. The solution was basified to pH 10 with 24% sodium hydroxide and the total volume was increased to 2L with water. The aqueous solution was extracted with methyl tert-butyl ether (3×, 650 mL). The organic layers were combined and extracted with 5% sodium hydroxide (100 mL). The aqueous phases were combined and acidified to pH 5.5 with 6N hydrochloric acid causing a suspension to form. This suspension was extracted with 2:1 ethyl acetate: THF (5×, 400 mL) ensuring all solid dissolved in the organic phase. The organic phases were combined and back washed with water (1 L). The organics were concentrated and triturated with methyl tert-butyl ether (1 L). The solid obtained was dried in a vacuum oven at 50°C for 18 h. This gave 25g (55%) of 6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid as an off-white solid.

MS (ESP): 375.0 (MH^+) for $C_{13}H_{14}BF_3N_4O_3S$

^1H NMR (300 MHz, DMSO-d_6): δ 0.90 (t, 3H), 1.45-1.52 (m, 2H), 3.07-3.16 (m, 2H), 7.81 (bt, 1H), 7.91 (s, 1H), 8.20 (br, 2H), 8.31 (d, 1H), 8.65 (m, 1H), 9.32 (s, 1H)

Intermediate 219

methyl 2-fluoro-6'-(3-propylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



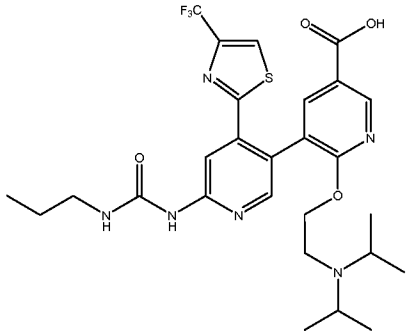
To a slurry of 6-(3-propylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 218, 4.2 g, 11.1 mmol), methyl 5-bromo-6-fluoronicotinate (2.0 g, 8.5 mmol) and trans dichlorobis(triphenylphosphine)palladium (II) (597 mg, 0.85 mmol) in 1,4-dioxane (72 mL) was added a solution of potassium carbonate (2.4 g, 17.0 mmol) in water (27 mL) and the mixture was stirred at 70°C for 1 h. The reaction was cooled to room temperature, and ethyl acetate (100 mL) and water (10 mL) were added to help separate the layers. The water was removed, and the organic phase was washed with water (10 mL). The organic layer was then concentrated and the resulting residue was triturated with a mixture of ethanol (20 mL) and methyl tert-butyl ether (50 mL). The solid was dried in a vacuum oven at 50°C for 3 h to give 1.7g (42% yield) of methyl 2-fluoro-6'-(3-propylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate as an off white solid.

MS (ESP): 484.2 (MH^+) for $C_{20}H_{17}F_4N_5O_3S$

^1H NMR (300 MHz, DMSO-d_6): δ 0.91 (t, 3H), 1.49 (m, 2H), 3.16 (m, 2H), 3.93 (s, 3H), 7.58 (bt, 1H), 8.23 (s, 1H), 8.39 (s, 1H), 8.48 (dd, 1H), 8.60 (s, 1H), 8.81 (d, 1H), 9.56 (bs, 1H).

Intermediate 220

2-(2-(diisopropylamino)ethoxy)-6'-(3-propylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid

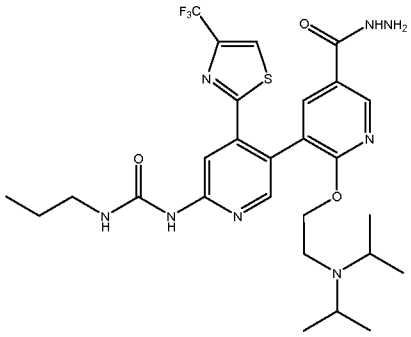


A suspension of methyl 6'-(3-propylureido)-2-fluoro-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 219, 0.3 g, 6 mmol) in diisopropylaminoethanol (2-3 mL, ~50 equiv.) in small vial was stirred for 2 min at room temperature. Sodium hydride (0.150 g, 60 mmol) was added over 5 minutes and the reaction was stirred for a further 5 h at room temperature. The reaction mixture was cooled with an ice bath and slowly quenched with HCl (0.1N) solution until pH 7. The aqueous layer was extracted twice with ether to remove excess alcohol. The aqueous layer was concentrated *in vacuo* to almost dryness, then loaded on Analogix C18-column for reverse phase purification (water-methanol) to remove excess of salt.

MS (ESP): 594.22 ($M+H^+$) for $C_{27}H_{33}F_3N_6O_4S$.

Intermediate 221

1-(2'-(2-(diisopropylamino)ethoxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-propylurea



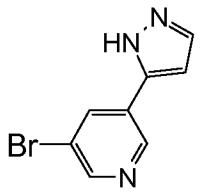
A suspension of 2-(2-(diisopropylamino)ethoxy)-6'-(3-propylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 220, 0.3 mmol) in thionyl chloride (2 mL) was heated at 50°C for 1 h. The solution was then cooled and concentrated to dryness. The crude suspended in tetrahydrofuran (2 mL) was added slowly to a solution of hydrazine/ tetrahydrofuran (1/2 vol., 3 mL) and stirred at room temperature for 12 h. The crude reaction mixture was concentrated under reduced pressure to dryness and

purified by reverse phase on Analogix C18-column (water-methanol) to give the hydrazide as off-white solid.

MS (ESP): 609.2 (MH^+) for $C_{27}H_{35}F_3N_8O_3S$

Intermediate 222

3-Bromo-5-(1H-pyrazol-5-yl)pyridine



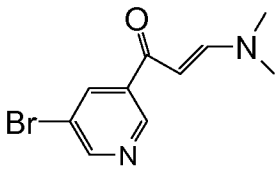
A mixture of 1-(5-Bromopyridin-3-yl)-3-(dimethylamino)prop-2-en-1-one (Intermediate 223, 300 mg, 1.18 mmol) and hydrazine (0.111 mL, 3.53 mmol) in ethanol (3 mL) was heated to reflux for 1.5 h. The solvent was removed and the crude light yellow solid (245 mg), which was used without further purification.

MS (ESP): 226 (M+2) for $C_8H_6BrN_3$

^{1}H-NMR (DMSO-d_6) δ: 6.94 (d, 1H); 7.85 (brs, 1H); 8.41 (s, 1H); 8.62 (d, 1H); 9.04 (d, 1H); 13.20 (brs, 1H)

Intermediate 223

1-(5-Bromopyridin-3-yl)-3-(dimethylamino)prop-2-en-1-one

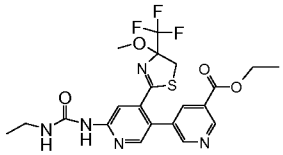
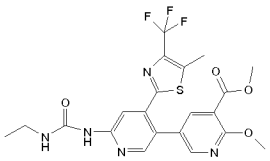


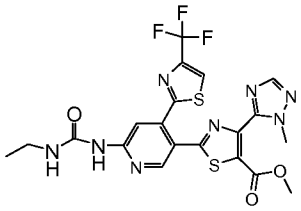
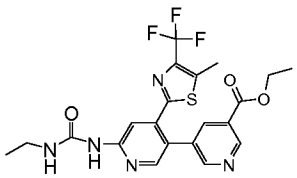
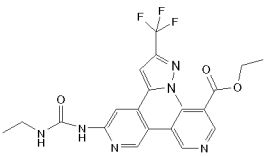
1-(5-Bromopyridin-3-yl)ethanone (1.3 g, 6.50 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (5 mL, 6.50 mmol) were taken in a round bottomed flask and heated at 120 °C for 1 h. The reaction mixture was cooled to room temperature and then partitioned between water and ethyl acetate. The layers were separated and the organic layer was washed with water two times, then dried over magnesium sulfate and concentrated under reduced pressure to give a bright orange colored solid (1.4 g) as the product.

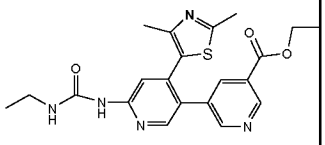
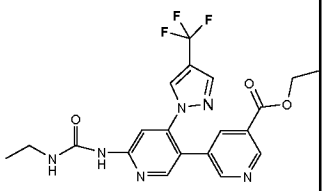
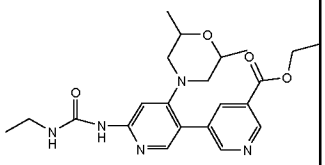
MS (ESP): 257 (M+2) for $C_{10}H_{11}BrN_2O$

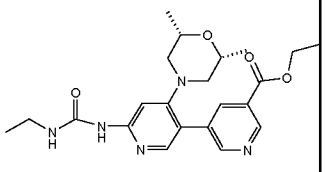
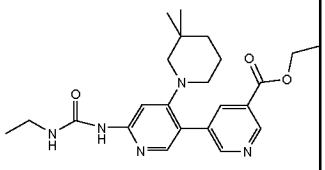
Intermediates 224-233

The following compounds have been synthesized as described for Example 21 from the starting materials indicated in the table below.

Int	Compound	Data	SM
224	Ethyl 6'-(3-ethylureido)-4'-(4-methoxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 498 (M+1) for $C_{21}H_{22}F_3N_5O_4S$	Intermediate 244 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate
225	Methyl 6'-(3-ethylureido)-6-methoxy-4'-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 496 (M+1) for $C_{21}H_{20}F_3N_5O_4S$	Intermediate 245 and methyl 5-bromo-2-methoxynicotinate.

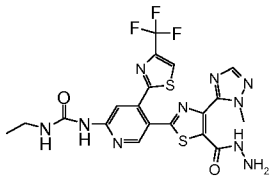
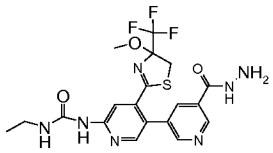
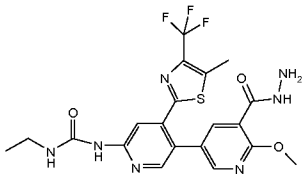
Int	Compound	Data	SM
226	Methyl 2-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazole-5-carboxylate 	MS (ESP): 539 (M+1) for $C_{20}H_{17}F_3N_8O_3S_2$	Intermediate 12 and Intermediate 44
227	Ethyl 6'-(3-ethylureido)-4'-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 480 (M+1) for $C_{21}H_{20}F_3N_5O_3S$ ^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 1.32 (t, 3H); 2.53 (s, 3H); 3.12-3.24 (m, 2H); 4.35 (q, 2H); 7.58 (brs, 1H); 8.15 (s, 1H); 8.25 (d, 1H); 8.34 (s, 1H); 8.74 (d, 1H); 9.10 (d, 1H); 9.50 (s, 1H)	ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate and Intermediate 247
228	Ethyl 6'-(3-ethylureido)-4'-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 463 (M+1) for $C_{21}H_{21}F_3N_6O_3$	Intermediate 472 and 1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-ylboronic acid

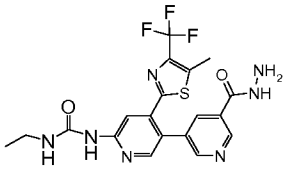
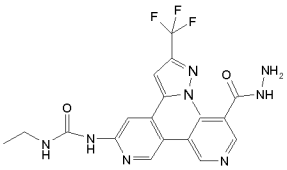
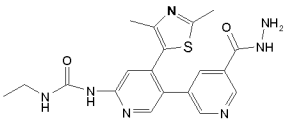
Int	Compound	Data	SM
229	Ethyl 4'-(2,4-dimethylthiazol-5-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 426 (M+1) for $C_{21}H_{23}N_5O_3S$	Intermediate 472 and 2,4-dimethylthiazol-5-ylboronic acid
230	Ethyl 6'-(3-ethylureido)-4'-(3-(trifluoromethyl)-1H-pyrazol-1-yl)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 449 (M+1) for $C_{20}H_{19}F_3N_6O_3$	ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate and Intermediate 250
231	Ethyl 4'-(2,6-dimethylmorpholino)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 428 (M+1) for $C_{22}H_{29}N_5O_4$	ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate and Intermediate 251

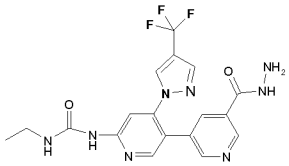
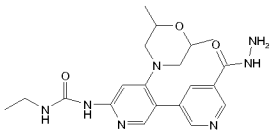
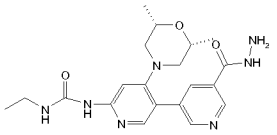
Int	Compound	Data	SM
232	Ethyl 4'-((2R,6S)-2,6-dimethylmorpholino)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 428 (M+1) for $C_{22}H_{29}N_5O_4$	ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate Intermediate 252
233	Ethyl 4'-(3,3-dimethylpiperidin-1-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate 	MS (ESP): 426 (M+1) for $C_{23}H_{31}N_5O_3$	ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate and Intermediate 249

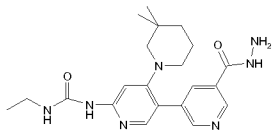
Intermediates 234-243

The following compounds have been synthesized as described for Intermediate 9 from the starting materials indicated in the table below.

Int	Compound	Data	SM
234	1-Ethyl-3-(5-(5-(hydrazinecarbonyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	MS (ESP): 539 (M+1) for $C_{19}H_{17}F_3N_{10}O_2S_2$	Intermediate 226
235	1-Ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-methoxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 484 (M+1) for $C_{19}H_{20}F_3N_7O_3S$	Intermediate 224
236	1-Ethyl-3-(5'-(hydrazinecarbonyl)-6'-methoxy-4-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 496 (M+1) for $C_{20}H_{20}F_3N_7O_3S$.	Intermediate 225

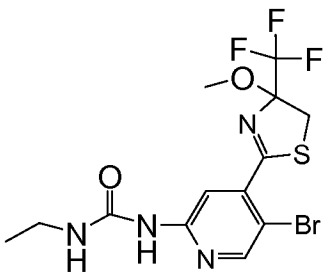
Int	Compound	Data	SM
237	1-Ethyl-3-(5'-(hydrazinecarbonyl)-4-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 466 (M+1) for $C_{19}H_{18}F_3N_7O_2S$	Intermediate 227
238	1-Ethyl-3-(5'-(hydrazinecarbonyl)-4-(1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 449 (M+1) for $C_{19}H_{19}F_3N_8O_3$	Intermediate 228
239	1-(4-(2,4-Dimethylthiazol-5-yl)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 412 (M+1) for $C_{19}H_{21}N_7O_2S$	Intermediate 229

Int	Compound	Data	SM
240	1-Ethyl-3-(5'-(hydrazinecarbonyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)-3,3'-bipyridin-6-yl)urea 	MS (ESP): 435 (M+1) for $C_{18}H_{17}F_3N_8O_2$	Intermediate 230
241	1-(4-(2,6-Dimethylmorpholino)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 414 (M+1) for $C_{20}H_{27}N_7O_3$	Intermediate 231
242	1-(4-((2R,6S)-2,6-dimethylmorpholino)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 414 (M+1) for $C_{20}H_{27}N_7O_3$	Intermediate 232

Int	Compound	Data	SM
243	1-(4-(3,3-dimethylpiperidin-1-yl)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (ESP): 412 (M+1) for $C_{21}H_{29}N_7O_2$	Intermediate 233

Intermediate 244

1-(5-Bromo-4-(4-methoxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-yl)-3-ethylurea



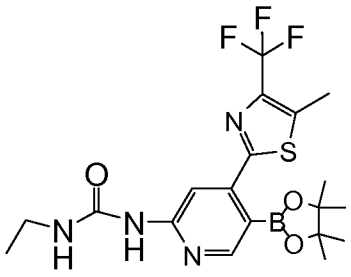
To a suspension of 5-bromo-2-(3-ethylureido)pyridine-4-carbothioamide (Intermediate 5, 25 g, 82.46 mmol) in acetonitrile (150 mL), 3-bromo-1,1,1-trifluoropropan-2-one (12.84 mL, 123.69 mmol) was added and the mixture was heated to reflux for 5 h. The reaction mixture was cooled to room temperature, filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was slurried in ethylaceate, filtered, and washed with methanol. The solid obtained was taken to the next step.

MS (ESP): 429 (M+2) for $C_{13}H_{14}BrF_3N_4O_2S$

^{1}H-NMR (DMSO-d_6) δ: 1.07 (t, 3H); 3.08-3.24 (m, 2H); 3.40 (s, 3H); 3.93 (s, 1H); 3.96 (s, 1H); 7.13 (t, 1H); 7.99 (s, 1 H); 8.51 (s, 1H); 9.43 (s, 1H).

Intermediate 245

1-Ethyl-3-(4-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)urea

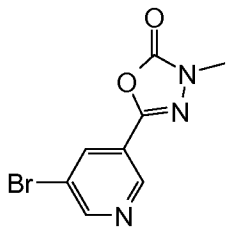


The title compound was synthesized by a method analogous to the synthesis of the Iintermediate 12 starting with 1-(5-bromo-4-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 244) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane).

MS (ESP): 457 (M+1) for $C_{19}H_{24}BF_3N_4O_3S$

Intermediate 246

5-(5-Bromopyridin-3-yl)-3-methyl-1,3,4-oxadiazol-2(3H)-one

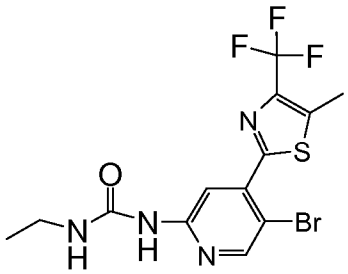


To a 1 M solution of potassium tert-butoxide (413 µl, 0.41 mmol) in THF, 5-(5-bromopyridin-3-yl)-1,3,4-oxadiazol-2(3H)-one (Intermediate 485 100 mg, 0.41 mmol) was added. To this mixture 2 mL of THF was added and the mixture was stirred for 30 min at room temperature. Then methyl iodide (51.7 µl, 0.83 mmol) was added and DMF (2mL) was added as a co-solvent in order to dissolve the starting material, and the resulting suspension was stirred for an additional 30 min. Then water was added and the precipitated product was isolated by filtration. The precipitate was slurried with acetonitrile, filtered and dried to give a nice white solid (75 mg). MS (ESP): 258 (M+2) for $C_8H_6BrN_3O_2$

^{1}H-NMR (DMSO-d_6) δ: 3.44 (s, 3H); 8.37 (t, 1H); 8.91 (d, 1H); 8.95 (d, 1H).

Intermediate 247

1-(5-Bromo-4-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea



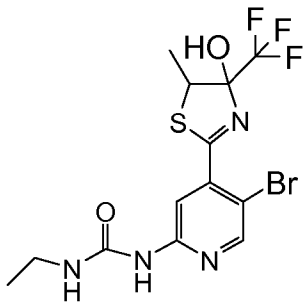
The title compound was synthesized by a method analogous to the synthesis of the Intermediate 3 starting with 1-(5-bromo-4-(4-hydroxy-5-methyl-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 248).

MS (ESP): 411 (M+2) for $C_{13}H_{12}BrF_3N_4OS$

^{1}H-NMR (DMSO-d_6) δ: 1.08 (t, 3H); 2.69 (s, 3H); 3.10-3.24 (m, 2H); 7.26 (t, 1H); 8.39 (s, 1H); 8.54 (s, 1H); 9.39 (s, 1H).

Intermediate 248

1-(5-Bromo-4-(4-hydroxy-5-methyl-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-yl)-3-ethylurea

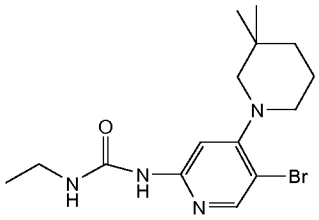


The title compound was synthesized by a method analogous to the synthesis of the intermediate 4 starting with 5-bromo-2-(3-ethylureido)pyridine-4-carbothioamide (Intermediate 5) and 3-bromo-1,1,1-trifluorobutan-2-one.

MS (ESP): 429 (M+2) for $C_{13}H_{14}BrF_3N_4O_2S$.

Intermediate 249

1-(5-Bromo-4-(3,3-dimethylpiperidin-1-yl)pyridin-2-yl)-3-ethylurea

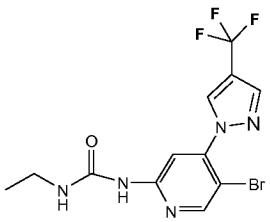


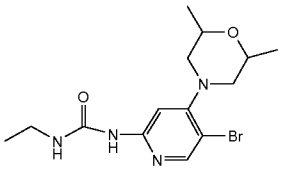
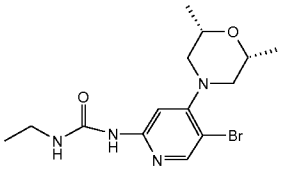
To a solution of 1-(4-(3,3-dimethylpiperidin-1-yl)pyridin-2-yl)-3-ethylurea (Intermediate 253, 200 mg, 0.72 mmol), in DMF (3 mL), N-bromo-succinamide (NBS,129 mg, 0.72 mmol) was added. The resulting solution was heated at 80 °C for 1 hr. The reaction was then partitioned between water and ethyl acetate. The layers separated and the organic layer was washed with water and brine, then dried over magnesium sulfate, concentrated and the crude was purified by normal phase (ethyl acetate/hex) chromatography. The fractions containing the product were combined and concentrated to give an off-white solid (160 mg).

MS (ESP): 357(M+2) for $C_{15}H_{23}BrN_4O$.

Intermediates 250-252

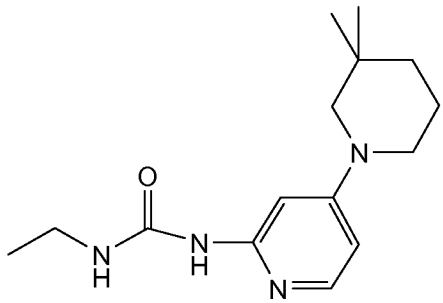
The following compounds have been synthesized as described for Intermediate 249 from the starting materials indicated in the table below.

Int	Compound	Data	SM
250	1-(5-Bromo-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyridin-2-yl)-3-ethylurea 	MS (ESP): 380 (M+2) for $C_{12}H_{11}BrF_3N_5O$ ^{1}H-NMR (DMSO-d_6) δ: 1.07 (t, 3H); 3.07-3.28 (m, 2H); 7.11 (d, 1H); 7.16 (brs, 1H); 7.96 (s, 1H); 8.53 (s, 1H); 8.59 (s, 1H); 9.50 (s, 1H)	Intermediate 254

Int	Compound	Data	SM
251	1-(5-Bromo-4-(2,6-dimethylmorpholino)pyridin-2-yl)-3-ethylurea 	MS (ESP): 359 (M+2) for $C_{14}H_{21}BrN_4O_2$ ^{1}H-NMR (DMSO-d_6) δ: 1.07 (t, 3H); 1.13 (d, 6H); 2.35 (dd, 2H); 3.08-3.20 (m, 2H); 3.41 (d, 2H); 3.56-3.98 (m, 2H); 7.25 (s, 1H); 7.57 (brs, 1H); 8.14 (s, 1H); 9.03 (s, 1H)	Intermediate 255
252	1-(5-Bromo-4-((2R,6S)-2,6-dimethylmorpholino)pyridin-2-yl)-3-ethylurea 	MS (ESP): 359 (M+2) for $C_{14}H_{21}BrN_4O_2$	Intermediate 256

Intermediate 253

1-(4-(3,3-Dimethylpiperidin-1-yl)pyridin-2-yl)-3-ethylurea

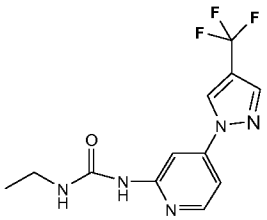
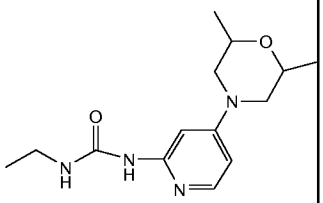
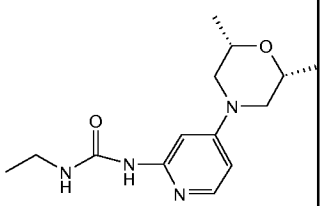


1-(4-Bromopyridin-2-yl)-3-ethylurea (Intermediate 14, 500 mg, 2.05 mmol), 3,3-dimethylpiperidine (301 mg, 2.66 mmol), copper(I) iodide (39.0 mg, 0.20 mmol) and pyrrolidine-2-carboxylic acid (47.2 mg, 0.41 mmol) and potassium carbonate (566 mg, 4.10 mmol) were taken in a round bottomed flask and degassed with argon. DMSO (8 mL) was added, and the mixture was degassed with argon again, then heated at 105 °C for 4 h. The reaction was partitioned between water and ethyl acetate. The layers were separated and the aqueous was extracted with ethyl acetate. The combined extract was washed with water and

brine, dried over magnesium sulfate and concentrated. The crude was purified by normal phase (Hex/ethyl acetate) chromatography to give an off-white solid (200 mg).
MS (ESP): 277 (M+1) for $C_{15}H_{24}N_4O$

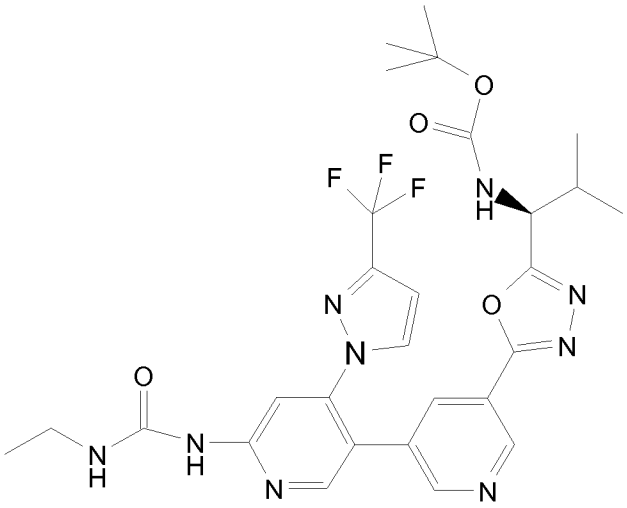
Intermediates 254-256

The following compounds have been synthesized as described for Intermediate 253 from the starting materials indicated in the table below.

Int	Compound	Data	SM
254	1-Ethyl-3-(4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pyridin-2-yl)urea 	MS (ESP): 300 (M+1) for $C_{12}H_{12}F_3N_5O$ ^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 3.07-3.28 (m, 2H); 7.13 (d, 1H); 7.49 (dd, 1H); 7.72 (brs, 1H); 8.07 (d, 1H); 8.31 (d, 1H); 8.85 (d, 1H); 9.35 (s, 1H)	Intermediate 14 and 3-(trifluoromethyl)-1H-pyrazole
255	1-(4-(2,6-Dimethylmorpholino)pyridin-2-yl)-3-ethylurea 	MS (ESP): 279 (M+1) for $C_{14}H_{22}N_4O_2$	Intermediate 14 and 2,6-dimethylmorpholine
256	1-(4-((2R,6S)-2,6-Dimethylmorpholino)pyridin-2-yl)-3-ethylurea 	MS (ESP): 279 (M+1) for $C_{14}H_{22}N_4O_2$	Intermediate 14 and 2R,6S)-2,6-Dimethylmorpholine

Intemediate 257

(S)-tert-Butyl 1-(5-(6'-(3-ethylureido)-4'-(3-(trifluoromethyl)-1H-pyrazol-1-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)-2-methylpropylcarbamate

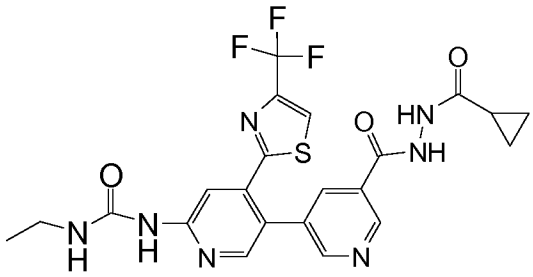


To a solution of 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(3-(trifluoromethyl)-1H-pyrazol-1-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 238, 80 mg, 0.18 mmol) in DMF (3 mL), DIPEA (0.032 mL, 0.18 mmol) was added followed by (S)-2-(tert-butoxycarbonylamino)-3-methylbutanoic acid (40.0 mg, 0.18 mmol) and HATU (180mg, 0.47 mmol) and the solution was stirred for 30 min at RT. The reaction was partitioned between water and ethyl acetate. The layers separated and the aqueous layer was back extracted with ethyl acetate twice. Then the combined extracts were washed with water and brine, dried over magnesium sulfate and concentrated to give a clear oil. The oil was taken up in acetonitrile (5 mL) and DBU (0.042 mL, 0.28 mmol) was added followed by triphenylphosphine (97 mg, 0.37 mmol) and carbon tetrachloride (0.036 mL, 0.37 mmol). The resulting solution was stirred at room temperature overnight. The reaction was concentrated and the crude was partitioned between water and ethyl acetate. The layers separated and the aqueous was back extracted twice. The combined extracts were washed with water and dried over magnesium sulfate, concentrated and purified by normal phase (hex/ethyl acetate) chromatography to give a white solid (95 mg) which was slurried in acetonitrile, and filtered and dried (65 mg white solid).

MS (ESP): 616 (M+1) for $C_{28}H_{32}F_3N_9O_4$

Intermediate 258

1-(5'-(2-(Cyclopropanecarbonyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



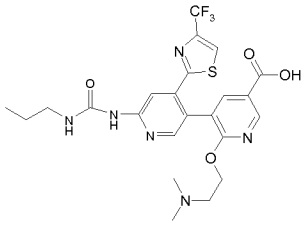
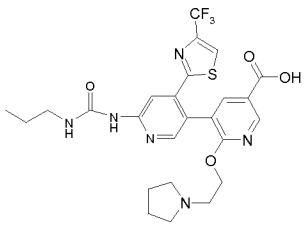
To a suspension of 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 9, 70 mg, 0.16 mmol) in acetonitrile (3 mL), potassium carbonate (25.7 mg, 0.19 mmol) was added, followed by a slow addition of cyclopropanecarbonyl chloride (0.014 mL, 0.16 mmol) and the resulting mixture was stirred at room temperature for 30 minutes. The precipitated product was filtered and the residue was washed with acetonitrile and water to give 72 mg of the desired product as a tan colored solid. MS (ESP): 520 (M+1) for $C_{22}H_{20}F_3N_7O_3S$.

Intermediates 259-260

The following Intermediates were prepared by the general procedure described below from the starting materials indicated in the Table.

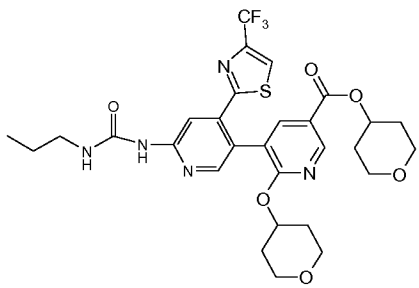
General Procedure

A suspension of ester (0.3g, 6 mmol, 1 eq) in the corresponding alcohol (2-3 mL, ~50 equiv.) in a small vial was stirred for 2 min at room temperature. Sodium hydride (0.150 g, 60 mmol) was added over 5 min and the reaction was stirred for a further 5 h at room temperature. The reaction was cooled with an ice bath and slowly quenched with HCl (0.1N) solution until pH 7. The aqueous layer was extracted twice with ether to remove excess alcohol. The aqueous layer was concentrated *in vacuo* to almost dryness than loaded on Analogix C18-column for reverse phase purification (water-methanol) to remove excess salt.

Int	Compound	Data	SM
259	2-(2-(dimethylamino)ethoxy)-6'-(3-propylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid 	MS (ESP): 539.1 (MH^+) for $C_{23}H_{25}F_3N_6O_4S$	Intermediate 219 and 2-(2-(diisopropylamino)ethanol
260	6'-(3-propylureido)-2-(2-(pyrrolidin-1-yl)ethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid 	MS (ESP): 565.1 (MH^+) for $C_{25}H_{27}F_3N_6O_4S$	Intermediate 219 and 2-(pyrrolidin-1-yl)ethanol

Intermediate 261

tetrahydro-2H-pyran-4-yl 6'-(3-propylureido)-2-(tetrahydro-2H-pyran-4-yloxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate

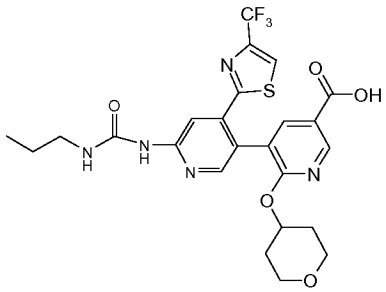


To a slurry of 6-(3-propylureido)-4-(4-trifluoromethylthiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 218, 0.63 g, 1.7 mmol), tetrahydro-2H-pyran-4-yl 5-bromo-6-(tetrahydro-2H-pyran-4-yloxy)nicotinate (Intermediate 281, 0.5 g, 1.3 mmol) and trans dichlorobis(triphenylphosphine)palladium (II) (597 mg, 0.85 mmol) in 1,4-dioxane (72 mL) was added a solution of potassium carbonate (2.4 g, 17.0 mmol) in water (27 mL). The reaction was stirred at 70°C for 1 h. The reaction was cooled to room temperature, and ethyl acetate (100 mL) and water (10 mL) were added to help separate the layers. The water was removed, and the organic phase was washed with water (10 mL). The reaction was then concentrated and the residue was triturated with a mixture of ethanol (20 mL) and methyl tert-butyl ether (50 mL). The solid was dried in a vacuum oven at 50°C for 3 hours. This gave tetrahydro-2H-pyran-4-yl 6'-(3-propylureido)-2-(tetrahydro-2H-pyran-4-yloxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (~80% yield) as an off white solid.

MS (ESP): 635.20 (MH^+) for $C_{29}H_{32}F_3N_5O_6S$.

Intermediate 262

6'-(3-propylureido)-2-(tetrahydro-2H-pyran-4-yloxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid

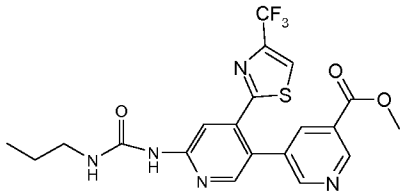


Tetrahydro-2H-pyran-4-yl 6'-(3-propylureido)-2-(tetrahydro-2H-pyran-4-yloxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 261, ~0.3 mmol) was dissolved in tetrahydrofuran-water and treated with lithium hydroxide (10 eq) at room temperature for 24 h. After this period of time, the organic was removed under vacuum. Dilute HCl was added to adjust the pH to 7 and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated to dryness to give the corresponding acid which was used directly for the next step.

MS (ESP): 552.1 (MH^+) for $C_{24}H_{24}F_3N_5O_5S$

Intermediate 263

Methyl 6'-(3-propylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



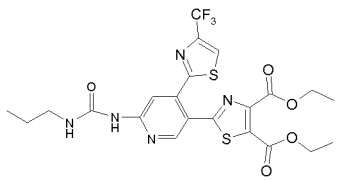
1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-propylurea (Intermediate 218, 200 mg, 0.51 mmol), methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (173 mg, 0.65 mmol), and trans dichlorobis(triphenylphosphine)palladium (II) (36 mg, 0.05 mmol) were dissolved in 1,4-dioxane (8 mL). Sodium bicarbonate (170 mg, 2 mmol) was dissolved in water (3 mL) and added to the above mixture. The reaction was heated at 65˚C for 60 min. Ethyl acetate (10 mL) was then added to the reaction and the layers were separated. The solvent was removed *in vacuo* and the residue was triturated with ethanol (5 mL). The solid was dried in a vacuum oven at 60˚C for 1 hour to give 145 mg (64% yield) of methyl 6'-(3-propylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate as an off white powder.

MS (ESP): 466.2 ($M+H^+$) for $C_{20}H_{18}F_3N_5O_3S$

^1H NMR (300 MHz, DMSO-d_6): δ 0.88 (t, 3H), 1.49 (m, 2H), 3.17 (m, 2H), 3.87 (s, 3H), 7.59 (bt, 1H), 8.20 (s, 1H), 8.21 (s, 1H), 8.37 (s, 1H), 8.37 (s, 1H), 8.75 (d, 1H), 9.07 (d, 1H), 9.54 (bs, 1H).

Intermediate 264

Diethyl 2-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)thiazole-4,5-dicarboxylate



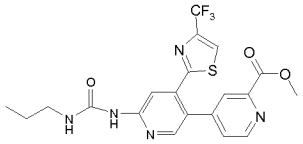
6-(3-Propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 218, 200 mg, 0.54 mmol), diethyl 2-chlorothiazole-4,5-dicarboxylate (110 mg, 0.41 mmol), and trans dichlorobis(triphenylphosphine)palladium (II) (30 mg, 0.041 mmol) were dissolved in 1,4-dioxane (8 mL). Sodium bicarbonate (170 mg, 2 mmol) was dissolved in water (3 mL) and added to the above mixture. The reaction was heated at 80˚C in a microwave for 60 min. Ethyl acetate (10 mL) was then added to the reaction and the layers were separated. The

solvent was removed *in vacuo* and the residue was chromatographed on an Analogix 4g column using 1-100% ethyl acetate in heptane. This gave 73 mg (31% yield) of diethyl 2-(6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)thiazole-4,5-dicarboxylate as an off white powder.

MS (ESP): 558.2 ($M+H^+$) for $C_{22}H_{22}F_3N_5O_5S_2$

Intermediate 265

Methyl 6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate

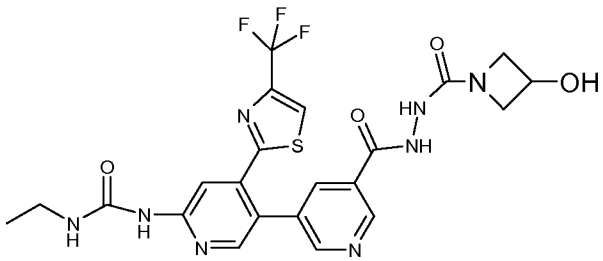


6-(3-Propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 218, 311 mg, 0.86 mmol), methyl 4-chloropicolinate (135 mg, 0.78 mmol), and trans dichlorobis(triphenylphosphine)palladium (II) (32 mg, 0.04 mmol) were dissolved in 1,4-dioxane (4 mL). Sodium bicarbonate (131 mg, 1.5 mmol) was dissolved in water (1 mL) and added to the above mixture. The reaction was heated at 80°C for 60 min in the microwave. Ethyl acetate (10 mL) was then added to the reaction and the layers were separated. The solvent was removed *in vacuo* and the residue was chromatographed on an Analogix 4g column using 0-100% ethyl acetate in heptane. The solid was dried in a vacuum oven at 60°C for 1 hour to give 102 mg (26% yield) of methyl 6-(3-propylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate as an off white powder.

MS (ESP): 466.2 ($M+H^+$) for $C_{20}H_{18}F_3N_5O_3S$

Intermediate 266

1-Ethyl-3-(5'-(2-(3-hydroxyazetidine-1-carbonyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl) urea

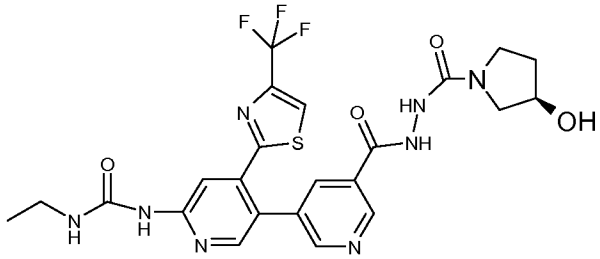


To a suspension of 1-ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Example 6, 235 mg, 0.49 mmol) in

ethanol (3 mL) was added azetidin-3-ol (162 mg, 1.48 mmol) followed by TEA (0.206 mL, 1.48 mmol) and heated to 100°C for 2 h in a microwave. The reaction mixture was concentrated and used without further purification.

Intermediate 267

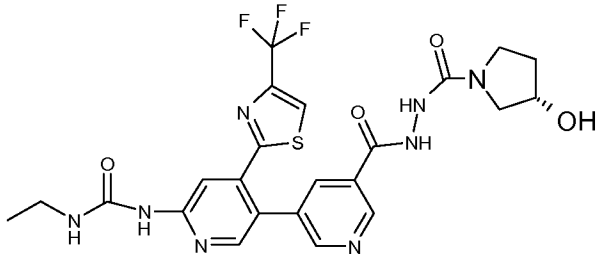
(R)-1-Ethyl-3-(5'-(2-(3-hydroxypyrrolidine-1-carbonyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



The title compound was synthesized by method analogous to Intermediate 266 starting with Example 6 and (R)-pyrrolidin-3-ol.

Intermediate 268

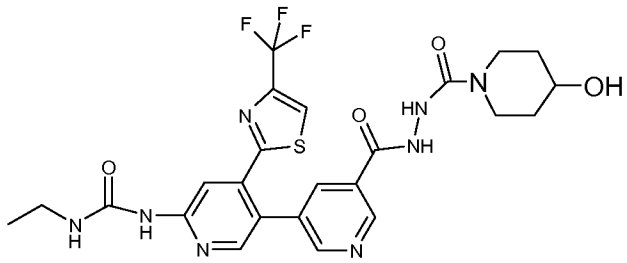
(S)-1-ethyl-3-(5'-(2-(3-hydroxypyrrolidine-1-carbonyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



The title compound was synthesized by method analogous to Intermediate 266 starting with Example 6 and (S)-pyrrolidin-3-ol.

Intermediate 269

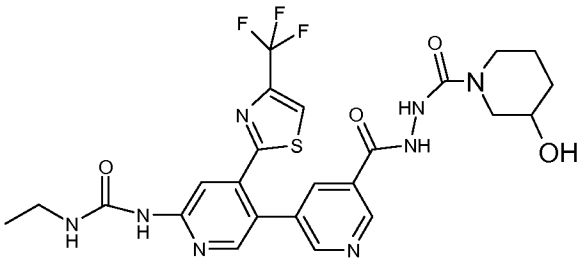
1-Ethyl-3-(5'-(2-(4-hydroxypiperidine-1-carbonyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



The title compound was synthesized by method analogous to Intermediate 266 starting with Example 6 and piperidin-4-ol.

Intermediate 270

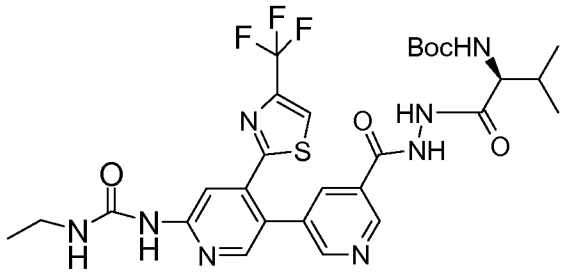
1-Ethyl-3-(5'-(2-(3-hydroxypiperidine-1-carbonyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



The title compound was synthesized by method analogous to Intermediate 266 starting with Example 6 and piperidin-3-ol.

Intermediate 271

(S)-tert-butyl 1-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-3-methyl-1-oxobutan-2-ylcarbamate

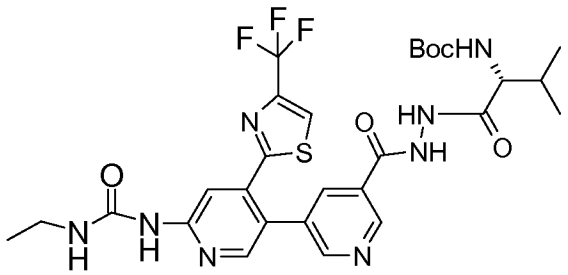


To a solution of 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 9, 340 mg, 0.75 mmol) in DMF (5 mL) was added (S)-2-(tert-butoxycarbonylamino)-3-methylbutanoic acid (245 mg, 1.13 mmol), HATU (573 mg, 1.51 mmol) and DIEA (0.329 mL, 1.88 mmol). After stirring overnight, the reaction mixture

was diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to give light yellow color solid.

Intermediate 172

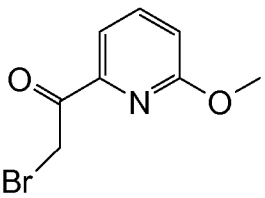
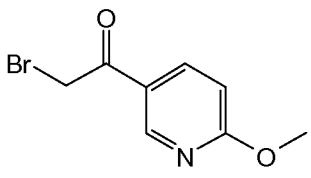
(R)-tert-butyl 1-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-3-methyl-1-oxobutan-2-ylcarbamate

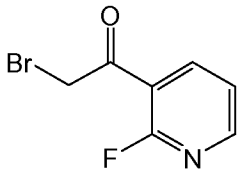
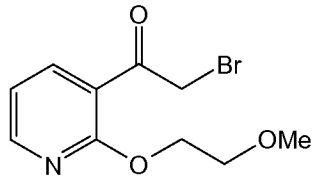
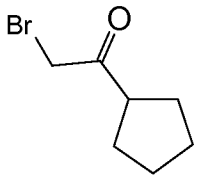
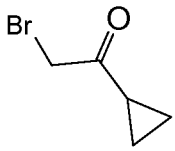
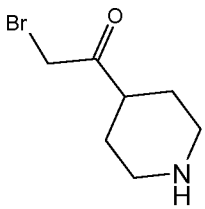


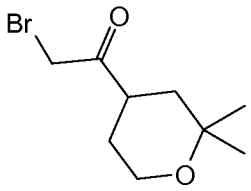
The title compound was synthesized by method analogous to Intermediate 271 starting with Intermediate 9 and (R)-2-(tert-butoxycarbonylamino)-3-methylbutanoic acid.

Intermediates 273-280

The following Intermediates were prepared according to the procedure described for Intermediate 28 from the starting materials indicated in the Table.

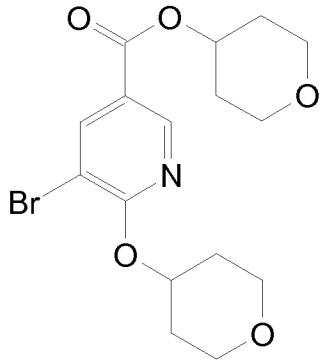
Int	Compound	Data	SM
273	2-bromo-1-(6-methoxypyridin-2-yl)ethanone 	LC/MS (ES^+)$(M+H)^+$: 230 232 for $C_8H_8BrNO_2$. ^1H NMR (300 MHz, CDCl3): 4.01 (s, 3H), 4.81 (s, 2H), 7.0 (d, 1H), 7.73 (m, 2H).	1-(6-methoxypyridin-2-yl)ethanone
274	2-bromo-1-(6-methoxypyridin-3-yl)ethanone 	LC/MS (ES)$(M+H)^+$: 230 232 for $C_8H_8BrNO_2$. ^1H NMR (300 MHz, d_6-DMSO): 3.95 (s, 3H), 4.90 (s, 2H), 6.96 (d, 1H), 8.21 (m, 1H), 8.88 (s, 1H).	1-(6-methoxypyridin-3-yl)ethanone

Int	Compound	Data	SM
275	2-bromo-1-(2-fluoropyridin-3-yl)ethanone 	LC/MS (ES^+)[$(M+H)^+$]: 216 218 for C_7H_5BrFNO. ^1H NMR (300 MHz, d_6-DMSO): 4.86 (s, 2H), 6.41 (m, 1H), 7.82 (m, 1H), 8.17 (m, 1H).	1-(2-fluoropyridin-3-yl)ethanone
276	2-bromo-1-(2-(2-methoxyethoxy)pyridin-3-yl)ethanone 	LC/MS (ES^+)[$(M+H)^+$]: 274, 276 for $C_{10}H_{12}BrNO_3$. ^1H NMR (300 MHz, d_6-DMSO): 3.33 (s, 3H), 3.74 (m,2H), 4.53 (m, 2H), 4.84 (s, 2H), 7.18 (m, 1H), 8.14 (m, 1H), 8.41 (m, 1H).	1-(2-(2-methoxyethoxy)pyridin-3-yl)ethanone
277	2-bromo-1-cyclopentylethanone 	^1H NMR (300 MHz, CDCl3): 1.69 (m, 8H), 3.18 (m, 1H), 3.99 (s, 2H).	1-cyclopentyl-ethanone
278	2-bromo-1-cyclopropylethanone 	^1H NMR (300 MHz, CDCl3): 1.02 (m, 2H), 1.14 (m, 2H), 2.22 (m, 1H), 4.02 (s, 2H).	1-cyclopropyl-ethanone
279	2-bromo-1-(piperidin-4-yl)ethanone 	^1H NMR (300 MHz, CDCl3): 1.69 (m, 8H), 3.18 (m, 1H), 3.99 (s, 2H).	benzyl 4-acetylpiperidine-1-carboxylate

Int	Compound	Data	SM
280	2-bromo-1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)ethanone 	^{1}H NMR (300 MHz, CDCl3): 1.26 (s, 3H), 1.27 (s, 3H), 1.56 (m, 2H), 1.73 (m, 2H), 3.15 (m, 1H), 3.75 (m, 2H), 3.96 (s, 2H).	1-(2,2-dimethyltetrahydro-2H-pyran-4-yl)ethanone

Intermediate 281

Tetrahydro-2H-pyran-4-yl 5-bromo-6-(tetrahydro-2H-pyran-4-yloxy)nicotinate

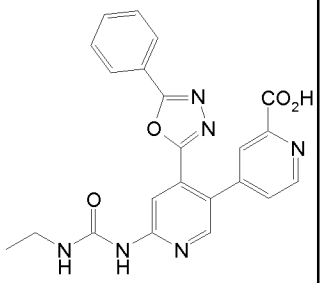
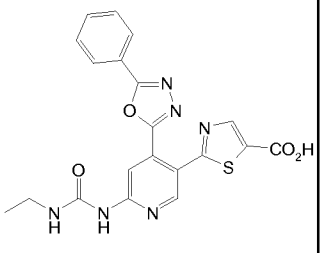


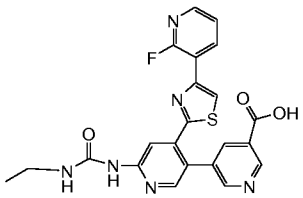
In a dried 250 mL glass round bottom flask, sodium hydride (0.878 g, 21.96 mmol) was suspended in 20 mL of anhydrous DMF. Tetrahydro-2H-pyran-4-ol (1.838 mL, 19.32 mmol) was added to the suspension dropwise. Upon reacting, the suspension became homogenous and a clear yellow solution was obtained. Methyl 5-bromo-6-chloronicotinate (2.2 g, 8.78 mmol) was then added in a single portion. The resultant reaction mixture was stirred at room temperature for 1 hour. A brown precipitate began to form. The reaction was monitored by LC/MS and TLC (6:4 EtOAc / hexanes). When the reaction was complete the mixture was diluted with Et_2O, cooled to 0°C (ice bath) and slowly quenched with water. The aqueous and organic phases were separated and the organic layer was dried over Na_2SO_4, filtered, concentrated by rotary evaporation and purified by flash column chromatography (1:1 EtOAc / hexanes). Isolation gave 441 mg of desired product.

LC/MS (ES^+): 386, 388 for $C_{16}H_{20}BrNO_5$.

Intermediates 282-284

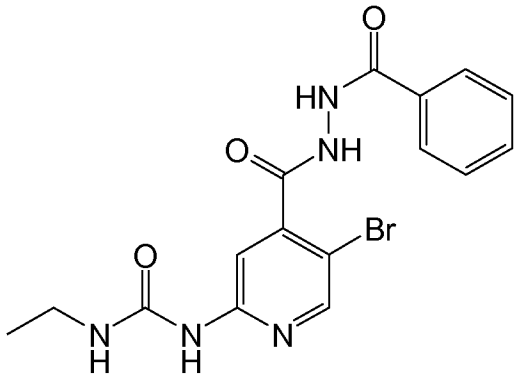
The following Intermediates were prepared according to the procedure described for Intermediate 51 using the starting material indicated in the table.

Int	Compound	Data	SM
282	6-(3-ethylureido)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,4'-bipyridine-2'-carboxylic acid 	LC/MS (ES^+)[$(M+H)^+$]: 431 for $C_{22}H_{18}N_6O_4$.	Intermediate 310
283	2-(6-(3-ethylureido)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-3-yl)thiazole-5-carboxylic acid 	LC/MS (ES^+)[$(M+H)^+$]: 437 for $C_{20}H_{16}N_6O_4S$.	Intermediate 312

Int	Compound	Data	SM
284	6'-(3-ethylureido)-4'-(4-(2-fluoropyridin-3-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid 	LC/MS (ES^+)[$(M+H)^+$]: 465 for $C_{22}H_{17}FN_6O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.23 (m, 2H), 7.44 (m, 1H), 7.62 (m, 1H), 8.13 (m, 1H), 8.16 (m, 1H), 8.19 (m, 1H), 8.23 (m, 1H), 8.24 (m, 1H), 8.34 (s, 1H), 8.75 (d, 1H), 9.08 (d, 1H), 9.49 (s, 1H), 13.52 (s, 1H).	Intermediate 320

Intermediate 285

1-(4-(2-benzoylhydrazinecarbonyl)-5-bromopyridin-2-yl)-3-ethylurea

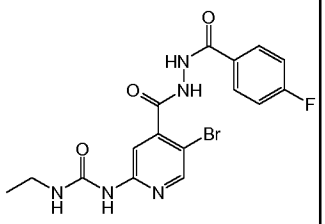


5-bromo-2-(3-ethylureido)isonicotinic acid (Intermediate 51, 6.25 g, 21.69 mmol) was dissolved in a DMF (60 mL) solution containing HATU (12.38 g, 32.54 mmol) and DIEA (7.54 mL, 43.39 mmol). After the mixture was stirred for 15 min, benzohydrazide (3.25 g, 23.86 mmol) was added in a single portion and the reaction mixture was stirred at room temperature for 1 h, the heated to 70°C for 1 hour. Solids precipitated from solution. The reaction was not complete after 12 hours, so another 2 grams of HATU was added and the mixture was heated until the reaction was complete. The reaction mixture was cooled to room temperature. The solids were filtered and washed with minimal DMF. The solids were then triturated in water, filtered and dried *in vacuo*. Isolation gave 3 grams of a white fluffy solid. LC/MS (ES^+): 406, 408 for $C_{16}H_{16}BrN_5O_3$.

^{1}H NMR (300 MHz, d_6-DMSO): 1.09 (t, 3H), 3.18 (m, 2H), 7.33 (t, 1H), 7.53 (m, 3H), 7.85 (s, 1H), 7.93 (d, 2H), 8.42 (s, 1H), 9.42 (s, 1H), 10.60 (s, 1H), 10.67 (s, 1H).

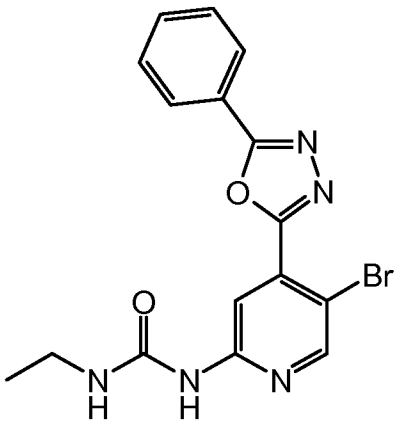
Interemediate 286

The following Intermediate was prepared according to the procedure described for Intermediate 285 using the starting materials indicated in the table.

Int	Compound	Data	SM
286	1-(5-bromo-4-(2-(4-fluorobenzoyl)hydrazinecarbonyl)pyridin-2-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 424, 426 for $C_{16}H_{15}BrFN_5O_3$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.08 (t, 3H), 3.17 (m, 2H), 7.38 (m, 3H), 7.87 (s, 1H), 8.01 (m, 2H), 8.41 (s, 1H), 9.46 (s, 1H), 10.62 (s, 1H), 10.72 (s, 1H).	Intermediate 51 and 4-fluorobenzohydrazide

Intermediate 287

1-(5-bromo-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl)-3-ethylurea



1-(4-(2-benzoylhydrazinecarbonyl)-5-bromopyridin-2-yl)-3-ethylurea (Intermediate 285, 4.73 g, 11.64 mmol) was suspended in a methylene chloride (20 mL) solution containing triphenyl phosphine (3.36 g, 12.81 mmol), carbon tetrabromide (4.25 g, 12.81 mmol) and triethylamine (1.790 mL, 12.81 mmol) (pre-mixed and stirred for 10 minutes). The mixture was stirred at room temperature and monitored by LC/MS. The reaction was not complete after 12 hours,

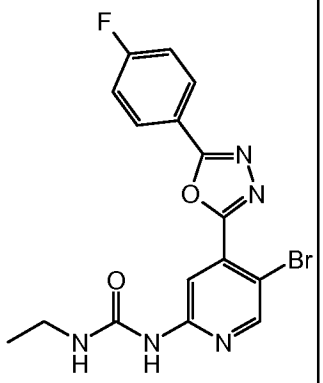
so a second CH_2Cl_2 (20 mL) solution containing triphenyl phosphine (3.36 g, 12.81 mmol), carbon tetrabromide (4.25 g, 12.81 mmol) and triethylamine (1.790 mL, 12.81 mmol) was prepared and added to the reaction mixture. This procedure was repeated a third time. Once the reaction was deemed complete, the precipitate was filtered off, and washed with CH_2Cl_2. The filtration yielded 970 mg of the product. The mother liquor was purified by flash column chromatography (95:5 CH_2Cl_2 / MeOH). Isolation gave another 1.2 gram of product. Total isolated weight was 2.1 g.

LC/MS (ES^+): 388, 340 for $C_{16}H_{14}BrN_5O_2$.

^1H NMR (300 MHz, d_6-DMSO): 1.09 (t, 3H), 3.19 (m, 2H), 7.21 (t, 1H), 7.66 (m, 2H), 7.69 (s, 1H), 8.08 (m, 2H), 8.45 (s, 1H), 8.61 (s, 1H), 9.49 (s, 1H).

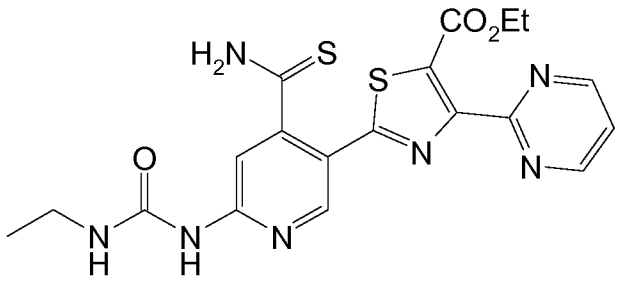
Intermediate 288

The following Intermediate was prepared according to the procedure described for Intermediate 287 using the starting materials indicated in the table.

Int	Compound	Data	SM
288	1-(5-bromo-4-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)pyridin-2-yl)-3-ethylurea 	LC/MS (ES^+): 406, 408 for $C_{16}H_{13}BrFN_5O_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.09 (t, 3H), 3.17 (m, 2H), 7.19 (t, 1H), 7.53 (m, 2H), 8.15 (m, 2H), 8.46 (s, 1H), 8.62 (s, 1H), 9.49 (s, 1H).	Intermediate 286

Intermediate 289

Ethyl 2-(4-carbamothioyl-6-(3-ethylureido)pyridin-3-yl)-4-(pyrimidin-2-yl)thiazole-5-carboxylate

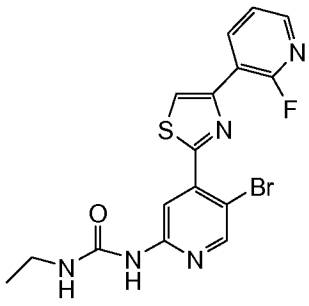


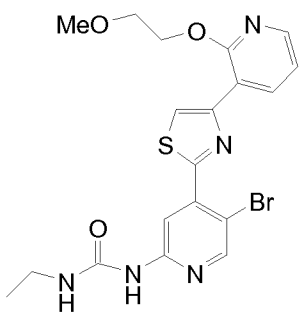
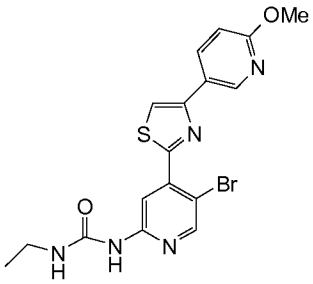
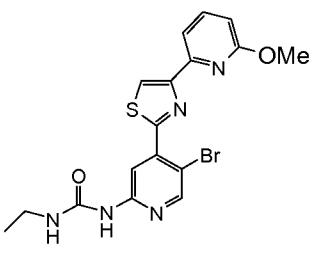
Ethyl 2-(4-carbamoyl-6-(3-ethylureido)pyridin-3-yl)-4-(pyrimidin-2-yl)thiazole-5-carboxylate (Intermediate 319, 132 mg, 0.30 mmol) was suspended in THF. Lawesson's reagent (145 mg, 0.36 mmol) was added in a single portion. The suspension was heated to reflux for 1 h. The reaction mixture concentrated to dryness.

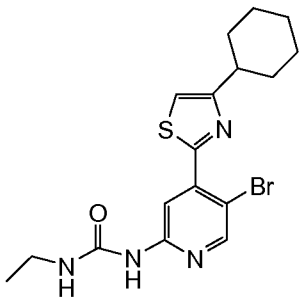
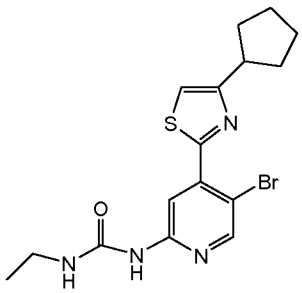
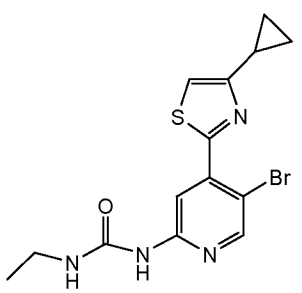
LC/MS (ES^+)[$(M+H)^+$]: 458 for $C_{19}H_{19}N_7O_3S_2$.

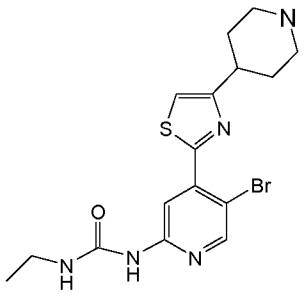
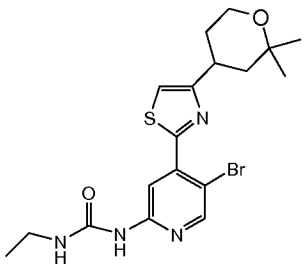
Intermediates 290-299

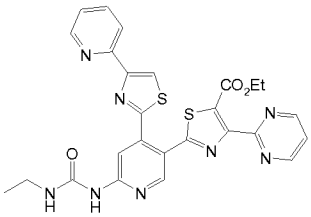
The following Intermediates were prepared according to the procedure described for Intermediate 16 using the starting materials indicated.

Int	Compound	Data	SM
290	1-(5-bromo-4-(4-(2-fluoropyridin-3-yl)thiazol-2-yl)pyridin-2-yl)-3-ethylureaethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 420, 422 for $C_{16}H_{13}BrN_5OS$. ^1H NMR (300 MHz, d_6-DMSO): 1.09 (t, 3H), 3.18 (m, 2H), 6.45 (m, 1H), 7.37 (m, 1H), 8.51 (m, 1H), 8.46 (s, 1H), 8.47 (m, 1H), 8.54 (s, 1H), 8.83 (s, 1H), 9.38 (s, 1H).	Intermediate 5 and Intermediate 275

Int	Compound	Data	SM
291	1-(5-bromo-4-(4-(2-(2-methoxyethoxy)pyridin-3-yl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 478, 480 for $C_{19}H_{20}BrN_5O_3S$.	Intermediate 5 and Intermediate 276
292	1-(5-bromo-4-(4-(6-methoxypyridin-3-yl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 434, 436 for $C_{17}H_{16}BrN_5O_2S$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.09 (t, 3H), 3.18 (m, 2H), 3.92 (s, 3H), 6.98 (d, 1H), 7.34 (m, 1H), 8.32 (m, 1H), 8.45 (s, 1H), 8.53 (s, 1H), 8.54 (s, 1H), 8.87 (d, 1H), 9.38 (s, 1H).	Intermediate 5 and Intermediate 274
293	1-(5-bromo-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 434, 436 for $C_{17}H_{16}BrN_5O_2S$.	Intermediate 5 and Intermediate 273

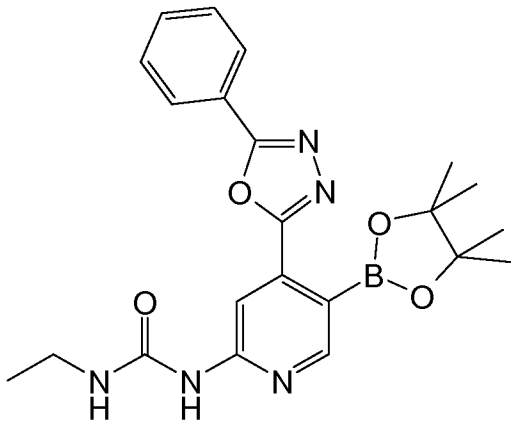
Int	Compound	Data	SM
294	1-(5-bromo-4-(4-cyclohexylthiazol-2-yl)pyridin-2-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 409, 411 for $C_{17}H_{21}BrN_4OS$. ^1H NMR (300 MHz, d_6-DMSO): 1.06 (t, 3H), 1.23 (m, 1H), 1.38 (m, 2H), 1.45 (m, 2H), 1.74 (m,3H), 2.03 (m, 2H), 2.81(m, 1H), 3.17 (m, 2H), 7.33 (m, 1H), 7.63 (s, 1H), 8.37 (s, 1H), 8.49 (s, 1H), 9.33 (s, 1H).	Intermediate 5 and 2-bromo-1-cyclohexylethanone
295	1-(5-bromo-4-(4-cyclopentylthiazol-2-yl)pyridin-2-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 395, 397 for $C_{16}H_{19}BrN_4OS$. ^1H NMR (300 MHz, d_6-DMSO): 1.26 (t, 3H), 1.57 (m, 4H), 1.82 (m, 4H), 3.30 (m, 1H), 3.43 (m, 2H), 7.19 (m, 1H), 7.31 (s, 1H), 7.61 (s, 1H), 8.41 (s, 1H), 8.80 (m, 1H).	Intermediate 5 and Intermediate 277
296	1-(5-bromo-4-(4-cyclopropylthiazol-2-yl)pyridin-2-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 367, 369 for $C_{14}H_{15}BrN_4OS$. ^1H NMR (300 MHz, d_6-DMSO): 0.88(m, 2H), 0.99(m, 2H), 1.08 (t, 3H), 2.19 (m, 1H), 3.17 (m, 2H), 7.38 (m, 1H), 7.82 (s, 1H), 8.30 (s, 1H), 8.48 (s, 1H), 9.32 (s, 1H).	Intermediate 5 and Intermediate 278

Int	Compound	Data	SM
297	1-(5-bromo-4-(4-(piperidin-4-yl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 410, 412 for $C_{16}H_{20}BrN_5OS$. ^1H NMR (300 MHz, d_6-DMSO): 1.07 (t, 3H), 1.89 (m, 2H), 2.17 (m, 2H), 3.08 (m, 2H), 3.14 (m, 2H), 3.37 (m, 2H), 3.40(m, 1H), 7.16 (m, 1H), 7.77 (s, 1H), 8.43 (s, 1H), 8.51 (s, 1H), 9.33 (s, 1H).	Intermediate 5 and Intermediate 279
298	1-(5-bromo-4-(4-(2,2-dimethyltetrahydro-2H-pyran-4-yl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 439 441 for $C_{18}H_{23}BrN_4O_2S$. ^1H NMR (300 MHz, d_6-DMSO): 1.08 (t, 3H), 1.11 (m, 2H), 1.19 (s, 3H), 1.27 (s, 3H), 1.53 (m, 2H), 1.87 (m, 2H), 3.16 (m, 1H), 3.74(m, 2H), 7.35 (m, 1H), 7.67 (s, 1H), 8.34 (s, 1H), 8.50 (s, 1H), 9.33 (s, 1H).	Intermediate 5 and Intermediate 280

Int	Compound	Data	SM
299	ethyl 2-(6-(3-ethylureido)-4-(4-(pyridin-2-yl)thiazol-2-yl)pyridin-3-yl)-4-(pyrimidin-2-yl)thiazole-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 559 for $C_{26}H_{22}N_8O_3S_2$.	Intermediate 289 and 2-bromo-1-(pyridin-2-yl)ethanone

Intermediate 300

1-ethyl-3-(4-(5-phenyl-1,3,4-oxadiazol-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)urea



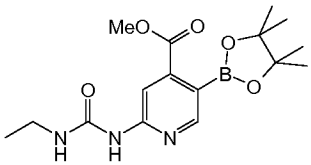
1-(5-Bromo-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 287, 1.17 g, 3.01 mml) and $PdCl_2(PPh_3)_2$ (0.2 g, 0.3 mmol) were suspended in 1,4 dioxane. The reaction mixture was degassed and purged with nitrogen. The suspension was gently warmed to 70 °C. 4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.3 g, 9.04 mmol) was added in a single portion and the mixture was stirred at 100 °C for 30 min. Triethylamine (0.91 g, 9.04 mmol) was added followed by KOAc (0.88 g, 9.04 mmol). The reaction mixture

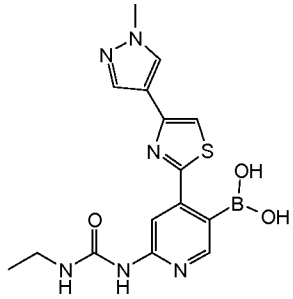
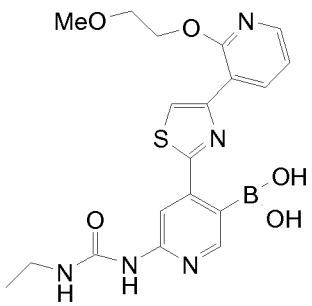
was then allowed to react for 12 hours, then the reaction was cooled to room temperature, filtered through a pad of Celite, and the mother liquor was concentrated to dryness. The residue was dissolved in ethyl acetate and the solution was washed with water, dried over Na_2SO_4, filtered and concentrated to a solid. The solid was triturated in EtOAc, filtered and dried *in vacuo* (isolated ~925 mg's). The mother liquor was concentrated further and then purified by flash column chromatography (0-100% EtOAc / hexanes) to give an additional 60 mg of product. Isolated weight and approximate purity as judged by LC/MS ratios (1:1 ratio of ester and acid): 925 mg (95% pure).

LC/MS (ES^+)[$(M+H)^+$]: 436 for $C_{22}H_{26}BN_5O_4$ (Boronic ester); 354 for $C_{16}H_{16}BN_5O_4$ (Boronic acid).

Intermediate 301-303

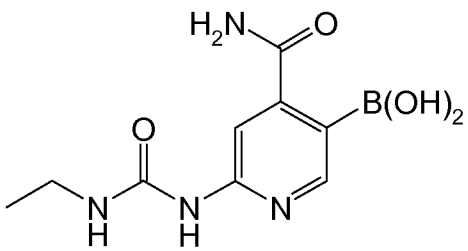
The following Intermediates were prepared by the procedure described for Intermediate 300 using the starting materials indicated in the table.

Int	Compound	Data	SM
301	methyl 2-(3-ethylureido)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isonicotinate 	LC/MS (ES^+)[$(M+H)^+$]: 350 for $C_{16}H_{24}BN_3O_5$	Intermediate 321

Int	Compound	Data	SM
302	6-(3-ethylureido)-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)pyridin-3-ylboronic acid 	LC/MS (ES^+)[$(M+H)^+$]: 373 for $C_{15}H_{17}BN_6O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.10 (t, 3H), 3.20 (m, 2H), 3.9(s, 3H), 7.81 (m, 1H), 7.84 (s, 1H), 7.91 (s, 1H), 7.92 (s, 1H), 8.12 (s, 1H), 8.33 (s, 1H), 8.37 (s, 2H), 9.27 (s, 1H).	Intermediate 29
303	6-(3-ethylureido)-4-(4-(2-(2-methoxyethoxy)pyridin-3-yl)thiazol-2-yl)pyridin-3-ylboronic acid 	LC/MS (ES^+)[$(M+H)^+$]: 444 for $C_{19}H_{22}BN_5O_5S$	Intermediate 291

Intermediate 304

4-carbamoyl-6-(3-ethylureido)pyridin-3-ylboronic acid

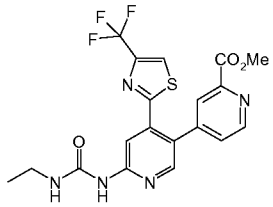
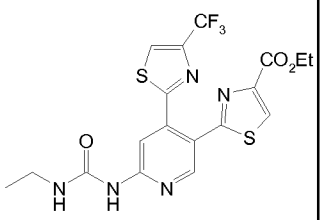


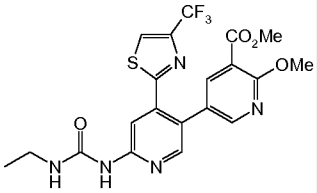
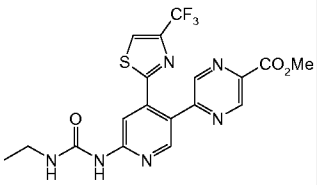
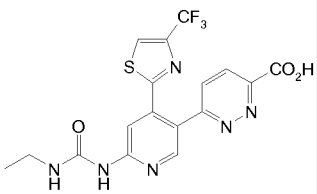
In a sealed microwave vessel, methyl 2-(3-ethylureido)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isonicotinate (Intermediate 301, 1.2 g, 3.44 mmol) was dissolved in a methanol solution containing ammonia (7N) (10 mL, 70.00 mmol). The solution was heated at 80°C for 15 minutes, the concentrated to dryness. The product was used without further purification.

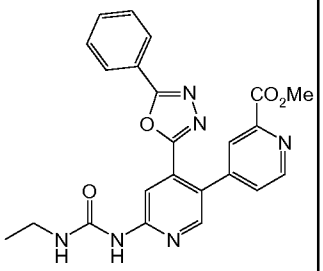
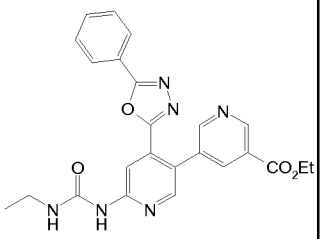
LC/MS (ES^+)[$(M+H)^+$]: 369 for $C_9H_{13}BN_4O_4$.

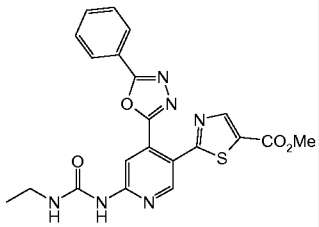
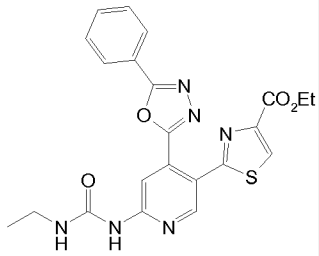
Intermediates 305-320

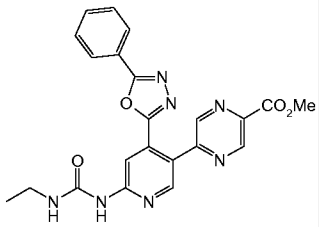
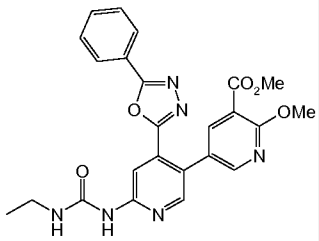
The following Intermediates were prepared according to the procedure described for Intermediate 2 using the starting materials indicated in the table.

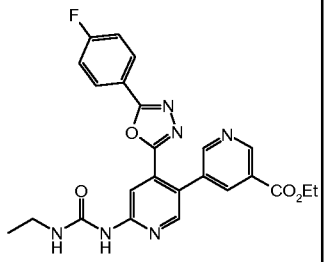
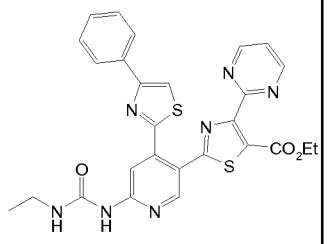
Int	Compound	Data	SM
305	methyl 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 452 for $C_{19}H_{16}F_3N_5O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.20 (m, 2H), 3.86 (s, 3H), 7.53 (t, 1H), 7.59 (dd, 1H), 7.98 (s, 1H), 8.16 (s, 1H), 8.38 (s, 1H), 8.61 (s, 1H), 8.70 (d, 1H), 9.55 (s, 1H).	Intermediate 12 and methyl 4-bromopicolinate
306	ethyl 2-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)thiazole-4-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 472 for $C_{18}H_{16}F_3N_5O_3S_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.29 (t, 3H), 3.22 (m, 2H), 4.28 (q, 2H), 7.49 (t, 1H), 8.14 (s, 1H), 8.65 (s, 2H), 8.69 (s, 1H), 9.67 (s, 1H).	Intermediate 12 and ethyl 2-bromothiazole-4-carboxylate

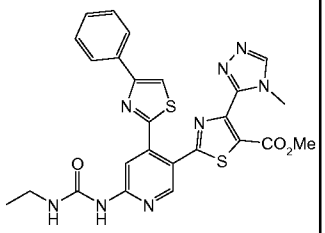
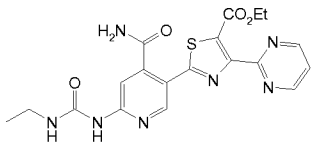
Int	Compound	Data	SM
307	methyl 6'-(3-ethylureido)-6-methoxy-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 482 for $C_{20}H_{18}F_3N_5O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.10 (t, 3H), 3.21 (m, 2H), 3.78 (s, 3H), 3.97 (s, 3H), 7.59 (m, 1H), 8.06 (s, 1H), 8.23 (s, 1H), 8.31 (s, 1H), 8.35 (s, 1H), 8.56 (s, 1H), 9.45 (s, 1H).	Intermediate 12 and methyl 5-bromo-2-methoxynicotinate
308	methyl 5-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)pyrazine-2-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 453 for $C_{18}H_{15}F_3N_6O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.17 (m, 2H), 3.94 (s, 3H), 7.53 (t, 1H), 8.16 (s, 1H), 8.61 (s, 1H), 8.63 (s, 1H), 8.88 (d, 1H), 9.13 (d, 1H), 9.66 (s, 1H).	Intermediate 12 and methyl 5-chloropyrazine-2-carboxylate
309	6-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-yl)pyridazine-3-carboxylic acid 	LC/MS (ES^+)[$(M+H)^+$]: 439 for $C_{17}H_{13}F_3N_6O_3S$.	Intermediate 12 and 6-chloropyridazine-3-carboxylic acid

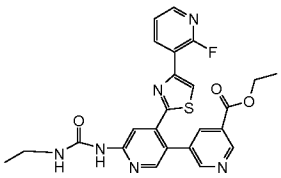
Int	Compound	Data	SM
310	methyl 6-(3-ethylureido)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,4'-bipyridine-2'-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 445 for $C_{23}H_{20}N_6O_4$.	Intermediate 300 and methyl 4-bromopicolinate
311	ethyl 6'-(3-ethylureido)-4'-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 459 for $C_{24}H_{22}N_6O_4$.	Intermediate 300 and ethyl 5-bromo-nicotinate

Int	Compound	Data	SM
312	methyl 2-(6-(3-ethylureido)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-3-yl)thiazole-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 451 for $C_{21}H_{18}N_6O_4S$.	Intermediate 300 and methyl 2-bromothiazole-5-carboxylate
313	ethyl 2-(6-(3-ethylureido)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-3-yl)thiazole-4-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 465 for $C_{22}H_{20}N_6O_4S$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.09 (m, 6H), 3.21 (m, 2H), 4.10 (q, 2H), 7.48 (t, 1H), 7.60 (m, 3H), 7.81 (d, 2H), 8.30 (s, 1H), 8.67 (s, 1H), 8.77 (s, 1H), 9.79 (s, 1H).	Intermediate 300 and ethyl 2-bromothiazole-4-carboxylate

Int	Compound	Data	SM
314	methyl 5-(6-(3-ethylureido)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-3-yl)pyrazine-2-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 446 for $C_{22}H_{19}N_7O_4$.	Intermediate 300 and methyl 5-bromopyrazine-2-carboxylate
315	methyl 6'-(3-ethylureido)-6-methoxy-4'-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 475 for $C_{24}H_{22}N_6O_5$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.12 (t, 3H), 3.22 (m, 2H), 3.78 (s, 3H), 4.00 (s, 3H), 7.52 (t, 1H), 7.68 (m, 3H), 7.77 (d, 2H), 8.22 (s, 1H), 8.38 (s, 1H), 8.45 (m, 2H), 9.53 (s, 1H).	Intermediate 300 and methyl 5-bromo-2-methoxynicotinate

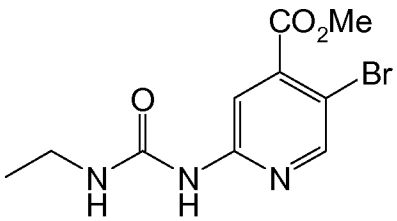
Int	Compound	Data	SM
316	ethyl 6'-(3-ethylureido)-4'-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 477 for $C_{24}H_{21}FN_6O_4$. ^1H NMR (300 MHz, d_6-DMSO): 1.07 (t, 3H), 1.11 (t, 3H), 3.21 (m, 2H), 4.13 (q, 2H), 7.43 (m, 3H), 7.51 (t, 1H), 7.59 (t, 1H), 7.88 (d, 2H), 8.21 (s, 1H), 8.39 (s, 1H), 8.73 (s, 1H), 8.92 (d, 2H), 9.68 (s, 1H).	Intermediate 288 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate
317	ethyl 2-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-4-(pyrimidin-2-yl)thiazole-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 558 for $C_{27}H_{23}N_7O_3S_2$. ^1H NMR (300 MHz, d_6-DMSO): 1.07 (t, 3H), 1.11 (t, 3H), 3.21 (m, 2H), 4.13 (q, 2H), 7.43 (m, 3H), 7.51 (t, 1H), 7.59 (t, 1H), 7.88 (d, 2H), 8.21 (s, 1H), 8.39 (s, 1H), 8.73 (s, 1H), 8.92 (d, 2H), 9.68 (s, 1H).	Intermediate 161 and Intermediate 43

Int	Compound	Data	SM
318	methyl 2-(6-(3-ethylureido)-4-(4-phenylthiazol-2-yl)pyridin-3-yl)-4-(4-methyl-4H-1,2,4-triazol-3-yl)thiazole-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 547 for $C_{25}H_{22}N_8O_3S_2$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.21 (m, 2H), 3.60 (s, 3H), 3.75 (s, 3H), 7.40 (m, 3H), 7.51 (t, 1H), 7.84 (d, 2H), 8.06 (s, 1H), 8.17 (s, 1H), 8.36 (s, 1H), 8.76 (s, 2H), 9.71 (s, 1H).	Intermediate 161 and Intermediate 44
319	ethyl 2-(4-carbamoyl-6-(3-ethylureido)pyridin-3-yl)-4-(pyrimidin-2-yl)thiazole-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 442 for $C_{19}H_{19}N_7O_4S$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.19 (m, 2H), 4.16 (q, 2H), 7.57 (t, 1H), 7.62 (t, 1H), 7.66 (s, 1H), 7.97 (s, 1H), 8.32 (s, 1H), 8.79 (s, 1H), 8.95 (d, 2H), 9.66 (s, 1H).	Intermediate 304 and Intermediate 43

Int	Compound	Data	SM
320	Ethyl 6'-(3-ethylureido)-4'-(4-(2-fluoropyridin-3-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 493 for $C_{24}H_{21}FN_6O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.27 (t, 3H), 3.22 (m, 2H), 4.32 (m, 2H), 7.26 (m, 1H), 7.43 (s, 1H), 7.61 (s, 1H), 8.11 (m, 1H), 8.20 (m, 1H), 8.22 (m, 1H), 8.25 (m, 1H), 8.36 (s, 1H), 8.79 (d, 1H), 9.10 (d, 1H), 9.50 (s, 1H).	Intermediate 290 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

Intermediate 321

Methyl 5-bromo-2-(3-ethylureido)isonicotinate



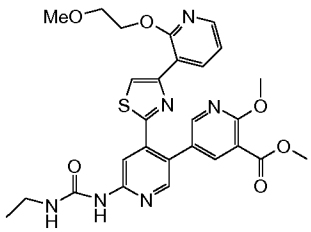
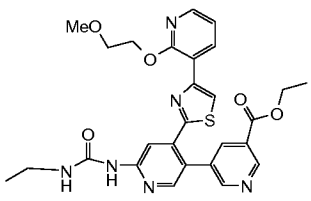
Methyl 2-amino-5-bromoisonicotinate (20 g, 86.56 mmol) was suspended in $CHCl_3$ (20 mL). Ethyl isocyanate (10.20 mL, 129.84 mmol) was added in a single portion and the reaction was heated in an oil bath to 80°C for 5 h. The reaction mixture was concentrated to dryness by rotary evaporation. The product crystallized from a mixture of CH_2Cl_2 and hexanes. Isolation gave 16.2 grams of the title compound.

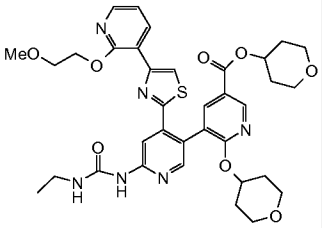
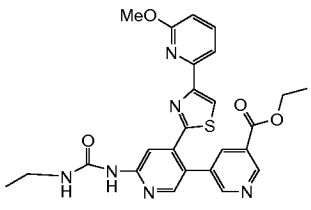
LC/MS (ES^+): 302, 304 for $C_{10}H_{12}BrN_3O_3$.

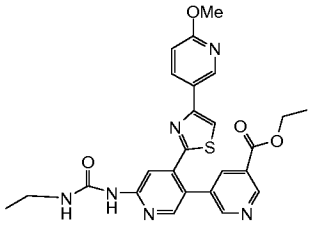
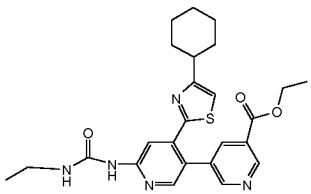
^1H NMR (300 MHz, d_6-DMSO): 1.07 (t, 3H), 3.18 (m, 2H), 3.89 (s, 3H), 7.18 (t, 1H), 8.02 (s, 1H), 8.46 (s, 1H), 9.42 (s, 1H).

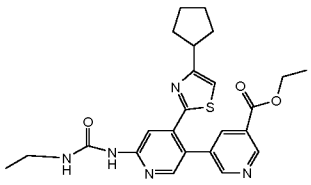
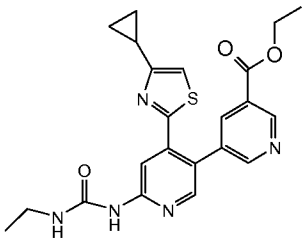
Intermediates 322-335

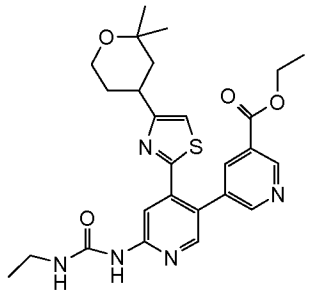
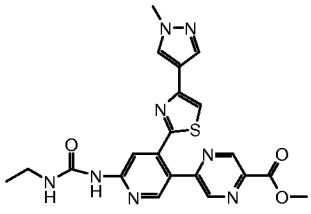
The following Intermediates were prepared according to the procedure described for Intermediate 2 using the starting materials indicated in the table.

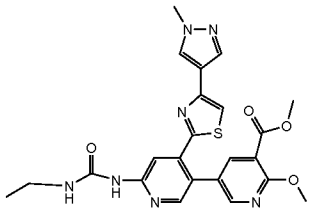
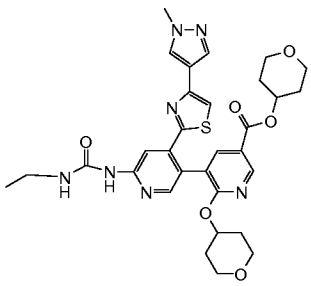
Int	Compound	Data	SM
322	methyl 6'-(3-ethylureido)-6-methoxy-4'-(4-(2-(2-methoxyethoxy)pyridin-3-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 565 for $C_{27}H_{28}N_6O_6S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.22 (m, 2H), 3.32 (s, 3H), 3.77 (s, 3H), 3.78 (m, 2H), 3.97 (s, 3H), 4.53 (m, 2H), 7.08 (m, 1H), 7.68 (m, 1H), 8.13 (d, 1H), 8.16 (m, 1H), 8.22 (m, 1H), 8.26 (s, 1H), 8.28 (s, 2H), 8.36 (d, 1H), 9.44 (s, 1H)	Intermediate 303 and methyl 5-bromo-2-methoxynicotinate
323	ethyl 6'-(3-ethylureido)-4'-(4-(2-(2-methoxyethoxy)pyridin-3-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 549 for $C_{27}H_{28}N_6O_5S$.	Intermediate 291 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

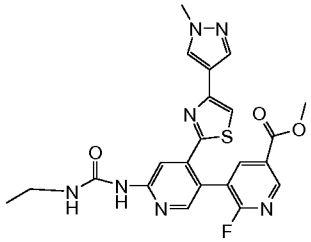
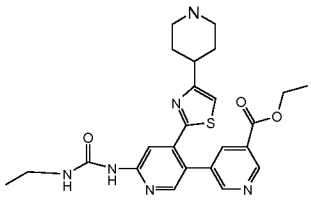
Int	Compound	Data	SM
324	tetrahydro-2H-pyran-4-yl 6'-(3-ethylureido)-4'-(4-(2-(2-methoxyethoxy)pyridin-3-yl)thiazol-2-yl)-2-(tetrahydro-2H-pyran-4-yloxy)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 705 for $C_{35}H_{40}N_6O_8S$.	Intermediate 303 and Intermediate 281
325	Ethyl 6'-(3-ethylureido)-4'-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 505 for $C_{25}H_{24}N_6O_4S$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.27 (t, 3H), 3.22 (m, 2H), 3.91 (s, 3H), 4.32 (m, 2H), 6.77 (m, 1H), 7.22 (m, 1H), 7.65 (m, 1H), 7.73 (m, 1H), 8.26 (m, 2H), 8.34 (s, 1H), 8.36 (s, 1H), 8.79 (s, 1H), 9.10 (s, 1H), 9.49 (s, 1H).	Intermediate 293 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

Int	Compound	Data	SM
326	Ethyl 6'-(3-ethylureido)-4'-(4-(6-methoxypyridin-3-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 505 for $C_{25}H_{24}N_6O4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.28 (t, 3H), 3.22 (m, 2H), 3.88 (s, 3H), 4.33 (m, 2H), 6.86 (m, 1H), 7.62 (m, 1H), 7.99 (m, 1H), 8.20 (m, 1H), 8.25 (s, 1H), 8.27 (t, 1H), 8.33 (s, 1H), 8.50 (m, 1H), 8.78 (d, 1H), 9.10 (d, 1H), 9.48 (s, 1H).	Intermediate 292 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate
327	ethyl 4'-(4-cyclohexylthiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 480 for $C_{25}H_{29}N_5O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.17 (m, 2H), 1.3 (m, 3H), 1.62 (m, 2H), 1.68(m, 2H), 2.55 (m, 2H), 3.20(m, 2H), 4.02 (m, 1H), 4.31 (m, 2H), 7.37 (s, 1H), 7.50 (m, 1H), 7.64(m, 2H), 8.09 (s, 1H), 8.10 (m, 1H), 8.29 (s, 1H), 8.69 (d, 1H), 9.05 (d, 1H), 9.43 (s, 1H).	Intermediate 294 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

Int	Compound	Data	SM
328	ethyl 4'-(4-cyclopentylthiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 466 for $C_{24}H_{27}N_5O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.28 (t, 3H), 1.33 (m, 2H), 1.50 (m, 4H), 1.76(m, 2H), 3.03 (m, 1H), 3.21(m, 2H), 4.32 (m, 2H), 7.40 (s, 1H), 7.66 (m, 1H), 8.08 (s, 1H), 8.10 (m, 1H), 8.30 (s, 1H), 8.69 (d, 1H), 9.05 (d, 1H), 9.45 (s, 1H).	Intermediate 295 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate
329	ethyl 4'-(4-cyclopropylthiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 438 for $C_{22}H_{23}N_5O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 0.42 (m, 2H), 0.74 (m, 2H), 1.11 (t, 3H), 1.33 (m, 3H), 1.97 (m, 1H), 3.21(m, 2H), 4.34 (m, 2H), 7.40 (s, 1H), 7.51 (m, 1H), 8.08 (s, 1H), 8.12 (m, 1H), 8.26 (s, 1H), 8.65 (d, 1H), 9.07 (d, 1H), 9.41 (s, 1H).	Intermediate 296 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

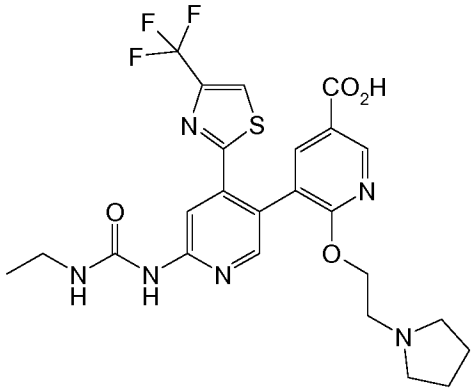
Int	Compound	Data	SM
330	Ethyl 4'-(4-(2,2-dimethyltetrahydro-2H-pyran-4-yl)thiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 510 for $C_{26}H_{31}N_5O_4S$.	Intermediate 298 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate
331	methyl 5-(6-(3-ethylureido)-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)pyridin-3-yl)pyrazine-2-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 465 for $C_{21}H_{20}N_8O_3S$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.21 (m, 2H), 3.80 (s, 3H), 3.94 (s, 3H), 7.50 (s, 1H), 7.56 (m, 1H), 7.74 (s, 1H), 7.81 (s, 1H), 8.15 (s, 1H), 8.51 (s, 1H), 8.79 (d, 1H), 9.19 (d, 1H), 9.58 (s, 1H).	Intermediate 302 and methyl 5-chloropyrazine-2-carboxylate

Int	Compound	Data	SM
332	methyl 6'-(3-ethylureido)-6-methoxy-4'-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 494 for $C_{23}H_{23}N_7O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.10 (t, 3H), 3.21 (m, 2H), 3.78 (s, 3H), 3.86 (s, 3H), 3.97 (s, 3H), 7.67 (s, 1H), 7.72 (s, 1H), 7.77 (s, 1H), 8.0 (s, 1H), 8.11 (d, 1H), 8.19(m, 1H), 8.25 (s, 1H), 8.34 (m, 1H), 9.42 (s, 1H).	Intermediate 302 and methyl 5-bromo-2-methoxynicotinate
333	tetrahydro-2H-pyran-4-yl 6'-(3-ethylureido)-4'-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-2-(tetrahydro-2H-pyran-4-yloxy)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 634 for $C_{31}H_{35}N_7O_6S$.	Intermediate 281 and Intermediate 302

Int	Compound	Data	SM
334	methyl 6'-(3-ethylureido)-2-fluoro-4'-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 482 for $C_{22}H_{20}FN_7O_3S$.	Intermediate 302 and methyl 5-bromo-6-fluoronicotinate
335	ethyl 6'-(3-ethylureido)-4'-(4-(piperidin-4-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 481 for $C_{24}H_{28}N_6O_3S$.	Intermediate 297 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate

Intermediate 336

6'-(3-ethylureido)-2-(2-(pyrrolidin-1-yl)ethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid

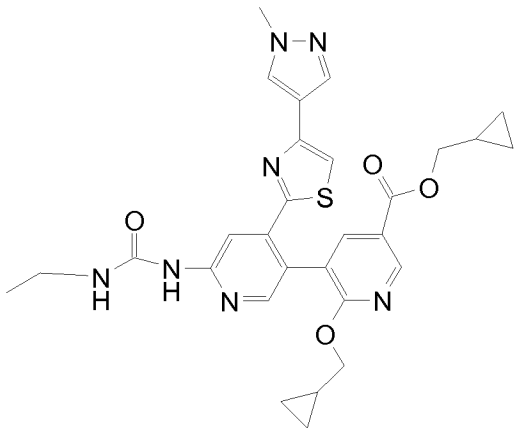


Methyl 6'-(3-ethylureido)-2-fluoro-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 162, 200 mg, 0.43 mmol) was added to a THF solution containing sodium hydride (85 mg, 2.13 mmol). The mixture was stirred at room temperature for 18 h. The reaction was neutralized with 2N HCl. The reaction mixture was concentrated to dryness by rotary evaporation. Purified by silica gel flash column chromatography (95:5 CH_2Cl_2 / MeOH) gave 220 mg of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 551 for $C_{24}H_{25}F_3N_6O_4S$.

Intermediate 337

cyclopropylmethyl 2-(cyclopropylmethoxy)-6'-(3-ethylureido)-4'-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



Lithium bis(trimethylsilyl)-amide (0.841 mL, 0.84 mmol) was added to solution of cyclopropylmethanol (0.033 mL, 0.42 mmol) in THF (1.5 mL). Methyl 6'-(3-ethylureido)-2-fluoro-4'-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 334, 0.081 g, 0.17 mmol) was added after 30 min. The mixture was stirred at room temperature overnight. The reaction was quenched with NH_4OH, partitioned between water and ethyl acetate, the layers were separated, and the organic phase was washed with

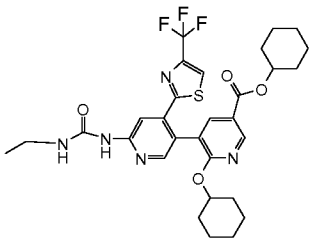
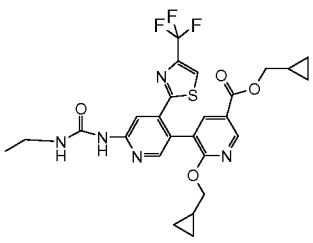
water and brine, dried over magnesium sulfate, concentrated under reduced pressure, and purified by column chromatography (Silica gel, 0-10% MeOH in CH_2Cl_2) to give 59 mg of crude compound.

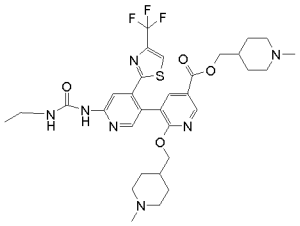
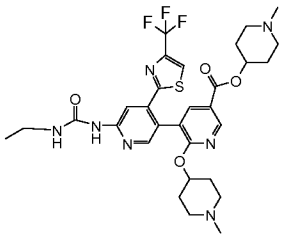
LC/MS (ES^+)[$(M+H)^+$]: 574 for $C_{29}H_{31}N_7O_4S$.

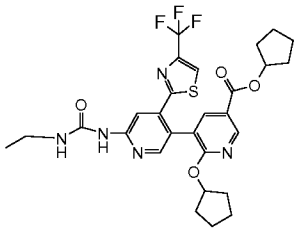
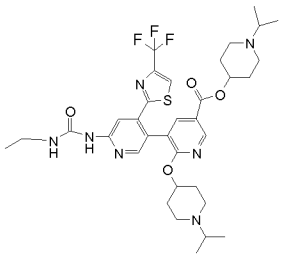
5

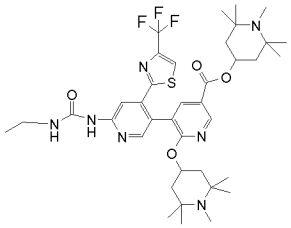
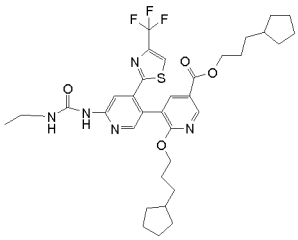
Intermediates 338-349

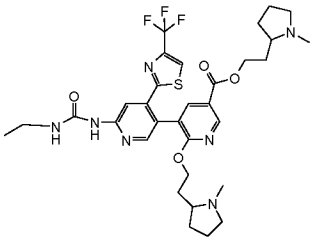
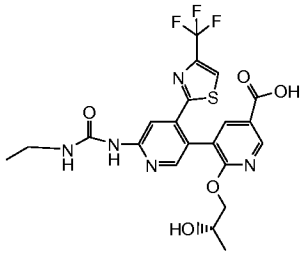
The following Intermediates were prepared according to the procedure described for Intermediate 337 using the starting materials indicated in the table.

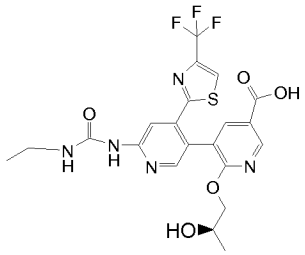
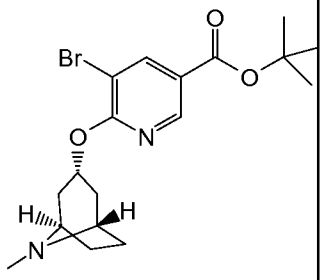
Int	Compound	Data	SM
338	cyclohexyl 2-(cyclohexyloxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 618 for $C_{30}H_{34}F_3N_5O_4S$.	Intermediate 162 and cyclohexanol
339	cyclopropylmethyl 2-(cyclopropylmethoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 562 for $C_{26}H_{26}F_3N_5O_4S$.	Intermediate 162 and cyclopropylmethanol

Int	Compound	Data	SM
340	(1-methylpiperidin-4-yl)methyl 6'-(3-ethylureido)-2-((1-methylpiperidin-4-yl)methoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 676 for $C_{32}H_{40}F_3N_7O_4S$.	Intermediate 162 and (1-methylpiperidin-4-yl)methanol
341	1-methylpiperidin-4-yl 6'-(3-ethylureido)-2-(1-methylpiperidin-4-yloxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 648 for $C_{30}H_{36}F_3N_7O_4S$.	Intermediate 162 and 1-methylpiperidin-4-ol

Int	Compound	Data	SM
342	cyclopentyl 2-(cyclopentyloxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 590 for $C_{28}H_{30}F_3N_5O_4S$.	Intermediate 162 and cyclopentanol
343	1-isopropylpiperidin-4-yl 6'-(3-ethylureido)-2-(1-isopropylpiperidin-4-yloxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 704 for $C_{34}H_{44}F_3N_7O_4S$.	Intermediate 162 and 1-isopropylpiperidin-4-ol

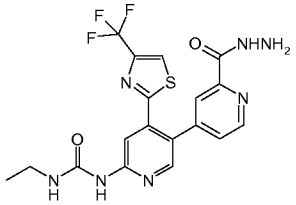
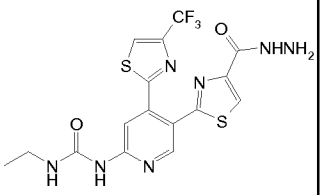
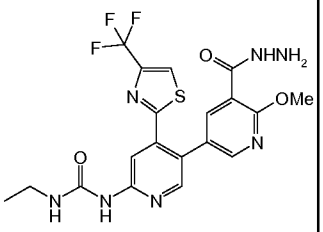
Int	Compound	Data	SM
344	1,2,2,6,6-pentamethylpiperidin-4-yl 6'-(3-ethylureido)-2-(1,2,2,6,6-pentamethylpiperidin-4-yloxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 760 for $C_{38}H_{52}F_3N_7O_4S$.	Intermediate 162 and 1,2,2,6,6-pentamethylpiperidin-4-ol
345	3-cyclopentylpropyl 2-(3-cyclopentylpropoxy)-6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 674 for $C_{34}H_{42}F_3N_5O_4S$.	Intermediate 162 and 3-cyclopentylpropan-1-ol

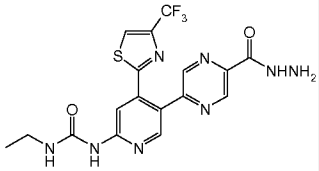
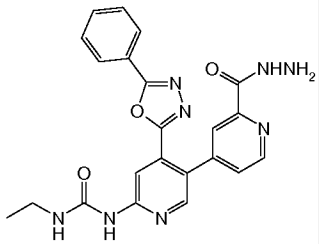
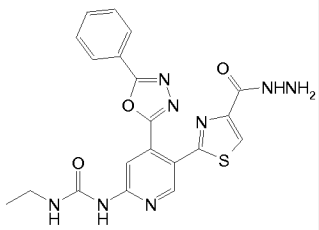
Int	Compound	Data	SM
346	2-(1-methylpyrrolidin-2-yl)ethyl 6'-(3-ethylureido)-2-(2-(1-methylpyrrolidin-2-yl)ethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 676 for $C_{32}H_{40}F_3N_5O_4S$.	Intermediate 162 and 2-(1-methylpyrrolidin-2-yl)ethanol
347	6'-(3-ethylureido)-2-((S)-2-hydroxypropoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid 	LC/MS (ES^+)[$(M+H)^+$]: 512 for $C_{21}H_{20}F_3N_5O_4S$.	Intermediate 162 and (S)-propane-1,2-diol

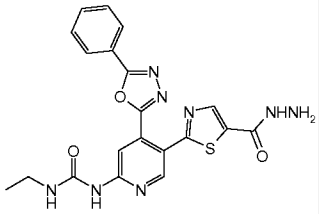
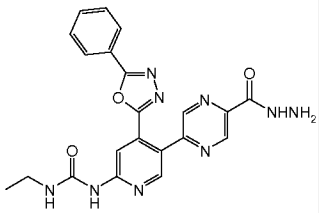
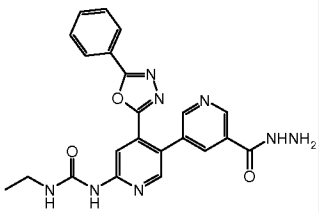
Int	Compound	Data	SM
348	6'-(3-ethylureido)-2-((R)-2-hydroxypropoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid 	LC/MS (ES^+)[$(M+H)^+$]: 512 for $C_{21}H_{20}F_3N_5O_4S$.	Intermediate 162 and (R)-propane-1,2-diol
349	tert-butyl 5-bromo-6-((1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yloxy)nicotinate 	LC/MS (ES^+)[$(M+H)^+$]: 397, 399 for $C_{18}H_{25}BrN_2O_3$.	tert-butyl 5-bromo-6-fluoronicotinate and (1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-ol

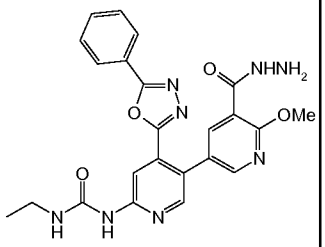
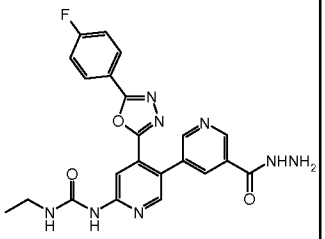
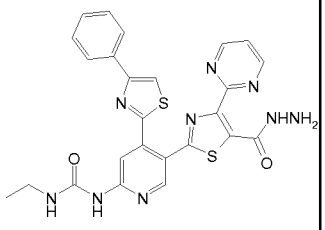
Intermediates 350-386

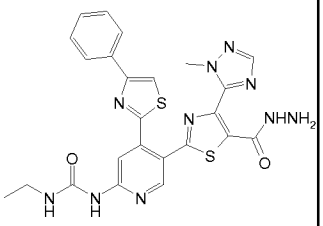
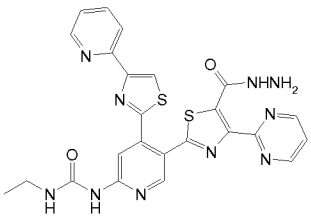
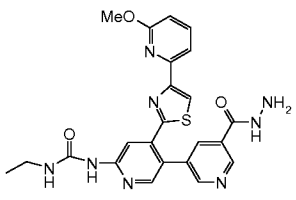
The following Intermediates were prepared according to the procedure described Intermediate 9 using the starting material indicated in the table.

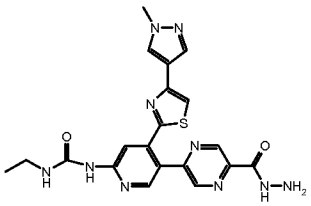
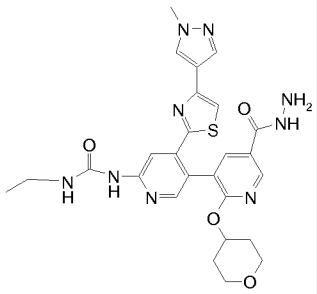
Int	Compound	Data	SM
350	methyl 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 452 for $C_{18}H_{16}F_3N_7O_2S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.21 (m, 2H), 4.57 (s, 2H), 7.52 (m, 2H), 7.82 (s, 1H), 8.16 (s, 1H), 8.37 (s, 1H), 8.58 (s, 1H), 8.60 (d, 1H), 9.51 (s, 1H), 9.91 (s, 1H).	Intermediate 305
351	1-ethyl-3-(5-(4-(hydrazinecarbonyl)thiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 458 for $C_{16}H_{14}F_3N_7O_2S_2$.	Intermediate 306
352	1-ethyl-3-(5'-(hydrazinecarbonyl)-6'-methoxy-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 482 for $C_{19}H_{18}F_3N_7O_3S$.	Intermediate 307

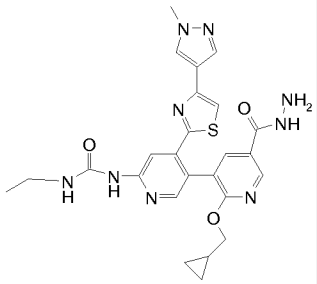
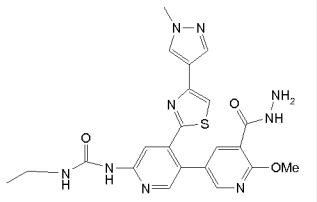
Int	Compound	Data	SM
353	1-ethyl-3-(5-(5-(hydrazinecarbonyl)pyrazin-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 453 for $C_{17}H_{15}F_3N_8O_2S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.22 (m, 2H), 4.66 (m, 2H), 7.45 (t, 1H), 8.15 (s, 1H), 8.59 (s, 1H), 8.61 (m, 1H), 8.76 (d, 1H), 9.04 (d, 1H), 9.62 (s, 1H), 10.18 (s, 1H).	Intermediate 308
354	1-ethyl-3-(2'-(hydrazinecarbonyl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,4'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 445 for $C_{22}H_{20}N_8O_3$.	Intermediate 310
355	1-ethyl-3-(5-(4-(hydrazinecarbonyl)thiazol-2-yl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 451 for $C_{20}H_{18}N_8O_3S$.	Intermediate 313

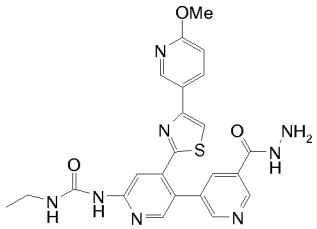
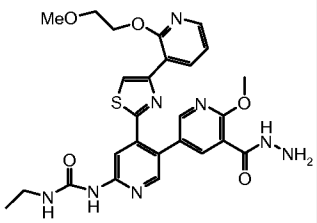
Int	Compound	Data	SM
356	1-ethyl-3-(5-(5-(hydrazinecarbonyl)thiazol-2-yl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 451 for $C_{20}H_{18}N_8O_3S$.	Intermediate 312
357	1-ethyl-3-(5-(5-(hydrazinecarbonyl)pyrazin-2-yl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 446 for $C_{21}H_{19}N_9O_3$	Intermediate 314
358	1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 455 for $C_{22}H_{20}N_8O_3$.	Intermediate 311

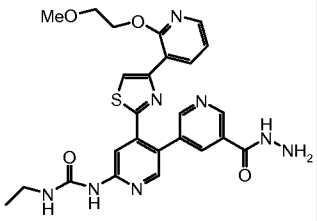
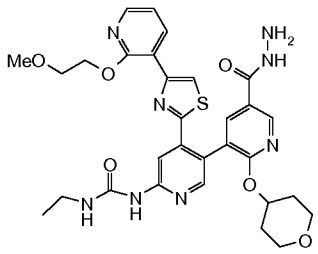
Int	Compound	Data	SM
359	1-ethyl-3-(5'-(hydrazinecarbonyl)-6'-methoxy-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 475 for $C_{23}H_{22}N_8O_4$.	Intermediate 315
360	1-ethyl-3-(4-(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 463 for $C_{22}H_{19}FN_8O_3$	Intermediate 316
361	1-ethyl-3-(5-(5-(hydrazinecarbonyl)-4-(pyrimidin-2-yl)thiazol-2-yl)-4-(4-phenylthiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 544 for $C_{25}H_{21}N_9O_2S_2$.	Intermediate 317

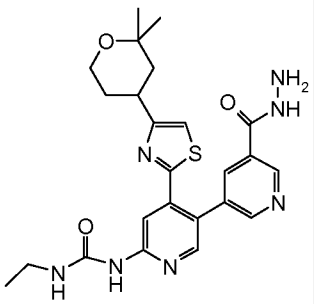
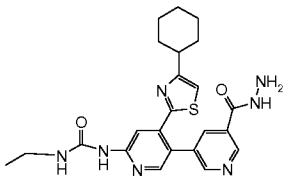
Int	Compound	Data	SM
362	1-ethyl-3-(5-(5-(hydrazinecarbonyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazol-2-yl)-4-(4-phenylthiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 547 for $C_{24}H_{22}N_{10}O_2S_2$.	Intermediate 318
363	1-ethyl-3-(5-(5-(hydrazinecarbonyl)-4-(pyrimidin-2-yl)thiazol-2-yl)-4-(4-(pyridin-2-yl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 545 for $C_{24}H_{20}N_{10}O_2S_2$.	Intermediate 299
364	1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 491 for $C_{23}H_{22}N_8O_3S$.	Intermediate 325

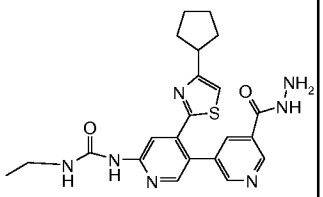
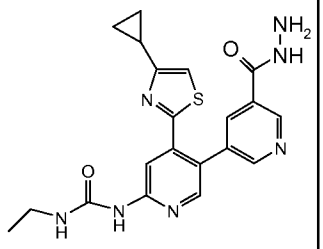
Int	Compound	Data	SM
365	1-ethyl-3-(5-(5-(hydrazinecarbonyl)pyrazin-2-yl)-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 465 for $C_{20}H_{20}N_{10}O_2S$.	Intermediate 331
366	1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-yloxy)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 564 for $C_{26}H_{29}N_9O_4S$.	Intermediate 333

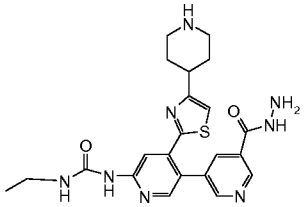
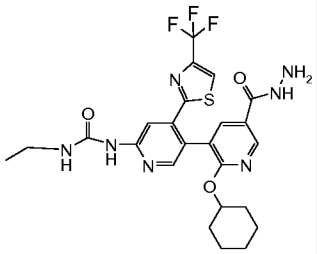
Int	Compound	Data	SM
367	1-(2'-(cyclopropylmethoxy)-5'-(hydrazinecarbonyl)-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 534 for $C_{25}H_{27}N_9O_3S$	Intermediate 337
368	1-ethyl-3-(5'-(hydrazinecarbonyl)-6'-methoxy-4-(4-(1-methyl-1H-pyrazol-4-yl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 494 for $C_{22}H_{23}N_9O_3S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 3.19 (m, 2H), 3.87 (s, 3H), 4.00(s, 3H), 4.6 (s, 2H), 7.68 (m, 1H), 7.75 (s, 1H), 7.76 (s, 1H), 8.03 (s, 1H), 8.05 (m, 1H), 8.18 (s, 1H), 8.23 (s, 1H), 8.24 (m, 1H), 8.98 (d, 1H), 9.41 (s, 1H).	Intermediate 332

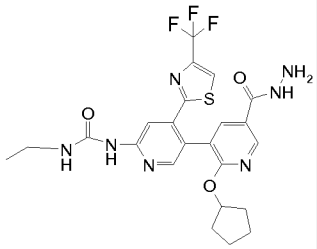
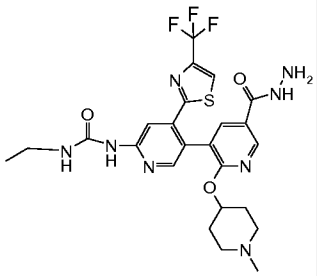
Int	Compound	Data	SM
369	1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(6-methoxypyridin-3-yl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 491 for $C_{23}H_{22}N_8O_3S$.	Intermediate 326
370	1-ethyl-3-(5'-(hydrazinecarbonyl)-6'-methoxy-4-(4-(2-(2-methoxyethoxy)pyridin-3-yl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 565 for $C_{26}H_{28}N_8O_5S$.	Intermediate 322

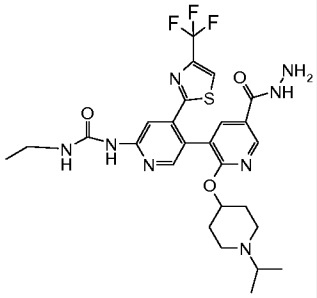
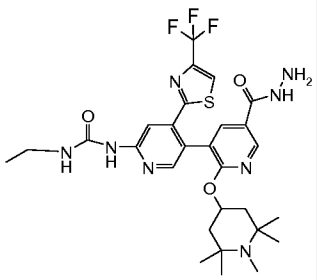
Int	Compound	Data	SM
371	1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(2-(2-methoxyethoxy)pyridin-3-yl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 535 for $C_{25}H_{26}N_8O_4S$.	Intermediate 323
372	1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(2-(2-methoxyethoxy)pyridin-3-yl)thiazol-2-yl)-2'-(tetrahydro-2H-pyran-4-yloxy)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 635 for $C_{30}H_{34}N_8O_6S$	Intermediate 324

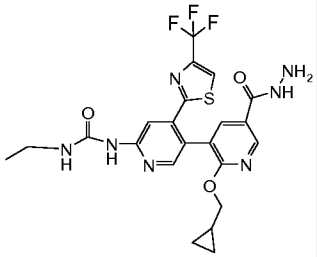
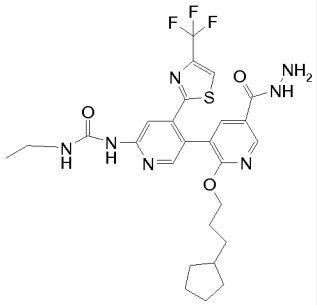
Int	Compound	Data	SM
373	1-(4-(4-(2,2-dimethyltetrahydro-2H-pyran-4-yl)thiazol-2-yl)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 496 for $C_{24}H_{29}N_7O_3S$.	Intermediate 330
374	1-(4-(4-cyclohexylthiazol-2-yl)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 466 for $C_{23}H_{27}N_7O_2S$.	Intermediate 327

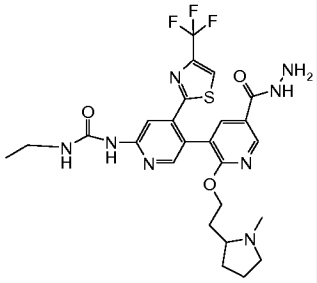
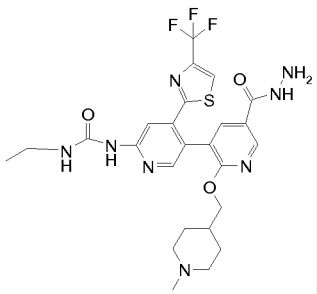
Int	Compound	Data	SM
375	1-(4-(4-cyclopentylthiazol-2-yl)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 452 for $C_{22}H_{25}N_7O_2S$. ^1H NMR (300 MHz, d_6-DMSO): 1.10 (t, 3H), 1.40 (m, 2H), 1.52 (m, 4H), 1.81 (m, 2H), 3.06 (m, 1H), 3.20 (m, 2H), 4.56(s, 2H), 7.39 (s, 1H), 7.66(m, 1H), 8.07 (m, 1H), 8.10 (s, 1H), 8.28 (s, 1H), 8.51 (d, 1H), 8.94 (d, 1H), 9.43 (s, 1H), 9.95 (s, 1H).	Intermediate 328
376	1-(4-(4-cyclopropylthiazol-2-yl)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 424 for $C_{20}H_{21}N_7O_2S$.	Intermediate 329

Int	Compound	Data	SM
377	1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(piperidin-4-yl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 467 for $C_{22}H_{26}N_8O_2S$.	Intermediate 335
378	1-(2'-(cyclohexyloxy)-5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 467 for $C_{24}H_{26}F_3N_7O_3S$.	Intermediate 338

Int	Compound	Data	SM
379	1-(2'-(cyclopentyloxy)-5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 536 for $C_{23}H_{24}F_3N_7O_3S$.	Intermediate 342
380	1-ethyl-3-(5'-(hydrazinecarbonyl)-2'-(1-methylpiperidin-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 565 for $C_{24}H_{27}F_3N_8O_3S$.	Intermediate 341

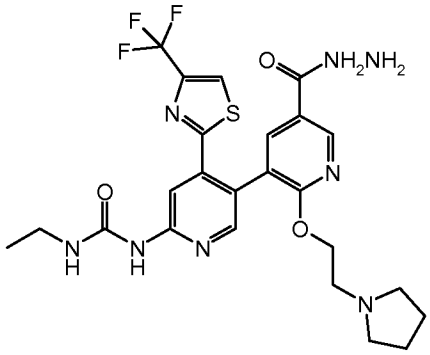
Int	Compound	Data	SM
381	1-ethyl-3-(5'-(hydrazinecarbonyl)-2'-(1-isopropylpiperidin-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 593 for $C_{26}H_{31}F_3N_8O_3S$.	Intermediate 343
382	1-ethyl-3-(5'-(hydrazinecarbonyl)-2'-(1,2,2,6,6-pentamethylpiperidin-4-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 621 for $C_{28}H_{35}F_3N_8O_3S$.	Intermediate 344

Int	Compound	Data	SM
383	1-(2'-(cyclopropylmethoxy)-5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 522 for $C_{22}H_{22}F_3N_7O_3S$.	Intermediate 339
384	1-(2'-(3-cyclopentylpropoxy)-5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 578 for $C_{26}H_{30}F_3N_7O_3S$.	Intermediate 345

Int	Compound	Data	SM
385	1-ethyl-3-(5'-(hydrazinecarbonyl)-2'-(2-(1-methylpyrrolidin-2-yl)ethoxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 579 for $C_{25}H_{29}F_3N_8O_3S$.	Intermediate 346
386	1-ethyl-3-(5'-(hydrazinecarbonyl)-2'-((1-methylpiperidin-4-yl)methoxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 579 for $C_{25}H_{29}F_3N_8O_3S$.	Intermediate 340

Intermediate 387

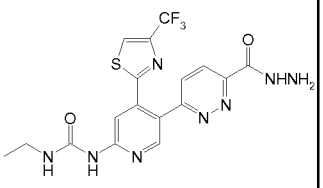
1-ethyl-3-(5'-(hydrazinecarbonyl)-2'-(2-(pyrrolidin-1-yl)ethoxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea

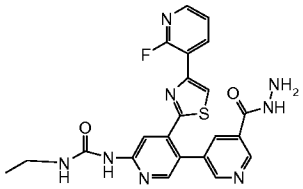
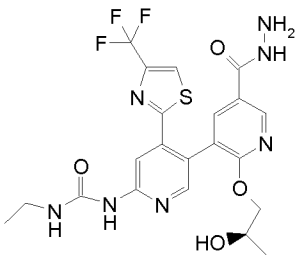


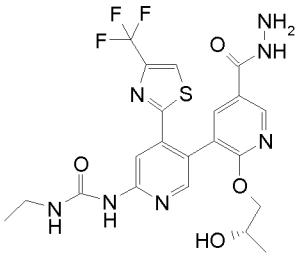
6'-(3-ethylureido)-2-(2-(pyrrolidin-1-yl)ethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylic acid (Intermediate 336, 220 mg, 0.40 mmol) was dissolved in a DMF solution containing HATU (152 mg, 0.40 mmol) and diisopropylethyl amine (0.139 mL, 0.80 mmol). The solution was stirred for 30 minutes. Hydrazine (0.015 mL, 0.48 mmol) was added in a single portion. The reaction mixture was stirred for 0.5 hour. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to give the title compound which was used without further purification. LC/MS (ES^+)[$(M+H)^+$]: 565 for $C_{24}H_{27}F_3N_8O_3S$.

Intermediates 388-391

The following Intermediates were prepared according to the synthesis described for Intermediate 387 using the starting materials indicated in the table.

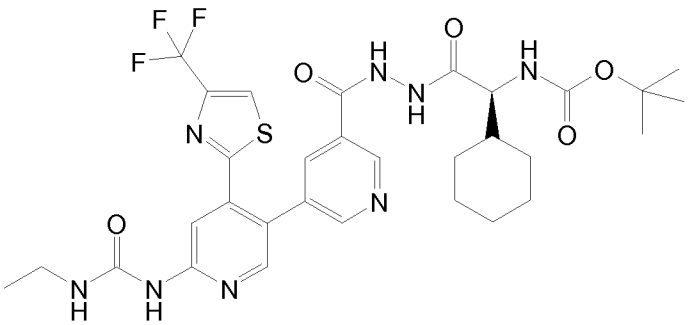
Int	Compound	Data	SM
388	1-ethyl-3-(5-(6-(hydrazinecarbonyl)pyridazin-3-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 453 for $C_{17}H_{15}F_3N_8O_2S$.	Intermediate 309

Int	Compound	Data	SM
389	1-ethyl-3-(4-(4-(2-fluoropyridin-3-yl)thiazol-2-yl)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$] 479 for $C_{22}H_{19}N_8O_2S$.	Intermediate 284
390	1-ethyl-3-(5'-(hydrazinecarbonyl)-2'-((R)-2-hydroxypropoxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 526 for $C_{21}H_{22}F_3N_7O_4S$.	Intermediate 348

Int	Compound	Data	SM
391	1-ethyl-3-(5'-(hydrazinecarbonyl)-2'-((S)-2-hydroxypropoxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 526 for $C_{21}H_{22}F_3N_7O_4S$.	Intermediate 347

Intermediate 392

(S)-tert-butyl 1-cyclohexyl-2-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-2-oxoethylcarbamate

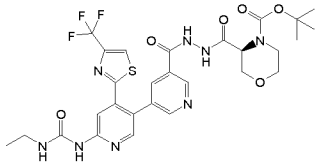
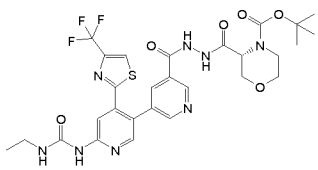


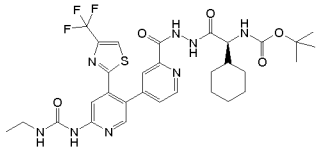
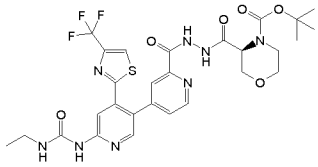
In a glass vial, 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 9, 300 mg, 0.66 mmol) and (S)-2-(tert-butoxycarbonylamino)-2-cyclohexylacetic acid (188 mg, 0.73 mmol) were combined and dissolved in a DMF solution containing diisopropylethyl amine (0.173 mL, 1.00 mmol). The reaction mixture was stirred for 5 min, then HATU (329 mg, 0.86 mmol) was added in a single portion. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to a residue which was purified by silica gel flash column chromatography (95:5 CH_2Cl_2 / MeOH).

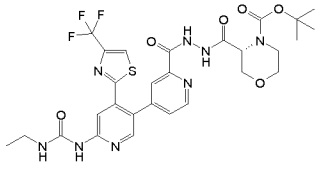
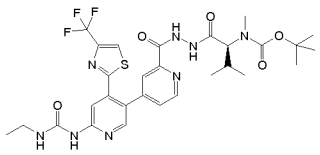
LC/MS (ES^+)[$(M+H)^+$]: 691 for $C_{31}H_{37}F_3N_8O_5S$.

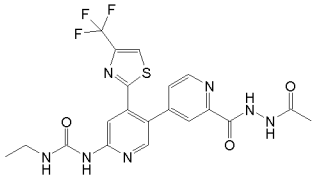
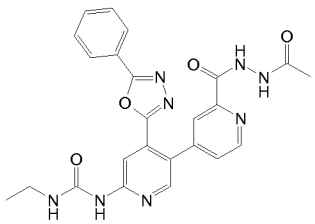
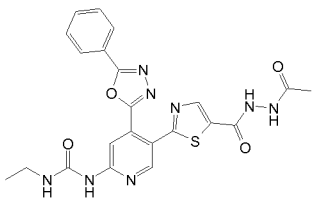
Intermediates 393-402

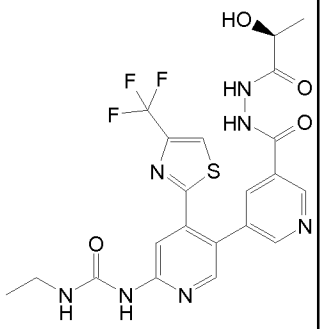
The following Intermediates were prepared according to the procedure described for Intermediate 392 using the starting materials indicated in the table.

Int	Compound	Data	SM
393	(S)-tert-butyl 3-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinecarbonyl)morpholine-4-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 665 for $C_{28}H_{31}F_3N_8O_6S$.	Intermediate 9 and (S)-4-(tert-butoxycarbonyl)morpholine-3-carboxylic acid
394	(R)-tert-butyl 3-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinecarbonyl)morpholine-4-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 665 for $C_{28}H_{31}F_3N_8O_6S$.	Intermediate 9 and (R)-4-(tert-butoxycarbonyl)morpholine-3-carboxylic acid

Int	Compound	Data	SM
395	(S)-tert-butyl 1-cyclohexyl-2-(2-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carbonyl)hydrazinyl)-2-oxoethylcarbamate 	LC/MS (ES^+)[$(M+H)^+$]: 691 for $C_{31}H_{37}F_3N_8O_5S$.	Intermediate 350 and (S)-2-(tert-butoxycarbonylamino)-2-cyclohexylacetic acid
396	(S)-tert-butyl 3-(2-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carbonyl)hydrazinecarbonyl)morpholine-4-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 665 for $C_{28}H_{31}F_3N_8O_6S$.	Intermediate 350 and (S)-4-(tert-butoxycarbonyl)morpholine-3-carboxylic acid

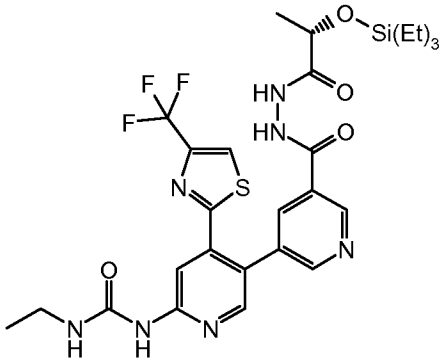
Int	Compound	Data	SM
397	(R)-tert-butyl 3-(2-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carbonyl)hydrazinecarbonyl)morpholine-4-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 665 for $C_{28}H_{31}F_3N_8O_6S$.	Intermediate 350 and (R)-4-(tert-butoxycarbonyl)morpholine-3-carboxylic acid
398	(S)-tert-butyl 1-(2-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridine-2'-carbonyl)hydrazinyl)-3-methyl-1-oxobutan-2-yl(methyl)carbamate 	LC/MS (ES^+)[$(M+H)^+$]: 665 for $C_{29}H_{35}F_3N_8O_5S$..	Intermediate 350 and (S)-2-(tert-butoxycarbonyl(methyl)amino)-3-methylbutanoic acid

Int	Compound	Data	SM
399	1-(2'-(2-acetylhydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 494 for $C_{20}H_{18}F_3N_7O_3S$.	Intermediate 50 and acetohydrazide
400	1-(2'-(2-acetylhydrazinecarbonyl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)-3,4'-bipyridin-6-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 487 for $C_{24}H_{22}N_8O_4$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.91 (s, 3H), 3.21 (m, 2H), 7.60 (m, 4H), 7.69 (m, 3H), 8.07 (s, 1H), 8.42 (s, 1H), 8.53 (s, 1H), 8.71 (d, 1H), 9.77 (s, 1H), 10.08 (s, 1H), 10.51 (s, 1H).	Intermediate 282 and acetohydrazide
401	1-(5-(5-(2-acetylhydrazinecarbonyl)thiazol-2-yl)-4-(5-phenyl-1,3,4-oxadiazol-2-yl)pyridin-2-yl)-3-ethylurea 	LC/MS (ES^+)[$(M+H)^+$]: 493 for $C_{22}H_{20}N_8O_4S$. ^{1}H NMR (300 MHz, d_6-DMSO): 1.10 (t, 3H), 1.92 (s, 3H), 3.20 (m, 2H), 7.63 (m, 2H), 7.71 (t, 1H), 7.82 (m, 2H), 8.37 (s, 1H), 8.44 (s, 1H), 8.76 (s, 1H), 9.95 (s, 1H), 10.06 (s, 1H), 10.64 (s, 1H).	Intermediate 283 and acetohydrazide

Int	Compound	Data	SM
402	(S)-1-ethyl-3-(5'-(2-(2-hydroxypropanoyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 524 for $C_{21}H_{20}F_3N_7O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 1.11 (t, 3H), 1.30 (d, 3H), 3.21 (m, 2H), 4.15 (m, 1H), 5.56 (d, 1H), 7.55 (t, 1H), 8.21 (t, 1H), 8.26 (s, 1H), 8.37 (s, 1H), 8.56 (s, 1H), 8.64 (d, 1H), 9.06 (d, 1H), 9.49 (s, 1H), 9.81 (s, 1H), 10.53 (s, 1H).	Intermediate 9 and (S)-2-hydroxypropanoic acid

Intermediate 403

S)-1-ethyl-3-(5'-(2-(2-(triethylsilyloxy)propanoyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



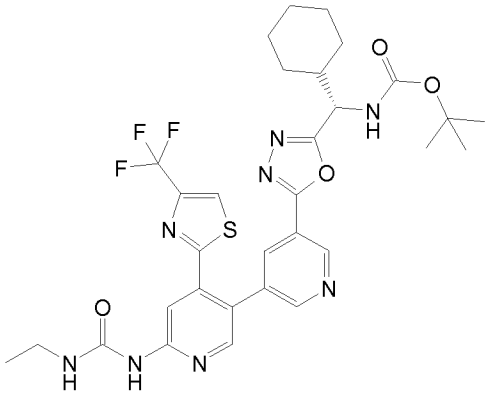
(S)-1-ethyl-3-(5'-(2-(2-hydroxypropanoyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 402, 260 mg, 0.50 mmol) was suspended in a CH_2Cl_2 (10 mL) solution containing 2,6-lutidine (213 mg, 1.99 mmol). The suspension was cooled to 0°C (ice-water bath). Triethylsilyl trifluoromethanesulfonate (0.337 mL, 1.49 mmol) was added in a single portion via a micro syringe. The reaction mixture was slowly warmed to room temperature where it was allowed to react for 5 h. The reaction mixture

became homogeneous, and analysis showed complete conversion to the silyl protected compound. The reaction mixture was diluted with CH_2Cl_2, washed with $NaHCO_3$ (sat.) and brine, dried organic over Na_2SO_4, filtered and concentrate by rotary evaporation. The crude reaction mixture was purified by silica gel flash column chromatography (95:5 CH_2Cl_2 / MeOH) to give 205 mg of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 638 for $C_{27}H_{34}F_3N_7O_4SSi$.

Intermediate 404

(S)-tert-butyl cyclohexyl(5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)methylcarbamate



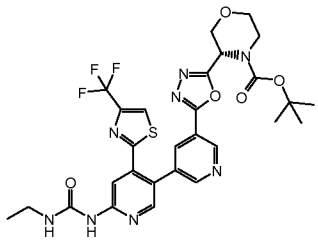
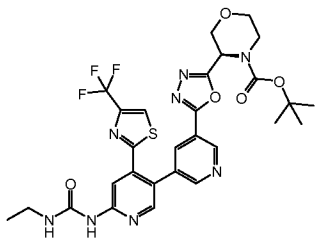
In a glass vial, (S)-tert-butyl 1-cyclohexyl-2-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-2-oxoethylcarbamate (Intermediate 392, 459 mg, 0.66 mmol) was dissolved in a ACN solution containing carbon tetrachloride (0.321 mL, 3.32 mmol) and DBU (1,8-Diazabicyclo[5.4.0]-undec-7-ene) (0.497 mL, 3.32 mmol). Triphenyl phosphine (349 mg, 1.33 mmol) was added in a single portion, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc, washed with water / brine, dried over Na_2SO_4, filtered and concentrated to dryness by rotary evaporation. The concentrate was purified by silica gel flash column chromatography (95:5 CH_2Cl_2 / MeOH).

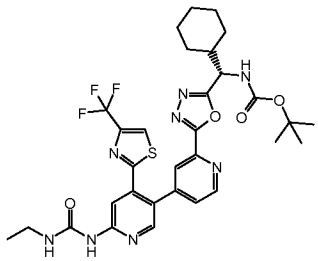
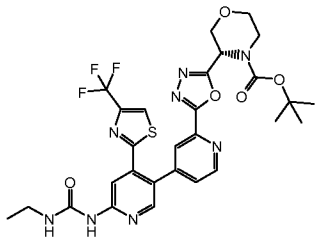
LC/MS (ES^+)[$(M+H)^+$]: 673 for $C_{31}H_{35}F_3N_8O_4S$.

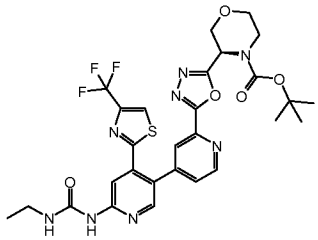
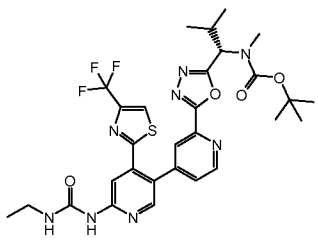
^1H NMR (300 MHz, d_6-DMSO): 0.95 - 1.45 (m, 6H), 1.12 (t, 3H), 1.37 (s, 9H), 1.62 - 1.89 (m, 5H), 3.22 (m, 2H), 4.71 (m, 1H), 7.55 (t, 1H), 7.66 (d, 1H), 8.25 (s, 1H), 8.27 (s, 1H), 8.42 (s, 1H), 8.56 (s, 1H), 8.73 (s, 1H), 9.18 (s, 1H), 9.51 (s, 1H).

Intermediates 405-410

The following Intermediates were prepared according to the procedure described for Intermediate 404 using the starting materials indicated in the table.

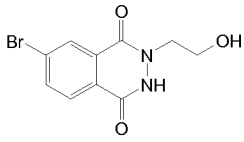
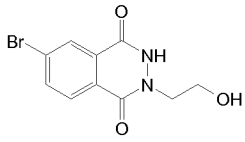
Int	Compound	Data	SM
405	(S)-tert-butyl 3-(5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)morpholine-4-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 647 for $C_{28}H_{29}F_3N_8O_5S$.	Intermediate 393
406	(R)-tert-butyl 3-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinecarbonyl)morpholine-4-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 647 for $C_{28}H_{29}F_3N_8O_5S$.	Intermediate 394

Int	Compound	Data	SM
407	(S)-tert-butyl cyclohexyl(5-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-2'-yl)-1,3,4-oxadiazol-2-yl)methylcarbamate 	LC/MS (ES^+)[$(M+H)^+$]: 673 for $C_{31}H_{35}F_3N_8O_4S$.	Intermediate 395
408	(S)-tert-butyl 3-(5-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-2'-yl)-1,3,4-oxadiazol-2-yl)morpholine-4-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 647 for $C_{29}H_{33}F_3N_8O_4S$.	Intermediate 396

Int	Compound	Data	SM
409	(R)-tert-butyl 3-(5-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-2'-yl)-1,3,4-oxadiazol-2-yl)morpholine-4-carboxylate 	LC/MS (ES^+)[$(M+H)^+$]: 647 for $C_{29}H_{33}F_3N_8O_4S$.	Intermediate 397
410	(S)-tert-butyl 1-(5-(6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,4'-bipyridin-2'-yl)-1,3,4-oxadiazol-2-yl)-2-methylpropyl(methyl)carbamate 	LC/MS (ES^+)[$(M+H)^+$]: 647 for $C_{29}H_{33}F_3N_8O_4S$. ^1H NMR (300 MHz, d_6-DMSO): 0.95 (m, 6H), 1.11 (t, 3H), 1.40 (s, 9H), 2.77 (s, 3H), 3.22 (m, 2H), 4.90 (m, 1H), 5.18 (m, 1H), 7.52 (t, 1H), 7.59 (dd, 1H), 8.01 (s, 1H), 8.18 (s, 1H), 8.43 (s, 1H), 8.61 (s, 1H), 8.77 (d, 1H), 9.55 (s, 1H).	Intermediate 398

Intermediate 411 and Intermediate 412

7-bromo-2-(2-hydroxyethyl)-2,3-dihydrophthalazine-1,4-dione and 6-bromo-2-(2-hydroxyethyl)-2,3-dihydrophthalazine-1,4-dione

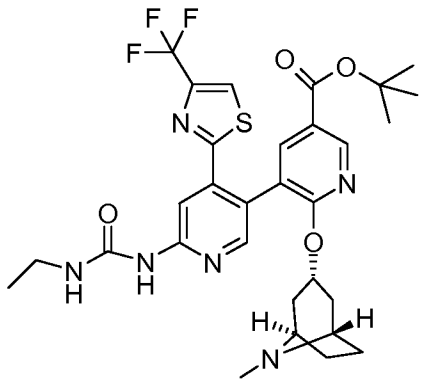
In a microwave vessel, 5-bromoisobenzofuran-1,3-dione (500 mg, 2.20 mmol) was suspended in an ethanolic solution containing 2-hydrazinylethanol (0.332 mL, 4.41 mmol). The vial was sealed and heated to reflux. The reaction mixture became homogeneous upon heating. After for 12 hours, the reaction was cooled to room temperature. Solids precipitated from solution and were collected by filtration, washed with ethanol, and dried *in vacuo*. Analysis showed the ratio of desired products to be 1:1 with about 30% of an unidentified side product. Isolation gave 340 mg of a 1:1 mixture of the title compounds which were not further purified.

LC/MS (ES^+)[$(M+H)^+$]: 285, 287 for $C_{10}H_9BrN_2O_3$.

Intermediate 413

tert-butyl 6'-(3-ethylureido)-2-((1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yloxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate

The title compound was prepared as described for Intermediate 2 from Intermediate 12 and Intermediate 349.

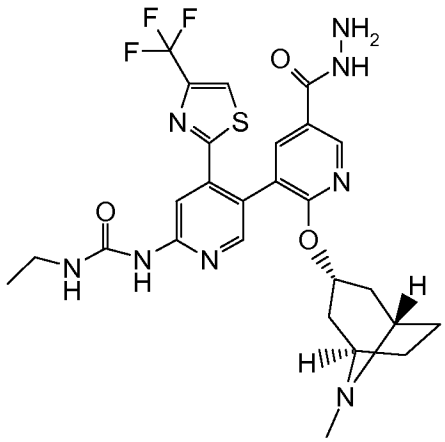


LC/MS (ES^+)[$(M+H)^+$]: 633 for $C_{30}H_{35}F_3N_6O_4S$.

Intermediate 414

1-ethyl-3-(5'-(hydrazinecarbonyl)-2'-((1R,3r,5S)-8-methyl-8-azabicyclo[3.2.1]octan-3-yloxy)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea

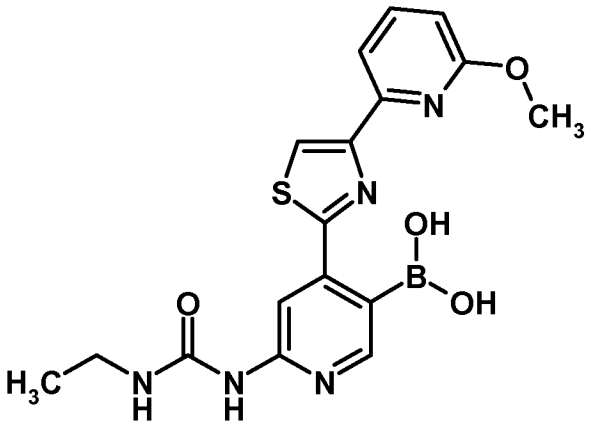
The title compound was prepared as described for Intermediate 9 from Intermediate 413 and hydrazine hydrate.



LC/MS (ES^+)[$(M+H)^+$]: 591 for $C_{26}H_{29}F_3N_8O_3S$

Intermediate 415

6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-3-ylboronic acid



DMSO (36 mL) was added to a dry suspension of 1-(5-bromo-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 293, 2.5 g, 5.76 mmol), $PdCl_2$(dppf)-CH_2Cl_2 adduct (430 mg, 0.53 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3 g, 11.81 mmol), and potassium acetate (1 g, 10.19 mmol) under vacuum. The resulting suspension was warmed to 80 °C and treated with triethyl amine(1 ml, 7.17 mmol) and stirred under nitrogen at this temperature for 16 hours. The reaction was diluted with water (100 ml), and held at 100 °C for 1hr, cooled to room temperature, and filtered to give crude product as a peach filter cake. This material was suspended in ethyl acetate (200

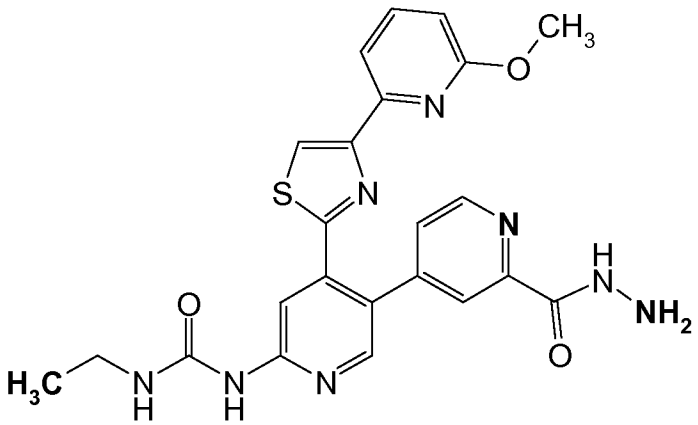
ml), warmed to 70 °C for 1 hour, and filtered hot to give (1.44 g, 62.7%) of a peach solid as a 3:1 mixture of title boronic acid and the reduced material.

MS (EI) $(M+H)^+$ 400 for $C_{17}H_{19}BN_5O_4S$ $(M-H)^-$ 398 for $C_{17}H_{17}BN_5O_4S$

^{1}H NMR (DMSO-*d6*) δ: 8.41 (t, *J*=5.46 Hz, 1 H), 8.25 (s, 1 H), 7.96 (s, 1 H), 7.86 (s, 1 H), 7.77 (d, *J*=7.16 Hz, 1 H), 6.84 (d, *J*=7.72 Hz, 1 H), 3.97 (s, 3 H), 3.21 (d, *J*=7.35 Hz, 2 H), 1.08 - 1.14 (m, 3 H).

Intermediate 416

1-ethyl-3-(2'-(hydrazinecarbonyl)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-3,4'-bipyridin-6-yl)urea

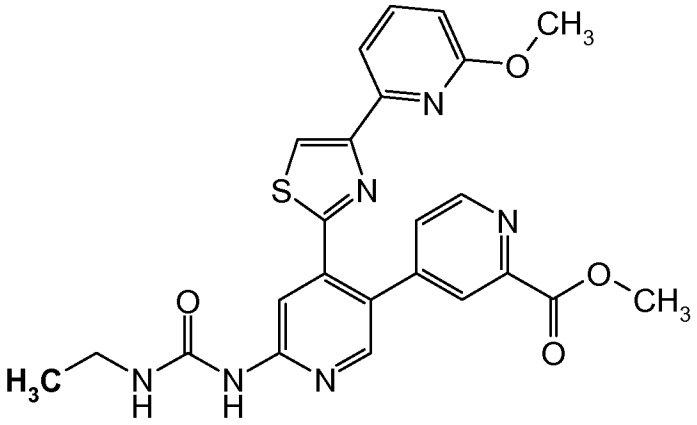


Intermediate 416 was synthesized according to the procedure described for intermediate 22 from Intermediate 417 and hydrazine.

MS (EI) $(M+H)^+$ 491 for $C_{23}H_{23}N_8O_3S$ $(M-H)^-$ 489 for $C_{23}H_{21}N_8O_3S$;

Intermediate 417

methyl 6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)-3,4'-bipyridine-2'-carboxylate



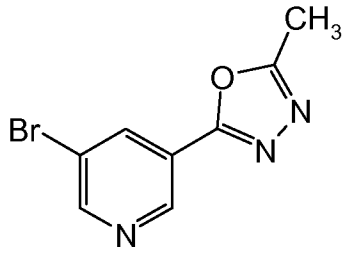
A mixture of 6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 415, 400 mg, 1.00 mmol), methyl 4-bromopicolinate (216 mg, 1.00 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (143 mg, 0.30 mmol), Pd_2dba_3 (45.9 mg, 0.05 mmol) and Cs_2CO_3 (392 mg, 1.20 mmol), under vacuum was treated with 1,4-dioxane (20 mL) and water (5 mL). The reaction mixture was placed in oil bath at 80 °C, and held at that temperature for 2 hours, The reaction was cooled to room temperature, diluted with ethyl acetate (100 ml), water (50 ml), and brine (5ml), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3X50ml), and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and the solvents were removed under reduced pressure. The resulting residue was purified by chromatography on silica gel eluting with a gradient of methanol in methylene chloride. The major peak was concentrated, and precipitated by the addition of acetonitrile to give the title compound as a tan solid (480 mg, 98 %)

MS (EI) $(M+H)^+$ 491 for $C_{23}H_{23}N_6O_4S$ $(M-H)^-$ 489 for $C_{23}H_{21}N_6O_4S$

^{1}H NMR (DMSO-*d*6) δ: 9.52 (s, 1 H), 8.72 (d, J=4.90 Hz, 1 H), 8.35 - 8.37 (m, 1 H), 8.33 (br. s., 1 H), 8.21 (s, 1 H), 8.01 (s, 1 H),7.71 (t, J=7.82 Hz, 1 H), 7.63 (d, J=5.09 Hz, 1 H), 7.58 (t, J=5.18 Hz, 1 H), 7.16 (d, J=7.35 Hz, 1 H), 6.78 (d, J=8.10 Hz, 1 H), 3.91 (s, 3 H), 3.84(s, 3 H), 3.22 (tt, J=7.16, 6.40 Hz, 2 H), 1.11 (t, J=7.06 Hz, 3 H).

Intermediate 418

2-(5-bromopyridin-3-yl)-5-methyl-1,3,4-oxadiazole



A suspension of 5-bromonicotinohydrazide (Intermediate 433, 2.3 g, 10.65 mmol) in 1,1,1-trimethoxyethane (20 ml, 166.46 mmol) was heated reflux and treated with concentrated aqueous HCl (drop), the resulting clear colorless solution was refluxed for 20 minutes, treated with DBU (0.2 ml, 1.33 mmol) and refluxed an additional 20 min. The material was concentrated under reduced pressure to give a tan gum which was purfied by flash chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes to give the title compound as a white solid (2.47 g, 97 %)

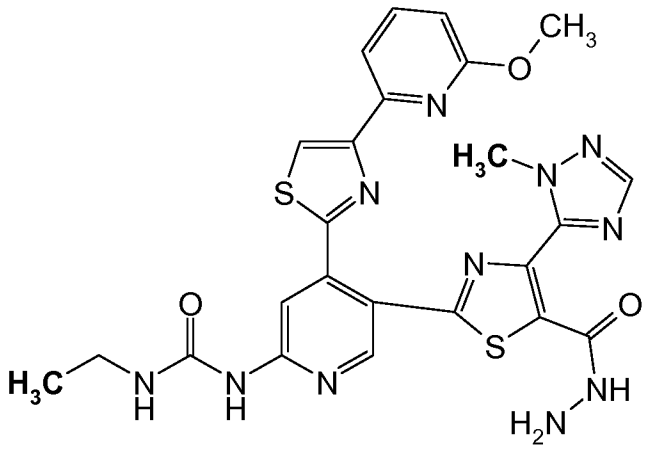
MS (EI) $(M+H)^+$ 240/242 for $C_8H_7BrN_3O$

^{1}H NMR (DMSO-*d*6) δ: 9.10 (d, *J*=1.51 Hz, 1 H), 8.93 (d, *J*=2.07 Hz, 1 H), 8.52 (t, *J*=1.60 Hz, 1 H), 2.61 (s, 3 H);

^{13}C NMR (DMSO-*d*6) δ: 164.75 (s, 1 C), 160.98 (s, 1 C), 152.90 (s, 1 C), 145.43 (s, 1 C), 135.97 (s, 1 C), 121.60 (s, 1 C), 120.58 (s,1 C), 10.61 (s, 1 C).

Intermediate 419

1-ethyl-3-(5-(5-(hydrazinecarbonyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazol-2-yl)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-2-yl)urea



A solution of crude methyl 2-(6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-3-yl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazole-5-carboxylate (Intermediate 420, 250 mg, 0.43 mmol) in ethanol was treated with hydrazine (0.5 mL, 0.43 mmol), and the pale

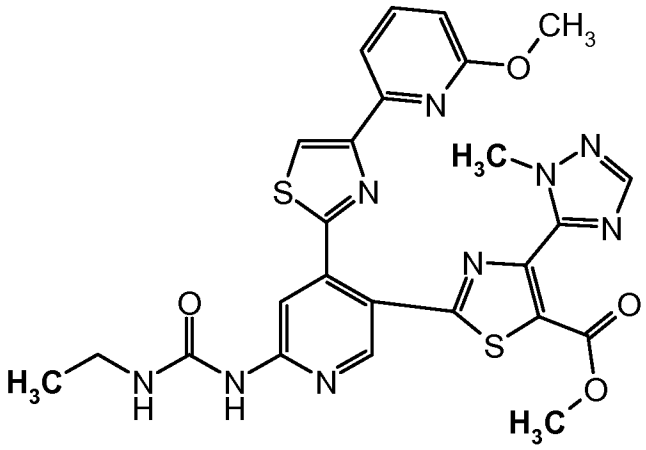
grey solution was heated to reflux for 16hours. The resulting pale grey suspension was filtered to give the title compound as a grey solid (200 mg, 0.35 mmol, 80 %).

MS (EI) $(M+H)^+$ 578 for $C_{24}H_{24}N_{11}O_3S_2$) $(M-H)^-$ 576 for $C_{24}H_{22}N_{11}O_3S_2$

^{1}H NMR (DMSO-*d6*) δ: 11.81 (br. s., 1 H), 9.68 (s, 1 H), 8.82 (s, 1 H), 8.47 (s, 1 H), 8.24 (s, 1 H), 8.12 (s, 1 H), 7.74 (t, *J*=7.72 Hz,1 H), 7.56 (br. s., 1 H), 7.42 (d, *J*=7.35 Hz, 1 H), 6.81 (d, *J*=8.29 Hz, 1 H), 3.95 (d, *J*=3.01 Hz, 6 H), 3.12 - 3.26 (m, 2 H), 1.09 - 1.16 (m, 3 H).

Intermediate 420

methyl 2-(6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-3-yl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazole-5-carboxylate



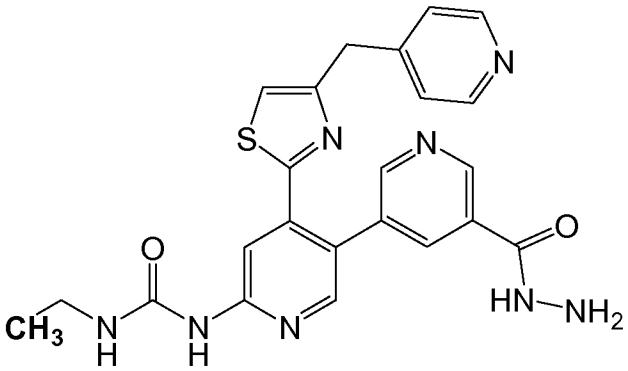
1,4-Dioxane (20 mL) and water (5 mL) were added to a mixture of 6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 415, 400 mg, 1.00 mmol), methyl 2-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)thiazole-5-carboxylate (Intermediate 44, 259 mg, 1.00 mmol), Pd_2dba_3 (45.9 mg, 0.05 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (143 mg, 0.30 mmol), and Cs_2CO_3 (392 mg, 1.20 mmol), under vacuum. The suspension was placed in oil bath at 80 °C, purged with nitrogen, and heated for 30 minutes. When the reaction was complete by LCMS, it was cooled to room temperature, diluted with water (100 ml), and extracted with ethyl acetate (4X75ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressured, and the residue was purified by silica gel chromatography eluting with a gradient of methanol in methylene chloride to give the title compound as a beige solid (265 mg, 0.46 mmol, 45.8 %).

MS (EI) $(M+H)^+$ 578 for $C_{25}H_{23}N_9O_4S_2$ $(M-H)^-$ 576 for $C_{25}H_{21}N_9O_4S_2$

^{1}H NMR (DMSO-*d6*) δ:□9.71 (s, 1 H), 8.78 (s, 1 H), 8.48 (s, 1 H), 8.17 (s, 1 H), 8.06 (s, 1 H), 7.75 (t, *J*=7.82 Hz, 1 H), 7.49 (br. s., 1H), 7.43 (d, *J*=7.35 Hz, 1 H), 6.81 (d, *J*=8.10 Hz, 1 H), 3.95 (s, 3 H), 3.74 (s, 3 H), 3.65 (s, 3 H), 3.10 - 3.28 (m, 2 H), 1.11 (t, *J*=7.16 Hz, 3 H);

Intermediate 421

1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(pyridin-4-ylmethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



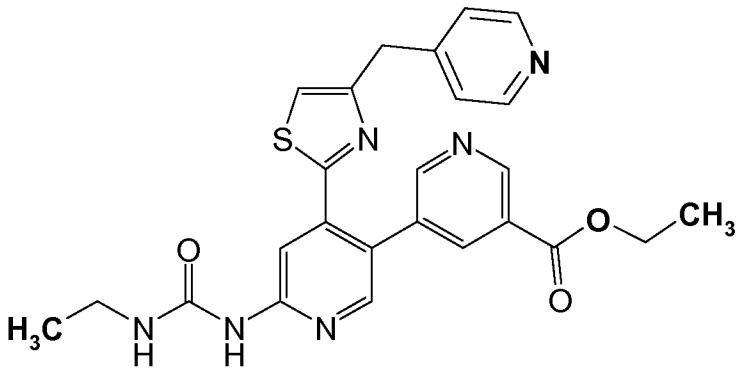
Intermediate 421 was synthesized according to the procedure described for Intermediate 22 from Intermediate 422 and hydrazine.

MS (EI) $(M+H)^+$ 475 for $C_{23}H_{23}N_8O_2S$ $(M-H)^-$ 473 for $C_{23}H_{21}N_8O_2S$;

^{1}H NMR (DMSO-*d6*) δ: 9.98 (s, 1 H), 9.45 (s, 1 H), 8.97 (d, *J*=1.88 Hz, 1 H), 8.52 (d, *J*=1.88 Hz, 1 H), 8.41 (d, *J*=5.84 Hz, 2 H),8.28 (s, 1 H), 8.09 (s, 2 H), 7.66 (t, *J*=4.99 Hz, 1 H), 7.53 (s, 1 H), 7.08 (d, *J*=5.65 Hz, 2 H), 4.59 (br. s., 2 H), 4.03 (s, 2 H), 3.20 (quin, *J*=6.97 Hz,2 H), 1.10 (t, *J*=7.16 Hz, 3 H)

Intermediate 422

ethyl 6'-(3-ethylureido)-4'-(4-(pyridin-4-ylmethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



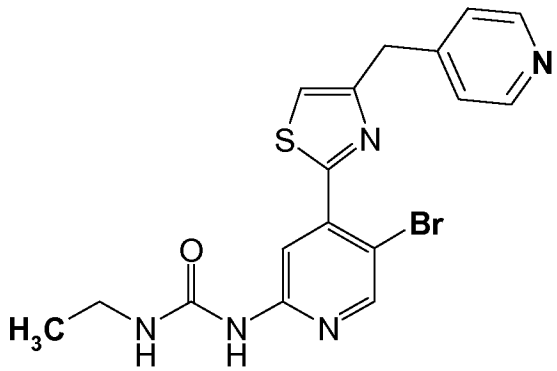
Intermediate 422 was synthesized as described for Intermediate 20 from Intermediate 423 and ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate.

MS (EI) $(M+H)^+$ 489 for $C_{25}H_{25}N_6O_3S$ $(M-H)^-$ 487 for $C_{25}H_{23}N_6O_3S$;

^{1}H NMR (DMSO-*d6*) δ: 9.46 (s, 1 H), 9.02 (d, *J*=2.07 Hz, 1 H), 8.67 (d, *J*=2.26 Hz, 1 H), 8.38 (d, *J*=5.46 Hz, 2 H), 8.29 (s, 1 H),8.01 - 8.12 (m, 2 H), 7.66 (t, *J*=5.27 Hz, 1 H), 7.57 (s, 1 H), 7.03 (d, *J*=5.65 Hz, 2 H), 4.32 (q, *J*=6.78 Hz, 2 H), 3.99 (s, 2 H), 3.18 - 3.25 (m, 2 H),1.31 (t, *J*=7.06 Hz, 3 H), 1.10 (t, *J*=7.16 Hz, 3 H).

Intermediate 423

1-(5-bromo-4-(4-(pyridin-4-ylmethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea



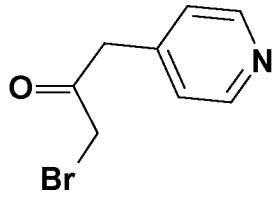
A solution of 1-bromo-3-(pyridin-4-yl)propan-2-one hydrobromide (Intermediate 424, 434 mg, 1.47 mmol) and 5-bromo-2-(3-ethylureido)pyridine-4-carbothioamide (Intermediate 5, 500 mg, 1.65 mmol) in ethanol (25 mL) was heated to reflux for 1 hour. The mixture was then cooled, diluted with water (100 ml), ethyl acetate (100 ml) and saturated aqueous sodium hydrogen carbonate, the layers were separated and the aqueous phase extracted with ethyl acetate (3X100ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, concentrated under reduced pressure, and the resulting residue was purified by normal phase chromatography on silica gel, eluting with a gradient of ethyl acetate in hexanes to afford as a tan solid after trituration from dichloromethane with hexanes 364 mg (59%) of the title compound as a pale yellow powder.

MS (EI) $(M+H)^+$ 418/420 for $C_{17}H_{17}BrN_5OS$ $(M-H)^-$ 416/418 for $C_{17}H_{15}BrN_5OS$;

^{1}H NMR (DMSO-*d6*) δ: 9.36 (s, 1 H), 8.45 - 8.56 (m, 3 H), 8.33 (s, 1 H), 7.75 (s, 1 H), 7.28 - 7.40 (m, 3 H), 4.23 (s, 2 H), 3.17(quin, *J*=6.64 Hz, 2 H), 1.08 (t, *J*=7.16 Hz, 3 H);

Intermediate 424

1-bromo-3-(pyridin-4-yl)propan-2-one



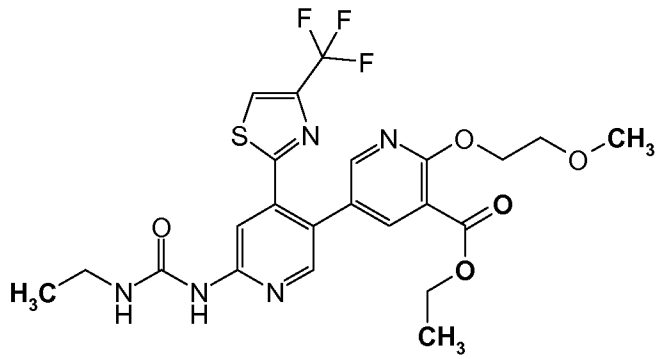
Bromine (0.65 ml, 12.5 mmol) was added to a solution of 1-(pyridin-4-yl)propan-2-one (770 mg, 5.70 mmol) in HBr (10 mL, 184.15 mmol, 33% in acetic acid). After 5 hours, the reaction was diluted with acetone (40 ml) and the resulting solution was stirred at room temperature for 19 hours. The resulting tan suspension was filtered to afford as a tan solid 755 mg of the title compound as a 2:1 mixture with 1,3-dibromo-1-(pyridin-4-yl)propan-2-one.

MS (EI) $(M+H)^+$ 214/216 for C_8H_9BrNO

^{1}H NMR (DMSO-*d*6) δ: 8.82 - 8.95 (m, 2 H), 8.65 (d, *J*=6.22 Hz, 1 H), 8.05 (d, *J*=6.03 Hz, 1 H), 7.92 (d, *J*=6.03 Hz, 2 H), 5.89 (s, 1H), 4.57 (s, 2 H), 4.38 (s, 1 H), 4.30 (s, 2 H)

Intermediate 425

ethyl 6'-(3-ethylureido)-6-(2-methoxyethoxy)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate



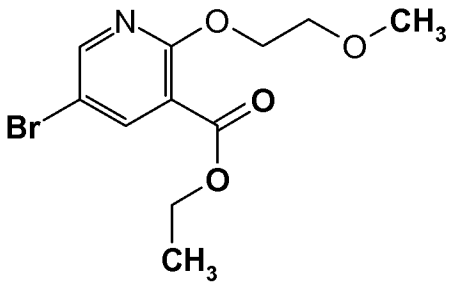
A mixture of ethyl 5-bromo-2-(2-methoxyethoxy)nicotinate (Intermediate 426, 500 mg, 1.64 mmol), 1-ethyl-3-(5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea (Intermediate 12, 500 mg, 1.13 mmol), Cs2CO3 (370 mg, 1.14 mmol), Pd_2dba_3 (27 mg, 0.03 mmol), and dicyclohexyl triisopropylbiphenylphosphine (170 mg, 0.36 mmol) in 1,4-dioxane (12 mL) was degassed, treated with water (3.00 mL), and then heated to 80 °C for 30 minutes. The reaction mixture was diluted with water (100 ml), brine (10 ml), and ethyl acetate (100 ml), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3x50ml), and the combined

organics were washed with brine, dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified by normal phase chromatography eluting with a gradient of ethyl acetate in hexanes to afford 90 mg of the title compound as a pale amber oil, which was used without further purification.

MS (EI) $(M+H)^+$ 540 for $C_{23}H_{25}F_3N_5O_5S$ $(M-H)^-$ 538 for $C_{23}H_{23}F_3N_5O_5S$.

Intermediate 426

ethyl 5-bromo-2-(2-methoxyethoxy)nicotinate

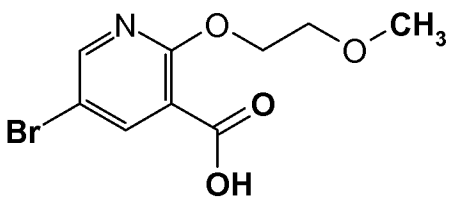


A solution of 5-bromo-2-(2-methoxyethoxy)nicotinic acid (Intermediate 427, 800 mg, 2.90 mmol) in ethanol (10 ml) was treated with sulfuric acid (drop), trimethoxymethane (10 ml) and refluxed for 1hour. The resulting solution was cooled, diluted with water (100 ml), ethyl acetate (100 ml), and saturated bicarbonate (20 ml), and the layers were separated. The organic layers were washed with water and brine, then dried over magnesium sulfate, filtered, concentrated, and purified by normal phase chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes to afford 500 mg of the title compound as a mixture of ethyl and methyl esters, as a colorless oil.

MS (EI) $(M+H)^+$ 304/306 for $C_{11}H_{15}BrNO_4$ $(M-H)^-$ 302/304 for $C_{11}H_{15}BrNO_4$;

Intermediate 427

5-bromo-2-(2-methoxyethoxy)nicotinic acid



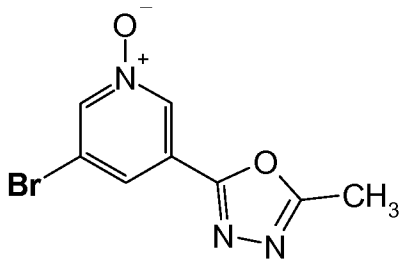
A solution of 2,5-dibromonicotinic acid (1g, 3.5 mmol), 2-methoxyethanol (1.686 mL, 21.36 mmol) in DMF (10 mL) was treated with sodium hydride then warmed to 60 °C for 30 minutes. The reaction was diluted with water (100 ml), acidified (1N HCl), and extracted

with ethyl acetate (3x100 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and the solvents were removed under reduced pressure. The resulting orange oil was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in dichloromethane to give the title compound in solution with DMF, which was carried forward without further purification.

MS (EI) $(M+H)^+$ 276/278 for $C_9H_{11}BrNO_4$ $(M-H)^-$ 274/276 for $C_9H_9BrNO_4$

Intermediate 428

3-bromo-5-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine 1-oxide

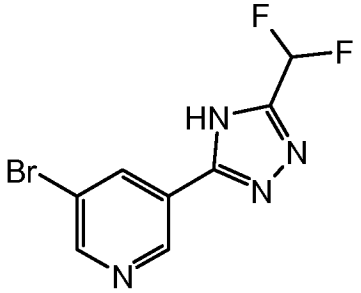


A solution of 2-(5-bromopyridin-3-yl)-5-methyl-1,3,4-oxadiazole (Intermediate 418, 870 mg, 3.62 mmol) in dichloromethane(25 mL) was treated with 3-chlorobenzoperoxoic acid (2031 mg, 9.06 mmol) and stirred at room temperate for 16 hours. Solvents were removed under reduced pressure and the residue was purified by normal phase chromatography on silica gel, eluting with a gradient of methanol in dichloromethane to give 900 mg of the title compound as a off white solid.

MS (EI) $(M+H)^+$ 256/258 for $C_8H_7BrN_3O_2$;

Intermediate 429

3-bromo-5-(5-(difluoromethyl)-4H-1,2,4-triazol-3-yl)pyridine



A mixture of 2-(5-bromopyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole 2,2-difluoroacetate (Intermediate 430, 350 mg, 0.96 mmol) in ammonia (6 mL, 42.00 mmol, 7M in methanol) was heated to 130 °C for 15 min in a microwave reactor. The solvents were removed and the residue was purified by normal phase chromatography eluting with a gradient of ethyl acetate in hexanes to give 113 mg of the title compound as a white solid.

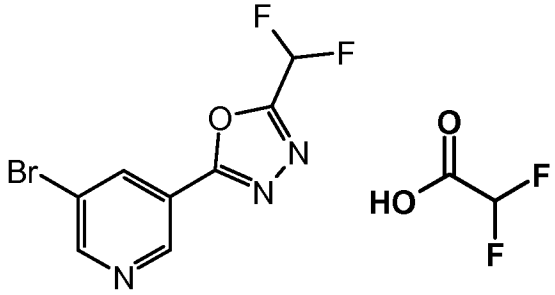
MS (EI) $(M+H)^+$ 275/277 for $C_8H_6BrF_2N_4$ $(M-H)^-$ 273/275for $C_8H_6BrF_2N_4$;

^{1}H NMR (DMSO-*d6*) δ: 15.28 (br. s., 1 H), 9.16 (d, *J*=1.51 Hz, 1 H), 8.87 (d, *J*=2.07 Hz, 1 H), 8.58 (s, 1 H), 7.21 (d, *J*=53.31 Hz, 1H);

^{19}F NMR (DMSO-*d6*) δ: -116.28 (br. s., 2 F);

Intermediate 430

2-(5-bromopyridin-3-yl)-5-(difluoromethyl)-1,3,4-oxadiazole 2,2-difluoroacetate



A suspension of 5-bromonicotinohydrazide (Intermediate 433, 2 g, 9.26 mmol) in toluene (10 mL) was treated with 2,2-difluoroacetic anhydride (1.611 g, 9.26 mmol) drop wise, the resulting suspension was heated to 70 °C for 30 minutes. The reaction was cooled to room temperature and let stir for 16 hours. The solvent was removed under reduced pressure and the residue was purified by normal phase chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes to give the title compound as a white solid.

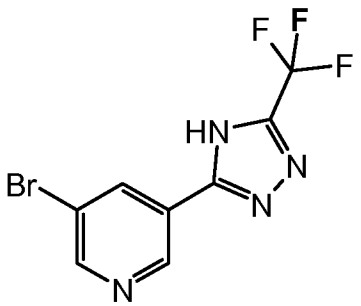
MS (EI) $(M+H)^+$ 276/278 for $C_8H_5BrF_2N_3O$;

^{1}H NMR (DMSO-*d6*) δ: 14.22 (br. s., 1 H), 9.19 (s, 1 H), 9.00 (s, 1 H), 8.63 (s, 1 H), 7.58 (t, *J*=51.05 Hz, 1 H), 6.28 (t, *J*=53.12 Hz,1 H);

^{19}F NMR (DMSO-*d6*) δ: -120.83 (s, 2 F), -127.59 (s, 2 F);

Intermediate 431

3-bromo-5-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)pyridine



Example 431 was synthesized as described for Example 429 from Intermediate 432. The product was obtained as a white solid.

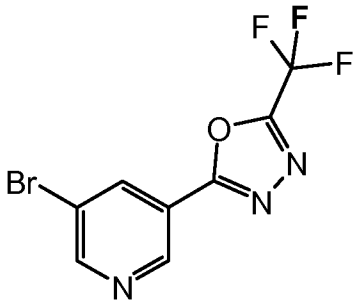
MS (EI) $(M+H)^+$ 293/295 for $C_8H_5BrF_3N_4$ $(M-H)^-$ 291/293for $C_8H_3BrF_3N_4$;

^{1}H NMR (DMSO-*d6*) δ: 15.63 (br. s., 1 H), 9.17 (d, *J*=1.51 Hz, 1 H), 8.91 (d, *J*=2.07 Hz, 1 H), 8.61 (t, *J*=1.98 Hz, 1 H);

^{19}F NMR (DMSO-*d6*) δ: -63.79 (br. s., 3 F);

Intermediate 432

2-(5-bromopyridin-3-yl)-5-(trifluoromethyl)-1,3,4-oxadiazole



A mixture of trifluoroacetic anhydride (5 ml) and 5-bromonicotinohydrazide (Intermediate 433, 1g, 3.24 mmol) was warmed to reflux for 5 minutes to afford an amber solution which was diluted with toluene (12 ml) and heated to reflux for an additional one hour. Solvents were removed under reduced pressure and the residue was purified by normal phase chromatography on silica gel, eluting with a gradient of dichloromethane in hexanes to afford 780 mg of the title compound as a white solid.

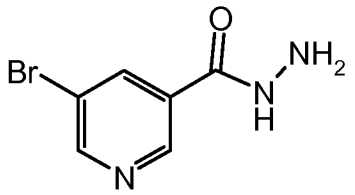
MS (EI) $(M+H)^+$ 294/296 for $C_8H_5BrF_3N_3O$;

^{1}H NMR (DMSO-*d6*) δ: 9.24 (s, 1 H), 9.05 (d, *J*=1.32 Hz, 1 H), 8.70 (s, 1 H);

^{19}F NMR (DMSO-*d6*) δ: -64.21 (s, 3 F);

Intermediate 433

5-bromonicotinohydrazide



Hydrazine (0.8g, 24 mmol) was added to a solution of methyl 5-bromonicotinate (5.15g, 24 mol) in toluene (10 ml) and the mixture was heated to 80 °C for 16 hours. The reaction

mixture was then diluted with ethyl acetate (30 ml), cooled to RT, filtered, and the white solid that was collected was washed with ethyl acetate to give 4.64g of the title compound as off-white solid.

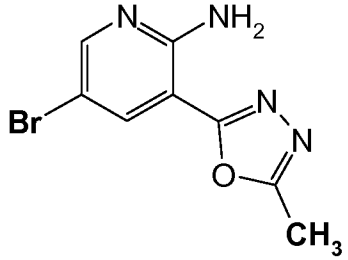
MS (EI) $(M+H)^+$ 216/218 for $C_6H_7BrN_3O$ $(M-H)^-$ 214/216 for $C_6H_5BrN_3O$;

^{1}H NMR (DMSO-*d6*) δ: 10.00 (br. s., 1 H), 8.94 (d, *J*=1.70 Hz, 1 H), 8.82 (d, *J*=2.26 Hz, 1 H), 8.31 - 8.40 (m, 1 H), 4.63 (br. s., 2H);

^{13}C NMR (DMSO-*d6*) δ: 162.72 (s, 1 C), 152.35 (s, 1 C), 146.63 (s, 1 C), 137.02 (s, 1 C), 130.46 (s, 1 C), 120.04 (s, 1 C);

Intermediate 434

5-bromo-3-(5-methyl-1,3,4-oxadiazol-2-yl)pyridin-2-amine



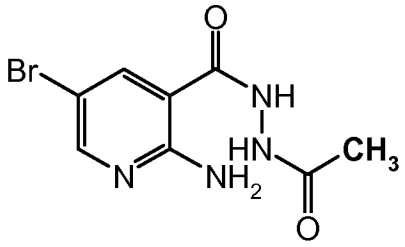
Carbontetrachloride (600 µl, 6.06 mmol) was added to a solution of N'-acetyl-2-amino-5-bromonicotinohydrazide (Intermediate 435, 270 mg, 0.99 mmol), triphenylphosphine (520 mg, 1.98 mmol), and DBU (300 µl, 1.99 mmol) in acetonitrile (50 mL). After stirring for 16 hours at RT the mixture was purified by normal phase chromatography on silica gel, eluting with a gradient of ethyl acetate in hexanes to afford 240 mg of the title compound as an off white solid.

MS (EI) $(M+H)^+$ 255/257 for $C_8H_8BrN_4O$;

^{1}H NMR (DMSO-*d6*) δ: 8.27 (d, *J*=2.45 Hz, 1 H), 8.08 (d, *J*=2.45 Hz, 1 H), 7.45 (br. s., 2 H), 2.58 (s, 3 H);

Intermediate 435

N'-acetyl-2-amino-5-bromonicotinohydrazide



HATU (2.76g, 7.26 mmol) was added to a solution of 2-amino-5-bromonicotinic acid (1.05 g, 4.84 mmol), acetohydrazide (0.466 g, 6.29 mmol), and DIEA (1.690 mL, 9.68 mmol) in DMF (20 mL) and the resulting solution was stirred at RT for 16 hours. The reaction was then diluted with water (250ml) and let stir at RT for 60 hrs then filtered to afford 314 mg of the title compound as a white solid.

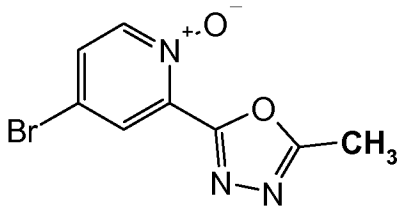
MS (EI) $(M+H)^+$ 273/275 for $C_8H_{10}BrN_4O_2$ $(M-H)^-$ 271/273 for $C_8H_8BrN_4O_2$;

^{1}H NMR (DMSO-*d6*) δ: 10.30 (s, 1 H), 9.89 (s, 1 H), 8.20 (d, *J*=2.26 Hz, 1 H), 8.10 (d, *J*=2.07 Hz, 1 H), 7.22 (s, 2 H), 1.91 (s, 3 H);

^{13}C NMR (DMSO-*d6*) δ: 168.58 (s, 1 C), 165.53 (s, 1 C), 157.38 (s, 1 C), 151.98 (s, 1 C), 138.33 (s, 1 C), 109.02 (s, 1 C), 103.80 (s,1 C), 20.47 (s, 1 C);

Intermediate 436

4-bromo-2-(5-methyl-1,3,4-oxadiazol-2-yl)pyridine 1-oxide

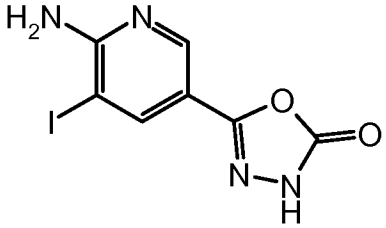


Intermediate 436 was synthesized according to the procedure for Intermediate 428 from Intermediate 176.

MS (EI) $(M+H)^+$ 256/258 for $C_8H_7BrN_3O_2$;

Intermediate 437

5-(6-amino-5-iodopyridin-3-yl)-1,3,4-oxadiazol-2(3H)-one



Hydrazine (2 ml) was added to a solution of (Z)-ethyl 5-iodo-6-(1-methoxyethylideneamino)nicotinate (Intermediate 437, 3 g, 8.62 mmol) in ethanol (50 mL) and warmed to 80 °C for 2 hours. Hydrochloric acid (1M in 1,4- dioxane, 1ml) was added and heating continued for 2 hours. Additional hydrazine (2ml) was added and heating continued for 16 hours. Solvents were removed and the crude mixture was dissolved in DMF (20 ml), treated with DIEA (3 ml), and 1,1'-carbonyl diimidazole (4g). After stirring at RT

for 8 hours, ethyl acetate (200 ml) was added and a solid was removed by filtration. The organic solution was washed with water (150 ml, then 50 ml) and brine (50 ml) then dried over magnesium sulfate. The solvents were removed under reduced pressure, and the residue was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in methylene chloride. The major peak was precipitated from methylene chloride with hexanes to afford 200 mg (7.6%) of the title compound as a white powder.

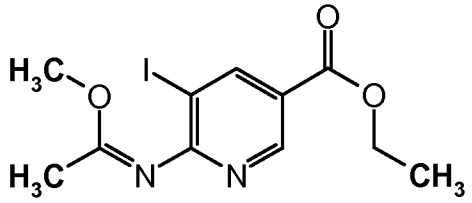
MS (EI) $(M+H)^+$ 305 for $C_7H_6IN_4O_2$ $(M-H)^-$ 303 for $C_7H_4IN_4O_2$;

^{1}H NMR (DMSO-*d6*) δ: 12.41 (br. s., 1 H), 8.33 (d, *J*=2.07 Hz, 1 H), 8.15 (d, *J*=2.07 Hz, 1 H), 6.85 (d, *J*=0.94 Hz, 2 H)

^{13}C NMR (DMSO-*d6*) δ: 160.20 (s, 1 C), 154.27 (s, 1 C), 151.80 (s, 1 C), 145.55 (s, 1 C), 142.93 (s, 1 C), 10.28 (s, 1 C), 76.86 (s, 1C)

Intermediate 438

(Z)-ethyl 5-iodo-6-(1-methoxyethylideneamino)nicotinate



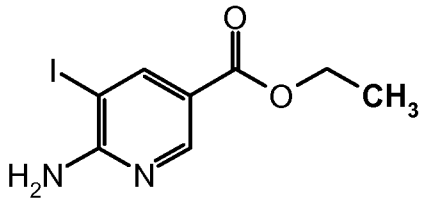
Hydrazine (2 ml) was added to a solution of ethyl 6-amino-5-iodonicotinate (Intermediate 439, 13 g, 31.16 mmol) in 2-methoxy ethanol (50 mL) and the mixture was heated to 135 °C for three hours. Solvents were removed and trimethylorthoacetate (10 ml), HCl (1 drop), and DBU (1ml) were added and the mixture warmed to refluxed for 2 hours. The reaction was diluted with ethyl acetate (200 ml), washed sequentially with 100 ml each of water, saturated aqueous bicarbonate, and brine then dried over magnesium sulfate. The solvents were removed under reduced pressure and the resulting material was purified by normal phase chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes to give 3.1 g of the title compound as an amber oil.

MS (EI) $(M+H)^+$ 349 for $C_{11}H_{14}IN_2O_3$;

^{1}H NMR (DMSO-*d6*) δ: 8.80 - 8.83 (m, 1 H), 8.56 - 8.60 (m, 1 H), 4.32 (q, *J*=7.10 Hz, 2 H), 3.83 (s, 3 H), 1.87 (s, 3 H), 1.32 (t,*J*=7.06 Hz, 3 H)

Intermediate 439

ethyl 6-amino-5-iodonicotinate



Ethyl 6-aminonicotinate (Intermediate 440, 8.7 g, 52.35 mmol) was suspended in ethanol (150 mL), and treated sequentially with Silver (I) sulfate (16.32 g, 52.35 mmol) and then diiodine (13.29 g, 52.35 mmol). The dark suspension was warmed to 80 °C for 5 hours then additional diiodine(1.4 g) and silver sulfate (1.7g) were added. After 2 hours, the reaction mixture was cooled to rt, and a yellow solid was removed by filtration. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by normal phase chromatography eluting with a gradient of ethyl acetate in hexanes. 2.8 grams of the title compound was precipitated from a mixture of hot ethyl acetate and hexanes as an off-white solid.

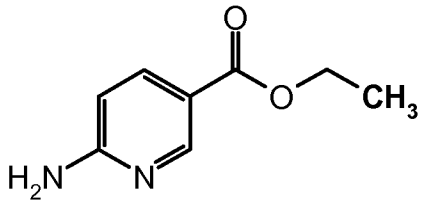
MS (EI) $(M+H)^+$ 293 for $C_8H_{10}IN_2O_2$;

^{1}H NMR (DMSO-*d6*) δ: 10.31 (br. s., 2 H), 8.51 (s, 1 H), 8.45 (s, 1 H), 4.26 (q, *J*=6.97 Hz, 2 H), 1.28 (t, *J*=7.06 Hz, 3 H)

^{13}C NMR (DMSO-*d6*) δ: 162.90 (s, 1 C), 158.53 (s, 1 C), 148.93 (s, 1 C), 145.52 (s, 1 C), 115.80 (s, 1 C), 78.35 (s, 1 C), 60.83 (s, 1C), 14.12 (s, 1 C).

Intermediate 440

ethyl 6-aminonicotinate



Thionyl chloride (15 ml) was added drop wise to a refluxing suspension of 6-aminonicotinic acid (10 g, 72.40 mmol) and sulfuric acid (0.5 mL, 9.38 mmol) in ethanol (300 mL, 72.40 mmol). The suspension was heated for an additional 16 hours at which time the solution was concentrated to dryness. The material was then suspended in ethyl acetate (250 ml) and washed with sodium hydroxide (6x50 ml, 1N), until the aqueous washes were basic, then with saturated aqueous bicarbonate and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 8.7g of the title compound as a white solid.

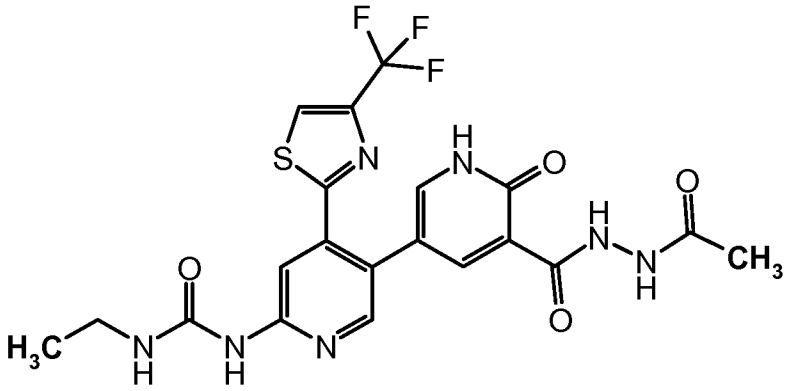
MS (EI) $(M+H)^+$ 167 for $C_8H_{11}N_2O_2$;

^{1}H NMR (DMSO-*d*6) δ: 8.49 (d, *J*=2.07 Hz, 1 H), 7.81 (dd, *J*=8.67, 2.26 Hz, 1 H), 6.83 (s, 2 H), 6.44 (d, *J*=8.67 Hz, 1 H), 4.22 (q,*J*=7.16 Hz, 2 H), 1.27 (t, *J*=7.16 Hz, 3 H);

^{13}C NMR (DMSO-*d*6) δ: 165.18 (s, 1 C), 162.48 (s, 1 C), 150.97 (s, 1 C), 137.49 (s, 1 C), 113.42 (s, 1 C), 107.01 (s, 1 C), 59.74 (s, 1C), 14.24 (s, 1 C);

Intemediate 441

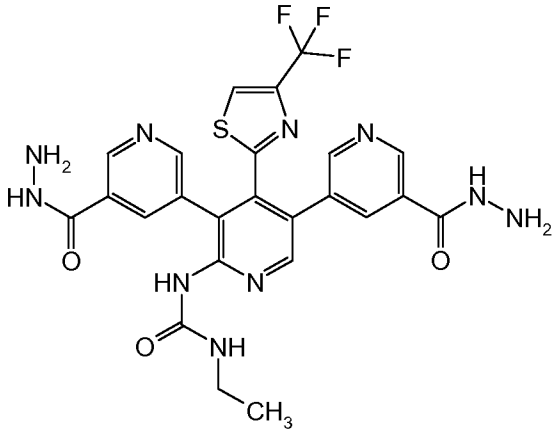
1-(5-(5-(2-acetylhydrazinecarbonyl)-6-oxo-1,6-dihydropyridin-3-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea



A solution of sodium nitrite (350 mg) in water (5 ml) was added dropwise to a suspension of 1-(6'-amino-5'-(5-methyl-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Example 258, 40 mg, 0.08 mmol) and sulfuric acid (1 ml) in water (5.00 mL) at 0 °C, the mixture was allowed to warm to RT over 16 hours. The reaction was diluted with saturated aqueous sodium bicarbonate (50 ml), extracted with ethyl acetate (3x50ml), combined organics were washed with brine, dried over magnesium sulfate, filtered, and the solvents removed under reduced pressure. The residue was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in dichloromethane to afford 25 mg of the title compound crude as a tan gum which was used without further purification.
MS (EI) $(M+H)^+$ 510 for $C_{20}H_{19}F_3N_7O_4S$ $(M-H)^-$ 508 for $C_{20}H_{17}F_3N_7O_4S$;

Intermediate 442

1-{5,5"-bis(hydrazinocarbonyl)-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3':5',3"-terpyridin-2'-yl}-3-ethylurea

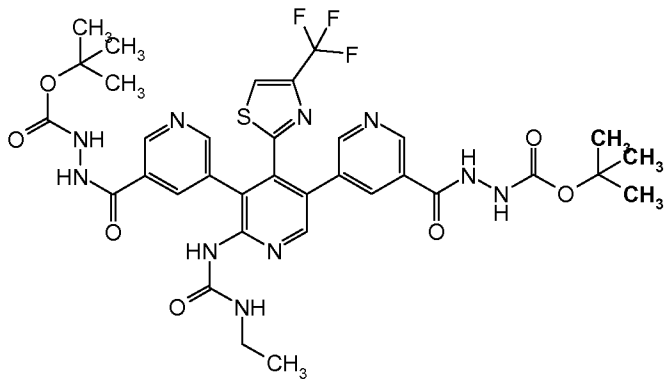


Acetyl chloride (0.4 ml) was added drop wise to a solution of di-*tert*-butyl 2,2'-({2'-[(ethylcarbamoyl)amino]-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3':5',3"-terpyridine-5,5"-diyl}dicarbonyl) dihydrazine carboxylate (Intermediate 443, 38 mg, 0.05 mmol), and stirred at RT for 18 hours, solvent was removed and the material was used in the next step without purification.

MS (EI) $(M+H)^+$ 587 for $C_{24}H_{22}F_3N_{10}O_3S$;

Intermediate 443

di-*tert*-butyl 2,2'-({2'-[(ethylcarbamoyl)amino]-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3':5',3"-terpyridine-5,5"-diyl}dicarbonyl) dihydrazine carboxylate

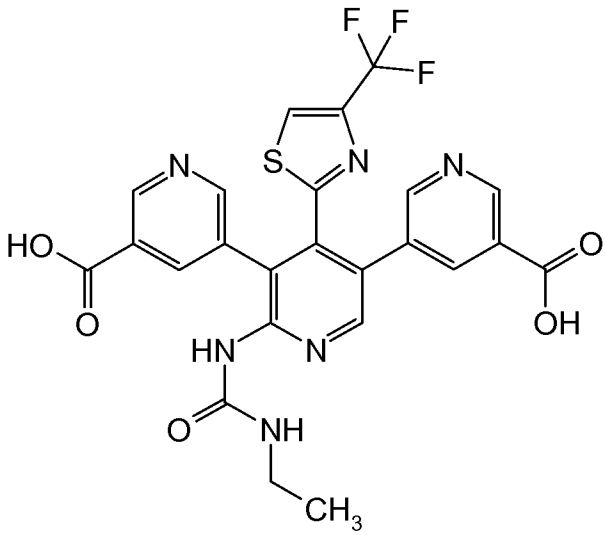


HATU (80 mg, 0.21 mmol) was added to a solution of 2'-[(ethylcarbamoyl)amino]-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3':5',3"-terpyridine-5,5"-dicarboxylic acid (Intermediate 444, 60 mg, 0.11 mmol), tert-butyl hydrazinecarboxylate (50 mg, 0.38 mmol) and DIEA (0.2 mL, 1.15 mmol) in DMF (3 ml) and the resulting solution was stirred at RT for 20 hours. Ethyl acetate (50 ml) was added, followed by water (50 ml), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3x50m ml), and the combined organic layers were washed sequentially with saturated aqueous bicarbonate and brine, then dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The material

was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in dichloromethane to afford 40 mg of the title compound as a tan solid.
MS (EI) $(M+H)^+$ 787 for $C_{34}H_{38}F_3N_{10}O_7S$ $(M-H)^-$ 785 for $C_{34}H_{36}F_3N_{10}O_7S$;
^{1}H NMR (DMSO-*d6*) δ: 10.41 (d, *J*=0.75 Hz, 2 H), 9.03 (d, *J*=8.48 Hz, 2 H), 8.94 (s, 1 H), 8.90 (s, 1 H), 8.79 (s, 1 H), 8.63 (s, 1 H),8.45 (d, *J*=5.84 Hz, 2 H), 8.36 (d, *J*=0.94 Hz, 1 H), 8.13 (d, *J*=11.30 Hz, 3 H), 3.16 (d, *J*=5.27 Hz, 2 H), 1.43 (s, 18 H), 1.02 - 1.13 (m, 3 H)

Intermediate 444

2'-[(ethylcarbamoyl)amino]-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3':5',3"-terpyridine-5,5"-dicarboxylic acid



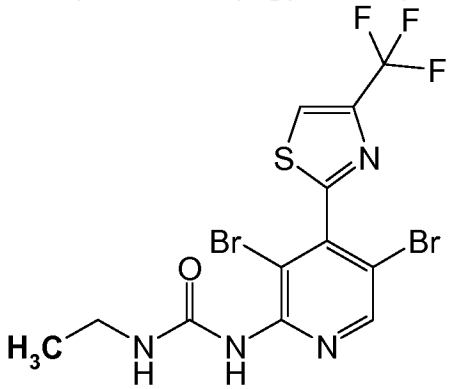
A degassed solution of 1-(3,5-dibromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 445, 60 mg, 0.13 mmol), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (77 mg, 0.28 mmol), diphenylphospinoferocenyl palladium dichloride(10.34 mg, 0.01 mmol), and potassium carbonate (26.2 mg, 0.19 mmol) in acetonitrile (3 ml) and water (3.00 ml) under nitrogen was heated in a microwave reactor for 1 hour at 100 °C. Lithium hydroxide (0.3 ml, 2N in water) was added and the solution was heated to 100 °C in a microwave reactor. The reaction was then diluted with ethyl acetate (50 ml) and water (50 ml), and the layers were separated. The aqueous phase was washed with ethyl acetate (50 ml), filtered then acidified with 1N hydrochloric acid and extracted with ethyl acetate (3x50 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and the solvents removed under reduced pressure to give 50 mg of the title compound as a pale yellow gum, which was used in the next step with no further purification.
MS (EI) $(M+H)^+$ 559 for $C_{24}H_{18}F_3N_6O_5S$ $(M-H)^-$ 557 for $C_{24}H_{16}F_3N_6O_5S$;

^{1}H NMR (DMSO-*d6*) δ: 13.47 (br. s., 2 H), 8.95 (d, *J*=1.88 Hz, 3 H), 8.66 (d, *J*=2.07 Hz, 1 H), 8.64 (s, 1 H), 8.53 (d, *J*=1.88 Hz, 1H), 8.36 (s, 1 H), 8.28 (s, 1 H), 8.06 - 8.13 (m, 1 H), 7.96 - 8.03 (m, 1 H), 3.12 - 3.25 (m, 2 H), 1.02 - 1.11 (m, 3 H)

^{19}F NMR (DMSO-*d6*) δ: -62.73 (s, 3 F)

Intermediate 445

1-(3,5-dibromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea



A mixture of 1-ethyl-3-(4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)urea (from synthesis of Intermediate 12, 350 mg, 1.11 mmol) and 1-bromopyrrolidine-2,5-dione (350 mg, 1.97 mmol) in DMF (30 mL) was heated to 70 °C for 2 hours. The reaction was diluted with water (300 ml) to afford a brown precipitate which was recovered by filtration. This solid was purified by normal phase chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes to give 90 mg of the title compound as a brown solid.

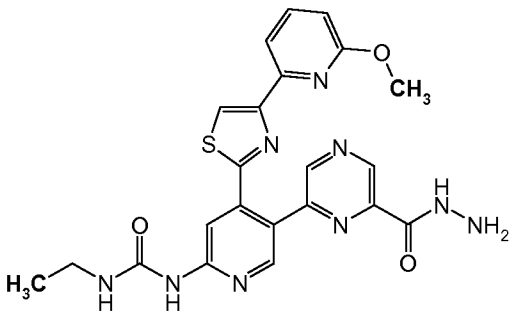
MS (EI) $(M+H)^+$ 475 for $C_{12}H_{10}Br_2F_3N_4OS$ $(M-H)^-$ 473 for $C_{12}H_8Br_2F_3N_4OS$;

^{1}H NMR (DMSO-*d6*) δ: 8.87 (s, 1 H), 8.60 (s, 1 H), 8.24 (br. s., 2 H), 3.23 (qd, *J*=6.97, 6.03 Hz, 2 H), 1.11 (t, *J*=7.16 Hz, 3 H);

^{19}F NMR (DMSO-*d6*) δ: -61.99 (s, 3 F);

Intermediate 446

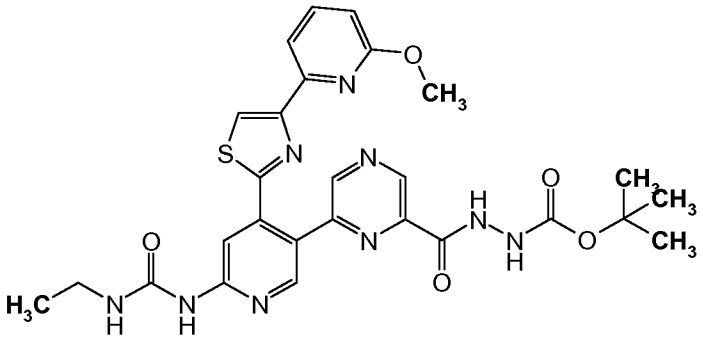
1-ethyl-3-(5-(6-(hydrazinecarbonyl)pyrazin-2-yl)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-2-yl)urea



A solution of tert-butyl 2-(6-(6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-3-yl)pyrazine-2-carbonyl)hydrazinecarboxylate (Intermediate 447, 30 mg, 0.05 mmol) in MeOH (20 mL), was treated with acetyl chloride (1 mL, 0.05 mmol) drop wise. After stirring at RT for 18 hours, solvents were removed under reduced pressure to give 26 mg of the title compound as a white solid, which was used without further purification. MS (EI) $(M+H)^+$ 492 for $C_{22}H_{22}N_9O_3S$ $(M-H)^-$ 490 for $C_{22}H_{20}N_9O_3S$;

Intermediate 447

tert-butyl 2-(6-(6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-3-yl)pyrazine-2-carbonyl)hydrazinecarboxylate



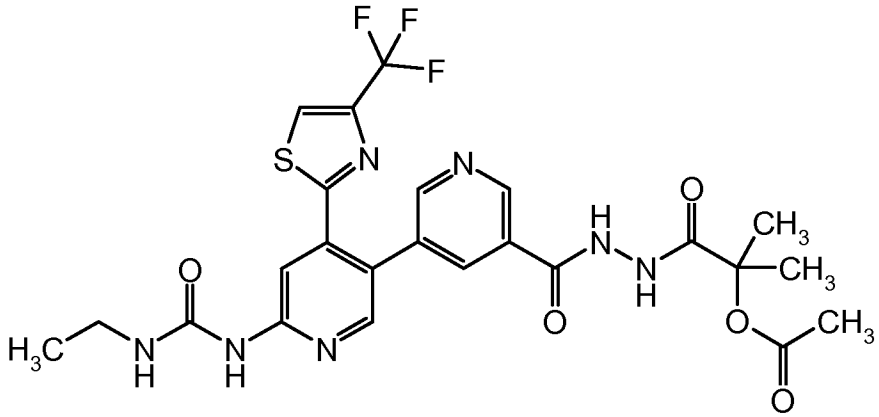
HATU (50 mg, 0.13 mmol) was added to a solution of 6-(6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-3-yl)pyrazine-2-carboxylic acid (Intermediate 486, 25 mg, 0.05 mmol), tert-butyl hydrazinecarboxylate (30 mg, 0.23 mmol), and DIEA (50 μL, 0.29 mmol) in DMF (6 mL), and the mixture stirred at RT for 48 hours. The reaction was diluted with ethyl acetate (50 ml) and water (50 ml), and the layers were separated. The aqueous phase was extracted with ethyl acetate (3x50 ml), and the combined organic layers were washed sequentially with saturated aqueous bicarbonate and brine then dried over magnesium sulfate, filtered, and the solvents were removed under reduced pressure. The resulting residue was purified by normal phase chromatography on silica gel, eluting with a gradient of ethyl acetate in hexanes to afford 30 mg of the title compound as a white solid.

MS (EI) $(M+H)^+$ 592 for $C_{27}H_{30}N_9O_5S$ $(M-H)^-$ 590 for $C_{27}H_{28}N_9O_5S$;

^{1}H NMR (DMSO-*d6*) δ: 10.53 (s, 1 H), 9.60 (s, 1 H), 9.08 (s, 1 H), 9.03 (s, 1 H), 8.76 (s, 1 H), 8.69 (s, 1 H), 8.40 (s, 1 H), 8.23 (s, 1H), 7.85 (br. s., 1 H), 7.70 (s, 1 H), 7.54 (br. s., 1 H), 6.76 (d, *J*=8.29 Hz, 1 H), 3.92 (s, 3 H), 3.10 - 3.28 (m, 2 H), 1.38 (s, 9 H), 1.17 (t, *J*=7.16 Hz, 3 H).

Intermediate 448

1-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-2-methyl-1-oxopropan-2-yl acetate



A solution of 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 9, 100 mg, 0.22 mmol) in pyridine (1.5 ml) was treated with 1-chloro-2-methyl-1-oxopropan-2-yl acetate (0.5 ml) and allowed to stir at RT for 30 minutes. Volatiles were removed under reduced pressure and the residue was purified by normal phase chromatography on silica gel eluting with ethyl acetate in hexanes to afford 100 mg of the title compound as an amber gum.

MS (EI) $(M+H)^+$ 580 for $C_{24}H_{25}F_3N_7O_5S$ $(M-H)^-$ 578 for $C_{24}H_{23}F_3N_7O_5S$;

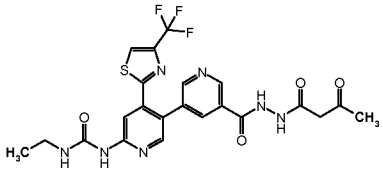
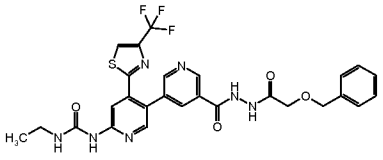
^{1}H NMR (DMSO-*d6*) δ: 10.60 (s, 1 H), 9.95 (s, 1 H), 9.50 (s, 1 H), 9.06 (d, *J*=1.88 Hz, 1 H), 8.65 (d, *J*=1.88 Hz, 1 H), 8.57 (s, 1 H),8.37 (s, 1 H), 8.25 (s, 1 H), 8.22 (s, 1 H), 7.55 (t, *J*=5.37 Hz, 1 H), 3.12 - 3.27 (m, 2 H), 2.03 (s, 3 H), 1.56 (s, 6 H), 1.11 (t, *J*=7.16 Hz, 3 H);

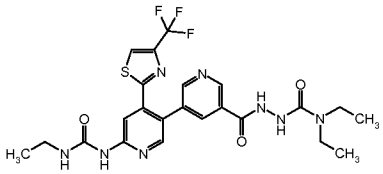
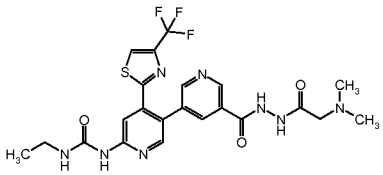
^{19}F NMR (DMSO-*d6*) δ: -62.41 (s, 3 F);

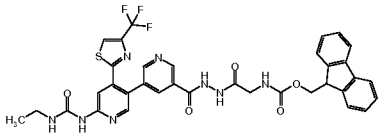
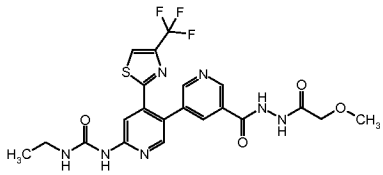
Intermediates 449-463

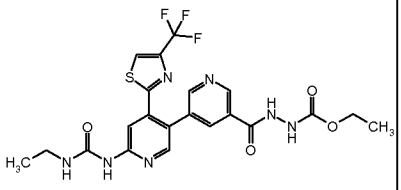
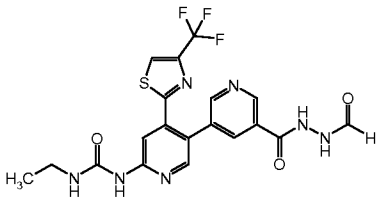
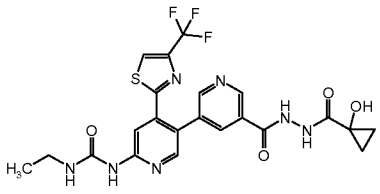
The following Intermediates were prepared as described for Intermediate 448 using the starting materials indicated in the table.

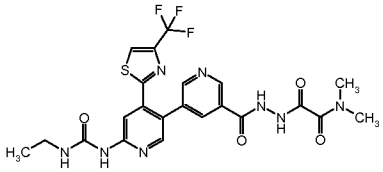
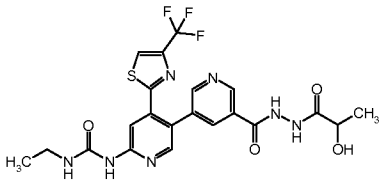
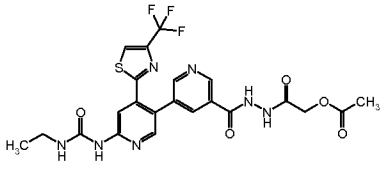
Int	Compound	Data	SM

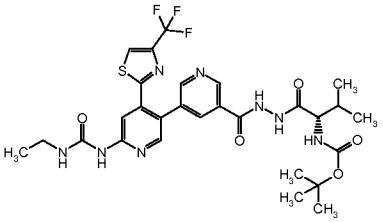
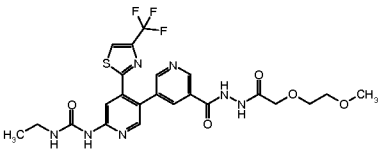
Int	Compound	Data	SM
449	1-ethyl-3-(5'-(2-(3-oxobutanoyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (EI) $(M+H)^+$ 536 for $C_{22}H_{21}F_3N_7O_6S$ $(M-H)^-$ 534 for $C_{22}H_{19}F_3N_7O_6S$; ^{1}H NMR (DMSO-*d*6) δ: 10.74 (s, 0 H), 10.26 (s, 1 H), 9.51 (s, 1 H), 9.05 (d, *J*=1.88 Hz, 1 H), 8.65 (d, *J*=1.88 Hz, 1 H), 8.57 (s, 1H), 8.38 (s, 1 H), 8.25 (s, 1 H), 8.22 (s, 1 H), 7.55 (br. s., 0 H), 3.45 (s, 2 H), 3.17 - 3.26 (m, 2 H), 2.22 (s, 3 H), 1.11 (t, *J*=7.25 Hz, 3 H); ^{19}F NMR (DMSO-*d*6) δ: -62.42 (s, 3 F)	Intermediate 9 and 4-methyleneoxetan-2-one
450	1-(5'-(2-(2-(benzyloxy)acetyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (EI) $(M+H)^+$ 600 for $C_{27}H_{25}F_3N_7O_4S$ $(M-H)^-$ 598 for $C_{27}H_{22}F_3N_7O_4S$; ^{1}H NMR (DMSO-*d*6) δ: 10.63 (br. s., 1 H), 10.08 (s, 1 H), 9.51 (s, 1 H), 9.06 (d, *J*=1.88 Hz, 1 H), 8.66 (d, *J*=2.07 Hz, 1 H), 8.57 (s,1 H), 8.37 (s, 1 H), 8.25 (s, 1 H), 8.21 (t, *J*=2.07 Hz, 1 H), 7.55 (t, *J*=4.90 Hz, 1 H), 7.22 - 7.46 (m, 5 H), 4.61 (s, 2 H), 4.08 (s, 2 H), 3.21 (qd,*J*=7.16, 5.84 Hz, 2 H), 1.11 (t, *J*=7.16 Hz, 3 H); ^{19}F NMR (DMSO-*d*6) δ: -62.41 (s, 3 F);	Intermediate 9 and 2-(benzyloxy)acetyl chloride

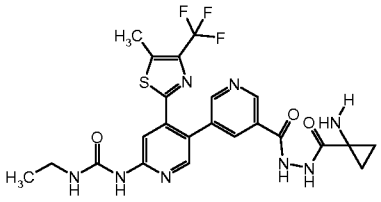
Int	Compound	Data	SM
451	N,N-diethyl-2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinecarboxamide 	MS (EI) $(M+H)^+$ 551 for $C_{23}H_{26}F_3N_8O_3S$ $(M-H)^-$ 549 for $C_{23}H_{24}F_3N_8O_3S$; ^{1}H NMR (DMSO-*d*6) δ: 10.28 (s, 1 H), 9.50 (s, 1 H), 9.06 (s, 1 H), 8.64 (s, 1 H), 8.57 (s, 1 H), 8.43 (s, 1 H), 8.37 (s, 1 H), 8.25 (s, 1H), 8.19 (s, 1 H), 7.56 (t, *J*=5.65 Hz, 1 H), 3.12 - 3.30 (m, 6 H), 0.94 - 1.18 (m, 9 H); ^{19}F NMR (DMSO-*d*6) δ: -62.40 (s, 3 F);	Intermediate 9 and diethylcarbamic chloride
452	1-(5'-(2-(2-(dimethylamino)acetyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (EI) $(M+H)^+$ 537 for $C_{22}H_{24}F_3N_8O_3S$ $(M-H)^-$ 535 for $C_{22}H_{22}F_3N_8O_3S$; ^{1}H NMR (DMSO-*d*6) δ: 10.57 (br. s., 1 H), 9.88 (s, 1 H), 9.50 (s, 1 H), 9.05 (d, *J*=2.07 Hz, 1 H), 8.65 (d, *J*=1.88 Hz, 1 H), 8.57 (s, 1H), 8.37 (s, 1 H), 8.25 (s, 1 H), 8.21 (t, *J*=1.98 Hz, 1 H), 7.92 (s, 1 H), 7.55 (t, *J*=5.18 Hz, 1 H), 3.13 - 3.27 (m, *J*=7.16, 7.16, 7.16, 6.03 Hz, 2 H),3.02 (s, 2 H), 2.27 (s, 6 H), 1.11 (t, *J*=7.16 Hz, 3 H); ^{19}F NMR (DMSO-*d*6) δ: -62.41 (s, 3 F);	Intermediate 9 and 2-(dimethylamino)acetyl chloride

Int	Compound	Data	SM
453	(9H-fluoren-9-yl)methyl 2-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-2-oxoethylcarbamate 	MS (EI) $(M+H)^+$ 731 for $C_{35}H_{30}F_3N_8O_5S$ $(M-H)^-$ 729 for $C_{35}H_{28}F_3N_8O_5S$; ^1H NMR (DMSO-*d*6) δ: 10.64 (br. s., 1 H), 10.13 (s, 1 H), 9.51 (s, 1 H), 9.05 (s, 1 H), 8.65 (s, 1 H), 8.56 (s, 1 H), 8.37 (s, 1 H), 8.24(s, 1 H), 8.20 (br. s., 1 H), 7.89 (d, *J*=7.35 Hz, 2 H), 7.72 (d, *J*=7.35 Hz, 2 H), 7.68 (d, *J*=6.22 Hz, 1 H), 7.55 (br. s., 1 H), 7.42 (t, *J*=7.35 Hz, 2 H),7.33 (t, 2 H), 4.12 - 4.42 (m, 3 H), 3.75 (d, *J*=5.65 Hz, 2 H), 3.21 (quin, *J*=6.64 Hz, 2 H), 1.10 (t, *J*=7.16 Hz, 3 H); ^{19}F NMR (DMSO-*d*6) δ: -62.39 (s, 3 F)	Intermediate 9 and (9H-fluoren-9-yl)methyl 2-chloro-2-oxoethylcarbamate
454	1-ethyl-3-(5'-(2-(2-methoxyacetyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (EI) $(M+H)^+$ 524 for $C_{21}H_{21}F_3N_7O_4S$ $(M-H)^-$ 522 for $C_{21}H_{19}F_3N_7O_4S$; ^1H NMR (DMSO-*d*6) δ: 10.59 (s, 1 H), 10.02 (s, 1 H), 9.50 (s, 1 H), 9.06 (d, J=1.88 Hz, 1 H), 8.65 (d, J=1.88 Hz, 1 H), 8.57 (s, 1H), 8.37 (s, 1 H), 8.25 (s, 1 H), 8.21 (s, 1 H), 7.56 (br. s., 1 H), 3.98 (s, 2 H), 3.36 (s, 3 H), 3.14 - 3.27 (m, 2 H), 1.10 (t, J=7.16 Hz, 3 H); ^{19}F NMR (DMSO-*d*6) δ: -62.42 (s, 3 F);	Intermediate 9 and 2-methoxyacetyl chloride

Int	Compound	Data	SM
455	ethyl 2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinecarboxylate 	MS (EI) $(M+H)^+$ 524 for $C_{21}H_{21}F_3N_7O_4S$ $(M-H)^-$ 522 for $C_{21}H_{19}F_3N_7O_4S$; ^1H NMR (DMSO-*d*6) δ: 10.53 (s, 1 H), 9.51 (s, 1 H), 9.31 (br. s., 1 H), 9.04 (s, 1 H), 8.66 (s, 1 H), 8.57 (s, 1 H), 8.37 (s, 1 H), 8.24 (s, 1 H), 8.19 (br. s., 1 H), 7.55 (t, J=5.56 Hz, 1 H), 4.08 (dt, J=9.23, 6.97 Hz, 2 H), 3.21 (qd, J=7.16, 6.03 Hz, 2 H), 1.16 - 1.26 (m, 3 H), 1.11 (t,J=7.16 Hz, 3 H); ^{19}F NMR (DMSO-*d*6) δ: -62.43 (s, 3 F);	Intermediate 9 and ethyl carbonochloridate
456	1-ethyl-3-(5'-(2-formylhydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (EI) $(M+H)^+$ 480 for $C_{19}H_{17}F_3N_7O_3S$ $(M-H)^-$ 478 for $C_{19}H_{15}F_3N_7O_3S$;	Intermediate 9, formic acid and HATU
457	1-ethyl-3-(5'-(2-(1-hydroxycyclopropanecarbonyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (EI) $(M+H)^+$ 536 for $C_{22}H_{21}F_3N_7O_4S$ $(M-H)^-$ 534 for $C_{22}H_{19}F_3N_7O_4S$;	Intermediate 9, 1-hydroxycyclopropanecarboxylic acid and HATU

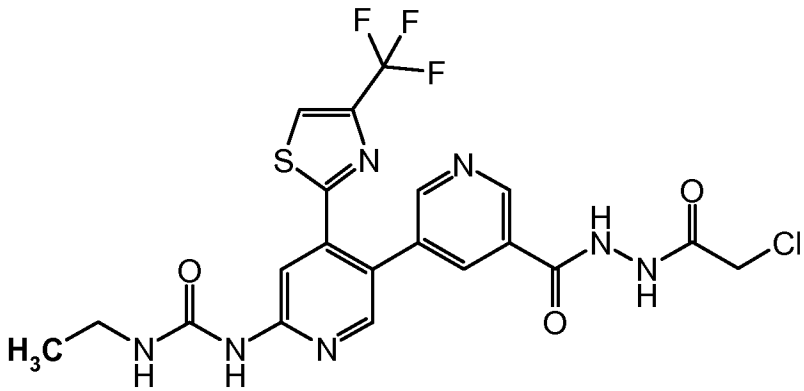
Int	Compound	Data	SM
458	2-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-N,N-dimethyl-2-oxoacetamide 	MS (EI) $(M+H)^+$ 551 for $C_{22}H_{22}F_3N_8O_4S$ $(M-H)^-$ 549 for $C_{22}H_{20}F_3N_8O_4S$;	Intermediate 9, 2-(dimethylamino)-2-oxoacetic acid and HATU
459	1-ethyl-3-(5'-(2-(2-hydroxypropanoyl)hydrazine carbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (EI) $(M+H)^+$ 524 for $C_{21}H_{21}F_3N_7O_4S$ $(M-H)^-$ 522 for $C_{21}H_{19}F_3N_7O_4S$;	Intermediate 9, 2-hydroxypropanoic acid and HATU
460	2-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-2-oxoethyl acetate 	MS (EI) $(M+H)^+$ 552 for $C_{22}H_{21}F_3N_7O_5S$ $(M-H)^-$ 550 for $C_{22}H_{19}F_3N_7O_5S$;	Intermediate 9, 2-acetoxyacetic acid and HATU

Int	Compound	Data	SM
461	(S)-tert-butyl 1-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-3-methyl-1-oxobutan-2-ylcarbamate 	MS (EI) $(M+H)^+$ 651 for $C_{28}H_{34}F_3N_8O_5S$ $(M-H)^-$ 649 for $C_{28}H_{32}F_3N_8O_5S$; ^1H NMR (DMSO-*d*6) δ: 10.62 (s, 1 H), 10.11 (s, 1 H), 9.50 (s, 1 H), 9.06 (s, 1 H), 8.64 (s, 1 H), 8.57 (s, 1 H), 8.37 (s, 1 H), 8.25 (s,1 H), 8.23 (br. s., 1 H), 7.55 (br. s., 1 H), 6.83 (d, *J*=8.85 Hz, 1 H), 3.88 (t, *J*=7.91 Hz, 1 H), 3.09 - 3.28 (m, 2 H), 1.84 - 2.07 (m, 1 H), 1.39 (s, 9 H),1.10 (t, *J*=7.16 Hz, 3 H), 0.97 (d, *J*=6.59 Hz, 3 H), 0.90 (d, *J*=6.59 Hz, 3 H); ^{19}F NMR (DMSO-*d*6) δ: -62.42 (s, 3 F)	Intermediate 9 and (S)-tert-butyl 4-isopropyl-2,5-dioxooxazolidine-3-carboxylate
462	1-ethyl-3-(5'-(2-(2-(2-methoxyethoxy)acetyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	MS (EI) $(M+H)^+$ 568 for $C_{23}H_{25}F_3N_7O_5S$ $(M-H)^-$ 566 for $C_{23}H_{23}F_3N_7O_5S$;	Intermediate 9 and 2-(2-methoxyethoxy)acetyl chloride

Int	Compound	Data	SM
463	1-(5'-(2-(1-aminocyclopropanecarbonyl) hydrazinecarbonyl)-4-(5-methyl-4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea 	MS (EI) $(M+H)^+$ 549 for $C_{23}H_{24}F_3N_8O_3S$ $(M-H)^-$ 547 for $C_{23}H_{24}F_3N_8O_3S$;	Intermediate 237, 1-(tert-butoxycarbonylamino)cyclopropanecarboxylic acid and HATU, followed by HCl in methanol.

Intermediate 464

1-(5'-(2-(2-chloroacetyl)hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



N,N'-methanediylidenedicyclohexanamine (120 mg, 0.58 mmol) was added to a solution of 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 9, 200 mg, 0.44 mmol), and sodium 2-chloroacetate (51.6 mg, 0.44 mmol) in 1,4-dioxane (10 mL). After stirring at RT for 16 hours the solution was warmed to 50 °C and HATU (200 mg) was added. After stirring for 1 hour, potassium carbonate (100 mg)was added and one hour later pyridine (0.5 ml) was added, and the mixture stirred at 1 hr at 50 °C. The solvents were then removed under reduced pressure and the residue was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in

dichloromethane to give crude title compound as a pale yellow solid, which was used without further purification.

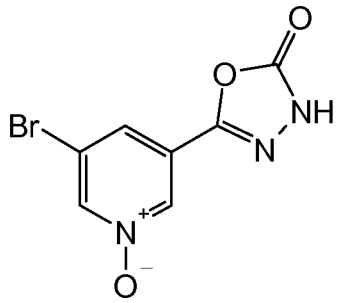
MS (EI) $(M+H)^+$ 528 for $C_{20}H_{18}ClF_3N_7O_3S$ $(M-H)^-$ 526 for $C_{20}H_{18}ClF_3N_7O_3S$;

^{1}H NMR (DMSO-*d*6) δ: 10.80 (s, 1 H), 10.50 (s, 1 H), 9.51 (s, 1 H), 9.05 (d, *J*=1.88 Hz, 1 H), 8.66 (d, *J*=1.88 Hz, 1 H), 8.57 (s, 1H), 8.38 (s, 1 H), 8.24 (s, 1 H), 8.21 (t, *J*=2.07 Hz, 1 H), 7.55 (t, *J*=5.37 Hz, 1 H), 4.21 (s, 2 H), 3.05 - 3.27 (m, 2 H), 1.11 (t, *J*=7.16 Hz, 3 H);

^{19}F NMR (DMSO-*d*6) δ: -62.43 (s, 3 F)

Intermediate 465

3-bromo-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyridine 1-oxide



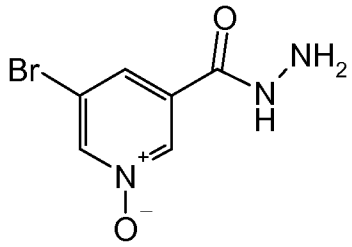
Di(1H-imidazol-1-yl)methanone (295 mg, 1.82 mmol) was added to a solution of 3-bromo-5-(hydrazinecarbonyl)pyridine 1-oxide (Intermediate 466, 310 mg, 1.34 mmol) in DMF (10 mL) and the mixture was stirred for 20 hours. The reaction was then diluted with ethyl acetate (100 ml), water (100 ml), and hydrochloric acid (1N, 10 ml), and the layers were separated. The aqueous phase extracted with ethyl acetate (3x100 ml), and the combined organic layers were washed with brine, dried over magnesium sulfate, and the solvents removed under reduced pressure. The resulting residue was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in dichloromethane to afford 150 mg of the title compound as a pale yellow solid.

MS (EI) $(M+H)^+$ 258/2260 for $C_7H_5BrN_3O_3$ $(M-H)^-$ 256/258 for $C_7H_3BrN_3O_3$;

^{1}H NMR (DMSO-*d*6) δ: 13.02 (br. s., 1 H), 8.77 (s, 1 H), 8.48 (s, 1 H), 7.88 (s, 1 H);

Intermediate 466

3-bromo-5-(hydrazinecarbonyl)pyridine 1-oxide



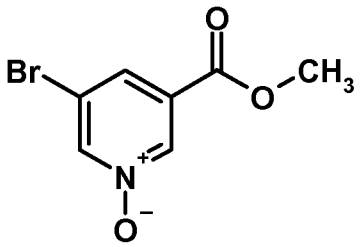
Hydrazine (0.120 g, 3.75 mmol) was added to a solution of 3-bromo-5-(methoxycarbonyl)pyridine 1-oxide (Intermediate 467, 16 g, 3.75 mmol) in ethanol (50 mL), and heated to 70 °C for 19 hours, solvents were removed under reduced pressure and the residue was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in dichloromethane to afford 310 mg of the title compound as a brown gummy solid.

MS (EI) $(M+H)^+$ 232/234 for $C_6H_7BrN_3O_2$ $(M-H)^-$ 230/232 for $C_6H_5BrN_3O_2$;

^{1}H NMR (DMSO-*d6*) δ: 10.11 (br. s., 1 H), 8.72 (s, 1 H), 8.50 (s, 1 H), 7.89 (s, 1 H), 4.65 (br. s., 2 H);

Intermediate 467

3-bromo-5-(methoxycarbonyl)pyridine 1-oxide



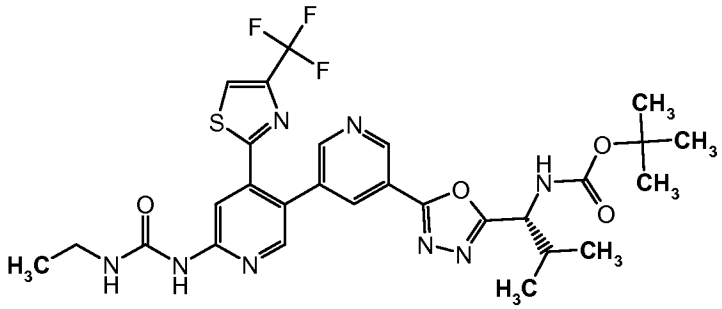
A solution of methyl 5-bromonicotinate (1.6 g, 7.41 mmol) in dichloromethane (25 mL) was treated with 3-chlorobenzoperoxoic acid (1.992 g, 8.89 mmol) and stirred at room temperature for 16 hours. The resulting suspension was filtered, and the filtrate purified by normal phase chromatography on silica gel eluting with a gradient of ethyl acetate in hexane. The major peak was triturated from ethyl acetate with hexanes to give the title compound as a peach solid (1.4 g, 6.03 mmol, 81 %).

MS (EI) $(M+H)^+$ 232/234 for $C_7H_7BrNO_3$;

^{1}H NMR (DMSO-*d6*) δ: 8.85 (s, 1 H), 8.51 (d, *J*=1.13 Hz, 1 H), 7.94 (d, *J*=1.13 Hz, 1 H), 3.89 (s, 3 H);

Intermediate 468

(R)-tert-butyl 1-(5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-1,3,4-oxadiazol-2-yl)-2-methylpropylcarbamate

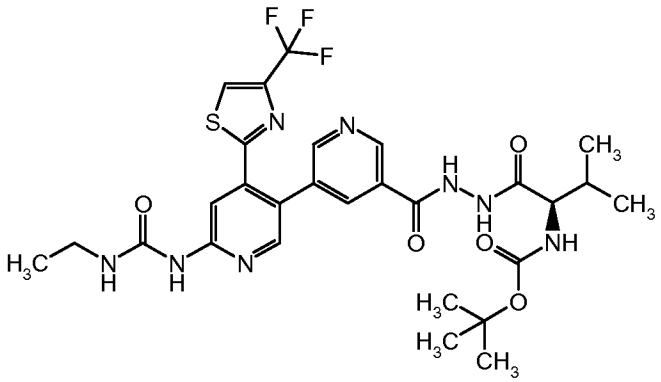


Intermediate 468 was synthesized according to the procedure for Example 264 from Intermediate 461.

MS (EI) $(M+H)^+$ 633 for $C_{28}H_{32}F_3N_8O_4S$ $(M-H)^-$ 631 for $C_{28}H_{30}F_3N_8O_4S$;

Intermediate 469

(R)-tert-butyl 1-(2-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carbonyl)hydrazinyl)-3-methyl-1-oxobutan-2-ylcarbamate

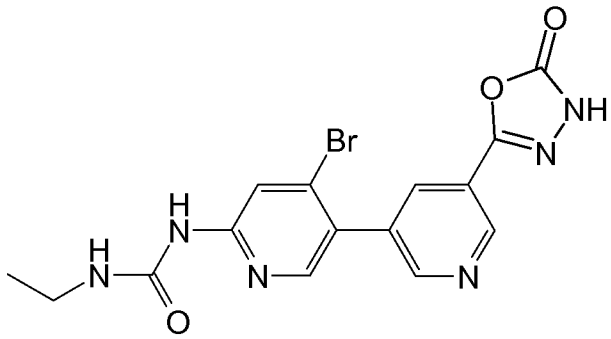


Intermediate 469 was synthesized according to the procedure for Intermediate 268 from Intermediate 9 and (R)-2-(tert-butoxycarbonylamino)-3-methylbutanoic acid.

MS (EI) $(M+H)^+$ 651 for $C_{28}H_{34}F_3N_8O_5S$ $(M-H)^-$ 649 for $C_{28}H_{32}F_3N_8O_5S$;

Intermediate 470

1-(4-bromo-5'- (5-oxo-4, 5-dihydro-1, 3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



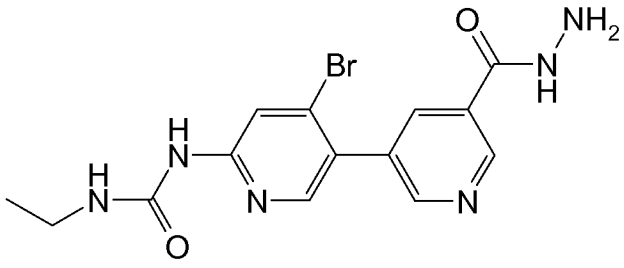
A mixture of (1-(4-bromo-5'- (hydrazine carbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea (Intermediate 471, 60mg, 0.16 mmol), 1,1'-carbonyldiimmidazol (34.4mg, 0.21mmol) and diisopropyl ethylamine (0.041 ml, 0.24 mmol) in DMF (3ml) was heated at 50 °C for 4 hours, cooled down to room temperature. The crude was concentrated and purified by column chromatography on silica gel (5% methanol in dichloromethane) to give the desired product as a solid (62 mg).

MS (ESP) 407.2(MH^+) for $C_{15}H_{13}BrN_6O_3$.

^{1}H-NMR (DMSO-d_6) δ: 1.09 (t, 3H); 3.19 (t, 2H); 7.48 (t, 1H); 8.04 (s, 1H); 8.23 (t, 1H); 8.29 (s, 1H); 8.80 (d, 1H); 9.0 (d, 1H); 9.45 (s, 1H).

Intermediate 471

1-(4-bromo-5'- (hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea- (hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea



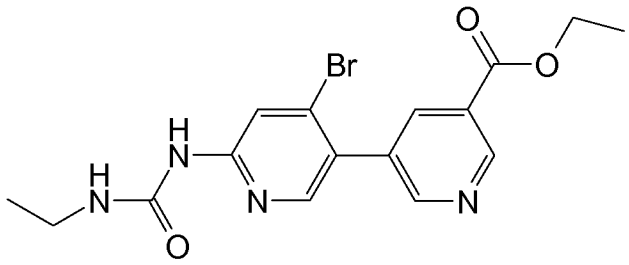
Ethyl 4'-bromo-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate (Intermediate 472, 1.32g, 2.85 mmol), hydrazine hydrate (1.416 ml, 28.53 mmol) were mixed in ethanol (20 ml), heated at 80 °C for 2 d, cooled down to room temperature. The crude was diluted with ethyl acetate; the resulting precipitate was filtered and washed with ethyl acetate, collected as the desired product (920mg).

MS (ESP) 381.06 (MH^+) for $C_{14}H_{15}BrN_6O_2$

^{1}H-NMR (DMSO-d_6): 1.08 (t, 3H); 3.17 (q, 2H); 3.58 (br, 2H); 7.43 (t, 1H); 8.05 (s, 1H); 8.27 (s, 2H); 8.85 (s, 1H); 9.03 (s, 1H); 9.43 (s, 1H); 11.15 (br, 1H).

Intermediate 472

Ethyl 4'-bromo-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate



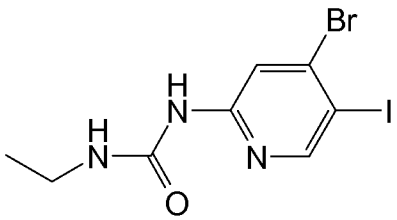
1-(4-Bromo-5-iodopyridin-2-yl)-3-ethylurea (Intermediate 473, 1.33g, 3.59 mmol), ethyl 5-(4,4,5,5-tetramethyl-1, 3,2-dioxaborolan-2-yl) nicotinate (1.049 g, 3.59 mmol), paladium-tetrakistriphenylphosphine (0.415 g, 0.36 mmol) and K_2CO_3 (0.745 g, 5.39 mmol) were suspended in a mixture of DMF (10ml) and water (1.000 ml). The suspension was degassed and purged with nitrogen then heated at 100°C for 1.5 h. The reaction mixture was cooled down to room temperature and filtered; the filtrate was concentrated and purified by column chromatography on silica gel to give the desired product (1.32g).

MS (ESP) 395.02 (MH^+) for $C_{16}H_{17}BrN_4O_3$.

^{1}H-NMR ($CDCl_3$): 1.29 (t, 3H); 1.45 (t, 3H); 3.45 (q, 2H); 4.47 (q, 2H); 7.30 (br, 1H); 8.12 (s, 1H); 8.38 (t, 1H); 8.84 (2s, 2xH); 9.29 (s, 1H).

Intermediate 473

1-(4-bromo-5-iodopyridin-2-yl)-3-ethylurea



4-bromo-5-iodopyridin-2-amine (Intermediate 474, 3.2g, 10.71 mmol) was dissolved in dry chloroform (15 mL). Isocyanatoethane (2.52 mL, 32.12 mmol) was added and the reaction mixture was refluxed for 24 hrs. The reaction was cooled down to room temperature and

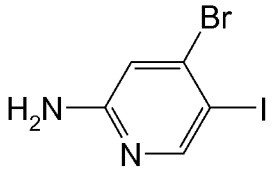
hexanes was added. The resulting precipitate was collected by filtration to give the desired product (3.14g).

MS (ESP+) 371.99 (MH^+) for $C_8H_9BrIN_3O$.

^{1}H-NMR (DMSO-d_6): 1.06 (t, 3H); 3.32 (q, 2H); 7.24 (br, 1H); 8.05 (s, 1H); 8.52 (s, 1H); 9.31 (s, 1H).

Intermediate 474

4-bromo-5-iodopyridin-2-amine



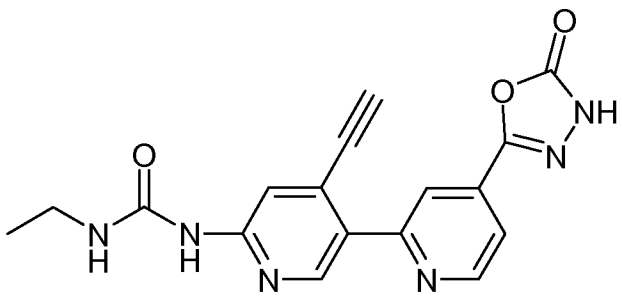
4-Bromopyridin-2-amine (2.5g, 14.45 mmol) was dissolved in DMF (6 mL)/$CHCl_3$ (20 mL), 1-iodopyrrolidine-2,5-dione (6.50 g, 28.90 mmol) was added, and the mixture was stirred at 45 °C for 2 days. $CHCl_3$ was evaporated and the remaining solution was poured into water (15ml) and extracted with EtOAc(15ml x 3). The organic phase was concentrated and purified by ISCO eluted with Hex/EtOAc(gradiant) to give the title compound (3.2g).

MS (ESP) 298.88 (MH^+) for $C_5H_4BrIN_2$.

^{1}H-NMR (DMSO-d_6): 4.51 (br, 2H); 6.80 (s, 1H); 8.35 (s, 1H).

Intermediate 475

1-ethyl-3- (4-ethynyl-5'- (5-oxo-4, 5-dihydro-1, 3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl) urea



1-ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-((trimethylsilyl)ethynyl)-3,3'-bipyridin-6-yl)urea (Intermediate 476, 84mg, 0.20 mmol) was suspended in methanol (5ml), and NaOH (2 ml, 2.00 mmol) was added. The mixture was stirred at room temperature for 2 hrs, aqueous HCl solution (2N) was added to adjust the ph to 6.5. DCM (10ml) was added and the organic layer was washed with brine and dried over $MgSO_4$, and concentrated to a

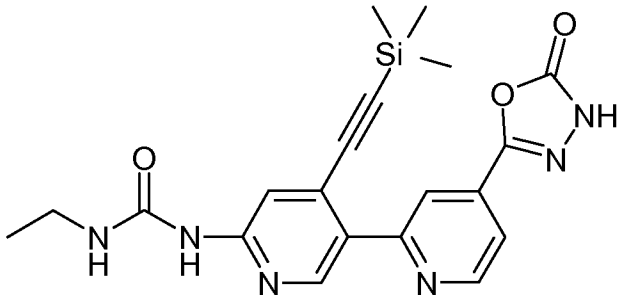
volume of 2 ml. Hexanses was added and the resulting precipitate was filtered and washed with DCM, collected as the desired product (25mg).

MS (ESP) 351 (MH^+) for $C_{17}H_{14}N_6O_3$

^{1}H-NMR (DMSO-d_6): 1.10 (t, 3H); 3.20 (m, 2H); 4.66 (s, 1H); 7.61 (m, 1H); 7.78 (s, 1H); 8.34 (m, 1H); 8.41 (s, 1H); 8.92 (d, 1H); 8.98 (d, 1H); 9.43 (s, 1H); 12.84 (br, 1H) ppm

Intermediate 476

1-ethyl-3- (5'-(5-oxo-4, 5-dihydro-1, 3,4-oxadiazol-2-yl)-4-((trimethylsilyl) ethynyl)-3,3'-bipyridin-6-yl) urea



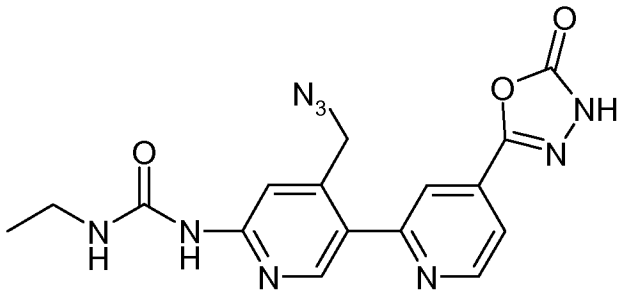
1-(4-bromo-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Intermediate 470, 400mg, 0.99 mmol), ethynyltrimethylsilane (116 mg, 1.18 mmol), copper(I) iodide (18.80 mg, 0.10 mmol), Et_3N (0.550 mL, 3.95 mmol), and $Pd(PPh_3)4$ (57.1 mg, 0.05 mmol) were combined in anhydrouse DMF (10 mL) and heated at 80 °C for 4 hours. After cooling down to room temperature, the crude sample was filtered through celite and the filtrate was concentrated and purified by column chromatography on silica gel(Hex/EtOAc) to give the tile compound (160mg).

MS (ESP) 423 (MH^+) for $C_{20}H_{22}N_6O_3Si$

^{1}H-NMR (DMSO-d_6): 0.12 (s, 9H); 1.10 (t, 3H); 3.20 (m, 2H); 7.57 (m, 1H); 7.72 (s, 1H); 8.41 (m, 1H); 8.45 (s, 1H); 8.92 (d, 1H); 8.99 (d, 1H); 9.41 (s, 1H); 12.86 (s, 1H) ppm

Intermediate 477

1-(4-(azidomethyl)-5'-(5-oxo-4, 5-dihydro-1, 3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



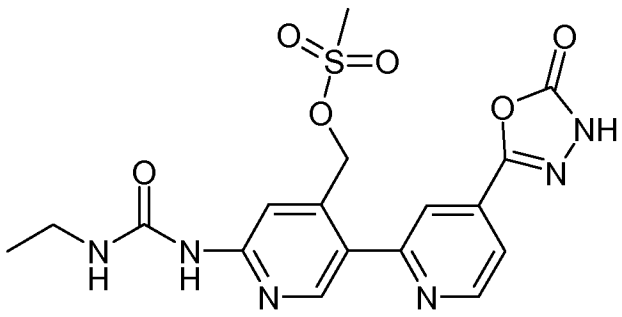
(6-(3-Ethylureido)-5'-(5-oxo-4, 5-dihydro-1, 3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl) methyl methanesulfonate (Intermediate 478, 350mg, 0.81 mmol), sodium azide (52.4 mg, 0.81 mmol) were mixed in DMF (4ml), stirred at 60 °C for 2 hr, diluted with dichloromethane, the solvent was evaporated and the residue was mixed with silica gel and dry loaded onto isco column (silica gel), eluted with 10%MeOH in dichloromethane to give the title product as a white solid (206mg).

MS (ESP) 382 (MH^+) for $C_{16}H_{15}N_9O_3$

^{1}H-NMR (DMSO-d_6): 1.10 (t, 3H); 3.20 (m, 2H); 4.55 (s, 2H); 7.69 (s, 1H); 7.81 (t, 1H); 8.18 (m, 2H); 8.77 (d, 1H); 9.00 (d, 1H); 9.40 (s, 1H); 12.84 (s, 1H) ppm

Intermediate 478

(6-(3-ethylureido)-5'-(5-oxo-4, 5-dihydro-1, 3,4-oxadiazol-2-yl)-3,3'-bipyridin-4-yl) methyl methanesulfonate

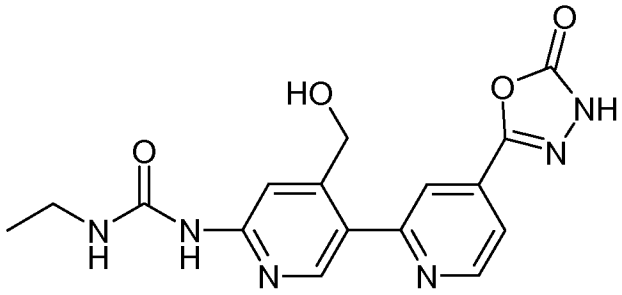


1-Ethyl-3- (4-(hydroxymethyl)-5'-(5-oxo-4, 5-dihydro-1, 3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl) urea (Intermediate 479, 420mg, 1.18 mmol), methane sulfonyl chloride (0.137 ml, 1.77 mmol) were mixed in DMF (4ml)/DCM (15ml) and stirred at 25 °C for 2 hr. The reaction mixture was then diluted with DCM (10ml), washed with brine and the organic phase was concentrated and diluted in dichloromethane. Hexanses was added and the resulting precipitate was filtered and collected as the desired product (350mg).

MS (ESP) 435 (MH^+) for $C_{17}H_{18}N_6O_6S$

Intermediate 479

1-Ethyl-3- (4-(hydroxymethyl)-5'-(5-oxo-4, 5-dihydro-1, 3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl) urea



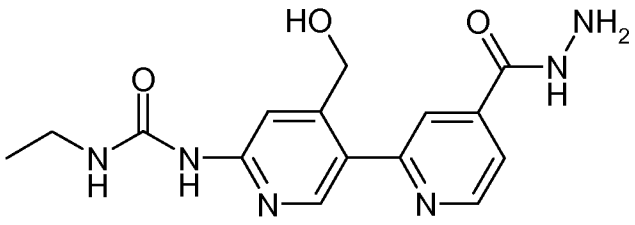
1-Ethyl-3- (5'-(hydrazine carbonyl)-4-(hydroxymethyl)-3,3'-bipyridin-6-yl) urea (Intermediate 480, 470mg, 1.42 mmol), CDI (476 mg, 2.85 mmol) and DIEA (0.497 ml, 2.85 mmol) were suspended in DMF (5ml) and stirred at room temperature for 12 hours. The reaction mixture turned into solution, and sodium hydroxide (aqueous solution, 2N, 1ml) was added, and the reaction was stirred for 30 min. Hydrogen chloride (aqueous, 2N, ~1ml) was added, and the mixture was extracted with 10% methanol in dichloromethane (10 ml x 5). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to volume of ~3ml, ether (10ml) was added, the resulting precipitates was filtered and washed with ether and DCM, collected to give the title compound (425mg).

MS (ESP) 357 (MH^+) for $C_{16}H_{16}N_6O_4$

^{1}H-NMR (DMSO-d_6): 1.10 (t, 3H); 3.19 (m, 2H); 4.41 (s, 2H); 5.47 (m, 1H); 7.65 (s, 1H); 8.10 (s, 1H); 8.18 (m, 2H); 8.70 (br, 1H); 8.95 (d, 1H); 9.36 (s, 1H); 12.84 (s, 1H) ppm

Intermediate 480

1-ethyl-3- (5'-(hydrazine carbonyl)-4-(hydroxymethyl)-3,3'-bipyridin-6-yl) urea



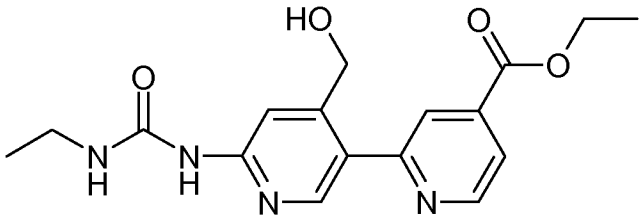
Ethyl 6'-(3-ethylureido)-4'-(hydroxymethyl)-3,3'-bipyridine-5-carboxylate (Intermediate 481, 500 mg, 1.45 mmol), hydrazine hydrate (0.721 ml, 14.52 mmol) were mixed in ethanol (10ml), heated at 80 °C for 25 hr., cooled down to room temperature, ethyl acetate was added

and the resulting solid was filtered and washed with ethyl acetate, to give the desired product (440 mg).

MS (ESP) 331 (MH^+) for $C_{15}H_{18}N_6O_3$

Intermediate 481

Ethyl 6'-(3-ethylureido)-4'-(hydroxymethyl)-3,3'-bipyridine-5-carboxylate



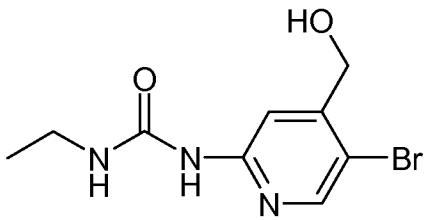
In a round bottom flask, 1-(5-bromo-4- (hydroxymethyl) pyridin-2-yl)-3-ethylurea (Intermediate 482, 5.26g, 19.19 mmol), ethyl 5-(4,4,5,5-tetramethyl-1, 3,2-dioxaborolan-2-yl) nicotinate (5.60 g, 19.19 mmol), $Pd(PPh_3)_4$ (2.217 g, 1.92 mmol) and cesium carbonate (12.50 g, 38.38 mmol) were suspended in a 4:1 mixture of 1,4 dioxane / water. The suspension was degassed and purged with nitrogen then heated in the microwave at 100°C for 2 hours. The reaction was cooled to room temperature. Diluted with DCM(20ml)/MeOH(5ml) and washed with brine. The organic phase was dried and concentrated then purified by column chromatography on silica gel eluted with DCM/MeOH (95/5%) to give the title compound as a solid. (3.5g)

MS (ESP) 345 (MH^+) for $C_{17}H_{20}N_4O_4$

^{1}H-NMR (DMSO-d_6): 1.27 (t, 3H); 1.45 (t, 3H); 3.43 (m, 2H); 4.46 (q, 2H); 4.65 (s, 2H); 8.02 (br, 1H); 8.30 (br, 2H); 8.77 (s, 1H); 9.28 (s, 1H).

Intermediate 482

1-(5-bromo-4- (hydroxymethyl)pyridin-2-yl)-3-ethylurea



Methyl 5-bromo-2- (3-ethylureido) isonicotinate (Intermediate 483, 5g, 15.82 mmol), $NaBH_4$ (1.795 g, 47.45 mmol) were mixed in EtOH (20ml), and the mixture was refluxed for over night. The solvent was evaporated and the residue was mixed with DCM (50ml). A 2N HCl

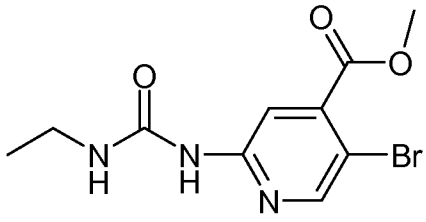
aqueous solution was added (10ml), and the mixture was stirred for 10min, then the saturated $NaHCO_3$ was added and the mixture was extracted with DCM (20 ml x 3), the organic layer was dried over $MgSO_4$, filtered and the volume was reduced to 10ml. The precipitate that formed was filtered and collected as the desired product (2.34g).

MS (ESP) 275 (MH^+) for $C_9H_{12}BrN_3O_2$

^{1}H-NMR (CD_3OD): 1.20 (t, J=7.33 Hz, 3H); 4.59 (s, 2H); 7.35 (s, 1H); 8.22 (s, 1H) ppm.

Intermediate 483

Methyl 5-bromo-2- (3-ethylureido) isonicotinate



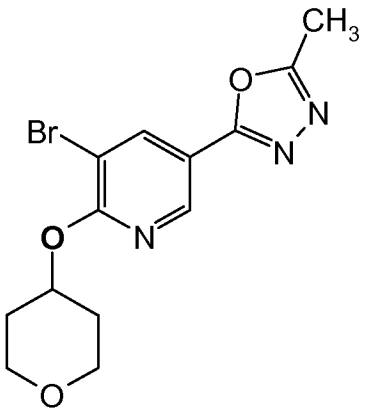
To a solution of methyl 2-amino-5-bromoisonicotinate (25 g, 108.20 mmol) in chloroform (20 mL) was added ethyl isocyanate (17.00 mL, 216.41 mmol), and the reaction mixture heated to reflux for 16 h then cooled to ambient temperature. The product was precipitated with hexane (200 mL), filtered, washed with hexane (2x50 mL) and dried to give 27.5 g light yellow color solid as the desired product.

MS (ESP): 304.00 (M+2) for $C_{10}H_{12}BrN_3O_3$

^{1}H NMR (DMSO-d_6): 1.07 (t, J=7.20 Hz, 3H); 3.01 - 3.25 (m, 2H); 3.91 (s, 3H); 7.17 (t, J=5.31 Hz, 1H); 8.02 (d, J=1.52 Hz, 1H); 8.46 (s, 1H); 9.41 (s, 1H)

Intermediate 484

2-(5-bromo-6-(tetrahydro-2H-pyridin-3-yl)-5-methyl-1,3,4-oxadiazole

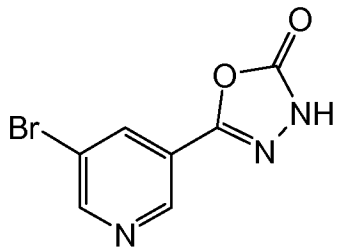


A solution of tetrahydro-2H-pyran-4-yl 5-bromo-6-(tetrahydro-2H-pyran-4-yloxy)nicotinate (Intermediate 281, 2 g) and hydrazine (2 mL) in ethanol (20 mL) was heated to reflux for 20 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude product and 1,1,1-trimethoxyethane (20 ml, 166.46 mmol) was heated reflux and treated with concentrated aqueous HCl (drop), the resulting clear colorless solution was refluxed for 20 minutes, treated with DBU (0.2 ml, 1.33 mmol) and refluxed an additional 20 min. The material was concentrated under reduced pressure to give a tan gum which was purfied by flash chromatography on silica gel eluting with a gradient of ethyl acetate in hexanes to give the title compound as a white solid (1.77 g)

MS (EI) $(M+H)^+$ 340/342 for $C_{13}H_{14}BrN_3O_3$;

Intermediate 485

3-bromo-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)pyridine

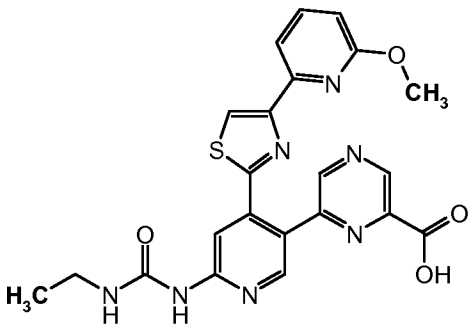


Di(1H-imidazol-1-yl)methanone (290 mg, 1.82 mmol) was added to a solution of 3-bromo-5-(hydrazinecarbonyl)pyridine (Intermediate 433, 300 mg, 1.34 mmol) in DMF (10 mL) and the reaction was allowed to preceed for 20 hours. The reaction was then diluted with ethyl acetate (100 ml), water (100 ml), and hydrochloric acid (1N, 10 ml), and the layers were separated. The aqueous phase extracted with ethyl acetate (3x100 ml), and the combined organics were washed with brine, dried over magnesium sulfate, filtered and the solvents were removed under reduced pressure. The resulting residue was purified by normal phase chromatography on silica gel eluting with a gradient of methanol in dichloromethane to afford 150 mg of the title compound as a pale yellow solid.

MS (EI) $(M+H)^+$ 242/250 for $C_7H_5BrN_3O_2$;

Intermediate 486

6-(6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-3-yl)pyrazine-2-carboxylic acid



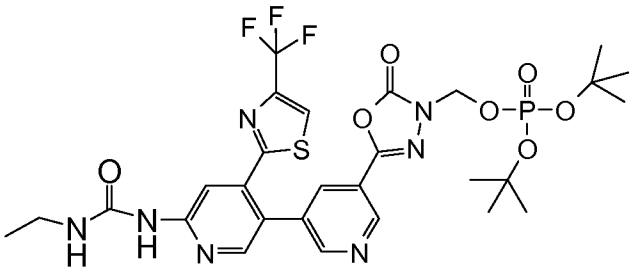
A mixture of 6-(3-ethylureido)-4-(4-(6-methoxypyridin-2-yl)thiazol-2-yl)pyridin-3-ylboronic acid (Intermediate 415, 700 mg, 0.88 mmol), 6-chloropyrazine-2-carboxylic acid (278 mg, 1.75 mmol), cesium carbonate (571 mg, 1.75 mmol), dipalladium tridibenzilidine acetone (40.1 mg, 0.04 mmol), Dicyclohexyl TriisopropylBiphenyl phosphine (84 mg, 0.18 mmol), in 1,4-dioxane (12 mL) and water (3.0 mL) was degassed, then heated in a microwave reactor at 110 °C for 1hr. The reaction was diluted with ethyl acetate (25 ml), and the resulting solid was removed by filtration, the solid was washed with ethyl acetate, ethyl acetate/methanol, and 1N sodium hydroxide. The combined filtrates were extracted with 1N sodium hydroxide (3x50 ml). The combined aqueous extracts were acidified (con. HCl), and the aqueous phase was extracted with ethyl acetate (3x50 ml). The combined organics were washed with brine, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The resulting solid was washed exhaustively with methanol solutions in methylene chloride to afford 30 mg of the title compound as a beige solid.

MS (EI) $(M+H)^+$ 478 for $C_{25}H_{20}N_7O_4S$ $(M-H)^-$ 476 for $C_{25}H_{18}N_7O_4S$;

^{1}H NMR (DMSO-*d*6) δ: 9.62 (s, 1 H), 9.13 (s, 1 H), 8.85 (s, 1 H), 8.49 (s, 1 H), 8.36 (s, 1 H), 8.28 (s, 1 H), 7.70 (t, *J*=7.82 Hz, 1 H),7.63 (br. s., 1 H), 6.96 (d, *J*=7.35 Hz, 1 H), 6.76 (d, *J*=8.29 Hz, 1 H), 3.91 (s, 3 H), 3.13 - 3.28 (m, 2 H), 1.12 (t, *J*=7.25 Hz, 3 H)

Intermediate 487

di-tert-Butyl (5-(6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-yl)methyl phosphate



To a solution of 1-ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 515, 2.5 g, 5.24 mmol) in DMF (30 mL), sodium hydride (0.314 g, 7.85 mmol) was added at room temperature. The reaction mixture was stirred at that temperature for 15 min and then a solution of di-tert-butyl chloromethyl phosphate (2.032 g, 7.85 mmol) in DMF (3 mL) was added slowly at room temperature . The reaction mixture was then heated to 75 °C for 2 h . The reaction mixture was cooled to room temperature and 100 mg of sodium hydride followed by a solution of di-tert-butyl chloromethyl phosphate (500 mg) in DMF (2 mL) was added and the reaction mixture was heated for 1 h. The reaction mixture was cooled to room temperature, treated with water (75 mL) and ethyl acetate. The organic layer was washed with water and brine and dried over magnesium sulfate and concentrated under reduced pressure to give a light yellow soild. Purification by column chromatogrpahy (silica deactivated with TEA, ethyl acetate:hexanes:5% TEA) provided a crude solid. The solid was slurried with acetonitrile for 30 min and the resulting white solid (1.2 g) was collected by filtration and dried under vacuum overnight.

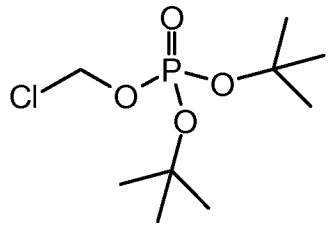
MS (ESP): 700 (M+1) for $C_{28}H_{33}F_3N_7O_7PS$

^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 1.41 (s, 18 H); 3.16-3.28 (m, 2H); 5.52 (d, 2H); 7.55 (brs, 1H); 8.15 (d, 1H); 8.23 (s, 1H); 8.39 (s, 1H); 8.59 (s, 1H); 8.72 (s, 1H); 9.03 (s, 1H); 9.51 (s, 1H).

^{13}P-NMR (DMSO-d_6) δ: -11.76

Intermediate 488

di-tert-Butyl chloromethyl phosphate



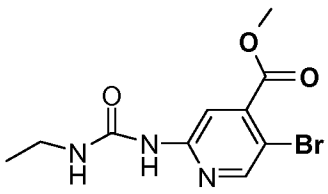
Potassium di-tert-butyl phosphate (10 g, 40.27 mmol), sodium carbonate (17.07 g, 161.10 mmol) and tet-n-butylammonium bisulfate (0.712 g, 2.01 mmol) were combined and dissolved in water (37 mL). Dichloromethane was added as a solvent and the resulting mixture was placed in a ice bath, and a solution of chloromethyl sulfochloridate (8 g, 48.49 mmol) in dichloromethane (6 mL) was added while the reaction mixture was agitated vigorously. The reaction mixture was warmed to room temperature slowly and stirred for additional 5 h, diluted with water (120 mL) and stirred for about 30 min The phases were separated and the aqueous was back extracted with dichloromethane. The organic phases were combined, washed with water, dried over magnesium sulfate, filtered and concentrated under reduced pressure to give a clear oil (8.5 g).

^{1}H-NMR ($CDCl_3$) δ: 1.52 (s, 18 H), 5.63 (d, 2H)

^{13}P-NMR ($CDCl_3$) δ: -11.76.

Intermediate 489

Methyl 5-bromo-2-(3-ethylureido)isonicotinate



A solution of methyl 2-amino-5-bromoisonicotinate (50 g, 216 mmol) in chloroform (500mL) was placed into a sealed tube. Ethyl isocyanate (51 mL, 649 mmol) was then added in two parts over the course of 6 h. The sealed tube was insulated and heated at 40°C for 3 d. The reaction mixture was then cooled to room temperature, concentrated under reduced pressure, and extracted with ethyl acetate (3 L) and water (1 L). The extracted organic layer was then

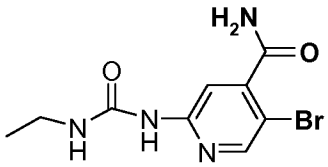
dried with sodium sulfate, filtered, and concentrated under reduced pressure to yield 68.4 g of a pale yellow solid (96%).

MS (ESP): 302 ($M+H^+$) for $C_{10}H_{12}BrN_3O_3$

^1H NMR ($CDCl_3$): δ 1.22 (t, 3H), 3.41 (q, 2H), 7.22 (s, 1H), 7.30 (s, 1H), 8.38 (s, 1H), 8.70 (s, 1H), 9.42 (s, 1H).

Intermediate 490

5-Bromo-2-(3-ethylureido)isonicotinamide



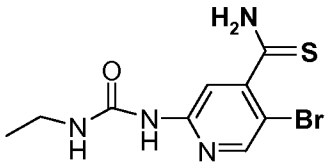
A solution of methyl 5-bromo-2-(3-ethylureido)isonicotinate (Intermediate 489, 56.22 g, 186 mmol) in 7 N ammonia in methanol (1 L) was allowed to stir at room temperature in a sealed flask for 1.5 d. The precipitate that formed was collected by filtration, rinsed with acetonitrile (500 mL), and then dried on the high vacuum pump overnight, yielding 50.8 g of a solid (95.1%).

MS (ESP): 287 ($M+H^+$) for $C_9H_{11}BrN_4O_2$

^1H NMR (DMSO-d_6): δ 1.1 (t, 3H), 3.18 (q, 2H), 7.40 (s, 1H), 7.60 (s, 1H), 7.80 (s, 1H), 8.1 (s, 1H), 8.38 (s, 1H), 9.39 (s, 1H).

Intermediate 491

5-Bromo-2-(3-ethylureido)pyridine-4-carbothioamide



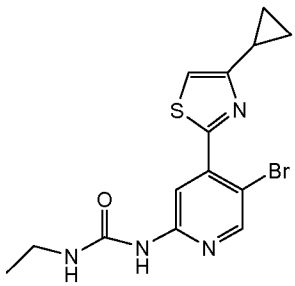
A solution of 5-bromo-2-(3-ethylureido)isonicotinamide (Intermediate 490, 52.2 g, 181 mmol), Lawesson's Reagent (73.5 g, 181 mmol), and tetrahydrofuran (840 mL) was prepared and stirred with heating at reflux overnight. After approximately 12 h, the reaction mixture was cooled to room temperature. The precipitate that formed was collected by filtration and subsequently washed with 500 mL of additional tetrahydrofuran. The solid was then dried in the vacuum oven at 50°C for 30 min, yielding 51 g of a bright yellow solid (92.5%).

MS (ESP): 304 ($M+H^+$) for $C_9H_{11}BrN_4OS$

^{1}H NMR (DMSO-d_6): δ 1.1 (t, 3H), 3.18 (q, 2H), 7.38 (s, 1H), 7.50 (s, 1H), 8.28 (s, 1H), 9.25 (s, 1H), 9.80 (s, 1H), 10.28 (s, 1H)

Intermediate 492

1-(5-bromo-4-(4-cyclopropylthiazol-2-yl)pyridin-2-yl)-3-ethylurea



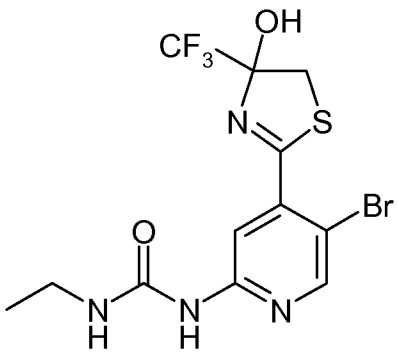
In a 25 mL flask 5-bromo-2-(3-ethylureido)pyridine-4-carbothioamide (Intermediate 491, 51.24 g, 169 mmol) and 2-bromo-1-cyclopropylethanone (28.9 g, 177 mmol) were suspended in ethanol (700 mL). The reaction mixture was heated at 80 °C for 5 h, cooled to room temperature and concentrated to one half the volume under reduced pressure. The resulting solid was collected by filtered and washed with ethanol. Isolation gave 60.1g of the title compound.

LC/MS (ES$^+$)[(M+H)$^+$]: 367, 369 for $C_{14}H_{15}BrN_4OS$.

^{1}H NMR (300 MHz, d_6-DMSO): 0.88(m, 2H), 0.99(m, 2H), 1.08 (t, 3H), 2.19 (m, 1H), 3.17 (m, 2H), 7.35 (m, 1H), 7.62 (s, 1H), 8.30 (s, 1H), 8.48 (s, 1H), 9.32 (s, 1H).

Intermediate 493

1-(5-Bromo-4-(4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-yl)-3-ethylurea



A suspension of 5-bromo-2-(3-ethylureido)pyridine-4-carbothioamide (Intermediate 491, 160 g, 510 mmol), 3-bromo-1,1,1-trifluoroacetone (200g, 1.02 mol) in acetonitrile (3 L) was

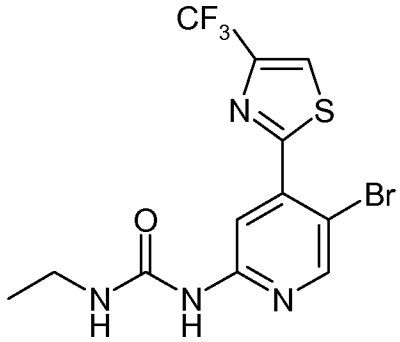
heated at 80°C for 20 h. The solution was then cooled down and concentrated under reduced pressure. The resulting mixture was dissolved in acetonitrile and methyl tert-butyl ether (2:1, 2.4 L), and concentrated to one half the volume under reduced pressure. The precipitate that formed was collected by filtration and dried in a vacuum oven at 40°C. .

MS (ESP): 413.0 (MH^+) for $C_{12}H_{12}BrF_3N_4O_2S$.

^1H NMR (300 MHz, DMSO-d_6): δ 1.05 (t, 3H), 3.10 (q, 2H), 3.60 (d, 1H), 3.85 (d, 1H), 7.58 (s, 1H), 7.95 (s, 1H), 8.42 (s, 1H), 9.42 (s, 1H).

Intermediate 494

1-(5-Bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea



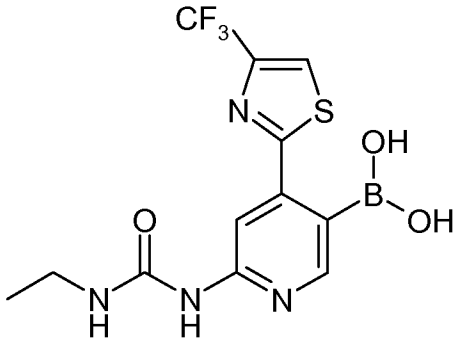
A suspension of 1-(5-bromo-4-(4-hydroxy-4-(trifluoromethyl)-4,5-dihydrothiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 493, 175 g, 430 mmol) and triethylamine (295 mL, 2.13 mol) in tetrahydrofuran (3 L) was prepared and stirred at room temperature. Methane sulfonyl chloride (106 mL, 1.36 mol) was added dropwise over the course of an hour. This reaction mixture was stirred at room temperature for 6 h. The solid was collected by filtration, rinsed with tetrahydrofuran (2 × 500 mL), and the filtrate was retained while the solid was discarded. The combined tetrahydrofuran layers were concentrated to a viscous, yellow semi-solid which was then washed with water (2 × 500 mL). This solid was further stirred with water (500 mL) for 18 hours, then filtered and dried in the vacuum oven at 50°C for 12 hours to give 121.8g (73%) of 1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea as an off-white solid.

MS (ESP): 395.0 (MH^+) for $C_{12}H_{10}BrF_3N_4OS$

^1H NMR (300 MHz, DMSO-d_6): δ 1.1 (t, 3H), 3.20 (q, 2H), 7.23 (s, 1H), 8.40 (s, 1H), 8.60 (s, 1H), 8.83 (s, 1H), 9.40 (s, 1H).

Intermediate 495

6-(3-Ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid



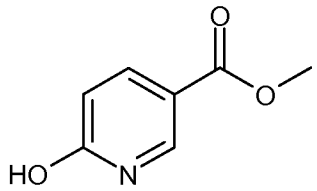
A suspension of 1-(5-bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 494, 50 g, 130 mmol) in tetrahydrofuran (1.25 L) was prepared and stirred at -50˚C. 2.0 M Isopropyl magnesium chloride in tetrahydrofuran (165 mL, 330 mmol) was added dropwise over 45 min so that the temperature never rose above -35˚C. The reaction was stirred for a further hour at -40˚C then was cooled to -78˚C. 2.5 M n-Butyl lithium in hexanes (293 mL, 730 mmol) was then added dropwise to the reaction mixture over the course of 1 h so that the temperature never rose above -65˚C. This mixture was then allowed to return to -78˚C for 1.5 h. Boron methoxide (155 mL, 1.39 mol) was added in 1 portion and the cold bath was removed. At this point a sticky solid formed, and the reaction mixture was stirred vigorously. The reaction mixture was allowed to warm to room temperature and stir for 1 h. 6N Hydrochloric acid (300 mL) was then added slowly to minimize foaming and the reaction was stirred at room temperature for 30 minutes so that all of the solids were dissolved. The reaction was concentrated to remove the tetrahydrofuran then water (1L) was added. The solution was basified to pH 10 with 25% sodium hydroxide and the total volume was increased to 2L with water. The aqueous solution was extracted with methyl tert-butyl ether (3 × 650 mL). The organic layers were combined and extracted with 5% sodium hydroxide (500 mL). The aqueous phases were combined and acidified to pH 5.5 with 6N hydrochloric acid to form a suspension. This suspension was extracted with 2:1 ethyl acetate:THF (3 × 1.3L) making sure all of the solid dissolved in the organic layer. The organic layers were combined and back washed with water (1 L) then concentrated. The concentrate was triturated with methyl tert-butyl ether (1 L). The solid obtained was dried in a vacuum oven at 50˚C for 18 hours to give 35g (77%) of 6-(3-ethylureido)-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-3-ylboronic acid as an off-white solid.

MS (ESP): 361.2 ($M+H^+$) for $C_{12}H_{12}BF_3N_4O_3S$

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10 (t, 3H), 3.18 (m, 2H), 7.75 (brt, 1H), 7.91 (s, 1H), 8.18 (br, 2H), 8.31 (s, 1H), 8.64 (s, 1H), 9.31 (s, 1H).

Intermediate 496

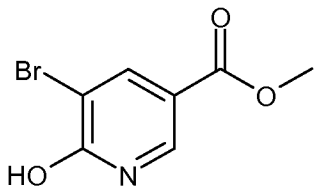
Methyl 6-hydroxynicotininate



6-Hydroxy-nicotinic acid (100 g, 719 mmol) was suspended in methanol (1 L). 18M Sulfuric acid (50 mL) was added and the reaction was heated at reflux for 16 h. The reaction mixture was then cooled, and sodium bicarbonate powder (45 g) was added slowly to neutralize some of the acid. Most of the methanol was then removed *in vacuo*. Water (1L) was added, and the pH adjusted to 7 with the careful addition of bicarbonate solution. The suspension was extracted with dichloromethane (4×, 200 mL), the organic phases were combined, dried over sodium sulfate, and the solvent was removed *in vacuo*. The solid was dried in a vacuum oven at 50°C for 1.5 hours. This gave 83g (75%) of methyl 6-hydroxynicotinate as a white solid.
MS (ESP): 154.2 (MH^+) for $C_7H_7NO_3$
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H), 6.59 (dd, 1H), 8.02 (dd, 1 H), 8.21 (m, 1H), 13.19 (bs, 1H)

Intermediate 497

Methyl 5-bromo-6-hydroxynicotininate



Methyl 6-hydroxynicotininate (Intermediate 496, 50 g, 327 mmol) was suspended in acetic acid (250 mL) and bromine (26.2 mL, 490.5 mmol) was added dropwise to the solution. The reaction mixture was heated at 60°C for 18 h. The reaction mixture was cooled to room temperature, and saturated sodium thiosulfate solution was added to remove remaining

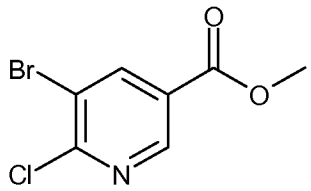
bromine. Saturated sodium bicarbonate solution (500 mL) was added slowly then 1N sodium hydroxide was added carefully until the pH was ~7. The solid that precipitated out of the solution was collected by filtration and dried in a vacuum oven at 50°C for 18 h. This gave 76 g (100%) of methyl 5-bromo-6-hydroxynicotininate as an off white solid.

MS (ESP): 231.9(MH^+) for $C_7H_6BrNO_3$

^1H NMR (300 MHz, DMSO-d_6): δ 3.80 (s, 3H), 8.12 (s, 1 H), 8.19 (s, 1H), 12.77 (bs, 1H)

Intermediate 498

Methyl 5-bromo-6-chloronicotinate



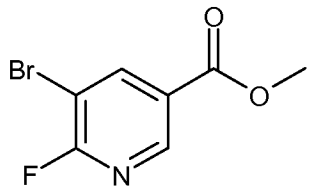
Methyl 5-bromo-6-hydroxynicotininate (Intermediate 497, 50 g, 215 mmol) was suspended in phosphorous oxychloride (100 mL). The reaction mixture was heated at reflux for 2 h. The phosphorous oxychloride was then removed *in vacuo*. The resulting residue was concentrated from toluene (200 mL) to remove any excess phosphorous oxychloride. This material was dried in a vacuum oven at 50°C for 5 h to give 44 g (82%) of methyl 5-bromo-6-chloronicotinate as an orange solid.

MS (ESP): 250.3 (MH^+) for $C_7H_5BrClNO_2$

^1H NMR (300 MHz, $CDCl_3$): δ 3.97 (s, 3H), 8.51 (d, 1H), 8.91 (d, 1 H).

Intermediate 499

Methyl 5-bromo-6-Fluoronicotinate



Methyl 5-bromo-6-chloronicotinate (Intermediate 498, 35 g, 139 mmol) was dissolved in acetonitrile (900 mL). Potassium fluoride (32 g, 560 mmol) and tetraphenyl

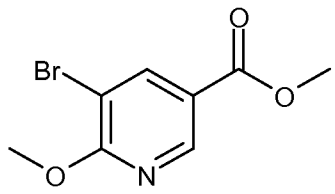
phosphoniumbromide (35 g, 84 mmol) were added and the reaction mixture was heated at reflux for 4.5 d. The reaction mixture was then cooled and the solid that formed was removed by filtration. The solution was concentrated under reduced pressure to give a pale orange oil. This resulting residue was chromatographed on 700g of silica gel using 5-7% ethyl acetate in heptane to give 19.6g (60%) of methyl 5-bromo-6-Fluoronicotinate as a white solid.

MS (ESP): 234.0(MH^+) for $C_7H_5BrFNO_2$

^{1}H NMR (300 MHz, $CDCl_3$): δ ppm 3.96 (s, 3H), 8.58 (m, 1H), 8.76 (m, 1H)

Intermediate 500

Methyl 5-bromo-6-methoxynicotinate

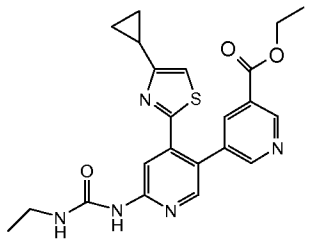


Methanol (0.173 mL, 4.27 mmol) and lithium bis(trimethylsilyl)-amide (4.27 mL, 4.27 mmol) were mixed in THF (4 mL). Methyl 5-bromo-6-fluoronicotinate (Intermediate 499, 0.5 g, 2.14 mmol) was added after 30 min. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure, partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The solid product was triturated from ACN, filtered off, washed with ACN. Isolation gave 0.5g of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 246, 248 for $C_8H_8BrNO_3$. ^{1}H NMR (300 MHz, $CDCl_3$): 3.93 (s, 3H), 4.09 (s, 3H), 8.41 (s, 1H), 8.75 (m, 1H).

Intermediate 501

Ethyl 4'-(4-cyclopropylthiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate



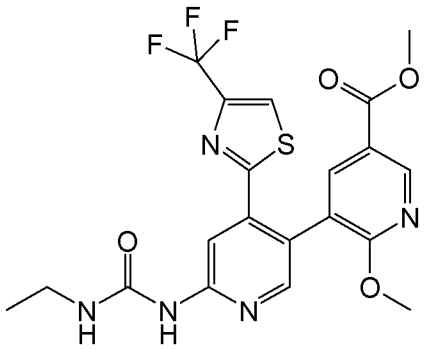
1-(5-bromo-4-(4-cyclopropylthiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 492, 20 g, 54.46 mmol), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (16.60g, 59.90 mmol), $Pd(PPh_3)_4$ (6.29g, 5.45 mmol) and cesium carbonate (26.6mg, 81.69 mmol) were combined in a 250 mL round bottom flask and suspended in a mixture of dioxane /water (4:1). The slurry was degassed and purged with nitrogen for 10 minutes. The reaction was then heated to 100°C for 1 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (250 mL) and washed with water then brine. The organic was dried over Na_2SO_4, filtered and concentrated to dryness by rotary evaporation. The concentrated solid residue was then suspended in minimal acetonitrile and filtered. Washed the filter cake with minimal acetonitrile. Dried in vacuo. Isolation gave 21.1g of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 438 for $C_{22}H_{23}N_5O_3S$.

^1H NMR (300 MHz, d_6-DMSO): 0.42 (m, 2H), 0.74 (m, 2H), 1.11 (t, 3H), 1.33 (m, 3H), 1.97 (m, 1H), 3.21(m, 2H), 4.34 (m, 2H), 7.40 (s, 1H), 7.64 (m, 1H), 8.08 (s, 1H), 8.12 (m, 1H), 8.26 (s, 1H), 8.65 (d, 1H), 9.07 (d, 1H), 9.41 (s, 1H).

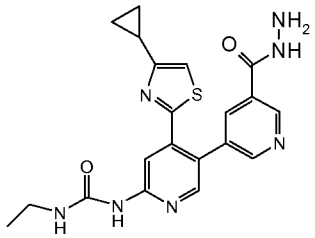
Intermediate 502

The following intermediate was prepared in accordance to the procedure described for Intermediate 501 using the starting materials indicated in the table.

Int	Compound	Data	SM
502	methyl 6'-(3-ethylureido)-2-methoxy-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate 	LC/MS $(ES^+)[(M+H)^+]$: 482 for $C_{20}H_{18}F_3N_5O_4S$.	Intermediate 495 and Intermediate 500

Intermediate 503

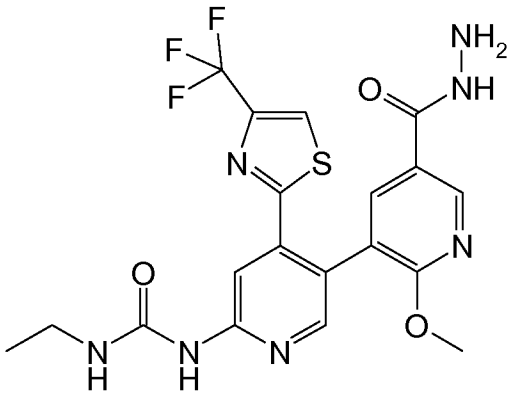
1-(4-(4-cyclopropylthiazol-2-yl)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea



Ethyl 4'-(4-cyclopropylthiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridine-5-carboxylate (Intermediate 501, 6.9 g, 15.77 mmol) was added to an ethanol solution (30 mL) containing hydrazine (4.95 mL, 157.71 mmol). The suspension was heated to reflux for 7 h. The reaction mixture was cooled to room temperature, filtered and the filter cake was washed with ethanol. The cake was dried in vacuo. Isolation gave 5.46g of the title compound.
LC/MS $(ES^+)[(M+H)^+]$: 424 for $C_{20}H_{21}N_7O_2S$.

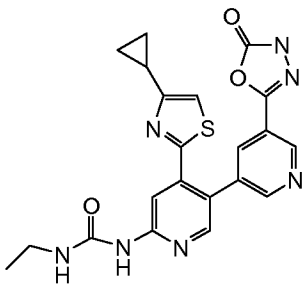
Intermediate 504

The following intermediates were prepared in accordance to the procedure described for Intermediate 503 using the starting materials indicated in the table.

Int	Compound	Data	SM
504	1-ethyl-3-(5'-(hydrazinecarbonyl)-2'-methoxy-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 482 for $C_{19}H_{18}F_3N_7O_3S$.	Intermediate 502

Intermediate 505

1-(4-(4-cyclopropylthiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea



1-(4-(4-cyclopropylthiazol-2-yl)-5'-(hydrazinecarbonyl)-3,3'-bipyridin-6-yl)-3-ethylurea (Intermediate 502, 5.46 g, 12.89 mmol) was suspended in a THF solution (50mL). Carbonyl diimidazole (3.14 g, 19.34 mmol) was added in a single portion. The reaction mixture was heated to 70°C for 30 min. The reaction mixture was cooled to room temperature, concentrated under reduced pressure, and diluted with EtOAc and water. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine. The organic layers were dried with Na_2SO_4, filtered and concentrated under reduced pressure. The concentrated solid residue was then suspended in minimal acetonitrile and filtered. The filter

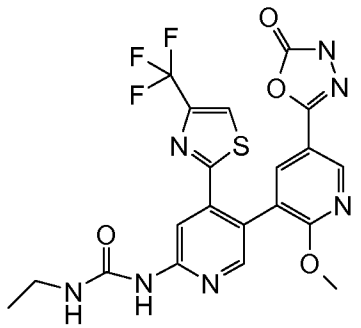
cake was washed with minimal acetonitrile, and then dried in vacuo. Isolation gave 3.52g of the title compound.

LC/MS (ES^+)[$(M+H)^+$]: 450 for $C_{21}H_{19}N_7O_3S$.

^1H NMR (300 MHz, d_6-DMSO): 0.45 (m, 2H), 0.76 (m, 2H), 1.10 (t, 3H), 1.97 (m, 1H), 3.21 (m, 2H), 7.40 (s, 1H), 7.63 (m, 1H), 8.02 (m, 1H), 8.08 (s, 1H), 8.27 (s, 1H), 8.55 (d, 1H), 8.95 (d, 1H), 9.41 (s, 1H), 12.74 (s, 1H).

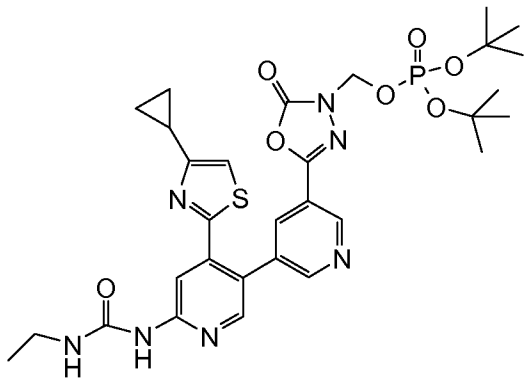
Intermediate 506

The following intermediates were prepared in accordance to the procedure described for Intermediate 505 using the starting materials indicated in the table.

Int	Compound	Data	SM
506	1-ethyl-3-(2'-methoxy-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea 	LC/MS (ES^+)[$(M+H)^+$]: 508 for $C_{20}H_{16}F_3N_7O_4S$. ^1H NMR (400 MHz, d_6-DMSO): 1.11 (t, 3H), 3.21 (m, 2H), 3.59 (s, 3H), 7.57 (t, 1H), 8.12 (d, 1H), 8.21 (s, 1H), 8.29 (s, 1H), 8.54(s, 1H), 8.65 (d, 1H), 9.45 (s, 1H), 12.32 (s, 1H).	Intermediate 504

Intermediate 507

di-tert-butyl (5-(4'-(4-cyclopropylthiazol-2-yl)-6'-(3-ethylureido)-3,3'-bipyridin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-yl)methyl phosphate



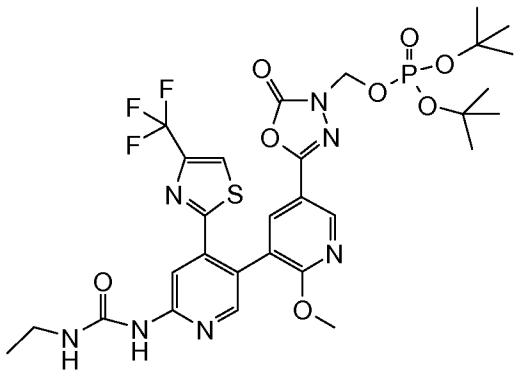
1-(4-(4-cyclopropylthiazol-2-yl)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Intermediate 505, 2.9 g, 6.45 mmol) was suspended in a solution of DMF(10mL). Cesium carbonate (2.52 g, 7.74 mmol) was added in one portion. The resulting mixture was stirred at room temperature for 5 min followed by addition of di-tert-butyl chloromethyl phosphate (Intermediate 2, 2.503 g, 7.74 mmol, Ref. US 2006/0047135 A1) was added. The reaction mixture was stirred at 45-50°C for 20 h. The reaction mixture was cooled to room temperature, poured onto ice, stirred in ice/water bath for 15 min. The yellow solid was filtered off, washed with water, and dried under reduced pressure. Isolation gave 3.71g of the title compound

LC/MS (ES^+)[$(M+H)^+$]: 672 for $C_{30}H_{38}N_7O_7PS$.

^1H NMR (300 MHz, d_6-DMSO): 0.43 (m, 2H), 0.77 (m, 2H), 1.11 (t, 3H), 1.41 (s, 18H), 1.97 (m, 1H), 3.21 (m, 2H), 5.50 (d, 2H), 7.41 (s, 1H), 7.62 (m, 1H), 8.07 (m, 1H), 8.09 (s, 1H), 8.28 (s, 1H), 8.62 (d, 1H), 8.99 (d, 1H), 9.42 (s, 1H).

Intermediate 508

The following intermediate was prepared in accordance to the procedure described for Intermediate 507 using the starting materials indicated in the table.

Int	Compound	Data	SM
508	di-tert-butyl (5-(6'-(3-ethylureido)-2-methoxy-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-yl)methyl phosphate 	LC/MS (ES^+)[$(M+H)^+$]: 730 for $C_{29}H_{35}F_3N_7O_8PS$. ^1H NMR (300 MHz, CDCl3): 1.28 (t, 3H), 1.52 (s, 18H), 3.43 (m, 2H), 3.73 (s, 3H), 5.59 (d, 2H), 7.46 (s, 1H), 7.76 (s, 1H), 8.03 (s, 1H), 8.04 (s, 1H), 8.17 (s, 1H), 8.74 (d, 1H), 8.87 (m, 1H).	Intermediate 488 and Intermediate 506

Intermediate 509

5-bromo-6-(1-methylpiperidin-4-yloxy)nicotinic acid

Methyl 5-bromo-6-fluoronicotinate (2 g, 8.6 mmol) was dissolved in 1-methylpiperidin-4-ol (49.5 g, 429 mmol) at 40˚C in a flask with a large head space. Sodium hydride (60% dispersion in oil, 3.09 g, 129 mmol) was added slowly over ~5 min under good stirring. After addition the mixture was heated at 40˚C overnight. Water (100 mL) was cautiously added and the pH adjusted to 7 with HCl. The material was extracted with ethyl acetate several times to remove any starting material and the aqueous was then subjected to reverse phase C18 chromatography (water/methanol) to give 1.4 g (52%) of product after drying.
MS (ESP): 315, 317.1 (MH^+) for $C_{12}H_{15}BrN_2O_3$

^{1}H NMR (300 MHz, CD_3OD): δ 2.1-2.3 (m, 4H), 2.85 (s, 3H), 3.2-3.4 (m, 4H), 5.41 (m, 1H), 8.39 (d, 1H), 8.64 (d, 1H).

Intermediate 510

tert-butyl 2-(5-bromo-6-(1-methylpiperidin-4yloxy)nicotinoyl)hydrazinecarboxylate

To a mixture of 5-bromo-6-(1-methylpiperidin-4-yloxy)nicotinic acid (Intermediate 509, 1.31 g, 4.2 mmol), tert-butyl hydrazinecarboxylate (1.12 g, 8.5 mmol) and triethylamine (1.81 mL, 12.6 mmol) in tetrahydrofuran (20 mL) was added HATU (1.91 g, 5.0 mmol) and the mixture stirred at room temperature overnight. The organics were removed in vacuo and the residue was washed with brine and chromatographed (dichloromethane/methanol) to give ~1.2 g (67%) of white solid.

MS (ESP): 429.0, 431.1 (MH^+) for $C_{17}H_{25}BrN_4O_4$

^{1}H NMR (300 MHz, CD_3OD): δ 1.50 (s, 9H), 2.0-2.25 (m, 4H), 2.73 (s, 3H), 3.06-3.22 (m, 4H), 5.43 (br s, 1H), 8.38 (br s, 1H), 8.60 (br s, 1H).

Intermediate 511

4-(4-cyclopropylthiazol-2-yl)-6-(3-ethylureido)pyridin-3-ylboronic acid

A suspension of 1-(5-bromo-4-(4-cyclopropylthiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 492, 2.2 g, 6.10 mmol) in tetrahydrofuran (60 mL) was cooled to -50°C. Isopropyl magnesium chloride in tetrahydrofuran (2.0 M, 7.6 mL, 15.2 mmol) was added dropwise over ~10 minutes so that the temperature never rose above -35°C. The reaction was stirred for a further hour at -40°C then was cooled to -78°C. 2.5M n-Butyl lithium in hexanes (13.6 mL, 34.2 mmol) was then added dropwise to the reaction solution so that the temperature never rose above -65°C. The dark red mixture was then allowed to stir at -78°C for 1 h. Boron methoxide (6.5 mL, 58.5 mmol) was added in 1 portion and the cold bath was removed. At this point a sticky solid formed, so good stirring is essential. The reaction was allowed to warm to room temperature and stir for 1 h. 6N Hydrochloric acid (10 mL) was then added and the stirring continued. The mixture was extracted with ethyl acetate (2×, 100 mL), dried and the solvent evaporated. The residue was triturated with methyl tert-butyl ether /water to give solids that were still impure. The material was taken back up into water with 24% sodium hydroxide (to pH 10) and washed with ethyl acetate. The mixture was acidified to pH 5-6 with HCl and the solids filtered and dried. More product precipitated from the ethyl

acetate layer and was recovered to give a total of ~800 mg of product. The triturates and aqueous that retained more product were kept for later re-processing if needed.

MS (ESP): 333.0 (MH^+) for $C_{14}H_{17}BN_4O_3S$

^1H NMR (300 MHz, dmso-d_6): δ 0.93 (m, 2H), 1.09 (m, 5H), 2.08 (m, 1H), 3.17 (m, 2H), 7.46 (s, 1H), 7.82 (m, 2H), 8.23 (brs, 2H), 8.27 (s, 1H), 9.20 (s, 1H).

Intermediate 512

tert-butyl 2-(4'-(4-cyclopropylthiazol-2-yl)-6'-(3-ethylureido)-2-(1-methylpiperidin-4-yloxy)-3,3'-bipyridine-5-carbonyl)hydrazinecarboxylate

A mixture of 4-(4-cyclopropylthiazol-2-yl)-6-(3-ethylureido)pyridin-3-ylboronic acid (Intermediate 511, 400 mg, 1.2 mmol), tert-butyl 2-(5-bromo-6-(1-methylpiperidin-4-yloxy)nicotinoyl)hydrazinecarboxylate (Intermediate 24, 340 mg, 0.8 mmol) and potassium carbonate (220 mg, 1.6 mmol) in dioxane (16 mL) and DIUF water (4 mL) was purged for ~10 min with N_2. Trans dichlorobis(triphenylphosphine)palladium (II) (56 mg, 0.08 mmol) was added and the mixture heated to 80°C in a heating block. After 1-2 h the reaction was complete and the material was cooled to room temperature. A second batch (~1 mmol boronic acid) was combined and the mixture filtered through Celite. The organics were evaporated and the residue diluted with DIUF water and filtered. This gave ~1.1 g of brownish foam which was used 'as is' in the next reaction.

MS (ESP): 637.2 (MH^+) for $C_{31}H_{40}N_8O_5S$

Intermediate 513

1-(4-(4-cyclopropylthiazol-2-yl)-2'-(1-methylpiperidin-4-yloxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea

To crude tert-butyl 2-(4'-(4-cyclopropylthiazol-2-yl)-6'-(3-ethylureido)-2-(1-methylpiperidin-4-yloxy)-3,3'-bipyridine-5-carbonyl)hydrazinecarboxylate (~2.2 mmol) in dichloromethane (5 mL) was added 4 M HCl in dioxane (2 mL) and the reaction stirred at room temperature for ~1 h at which time a gummy solid had formed. The dichloromethane was decanted away from the reaction and checked for product before discarding.

The crude residue was then re-dissolved in tetrahydrofuran (10 mL) and triethyl amine added (~500 μL). To this was added 1,1'-carbonyl diimidazole (900 mg) and the reaction

stirred at room temperature monitoring by LCMS. The crude was then chromatographed on an Analogix 4 g column using 0-10% methanol in dichloromethane as an eluent. This gave ~230 mg of product.

MS (ESP): 563.1 (MH^+) for $C_{27}H_{30}N_8O_4S$

^1H NMR (300 MHz, dmso-d_6): δ 0.46 (brs, 2H), 0.76 (brd, 2H), 1.10 (t, 3H), 1.15-1.35 (brs, 2H), 1.60 (brs, 2H), 2.06 (s, 3H), 1.98-2.26 (m, 5H), 3.22 (m, 2H), 4.86 (brs, 1H), 7.34 (s, 1H), 7.70 (t, 1H), 8.02 (d, 1H), 8.08 (s, 1H), 8.16 (s, 1H), 8.58 (d, 1H), 9.38 (s, 1H).

Intermediate 514

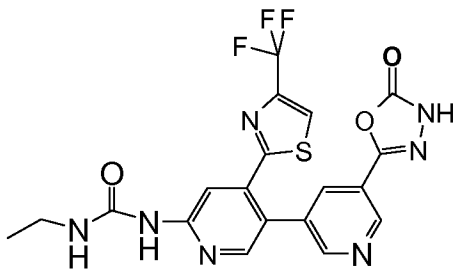
di-tert-butyl (5-(4'-(4-cyclopropylthiazol-2-yl)-6'-(3-ethylureido)-2-(1-methylpiperidin-4-yloxy)-3,3'-bipyridin-5-yl)-2-oxo-1,3,4-oxadiazol-3(2H)-yl)methyl phosphate

A solution of 1-(4-(4-cyclopropylthiazol-2-yl)-2'-(1-methylpiperidin-4-yloxy)-5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-3,3'-bipyridin-6-yl)-3-ethylurea (Intermediate 513, 250 mg, 0.44 mmol), cesium carbonate (159 mg, 0.49 mmol) and di-tert-butyl chloromethyl phosphate (Intermediate 2, 138 mg, 0.53 mmol) in dimethylformamide (2 mL) was allowed to stir at room temperature for several days until no further reaction was observed. The mixture was then diluted with water, filtered and mostly dried to give 167 mg of yellow solid which was used without further purification.

MS (ESP): 785 ($M+H^+$) for $C_{36}H_{49}N_8O_8PS$.

Intermediate 515

1-Ethyl-3-(5'-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



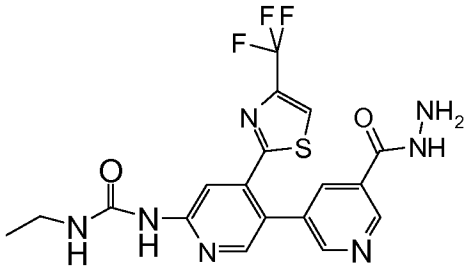
Diisopropylethylamine (0.061 mL, 0.35 mmol) and carbonyldiimidazole (56.6 mg, 0.35 mmol) were added to a solution of 1-ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea (Intermediate 516, 105 mg, 0.23 mmol) in DMF (1.5 mL), and the mixture was stirred at room temperature for 1.5 hours. The reaction was diluted with water and extracted with 5% methanol in dichloromethane. The combined extract was washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. The crude residue obtained was purified by normal phase chromatography (2 % MeOH in dichloromethane to 8 % MeOH) to give the desired compound as a white solid (65 mg).

MS (ESP): 478 (M+1) for $C_{19}H_{14}F_3N_7O_3S$

^{1}H-NMR (DMSO-d_6) δ: 1.10 (t, 3H); 3.16-3.28 (m, 2H); 7.55 (brs, 1H); 8.09 (s, 1H); 8.22 (s, 1H); 8.37 (s, 1H); 8.57 (s, 1H); 8.62 (s, 1H); 8.97 (s, 1H); 9.50 (s, 1H); 12.80 (s, 1H).

Intermediate 516

1-Ethyl-3-(5'-(hydrazinecarbonyl)-4-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridin-6-yl)urea



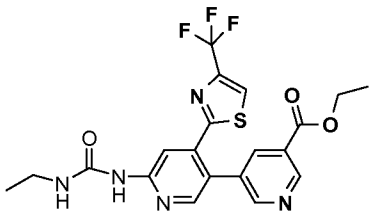
Ethyl 6'-(3-ethylureido)-4'-(4-(trifluoromethyl)thiazol-2-yl)-3,3'-bipyridine-5-carboxylate (Intermediate 517, 150 mg, 0.32 mmol) and hydrazine hydrate (31 mg, 0.97 mmol) were taken in ethanol (6 ml) and heated at 80 °C for 5 h. The reaction mixture was cooled down and concentrated under reduced pressure to give tan colored solid that was washed with 10% MeOH in dichloromethane and dried to give the title compound (101 mg).

MS (ESP): 452 (M+1) for $C_{18}H_{16}F_3N_7O_3S$

^{1}H-NMR (DMSO-d_6) δ: 1.09 (t, 3H); 3.10-3.25 (m, 2H); 4.57 (brs, 2H); 7.55 (brs, 1H); 8.13 (s, 1H); 8.23 (s, 1H); 8.34 (s, 1H); 8.55 (s, 1H); 8.59 (s, 1H); 8.99 (s, 1H); 9.48 (s, 1H); 9.97 (s, 1H).

Intermediate 517

Ethyl 6'-{[(ethylamino)carbonyl]amino}-4'-[4-(trifluoromethyl)-1,3-thiazol-2-yl]-3,3'-bipyridine-5-carboxylate



1-(5-Bromo-4-(4-(trifluoromethyl)thiazol-2-yl)pyridin-2-yl)-3-ethylurea (Intermediate 494, 500 mg, 1.27 mmol), cesium carbonate (618 mg, 1.90 mmol), tetrakis(triphenylphosphine)palladium(0) (146 mg, 0.13 mmol), ethyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinate (526 mg, 1.52 mmol) were taken in a microwave vial and degassed with Argon. Then dioxane:water (4:1, 8 mL) was added to it and microwaved at 100 °C for half an hour. The reaction mixture was partitioned between water and ethyl acetate and layers separated. The organic layer was washed with saturated sodium bicarbonate solution, water, brine and dried over magnesium sulfate. The solvent was removed and the residue was purified by flash chromatography eluting with 2% MeOH in dichloromethane to 3 % MeOH in dichloromethane to give 330 mg of the title compound.

MS (ES) MH^+: 466 for $C_{20}H_{18}F_3N_5O_3S$;

^{1}H-NMR (DMSO-d_6) δ: 1.11 (t, 3H); 1.31(t , 3H); 3.18- 3.24 (m, 2H); 4.34 (q, 2H); 7.57 (brs, 1H); 8.16-8.18 (m, 1H); 8.21 (s, 1H); 8.39 (s, 1H); 8.58 (s, 1H); 8.75 (d, 1H); 9.10 (s, 1H); 9.52 (s, 1H).

Incorporation By Reference

The entire contents of all patents, published patent applications and other references cited herein are hereby expressly incorporated herein in their entireties by reference.

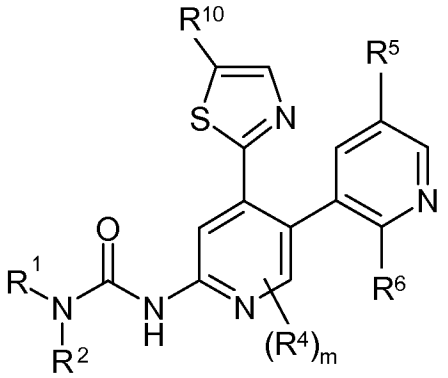
Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents were considered to be within the scope of this invention and are covered by the following claims. Moreover, any numerical or alphabetical ranges provided herein are intended to include both the upper and lower value of those ranges. In addition, any listing or grouping is intended, at least in one embodiment, to represent a shorthand or convenient

manner of listing independent embodiments; as such, each member of the list should be considered a separate embodiment.

Claims

1. A compound of formula **(I)**:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more R^7;

R^2 is selected from hydrogen or C_{1-6}alkyl; wherein said C_{1-6}alkyl may be optionally substituted by one or more groups independently selected from halo, cyano, hydroxy, nitro and amino;

or **R^1 and R^2 together** with the nitrogen to which they are attached form a heterocyclyl; wherein said heterocyclyl may be optionally substituted on one or more carbon atoms with one or more R^8; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^4, for each occurrence, is independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, mercapto, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, and C_{1-6}alkylsulfanyl; wherein R^4, for each occurrence, is independently optionally substituted on one or more carbon atoms with one or more R^{12};

R^5 is a nitrogen-containing heterocyclyl, wherein said nitrogen is substituted by a methyl dihydrogen phosphate group; wherein the heterocyclyl may be optionally substituted on one or more carbon atoms with an =O, =S, or one or more R^{14}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups;

R^6, for each occurrence, is independently selected from the group consisting of halo, nitro, cyano, hydroxy, amino, mercapto, sulphamoyl, =O, =S, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkylS(O)$_a$- wherein a is 0, 1 or 2, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, *N'*-hydroxycarbamimidoyl, carbamimidoyl, C_{3-14}carbocyclyl-L- and heterocyclyl-L-; wherein R^6, for each occurrence, is independently optionally substituted on one or more carbon atoms with one or more R^{16}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

m is 0 or 1;

R^7, R^8, R^{10}, R^{12}, R^{14} and R^{16} are substituents on carbon which, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$- wherein a is 0, 1 or 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino, C_{3-6}carbocyclyl-L- or heterocyclyl-L-; wherein R^7, R^8, R^{10}, R^{12}, R^{14} and R^{16} independently of each other may be optionally substituted on one or more carbon by one or more R^{19}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{20}; and wherein if said heterocyclyl contains an =N- or a –S- moiety that nitrogen may be optionally substituted by one oxo group and that sulfur may be optionally substituted by one or two oxo groups

R^9, R^{13}, and R^{20}, for each occurrence, are independently selected from C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkanoyl, C_{1-6}alkylsulphonyl, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, imidazolylcarbonyl, amino, benzoyl and phenylsulphonyl; wherein R^9, R^{13}, and R^{20} independently of each other may be optionally substituted on carbon by one or more R^{23};

R^{19} and R^{23}, for each occurrence, are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, 2-methoxyethoxy, morpholinyl, piperazinyl, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino,

N-methyl-*N*-ethylamino, N-(2-morpholinoethyl)-amino, cyclohexylamino, cyclopentylamino, cyclohexyl, acetylamino, 2-methyoxyethylamino, tetrahydropyran-4-ylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, benzyloxy, 9*H*-fluoren-9-ylmethoxycarbonylamino, t-butoxycarbonylamino, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

L is a direct bond, -O-, -C(O)-, -C(O)NR^{25}-, -NR^{25}C(O)-, or $–CH_2$-; and

R^{25} is H or a C_{1-6}alkyl.

2. The compound of Claim 1, or pharmaceutically acceptable salts thereof, wherein R^1 is a C_{1-6}alkyl.

3. The compound of Claim 2, or pharmaceutically acceptable salts thereof, wherein R^1 is ethyl.

4. The compound of any one of Claims 1-3, or pharmaceutically acceptable salts thereof, wherein R^2 is hydrogen.

5. The compound of any one of Claims 1-4, or pharmaceutically acceptable salts thereof, wherein m is 0.

6. The compound of any one of Claims 1-5, or pharmaceutically acceptable salts thereof, wherein R^{10} is selected from the group consisting of methyl, cyclopropyl, phenyl, trifluoromethyl, and pyridinyl.

7. The compound of any one of Claims 1-6, or pharmaceutically acceptable salts thereof, wherein R^5 is a nitrogen-containing five membered aromatic heterocyclyl, wherein said nitrogen is substituted by a methyl dihydrogen phosphate group.

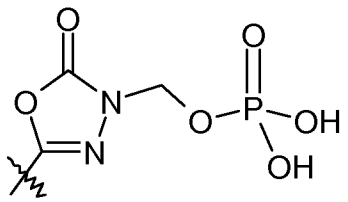
8. The compound of Claim 7, or pharmaceutically acceptable salts thereof, wherein R^{14} is selected from the group consisting of C_{1-4}alkyl or hydroxy.

9. The compound of Claim 7 or 8, or pharmaceutically acceptable salts thereof, wherein R^{15} is a C_{1-4}alkyl.

10. The compound of Claim 7, or pharmaceutically acceptable salts thereof, wherein R^5 is a nitrogen-containing heterocyclyl, wherein said nitrogen is substituted by a methyl dihydrogen phosphate group, and wherein the heterocyclyl is selected from the group consisting of 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1*H*-tetrazolyl, 1,2,4-oxadiazolyl, 1*H*-pyrazolyl, 3*H*-1,2,3,5-oxathiadiazolyl, 1*H*-imidazolyl, morpholinyl, 4,5-dihydro-oxazolyl, and 1*H*-1,2,4-triazolyl, wherein the 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1*H*-tetrazolyl, 1,2,4-oxadiazolyl, 1*H*-pyrazolyl, 3*H*-1,2,3,5-oxathiadiazolyl, 1*H*-imidazolyl, morpholinyl, 4,5-dihydro-oxazolyl, and 1*H*-1,2,4-triazolyl may be optionally substituted on one or more carbon atoms with one or more R^{14}; and wherein the =N- moiety of 1,3,4-oxadiazolyl, 1,3,4-thiadiazolyl, 1*H*-tetrazolyl, 1,2,4-oxadiazolyl, 1*H*-pyrazolyl, 3*H*-1,2,3,5-oxathiadiazolyl, 1*H*-imidazolyl, 4,5-dihydro-oxazolyl, and 1*H*-1,2,4-triazolyl may be optionally substituted with one oxo group and the –S- moiety of 1,3,4-thiadiazolyl or the 3*H*-1,2,3,5-oxathiadiazolyl, may be optionally substituted by one or two oxo groups; and wherein the -NH- moiety of the 1*H*-tetrazolyl, 1*H*-pyrazolyl, 3*H*-1,2,3,5-oxathiadiazolyl, 1*H*-imidazolyl, morpholinyl, or the 1*H*-1,2,4-triazolyl may be optionally substituted by a group selected from R^{15}.

11. The compound of Claim 10, or pharmaceutically acceptable salts thereof, wherein the heterocyclyl is 5-oxo-4,5-dihydro-1,3,4-oxadiazo-2-yl.

12. The compound of Claim 10, or pharmaceutically acceptable salts thereof, wherein R^5 is



13. The compound of any one of Claims 1-12, or pharmaceutically acceptable salts thereof, wherein R^6 is hydrogen or C_{1-6}alkoxy.

14. A pharmaceutical composition comprising a compound of any one of Claims 1-13, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient or carrier.

15. A method of inhibiting bacterial DNA gyrase and/or bacterial topoisomerase IV in a warm-blooded animal in need of such treatment, comprising administering to the animal an effective amount of a compound of any one of Claims 1-13, or a pharmaceutically acceptable salt thereof.

16. A method of producing an antibacterial effect in a warm-blooded animal in need of such treatment, comprising administering to the animal an effective amount of a compound of any one of Claims 1-13, or a pharmaceutically acceptable salt thereof.

17. A method of treating a bacterial infection in a warm-blooded animal in need thereof, comprising administering to the animal an effective amount of a compound of any one of Claims 1-13, or a pharmaceutically acceptable salt thereof.

18. The method of Claim 17, wherein the bacterial infection is selected from the group consisting of community-acquired pneumoniae, hospital-acquired pneumoniae, skin and skin structure infections, acute exacerbation of chronic bronchitis, acute sinusitis, acute otitis media, catheter-related sepsis, febrile neutropenia, osteomyelitis, endocarditis, urinary tract infections and infections caused by drug resistant bacteria such as Penicillin-resistant Streptococcus pneumoniae, methicillin-resistant Staphylococcus aureus, methicillin-resistant Staphylococcus epidermidis and Vancomycin-Resistant Enterococci.

19. The method of Claim 17, wherein the warm-blooded animal is a human.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/051417

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/14 A61P31/04 A61K31/444 C07F9/09
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07F C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/068470 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BASARAB GREGORY STEVEN [) 12 June 2008 (2008-06-12) page 1, paragraph 1 claim 1	1-19
A	WO 2006/092599 A2 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BASARAB GREG [US]; GRAVE) 8 September 2006 (2006-09-08) page 1 claim 1	1-19
A	WO 2007/071965 A2 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; BASARAB GREGORY [US]; NI) 28 June 2007 (2007-06-28) page 1 claim 2	1-19

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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 :

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 2010	18/11/2010

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	Fanni, Stefano

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No
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